Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

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ABSTRACT

The study aimed to develop evidence-based recommendations regarding the evaluation and use of biosimilars to treat rheumatological diseases. The task force comprised an expert group of specialists in rheumatology, dermatology and gastroenterology, and pharmacologists, patients and a regulator from ten countries. Four key topics regarding biosimilars were identified through a process of discussion and consensus. Using a Delphi process, specific questions were then formulated to guide a systematic literature review. Relevant English-language publications through November 2016 were searched systematically for each topic using Medline; selected papers and pertinent reviews were examined for additional relevant references; and abstracts presented at the 2015 and 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual scientific meetings were searched for those about biosimilars. The experts used evidence obtained from these studies to develop a set of overarching principles and consensus recommendations. The level of evidence and grade of recommendation were determined for each. By the search strategy, 490 references were identified. Of these, 29 full-text papers were included in the systematic review. Additionally, 20 abstracts were retrieved from the ACR and EULAR conference abstract databases. Five overarching principles and eight consensus recommendations were generated, encompassing considerations regarding clinical trials, immunogenicity, extrapolation of indications, switching between bio-originators and biosimilars and among biosimilars, and cost. The level of evidence and grade of recommendation for each varied according to available published evidence. Five overarching principles and eight consensus recommendations regarding the evaluation and use of biosimilars to treat rheumatological diseases were developed using research-based evidence and expert opinion.

INTRODUCTION

Treatment with biological agents (biologics) has dramatically improved the outcome for patients with inflammatory diseases. However, the high cost of these medications has limited access for many patients.[1] To make effective biologics more widely available, biosimilars of products that no longer are protected by patent have been developed and have been made available to patients at costs lower than those of the bio-originator. In the European Union (EU), the USA, Japan and other countries, biosimilars of adalimumab, etanercept, infliximab and rituximab have been approved, and those for which the bio-originator no longer is protected by patent have been marketed.

Over the past decade, several publications have examined the scientific, legal and regulatory aspects of biosimilar development.[1–6] However, little has been published to guide healthcare providers in critically evaluating and differentiating the scientific data available for each of these molecules. Thus, a multidisciplinary group was convened to develop consensus, at an international level, among patients and physicians regarding the evaluation and use of biosimilars to treat rheumatological diseases.

METHODS

Participants

An international multidisciplinary task force on biosimilars was convened in 2016, consisting of 25 experts from eight European countries, Japan and the USA (17 rheumatologists, 1 rheumatologist/regulator, 1 dermatologist, 1 gastroenterologist, 2 pharmacologists, 2 patients with rheumatic diseases as patients' representatives and 1 research fellow). The objective was to develop an evidence-based and consensus-based statement about the use of biosimilars to treat inflammatory diseases by identifying and critically appraising evidence in the literature. This statement was intended both to guide clinicians and to serve as a framework for future educational efforts.

Experts' consensus

In August 2016, a steering committee consisting of six rheumatologists and one research fellow, all of whom were members of this task force, held a preliminary meeting in Vienna, Austria. At this meeting, they identified four key topics for further discussion by the task force: issues related to clinical trials of biosimilars, extrapolation of indications, immunogenicity of biosimilars compared with their bio-originators, and switching between bio-originators and biosimilars and among biosimilars. Using a Delphi process, specific questions were formulated about these subjects to guide a systematic literature review (SLR), which was then performed to identify relevant publications through November 2016.

The Medline database was searched for English-language publications about biosimilars; selected papers and pertinent reviews were examined for additional relevant references. Abstracts presented at the 2015 and 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual scientific

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meetings were searched for those about biosimilars. The European public assessment reports for human medicines, published by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) publications (Drugs@FDA), were reviewed to identify those about biosimilars approved by the EMA and/or the FDA to treat rheumatological diseases, as of December 2016 (online supplementary table S1). The EU clinical trials register and ClinicalTrials.gov databases were queried to identify clinical trials in which a biosimilar was studied in patients with an inflammatory disease. We included publications on biosimilars that were approved to treat rheumatological diseases. During the initial search process, no quality criteria were applied for inclusion, but all relevant studies were later rated using the Oxford Centre for Evidence-Based Medicine Levels of Evidence 1.[7]

The findings of the SLR were communicated to the steering committee members, augmented by two pharmacologists and a rheumatologist/regulator, at a second meeting that was held in Leiden, the Netherlands, in December 2016. Additional presentations were made about the relative immunogenicity of biosimilars to their bio-originators and about regulatory issues related to approval of biosimilars by the EMA. Group discussion followed these talks, during which overarching principles and consensus statements were developed to propose to the entire task force.

On the following day, a consensus conference took place, at which all but two members of the full task force were in attendance. At this face-to-face meeting, a summary of the evidence obtained through the SLR was presented to the entire task force. Subsequently, the proposed overarching principles and consensus statements that had been developed by the augmented steering committee were presented. The task force members deliberated on each statement and modified the wording, if necessary. Each statement was then voted on and high-level agreement was achieved for all statements. The two members of the task force who were absent from the Leiden meeting subsequently voted on each statement by email and their votes were combined with those of the other task force members (table 1). Overarching principles and recommendations were accepted when ≥80% of the experts agreed.

RESULTS

Systematic literature review

The initial search strategy (online supplementary table S2) identified 490 publications in Medline, as of December 2016. After the selection process had been applied, 29 full-text papers were included. From the ACR and EULAR conference abstract databases, 20 abstracts were retrieved (online supplementary figure S1).

Experts' opinion approach

After discussing the results of the SLR, the consensus process was initiated. The full task force agreed on five overarching principles and eight consensus recommendations (table 1).

Table 1 Overarching principles (A–E) and consensus recommendations (1–8) for biosimilars

		Agreement* (%)	Level of evidence†	Grade of recommendation‡
Overarching principles				
A.	Treatment of rheumatic diseases is based on a shared decision-making process between patients and their rheumatologists.	100	5	D
B.	The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made.	100	5	D
C.	A biosimilar, as approved by authorities in a highly regulated area, is neither better nor worse in efficacy and not inferior in safety to its bio-originator.	88	5	D
D.	Patients and healthcare providers should be informed about the nature of biosimilars, their approval process, and their safety and efficacy.	96	5	D
E.	Harmonised methods should be established to obtain reliable pharmacovigilance data, including traceability, about both biosimilars and bio-originators.	100	5	D
Consensus recommendations				
1.	The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases.	100	5	D
2.	Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators.	100	1b	A
3.	As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, antidrug antibodies to biosimilars need not be measured in clinical practice.	100	2b	B
4.	Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published.	100	5	D
5.	Since the biosimilar is equivalent to the bio-originator in its physicochemical, functional and pharmacokinetic properties, confirmation of efficacy and safety in a single indication is sufficient for extrapolation to other diseases for which the bio-originator has been approved.	100	5	D
6.	Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered.	96	1b	A
7.	Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries.	100	5	D
8.	No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider.	91	5	D

*Agreement indicates percentage of experts who approved the recommendation during the final voting round of the consensus meeting.
†1a: systematic review of randomised clinical trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT; eg, <80% follow-up); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case-series (and poor quality cohort and case–control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
‡A: based on consistent level 1 evidence; B: based on consistent level 2 or 3 evidence or extrapolations from level 1 evidence; C: based on level 4 evidence or extrapolations from level 2 or 3 evidence; D: based on level 5 evidence or on troublingly inconsistent or inconclusive studies of any level.

RECOMMENDATIONS

Five main topics related to biosimilars were identified: considerations regarding clinical trials, immunogenicity, extrapolation of indications, switching between bio-originators and biosimilars and among biosimilars, and cost. Within each of these areas, key issues were identified that form the basis for the overarching principles and consensus recommendations described here (table 1). We present the overarching principles and consensus statements in the sequence listed in table 1, followed by an explanatory discussion of each.

Overarching principles

Treatment of rheumatic diseases is based on a shared decision-making process between patients and their rheumatologists

A fundamental principle underlying the treatment of all diseases is that informed patients share in making decisions about therapy with their healthcare providers. For the rheumatic diseases, the rheumatologist is obliged to educate the patient both about the disease process and about appropriate treatment options. Once informed, the patient can then engage the healthcare provider in a dialogue in which personal preferences, treatment goals, and the potential risks and benefits of each treatment option are discussed and evaluated relative to one another. Such a discussion should result in optimal treatment of the disease process and empower patients to remain in control of their health.

The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made

The structure of healthcare systems varies in different countries. In some countries, the government oversees the healthcare system and serves as a single payer to cover the costs of medical treatment for its citizens. In other countries, such as the USA, a variety of systems are in place to support access to healthcare: some patients are covered by government-supported insurance plans, others purchase private insurance coverage, and some have no health insurance coverage at all. In single-payer systems, the payer often supports the cost of medications. However, in countries in which coverage for healthcare expenses is provided by a variety of systems, there often is a similar range of approaches to subsidise the cost of medications. Among those individuals who have prescription coverage, the proportion of the drug acquisition cost that is subsidised varies. Although only a small monetary copayment is required of some patients, others are expected to pay 20% or more of the cost of medications. This can place a significant burden on some individuals and may make necessary treatment inaccessible to some. These contextual aspects must be considered when choosing appropriate drug therapy for a given patient, since lower drug costs increase affordability.

A biosimilar, as approved by authorities in a highly regulated area, is neither better nor worse in efficacy and not inferior in safety to its bio-originator

A biosimilar is a replica of a biopharmaceutical that has met criteria for biosimilarity, according to a defined pathway established to demonstrate equivalent pharmacokinetics (PK), pharmacodynamics (PD) and efficacy and comparable safety and immunogenicity, and has been reviewed and approved by a regulatory authority in a highly regulated area. Many such regulatory agencies are members or observers of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[8] ICH aims to recommend guidelines and requirements for approval of pharmaceutical products to achieve harmonisation among regulatory agencies worldwide.

The EMA defines a biosimilar as 'a biological medicinal product that contains a version of the active substance of an already authorised' bio-originator, for which 'similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy' has been demonstrated.[9] In the USA, a biosimilar is defined in the Biologics Price Competition and Innovation Act of 2009 as a biological product that is 'highly similar to the reference product notwithstanding minor differences in clinically inactive components' and that 'there are no clinically meaningful differences between the reference product and the biologic product in terms of the safety, purity and potency of the product'.[10] In 2005, the EMA proposed a pathway by which to approve similar biological products.[11] Five years later, the US Congress established a pathway for the approval of biological products that are 'highly similar' to their bio-originators.[10]

The regulatory pathways for approval of a biosimilar differ slightly between the EMA and the US FDA, but both follow a 'stepwise approach' and require extensive analytical studies followed by clinical studies comparing PK and PD parameters, immunogenicity, efficacy and safety of the proposed biosimilar to its bio-originator to confirm that there are 'no clinical meaningful differences' between the bio-originator and the biosimilar. The US FDA has articulated a 'totality of the evidence' approach to evaluating the accumulated data, in which all of the information is considered in its entirety without giving greater importance to any one aspect.[12] The EMA follows a similar process.[13] Many other countries have conformed to this approach and established comparable pathways to approve biosimilars.[3]

Biosimilarity is established, following a stepwise approach, by a series of comparative studies with high face validity. Analyses must demonstrate that the biosimilar and its bio-originator have the same primary amino acid sequence. Comparing multiple batches of a biosimilar candidate with many batches of its bio-originator, acquired over time, there must be no significant differences in charge isoforms, glycosylation, other post-translational modifications or impurities. There may be minor differences, but these must not affect critical quality attributes of the biologic. For therapeutic monoclonal antibodies, essential functional properties include Fc receptor binding, complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, on which their mechanism of action may depend. Subsequent clinical studies must demonstrate PK and PD equivalence and equivalent efficacy in at least one disease for which the bio-originator is approved, as well as comparable safety and no greater immunogenicity of the biosimilar.

Because a biosimilar can rely on data generated for approval of its bio-originator, the clinical data required by regulatory pathways for biosimilar approval in the EU, the USA and most other countries are abbreviated, contrasted to those required for approval of bio-originators. PK typically is studied by comparing single doses of a biosimilar and its bio-originator in healthy subjects[14–20]; multiple dosing is subsequently assessed in patients.[21–24] Most regulatory agencies define PK equivalence of a biosimilar to its bio-originator as when the 90% CIs for the ratio of geometric means for area under the curve and maximal concentration between the biosimilar and its bio-originator fall within the log-transformed range of 80%–125% (±20%).[5 6] In published PK studies of approved biosimilar tumour necrosis factor (TNF) inhibitors, serum concentration time profiles of the biosimilar and its bio-originator have overlapped closely, and variability of the ratio of geometric means for PK parameters has been much less than that allowed by regulatory requirements.[7–12]

Phase III randomised controlled trials (RCTs) comparing the efficacy of a candidate biosimilar with its bio-originator should be conducted in a disease that is sensitive for detecting potential differences in efficacy between the biosimilar and its bio-originator. However, the same condition may not be the most sensitive in which to detect potential differences in safety, including immunogenicity. RCTs comparing a candidate biosimilar with its bio-originator should be of adequate duration to assess durability of response, safety and immunogenicity. These trials should use endpoints that are sensitive to detecting potential differences between a biosimilar and its bio-originator. Assessment of an outcome measure at early time points, during the rapid rise phase of the time–response curve, provides additional information.[25] Assessing response to treatment during the first 3 months allows comparison of the rapidity of onset. These issues must be taken into consideration when designing phase III RCTs comparing biosimilar with their bio-originators.

Since a phase III RCT comparing a biosimilar with its bio-originator is designed to demonstrate equivalence and aims to prove the null hypothesis, the primary analysis should be performed on the per protocol set.[26] Although an intention-to-treat analysis would bias towards the null hypothesis concluding that the two drugs are equivalent, secondary analyses should be performed on each endpoint using the intention-to-treat approach to account for possible differential dropout in the two treatment arms. The equivalence margin for RCTs comparing the efficacy of a biosimilar with its bio-originator is derived from a meta-analysis of the therapeutic effect of the bio-originator in the original placebo-controlled RCTs, calculated as the risk difference in the endpoint of interest between active drug and placebo. To preserve a proportion of the therapeutic effect of the bio-originator, the equivalence margin used in a comparative effectiveness RCT is usually half or less of the mean absolute difference derived in the meta-analysis.[19] Equivalence margins should be standardised for each bio-originator.[27] The EMA defines two-sided therapeutic equivalence in RCTs comparing a biosimilar with its bio-originator as when the 95% CI for the mean absolute difference in the primary endpoint between the biosimilar and its bio-originator falls within the predefined equivalence margin.[13] However, the US FDA prefers use of the narrower 90% CI to demonstrate therapeutic equivalence.[14]

A biosimilar that has satisfied the requirements of a dedicated pathway for regulatory approval will be neither better nor worse in efficacy and not inferior in safety to the various batches of the bio-originator. Since the processes for manufacturing biologics, including highly sensitive methods to assess quality, have matured over the past decades, major changes in the manufacturing process of the bio-originator are not likely and its efficacy and safety are unlikely to drift. Thus, efficacy and safety of a biosimilar can be expected to remain highly comparable to those of its bio-originator over time.

Patients and healthcare providers should be informed about the nature of biosimilars, their approval process, and their safety and efficacy

Given that biosimilars have only recently become available, many patients and healthcare providers are unfamiliar with this concept. Since biosimilars are usually marketed at a price lower than that of their bio-originators, some presume that biosimilars are of lesser quality. This misconception can and must be corrected by informing patients and healthcare providers about the nature of biosimilars, the rigorous approval process to which they are subjected by regulatory agencies, and the equivalent efficacy and comparable safety of approved biosimilars to their bio-originators.

Harmonised methods should be established to obtain reliable pharmacovigilance data, including traceability, about both biosimilars and bio-originators

During the development of a pharmaceutical product, a limited number of patients receive treatment with the investigational drug. Thus, it is important to gather safety and efficacy data after a drug has been approved and is commercially available. Especially since the clinical part of the development process for biosimilars is abbreviated relative to that for bio-originators, it is critical that postmarketing pharmacovigilance be conducted to confirm the efficacy and safety of a biosimilar over time in a much larger number of patients than were studied in RCTs.

Traceability is an issue for all drugs, not only for biosimilars. To facilitate postmarketing pharmacovigilance, the non-proprietary name of a biosimilar must be readily distinguishable from that of its bio-originator. In 2012, the WHO proposed that a unique four-letter 'biological qualifier' code be appended as a suffix to the core name. This nomenclature system would be applied retrospectively to the bio-originator and prospectively to designate biosimilars.[28] The US FDA has followed these WHO recommendations and, in 2017, issued guidance regarding non-proprietary naming of biological products, in which it specifies that the 'biological qualifier' code suffix consists of four lower-case letters and that it is unique and 'devoid of meaning'.[29] The five biosimilars approved in the USA to treat inflammatory diseases have been designated as adalimumab-adbm, adalimumab-atto, etanercept-szzs, infliximab-abda, and infliximab-dyyb. Similarly, a 'biological qualifier' code suffix will be appended retroactively to the core name of each bio-originator, so that these may be distinguished from biosimilars. This naming convention for biologics should facilitate traceability and allow effective postmarketing surveillance of the safety and efficacy of both biosimilars and their bio-originators. Within the European medicines regulatory network, pharmacovigilance is organised primarily at a national level in the Member States of the EU and the European Economic Area using brand names for postmarketing surveillance of both biosimilars and bio-originators. An advantage of using brand names is that these can be easily recalled and reported by both patients and their healthcare providers. Suspected adverse events are submitted to the EudraVigilance database, which allows monitoring safety of medications across the entire network. However, it is unfortunate that there has not yet been global agreement on nomenclature for all biologics. Regardless of the method used to distinguish among biosimilars and bio-originators, batch numbers are essential for tracing potential problems. However, although recorded by the dispensing pharmacist, batch numbers are infrequently noted by patients or healthcare providers and may be difficult to obtain when an adverse event occurs.

Consensus recommendations

The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases

As the prevalence of chronic disease increases in both high-income and lower-income countries, pharmaceutical consumption must shift to lower cost products so as to improve access to all who need these medications.[30] An approved biosimilar should provide patients with an equivalent biologic at a cost lower than that of the bio-originator. Unlike a new medication, a biosimilar

of equivalent efficacy and comparable safety has no attribute other than price to distinguish it from its bio-originator.

The expenses associated with developing a biosimilar are but a fraction of those incurred during the development of a bio-originator. Thus, once patents for bio-originators have expired, the use of less expensive biosimilars should help to offset the necessary expense of using other medications to fulfil unmet therapeutic needs. Regardless, payers must transfer the savings realised from the reduced cost of developing a biosimilar back to the patient by improving access to treatment with lower copayments for medications or by lowering insurance premiums.[31]

A 2014 RAND Corporation study estimated the potential cost savings of biosimilars in the US market to be $44.2 billion over the subsequent decade, of which TNF inhibitors would account for 21% ($9.3 billion).[32] This study assumed that market competition would result in the price of a biosimilar being 35% lower than that of its bio-originator. However, at the time of the launch in September 2015 of filgrastim-sndz (Zarxio), the first biosimilar approved in the USA, its wholesale acquisition cost (WAC) was only 15% lower than that of bio-originator filgrastim.[33] Similarly, at the time of its launch in November 2016, the WAC of infliximab-dyyb (Inflectra) in the USA was only 15% lower than that of bio-originator infliximab.[34] However, discounts and ex-post rebates provided to third-party payers and pharmacy benefit management companies by bio-originator manufacturers might reduce or even eliminate the price differential between a biosimilar and its bio-originator. Small price differentials between biosimilars and bio-originators likely will decrease the market penetration of biosimilars and further reduce direct cost savings. A price discounted only 15% below that of the bio-originator may not be sufficient to motivate use of a biosimilar. Thus, to ensure market uptake of biosimilars, it is important that they be priced considerably lower than bio-originators.

In other countries, the price of biosimilars is lowest where market competition is greatest. In Canada, at the time of its launch in March 2015, the price of Inflectra was 34% lower than that of bio-originator infliximab.[35] The prices of biosimilars in the EU typically have been 20%–40% lower than those of the corresponding bio-originators, but this is much less than the 80% price reduction realised with generic small molecule drugs.[36] However, in Norway, where the national hospital system has a competitive tender process for the exclusive contracts to supply medications that are administered in-hospital, the tender accepted for Remsima in 2014 was 39% lower than that offered for bio-originator infliximab and that accepted in 2015 was 69% lower.[37] As expected, the market share of biosimilar infliximab is much larger in those countries where the price of the biosimilar is much lower than that of bio-originator infliximab.[38] The use of a tender system has important implications for maintaining a competitive environment and is likely to reduce both the price of biologics that no longer are protected by patent and that of biosimilars. However, such a system may also pose a threat to the level of market competition over the long term and might ultimately result in a market in which only one version of a biologics (biosimilar or bio-originator) is available (ie, 'winner-take-all').

In the EU5 (France, Germany, Italy, Spain and the UK), using a conservative budget impact model, the introduction of an etanercept biosimilar priced 10%–25% lower than bio-originator etanercept could yield net savings of €286 to €728 million over the subsequent 5 years.[39] Such savings could fund treatment with the biosimilar for many more patients. Presumably, the proportion of the cost of a biosimilar that is shared by the patient will be lower than that shared for a bio-originator. Thus, with more affordable drugs, patients may be more likely to adhere to their prescribed medication regimens. Moreover, in developing markets in which access to biologics is restricted by cost, the availability of a lower cost biosimilar might allow a patient to receive a treatment that previously was more difficult to obtain or unavailable. Thus, biosimilars should increase global access to effective treatments for inflammatory diseases.

Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators

Once a biosimilar has demonstrated high structural similarity and clinical equivalence to its bio-originator in a sensitive population and has been granted marketing authorisation, it can be considered to be essentially the same biologic as a new batch of the bio-originator. The finding of biosimilarity justifies use of an approved biosimilar in all the indications for which the bio-originator is authorised.

As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, antidrug antibodies to biosimilars need not be measured in clinical practice

Antidrug antibodies (ADAs) typically develop in patients who are treated protractedly with biologics. Virtually all monoclonal antibodies induce an immune response with production of ADAs, often to the antigen-combining region (anti-idiotype antibodies).[40] ADAs bound to therapeutic monoclonal antibodies may form immune complexes which, when cleared by the reticuloendothelial system, result in lower trough drug concentrations and potentially decreased efficacy.[41] When the titre and affinity of ADAs for the biologic are high, the therapeutic effect is neutralised. Neutralising ADAs may be detected within 6 months after initial exposure to the biologic.[42]

Assays to detect ADAs have evolved over time to become more sensitive and specific.[41] Early studies of therapeutic monoclonal anti-TNF antibodies, using a bridging ELISA, identified ADAs in a small proportion of patients.[43] Subsequent studies have used assays that are less sensitive to drug interference, such as the homogeneous mobility shift assay method or the pH-shift anti-idiotype antigen-binding test, in which acid dissociation of drug–ADA complexes allows detection both of free ADAs and of those bound to drug.[44 45] In recent clinical trials, ADAs have been detected in a larger proportion of patients using the sensitive electrochemiluminescence bridging immunoassay.[46] However, the clinical relevance of ADAs, especially as to how they might differentiate biosimilars from their reference drugs, remains unclear.

The immunogenicity of a candidate biosimilar is best compared with that of its bio-originator in a clinical trial conducted in treatment-naïve patients.[12 47] These trials often have included a single crossover from the bio-originator to the candidate biosimilar. Thus far, such switches have not induced ADA formation. The proportion of subjects that develop ADAs to a biosimilar and to its bio-originator should be similar. Since neutralising ADAs are more clinically relevant, proportion of subjects developing these should also be reported.[48] If immunogenicity findings are to be extrapolated from a clinical trial in one disease to other indications, the patient population chosen for study should be that which is most likely to develop an immune response to the biologic.[12] Accordingly, patients not receiving concomitant immunosuppressive medications are preferred. However, in the clinical trials comparing the infliximab biosimilar CT-P13 with bio-originator infliximab, the prevalence of ADAs was higher in patients with rheumatoid arthritis receiving infliximab 3 mg/kg intravenously with concomitant methotrexate than in patients

with ankylosing spondylitis receiving infliximab 5 mg/kg as monotherapy.[21 46] Thus, genetic factors, the underlying disease process and the dose of the biologic administered may be more important than concomitant immunosuppressive medications in determining the predisposition to develop ADAs.

Although not typically measured in clinical practice by rheumatologists, trough drug concentrations provide a more relevant, indirect comparative assessment of immunogenicity between a biosimilar and its bio-originator than does detection of ADAs. As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, ADAs to biosimilars need not be measured in clinical practice.[49 50] However, the assessment of immunogenicity should not be dismissed completely, as it is a useful measure for active pharmacovigilance. Evaluating comparative immunogenicity data, acquired in both clinical and postmarketing studies of biosimilars, should help to increase confidence in using biosimilars among healthcare providers.[51]

Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published

As substantial emphasis has been placed on analytical and PK comparisons in the development of biosimilars, preclinical analytical data and phase 1 PK data should be available in peer-reviewed journals when data from phase III RCTs are published. Data from relevant physicochemical, in vitro functional and PK studies of a biosimilar should be published before or simultaneously with those from the phase III comparative effectiveness RCT. Physicochemical and in vitro functional data comparing the biosimilar with its bio-originator have been published in peer-reviewed journals for the infliximab biosimilar SB2, the etanercept biosimilars SB4 and GP 2015, and the adalimumab biosimilar ABP 501.[52–56] For the infliximab biosimilar CT-P13, selected physicochemical and in vitro functional data were published as supplementary data in appendices to the primary publications reporting the results of the phase I and phase III studies that compared CT-P13 with bio-originator infliximab.[21 46]

Phase I PK data comparing biosimilars with their bio-originators have usually been published in a peer-reviewed journal before or simultaneously with publication of the results of the phase III study in manuscript form. Results of the phase I PK study comparing ABP 501 with bio-originator adalimumab were published before publication of a manuscript reporting the phase III data.[18 57] Similarly, results of the phase I PK study comparing SB2 with bio-originator infliximab were published before the phase III study was published,[17 58] and results of the phase I PK study comparing SB4 with bio-originator etanercept were published before the phase III study was published.[19 59] The phase I and phase III studies comparing CT-P13 with bio-originator infliximab,[21 46] and those comparing GP2015 with bio-originator etanercept both were published simultaneously.[20 60] The availability of this information, when the phase III RCT data are published, facilitates assessment of biosimilarity based on a 'totality-of-the-evidence' approach.[61]

Since the biosimilar is equivalent to the bio-originator in its physicochemical, functional and pharmacokinetic properties, confirmation of efficacy and safety in a single indication is sufficient for extrapolation to other diseases for which the bio-originator has been approved

Based on the extensive historical clinical experience with the bio-originator in each of its licensed indications, regulatory agencies allow efficacy and safety data for a biosimilar to be extrapolated from one approved indication to others in which the biosimilar has not been studied, if the mechanism of action of the bio-originator is considered to be the same in each disease.[62 63] The comprehensive preclinical comparison of the biosimilar to its bio-originator, in which their similarity is confirmed by many different analytical and functional assays, forms the basis for this 'extrapolation of indications.' Thus, after having demonstrated efficacy and safety equivalent to its bio-originator in at least one RCT conducted in patients with a disease for which the bio-originator is authorised, a biosimilar may apply for approval in any or all indications for which its bio-originator already has been authorised without an RCT in each indication.

By this process, biosimilars have usually been granted marketing authorisation in all indications for which the bio-originator has been approved but in which the biosimilar has not been studied. In this context, experts from national and international organisations have argued that convincing data from RCTs are needed for each individual indication.[64–72] However, biosimilars have always demonstrated efficacy equivalent to that of their bio-originators when studied in more than one indication.[21 46 73 74] Also, the biosimilar infliximab, CT-P13, has exhibited efficacy and safety comparable to bio-originator infliximab in several small, prospective case series of patients with indications for which approval had been based on extrapolation of data from the RCTs.[75–78] Although Health Canada initially denied the biosimilar infliximab CT-P13 extrapolation of data from clinical trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis to inflammatory bowel diseases, this decision was ultimately reversed by the same regulatory authority.[79] Nonetheless, biosimilars have demonstrated efficacy and safety when used in clinical practice to treat approved indications in which they had not been studied in comparison to their bio-originators.[78]

Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered

Switching patients from bio-originators to their biosimilars and from one biosimilar to another should be evidence-based. Current data suggest that treating a patient with an approved biosimilar should yield results comparable to those achieved when the patient is treated with the bio-originator. However, no study to date has evaluated the efficacy or safety of switching between different biosimilars of the same bio-originator.

Ideally, the consequences of switching from a bio-originator to a biosimilar should be compared with that of continued treatment with the bio-originator in an RCT, conducted in patients who are receiving stable treatment with the bio-originator. Extensions to phase III RCTs of several biosimilars, in which subjects treated initially with the bio-originator were switched to the biosimilar, have been published.[80–84] Observing no loss of efficacy and no increase in the rate of adverse events following this single switch supports making this switch in clinical practice, only if the biosimilar costs less than the bio-originator. However, if a patient has failed to respond to a specific biologic, a biosimilar of that product should not subsequently be prescribed.

An RCT was conducted in Norway to assess the effect of switching from bio-originator infliximab (Remicade) to the biosimilar infliximab CT-P13 on efficacy and safety in the various indications for which both had been approved. NOR-SWITCH was a 52-week, double blind, non-inferiority, phase IV RCT that

enrolled 482 patients with a variety of diseases: Crohn's disease (n=155), ulcerative colitis (n=93), spondyloarthritis (n=91), rheumatoid arthritis (n=78), psoriasis (n=35) and psoriatic arthritis (n=30), each of whom had been on stable treatment with bio-originator infliximab for at least 6 months.[78] The primary endpoint was worsening in disease-specific composite measures and/or agreement between the investigator and the patient that increased disease activity required a change in treatment by week 52. This study demonstrated non-inferiority of switching from the bio-originator to the biosimilar, using a non-inferiority margin of 15%, as compared with continuation of treatment with the bio-originator for the aggregate of subjects with the various diseases enrolled. However, NOR-SWITCH was not powered to compare these two treatment strategies in subjects with any individual disease. Similar proportions of patients in each group developed treatment-emergent adverse events (TEAEs), serious adverse events and TEAEs resulting in study drug discontinuation, and the prevalence and incidence of ADAs, as well as trough drugs levels, were similar between the two groups. Thus, NOR-SWITCH supports the practice of switching patients with stable disease activity from bio-originator infliximab to the biosimilar CT-P13. However, these results cannot be generalised to other biologics and their biosimilars or to frequent switching back-and-forth between bio-originator and biosimilar. For each new biosimilar and application device, an RCT should be conducted to evaluate safety and continued efficacy after switching from the bio-originator or to another biosimilar. However, once sufficient experience has been gained, additional switching studies may no longer be necessary.

Even if data from RCTs support the practice of switching from a bio-originator to its biosimilar or between biosimilars, patients must feel comfortable receiving the treatment that they have been prescribed. To achieve this, rheumatologists should inform patients about the rigorous development process during which biosimilars have been assessed and shown to be highly similar to their bio-originators. Patient perspectives must be taken into account. Patients should understand that an approved biosimilar may be like another batch of its bio-originator and should provide similar therapeutic benefit with comparable safety. They also should be informed about the economic implications of switching, which should allow more patients to benefit from treatment with biologics. However, if some patients remain uneasy about switching from the bio-originator to a biosimilar, even with this information, their preferences must be considered when making a therapeutic decision.

Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries

Substitution, in which a biosimilar is prescribed in place of its bio-originator, must be distinguished from interchangeability, wherein someone other than the prescribing healthcare provider initiates the switch from bio-originator to biosimilar or between two biosimilars. Of note, in the EU, the term 'substitution' implies what is considered in the USA to be 'interchange'. Thus, terminology must be harmonised worldwide. In the EU, the EMA does not have the authority to designate a biosimilar as being interchangeable; rather, this judgement must be made by regulatory agencies in each Member State.[85]

To support the designation of interchangeability, an RCT that incorporates multiple switches between the two biologics must be conducted. The US FDA has issued draft guidance on demonstrating interchangeability of a biosimilar with its bio-originator, in which it suggests that postmarketing pharmacovigilance data should be combined with data from at least one prospective RCT that compares repeated switching between the bio-originator and the biosimilar to continuous treatment with the bio-originator.[86] Subjects in the 'switching arm' of such a study switch at least three times between the bio-originator and the biosimilar, whereas subjects in the 'non-switching arm' continue treatment with only the bio-originator. After the last switch from the bio-originator to the biosimilar, subjects in the 'switching arm' should remain on the biosimilar. The primary endpoints for such a study should be PK parameters; secondary endpoints should evaluate efficacy, safety and immunogenicity. However, to date, no biosimilar has been evaluated according to this study design.

Systematic postmarketing pharmacovigilance should be carried out using biologics registries and by conducting long-term, observational cohort studies to which data are reported regularly by prescribing healthcare providers and patients who are treated with specific products. Biologics registries in many countries have provided insight into the short-term and long-term safety of biologics.[87–93] Data collected about the use of biosimilars should be integrated into these existing biologics registries. Pertinent standardised data must be collected to address any remaining uncertainty regarding the safety of biosimilars. Although not designed primarily to assess efficacy, the durability or potential loss of efficacy after switching from a bio-originator to its biosimilar might become evident in such a registry.

No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider

Patients with rheumatological diseases may be reluctant to switch medications, even when their disease remains active, because of fear of disease worsening or of developing an adverse effect on a new medication.[94] However, the concern that therapeutic efficacy might be lost after switching from a bio-originator to its biosimilar has not been supported by currently available data.

In the EU, the introduction of infliximab and etanercept biosimilars has generated market competition, which has resulted in price reductions for their reference products and for the other bio-originator TNF inhibitors.[38] Patients and their healthcare providers share the responsibility to consider equity when choosing a course of treatment and must consider cost in the decision-making process. However, in some countries, the choice of biologic is often imposed by payers rather than being made by either the patient or his or her treating healthcare provider.

Transparency is of utmost importance in the therapeutic relationship between a patient and his or her healthcare provider. Therapeutic decisions must be made jointly by the patient in consultation with the healthcare provider. As with all changes in treatment, the patient and the healthcare provider should be fully aware of any change and should agree with its implementation.

CONCLUSION

The differing opinions about biosimilars that have been published by various national and international medical subspecialty organisations illustrate the lack of confidence shared by many clinicians regarding the appropriate use of biosimilars.[64–72 95–98] However, a rapidly growing body of evidence has begun to reduce residual uncertainty about their use. This consensus statement aims to raise awareness about biosimilars and to discuss the key issues that healthcare providers must consider when using biosimilars to treat their patients. The assembled group of experts and patients achieved a high level of agreement about the evaluation of biosimilars and their use to treat rheumatological diseases.

The participants were confident that biosimilars approved by authorities in a highly regulated area are unlikely to differ from their bio-originators in clinically meaningful ways. Nevertheless, given the complex nature of all biopharmaceuticals, the treating clinician must be the only one to decide whether to prescribe a biosimilar in place of a bio-originator on a case-by-case basis with full awareness of the patient. The group believed that adequate evidence exists to support the decision to switch from a biologic, which no longer is protected by patent, to its biosimilar. In addition, the group concluded that there is sufficient evidence about safety and efficacy of biosimilars to allow for extrapolation of indications. However, there remained concern about switching between two biosimilars or between a bio-originator and its biosimilar on multiple occasions because adequate studies have not yet been conducted to assess these circumstances. To facilitate making informed decisions about therapeutic substitution with biosimilars, healthcare providers are encouraged to gather pharmacovigilance data in registries about the outcome of such switches made in the context of clinical practice. Data available as of December 2016 support the use of biosimilars by rheumatologists to encourage a fair and competitive market for biologics. Biosimilars now provide an opportunity to expand access to effective but expensive medications, increasing the number of available treatment choices and helping to control rapidly increasing drug expenditures.

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REFERENCES

1 Kay J. Biosimilars: a regulatory perspective from America. *Arthritis Res Ther* 2011;13:112.
2 Kay J, Feagan BG, Guirguis MS, *et al*. Health Canada/BIOTECanada Summit on regulatory and clinical topics related to subsequent entry biologics (biosimilars), Ottawa, Canada, 14 May 2012. *Biologicals* 2012;40:517–27.
3 Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology--"O brave new world". *Nat Rev Rheumatol* 2012;8:430–6.
4 Dörner T, Strand V, Castañeda-Hernández G, *et al*. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis* 2013;72:322–8.
5 Dörner T, Kay J. Biosimilars in rheumatology: current perspectives and lessons learnt. *Nat Rev Rheumatol* 2015;11:713–24.
6 Dörner T, Strand V, Cornes P, *et al*. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75:974–82.
7 OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). 2009 http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (accessed 18 Jul 2017).
8 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH official website. 2017 http://www.ich.org/ (accessed 28 Jan 2017).
9 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (accessed 20 Nov 2016).
10 Biologics Price Competition and Innovation Act of 2009. *United States Code. 111th Congress*. 2nd Session edn. United States, 2010:804–21.
11 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. 2005 http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf (accessed 20 Nov 2016).
12 US Food & Drug Administration. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. 2015 http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed 22 Jun 2016).
13 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf (accessed 10 Nov 2016).
14 Gu N, Yi S, Kim TE, *et al*. Comparative pharmacokinetics and tolerability of branded etanercept (25 mg) and its biosimilar (25 mg): a randomized, open-label, single-dose, two-sequence, crossover study in healthy Korean male volunteers. *Clin Ther* 2011;33:2029–37.
15 Yi S, Kim SE, Park MK, *et al*. Comparative pharmacokinetics of HD203, a biosimilar of etanercept, with marketed etanercept (Enbrel®): a double-blind, single-dose, crossover study in healthy volunteers. *BioDrugs* 2012;26:177–84.
16 Park W, Lee SJ, Yun J, *et al*. Comparison of the pharmacokinetics and safety of three formulations of infliximab (CT-P13, EU-approved reference infliximab and the US-licensed reference infliximab) in healthy subjects: a randomized, double-blind, three-arm, parallel-group, single-dose, Phase I study. *Expert Rev Clin Immunol* 2015;11(Suppl 1):25–31.
17 Shin D, Kim Y, Kim YS, *et al*. A randomized, Phase I pharmacokinetic study comparing SB2 and Infliximab reference product (Remicade(®)) in healthy subjects. *BioDrugs* 2015;29:381–8.
18 Kaur P, Chow V, Zhang N, *et al*. A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Ann Rheum Dis* 2017;76:526–33.

19 Park W, Yoo DH, Jaworski J, *et al*. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. *Arthritis Res Ther* 2016;18:25.
20 von Richter O, Skerjanec A, Afonso M, *et al*. GP2015, a proposed etanercept biosimilar: Pharmacokinetic similarity to its reference product and comparison of its autoinjector device with prefilled syringes. *Br J Clin Pharmacol* 2017;83:732–41.
21 Park W, Hrycaj P, Jeka S, *et al*. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis* 2013;72:1605–12.
22 Takeuchi T, Yamanaka H, Tanaka Y, *et al*. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2015;25:817–24.
23 Cohen S, Emery P, Greenwald M, *et al*. A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. *Br J Clin Pharmacol* 2016;82:129–38.
24 Yoo DH, Suh CH, Shim SC, *et al*. A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2017;76:566–70.
25 Kay J, Smolen JS. Biosimilars to treat inflammatory arthritis: the challenge of proving identity. *Ann Rheum Dis* 2013;72:1589–93.
26 Rutherford AI, Galloway JB. Biosimilars in rheumatology: out of the laboratory and into practice. *Expert Rev Clin Immunol* 2016;12:697–9.
27 Kay J, Isaacs JD. Clinical trials of biosimilars should become more similar. *Ann Rheum Dis* 2017;76:4–6.
28 World Health Organization Programme on International Nonproprietary Names (INN). Biological qualifier: An INN proposal. 2014 http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf (accessed 18 Nov 2016).
29 US Food & Drug Administration. Guidance for industry: Nonproprietary naming of biological products. 2017 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf (accessed 27 Jan 2017).
30 Hoebert J, Laing R, Stephens P. *The world medicines situation 2011: pharmaceutical consumption*. Geneva, Switzerland: World Health Organization, 2011:1–17.
31 MacDougall D, Crowell K, Prager S, *et al*. IMS health white paper: biosimilars: who saves? 2016 https://structurecms-staging-psyclone.netdna-ssl.com/client_assets/dwonk/media/attachments/57dc/387d/6970/2d6c/ad6f/0000/57dc387d69702d6cad6f0000.pdf?1474050173 (accessed 25 Feb 2017).
32 Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States. Perspectives. 2014 http://www.rand.org/pubs/perspectives/PE127.html (accessed 18 Nov 2016).
33 Raedler LA, Zarxio RLA. Zarxio (Filgrastim-sndz): First Biosimilar Approved in the United States. *Am Health Drug Benefits* 2016;9:150–4.
34 Pfizer IncPfizer announces the U.S. availability of biosimilar INFLECTRA® (infliximab-dyyb). Company to begin shipping to wholesalers in late November, 2016Pfizer Inc, 2016 New York, NY. http://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_the_u_s_availability_of_biosimilar_inflectra_infliximab_dyyb (accessed 7 Jan 2017).
35 Canadian Drug Expert Committee. CDEC final recommendation: Infliximab (Inflectra - Hospia Healthcare Corporation). Common Drug Review. 2014 https://www.cadth.ca/media/cdr/complete/cdr_complete_SE0384_Inflectra_Dec-23-14.pdf (accessed 7 Jan 2017).
36 Haustein R, *et al*. Saving money in the European healthcare systems with biosimilars. *GaBI J* 2012;1:120–6.
37 Mack A. Norway, biosimilars in different funding systems. What works? *GaBI J* 2015;4:90–2.
38 IMS Health. *The impact of biosimilar competition*. London, UK: IMS Health Inc., 2016:1–30.
39 Ruff L, Rezk MF, Uhlig T, *et al*. Budget impact analysis of an etanercept biosimilar for the treatment of all licensed etanercept indications for adults in Europe. *Value Health* 2015;18:A639.
40 van Schouwenburg PA, van de Stadt LA, de Jong RN, *et al*. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. *Ann Rheum Dis* 2013;72:104–9.
41 van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* 2013;9:164–72.
42 Bartelds GM, Krieckaert CL, Nurmohamed MT, *et al*. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* 2011;305:1460–8.
43 Lipsky PE, van der Heijde DM, St Clair EW, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343:1594–602.
44 van Schouwenburg PA, Krieckaert CL, Rispens T, *et al*. Long-term measurement of anti-adalimumab using pH-shift-anti-idiotype antigen binding test shows predictive value and transient antibody formation. *Ann Rheum Dis* 2013;72:1680–6.
45 Wang S-L, Hauenstein S, Ohrmund L, *et al*. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal* 2013;78-79:39–44.
46 Yoo DH, Hrycaj P, Miranda P, *et al*. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;72:1613–20.
47 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. 2012 https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf (accessed 20 Nov 2016).
48 Shankar G, Devanarayan V, Amaravadi L, *et al*. Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. *J Pharm Biomed Anal* 2008;48:1267–81.
49 Ben-Horin S, Yavzori M, Benhar I, *et al*. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut* 2016;65:1132–8.
50 Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, *et al*. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. *Ann Rheum Dis* 2016;75:1693–6.
51 Gonçalves J, Araújo F, Cutolo M, *et al*. Biosimilar monoclonal antibodies: preclinical and clinical development aspects. *Clin Exp Rheumatol* 2016;34:698–705.
52 Hong J, Lee Y, Lee C, *et al*. Physicochemical and biological characterization of SB2, a biosimilar of Remicade® (infliximab). *MAbs* 2017;9:365–83.
53 Cho IH, Lee N, Song D, *et al*. Evaluation of the structural, physicochemical, and biological characteristics of SB4, a biosimilar of etanercept. *MAbs* 2016;8:1136–55.
54 Hofmann HP, Kronthaler U, Fritsch C, *et al*. Characterization and non-clinical assessment of the proposed etanercept biosimilar GP2015 with originator etanercept (Enbrel(®)). *Expert Opin Biol Ther* 2016;16:1185–95.
55 Liu J, Eris T, Li C, *et al*. Assessing analytical similarity of proposed Amgen biosimilar ABP 501 to adalimumab. *BioDrugs* 2016;30:321–38.
56 Velayudhan J, Chen YF, Rohrbach A, *et al*. Demonstration of functional similarity of proposed biosimilar ABP 501 to adalimumab. *BioDrugs* 2016;30:339–51.
57 Cohen S, Genovese MC, Choy E, *et al*. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. *Ann Rheum Dis* 2017;76:1679–87.
58 Choe JY, Prodanovic N, Niebrzydowski J, *et al*. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:58–64.
59 Emery P, Vencovský J, Sylwestrzak A, *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:51–7.
60 Griffiths CEM, Thaçi D, Gerdes S, *et al*. The EGALITYch study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *Br J Dermatol* 2017;176:928–38.
61 Kozlowski S, Woodcock J, Midthun K, *et al*. Developing the nation's biosimilars program. *N Engl J Med* 2011;365:385–8.
62 US Food & Drug Administration. Guidance for industry. Biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. 2015 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf (accessed 31 Oct 2016).
63 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2006 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf (accessed 20 Nov 2016).
64 Argüelles-Arias F, Barreiro-de-Acosta M, Carballo F, *et al*. Joint position statement by "Sociedad Española de Patología Digestiva" (Spanish Society of Gastroenterology) and "Sociedad Española de Farmacología" (Spanish Society of Pharmacology) on biosimilar therapy for inflammatory bowel disease. *Rev Esp Enferm Dig* 2013;105:37–43.
65 Danese S, Gomollon F. Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis* 2013;7:586–9.
66 Gecse KB, Khanna R, van den Brink GR, *et al*. Biosimilars in IBD: hope or expectation? *Gut* 2013;62:803–7.
67 Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. *J Crohns Colitis* 2014;8:1548–50.
68 Fiorino G, Danese S. The biosimilar road in inflammatory bowel disease: the right way? *Best Pract Res Clin Gastroenterol* 2014;28:465–71.
69 Fiorino G, Girolomoni G, Lapadula G, *et al*. The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology

(SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. *Autoimmun Rev* 2014;13:751–5.
70 Hlavaty T, Letkovsky J. Biosimilars in the therapy of inflammatory bowel diseases. *Eur J Gastroenterol Hepatol* 2014;26:1–587.
71 Schreiber S, Luger T, Mittendorf T, *et al*. [Evolution of biologicals in inflammation medicine--biosimilars in gastroenterology, rheumatology and dermatology]. *Dtsch Med Wochenschr* 2014;139:2399–404.
72 Committee on Rheumatologic Care. American College of Rheumatology position statement: Biosimilars. 2016 http://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf (accessed 20 Nov 2016).
73 Cohen SB, Genovese MC, Choy EH, *et al*. Randomized, double-blind, Phase 3 study of efficacy and safety of ABP 501 compared with adalimumab in subjects with moderate to severe rheumatoid arthritis [abstract]. *Arthritis Rheumatol* 2015;67(suppl 10() http://acrabstracts.org/abstract/randomized-double-blind-phase-3-study-of-efficacy-and-safety-of-abp-501-compared-with-adalimumab-in-subjects-with-moderate-to-severe-rheumatoid-arthritis/.
74 Papp K, Bachelez H, Costanzo A, *et al*. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *J Am Acad Dermatol* 2017;76:1093–102.
75 Nikiphorou E, Kautiainen H, Hannonen P, *et al*. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert Opin Biol Ther* 2015;15:1677–83.
76 Benucci M, Gobbi FL, Bandinelli F, *et al*. Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study. *Immunol Res* 2017;65:419-422.
77 Gentileschi S, Barreca C, Bellisai F, *et al*. Switch from infliximab to infliximab biosimilar: efficacy and safety in a cohort of patients with different rheumatic diseasesResponse to: Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15:1677-1683. *Expert Opin Biol Ther* 2016;16:1311–2.
78 Jørgensen KK, Olsen IC, Goll GL, *et al*. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304–16.
79 Health Canada. Regulatory decision summary INFLECTRA. 2016 http://www.hc-sc.gc.ca/dhp-mps/prodpharma/rds-sdr/drug-med/rds-sdr-infectra-184564-eng.php (accessed 29 Sep 2016).
80 Kay J, Wyand M, Chandrashekara S, *et al*. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study [abstract]. *Arthritis Rheumatol* 2014;66:3538.
81 Weinblatt ME, Baranauskaite A, Niebrzydowski J, *et al*. Sustained efficacy and comparable safety and immunogenicity after transition to SB5 (an adalimumab biosimilar) vs. continuation of SB5 or reference adalimumab (Humira®) in patients with rheumatoid arthritis: Results of phase III study [abstract]. 2016 http://acrabstracts.org/abstract/sustained-efficacy-and-comparable-safety-and-immunogenicity-after-transition-to-sb5-an-adalimumab-biosimilar-vs-continuation-of-sb5-or-reference-adalimumab-humira-in-patients-with-rheumatoi/ (accessed 7 Jan 2017).
82 Park W, Yoo DH, Miranda P, *et al*. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann Rheum Dis* 2017;76:346–54.
83 Yoo DH, Prodanovic N, Jaworski J, *et al*. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis* 2017;76:355–63.
84 Emery P, Vencovský J, Sylwestrzak A, *et al*. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. *Ann Rheum Dis* 2017;76:1986–91.
85 Thimmaraju PK, Rakshambikai R, Farista R, *et al*. Legislations on biosimilar interchangeability in the US and EU – developments far from visibility. GaBI Online - Generics and Biosimilars Initiative 2015. 2015 http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility (accessed 20 Nov 2016).
86 Food US, Administration D. Guidance for industry: Considerations in demonstrating interchangeability with a reference product, draft guidance. 2017 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery (accessed 17 Jan 2017).
87 Gómez-Reino JJ, Carmona L, Angel Descalzo M, *et al*. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum* 2007;57:756–61.
88 Askling J, van Vollenhoven RF, Granath F, *et al*. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009;60:3180–9.
89 Greenberg JD, Reed G, Kremer JM, *et al*. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010;69:380–6.
90 Salmon-Ceron D, Tubach F, Lortholary O, *et al*. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2011;70:616–23.
91 Sakai R, Komano Y, Tanaka M, *et al*. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1125–34.
92 Zink A, Manger B, Kaufmann J, *et al*. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014;73:1673–6.
93 Mercer LK, Galloway JB, Lunt M, *et al*. BSRBR Control Centre Consortium. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2017;76:497–503.
94 Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis Rheum* 2007;56:2135–42.
95 Fonseca JE, Gonçalves J, Araújo F, *et al*. The Portuguese Society of Rheumatology position paper on the use of biosimilars. *Acta Reumatol Port* 2014;39:60–71.
96 Abad Hernández MÁ, Andreu JL, Caracuel Ruiz MÁ, *et al*. Position paper from the Spanish Society of Rheumatology on biosimilar drugs. *Reumatol Clin* 2015;11:269–78.
97 Azevedo VF, Meirelles ES, Kochen JA, *et al*. Recommendations on the use of biosimilars by the Brazilian Society of Rheumatology, Brazilian Society of Dermatology, Brazilian Federation of Gastroenterology and Brazilian Study Group on Inflammatory Bowel Disease--Focus on clinical evaluation of monoclonal antibodies and fusion proteins used in the treatment of autoimmune diseases. *Autoimmun Rev* 2015;14:769–73.
98 British Society for Rheumatology. Position statement on biosimilar medicines (Revised January 2017). 2017 http://www.rheumatology.org.uk/includes/documents/cm_docs/2017/r/revised_bsr_biosimilars_position_statement_jan_2017.pdf (accessed 14 Mar 2017).

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

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Notes

2016 update of the EULAR recommendations for the management of early arthritis

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ABSTRACT

Objectives Since the 2007 recommendations for the management of early arthritis have been presented, considerable research has been published in the field of early arthritis, mandating an update of the 2007 European League Against Rheumatism (EULAR) recommendations for management of early arthritis.

Methods In accordance with the 2014 EULAR Standardised Operating Procedures, the expert committee pursued an approach that was based on evidence in the literature and on expert opinion. The committee involved 20 rheumatologists, 2 patients and 1 healthcare professional representing 12 European countries. The group defined the focus of the expert committee and target population, formulated a definition of 'management' and selected the research questions. A systematic literature research (SLR) was performed by two fellows with the help of a skilled librarian. A set of draft recommendations was proposed on the basis of the research questions and the results of the SLR. For each recommendation, the categories of evidence were identified, the strength of recommendations was derived and the level of agreement was determined through a voting process.

Results The updated recommendations comprise 3 overarching principles and 12 recommendations for managing early arthritis. The selected statements involve the recognition of arthritis, referral, diagnosis, prognostication, treatment (information, education, pharmacological and non-pharmacological interventions), monitoring and strategy. Eighteen items were identified as relevant for future research.

Conclusions These recommendations provide rheumatologists, general practitioners, healthcare professionals, patients and other stakeholders with an updated EULAR consensus on the entire management of early arthritis.

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Peripheral inflammatory arthritis is among the most common features with which patients present in clinical rheumatology. Identifying the underlying disease can be difficult, particularly at an early stage. In clinical practice, early inflammatory arthritis is frequently undifferentiated.[1] Early arthritis can develop into established rheumatoid arthritis (RA) or another definite arthropathy, can resolve spontaneously, or may remain undifferentiated for indefinite periods. To better evaluate diagnosis and outcome in arthritis, it has been proposed to first recognise inflammatory arthritis; then search for a definite diagnosis (eg, peripheral or axial spondyloarthritis; psoriatic arthritis (PsA); systemic lupus erythematosus, etc), and finally estimate the risk of developing persistent and/or erosive arthritis and propose an optimal therapeutic strategy.[2 3] Although the prognosis of early arthritis is still difficult to define, a combination of clinical, laboratory and radiographic parameters may help to predict patients' outcomes with acceptable accuracy.

The management of early arthritis has changed considerably in the past few years under the influence of new concepts for diagnosis and new effective therapies. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have been shown to slow disease progression in chronic inflammatory arthritides such as RA and PsA.[4–6] Furthermore, biological (b) DMARDs have demonstrated rapid and sustained disease control associated with an arrest of joint destruction.[7 8] A large body of evidence points to the usefulness of very early DMARD-start for early chronic inflammatory arthritis, preferably before the onset of erosions, in order to reduce or even prevent the risk of (further) joint damage and disability.[5 9 10] Also, the assessment and tight monitoring of patients with early arthritis serves to better adapt therapeutic strategies.[9 11] Beyond doubt, the treatment goal of early arthritis should now be clinical remission and prevention of joint destruction.

Patients with early arthritis should be identified and referred to rheumatologists to confirm the presence of arthritis, the (potential) diagnosis and its prognosis and initiate appropriate treatment strategies based on these findings. Furthermore, management of early arthritis should include more than drug treatment alone, with education, shared decision making and the role of allied healthcare professionals as important themes.

A set of recommendations for the management of arthritis should address all these different aspects.

The European League Against Rheumatism (EULAR) recommendations for the management of early arthritis have been published in 2007.[9] In 2010, EULAR presented recommendations for the management of RA with synthetic and biological DMARDs, which have been updated in 2013 and

2016;[12 13] in addition, recommendations for the management of PsA were recently published.[6] While the latter recommendations focused on the pharmacological treatments of PsA and RA, both in advanced and in early disease, the 2007 recommendations for the management of early arthritis covered the entire spectrum of management of early arthritis, including the recognition of arthritis, referral, diagnosis, prognosis, classification, information, education, non-pharmacological interventions and monitoring of the disease process as well as pharmacological treatment. The systematic literature review (SLR) that has guided the 2007 EULAR recommendations included publications up to January 2005.[9] Between 2005 and 2015, research in early arthritis has been a major focus, and many studies have appeared in the peer-reviewed literature. This literature includes —but is not limited to—topics such as diagnosis and classification criteria, window of opportunity, imaging, prognostication, treatments and therapeutic strategies.

These developments mandated an update of the existing EULAR recommendations on early arthritis, which is reported here.

METHODS

The update of the EULAR recommendations for the management of early arthritis has followed the 2014 EULAR Standardised Operating Procedures.[14] The definitions (eg, management and early arthritis) of and the target populations (rheumatologists, general practitioners, medical students, healthcare professionals, patients) addressed by the 2007 expert committee[9] were considered. Briefly, the term 'management' was defined as 'all organisational, diagnostic, medical and educational procedures related to patients seeking help for arthritis of a peripheral joint' and 'early arthritis' was restricted to 'early inflammatory joint disease'.

The expert committee

The expert committee comprised 20 rheumatologists, including 2 research fellows (CID and CH), 1 healthcare professional and 2 patients, from 12 European countries.

Fifteen research questions derived from the 2007 process were proposed by the convenor (BC) and the methodologist (RL), and subsequently amended and approved by the whole committee. The selected topics included recognition of arthritis, referral, diagnosis, prognostics, classification, information, education, non-pharmacological interventions, pharmacological treatments, monitoring of the disease process, strategy and prevention.

Evidence-based approach

The research questions were adjusted for further literature research if appropriate, and structured according to the Patients-Intervention-Comparator-Outcome systematic by four of the authors (CID, CH, BC, RL). Eligible study types were also defined.

A systematic search of PubMed, Medline, Embase, CINAHL and the Cochrane library was performed, with the help of a skilled librarian (Louise Falzon, Columbia University Medical Centre, USA). All articles published in English up to December 2015 were included. Abstracts from the 2014 and 2015 EULAR and American College of Rheumatology (ACR) conferences were also considered. The search was completed by a hand search and by questioning experts for additional references. The SLR process is reported in detail in two separate articles.[15 16]

Expert opinion approach

Each member of the expert committee obtained insight into the results of the literature search and the accompanying levels of evidence before a meeting in January 2016. During the meeting, the results of the SLR were presented to the committee in aggregated format. Three break-out groups, chaired by one expert, were formed to amend the 2007 recommendations (1–4; 5–8 and 9–12) and to propose new recommendations if considered appropriate. Each group then reported its proposals and wording to the entire committee for discussion and consensus, and the final formulation of the recommendations was obtained after a vote with at least 85% agreement for each item's final wording.

After the meeting the recommendations were circulated by email to all expert committee members for further minor amendments if necessary. Categories of evidence and grades of recommendations were then determined (by CID, CH, RL, BC) according to the standards of the Oxford Centre for Evidence-Based Medicine.[17] To determine the level of agreement with recommendations, an anonymised email-based voting on a 0–10 scale was performed, a vote of 0 indicating complete disagreement with a particular recommendation and 10 indicating complete agreement. The means and SDs for scores from the whole group were calculated. The recommendations are presented in box 1 and figure 1.

RESULTS

The discussions of the expert committee resulted in 3 overarching principles and 12 recommendations (box 1) (in 2007, 12 recommendations were formulated).

Overarching principles

The expert committee considered that some of the principles on the care of patients with early arthritis are generic and should be stated first and separated from individual recommendations on diagnosis, prognosis and treatment. The committee decided unanimously on the following three overarching principles (box 1).

Principle A:

Management of early arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.

The term 'best care' is obviously a major principle in medicine. The wording 'shared decision between the patient and the rheumatologist' is more than informing the patient; it rather refers to the comprehensive process of communication, knowledge exchange and achieving consensus that should lead to a treatment decision, that is, optimal from the perspectives of both patient and clinical care provider.

Principle B:

Rheumatologists are the specialists who should primarily care for patients with early arthritis.

This statement, which was part of recommendation 1 in the 2007 recommendations, was also highlighted in the EULAR recommendations for the management of RA[14] and PsA.[6] Its basis is evidence that patients with chronic arthritis under rheumatologists' care receive an earlier diagnosis, start treatment earlier and have better outcomes, in particular with respect to joint damage and physical function.[18–20] Rheumatologists have the expertise to establish an accurate diagnosis of early arthritis, are familiar with monitoring disease activity and with the potential severity of the disease in their patients with inflammatory arthritis and are well aware of the indications, contraindications and adverse effects of specific therapies.

Box 1 2016 update of the EULAR recommendations for management of early arthritis: final recommendations based on evidence and expert opinion

Overarching principles

A. Management of early arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B. Rheumatologists are the specialists who should primarily care for patients with early arthritis
C. A definitive diagnosis in a patient with early arthritis should only be made after a careful history taking and clinical examination, which should also guide laboratory testing and additional procedures

Recommendations

1. Patients presenting arthritis (any joint swelling, associated with pain or stiffness) should be referred to, and seen by, a rheumatologist, within 6 weeks after the onset of symptoms
2. Clinical examination is the method of choice for detecting arthritis, which may be confirmed by ultrasonography
3. If a definite diagnosis cannot be reached and the patient has early undifferentiated arthritis, risk factors for persistent and/or erosive disease, including number of swollen joints, acute phase reactants, rheumatoid factor, ACPA and imaging findings, should be considered in management decisions
4. Patients at risk of persistent arthritis should be started on DMARDs as early as possible (ideally within 3 months), even if they do not fulfil classification criteria for an inflammatory rheumatologic disease
5. Among the DMARDs, methotrexate is considered to be the anchor drug and, unless contraindicated, should be part of the first treatment strategy in patients at risk of persistent disease
6. NSAIDs are effective symptomatic therapies but should be used at the minimum effective dose for the shortest time possible, after evaluation of gastrointestinal, renal and cardiovascular risks
7. Systemic glucocorticoids reduce pain, swelling and structural progression, but in view of their cumulative side effects, they should be used at the lowest dose necessary as temporary (<6 months) adjunctive treatment. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation
8. The main goal of DMARD treatment is to achieve clinical remission, and regular monitoring of disease activity, adverse events and comorbidities should guide decisions on choice and changes in treatment strategies to reach this target
9. Monitoring of disease activity should include tender and swollen joint counts, patient and physician global assessments, ESR and CRP, usually by applying a composite measure. Arthritis activity should be assessed at 1-month to 3-month intervals until the treatment target has been reached. Radiographic and patient-reported outcome measures, such as functional assessments, can be used to complement disease activity monitoring
10. Non-pharmacological interventions, such as dynamic exercises and occupational therapy, should be considered as adjuncts to drug treatment in patients with early arthritis
11. In patients with early arthritis smoking cessation, dental care, weight control, assessment of vaccination status and management of comorbidities should be part of overall patient care
12. Patient information concerning the disease, its outcome (including comorbidities) and its treatment is important. Education programmes aimed at coping with pain, disability, maintenance of ability to work and social participation may be used as adjunct interventions

ACPA, anticitrullinated peptide antibodies; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; NSAIDs, non-steroidal anti-inflammatory drugs.

However, the expert committee intentionally added the term 'primarily' to this statement for three reasons: (1) the management of patients with early arthritis includes the care by primary care physicians and other healthcare professionals in a multidisciplinary approach; (2) in some places care by rheumatologists is not always available and accessible. Some countries have a shortage of rheumatologists, and in such situations patients should receive treatment from other healthcare providers with experience in the care of patients with inflammatory arthritis; (3) in some countries, task shifting from rheumatologists to other healthcare professionals is actively supported in order to facilitate early access and optimal quality of care, and to make care cheaper. Such care is still primarily under the responsibility and supervision of rheumatologists, but may be provided by other care providers.

Principle C:

A definite diagnosis in a patient with early arthritis should only be made after a careful history taking and clinical examination, which should also guide laboratory testing and additional procedures.

In the 2007 recommendations, this important statement was included as bullet point 3. It was considered that 'good clinical practice' and a 'high level of training' suffices an opinion that was entirely expert-based. The expert group was of the unanimous opinion that the statement is so generic that it represents an overarching principle rather than a recommendation. To establish a definite diagnosis in a patient with early arthritis, the group proposed that the minimum diagnostic procedures should include careful history taking and clinical examination, keeping the different possible causes of inflammatory arthritis in mind. After excluding other causes of joint swelling and pain (eg, septic arthritis, trauma, osteoarthritis, gout), particular attention should be paid to age, geographical area and travel history, number and pattern of involved joints, axial/entheseal involvement and extra-articular features (eg, eye, skin, genitourinal and gastrointestinal symptoms), including recent infections.[1] A minimal laboratory testing panel was proposed in the 2007 recommendations and should include testing for C reactive protein (CRP)/erythrocyte sedimentation rate (ESR), full blood cell count, transaminase levels, renal function and urine analysis,

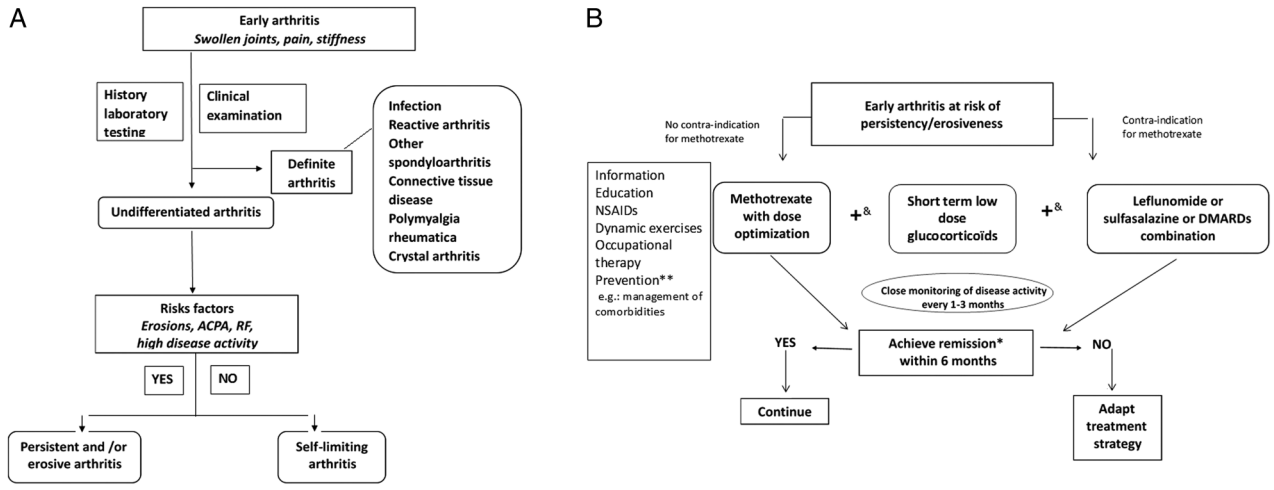

Figure 1 Algorithms based on the 2016 update of the European League Against Rheumatism recommendations for management of early arthritis. (A) Diagnosis and prognosis. (B) Treatment and strategy. &Combination with glucocorticoids preferred. *Low disease activity could be an alternative target in rare occasions. **Should also include weight loss, smoking cessation, dental care and vaccination. ACPA, anticitrullinated peptide antibodies; DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug, RF, rheumatoid factor.

rheumatoid factor (RF), anticitrullinated peptide antibodies (ACPA) and antinuclear antibodies. In addition, the diagnostic procedure may be expanded with microbiology and/or serological tests (reactive arthritis, synovial fluid microbial culture, Lyme disease, parvovirus infection, hepatitis B or C), uric acid testing, synovial fluid analysis (cell count and polarised light microscopy if needed), chest and joint radiographs, but dependent on the context and the country.

Recommendations

The discussions of the expert committee culminated into 12 recommendations (box 1). In comparison with 2007, the previous recommendation 3 was transformed into overarching principle C, while a recommendation for prevention (no. 11) was added. In addition, the order of the bullet points was slightly amended in order to better assure a logical sequence (and not for reasons of prioritisation). Table 1 displays the levels of evidence and grades for the following recommendations based on the Oxford Levels of Evidence assessment as well as level of agreement after anonymised voting by the expert committee.

Recommendation 1:

> Patients presenting with arthritis (any joint swelling, associated with pain or stiffness) should be referred to, and seen by, a rheumatologist, within 6 weeks after the onset of symptoms.

This recommendation is almost identical to its 2007 counterpart, but with subtle changes in the wording. After 2005, two studies have confirmed that patients with inflammatory arthritis in general, and those with suspected RA in particular, should be referred to rheumatologists as early as possible.[19 20] A delay in referral is one of the most important causes of late diagnosis and late start of effective treatment. Patients with early arthritis referred to a specialist within 3 months show better outcomes in terms of drug-free remission, radiographic damage and (less) need for orthopaedic surgery than those with late referral.[15] This is also fully in line with standards of care developed for patients with RA and quality indicators as established by European Expert committees.[21] On the basis of these data as well as the clinical experience of the committee members, it was recommended that diagnosis and start of treatment, both by a rheumatologist, should be established within a relatively short period after the onset of complaints which justifies the wording 'within 6 weeks' in this recommendation.

Joint swelling not due to trauma or bony swelling suggests early inflammatory arthritis, especially if associated with pain and morning stiffness >30 min.[22] Several referral questionnaires evaluating swelling, pain and stiffness have been developed to aid in the detection of early arthritis.[15] These questionnaires have a good sensitivity (86%–90%) and specificity (90%), but have been tested only in small patient samples and lack confirmation in independent validation cohorts. The committee was of the opinion that an appropriately validated tool to help general practitioners in adequately diagnosing and referring patients

Table 1 Updated EULAR recommendations for management of early arthritis, with LoE, GoR and LoA

		LoE*	GoR*	LoA*
A.	Shared decision	na	na	9.87±0.46
B.	Rheumatologists	na	na	9.78±0.67
C.	Diagnosis	na	na	9.78±0.67
1.	Early referral	Ib	B	9.43±1.16
2.	Clinical examination	IIb	C	9.48±0.99
3.	Prognosis	IIb	C	9.83±0.49
4.	Early treatment start	Ia	A	9.35±1.07
5.	MTX, the anchor drug	Ia	A	9.52±0.99
6.	NSAIDs	IV	D	9.00±1.13
7.	Glucocorticoids	Ia	A	9.00±1.28
8.	Remission and treatment strategies	Ib, IV†	A, D	9.52±0.9
9.	Regular monitoring	Ia, IV	A, D‡	9.13±1.06
10.	Non-pharmaceutical interventions	Ia	B	8.96±1.26
11.	Prevention	IIb, IV	C, D‡	8.96±1.19
12.	Patient information	Ia, Ib	B	9.35±0.98

*LoE and GoR are based on the recommendations of the Oxford Centre for Evidence-Based Medicine. LoA was based on an anonymised email voting system with a 0–10 scale by all members of the expert committee (data are mean±SD; 100% of voters).
†The general statement is evidence-based.
‡The place in the treatment algorithm is based on expert consensus.
EULAR, European League Against Rheumatism; GoR, grade of recommendation; LoA, level of agreement; LoE, level of evidence; MTX, methotrexate; na, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

with early arthritis is currently lacking. The strength of this recommendation was considered 'good' (category B) (table 1).

Recommendation 2:

Clinical examination is the method of choice for detecting arthritis, which may be confirmed by ultrasonography (US).

The expert committee unanimously appreciated the pivotal role of clinical examination. Clinical examination is still the cornerstone of detecting synovitis. This appreciation does not preclude that imaging modalities may be more sensitive in the detection of synovitis. US, including power Doppler techniques, may suggest synovitis by showing thickening of the synovial membrane, bursae and/or tendon sheaths with enhanced vascularity.[15] Several controlled studies have suggested a greater sensitivity of US than clinical examination in detecting synovitis in the knee and in small joints. US has been evaluated in detail in the 'EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis'.[23] The expert committee did not recommend a more prominent role for US in the detection of synovitis, since it was broadly felt that potentially decreased specificity and lack of knowledge regarding the long-term consequences of positive US in individual patients did not currently justify a more prominent position for US. Furthermore, wording specifically referring to power Doppler was deleted, because the group considered that power Doppler should be part of every US joint examination anyway.

MRI has also been suggested to be more sensitive than clinical examination in the early detection of synovitis,[23–25] but may face a lack of specificity as suggested by the prevalence of MRI abnormalities in the normal population.[26] In contrast with US, which is now a common tool in many rheumatologist practices, the long scanning time, limited access and the relatively high costs limit the widespread use of MRI. Therefore, the expert committee considered that MRI should be proposed only in very difficult cases or in patients with specific forms of arthritis, and that further research is needed to better determine the place of this imaging modality in the diagnosis of patients with early arthritis. MRI was part of the 2007 recommendations but was deleted from the current set.

Recommendation 3:

If a definite diagnosis cannot be reached and the patient has early undifferentiated arthritis, risk factors for persistent and/or erosive disease, including number of swollen joints, acute-phase reactants, RF, ACPA and imaging findings, should be considered in management decisions.

This recommendation was slightly rephrased because the group wanted to highlight that early undifferentiated arthritis should be clearly differentiated from early RA. In addition, 'imaging' was used instead of 'radiographic' to show that imaging modalities other than plain radiographs may provide prognostic information. For patients with early arthritis, after the exclusion of specific forms of arthritis, the working diagnosis is often undifferentiated arthritis. The next step in the diagnostic procedure is to evaluate the risk of persistent and/or erosive arthritis, usually corresponding to the definition of RA, in an individual patient.[27] This prognostic typing is now considered crucial to guide the optimal therapeutic strategy.

Since the 2007 exercise, many observational studies have evaluated the prognostic value of laboratory and imaging procedures for early arthritis. Most prognostic factors were analysed in a multivariate manner in these studies, to test their independent contribution. Commonly tested dependent variables were persistence, erosiveness or radiographic progression.

In most of the studies, ACPA and RF positivity and ACPA and RF levels have shown some predictive value for the development of persistent and erosive arthritis. This observation was clearly highlighted by EULAR and ACR since ACPAs, in addition to RF, have obtained an important weight in the 2010 ACR/EULAR classification criteria for RA.[27 28] In addition, several recent studies have confirmed the independent association of ACPAs with a diagnosis of RA as well as with radiographic progression in patients with early arthritis.[29–33] RF has been assigned a similar weight as ACPAs in the 2010 ACR/EULAR classification criteria for RA, although recent publications stemming from early arthritis cohorts and observational studies have suggested a lower predictive and diagnostic value of RF compared with ACPAs but RF has a stronger association with disease activity independent of the presence of ACPA.[15] The combination of RF and ACPAs does not provide additional value to RF or ACPAs alone.[28] In addition to ACPA, the number of swollen joints and the level of CRP and ESR are independent contributory factors.

Early erosion typical of RA is still a major prognostic factor in early arthritis and automatically leads to a classification of RA.[27 34] Synovitis and erosion detected by MRI or US may predict further joint damage in early arthritis, but false positivity has been reported.[26 35] MRI-detected bone marrow oedema and osteitis are independent predictors of radiographic progression in early RA,[23 24] but data are limited in early arthritis. Finally, two recent studies have shown that hand flexor or extensor tenosynovitis on US[36] or MRI[25] may be a specific—although not very sensitive—marker for RA classification.

Several combinations of diagnostic markers have been evaluated, but no one has been formally validated.[15] In addition, multibiomarker tests have been proposed to evaluate disease activity, prognosis and response to therapy, but current data are not convincing and further research is warranted.[15] Finally, it has been reported that substituting MRI for clinical examination in the 2010 ACR/EULAR criteria increases the sensitivity but decreases the specificity for a diagnosis of RA.[15] MRI is therefore of limited value in making a diagnosis of RA and is not recommended as a standard procedure.

Recommendation 4:

Patients at risk of persistent arthritis should be started on DMARDs as early as possible (ideally within 3 months), even if they do not fulfil classification criteria for an inflammatory rheumatologic disease.

This recommendation was slightly reworded and reiterates the unanimous opinion of the committee that an early treatment start is pivotal in the management of patients with early chronic arthritis such as early RA, early PsA or those at risk to develop persistent and erosive disease. The wording 'RA' is not used in this statement, but the implicit meaning is that persistent and/or erosive disease is factually synonymous to RA (see previous item) and justifies an early start with DMARDs. A new element is the maximum delay of 3 months after the onset of symptoms before starting the first DMARD. The expert committee was of the opinion that this time frame constitutes a 'window of opportunity' that should be considered to provide an optimal outcome in the patients at risk. Eight recent studies have endorsed an early treatment start. Four studies showed that introducing DMARDs within 3 months after the onset of symptoms leads to better outcome (remission, response to treatment, Health Assessment Questionnaire disability score or radiographic progression).[37–40] Very recently, van Nies *et al*[41] have suggested, based on data in the Etude et Suivi des Polyarthrites Indifferenciées Recentes (ESPOIR) and Leiden early arthritis cohorts, that 12–14 weeks represent an appropriate window within which therapy should be started in order to prevent

arthritis persistence. In addition, disease duration at the time of DMARD initiation was the most important determinant of response to DMARD therapy in another study.[15] This statement may raise questions about the best definition for 'early RA'. A duration of 3 months after the onset of symptoms may be the longest allowable delay in prescribing the first DMARD. However, this maximum delay is still difficult to meet in daily practice, while most of the recent 'early RA cohorts' allowed a delay of 6 months from the onset of symptoms (joint swelling usually) for inclusion.[28 29 41] A delay of not more than 6 months was also proposed in recent RA guidelines.[42] A delay of more than 1 year from symptom onset must not be considered 'early' anymore.

Recommendation 5:

> Among the DMARDs, methotrexate (MTX) is considered the anchor drug and unless contraindicated, should be part of the first treatment strategy in patients at risk of persistent disease.

This recommendation (previously no. 9) remains almost unchanged. Previous SLRs have confirmed the clinical and structural efficacy as well as the good safety profile of MTX.[4 43 44] An important argument to consider MTX an anchor drug as part of the first treatment strategy in patients at risk of persistent arthritis (eg, at risk of RA) is its good efficacy in early RA, and its 'practicability', both as monotherapy and in combination with glucocorticoids (GC), other csDMARDs and bDMARDs.[4 13 45] Recent trials in early DMARD-naïve patients with RA have evaluated MTX monotherapy versus csDMARDs combined with different dosages and routes of administration of GC. Verschueren *et al*[46] have recently reported similar 16-week remission rates in high-risk patients with early RA receiving MTX monotherapy, MTX plus sulfasalazine (SSZ) or MTX plus leflunomide (LEF), all in combination with high-dose prednisone bridging strategies. In another trial, MTX plus temporary high-dose prednisone was not less effective than MTX plus SSZ plus temporary high-dose prednisone after 26 weeks.[47] The Treatment in the Rotterdam Early Arthritis CoHort (tREACH) trial suggested short-lived superiority of MTX combined with SSZ, hydroxychloroquine and GC versus MTX and GC, but this superiority was not seen in all aspects, was not clinically meaningful and did ultimately not sustain after 1 year.[48] The Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial did not support a benefit of an intensive csDMARDs combination regimen over MTX monotherapy either.[49] In the absence of clear signals for superiority of a csDMARDs combination regimen, and guided by a trend towards lower tolerability for csDMARD combination,[16] the committee was of the opinion that the first treatment strategy should be MTX monotherapy with or without short-term high-dose GC as bridging therapy for most patients. In that regard, dose optimisation is an important aspect of first-line DMARD strategy, as previously reported[4 45] (MTX should be titrated rapidly to 20–30 mg/week, depending on clinical response and tolerability; parenteral administration should be considered in case of inadequate clinical response or intolerance).

The superiority of bDMARDs plus MTX over MTX monotherapy has been proven in many randomised controlled trials (RCTs) and was confirmed by eight recent studies in the current SLR.[16] In addition, two targeted synthetic DMARDs have recently demonstrated superiority to MTX, both used as monotherapy, in patients with early RA.[50 51] Nevertheless, because the benefit-to-risk ratio of these biological and targeted synthetic DMARDs was not convincingly favourable in patients with early disease, because tight monitoring is anyway part of the current treatment strategy to identify those in need of adding biologics and also because of their high cost, the expert committee considered their use as a first treatment strategy inappropriate, except in rare situations.

Recent RCTs comparing other csDMARDs with MTX were lacking. The clinical efficacy of LEF, and to a lesser extent SSZ, is similar to MTX in established and recent RA.[9] LEF is as effective as MTX in slowing radiographic damage, and its therapeutic maintenance is similar to that of MTX.[9] In contrast, SSZ may be inferior to LEF and MTX in the long term. Although formal evidence prioritising MTX over other csDMARDs as the first DMARD used in early arthritis and/or early RA is lacking, the expert committee does recommend MTX as first-choice treatment (unless contraindicated) in patients at risk of persistent disease. LEF and (to a lesser extent) SSZ are considered the best alternatives. Of note, SSZ is considered safe during pregnancy in contrast to MTX and LEF. Finally, the committee is of the opinion that antimalarial drugs, which have shown less clinical efficacy and may not retard radiographic progression in patients with RA but may have positive metabolic effects, can be considered as partner in combination therapy or as DMARD monotherapy in patients with mild disease and comorbidities or with persistent arthritis other than RA.[52]

Recommendation 6:

> Non-steroidal anti-inflammatory drugs (NSAIDs) are effective symptomatic therapies, but should be used at the minimum effective dose for the shortest time possible, after evaluation of gastrointestinal, renal and cardiovascular risks.

The SLR did not yield new data on NSAIDs in patients with early arthritis. The expert committee felt that symptomatic therapy with NSAIDs is still of value in patients presenting with early arthritis, but only after a careful consideration of gastrointestinal, renal and cardiovascular contraindications. In addition to the previous item no. 7 about NSAIDs, the group now reinforces the need to follow the US Food and Drug Administration and European Medicines Agency guidelines about NSAIDs, which includes wording about the shortest possible treatment duration, the minimum effective dose and the contraindications for patients at risk (http://www.fda.gov; http://www.ema.europa.eu).

Recommendation 7:

> Systemic GC reduce pain, swelling and structural progression, but in view of their cumulative side effects, they should be used at the lowest dose necessary as temporary (<6 months) adjunctive treatment. Intra-articular glucocorticoid injections should be considered for the relief of local symptoms of inflammation.

The expert committee has intensively debated the role of GC in the management of early arthritis. This discussion was based on expert opinion and on new information obtained by the SLR.[16] Recently, one meta-analysis of 14 RCTs in patients with RA and 2 RCTs in patients with 'early RA' has confirmed that systemic GC improve clinical and radiographic outcomes.[16 53 54] Preferably, therapy with systemic GC is temporary because of the risk of side effects, including weight gain, hypertension, diabetes, cataracts and osteoporosis, which justify careful monitoring and appropriate prevention. New data stemming from registries, observational studies and extensions of RCTs have also suggested an increased risk of severe infections, cardiovascular events and mortality.[16 55–60] In addition, there is evidence that intra-articular steroids may be an effective adjunct to DMARDs in relieving joint symptoms in patients presenting with early arthritis and may improve disease activity up to 24 months.[16]

The committee has reworded this item (no. 8 in the previous recommendations) in order to highlight the effectiveness of

systemic GC for relieving symptoms and disease progression but also in order to point to the risks of cumulative side effects in the medium to long term. The committee is of the opinion that GC can only be justified if used at the lowest possible cumulative dose, for the shortest possible duration and exclusively as adjunct (or bridge) therapy to csDMARDs. GC monotherapy may mask disease activity before a diagnosis has been established and should be avoided in patients with early arthritis, in order to expedite a proper diagnosis, and secure an adequate prognosis and a prompt DMARD treatment start. Despite a fierce debate, this recommendation was finally approved by 95% of the members and obtained a high level of agreement (mean of 9.00 ±1.28) with anonymous voting. The wording 'low dose' and the optimal regimen (low daily dose or high dose then step-down or parenteral boosts) in early arthritis are still under debate and will be mentioned in the research agenda (box 2).

Recommendation 8:

The main goal of DMARD treatment is to achieve clinical remission, and regular monitoring of disease activity, adverse events and comorbidities should guide decisions on choice and changes in treatment strategies to reach this target.

The 2007 recommendations for patients with early arthritis were among the first guidelines to highlight clinical remission as the main objective in the care of these patients. In the past 10 years, accumulating data have supported this as a major goal for the treatment of RA and other inflammatory arthritides.[6 9 11 13 61]

The expert committee has decided to keep the wording of the previous recommendation no. 10 unchanged. A few new studies have confirmed that achieving clinical remission as early as possible results in better clinical outcomes and quality of life, and helps to prevent further structural damage, functional disability and job loss in patients with early arthritis and early RA.[62] Which particular remission criteria should be used in practice remains unclear. Composite scores (disease activity score (DAS), DAS28, Clinical Disease Activity Index, Simplified Disease Activity Index (SDAI)) should be used, and the ACR-EULAR remission criteria (Boolean or SDAI) is likely the most stringent.[63] An interesting definition for daily practice is 'the absence of signs and symptoms of significant inflammatory disease activity'.[11] Recent evidence has suggested that remission leads to a better outcome than low disease activity (LDA),[62 64 65] and the committee was of the opinion that clinical remission according to the ACR-EULAR Boolean or index-based definition is the target for every patient presenting with early arthritis. A LDA state could be an appropriate alternative goal only in cases in which remission is considered unfeasible. In this respect, factors such as comorbidities, age or adverse events must be considered, and may determine the desired treatment target, which will form the basis for the process of shared decision making with the patient.

The expert committee also discussed whether imaging remission should be included in the target, as suggested by some recent recommendations.[23] Studies have suggested that ongoing inflammation seen by US, and to a lesser extent by MRI, in patients with clinical remission may predict structural progression. However, the significance thereof and its clinical utility are questionable and is associated with significant overtreatment and thus potential waste of societal resources;[66] the SLR did not yield new information.[15 16] Therefore, the expert committee suggested that the value of imaging remission should be part of the research agenda.

Finally, the committee felt that disease activity should be closely monitored in order to allow a timely change in DMARD therapy when necessary. The benefits of the treat-to-target approach have now amply been shown in patients with RA and PsA[11 67] and there is no reason to assume that the situation is different for early arthritis.

Recommendation 9:

Monitoring of disease activity should include tender and swollen joint counts, patient's and physician's global assessments, ESR and CRP, usually by applying a composite measure. Arthritis activity should be assessed at 1-month to 3-month intervals until the treatment target has been reached.

Box 2 Research agenda for management of early arthritis

Diagnosis and prognosis

1. Which tools could help general practitioners to diagnose early arthritis and prioritise referral?
2. Can we better define the diagnostic and prognostic value of ultrasonography in early arthritis?
3. Can we better define the diagnostic and prognostic value of MRI in early arthritis?
4. What is the diagnostic value of the systematic screening of antinuclear antibodies in early arthritis?
5. Which new biomarkers/multibiomarkers may help to better evaluate disease activity, the prognosis and treatment response in early arthritis?

Treatment and outcome

1. Can we develop prediction models to better define the therapeutic strategy in early arthritis?
2. Can we define at what level of risk (for developing persistent arthritis) different pharmacological interventions have a favourable benefit-to-risk ratios?
3. Do combinations of csDMARDs provide a better benefit-to-risk ratio than csDMARD monotherapy in early arthritis?
4. Can we better define 'low dose' and 'short term' use of glucocorticoids for an optimal medium-term to long-term benefit-to-risk ratio?
5. What is the optimal regimen (low daily dosage or high dose then step-down, or parenteral boosts) of glucocorticoids for better outcome in early arthritis?
6. Does imaging remission have an added benefit to clinical remission in treatment decisions?
7. What is the optimal interval at which to monitor radiographic progression in early chronic inflammatory arthritis?
8. What is the effectiveness of different non-pharmacological interventions in early arthritis?
9. Can physical activity/exercise reduce cardiovascular risk in early chronic arthritis?
10. Which study designs can best be used to investigate the comparative effectiveness and cost-effectiveness of different therapeutic strategies?
11. Is smoking cessation, oral hygiene, diets or psychological interventions beneficial for the outcome of patients with early arthritis?
12. What are the most efficient and effective information and education interventions and exercise programmes for early arthritis?

csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DMARD, disease-modifying antirheumatic drug.

Radiographic and patient-reported outcome measures, such as functional assessments can be used to complement disease activity monitoring.

In every patient with active arthritis, closely monitoring disease activity is now considered of particular importance in the therapeutic strategy to provide a good outcome and this is highlighted by all of the most recent recommendations.[6 9 11 13 42 61] Monitoring disease activity should be as frequent as the level of disease activity mandates, usually every 1–3 months, then potentially less frequently (such as every 6–12 months) once the treatment target has been achieved.

Nevertheless, three changes were proposed to this item (previously no. 12). First, a composite measure was recommended as the method of choice to monitor disease activity; second, a specific time frame for monitoring structural damage was deliberately left out and third, patient-reported outcomes were expanded beyond functional assessments.

Swollen joint count and progression of joint damage have been consistently found to be associated.[68 69] In addition, many trials have supported the use of a tight control of disease activity assessed via composite measures that include joint count evaluation.[11 16 67 70] Although it is difficult to formally investigate, the expert committee was of the opinion that monitoring the occurrence of radiographic progression is useful in view of one of the key objectives of managing early arthritis: the prevention of joint destruction. The determination of an optimal window for monitoring progression was added as an item for the research agenda (box 2).

Finally, patient-reported outcomes such as quality of life, fatigue and physical function are key to evaluate outcome[71 72] and the committee has mandated them as part of disease monitoring.

Recommendation 10:

Non-pharmacological interventions, such as dynamic exercises and occupational therapy, should be considered as adjuncts to drug treatment in patients with early arthritis.

This recommendation has remained almost unchanged. The efficacy of non-pharmacological therapy has not been investigated in early arthritis and can only be extrapolated from the results of several RCTs in established RA. Hydrotherapy in patients with RA has been evaluated in some studies,[73 74] but with insufficient evidence to support a strong recommendation; consequently, hydrotherapy was not included in the current statement but may be considered at the individual patient level. Previous RCTs have shown that joint-specific dynamic exercises may improve strength and physical function in RA, but the current SLR identified some controversial effects on disease activity.[16 74] Occupational therapy may improve functional ability and self-management but does not have a positive effect on disease activity; recent studies were not found.[75]

Finally, psychological counselling can be considered in selected patients, but trials investigating the efficacy of psychological interventions are lacking, and the committee did not include counselling in the statement. Furthermore, the SLR did not identify appropriate trials that evaluated the effectiveness of diets.

Since dynamic exercises, occupational therapy and to a lesser extent hydrotherapy have been associated with symptom relief in patients with established RA, the expert committee has decided to include them as adjunct therapies to pharmaceutical therapies in patients with early arthritis.

Recommendation 11:

In patients with early arthritis, smoking cessation, dental care, weight control, assessment of vaccination status and management of comorbidities should be part of overall patient care.

This recommendation is new and largely based on expert opinion. The expert committee felt that during the last decade evidence has accumulated that highlights the importance of the management of comorbidities (eg, cardiovascular diseases, metabolic conditions (eg, hyperlipidaemia, diabetes), lung diseases, infections, malignancies, osteoporosis and depression) in the context of the management of early arthritis.[76–82] Comorbidities may affect life expectancy and outcomes (physical function, quality of life) independently of disease activity in patients with inflammatory arthritis. In addition, coexisting diseases may affect the efficacy and safety of antirheumatic therapies.[82] Obesity and smoking may affect the response to treatment in inflammatory arthritis.[80] Prevention is now considered key in the management of chronic inflammatory rheumatic diseases, but comorbidities are still not optimally managed.[76] Smoking is the best-established modifiable risk factor in the development of RA and spondyloarthritis.[83 84] Furthermore, tobacco use has been associated with the presence of extra-articular manifestations such as rheumatoid nodules and also serum RF and ACPAs. While smoking does not seem to be associated with the perpetuation of disease activity or progression of RA,[85] it may affect the outcome of spondyloarthritis.[84]

RA is associated with periodontal disease, although the direction of the relationship still remains unclear.[86] The microbiome may play a role in chronic arthritis risk and progression, and *Porphyromonas gingivalis* infection could promote aberrant citrullination and a local breach of tolerance to citrullinated peptides. The potentially beneficial contribution of oral hygiene has been put on the research agenda.

Although current data do not prove that risk-factor modification is beneficial to patients, the modifiable risk factors identified in the SLR are so generic in nature that the committee was unanimously of the opinion that a recommendation aiming at abolishing their potential influence on arthritis (and general health) would not harm patients and may convey some benefits.

In addition, the expert committee noted that fewer patients with chronic arthritis than recommended are currently vaccinated,[87] and that this should be specifically mentioned.

Recommendation 12:

Patient information concerning the disease, its outcome (including comorbidities) and its treatment is important. Education programmes aimed at coping with pain, disability, maintenance of ability to work and social participation may be used as adjunct interventions.

This recommendation was very similar to the previous item no. 6. Obviously, full transparency about the disease and its treatment options should be an integral part of the management of any chronic disease, and constitutes the core of overarching principle A. Other healthcare providers share the responsibility in the provision of information. Studies have suggested that adherence to treatment is dependent on the quality of information exchange and the quality of the interaction between the patient and healthcare professionals, including rheumatologists.[16]

EULAR has recently recommended that 'people with inflammatory arthritis should have access to and be offered patient education throughout the course of their disease, including as a minimum, at diagnosis, at pharmacological treatment change and when required by the patient's physical or psychological condition'.[88] The content and delivery of patient education should be individually tailored, with individual and group sessions representing different approaches to delivery. It is impossible to prioritise a single educational intervention since all tested interventions have only short-term benefits and feature

cross-national and cultural variations.[16] Improved quality of life is a major aim for patients and the committee proposed to add 'social participation' as one of the objectives of these education programmes. The expert committee also felt that patients should be aware that comorbidities may affect the outcome and treatment of inflammatory arthritis, and that their screening and management should be part of the global management of early arthritis.

DISCUSSION

The update of the EULAR recommendations for the management of early arthritis followed the 2014 EULAR Standardised Operating Procedures.[14] The committee has proposed an important revision of the items, but obviously most major recommendations have remained intact. These updated recommendations for management of early arthritis contain 3 overarching principles, 12 recommendations and 2 algorithms that integrate all the recent developments in the management of early arthritis. The definition of the term 'management' was unchanged and includes all spectra of management of early arthritis, including referral, diagnosis, prognosis, classification, information, education, non-pharmacological interventions and pharmacological treatments and monitoring of the disease. The term 'early arthritis' was restricted to 'early inflammatory arthritis' and mainly, but not only, focused on the risk of chronic arthritis.

The expert committee had to face a limitation in that most of the published data on treatment and strategy on which they could build their recommendations involved studies in patients with early RA or established RA, rather than specific studies of early arthritis. Despite this limitation, the committee considered much of the data for early RA sufficiently robust and relevant for extrapolating to 'early arthritis with a certain propensity to become persistent.' The scope was different compared with the EULAR recommendations for the management of RA,[13] which focussed on the use of DMARDs in both early and established disease. However, there are overlaps with regard to the first-line therapy for early arthritis at risk of persistence (figure 1) and for early RA (DMARD-naïve and usually <6 months disease duration). Not surprisingly, the two sets of recommendations are very congruent on these specific points.

These recommendations have important strengths including the composition of the expert committee comprising 20 rheumatologists, including 2 research fellows, from 12 European countries and new addition of 1 healthcare professional and 2 patient representatives. The committee chose to grade the level of evidence provided by every study, which was based on the methodology of the study, and took this grading into consideration when discussing the content and the strength of the recommendations. An important consideration in the discussions was always whether the type of study fitted the content of the research question that was at the basis of the literature search. The recommendations were based on the most recent evidence and on expert opinion. For example, the expert committee felt that evidence supported comorbidities as possibly affecting the outcome of arthritis and also treatment efficacy and safety and should be considered in the management of all early arthritis cases. Despite the sparse evidence, the expert committee also wanted to indicate that smoking cessation and dental care could be proposed to patients with early arthritis, and that both patients and healthcare professionals should be aware of the importance to improve vaccination coverage. In this respect, a new recommendation on prevention was added (item no. 11). Of note, the level of agreement among the experts was high for each item (means of 9.0–9.9), which support the appropriateness and validity of the recommendations.

In light of the current literature and despite important recent advances, the committee felt that further development of new tools is needed for early and accurate diagnosis and prognosis, including new biomarkers, better understanding of the added value of US and MRI and creation of prediction algorithms for long-term outcome (box 2). Finally, the expert committee felt that the comparative effectiveness and cost-effectiveness of the different strategic modalities in early arthritis, including the effectiveness of non-pharmacological interventions, need additional research.

While these 'recommendations' are deliberately not called 'guidelines', they do reflect a strong view of many European experts including patient representatives. They should provide rheumatologists, general practitioners, medical students, healthcare professionals, health authorities and patients a practical approach to the management of early arthritis, even though each healthcare professional should choose the most appropriate management strategy for each individual patient. To that end, it is hoped that the recommendations will be widely disseminated and discussed within the community of rheumatologists and other healthcare professionals caring for patients with early arthritis and that they will help improve the standard of care for patients with arthritis across different healthcare systems. Obviously, these recommendations will probably need amendment after about 5 years to incorporate new scientific evidence.

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REFERENCES

1 Machado P, Castrejon I, Katchamart W, *et al*. Multinational evidence-based recommendations on how to investigate and follow-up undifferentiated peripheral inflammatory arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2011;70:15–24.
2 Huizinga TWJ, Machold KP, Breedveld FC, *et al*. Criteria for early rheumatoid arthritis: from Bayes' law revisited to new thoughts on pathogenesis. *Arthritis Rheum* 2002;46:1155–9.
3 Combe B. Early rheumatoid arthritis: strategies for prevention and management. *Best Pract Res Clin Rheumatol* 2007;21:27–42.
4 Gaujoux-Viala C, Nam J, Ramiro S, *et al*. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:510–15.
5 Smolen JS, Aletaha D, Koeller M, *et al*. New therapies for treatment of rheumatoid arthritis. *Lancet* 2007;370:1861–74.
6 Gossec L, Smolen JS, Ramiro S, *et al*. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016;75:499–510.
7 Nam JL, Ramiro S, Gaujoux-Viala C, *et al*. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:516–28.
8 Avci AB, Feist E, Burmester G-R. Biologicals in rheumatoid arthritis: current and future. *RMD Open* 2015;1:e000127.
9 Combe B, Landewe R, Lukas C, *et al*. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:34–45.
10 Monti S, Montecucco C, Bugatti S, *et al*. Rheumatoid arthritis treatment: the earlier the better to prevent joint damage. *RMD Open* 2015;1(Suppl 1):e000057.
11 Smolen JS, Breedveld FC, Burmester GR, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
12 Smolen JS, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.
13 Smolen JS, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
14 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
15 Hua C, Daien CI, Combe B. Diagnosis, prognosis and classification of early arthritis: results of a systematic literature informing the 2016 update of the EULAR recommendations for the management of early arthritis. *RMD Open*.
16 Daïen CI, Hua C, Combe B, *et al*. Pharmacologic and non-pharmacologic therapies in early arthritis: results of a systematic literature informing the 2016 update of the EULAR recommendations for the management of early arthritis. *RMD Open* 2016.
17 OCEBM Levels of Evidence. CEBM. 2016 (cited 3 May 2016). http://www.cebm.net/ocebm-levels-of-evidence/
18 Bykerk V, Emery P. Delay in receiving rheumatology care leads to long-term harm. *Arthritis Rheum* 2010;62:3519–21.
19 van der Linden MPM, le Cessie S, Raza K, *et al*. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis Rheum* 2010;62:3537–46.
20 Feldman DE, Bernatsky S, Houde M, *et al*. Early consultation with a rheumatologist for RA: does it reduce subsequent use of orthopaedic surgery? *Rheumatology* 2013;52:452–9.
21 Stoffer MA, Smolen JS, Woolf A, *et al*. Development of patient-centred standards of care for rheumatoid arthritis in Europe: the eumusc.net project. *Ann Rheum Dis* 2014;73:902–5.
22 Emery P, Breedveld FC, Dougados M, *et al*. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. *Ann Rheum Dis* 2002;61:290–7.
23 Colebatch AN, Edwards CJ, Østergaard M, *et al*. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013;72:804–14.
24 Duer-Jensen A, Hørslev-Petersen K, Hetland ML, *et al*. Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. *Arthritis Rheum* 2011;63:2192–202.
25 Nieuwenhuis WP, Krabben A, Stomp W, *et al*. Evaluation of magnetic resonance imaging-detected tenosynovitis in the hand and wrist in early arthritis. *Arthritis Rheumatol* 2015;67:869–76.
26 Mangnus L, Schoones JW, van der Helm-van Mil AHM. What is the prevalence of MRI-detected inflammation and erosions in small joints in the general population? A collation and analysis of published data. *RMD Open* 2015;1:e000005.
27 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
28 Funovits J, Aletaha D, Bykerk V, *et al*. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. *Ann Rheum Dis* 2010;69:1589–95.
29 Mouterde G, Lukas C, Logeart I, *et al*. Predictors of radiographic progression in the ESPOIR cohort: the season of first symptoms may influence the short-term outcome in early arthritis. *Ann Rheum Dis* 2011;70:1251–6.
30 van den Broek M, Dirven L, Klarenbeek NB, *et al*. The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study. *Ann Rheum Dis* 2012;71:245–8.
31 Hetland ML, Stengaard-Pedersen K, Junker P, *et al*. Radiographic progression and remission rates in early rheumatoid arthritis—MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. *Ann Rheum Dis* 2010;69:1789–95.
32 Degboé Y, Constantin A, Nigon D, *et al*. Predictive value of autoantibodies from anti-CCP2, anti-MCV and anti-human citrullinated fibrinogen tests, in early rheumatoid arthritis patients with rapid radiographic progression at 1 year: results from the ESPOIR cohort. *RMD Open* 2015;1:e000180.
33 Akdemir G, Verheul MK, Heimans L, *et al*. Predictive factors of radiological progression after 2 years of remission-steered treatment in early arthritis patients: a post hoc analysis of the IMPROVED study. *RMD Open* 2016;2:e000172.

34 van der Heijde D, van der Helm-van Mil AHM, Aletaha D, *et al*. EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria. *Ann Rheum Dis* 2013;72:479–81.
35 Rezaei H, Torp-Pedersen S, af Klint E, *et al*. Diagnostic utility of musculoskeletal ultrasound in patients with suspected arthritis—a probabilistic approach. *Arthritis Res Ther* 2014;16:448.
36 Sahbudin I, Pickup L, Cader Z, *et al*. OP0015 ultrasound-defined tenosynovitis is a strong predictor of early rheumatoid arthritis. *Ann Rheum Dis* 2015;74(Suppl 2):69–70.
37 Bosello S, Fedele AL, Peluso G, *et al*. Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression. *Ann Rheum Dis* 2011;70:1292–5.
38 Gremese E, Salaffi F, Bosello SL, *et al*. Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann Rheum Dis* 2013;72:858–62.
39 Lukas C, Combe B, Ravaud P, *et al*. Favorable effect of very early disease-modifying antirheumatic drug treatment on radiographic progression in early inflammatory arthritis: data from the Étude et Suivi des polyarthrites indifférenciées récentes (study and follow-up of early undifferentiated polyarthritis). *Arthritis Rheum* 2011;63:1804–11.
40 Söderlin MK, Bergman S, BARFOT Study Group. Absent "Window of Opportunity" in smokers with short disease duration. Data from BARFOT, a multicenter study of early rheumatoid arthritis. *J Rheumatol* 2011;38:2160–8.
41 van Nies JAB, Tsonaka R, Gaujoux-Viala C, *et al*. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. *Ann Rheum Dis* 2015;74:806–12.
42 Singh JA, Saag KG, Bridges SL, *et al*. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
43 Ramiro S, Gaujoux-Viala C, Nam JL, *et al*. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:529–35.
44 Ramiro S, Smolen JS, Landewé R, *et al*. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2016;75:490–8.
45 Visser K, Katchamart W, Loza E, *et al*. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009;68:1086–93.
46 Verschueren P, De Cock D, Corluy L, *et al*. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. *Ann Rheum Dis* 2015;74:27–34.
47 den Uyl D, ter Wee M, Boers M, *et al*. A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. *Ann Rheum Dis* 2014;73:1071–8.
48 de Jong PH, Hazes JM, Han HK, *et al*. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann Rheum Dis* 2014;73:1331–9.
49 Moreland LW, O'Dell JR, Paulus HE, *et al*. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum* 2012;64:2824–35.
50 Lee EB, Fleischmann R, Hall S, *et al*. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377–86.
51 Fleischmann R, Schiff M, van der Heijde D. Baricitinib, Methotrexate, or Combination in Patients with Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. *Arthritis Rheumatol* 2016 Oct 9. doi:10.1002/art.39953.
52 Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol* 2011;23:278–81.
53 Verschueren P, De Cock D, Corluy L, *et al*. Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early rheumatoid arthritis: week 16 results from the randomized multicenter CareRA trial. *Arthritis Res Ther* 2015;17:97.
54 Seegobin SD, Ma MHY, Dahanayake C, *et al*. ACPA-positive and ACPA-negative rheumatoid arthritis differ in their requirements for combination DMARDs and corticosteroids: secondary analysis of a randomized controlled trial. *Arthritis Res Ther* 2014;16:R13.
55 Dixon WG, Abrahamowicz M, Beauchamp M-E, *et al*. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012;71:1128–33.
56 del Rincón I, Battafarano DF, Restrepo JF, *et al*. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheumatol* 2014;66:264–72.
57 Listing J, Kekow J, Manger B, *et al*. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann Rheum Dis* 2015;74:415–21.
58 Roubille C, Richer V, Starnino T, *et al*. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:480–9.
59 Ajeganova S, Svensson B, Hafström I. Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: 10-year follow-up of a 2-year randomised trial. *BMJ Open* 2014;4:e004259.
60 de Hair M. Long-Term Adverse Events after Daily Concomitant Treatment with 10mg Prednisone in the 2-Year Computer Assisted Management in Early Rheumatoid Arthritis Trial-II. *ACR Meeting Abstracts* [cited 10 May 2016].
61 Smolen JS, Braun J, Dougados M, *et al*. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2014;73:6–16.
62 Combe B, Logeart I, Belkacemi MC, *et al*. Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. *Ann Rheum Dis* 2015;74:724–9.
63 Felson DT, Smolen JS, Wells G, *et al*. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.
64 Ruyssen-Witrand A, Guernec G, Nigon D, *et al*. Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes. *Ann Rheum Dis* 2015;74:1676–83.
65 Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. *Arthritis Res Ther* 2014;16:R56.
66 Dale J, Stirling A, Zhang R, *et al*. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. *Ann Rheum Dis* 2016;75:1043–50.
67 Coates LC, Moverley AR, McParland L, *et al*. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet* 2015;386:2489–98.
68 Klarenbeek NB, Güler-Yüksel M, van der Heijde DMFM, *et al*. Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. *Ann Rheum Dis* 2010;69:2107–13.
69 Gärtner M, Sigmund IK, Alasti F, *et al*. Clinical joint inactivity predicts structural stability in patients with established rheumatoid arthritis. *RMD Open* 2016;2:e000241.
70 Akdemir G, Markusse IM, Dirven L, *et al*. Effectiveness of four dynamic treatment strategies in patients with anticitrullinated protein antibody-negative rheumatoid arthritis: a randomised trial. *RMD Open* 2016;2:e000143.
71 van Steenbergen HW, Tsonaka R, Huizinga TWJ, *et al*. Fatigue in rheumatoid arthritis; a persistent problem: a large longitudinal study. *RMD Open* 2015;1:e000041.
72 Gossec L, Dougados M, Dixon W. Patient-reported outcomes as end points in clinical trials in rheumatoid arthritis. *RMD Open* 2015;1:e000019.
73 Verhagen AP, Bierma-Zeinstra SM, Boers M, *et al*. Balneotherapy (or spa therapy) for rheumatoid arthritis. An abridged version of Cochrane Systematic Review. *Eur J Phys Rehabil Med* 2015;51:833–47.
74 Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, *et al*. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst Rev* 2009;(4):CD006853.
75 Ekelman BA, Hooker L, Davis A, *et al*. Occupational therapy interventions for adults with rheumatoid arthritis: an appraisal of the evidence. *Occup Ther Health Care* 2014;28:347–61.
76 Dougados M, Soubrier M, Antunez A, *et al*. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis* 2014;73:62–8.
77 Baillet A, Gossec L, Carmona L, *et al*. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis* 2016;75:965–73.
78 Peters MJL, Symmons DPM, McCarey D, *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
79 Gherghe AM, Dougados M, Combe B, *et al*. Cardiovascular and selected comorbidities in early arthritis and early spondyloarthritis, a comparative study: results from the ESPOIR and DESIR cohorts. *RMD Open* 2015;1:e000128.

80 Daïen CI, Sellam J. Obesity and inflammatory arthritis: impact on occurrence, disease characteristics and therapeutic response. *RMD Open* 2015;1:e000012.
81 Bacconnier L, Rincheval N, Flipo R-M, *et al*. Psychological distress over time in early rheumatoid arthritis: results from a longitudinal study in an early arthritis cohort. *Rheumatology* 2015;54:520–7.
82 Radner H, Yoshida K, Mjaavatten MD, *et al*. Development of a multimorbidity index: impact on quality of life using a rheumatoid arthritis cohort. *Semin Arthritis Rheum* 2015;45:167–73.
83 Sparks JA, Karlson EW. The roles of cigarette smoking and the lung in the transitions between phases of preclinical rheumatoid arthritis. *Curr Rheumatol Rep* 2016;18:15.
84 Poddubnyy D, Haibel H, Listing J, *et al*. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the German SPondyloarthritis Inception Cohort (GESPIC). *Ann Rheum Dis* 2013;72:1430–2.
85 Vesperini V, Lukas C, Fautrel B, *et al*. Association of tobacco exposure and reduction of radiographic progression in early rheumatoid arthritis: results from a French multicenter cohort. *Arthritis Care Res* 2013;65:1899–906.
86 Fuggle NR, Smith TO, Kaul A, *et al*. Hand to mouth: a systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. *Front Immunol* 2016;7:80.
87 Hua C, Morel J, Ardouin E, *et al*. Reasons for non-vaccination in French rheumatoid arthritis and spondyloarthritis patients. *Rheumatology (Oxford)* 2015;54:748–50.
88 Zangi HA, Ndosi M, Adams J, *et al*. EULAR recommendations for patient education for people with inflammatory arthritis. *Ann Rheum Dis* 2015;74:954–62.

2016 update of the EULAR recommendations for the management of early arthritis

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RHEUMATOLOGY

Guidelines

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The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults

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Key words: lupus, diagnosis, assessment, monitoring, management, immunosuppressants, treatment, efficacy, non-biologics, biologics.

GUIDELINES

Scope and purpose of the guideline

Background

SLE (or lupus for short) is a multisystem, autoimmune disease, involving complex pathogenetic mechanisms that can present at any age. It most commonly presents in women in the reproductive age group, although lupus is increasingly recognized after the age of 40 years, particularly in Europeans [1–3]. Lupus affected nearly 1 in 1000 of the population in the UK in 2012 [4] and was

NICE has accredited the process used by the BSR to produce its guidance on the management of systemic lupus erythematosus in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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most frequently observed in people of African-Caribbean and South Asian descent [4–6]. The age-standardized incidence in the UK according to the Clinical Practice Research Datalink is 8.3/100 000/year for females and 1.4/100 000/year for males [4], and the highest incidence rates are seen in those of African-Caribbean descent: 31.4/100 000/year, compared with 6.7/100 000/year for those of white European descent. The mean age at diagnosis is 48.9 years [4], but it is lower in those of African ancestry in the UK [4–6] and North America [2, 7].

The disease is prone to relapses and remissions, resulting in considerable morbidity due to flares of disease activity and accumulated damage, and an increased risk of premature death, mostly due to infection or cardiovascular disease [2, 8–14]. Death from active lupus is rare in the UK [15, 16]; however, a 10% mortality over 20 years and a mean age of death of 53.7 years was recently reported [16]. About one-third of SLE patients in the UK develop LN [16–18]. Patients of African ancestry tend to present young with LN in the UK, as in the USA and elsewhere [2, 17, 19], and are at considerable risk of developing end-stage renal disease (ESRD) and of dying prematurely. In another UK cohort, ESRD occurred in 20% of LN patients within 10 years of diagnosis, and the mean age at death in LN patients was 40.3 years, with an average of 7.5 years between development of LN and death [18].

The mainstay of therapy for active lupus until recently has been NSAIDs, CSs, antimalarials such as HCQ, and immunosuppressants such as AZA and CYC, although only prednisolone and HCQ are licensed for lupus [8, 20]. With the exception of LN, there were relatively few trials until the last 15 years, and in 2011, belimumab became the first drug to be licensed for the treatment of active lupus for over 50 years [20]. New therapies that will reduce the need for CSs to control lupus activity and to reduce the development of damage and infection are needed to improve outcome [10–12, 16, 21]. In the meantime it is important to manage patients optimally with the treatment strategies that are available.

Need for the guideline

Despite some improvement in survival data over the last 40 years [2, 13], lupus patients still die on average 25 years earlier than the mean for women and men in the UK [16]. The disease can present with slowly or rapidly progressive active disease at any age and can be associated with the rapid accumulation of damage if not promptly diagnosed, appropriately treated and regularly monitored [2, 8, 14, 19, 20]. An up-to-date comprehensive guideline to optimize these aspects of management that is consistent with current evidence and National Health Service (NHS) practice is warranted to improve the outcome of this variable and potentially life-threatening disease that

Table 1 Levels of evidence and grades of recommendation for diagnosis, assessment and monitoring of non-renal SLE

Statement/item	Number of studies	Overall SIGN level of evidence	Grade of recommendation	Selected references covering items discussed in text
Diagnosis from clinical and serological features				
Prognostic value of:				
Clinical features	29	2++	B	[7, 10, 26–35]
ANA	8	2++	B	[26–29, 34, 36–38]
Anti-dsDNA antibodies	17	2++	B	[26–29, 37, 39, 40]
Low C3/C4 levels	13	2+	C	[27, 41–46]
Anti-Ro/La antibodies	4	2+	C	[10, 27–29, 37]
aPLs	12	2++	B	[26, 27, 29, 47]
Assessment and monitoring of SLE disease activity and damage				
Clinical flare	6	2+	C	[48, 49]
Good diagnostic utility of:				
clinical and laboratory monitoring	28	2++	B	[11, 16, 21, 32, 50–57]
anti-dsDNA and C3/C4 levels	14	2++	B	[40, 43, 44, 46, 49, 58–60, 61–63]
aPL repeat	–	–	D	[47]
anti-Ro/La for neonatal lupus	6	1+	A	[64, 65]
CRP low or normal unless infection	4	2++	B	[66–69]
ESR correlates with active lupus	2	2+	C	[69, 70]
Prognostic value of lupus disease activity and damage indices	>60	2++	B	Reviewed in [12, 71] [11, 14–16, 32, 72, 73]
Monitoring and treating cardiovascular risk factors in SLE patients	6	2+	C	Reviewed in [22, 71, 74–76]
Frequency of monitoring SLE:				
For active disease, every 1–3 months after diagnosis or flare	2	2+	C	[72, 77]
Low/no disease activity, stable treatment: 6- to 12-monthly	–	–	D	Expert opinion
Monitoring for drug toxicity/levels	2	2+	C	[78, 79]

SIGN: Scottish Intercollegiate Guidelines Network

Table 2 Levels of evidence and grades of recommendation for medications used in the treatment of non-renal SLE

Treatment (recommended target dosage)	Main uses (unless contra-indications)	Total number of papers	Overall SIGN level of evidence	Grade of recommendation	Comments: including number of reports and references for RCTs, cohort studies and systematic reviews/meta-analyses (SRs)
Antimalarials: HCQ ⩽6.5 mg/kg/day	Mild lupus, prevent flare in all patients, prevent damage, steroid-sparing	45	1 ++	A	7 RCTs [80–86]; 36 cohort studies [87–120]; 2 SRs [121, 122]
MTX ⩽25 mg/week	Mild and moderate lupus, prevent flare, steroid sparing	12	1+	A	2 blind, 1 open-label RCTs [123–125]; 5 cohort studies [126–130]; 2 case series [131, 132]; 2 SRs [133, 319]
NSAIDs	Symptom control in mild non-renal lupus only	1	3	D	1 SR covers case series/reports [134]
Sunscreen (high-SPF UV-A and UV-B)	Prevents UV-induced rashes and other manifestations	7	2 ++	B	1 blind RCT [135]; 5 cohort studies [136–140]; 1 case series [141]
Low-dose oral prednisolone (⩽7.5 mg)	Mild lupus and to prevent flares	0	4	D	Expert opinion
Higher doses of oral prednisolone ⩽0.5 mg/kg/day	Moderate lupus and prevention of flares	0 2	4 2+	D C	To prevent flare: 1 blind RCT [46] and 1 open-label RCT [60]
I.m. triamcinolone	Moderate lupus	1	2+	C	1 open-label RCT [142]
I.m. methylprednisolone (80–120 mg)	Moderate lupus	0	4	D	Expert opinion
I.v. methylprednisolone (100–250 mg)	Moderate lupus	1	2+	C/D	1 blind RCT for 100 mg *vs* 1000 mg [143]
I.v. methylprednisolone (500 mg–1 g) × 1–3 pulses	Moderate and severe lupus	6	2+	C	2 small blind RCTs [143, 144]; 1 open-label trial [145]; 3 cohort studies [146–148]
AZA (if TPMT normal) 2–3 mg/kg/day	Moderate lupus, prevent flare, steroid sparing	10	2+	C	4 open-label RCTs [149–152]; 5 cohort studies [153–157]; 1 case series [158]
MMF 2–3 g/day	Moderate/severe lupus, prevent flare, steroid-sparing	13	2 ++	B	3 open-label RCTs [159–161]; 7 cohort studies [162–168]; 1 case series [169]; 2 SRs [133, 170]
Mycophenolic acid/sodium 1.44–2.16 g/day	For patients intolerant of MMF	2	3	D	1 open-label RCT [171]; 1 cohort study [172]

(continued)

Table 2 Continued

Treatment (recommended target dosage)	Main uses (unless contra-indications)	Total number of papers	Overall SIGN level of evidence	Grade of recommendation	Comments: including number of reports and references for RCTs, cohort studies and systematic reviews/meta-analyses (SRs)
Ciclosporin ⩽2.5 mg/kg/day	Moderate/severe lupus including cytopenias, prevent flare, steroid-sparing	11	2+	C	2 open-label RCTs [152, 173]; 8 cohort studies [174–181]; 1 SR [133]
Tacrolimus 1–3 mg/day (assess drug levels)	Moderate/severe lupus, steroid-sparing	3	3	D	2 cohort studies [182, 183]; 1 SR [133]
LEF (20 mg/day)	Moderate lupus without subacute rash	3	3	D	1 small blind RCT [184]; 1 cohort study [185]; 1 SR [133]
CYC (see text for dosing)	Severe lupus, including NPSLE, prevent flare, steroid-sparing	30	2 ++	B	4 open-label RCTs [186–189]; 25 cohort studies covered by 1 SR [133]
Rituximab 1000 mg × 2	Refractory severe and moderate lupus; steroid-sparing	33	2+	C	1 blind RCT [190, 191]; 3 open-label RCTs [192–194]; 24 cohort studies [195–198 not in SRs]; 2 case series [194, 199]; 2 SRs, including 1 meta-analysis [200, 201]; 1 SR with 26 extra case reports/series [202]
Belimumab 10 mg/kg/4 weeks	Refractory moderate/severe lupus; prevent flare and steroid-sparing (not NPSLE)	5	1+	B	2 phase III blind RCTs [203, 204]; 1 phase II blind RCT [205]; *post hoc* combined analysis [206]; 1 open-label extension [207, 208]; 1 meta-analysis [209]
IVIG (see text)	Refractory severe lupus (including catastrophic APS)	19	2−	D	Rarely indicated: 3 open-label trials [210–212]; 10 cohort studies [213–222]; 4 case series [223–226]; 2 SRs with 1 meta-analysis [227, 228]
Plasmapharesis	TTP; refractory severe SLE	10	2 ++ for TTP; 3 otherwise	B for TTP; D otherwise	Rarely indicated: 9 cohort/case series [229–237]; 1SR [238]

TPMT: thiopurine S-methyltransferase (see text); TTP: thrombocytopaenic purpura.

causes considerable morbidity. There have been no previous UK-based guidelines for lupus. The European (EULAR) recommendations for the management of lupus in general were not very detailed and were published in 2008 [22], although more specific recommendations were published for neuropsychiatric lupus in 2010 [23], and joint EULAR and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for LN were published in 2012 [24], as well as ACR guidelines for the management of LN in 2012 [25].

Objectives of the guideline

The aim of this guideline was to produce recommendations for the management of adult lupus patients in the UK that cover the diagnosis, assessment and monitoring of lupus and the treatment of mild, moderate and severe active lupus disease, but which do not imply a legal obligation. The resulting recommendations are based on an extensive review of the literature up to June 2015 to produce evidence-based guidelines, particularly for the treatment of non-renal lupus, supplemented as necessary by expert opinion and consensus agreement (Tables 1 and 2). The guideline development group recommended that patients with LN are managed according to the EULAR/ERA-EDTA recommendations for LN [24] and provide their strengths of agreement (SOAs) with a summary of the most important items in those recommendations (Table 3).

Target population, target audience and stakeholder involvement

The guidelines address the management of adult patients only and have been developed by a multidisciplinary guideline development group set up by the British Society for Rheumatology (BSR) and led by C.G., consisting of academic (C.G., I.N.B., D.D.C., M.K., D.I.) and NHS consultants in rheumatology (M.A., B.G.) and nephrology (D.J., L.L.), rheumatology trainees (M.G., K.S.), a GP (B.E.), a clinical nurse specialist (S.B.), a patient representative (Y.N.) and a lay member (P.N.). All participants declared any conflicts of interest and these are listed at the end of this article. The target audience includes rheumatologists and other clinicians such as nephrologists, immunologists and dermatologists, trainees in these specialties and emergency medicine, GPs, clinical nurse specialists and other allied health professionals involved in the care of adult lupus patients. Opinions of other key stakeholders such as other consultant members of the BSR, additional trainees, podiatrists, nurse specialists and representatives of Lupus UK were sought during the preparation of these guidelines.

Areas that the guideline does not cover

This guideline does not cover the evidence for topical or systemic therapy for isolated cutaneous lupus, nor does it discuss paediatric lupus, as there is relatively little literature on paediatric lupus. As the disease tends to come on after puberty, most of the recommendations are likely to be appropriate for children/adolescents, with suitable dose modifications. We provide only summary advice about the use of drugs in the management of pregnant lupus patients, and refer to the extensive review of drugs used in pregnancy and breast-feeding that have been recently published [239, 240]. The management of complications of lupus, including chronic fatigue, cardiovascular risk, osteoporosis, infection and cancer risk are not discussed in detail, as these issues should be managed as for other patients with similar risk factors according to national and international guidelines. Management of thrombosis will depend on whether or not the criteria for APS are met [241].

Rigor of development

Selection of questions for the literature review, and statement of extent of previous National Institute for Health and Care Excellence, Royal College of Physicians, and Scottish Intercollegiate Guidelines Network guidelines

A multidisciplinary guideline development group was formed and followed the BSR Protocol for Guidelines and EULAR standardized operating procedures to define the focus of the work, the target population and the target audience. Discussions were supplemented by consensus-building strategies, including a modified Delphi technique, in order to reduce and clearly define the list of research questions to be addressed by the literature search (see supplementary data section Search strategy, available at *Rheumatology* Online). There are no BSR, Royal College of Physicians (RCP), National Institute for Health and Care Excellence (NICE) or Scottish Intercollegiate Guidelines Network (SIGN) guidelines or recommendations for the management of lupus in the UK to help improve the outcome of this variable and potentially life-threatening disease, but lupus has been included in the on-line resource Map of Medicine.

Literature review: eligibility criteria and limitations of the search

A systematic search of MEDLINE (PubMed) and the Cochrane Database of Systematic Reviews was performed, and all publications in peer-reviewed English language journals up to June 2015 were considered. A detailed search was performed using an array of relevant terms (see supplementary data section Search strategy and supplementary Table S1, available at *Rheumatology* Online), and papers were screened for eligibility based on their title, abstract and/or full content. Studies were eligible if they had studied at least 50 patients for prevalence and prognosis of manifestations, 10 patients for diagnosis and monitoring, or 5 patients for therapy.

Studies on animals, children, review articles, commentaries, conference abstracts or statements, and expert opinion statements were excluded. Narrative review articles and existing guidelines were checked for references, but only meta-analyses and systematic reviews were included, together with original research articles, in the analysis. Over 8000 articles were identified during the literature search, and over 600 were deemed eligible for

Table 3 Strength of agreement of authors with the main EULAR/ERA-EDTA recommendations for the management of LN

Management of SLE patients with renal involvement	SOA[a]
Assessment of renal involvement	
1. Indications for first renal biopsy in SLE	97
Any sign of renal involvement—in particular, urinary findings such as reproducible proteinuria $\geqslant$0.5 g/24 h, especially with glomerular haematuria and/or cellular casts—should be an indication for renal biopsy. Renal biopsy is indispensable since, in most cases, clinical, serologic and laboratory tests cannot accurately predict renal biopsy findings.	
2. Pathological assessment of kidney biopsy	98
The use of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system is recommended, with assessment not only of active and chronic glomerular and tubulointerstitial changes, but also of vascular lesions associated with aPLs/APS.	
Treatment of renal involvement	
3. Indications and goals of immunosuppressive treatment in LN	98
3.1 Initiation of immunosuppressive treatment should be guided by a diagnostic renal biopsy. Immunosuppressive agents are recommended in class III_A or $III_{A/C}$ (±V) and IV_A or $IV_{A/C}$ (±V) nephritis, and also in pure class V nephritis if proteinuria exceeds 1 g/24 h despite the optimal use of renin–angiotensin–aldosterone system blockers.	
3.2 The ultimate goals of treatment in LN are long-term preservation of renal function, prevention of disease flares, avoidance of treatment-related harms and improved quality of life and survival. Treatment should aim for complete renal response with UPCR <50 mg/mol and normal or near-normal (within 10% of normal GFR if previously abnormal) renal function. Partial renal response, defined as $\geqslant$ 50% reduction in proteinuria to subnephrotic levels and normal or near-normal renal function, should be achieved preferably by 6 months but no later than 12 months following initiation of treatment.	98
4. **Treatment of adult LN—initial treatment**	
4.1 For patients with class III_A or $III_{A/C}$ (±V) and class IV_A or $IV_{A/C}$ (±V) LN, mycophenolic acid (MPA) (MMF target dose: 3 g/day for 6 months, or MPA sodium at equivalent dose) or low-dose i.v. CYC (total dose 3 g over 3 months), in combination with glucocorticoids, are recommended as initial treatment as they have the best efficacy/toxicity ratio.	93
4.2 In patients with adverse prognostic factors (acute deterioration in renal function, substantial cellular crescents and/or fibrinoid necrosis), similar regimens may be used, but CYC can also be prescribed monthly at higher doses (0.75–1 g/m^2) for 6 months or orally (2–2.5 mg/kg/day) for 3 months.	92
4.3 To increase efficacy and reduce cumulative glucocorticoid doses, treatment regimens should be combined initially with three consecutive pulses of i.v. methylprednisolone 500–750 mg, followed by oral prednisone 0.5 mg/kg/day for 4 weeks, reducing to $\leqslant$ 10 mg/day by 4–6 months	98
4.4 In pure class V nephritis with nephrotic-range proteinuria, MPA (MMF target dose 3 g/day for 6 months) in combination with oral prednisone (0.5 mg/kg/day) may be used as initial treatment based on better efficacy/toxicity ratio. CYC or calcineurin inhibitors (ciclosporin, tacrolimus) or rituximab are recommended as alternative options or for non-responders.	95
4.5 AZA (2 mg/kg/day) may be considered as an alternative to MPA or CYC in selected patients without adverse prognostic factors (as defined 4.2), or when these drugs are contraindicated, not tolerated or unavailable. AZA use is associated with a higher flare risk.	96
Subsequent treatment	
4.6 In patients improving after initial treatment, subsequent immunosuppression is recommended with either MPA at lower doses (initial target MMF dose 2 g/day) or AZA (2 mg/kg/day) for at least 3 years, in combination with low-dose prednisone (5–7.5 mg/day). Gradual drug withdrawal, glucocorticoids first, can then be attempted.	97
4.7 Patients who responded to initial treatment with MPA should remain on MPA unless pregnancy is contemplated, in which case they should switch to AZA at least 3 months prior to conception.	98
4.8 Calcineurin inhibitors can be considered in pure class V nephritis.	93
Refractory disease	
4.9 For patients who fail treatment with MPA or CYC, either because of lack of effect (as defined above) or due to adverse events, we recommend that the treatment is switched from MPA to CYC, or CYC to MPA, or that rituximab be given.	95
5. **Adjunct treatment in patients with LN**	
5.1 Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are indicated for patients with proteinuria (UPCR >50 mg/mmol) or hypertension.	98
6. **Management of end-stage renal disease in LN**	
6.1 All methods of renal replacement treatment can be used in lupus patients, but there may be increased risk of infections in peritoneal dialysis patients still on immunosuppressive agents, and vascular access thrombosis in patients with aPLs.	98
6.2 Transplantation should be performed when lupus activity has been absent, or at a low level, for at least 3–6 months, with superior results obtained with living donor and pre-emptive transplantation. aPLs should be sought during transplant preparation because they are associated with an increased risk of vascular events in the transplanted kidney.	96
7. **APS-associated nephropathy in SLE**	
7.1 In patients with lupus and APS-associated nephropathy (APSN), HCQ and/or antiplatelet/anticoagulant treatment should be considered.	91

[a]Reproduced from Bertsias *et al.* Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 71: 771–82. Copyright 2012, with permission from BMJ Publishing Group Ltd [24]. Numbers are mean (S.D.) and median (IQR) agreement level among authors. A score of 10 represents the highest SOA. GFR: glomerular filtration rate; SOA: strength of agreement; UPCR: urine protein:creatinine ratio.

detailed review by at least two members of the group. There was considerable overlap in the topics covered by the papers, which were reviewed by various members of the group.

Development of the guideline: levels of evidence and consensus agreement

The recommendations were developed in line with the BSR's Guidelines Protocol, using RCP, SIGN and AGREE II methodology to assess the level of evidence (LOE) and grade of recommendation (GOR). Papers selected for review and the evidence obtained from them were categorized by at least two members of the group, according to the study design, using the SIGN methodology (supplementary Table S2, available at *Rheumatology* Online), and the level of the evidence was graded by combining information on the design and validity of the available research studies to provide the GOR for each component of each statement. The results of the literature search were summarized, aggregated and distributed to the expert committee by three of us (C.G., M.G., M.A.), and the GOR for each item was ratified by the expert committee. Draft recommendations were discussed and rephrased at a face-to-face meeting and subsequently by email, following an updated literature review. The LOEs and the GORs for the data supporting the guideline recommendations are shown in Tables 1 and 2. Finally, the six recommendations for the management of SLE and the main items in the EULAR/ERA-EDTA recommendations for LN [24] (Table 3) were voted on by clinical members of the guideline development group. For each recommendation, the SOA of all clinical members of the group was sought on a scale of 1 (no agreement) to 10 (complete agreement); the mean percentage agreement was calculated and is shown after each recommendation (all >90% and supported by other members of the group). The guideline will be reviewed in 5 years' time.

The guideline

Eligibility criteria

This guideline is designed to cover the management of adult patients with SLE by healthcare professionals. These recommendations are based on the literature review covering the diagnosis, assessment, monitoring and treatment of mild, moderate and severe lupus, including neuropsychiatric (NP) disease. The focus of the literature review was on non-renal disease, as the EULAR/ERA-EDTA recommendations for LN (see below) were published [24] close to the time that we started work on this guideline.

Exclusion criteria

Management of paediatric lupus, renal lupus, topical treatment for cutaneous lupus, and drug treatment in pregnancy have been excluded from our literature search and guideline development. BSR guidelines on the use of drugs in pregnant patients with rheumatic diseases (including lupus) have been developed in parallel with this guideline.

Introduction to the recommendations and supporting evidence

For each question addressed by the literature review (supplementary data section Search strategy, available at *Rheumatology* Online), we provide first the recommendations and the overall LOE, GOR and SOA for each, followed by the rationale. The rationale consists of a summary of the evidence supporting the statements (including cautions in the case of drug therapy). It is organized by topic and includes some key points about the studies leading to the recommendations and a conclusion for each topic discussed. The number of studies and types of studies (with references) leading to the LOE and GOR are summarized in Table 1 for the items contributing to the recommendations on diagnosis, assessment and monitoring of lupus, and in Table 2 for those relating to the treatment and prevention of mild, moderate and severe non-renal lupus. In Table 3 we provide our SOA with key points of the EULAR/ERA-EDTA recommendations for the management of LN [24], so that the management of the most important aspects of lupus are covered by this guideline in a single document.

Recommendations for clinical and serological features prompting consideration of a diagnosis of SLE

(i) SLE is a multisystem autoimmune disorder. The diagnosis requires a combination of clinical features and the presence of at least one relevant immunological abnormality. If there is a clinical suspicion of lupus, blood tests (including serological marker tests) should be checked (LOE 2++, GOR B, SOA 98%).

(ii) ANAs are present in ~95% of SLE patients. If the test is negative, there is a low clinical probability of the patient having SLE. A positive ANA test occurs in ~5% of the adult population, and alone it has poor diagnostic value in the absence of clinical features of autoimmune rheumatic disease (2++/B, SOA 96%).

(iii) The presence of anti-dsDNA antibodies (2++/B), low complement levels (2+/C) or anti-Smith (Sm) antibodies (2+/C) are highly predictive of a diagnosis of SLE in patients with relevant clinical features. Anti-Ro/La and anti-RNP antibodies are less-specific markers of SLE (2+/C) as they are found in other autoimmune rheumatic disorders as well as SLE (2+/C) (SOA 95%).

(iv) aPLs should be tested in all lupus patients at baseline, especially in those with an adverse pregnancy history or arterial/venous thrombotic events (2++/B). Confirmatory tests for APS are positive LA, aCL (IgG, IgM) and/or anti-beta-2 glycoprotein-1

(IgG, IgM) on two occasions at least 12 weeks apart (2 ++/B) (SOA 97%).

Rationale

Clinical manifestations

SLE is a multisystem autoimmune disease [1, 8] with considerable heterogeneity. This makes the diagnosis, assessment and monitoring a challenging process [10, 26–28, 41]. Delays in diagnosis are well recognized and remain a concern [242]. Some of the most typical features and their cumulative incidence are shown in supplementary Table S3, available at *Rheumatology* Online [7, 10, 26–29]. It is important to ensure that the diagnosis of lupus is appropriate before considering treatment [41, 243]. Given the variety of clinical manifestations that can occur, lupus should be considered in the differential diagnosis of many acute and sub-acute presentations, particularly, but not exclusively, in individuals at increased risk of the disease, such as women from African, South Asian or Chinese backgrounds [2, 244]. Lupus can also affect men, resulting in severe disease, including renal involvement and greater risk of damage compared with women in some but not all reports [15, 16, 30, 31].

Renal and neurological involvement are major causes for morbidity and mortality in SLE [2, 7, 15, 16, 32, 33]. Renal disease is clinically silent and must be actively sought to prevent renal damage as discussed below. A working party of the ACR distinguished 19 NP manifestations that may occur in SLE patients [245]. Not all are directly attributable to the SLE disease process, and the true incidence of these manifestations is hard to ascertain as most of them are uncommon [23, 246]. Gastrointestinal and hepatic features occur in 39–67% of patients [42, 247] and are often not recognized as being due to lupus. As with cardiorespiratory features, they must be distinguished carefully from infection, adverse events from drugs and co-morbid conditions. Ophthalmic manifestations of lupus are rare, but potentially sight-threatening, and need careful evaluation by an experienced ophthalmologist [248–250].

Serological (immunological) manifestations

The clinical features of acute lupus are mostly due to inflammatory processes triggered by the formation of immune complexes involving autoantibodies and complement consumption, although thrombosis associated with aPLs may contribute to the pathogenesis in some patients [1, 8, 10]. With a clinical suspicion of SLE, an initial autoantibody screen should be performed. Approximately 95% of lupus patients are ANA positive, and 98% of patients will have positive ANA and/or anti-dsDNA antibodies [26, 36, 37]. ANA tests, although sensitive, are not specific for the diagnosis of lupus, and ANAs can occur in a variety of other conditions, including SS, SSc, DM, viral infections (e.g. infectious mononucleosis) and malignancy [36, 41]. The ANA test can increase in titre over time or can become negative in treated patients, and the results can vary with different assays [34, 37].

If patients have a strong clinical likelihood of having lupus, anti-dsDNA antibody testing should be done [38]. Anti-dsDNA and anti-Sm antibodies are much more specific for lupus, being very rare in other conditions [36] but they are less sensitive than ANA (supplementary Table S3, available at *Rheumatology* Online) [10, 26–29, 251]. Both the Farr and the ELISA methods are acceptable for measuring anti-dsDNA antibodies, with the former yielding higher sensitivity and specificity rates [24, 39, 40]. The *Crithidia luciliae* immunofluorescence test also has a high specificity for SLE. Additional routine serological tests are the complement C3 and C4 levels [43]. C3 generally has a higher sensitivity than serum C4 for active LN, but both tests have modest specificity and their clinical utility lies in their high negative predictive value (>90%) to exclude active disease, especially renal disease [24, 44–46].

Anti-Ro (SSA), anti-La (SSB) and anti-RNP antibodies are less specific markers for the presence of SLE, as they are found in other autoimmune rheumatic disorders [41]. Anti-Ro and anti-La are most strongly associated with primary SS but do occur in lupus patients, especially those with photosensitivity and subacute cutaneous lupus. Anti-Ro and anti-La antibodies can cause neonatal lupus syndrome including congenital heart block (CHB) in children born to mothers with these antibodies (see Recommendations for monitoring of SLE section) [64, 65]. Anti-RNP antibodies are found in overlap conditions such as MCTD [41].

All lupus patients should be tested for aPLs because their presence indicates a group at increased risk of arterial/venous thrombotic events and adverse pregnancy outcomes [241, 252, 253]. As APS and SLE often overlap, and APS sometimes evolves in to SLE, the presence of APS should also prompt assessment for lupus. Confirmatory tests for APS are positive LA, aCL (IgG, IgM), and/or anti-beta-2 glycoprotein-1(IgG, IgM) antibodies on two occasions at least 12 weeks apart [241, 252]. The LA test is the most specific of the three tests and is associated with a higher positive predictive value. The most high-risk aPL profile (triple positivity including positive LA, aCL and anti-β2-glycoprotein-I antibody) is associated with a cumulative incidence of thrombosis after 10 years of 37.1% [254].

Classification criteria for lupus

Based on the ACR (previously the American Rheumatism Association) revised criteria for SLE published in 1982 [255] and the 1997 modification [256], a patient may be classified as having SLE if they have 4 or more of 11 criteria present (Table 4). However, not all patients who meet these criteria have lupus, and not all patients diagnosed clinically with lupus have four or more of these criteria, which may appear or disappear over time [7, 33, 35, 257]. There has been a tendency to consider patients who meet the ACR classification criteria for lupus to have the disease, even if they only have certain clinical features without evidence of one or more of the immunological abnormalities that are the hallmark of this autoimmune

Table 4 The ACR criteria for classification of SLE[a]

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
Serositis	Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >0.5 g/day or $>3+$ if quantitation not performed OR Cellular casts: may be red cell, haemoglobin, granular, tubular or mixed
Neurologic disorder	Seizures: in the absence of offending drugs or known metabolic derangements; e.g. uremia, ketoacidosis or electrolyte imbalance OR Psychosis: in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance
Haematologic disorder	Haemolytic anaemia with reticulocytosis OR Leukopenia $<4000/mm^3$ total on two or more occasions OR Lymphopenia $<1500/mm^3$ on two or more occasions OR Thrombocytopenia $<100\,000/mm^3$ in the absence of offending drugs
Immunologic disorder	Anti-DNA: antibody to native DNA in abnormal titre OR Anti-Sm: presence of antibody to Sm nuclear antigen OR Positive finding of aPLs on: an abnormal serum level of IgG or IgM aCL; a positive test result for LA using a standard method, or; a false positive test result for at least 6 months confirmed by *Treponema pallidum* immobilization or the fluorescent treponemal antibody absorption test
ANA	An abnormal titre of ANA by immunofluorescence, or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

[a]The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation. Adapted from Tan EM *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–7, copyright 1982 [255]; and Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725, copyright 1997 [256], with permission from John Wiley & Sons. Anti-Sm: anti-Smith antibody.

disease. Conversely, sometimes the disease has been diagnosed on the basis of auto-antibodies and haematological features, without consideration of whether the whole clinical and serological picture is consistent with lupus being the most likely diagnosis.

To address these and some other issues, the SLICC group devised alternative classification criteria for lupus [258]. These criteria introduced a requirement for at least one clinical and one immunological criterion and two others from an expanded list of items (Table 5) compared with the ACR criteria (Table 4) [256]. They also allowed biopsy-proven LN in the presence of ANA or anti-dsDNA antibodies to be classified as lupus, without the need for other criteria [258]. The serological criteria include low complement (C3 and/or C4), as this item reflects complement consumption due to the formation of immune complexes in active lupus disease.

These revised SLICC lupus criteria have been accepted by the European Medicines Agency, the US Food and Drug Administration and NHS England as being suitable for the inclusion of patients in clinical trials and in the commissioning policy for rituximab. They are more intuitive than the previous ACR classification criteria when considering a diagnosis of lupus, and allow a larger number of patients to meet criteria; however, diagnosis should not be restricted to patients who meet the classification criteria, as they can encompass other manifestations in the appropriate serological context [259]. The SLICC criteria have been tested in a number of cohorts and in most studies have shown an increase in sensitivity and reduced specificity, so care is needed if features are better explained by an alternative diagnosis [260–263].

Conclusions

When considering a patient with a possible diagnosis of lupus, a detailed clinical history and examination is required in order to identify relevant clinical features, including assessment of haematological and renal parameters. The diagnosis should not be made without evidence of at least one autoantibody or low complement levels to support the diagnosis of this autoimmune disease, consistent with the SLICC classification criteria. The ACR (Table 4) and SLICC (Table 5) classification criteria are not diagnostic criteria but may be helpful when considering the diagnosis;

Table 5 Clinical and Immunologic Criteria Used in the SLICC Classification Criteria for SLE[a]

Clinical Criteria
Acute cutaneous lupus including:
lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, (in the absence of dermatomyositis), or subacute cutaneous lupus, nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Chronic cutaneous lupus including:
classical discoid rash, localized (above the neck), generalized (above and below the neck), hypertrophic, (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap
Oral ulcers:
Palate, buccal, tongue, or nasal ulcers (in the absence of other causes, such as vasculitis, Behcet's disease, infection (herpes viruses), inflammatory bowel disease, reactive arthritis, acidic foods)
Nonscarring alopecia:
diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia)
Synovitis involving two or more joints:
characterized by swelling or effusion or tenderness in 2 or more joints and thirty minutes or more of morning stiffness.
Serositis:
typical pleurisy for $>$ 1 day or pleural effusions or pleural rub or typical pericardial pain (pain with recumbency improved by sitting forward) for $>$ 1 day or pericardial effusion or pericardial rub or pericarditis by EKG (in the absence of other causes, such as infection, uremia, and Dressler's pericarditis)
Renal:
Urine protein:creatinine ratio (or 24 hr urine protein) representing 500 mg of protein/24 hr or red blood cell casts
Neurologic:
seizures, psychosis, mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic-metabolic, uremia, drugs)
Hemolytic anemia
Leukopenia: $<$ 4000/mm^3 at least once (in the absence of other known causes such as Felty's, drugs, portal hypertension) OR
Lymphopenia: $<$ 1000/mm^3 at least once (in the absence of other known causes such as corticosteroids, drugs and infection)
Thrombocytopenia: $<$100,000/mm^3 at least once (in the absence of other known causes such as drugs, portal hypertension, TTP)
Immunologic Criteria
ANA level above laboratory reference range
Anti-dsDNA antibody level above laboratory reference range (or $>$ 2 fold the laboratory reference range if tested by ELISA)
Anti-Sm
Antiphospholipid antibody:
any of the following: lupus anticoagulant, false-positive rapid plasma regain (RPR), medium or high titer, nticardiolipin antibody level (IgG, IgM or IgA), anti-β_2 glycoprotein I (IgG, IgM or IgA)
Low complement:
low C3, low C4, low CH50
Direct Coombs' test (in the absence of hemolytic anemia)

[a]Patients can be classified as having SLE if they satisfy four of the clinical and immunological criteria, including at least one clinical criterion and one immunologic criterion, OR if they have biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies. Reproduced from Petri M *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 64:2677–86. Copyright 2012. With permission from John Wiley & Sons [258]. TTP: thrombocytopaenic purpura; anti-Sm: anti-Smith antibodies.

however, they do not cover all the clinical manifestations of lupus. The LOEs and GORs for parameters supporting the diagnosis of lupus are shown in Table 1.

Recommendations for the assessment of SLE patients

(i) Clinical manifestations in SLE patients may be due to disease activity, damage, drug toxicity or the presence of co-morbidity. In the case of disease activity, it is important to ascertain whether this is due to active inflammation or thrombosis, as this will define treatment strategies (LOE 2++, GOR B, SOA 97%).

(ii) Clinical assessment of a lupus patient should include a thorough history and review of systems, full clinical examination and monitoring of vital signs, urinalysis, laboratory tests, assessment of

health status and quality of life, and measurement of disease activity and damage using standardized SLE assessment tools (2++/B). Imaging (4/D), renal (2++/B) and other biopsies (4/D) should be performed where indicated (SOA 100%).

(iii) Disease activity is categorized into mild, moderate and severe, with the occurrence of flares (2+/C). Mild disease activity is clinically stable lupus with no life-threatening organ involvement, mainly manifesting as arthritis, mucocutaneous lesions and mild pleuritis. Patients with moderate disease activity have more serious manifestations, and severe disease is defined as organ- or life-threatening (4/D) (SOA 93%).

Rationale

Assessment of lupus

A systematic approach should be taken because of the diversity and complexity of clinical and laboratory manifestations (supplementary Table S3, available at *Rheumatology* Online) [264–266]. Clinical manifestations may be due to one or any combination of the following: disease activity from active inflammation or thrombosis, acute drug toxicity, chronic damage due to the effects of the disease or its treatment (such as lung fibrosis or atherosclerosis), or co-morbidity (e.g. infection). It is important to take a detailed history and to perform a clinical examination, including vital signs and urinalysis, to establish the likely differential diagnoses and then to organize the relevant investigations as suggested in Table 6, depending on the circumstances. In addition, when assessing disease activity with a view to planning treatment, it is necessary to determine the circumstances that may have led to a lupus flare (such as exposure to sunlight, concurrent or recent infection, hormonal changes, or timing of previous disease-related therapeutic change) as this will guide further investigation, treatment change (including non-drug measures) and disease monitoring required thereafter.

Validated instruments for the assessment of lupus

The most reliable way of assessing disease activity is to use a defined instrument for this purpose that has been validated and is available with an appropriate glossary and scoring instructions [265, 266]. For example, the NHS England Interim Clinical Commissioning Policy Statement for rituximab in lupus published in 2013 [267] recommended the use of two lupus-specific disease activity indices: the BILAG index and the SLEDAI. For such purposes, the currently recommended revised versions are the BILAG-2004 index [268, 269] (for BILAG-2004 index data collection form, glossary and scoring see supplementary data, available at *Rheumatology* Online) and SLEDAI-2K [270] or the SELENA-SLEDAI [271, 272] (see supplementary data, available at *Rheumatology* Online, for SLEDAI-2K and SELENA-SLEDAI index data collection forms). Modifications have been made for use in pregnancy [273, 274]. For optimal performance, training in the use of these instruments is advised. It is essential that only manifestations/items due to SLE disease activity are recorded and that the data collection forms are used in conjunction with the appropriate glossary and scoring rules. There is one validated instrument for assessing damage, the SLICC/ACR Damage Index (SDI) [275]. It is recommended that patients' assessment of their disease be captured using health status or quality of life questionnaires such as the generic Short-form36 (SF-36), which has been validated for use in lupus patients [276], or a lupus-specific questionnaire such as the Lupus Quality of Life (LupusQoL) [277]. There is agreement that for best practice these instruments should be used [74, 278], although there are no data confirming that their use improves the outcomes for patients. Better outcomes are achieved if lupus in-patients are managed in centres with experience in managing lupus [279–282].

Definitions of mild, moderate and severe lupus

For the purpose of planning appropriate treatment, disease activity has been broadly categorized as mild, moderate or severe [8], and worsening disease activity is termed flare, which can be similarly categorized as mild, moderate or severe [283, 284]. Examples are shown in Table 7. The term mild disease activity reflects clinically stable disease with no life-threatening organ involvement and that is not likely to cause significant scarring or damage. Examples of scores for such patients when using formal assessment tools would include a SLEDAI-2K score of <6 [270] and/or one BILAG B score [269]. Patients with moderate disease have more serious manifestations, which if left untreated would cause significant chronic scarring. Examples of scores for such patients when using formal assessment tools would include a SLEDAI-2K score in the range of 6–12 [270] and/or two or more BILAG B scores [269]. Severe disease is defined as organ or life threatening and reflects the most serious form of systemic disease that requires potent immunosuppression. Examples of scores for such patients when using formal assessment tools would include a SLEDAI-2K score of >12 [270] and/or at least one BILAG A score [269].

Conclusions

The assessment of a patient with lupus, as with making the initial diagnosis, is dependent on a careful history and examination of the patient, with relevant haematological, biochemical and immunological testing as well as other investigations as necessary (shown in Table 6) to establish the degree of disease activity and accumulation of chronic damage, and to identify other complications or co-morbid conditions that will influence the treatment plan. The LOEs and GORs for the components of the assessment and monitoring of lupus disease are shown in Table 1.

Recommendations for monitoring of SLE

(i) Patients with lupus should be monitored on a regular basis for disease manifestations, drug toxicity and co-morbidities (LOE 2++, GOR B, SOA 99%).

Table 6 Assessment and monitoring of SLE in lupus patients

Item	Initial assessment	Assessment (active disease) Patients with active disease should be reviewed at least every 1–3 months	Monitoring (stable disease) Patients with stable/low disease activity should be reviewed every 6–12 months	Pregnancy Pregnancy counselling and follow-up
History and examination				
Detailed history	X	focused history	focused history	obstetric history
Clinical examination	X	X	X[a]	X
Vital signs (Blood pressure, heart rate, weight)	X	X	X	X
Drug review including vaccination status	X	X	X	X
Bloods				
Full blood count	X	X	X	X
Other tests for anaemia	X[a]	X[a]	X[a]	X[a]
Renal function	X	X	X	X
Bone profile	X	X[a]	X[a]	X
Liver function tests	X	X[a]	X[a]	X
Creatine kinase	X	X[a]	X[a]	X[a]
CRP	X	X[a]	X[a]	X[a]
Vitamin D3	X	X[a]	Annually	X
Thyroid function	X	X[a]	X[a]	X
Immunology				
ANA	X	–	–	X[a]
Anti-dsDNA titre, C3/C4 level	X	X	X	X
aPL (LA, aCL, anti-beta2-glycoptroteinl)	X	X[a]	X[a]	Repeat if negative in the past
Anti-Ro/La, anti-RNP and anti-Sm antibodies	X	–	–	Repeat if negative in the past
Immunoglobulins	X	X[a]	Annually[a]	X[a]
Direct Coombs' test	X	X[a]	X[a]	X[a]
Urine				
Urinalysis (screen for proteinuria, haematuria, leucocyturia and nitrites to exclude infection)	X	X	X	X
Urine random protein:creatinine ratio Or 24-h urine collection for protein	X[a]	X[a]	X[a]	X[a]
Urine microscopy (and culture)	X[a]	X[a]	X[a]	X[a]
Other investigations				
Microbiology (other)	X[a]	X[a]	X[a]	X[a]
Biopsy (e.g. skin, kidney)	X[a]	X[a]	X[a]	X[b]
Lung function tests	X[a]	X[a]	X[a]	X[a]
Neurophysiology	X[a]	X[a]	X[a]	X[a]
ECG	X	X[a]	X[a]	X[a]
Imaging				
Chest X-ray	X	X[a]	X[a]	X[b]
Other imaging (US, CT, MRI)	X[a]	X[a]	X[a]	X[b]
Modifiable cardiovascular risk factors				
Hypertension	X	X[a]	Annually	X
Dyslipidaemia	X	X[a]	Annually	X[a]
Diabetes mellitus	X	X[a]	Annually	X
High BMI	X	X[a]	Annually	X
Smoking	X	X[a]	Annually	X
Disease activity and damage scores				
BILAG (BILAG 2004 index) or	X	X[a]	Annually	BILAG2004P[c]
SLEDAI (SLEDAI-2K or SELENA SLEDAI)	X	X[a]	Annually	SLEPDAI[d]
SLICC/ACR Damage Index	X	X[a]	Annually	X
Quality of life questionnaires				
Short-form 36 or LupusQoL	X	X[a]	Annually	X[a]

[a]When indicated; [b]when indicated and benefit > risks; [c]BILAG2004 pregnancy version; [d]SLEDAI pregnancy version. Anti-Sm antibodies: anti-Smith antibodies.

Table 7 SLE treatment strategies for examples of mild, moderate and severe lupus

Item	Mild activity/flare BILAG C scores or single B score; SLEDAI <6	Moderate activity/flare BILAG 2 or more systems with B scores, SLEDAI 6–12	Severe activity/flare (non-renal) BILAG 1 or more A scores; SLEDAI >12
Typical manifestations attributed to lupus	Fatigue, malar rash, diffuse alopecia, mouth ulcers, arthralgia, myalgia, platelets 50–149 × 10^9/l	Fever, lupus-related rash up to 2/9 body surface area, cutaneous vasculitis, alopecia with scalp inflammation, arthritis, pleurisy, pericarditis, hepatitis, platelets 25–49 × 10^9/l	Rash involving >2/9 body surface area, myositis, severe pleurisy and/or pericarditis with effusion, ascites, enteritis, myelopathy, psychosis, acute confusion, optic neuritis, platelets <25 × 10^9/l
Initial typical drugs and target doses if no contraindications	CSs[a]: topical preferred or oral prednisolone ⩽20 mg daily for 1–2 weeks or I.m. or IA methyl-prednisolone 80–120 mg and HCQ ⩽6.5 mg/kg/day and/or MTX 7.5–15 mg/week and/or NSAIDs (for days to few weeks only)	Prednisolone[a] ⩽0.5 mg/day or i.v. methyl- prednisolone ⩽250 mg × 1–3 or i.m. methyl-prednisolone 80–120 mg and AZA 1.5–2.0 mg/kg/day or MTX 10–25 mg/week or MMF 2–3 g/day or ciclosporin ⩽2.0 mg/kg/day and HCQ ⩽6.5 mg/kg/day	Prednisolone[a] ⩽0.5 mg/day and/or i.v. methyl-prednisolone 500 mg × 1–3 or prednisolone ⩽0.75–1 mg/kg/day and AZA 2–3 mg/kg/day or MMF 2–3 g/day or CYC i.v. or ciclosporin ⩽2.5 mg/kg/day and HCQ ⩽6.5mg/kg/day
Aiming for typical maintenance drugs/doses providing no contraindications	Prednisolone[a] ⩽ 7.5 mg/day and HCQ 200 mg/day and/or MTX 10 mg/week	Prednisolone[a] ⩽7.5 mg/day and AZA 50–100 mg/day or MTX 10 mg/week or MMF 1 g/day or ciclosporin 50–100 mg/day and HCQ 200 mg/day;	Prednisolone[a] ⩽7.5 mg/day and MMF 1.0–1.5 g/day or AZA 50–100 mg/day or ciclosporin 50–100 mg/day and HCQ 200 mg/day;
	Aim to reduce and stop drugs except HCQ eventually when in stable remission	Aim to reduce and stop drugs except HCQ eventually when in stable remission	Aim to reduce and stop drugs except HCQ eventually when in stable remission

[a]The lowest effective dose of prednisolone or other CSs should be used at all times.

(ii) Those with active disease should be reviewed at least every 1–3 months (2+, C/D), with blood pressure (1+/A), urinalysis (1+/A), renal function (1+/A), anti-dsDNA antibodies (2++/B), complement levels (2+/C), CRP (2+/C), full blood count (3/C), and liver function tests (4/D) forming part of the assessment, and further tests as necessary (4/D). Patients with stable low disease activity or in remission can be reviewed less frequently, for example, 6–12 monthly (4/D) (SOA 99%).

(iii) The presence of aPLs is associated with thrombotic events, damage, and adverse outcomes in pregnancy (2++/B). If previously negative, they should be re-evaluated prior to pregnancy or surgery, or in the presence of a new severe manifestation or vascular event (4/D) (SOA 96%).

(iv) Anti-Ro and anti-La antibodies are associated with neonatal lupus (including CHB) and should be checked prior to pregnancy (1+/A) (SOA 100%).

(v) Patients with lupus are at increased risk of comorbidities, such as atherosclerotic disease, osteoporosis, avascular necrosis, malignancy and infection (2+/C). Management of modifiable risk factors, including hypertension, dyslipidaemia, diabetes, high BMI and smoking, should be reviewed at baseline and at least annually (4/D) (SOA 98%).

(vi) Immunosuppressive therapy may lead to toxicities. Close monitoring of drugs by regular laboratory tests and clinical assessment should be performed in accordance with drug monitoring guidelines (4/D) (SOA 98%).

Rationale

Frequency of monitoring lupus/follow-up visits

There are no randomized controlled trials (RCTs) comparing different monitoring strategies in terms of frequency and details of assessments performed; however, data from various cohort studies have informed our expert opinion and previous guidelines in this respect [22, 71, 74, 278]. Patients should be told to report to clinicians if they develop any new or significant worsening of clinical manifestations. In most patients with active clinical disease, clinic visits should be approximately every 4 weeks initially, reducing gradually down to about 3-monthly reviews as the disease comes under control. There remains a significant risk of flare and the development of damage, even for patients who achieve early remission [72]. For most patients with mild features, including those who are clinically quiet but serologically active, 3-monthly visits are adequate [77]. Review should become more frequent if the disease becomes more active, especially if there is renal involvement,

as the patients will require clinical, renal and serological evaluation (see below) [285]. For patients with inactive disease, without previous renal involvement or organ damage (that can predict increased risk of further active disease and damage), review may be less frequent, for example every 6 months providing treatment is stable and suitable drug monitoring is in place [74]. Patients should be seen more regularly, however, if treatment is being withdrawn or has been stopped, due to the risk of disease flare, even if they appear to be in remission [72].

Reasons for clinical monitoring in lupus patients

Regular monitoring of clinical and laboratory features of active disease should take place, with additional investigations as necessary (Table 6), to assess and monitor changes in disease activity, the development of chronic damage, and to detect the presence of (and changes in) co-morbid conditions that may be confused with lupus (such as FM, hypothyroidism, iron deficiency anaemia, infection), and drug-induced conditions [22, 74, 265]. LOEs for the laboratory parameters are shown in Table 1. Proteinuria (and renal function in particular [24]), high DAS [16, 48, 73, 286], new and different types of cutaneous lesions [50], arthritis [72], NP disease [16, 51] and cytopenias [52, 53] have been shown to correlate with disease severity and can predict future flares and the development of damage [11, 32, 49, 54, 55]. Only measurement of proteinuria and renal function have been shown to have strong predictive value for outcome [22, 24, 56]. Chest X-ray, ECG and other specific tests such as lung function, echocardiography and neurophysiology should be repeated during the course of the disease as necessary. When major organs are involved, additional imaging (such as brain MRI) and pathology (renal/skin biopsy) can add significant prognostic information, particularly renal biopsy, and may need to be repeated to assess response to treatment [22–24, 287, 288].

Interpretation of haematological, renal and other biochemical parameters

Lymphopenia is a common manifestation of lupus (supplementary Table S3, available at *Rheumatology* Online), and some patients will have leucopenia and neutropenia regularly with active disease [53]. This needs to be remembered when monitoring patients on cytotoxic therapy, as a fall in cell counts may signify the need to increase therapy for lupus rather than reduce or discontinue therapy if drug toxicity is suspected. It also means that the usual drug-monitoring limits of tolerance may need to be reviewed and personalized in the context of an individual with SLE. Thrombocytopenia may be acute and indicative of a disease flare, or low grade and chronic as part of of lupus and/or associated with APS [57].

ESR is often raised in active SLE [70], but can also reflect persistent polyclonal hypergammaglobulinaemia, and is not a reliable marker of disease activity. CRP is usually normal [66–68] or slightly elevated in the presence of serositis or arthritis [69]. A significantly raised CRP is more likely to indicate infection, and patients with raised CRP will need therefore to be thoroughly screened for infection, given that infection is the commonest cause of death in lupus patients. In contrast, a raised ESR does not discriminate between active lupus and infection [69]. Immune complexes of CRP and anti-CRP antibodies may form in lupus patients, possibly explaining the low levels of CRP observed with active disease [67].

Proteinuria should be quantified using the urine protein:creatinine ratio or 24-h urine collection. Microscopic examination of the urine to look for red cells and red cell casts is useful for identifying active renal disease and renal flares, but the assessment of casts is now rarely done [24, 289, 290]. When assessing haematuria, it is important to exclude infection, menstrual blood loss and calculi. White cells in the urine are most often due to urine or vaginal infection and can be hard to interpret, but as an otherwise unexplained finding, are associated with active tubulointerstitial inflammation.

Serum immunoglobulins should be measured prior to starting drugs such as MMF, CYC and rituximab which have the most risk of inducing immunoglobulin deficiency that might increase the risk of infection. The initial repeat measurement of the serum immunoglobulins should take place about 3–6 months later and can then be spaced out to annual checks [74, 199, 291, 292, 293]. Specific antibodies, for example, pneumococcal antibodies, may be assessed (if tests are available) to assess the need for and response to immunization. Screening for chronic infections (such as TB, hepatitis B and C, HIV, HPV) is recommended before starting immunosuppressants and repeated if reactivation of infection is suspected.

It is important to measure creatinine kinase at baseline and to continue to follow it in patients with myositis or myalgias that might be due to lupus or statins used to prevent atherosclerosis [75]. Monitoring of cholesterol and of other lipids, and remaining vigilant for and treating the development of diabetes mellitus and features of the metabolic syndrome (which may increase cardiovascular risk, particularly in patients on glucocorticoids), are important and should be as successful as in the general population [71, 74, 76]. Additional monitoring investigations should include Vitamin D3, which is often low as a consequence of sun avoidance and/or chronic kidney disease [294]. Vitamin D is required for optimal bone health, especially in patients on chronic glucocorticoid therapy and/or following the menopause [295]. Clinicians should have a low threshold for assessing thyroid function, as hypothyroidism can present with similar features to lupus; it co-exists with lupus in ~7% of patients, and thyroid antibodies are found in 14% [296–298].

Monitoring of lupus autoantibodies and complement

Serial anti-dsDNA antibodies and C3 and C4 levels are useful because rising, high anti-dsDNA antibodies and falling, low complement levels are associated with flare [49, 58], particularly in patients with LN [24]. In general, concomitantly rising anti-dsDNA titres [39, 43, 46, 49, 59, 60] and decreasing C3 and/or C4 levels [43–46] are more important predictors of current or impending flares than the absolute levels, and levels of anti-dsDNA antibodies may actually fall at the time of flare [299].

It can be helpful to combine a sensitive but less specific anti-dsDNA antibody assay (e.g. ELISA) with one that only measures more specific, high affinity or high avidity antibodies (such as Farr radioimmunoassay or the *Crithidia* test), because only tests measuring high affinity and high avidity antibodies are strongly associated with renal disease; however, other ELISAs can be used to monitor disease activity [40]. Stable active serology without clinical features does not necessarily warrant therapy [71], but patients need to be followed closely, with individual care decisions made to prevent over- or undertreatment. Many physicians would avoid reducing therapy in this situation as patients may develop renal disease [300], but the serological tests do not always predict flare [61, 62, 71]. About 40% of lupus patients do not have anti-dsDNA antibodies, so for this group of patients, they are not useful for monitoring disease activity [63]. Some patients are heterozygous for the C4 allele and due to a null allele have a persistently low C4 level (at about 50% of normal), without having active disease, but C4 levels can still fluctuate with disease activity.

ANA, anti-Sm and anti-RNP antibodies tests should be carried out at baseline and do not need to be repeated at each visit, as levels do not fluctuate with disease activity. Anti-Ro and anti-La antibodies should be measured in women planning pregnancy or in early pregnancy, as they may be transferred across the placenta and are associated with CHB in ~1–2% of babies [64, 65]. Fetal heart-rate monitoring should be instituted from week 16 of pregnancy and continued throughout pregnancy in women with either of these antibodies. Neonatal lupus rash develops in ~10% of babies born to mothers with these antibodies (especially if exposed to UV light), and laboratory abnormalities (cytopenias and abnormal liver function tests) have also been observed in babies exposed to these antibodies [64].

aPLs should be assessed at baseline and, if previously negative, they should be re-evaluated in the presence of a new vascular event, adverse pregnancy outcome or other new manifestation that might have a thrombotic component, as well as prior to a planned pregnancy [47, 241, 252, 253]. Positive tests for APS include LA, aCL (IgG, IgM) and/or anti-beta-2 glycoprotein 1(IgG, IgM), and these tests should be repeated after 12 weeks to confirm positivity [241, 252], although LA cannot be evaluated if anticoagulation has been started, as this would interfere with the assay.

Monitoring for the development of co-morbidities

Patients with lupus are at increased risk of co-morbidities [71, 74], such as infection, premature cardiovascular and peripheral vascular disease, osteoporosis, avascular necrosis and some malignancies (non-Hodgkin's lymphoma, cervical, vulval, lung and thyroid cancer [301, 302]). The management of these issues is beyond the scope of this guideline and should follow national/international guidelines for each condition and include appropriate vaccinations [22, 71, 74, 278]. Nevertheless, screening for and managing these conditions is an integral part of the assessment and regular monitoring of lupus patients, as described in the EULAR recommendations for monitoring patients with SLE in clinical practice and in observational studies [74]. A preventative approach should be adopted, since the commonest causes of death in lupus patients in the UK are infection and cardiovascular disease, followed by malignancy [15, 16, 18]. Modifiable risk factors for co-morbidities to address include vaccination status, hypertension, dyslipidaemia, diabetes, high BMI and smoking. These should be reviewed at baseline and at least annually thereafter [22, 24, 71, 74]. These co-morbidities may occur at a younger age than in the normal population, and clinicians should screen regularly for them, even though there are no RCTs to suggest that more intense screening than that applied in the general population improves outcome in lupus patients [22, 24, 71, 74]. Routine cancer screening (particularly for cervical cancer, given the increased risk of HPV infection in lupus patients [303]) should not be forgotten due to emphasis on lupus disease management [304].

Monitoring of drugs

This should be similar to that for drugs used in other rheumatic diseases, but due to the occurrence of cytopenias and abnormal renal and liver function possibly caused by lupus disease itself, monitoring tests may need to be undertaken more frequently, and the interpretation of laboratory results is more difficult. Adherence to drugs may be confirmed by measuring drug levels (e.g. of ciclosporin, tacrolimus, mycophenolate [171] and HCQ [80]), but these tests are not widely available (except that for tacrolimus, which is tested in order to guide optimal dosing and to prevent renal toxicity). There is little lupus-specific data about target drug levels, and detailed discussion is beyond the scope of these recommendations, but this topic has been reviewed for rheumatic diseases in general [78] as well as for lupus [305]. It should be noted that, like other chronic conditions, adherence levels are suboptimal in lupus, and therefore specific consideration of this issue is needed in patients showing poor response to therapy [79].

Conclusions

It is important to monitor lupus patients regularly to assess and monitor changes in disease activity, chronic damage, and in drug-induced and co-morbid conditions that may be confused with lupus and that are associated with an increased risk of death. The LOEs and GORs for the main components of monitoring of lupus patients are shown together in Table 1, and a suggested protocol is shown in Table 6.

Recommendations for the management of mild SLE

(i) Treatments to be considered for the management of mild non-organ-threatening disease include the disease-modifying drugs HCQ (1++/A) and MTX (1+/A), and short courses of NSAIDs (3/D) for symptomatic control. These drugs allow for the avoidance of or dose reduction of CSs (SOA 94%).

(ii) Prednisolone treatment at a low dose of $\leqslant$7.5 mg/day may be required for maintenance therapy (2+/C). Topical preparations may be used for cutaneous manifestations, and IA injections for arthritis (4/D) (SOA 93%).
(iii) High–Sun Protection Factor (SPF) UV-A and UV-B sunscreen are important in the management and prevention of UV radiation–induced skin lesions (2++/B). Patients must also be advised about sun avoidance and the use of protective clothing (4/D) (SOA 97%).

Rationale

Overview of treatment of mild lupus

Mild lupus features (Table 7) are distressing for patients and warrant treatment to relieve symptoms and signs. Such treatment may prevent progression to severe manifestations requiring more intense immunosuppression. These manifestations can be managed with CSs, HCQ and other antimalarials, MTX, NSAIDs and sunscreens. The LOEs and GORs for the drugs used to treat lupus disease are summarized in Table 2, and the SOAs with the recommendations are above. There are little data to support the use of topical therapies, dapsone, retinoids, thalidomide or danazol in the treatment of refractory cutaneous lupus rashes and vasculitis, and as these drugs are not used for other systemic features of lupus, they are not discussed here but have been reviewed [287, 288].

CSs for mild lupus

Summary

Topical preparations should be used initially for cutaneous manifestations, and intra-articular (IA) or intramuscular (i.m.) injections of CSs for arthritis. Short courses of oral prednisolone (up to 20 mg/day) are used for short periods of time (up to 14 days and reduced rapidly) to induce remission in some cases of mild lupus where local treatment is not sufficient or practical (evidence discussed below in moderate lupus). Prednisolone can be used in women who are trying to conceive, are pregnant or are breast-feeding [239].

Evidence

There are no RCTs comparing different types of CS administration, such as skin creams and ointments, intralesional, IA and i.m. injections, and oral CS drugs (usually prednisolone in the UK). CSs contribute to the development of chronic damage and co-morbidities such as cataracts, osteoporotic fractures, diabetes, atherosclerosis and infection [12, 14]. It has been shown that a 1 mg/day increase in maintenance prednisone dose is associated with a 2.8% increase in the risk of new organ damage, and that prednisolone dosing of $\leqslant$7.5 mg/day is associated with less risk of cataracts, osteoporotic fractures and cardiovascular damage than higher doses [306].

Conclusions

The lowest possible dose/amount of CSs should be used due to their side effects, including the risk of contributing to chronic damage and infection. Prednisolone treatment at a low dose of $\leqslant$7.5 mg/day may be required for maintenance therapy and has less risk of side effects than higher doses (2+/C).

HCQ and other anti-malarial agents

Summary

There is good evidence (Table 2) for the efficacy and safety of HCQ, the most commonly prescribed anti-malarial agent and one of the few licensed drugs for lupus. Providing that the patient has normal renal and liver function, HCQ can be used at doses of up to 6.5 mg/kg/day and is compatible with pregnancy and breast-feeding. It is used (Table 7) for skin and joint involvement, myalgia, fever, fatigue, pleurisy, to reduce the development of renal disease and chronic damage [14, 121] and for its steroid-sparing properties (even in patients with more severe disease) [71]. Chloroquine is used if HCQ is not available or not tolerated; however, there is less evidence for benefit and it has a greater risk of retinal toxicity than HCQ [121]. Mepacrine (quinacrine) is used predominantly for cutaneous lupus and has the least risk of ocular toxicity [287, 307–309].

Evidence

The benefits of anti-malarials on lupus activity were reported in four RCTs [81–84], five prospective cohort studies [87–91], three retrospective cohort studies [92–94] and an open-label extension of the first RCT [95]. There have been two other double-blind RCTs confirming that lupus rashes significantly improve with HCQ [85] and chloroquine [86]. The cohort studies have shown that response often takes 3–4 months [94], but at 6 months only 60% of patients with discoid rash show some response [94]. Another study showed that 20% of patients with an adequate response lose it within 2 years and need other therapies [310]. Higher drug levels were associated with increased cutaneous response in a prospective study [311]. In a double-blind RCT [80], low drug levels were associated with increased disease activity. Systemic features and smoking are also associated with an increased risk of poor response [94, 96, 122].

Many of the studies showing increased flare rates in patients who discontinued HCQ involved pregnant patients. A RCT in lupus patients [84] and two prospective [87, 90] cohort studies support the use of this drug before conception and in pregnancy to reduce flares in the mother. Although HCQ can cross the placenta, exposure is not associated with significant adverse effects on the fetus [87, 90, 97–100]. HCQ has anti-thrombotic as well as anti-inflammatory properties and by reducing disease activity in the mother may improve the outcome for the child by improving placental function [101, 102]. There is increasing evidence that HCQ reduces the risk of CHB in babies born to mothers with anti-Ro antibodies [103, 312, 313]. Further evidence supporting the use of HCQ in pregnant women as well as in those planning pregnancy and breast-feeding is reviewed in the BSR Guidelines on drugs in pregnancy in the rheumatic diseases [239].

There is further evidence from high-quality prospective and retrospective cohort studies that patients treated with anti-malarials (particularly HCQ) not only have lower levels

of overall lupus activity and reduced rates of flare [80, 81, 84, 89, 90, 95], but can be managed with lower doses of CSs [83, 84, 90, 104]. The patients are more likely to stay clinically quiescent if HCQ is continued when the disease goes in to remission [105]. Patients on MMF are more likely to achieve renal remission if treated with HCQ [93]. Patients on HCQ are less likely to develop serious renal disease and have delayed time to renal damage [104], lower frequency of seizures [106] and less NP damage [107], greater delay in integument damage [108], less overall damage [109, 110] and, most importantly, improved survival [111, 112]. Some of the benefits on survival may be mediated by the beneficial effects of anti-malarials on total cholesterol, LDL-cholesterol, triglycerides, glucose [113] and/or by the prevention of thrombosis [101, 102, 121] and atherosclerotic plaque formation [114].

Patients take HCQ on average for about 6 years [115–118]. In general HCQ is well tolerated and better tolerated than chloroquine [86, 115, 116, 121]. The commonest adverse effects of anti-malarials are gastrointestinal, but a few patients stop because of headache, dizziness, itching, rash, non-retinal eye problems, hearing loss, myopathy or other rare neuromuscular side effects [121, 287]. The most serious adverse events are cardiac (which are very rare) [119] and retinopathy (which is more common with chloroquine than HCQ) [121, 314]. Retinopathy is unpredictable but unlikely with <7 years treatment with HCQ. It is more common thereafter [120] and with doses of HCQ above 6.5 mg/kg/day, or renal or liver impairment. It requires active screening to detect it early when it is asymptomatic and is most likely to be reversible [120, 314]. Policies on screening for ocular toxicity vary between countries and local guidelines should be followed [314, 315]. In general in the UK, baseline and yearly optician eye tests are recommended initially, with more detailed ophthalmological screening after 5 years of therapy [316].

Conclusions

There are good data from two systematic reviews and a meta-analysis including 7 RCTs and 36 cohort studies supporting the use of HCQ in lupus patients to reduce disease activity and as a steroid-sparing agent: overall LOE 1++, GOR A. HCQ should be given to all patients with mild lupus to prevent flares, the development of damage and to improve survival. It is recommended that HCQ be continued or started, even in those developing disease severe enough to warrant immunosuppressive therapies, including LN [22, 24, 25]. However patients with renal or liver dysfunction should have the dose reduced [314]. It is compatible with conception, pregnancy and breast-feeding. Unfortunately, it has a long half-life and takes at least 2 months to be effective [287, 309]. Patients need to be warned about this or they may discontinue the drug prematurely.

MTX in mild SLE

Summary

Although not licensed for the treatment of lupus, low-dose weekly MTX ($\leqslant$25 mg/week) has been used to reduce mild and moderate disease activity in lupus, particularly to control inflammatory arthritis and lupus skin rashes, originally on the basis of a variety of case series and cohort studies [317, 318]. MTX was originally used in patients who had failed HCQ and low-dose CSs, but it can be used with HCQ to avoid CSs or to promote CS dose reduction. Caution has been advised on the use of MTX in patients with LN, particularly as those with renal impairment will be at increased risk of MTX toxicity [317]. It is contra-indicated in women trying to conceive or pregnant as it is teratogenic. For these patients AZA would be more suitable (see section on moderate lupus for evidence).

Evidence

A systematic review by Sakthiswary and Suresh [319] summarizes the data from three controlled trials (two double-blind, placebo-controlled trials [123, 124], and a controlled open-label trial comparing MTX and chloroquine [125]) and five observational studies (two open-label prospective studies [126, 127]; a cross-sectional study [128]; a retrospective case–control cohort study [129]; and an open-label controlled study [130]). Another systematic review [133] includes two additional case series [131, 132]. These studies support the use of MTX to reduce mild and moderate lupus disease activity, and some demonstrated steroid-sparing properties. Some of these studies showed benefit specifically in treating lupus arthritis, rashes, vasculitis, serositis, myositis and constitutional symptoms, but there was little change in ESR, anti-dsDNA antibodies, C3 or C4 levels, except in a study with longer duration than previous studies [130]. The reduction in SLEDAI in the five controlled studies reporting these data included in the systematic review [319] was calculated to have an odds ratio = 0.444 (95% CI: 0.279, 0.707; $P = 0.001$). The analysis of the four controlled studies reporting steroid-sparing properties for MTX provided an odds ratio = 0.335 (95% CI: 0.202, 0.558; $P = 0.001$). Side effects led to discontinuation in $\sim$10% of patients but were not serious. It is teratogenic and should not be used in women within 3 months of planning to conceive, or who are pregnant or breast-feeding [239], nor in patients with renal impairment, because reduced renal function increases the risk of adverse events, particularly bone marrow suppression.

Conclusions

There are good data from two systematic reviews including three RCTs and seven cohort studies supporting the use of MTX in lupus to reduce disease activity and as a steroid-sparing agent: overall LOE 1+, GOR A.

NSAIDs in mild SLE

Summary

There are no RCTs of NSAIDs in SLE. Publications support the cautious use of NSAIDs for short periods of time for symptom control in SLE (inflammatory arthralgia, myalgia, chest pain and fever) where potential benefit outweighs the known risks of NSAIDs and paracetamol has been insufficient or not tolerated. The risk of NSAID-induced acute renal failure is increased in patients with LN, so NSAIDs

should be avoided in patients with renal involvement. NSAID-induced allergic reactions, aseptic meningitis, cutaneous reactions and hepatotoxicity are increased in SLE patients. Caution is required in pregnancy [240].

Evidence

A review of the literature on non-selective Cox inhibitors and selective Cox-2 inhibitors [320] highlighted the potential increased risk of renal, hepatic and neurological toxicity in lupus patients. A retrospective case series assessing celecoxib, with a detailed literature review of NSAIDs [321] and a more comprehensive systematic review addressing the risk–benefit ratio of non-selective and selective inhibitors of cyclooxygenases in SLE patients, were published subsequently [134]. More recently it has become clear that NSAIDs (except possibly naproxen) can predispose to acute myocardial infarction in individuals with coronary heart disease [322], which is an additional reason for caution in lupus patients.

Conclusions

Based on one systematic review of the evidence from case series and case reports, the overall LOE for NSAIDs in non-renal mild lupus is three and GOR is D.

High-SPF UV-A and UV-B sunblock in SLE

Summary

There is clear evidence that ultraviolet radiation (UV-A and UV-B) can induce various forms of cutaneous lupus [287]. Patients with systemic lupus without cutaneous features have also been found to have an abnormal reaction to UV irradiation [323].

Evidence

Sunscreens were shown to prevent discoid and subacute cutaneous lupus rashes in a case series [141] and to reduce systemic features such as renal disease, thrombocytopenia and hospitalization in a cohort study [136]. Three open-label controlled trials [137–139], a retrospective case series [140] and a double-blind, controlled trial [135] have shown that sunscreens that block UV-A and UV-B can reduce UV radiation–induced lesions of cutaneous lupus.

Conclusions

Lupus patients should be advised about avoidance of sun and other sources of UV irradiation, and about the use of sunscreens (UV-A protection five stars and UV-B protection from SPF factors 30 to 50 products, which can be prescribed on the NHS) and protective clothing. Overall, the LOE is 2++ for sunscreens (one small RCT and six other studies) in lupus patients to prevent cutaneous lesions, and the GOR is B.

Recommendations for the management of moderate SLE

(i) The management of moderate SLE involves higher doses of prednisolone (up to 0.5 mg/kg/day) (2+/C), or the use of i.m. (4/D) or i.v. doses of methylprednisolone (MP) (2+/C). Immunosuppressive agents are often required to control active disease and are steroid-sparing agents (2+/C). They can also reduce the risk of long-term damage accrual (4/D) (SOA 98%).

(ii) MTX (1+/A), AZA (2+/C), MMF (2++/B), ciclosporin (2+/C) and other calcineurin inhibitors (3/D) should be considered in cases of arthritis, cutaneous disease, serositis, vasculitis or cytopaenias if HCQ is insufficient (SOA 97%).

(iii) For refractory cases, belimumab (1+/B) or rituximab (2+/C) may be considered (SOA 98%).

Rationale

Overview of the management of moderate lupus

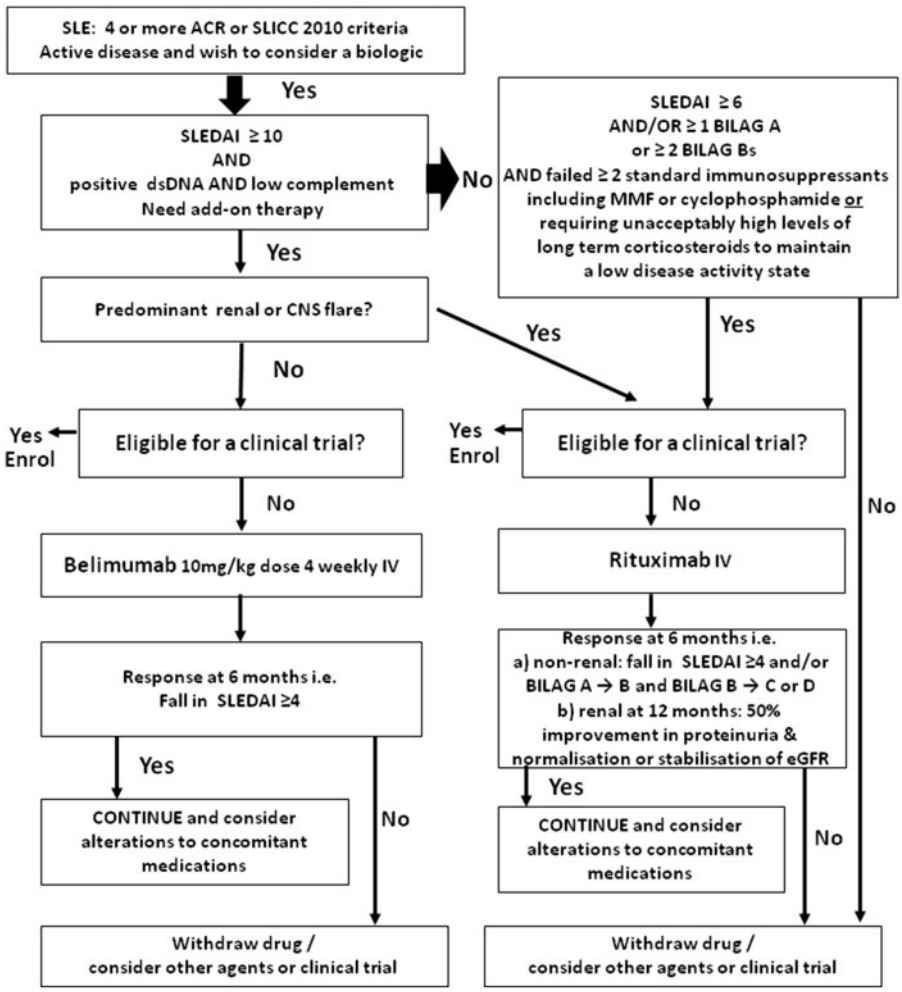
Immunosuppressive cytotoxic agents should be used with CSs, while continuing anti-malarials and avoidance of UV radiation, to reduce disease activity in moderate lupus (Table 7), prevent the risk of further flares and lower the risk of damage accrual due to disease and CSs, because they act as steroid-sparing agents. Despite their widespread use in clinical practice and as background standard of care therapy in clinical trials, there are only a few RCTs demonstrating the efficacy of CSs and other immunosuppressive agents for the management of moderate lupus. Additional drugs should be considered if HCQ is insufficient or not tolerated and can be used in addition to HCQ. The evidence supporting the use of MTX has been discussed above, and the evidence supporting the use of CSs, AZA, MMF, calcineurin inhibitors (ciclosporin and tacrolimus) and LEF are discussed in this section. For patients who do not respond to these drugs, the biologic drugs rituximab and belimumab may be considered. It should be noted that there is a specific NHS England 2013 Interim Clinical Commissioning Policy Statement for rituximab in adult SLE patients [267], and NICE guidance for the use of belimumab in active autoantibody-positive SLE in adults has been published in 2016 [324]. Patients being considered for these drugs should be discussed with and/or seen by a specialist lupus centre with experience in using these drugs. The patients should meet specific criteria and be entered in to the BILAG Biologics Register (see below and Fig. 1). For patients not requiring biologics, suggested initial target dosing regimens for active disease (as used in most studies) and lower maintenance dosing regimens to prevent recurrence of disease once patients are stable are shown in Table 7. The actual regimen used for individual patients will depend on the clinical picture and the treatment history. It is important to increase the dose and/or change treatment if patients fail to respond in the expected time frame. The LOEs and GORs for all the drugs used to treat lupus are summarized in Table 2.

CSs for moderate lupus

Summary

Higher doses of oral CSs are required initially than are required for mild lupus, for example prednisolone at up

Fig. 1 Summary of NICE and NHS England guidance for the use of belimumab and rituximab in patients with SLE



Belimumab is licensed and NICE-approved (Belimumab for active autoantibody-positive systemic lupus erythematosus: TA397, published June 2016) and should be considered first [324]. Rituximab is not licensed and should only be used according to the NHS England Interim Clinical Commissioning Policy Statement: rituximab for the treatment of systemic lupus erythematosus in adults: published September 2013 A13/PS/a [267]. All patients receiving either drug must be enrolled in the BILAG Biologics Register and be managed at or in collaboration with a specialized centre.

to 0.5 mg/kg/day, and intermittent treatment with i.m. 80–120 mg MP or even i.v. doses of MP (up to 250 mg) are used as well as, or instead of, oral prednisolone to promote a quicker response with less total CS exposure. Prednisolone dosing should be reduced, as disease activity improves, to the lowest possible maintenance dose and stopped, if possible, as other immunosuppressive agents take effect over several weeks or months.

Evidence

There are no data comparing different oral CS regimens for the treatment of moderate lupus. Two controlled studies have shown that treating patients who are clinically stable but showing serological deterioration with a short course of moderate-dose CSs (e.g. 30 mg/day) can prevent more flares than placebo and lead to improvement in serological markers [46, 60]. However, there is a risk of treating patients that will not flare, and this approach is not recommended due to the side effects of CSs.

There are some data supporting the use of 100 mg i.v. MP pulses in non-renal lupus as an alternative to 1000 mg pulses [143], and for 1000 mg pulses on three occasions in patients with moderate or severe lupus, with very little oral prednisolone [146]. The data supporting the use of i.v. pulses of 500 or 1000 mg are discussed further below in the section on the management of severe lupus [148, 326]. There is one open-label RCT [142] comparing triamcinolone 100 mg given as an i.m. injection with a short course of oral MP tapered over 1 week. Overall, there was little difference between the regimens but some improvement was seen more quickly with the triamcinolone injection.

Conclusions

Overall the LOE for CSs by i.m. or i.v. injection in non-renal moderate lupus is 2+ and GOR is C.

AZA for moderate lupus (non-renal disease)

Summary

AZA is not licensed for the treatment of lupus, but has been used for over 40 years, and it is the most frequently used cytotoxic agent [327] in lupus. AZA treatment (1–2.5 mg/kg/day orally) has been associated with prevention of flares and a reduction in CS dosage (see below and Table 2). It is usually started in patients with moderate lupus activity (Table 7) in conjunction with CSs, as it can take up to 3 months to be effective. It is also used for maintenance therapy after remission or significant response has been achieved with other agents used to treat severe lupus (such as CYC) that are less suitable for long-term therapy, particularly in women desiring pregnancy, or who are pregnant or breast-feeding [24, 25, 239, 328]. Most of the evidence (and the only double-blind RCTs) supporting its use relate to the management of LN [24, 25]. Only papers discussing the management of non-renal lupus with AZA are discussed here, although in some cases the studies included renal and non-renal patients. There is no evidence that it prevents atherosclerosis or other forms of damage [12, 329].

Evidence

The first reports of AZA being used for renal and non-renal manifestations of lupus with CSs appeared in the late 1960s and 1970s [149–151, 153, 330, 331]. Reduction in disease activity and flare rate and steroid-sparing effects were demonstrated in most of these open-label, controlled studies and in a case series [158]. AZA 200 mg daily was associated with an increased risk of significant liver dysfunction. There was no increased risk of infection, even starting at 3–4 mg/kg/day, but subsequent studies have used 2–2.5 mg/kg/day.

A prospective longitudinal open-label study [154] involving 17 SLE patients showed that AZA reduced lupus activity and anti-dsDNA antibody levels. Subsequently, in a retrospective study [155] with 61 SLE patients, suppression of anti-dsDNA antibodies by AZA (2 mg/kg/day) and low-dose prednisolone (7–12 mg/day) was associated with efficacy and better long-term outcome. However, the presence of renal disease, persistence of anti-dsDNA antibodies for at least 1 year after the beginning of treatment and reduction in AZA dosage to below 2 mg/kg/day predicted flares and was associated with a higher rate of lupus-related death.

An open-label, multicentre, RCT study of 89 SLE patients requiring 15 mg or more of prednisolone compared AZA (mean dose 2.1 mg/kg/day) with ciclosporin (mean dose 2.2 mg/kg/day) for its steroid-sparing properties [152]. The absolute mean change in prednisolone dose at 12 months, adjusted for baseline prednisolone dose, was not significantly different: 9.0 mg for ciclosporin (95% CI: 7.2, 10.8) and 10.7 mg for AZA (95% CI: 8.8, 12.7). There was no difference between groups in change in disease activity or number of flares, development of new damage, change in quality of life or numbers of patients discontinuing study drugs due to adverse events or lack of efficacy [152]. The conclusion was that both drugs can be used in lupus for their steroid-sparing properties, with appropriate monitoring.

AZA is usually well tolerated [332]. The main adverse events are nausea and vomiting, diarrhoea, flu-like illness with fever, rash, leucopenia and hepatotoxicity [156, 157, 332–334]. Side effects can occur soon after starting AZA and may require drug withdrawal [156, 335]. Hepatic veno-occlusive disease is a rare adverse event, but autoimmune hepatitis can improve on AZA, so this is not a contra-indication to its use [157]. AZA is not excreted by the kidney, and it can be used in patients with renal impairment. Managing patients with lupus-related leucopenia with AZA can be difficult [332, 336]. The enzyme thiopurine S-methyltransferase (TPMT) catalyses the inactivation of AZA. It is worth testing patients for TPMT [334] before starting AZA, as the very low level phenotype (homozygous deficiency that occurs in 0.3% Caucasians) is associated with potentially life-threatening bone marrow toxicity; otherwise, weekly full blood counts are required as the dose is increased over several weeks [337, 338]. Those patients with intermediate TPMT levels due to a heterozygous state have an increased risk of leucopenia as well, and such testing does not remove the need for monitoring the effects of the drug on the full blood count [156, 332] and liver function according to national or local guidelines [337, 338].

AZA does not cause infertility and has not been found to be teratogenic in clinical practice, despite theoretical concerns [339, 340]; thus, it can be used in women planning conception and is compatible with pregnancy and breast-feeding [24, 98, 239]. It may reduce the response to some immunizations [341–344], but this is not a contra-indication to immunization except with live viruses [74, 292]. There is no evidence that AZA increases the risk of malignancy in lupus patients [301, 345], but it may increase the risk of cervical dysplasia [346].

Conclusions

Although the data for AZA in non-renal lupus are much weaker than the data supporting its use in LN (see below), there are four open-label RCTs, three prospective cohort studies, two retrospective cohort studies and one case series supporting the use of AZA for non-renal lupus: overall LOE 2+, GOR C.

MMF for moderate lupus (non-renal disease)

Summary

There are increasing data showing that MMF in combination with CSs reduces moderate and severe lupus disease activity, reduces renal and non-renal flares, is associated with CS-sparing properties and is tolerated well (see Tables 2 and 7 for suggested treatment strategies). However, there are no placebo-controlled double-blind RCTs specifically designed to assess the use of MMF in non-renal lupus. It is teratogenic and is contra-

indicated in women trying to conceive, or who are pregnant or breast-feeding.

Evidence

The first systematic review of MMF (2–3 g daily) in non-renal lupus was published by Mok in 2007 [170] and reviewed 20 papers in terms of the response of specific clinical features (up to 2006) and steroid-sparing properties. This systematic review included patients mostly refractory to other therapies who were treated with MMF in uncontrolled studies for arthritis, renal, haematological and cutaneous manifestations, and a few with neuropsychiatric manifestations, and also covered the use of MMF in prevention of flare in a small prospective study of patients with rising anti-dsDNA antibody levels [162–164, 347].

A later systematic review [133] with a literature search up to end of October 2011 provided further evidence that MMF treatment is associated with reductions in disease activity, flare rate and prednisone dose and included data from five cohort studies [162–166] and from the Aspreva Lupus Management Study (ALMS) trial in LN that specifically reported on non-renal lupus manifestations (see below) [159]. Further supporting evidence for MMF comes from a small case series [169] and a study [348] showing that mycophenolic acid (MPA) levels vary between patients and that higher trough levels were associated with less risk of disease flare. MPA levels were more closely associated with efficacy and safety than the dose of MMF. This test is available in some hospitals, but the target trough level of 3.5–4.5 mg/l was recommended to be tested in a controlled trial before being widely applied.

The beneficial effects of MMF on non-renal disease activity [159] were demonstrated in a 6-month open-label RCT (ALMS) that compared oral MMF (target dose 3 g/day, median exposure 2.6 g/day) with pulses of i.v. CYC (0.5–1.0 g/month) as induction treatment for biopsy-proven LN [349]. All patients received prednisone starting at 60 mg/day that was tapered to 10 mg/day. There was induction of remission in >80% of patients treated with MMF for active disease at baseline in mucocutaneous, musculoskeletal, cardiorespiratory and vasculitis systems in addition to renal response in 56% (the primary end point) [349]. There were no flares in the patients on MMF, and complement levels and titres of anti-dsDNA antibodies normalized. Very similar renal and non-renal responses were seen in those given CYC [159]. However, more Black and Hispanic patients responded to MMF than i.v. CYC, and further trials are required to assess the role of race, ethnicity and geographical region on treatment response [350].

In the maintenance phase of ALMS [160], 227 patients from the 6-month induction study who met the renal clinical response criteria were randomized again to MMF (2 g/day) or AZA (2 mg/kg/day) in a 36-month, double-blind, double-dummy, phase III RCT [160]. Prednisolone ⩽10 mg/day or its equivalent was allowed and was taken by 90% of the MMF group ($n = 116$) and 87% of the AZA group ($n = 111$). Secondary end points included an analysis of non-renal severe flare. Severe non-renal flare rates did not differ between groups: 6.9% for the MMF group and 6.3% for the AZA group. There were no significant differences in the changes in anti-dsDNA antibodies or complement levels between groups. However, MMF was superior to AZA in various renal parameters related to maintaining a renal response and in preventing renal relapse in these LN patients, irrespective of which induction treatment had led to their initial response, race and geographical region [160]. Adverse events were common in both groups (>95%) (mostly minor infections and gastrointestinal disorders). Serious adverse events occurred in 24% of the MMF group and 33% of the AZA group ($P = 0.11$). The rate of withdrawal due to adverse events was lower with MMF than AZA (25% *vs* 40%, $P = 0.02$).

Another randomized open-label controlled trial [161], in Caucasians predominantly, compared MMF (mean 2 g/day) and AZA (mean 124 mg/day) for maintenance therapy over 36 months, starting at week 12 after induction with a short course of i.v. CYC (6 × 500 mg over 10 weeks) for the management of biopsy-proven proliferative LN. All patients initially received three i.v. pulses of MP and were tapered from 0.5 mg/kg/day prednisone down to 5 mg/day at week 52 and then tapered further and stopped if possible. Both regimens were well tolerated, and there was comparable improvement in renal end points and non-renal parameters, including disease activity indices and C3 levels in both groups. There were less renal flares and less haematological adverse events with MMF than AZA (though this was not statistically significant in this study).

Since the systematic review [133], further studies reporting reduction in disease activity included a retrospective review of patients treated with MMF that found a significant reduction in mean weekly steroid dosage (from about 12.5 to 3 mg/day prednisone) [167]. A single-centre retrospective cohort study [168] involving 135 patients with SLE (50% with renal disease) and 43 patients with systemic vasculitis treated with MMF reported good responses in 46% of patients, and the mean prednisolone dosage was significantly reduced from 22 to 8 mg/day at 12 months. These and other studies have shown that adverse events occur in up to 44% of patients over 5 years: mostly mild gastrointestinal intolerance and infections, with leucopenia and hospitalization rare. In one study most patients tolerated the drug well, with 73% of patients on the drug at 12 months, and there was no relationship between adverse events and dose (250 mg to 3 g daily) [351]. However, there have been increasing reports of teratogenicity, and it should be stopped at least 6 weeks before a planned pregnancy, and MMF should not be taken by women who are pregnant or breast-feeding [239].

Yahya *et al.* [172] reported on a small open-label prospective study of 14 non-renal lupus patients randomized to mycophenolate sodium (MS) or standard care and showed that MS treatment was safe and was associated with reduced disease activity. A randomized open-label

trial [171] of 40 patients with primary systemic vasculitis or SLE compared MMF (2000 mg/day) and enteric-coated MS (1440 mg/day). The composite primary end point was treatment failure and/or drug intolerance over 12 months. MS was anticipated to be tolerated better, but no difference in tolerance was observed. Although MS was associated with slightly better efficacy, this may have been due to imbalance in factors affecting remission and relapse, despite randomization with minimization. This study did not support the use of MS as a better tolerated and efficacious alternative to MMF for routine use, but MS could be considered in patients with gastrointestinal side effects from MMF.

Conclusions

The evidence that MMF reduces disease activity, lupus flare and has steroid-sparing properties in non-renal lupus comes from two systematic reviews, three open-label RCTs in LN and seven cohort studies: LOE 2++, GOR B. MPA/sodium (MS) may be considered in patients intolerant of MMF based on two studies (LOE three, GOR D).

Ciclosporin and tacrolimus for moderate lupus (non-renal disease)

Summary

Ciclosporin and tacrolimus do not cause myelosuppression and have the ability to reduce moderate disease activity (Tables 2 and 7). There is more evidence for ciclosporin in non-renal lupus, and it has been particularly helpful in the treatment of cytopenias, where there is likely to be difficulty distinguishing cytopenias due to lupus from cytopenias due to drugs such as AZA, MTX and MMF. Both ciclosporin and tacrolimus can be used (at the lowest possible dose) in women planning pregnancy, and in those who are pregnant or breast-feeding [239].

Evidence

There are two open-label RCTs [152, 173] and eight non-renal cohort studies supporting the use of ciclosporin at doses of $\leqslant$2.5 mg/kg/day in patients with normal renal function, although a systematic review [133] that included details of two open-label RCTs and a brief summary of six of the cohort studies reported that there was not much evidence supporting the use of ciclosporin in lupus because there were no double-blind, placebo-controlled RCTs.

Nevertheless, the open-label RCTs suggested that ciclosporin reduced disease activity as well as AZA did [152] and better than CSs alone [173], and that ciclosporin treatment was associated with significant CS-sparing properties in both RCTs, equivalent to that of AZA in one trial [152] as reported previously by the cohort studies. These included two prospective cohort studies [174, 175] that showed significant reduction in disease activity at 6 months, with most benefit in patients with renal and/or haematological manifestations, and response maintained to 24 months in one study [175]. Three retrospective studies [176–178] reported a reduction in disease activity and/or flares (particularly haematological manifestations such as thrombocytopenia), and significant steroid-sparing properties were reported in two of these studies [175, 177].

In the first of two additional studies not mentioned in the systematic review, ciclosporin was shown to treat thrombocytopenia in six patients [179], three of whom were able to stop CSs. In the second study [180], a retrospective cohort study, ciclosporin was used to manage 40 refractory lupus patients, including 11 patients with neurological conditions and 7 with overlap syndromes, as well as 18 with LN. The study showed reduction in disease activity and only mild transient adverse events not requiring discontinuation.

Adverse events were the focus of another study [181] with doses up to 5 mg/kg/day, so it was not surprising that adverse events were reported in 63%, but these led to discontinuation in only 16% and were reversible within 3 months of stopping the drug, consistent with many other reports. Ciclosporin treatment can cause hypertrichosis, gum hypertrophy, hypertension, paresthesiae, tremor, gastrointestinal symptoms and impaired renal function, especially at higher doses ($>$3 mg/kg/day). It is best used at lower doses ($\leqslant$2.5 mg/kg/day) as that is more tolerable and rarely causes permanent nephrotoxicity if carefully monitored. In the open-label RCT [152], there were no unexpected adverse events, and with appropriate monitoring of renal function and blood pressure, it was not discontinued due to adverse events or inefficacy more often than AZA.

There are two reports of tacrolimus in non-renal lupus and they were included in the systematic review [133]. The first was a small retrospective cohort study [182] with 10 non-renal patients showing significant reductions in SLEDAI and prednisolone over 1 year on 1–3 mg daily. The second was an open-label prospective study [183] with 21 mostly non-renal patients showing reduction in SLEDAI score over 6 months and no serious side effects, but 29% withdrew due to inefficacy and 10% due to adverse events.

Conclusions

Overall, the LOE for ciclosporin in non-renal lupus from two open-label RCTs, eight non-renal cohort studies and one systematic review is 2+ and GOR is C.

The LOE for tacrolimus from two studies in non-renal lupus and one systematic review is three and GOR is D.

LEF in moderate lupus

Summary

The systematic review [133] and our search found little evidence for efficacy and safety of LEF in lupus patients, with only two small studies in the literature. This drug can be considered in patients refractory to, not suitable for or intolerant of MTX, AZA, MMF and calcineurin inhibitors, for whom CYC, rituximab and belimumab are not suitable or not available. It is not suitable for women considering pregnancy, and a cholestyramine washout is required if pregnancy is desired or occurs while it is being taken [239].

Evidence

There was a randomized, double-blind, placebo-controlled trial in moderate SLE patients, with only six patients in each group [184]. A significant reduction in SLEDAI and prednisone occurred in both groups over 24 weeks. The LEF group showed significantly greater mean reduction in SLEDAI score, but there was no difference in steroid reduction between the groups. Side effects included transiently abnormal alanine aminotransferase (ALT), leucopenia and hypertension. There was a retrospective analysis of 18 patients who received LEF [185], but 4 patients withdrew (3 due to adverse events, including 1 with rash), and only 9/14 achieved lower SLEDAI scores after 2–3 months of therapy.

Conclusions

Overall the LOE for LEF for reducing non-renal lupus disease activity from two studies is three and the GOR is D. Caution is advised about its use in those with pre-existing subacute cutaneous lupus, as this may worsen as observed in other non-lupus studies.

Rituximab for refractory moderate lupus

Summary

Rituximab can be prescribed and reimbursed in the UK currently according to the NHS England 2013 Interim Clinical Commissioning Policy Statement for rituximab in adult SLE patients [267] who have two or more systems with BILAG B scores; or have severe BILAG A level disease activity, using the BILAG-2004 index [268, 269]; or have a SLEDAI-2 K score [270] >6 if they have failed two or more immunosuppressive agents (due to inefficacy or intolerance), at least one of which must be MMF or CYC; or need unacceptably high doses of steroids to achieve lower level of disease activity.

The patients must be managed in conjunction with a specialist centre for lupus and be entered in to the BILAG Biologics Register for standardized reporting of outcome (see Fig. 1 flowchart for eligibility and response criteria). This is essential for providing more open-label data in a prospective study with control patients treated with other immunosuppressive therapies, given the failure of the international double-blind, placebo-controlled lupus trials to meet their primary end points, as discussed below (EXPLORER for active non-renal disease [190, 191] and LUNAR for LN [352]). This policy was agreed as a result of the increasing published evidence supporting the efficacy of rituximab in refractory lupus patients, who are likely to differ from those recruited to trials where there was no requirement to have failed conventional therapy. Pregnancy should be avoided for at least 6 months after exposure to rituximab [239].

Evidence

The current evidence supporting the efficacy and safety of rituximab in non-renal lupus was most recently reported in a systematic review [200] in 2014 by Cobo-Ibanez with a literature search up to June 2013. This included the non-renal RCT EXPLORER [190] and its exploratory analysis [191], 2 open-label phase I/II trials [192, 193] and 22 cohort studies which analysed 1231 patients in total [200]. The 2 open-label trials [192, 193] and 5 of the cohort studies had been discussed in a previous systematic review summarizing off-label use in 188 cases (including non-renal and renal patients in 9 cohort studies and 26 case series/reports published up to December 2007) [202].

The non-renal patients discussed in the systematic review by Cobo-Ibáñez *et al.* [200] were heterogeneous, but in general had active lupus disease unresponsive to steroids and/or immunosuppressants prior to treatment with rituximab. Treatment with rituximab was associated with a reduction in global disease activity over 3–9 months, with 64–91% achieving response, including patients with a reduction in complement and anti-dsDNA antibody levels, arthritis and thrombocytopenia. Evidence for a steroid-sparing effect was based on the 2 open-label trials and 10 of the cohort studies [200]. There were few significant adverse events in the RCT, 2 open-label studies and 20 cohort studies [200]. Relapses/flares did occur at variable times (3.7–18 months), although in the RCT there were numerically fewer severe BILAG A flares and longer time to these flares in the rituximab group compared with the placebo group, and this almost achieved statistical significance (hazard ratio = 0.61, P = 0.052) [191]. Better clinical response after a second course was observed in 2 of the cohorts that studied retreatment [200], and a further report supported this observation and that steroid reduction occurred after each of two courses of rituximab [199]. The evidence for rituximab treating mucocutaneous involvement was deemed weak [200], and this may be explained by a recent report [353] specifically addressing 26 SLE patients with various subtypes of lupus rash, which observed that acute lupus rash responded whereas chronic cutaneous lupus (such as discoid rash) did not respond to rituximab and that new lesions with typical histology may appear despite confirmed B cell depletion.

Rituximab treatment early in the course of lupus disease, followed by AZA, was tried by Ezeonyeji *et al.* [194] specifically for its steroid-sparing effect in a pilot study with 8 SLE patients whose results were compared with 23 matched historical control patients treated conventionally [194]. Reduction in disease activity, a fall in anti-dsDNA antibodies and complement, and significant lower cumulative prednisolone at 6 months compared with controls was observed. There is also an open-label LN study suggesting that early rituximab with i.v. MP followed by MMF may avoid the use of oral CSs, and this regimen is currently being tested in a controlled randomized RCT called RITUXILUP [354].

The Duxbury systematic review and meta-analysis [201] reported response rates for various disease activity measures for patients in the open-label studies of refractory lupus treated with rituximab also reviewed by Cobo-Ibáñez *et al.* [200]. The Duxbury review and meta-analysis

did include a section on LN (not discussed here) and included a few non-renal studies not in the Cobo-Ibáñez review, although the latter also included a few not in the Duxbury review. The BILAG index was used in 188 patients treated with rituximab in 8 open-label studies (3 prospective, 4 retrospective and 1 small case–control) [201]. The pooled global response in seven of these studies was 83%. The complete response rate was 47% and the partial response rate was 38% in six studies. A significant reduction in anti-dsDNA antibodies was observed in 6 of the 8 studies and a significant rise in complement was observed in 5 of 6 studies. Various versions of the SLEDAI were used in 513 patients treated with rituximab in 12 open-label studies: 5 prospective, 6 retrospective and 1 open-label randomized trial, only 1 of which also analysed BILAG response. With SLEDAI the global response was 77% in 11 studies. In 6 studies the complete response rate was 57% and the partial response rate was 31%. Anti-dsDNA levels fell in 3 of 3 studies and complement rose in 2 of 3 studies [201].

Publications from cohorts in Germany [195], Italy [196] and Japan [197] have confirmed similar levels of efficacy with various disease activity measures and provided further safety data in another 264 patients. Long-term follow-up of 98 SLE patients treated with rituximab over a 12-year period has shown in a retrospective analysis that the group with longer duration of depletion ($\geqslant$12 months) was associated with a better response (greater decrease in BILAG score at 6 and 12 months) than those with shorter period of B cell depletion [198].

The results of these open-label studies are much better than the response rates observed in the EXPLORER RCT (for rituximab *vs* placebo: complete 12% *vs* 16%, partial 17% *vs* 13%) [190]. However, EXPLORER used more stringent BILAG response criteria than used in any other study [201], but did observe a reduced rate and time to severe BILAG A flare [191]. High-dose CSs and background immunosuppression were used in both arms of the EXPLORER trial and may have reduced the ability to discriminate benefit from rituximab [201]. Patients on MTX as the background immunosuppressant derived more benefit from rituximab in a *post hoc* analysis than those in the placebo group [190], and in contrast to those on background AZA or MMF [190]. Patients of Afro-American or Hispanic origin were also shown to benefit from rituximab in the RCT, in contrast to Caucasians [190].

However, two case series reports have suggested that repeat courses of rituximab may increase the risk of hypogammaglobulinaemia and infection [199, 293]. Progressive multifocal leukoencephalopathy (PML) has been reported in 17 SLE patients, of whom 5 had been treated with rituximab. It seems likely that immunosuppression, however it is achieved, is the key factor in the development of PML. Lupus patients may be at increased risk of developing PML compared with other rheumatic diseases [355]. The risk of rituximab causing PML in rheumatic diseases, including RA and SLE, has been estimated at 5/100 000, which is less than the risk observed with some other immunosuppressants in other diseases [356].

Conclusions

There is now considerable evidence for the ability of rituximab to reduce disease activity in refractory non-renal SLE of moderate and severe severity, albeit mostly from cohort studies. There have been relatively few concerns in the individual reports and systematic reviews about adverse events, including infections, in lupus patients on rituximab. There is increasing evidence that rituximab has steroid-sparing properties, but further evidence for its use early in the disease course is needed. Overall, the LOE for rituximab from 3 systematic reviews (including a meta-analysis and 30 studies, including 1 RCT and 3 open-label trials for reducing disease activity and for steroid-sparing properties) is 2+ and the GOR is C.

Belimumab for refractory moderate lupus

Summary

There have been two large phase III RCTs [203, 204] investigating the use of belimumab in moderate–severe seropositive lupus (mostly musculoskeletal and cutaneous disease; as severe active renal and NPSLE disease were exclusions). All patients received steroids, HCQ and/or immunosuppressive drugs, with specific criteria for dosing changes allowed or contra-indicated in the protocol. Both trials showed a significantly increased proportion of responders to belimumab at a 10 mg/kg dose in addition to standard care. A variety of secondary end points were met, and there were no significant differences in adverse events, leading to the drug being approved and licensed by the US Food and Drug Administration and the European Medicines Agency. NICE guidance for use of belimumab in active autoantibody-positive SLE in adults has been published [324] and is summarized in Fig. 1. Patients must have positive anti-dsDNA antibodies, low complement and a SELENA-SLEDAI score $\geqslant$10 despite standard therapy. Patients should be recruited to the BILAG Biologics Register so that outcomes can be recorded, and treatment with belimumab should not be continued for $>$24 weeks unless the SELENA-SLEDAI score has improved by 4 points or more. Pregnancy should not occur while on belimumab, but first trimester exposure is unlikely to be harmful [239].

Evidence

In the BLISS52 trial [203], at week 52 the response rate with placebo was 44%, with belimumab 1 mg/kg it was 51% ($P = 0.013$) and with 10 mg/kg it was 58% ($P = 0.001$). In the BLISS76 trial [204], the placebo response rate at week 52 was 34%, with belimumab 1 mg/kg it was 41% ($P = 0.089$) and with 10 mg/kg it was 43% ($P = 0.017$). The response rates at week 76 were a little lower in all groups. A meta-analysis of the response at 52 weeks in the phase II trial of belimumab [205] as well as BLISS 52 and BLISS 76 trials showed benefit for belimumab, with an odds ratio of 1.63 (95% CI: 1.27, 2.09) [209]. Safety data from the phase II trial and its open-label extension have not shown any significant concerns and continued benefit for up to 7 years [207, 208]. The most common side effects have been upper respiratory tract and urinary tract infections,

arthralgia, headaches, fatigue and nausea. Serious infusion reactions and infections have been rare [207, 208]. There have been two case reports of progressive multifocal leukoencephalopathy [357, 358], but there is no evidence that belimumab increases the risk more than other immunosuppressive regimens in SLE patients [356].

Further *post hoc* analyses [359, 360] on the pooled datasets from BLISS 52 and BLISS 76 trials have demonstrated that belimumab therapy was associated with significantly more patients showing improvements than with placebo in the most commonly affected musculoskeletal and mucocutaneous systems, and more immunological abnormalities normalized than with placebo [359]. Improvement was reported less consistently in other systems that were less often affected [359]. There was less worsening in haematological, immunological and renal parameters in those patients on belimumab than in those on placebo [359], but as with improvement, effects were not always dose related. Serological improvements (reduction in anti-dsDNA antibodies and increase in C3/C4 levels, without reduction in memory T or B cell numbers or levels of anti-pneumococcal or anti-tetanus toxoid antibodies) have been reported [361]. This is consistent with the low rate of serious infections in the long-term open-label study of belimumab [207, 208].

Another pooled analysis of BLISS 52 and BLISS 76 trials identified that belimumab had most therapeutic benefit compared with standard therapy alone in patients with higher disease activity (SELENA-SLEDAI $\geqslant$10), positive anti-dsDNA antibodies, low complement, or CS treatment at baseline [206]. Week 52 response rates in the low complement/anti-dsDNA–positive subgroup were 32% for placebo, 42% for belimumab 1 mg/kg ($P = 0.002$) and 52% for belimumab 10 mg/kg groups ($P < 0.001$). For the SELENA-SLEDAI $\geqslant$10 subgroup, the response rates were 44%, 58% ($P < 0.001$) and 63% ($P < 0.001$), respectively. Belimumab was also shown to reduce severe flares and CS use and to improve health-related quality of life most in these more severe subgroups [206]. These analyses contributed to the decision by the European Medicines Agency to limit the market authorization for belimumab (Benlysta) to add-on therapy in adult patients with active autoantibody-positive SLE with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy [362].

Conclusions

Treatment with belimumab in addition to standard therapy in autoantibody-positive SLE patients was associated with some improvements in clinical, laboratory and patient-reported outcome measures (compared with placebo in addition to standard therapy) and had a low risk of serious side effects. Based on the results of the two RCTs and the *post hoc* analyses, belimumab is considered by NICE to be cost-effective in the UK only for patients who meet the specific criteria [324] (see summary above and Fig. 1), so availability is limited. The drug is being used in other countries, particularly in the USA, where the licence covers patients with moderate disease activity and only specifies that patients must have active, autoantibody-positive lupus and be receiving standard therapy (such as CSs, antimalarials, immunosuppressives and NSAIDs) [363]. Overall, the LOE for belimumab in non-renal lupus from a meta-analysis, one phase II study, two phase III RCTs, their open-label extension study and *post hoc* analyses combining the data from the two RCTs is 1+ and the GOR is B.

Recommendations for the management of severe SLE

(i) Patients who present with severe SLE, including renal and NP manifestations, need thorough investigation to exclude other aetiologies, including infection (4/D). Treatment is dependent on the underlying aetiology (inflammatory and/or thrombotic), and patients should be treated accordingly with immunosuppression and/or anticoagulation, respectively (4/D) (SOA 98%).

(ii) Immunosuppressive regimens for severe active SLE involve i.v. MP (2+/C) or high-dose oral prednisolone (up to 1 mg/kg/day) (4/D) to induce remission, either on their own or more often as part of a treatment protocol with another immunosuppressive drug (4/D) (SOA 98%).

(iii) MMF or CYC are used for most cases of LN and for refractory, severe non-renal disease (2 ++/B) (SOA 98%).

(iv) Biologic therapies belimumab (1+/B) or rituximab (2+/C) may be considered, on a case-by-case basis, where patients have failed to respond to other immunosuppressive drugs, due to inefficacy or intolerance (SOA 98%).

(v) IVIG (2−/D) and plasmapheresis (3/D) may be considered in patients with refractory cytopaenias, thrombotic thrombocytopaenic purpura (TTP) (1+/B), rapidly deteriorating acute confusional state and the catastrophic variant of APS (SOA 93%).

Rationale

Overview of the management of severe lupus

Patients who have serious manifestations with organ- or life-threatening disease require treatment with intensive immunosuppression followed by a prolonged period of less aggressive maintenance therapy to prevent relapse (summarized with suggested dosing regimens in Table 7). In some cases there may be a thrombotic component to the clinical features that requires anticoagulation, for example in patients with APS as well as lupus. There is most evidence for the management of LN, less for neuropsychiatric disease and very little for other organ-specific manifestations.

The authors of this guideline have not reviewed the evidence for the management of LN as they suggest that the EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24] are followed. The main recommendations and SOAs with them are shown in Table 3. Further details about these recommendations and the evidence for them have been published [24].

For the management of severe non-renal SLE, the evidence for treatment with high-dose CSs, AZA, CYC, MMF, rituximab, IVIG and plasma exchange (plasmapheresis) is discussed below. The evidence for use of belimumab and of the calcineurin inhibitors ciclosporin and tacrolimus, particularly for cytopenias due to lupus, has already been reviewed above. Suggested initial target dosing regimens and lower maintenance regimens to prevent flares once patients are stable are shown in Table 7. The actual regimen used for individual patients will depend on the clinical picture and the treatment history. Patients with refractory disease, especially those being considered for belimumab and rituximab, should be discussed with and/or seen by a specialist lupus centre (see Fig. 1 flowchart for eligibility and response criteria). It is important to review the response regularly and to increase the dose and/or change the treatment if patients fail to respond.

CSs for severe SLE

Summary

The emphasis in the last 10 years has been on finding steroid-sparing regimens to treat severe lupus, using other immunosuppressants in conjunction with CSs (either orally, intravenously or both), to induce and maintain response with the least risk of adverse events, particularly infection. In general, there is an increasing tendency to use oral prednisolone at a dose of 0.5 mg/kg/day with i.v. MP pulses (3 × 500–750 mg) rather than higher doses of i.v. MP pulses and/or higher dose of oral prednisolone (e.g. 0.75–1 mg/kg/day) as done in the past for all severe manifestations of lupus.

Evidence

I.v. MP pulses as an alternative to, or in addition to, high-dose oral prednisolone was first reported as a treatment for LN [24, 325, 326]. I.v. MP pulses were introduced for the management of non-renal lupus in the early 1980s [147]. An open-label cohort study [146] and an open-label trial [145] using i.v. MP pulses followed by alternate day oral CSs found that pulse therapy led to rapid improvement in clinical symptoms and anti-dsDNA and C3 levels, but that an alternate day oral regimen was associated with relapses. A small double-blind, placebo-controlled RCT with mostly non-renal SLE patients [144] found that 3 i.v. MP pulses resulted in faster and more complete improvement in the first 2 weeks in 12 patients with SLE, but there was no significant difference in efficacy or safety parameters at 4 weeks or 6 months compared with the placebo group; however, all patients received 40–60 mg of oral prednisolone daily [144].

A double-blind RCT [143] comparing three daily i.v. MP pulses of either 1000 or 100 mg in 21 patients with SLE causing fever, cardiorespiratory, renal or NP manifestations (with individualized outcomes based on entry manifestations) suggested no difference in efficacy between the regimens. A retrospective study compared low-dose i.v. MP pulses (⩽1500 mg over 3 days) with high-dose pulses (3–5 g over 3–5 days) for the treatment of severe flares [148]. This study suggested that the lower dose was sufficient and safer for controlling SLE flares than the high-dose regimen, which was associated with an increased number of infections [148].

Conclusions

There is limited evidence for any particular CS regimen for specific manifestations of severe non-renal lupus. Overall the LOE for i.v. MP pulses and oral prednisolone in non-renal severe lupus is 2+ and the GOR is C.

AZA in severe SLE

Summary

AZA (2–3 mg/kg/day) is sometimes used as first-line therapy with CSs in severe non-renal lupus (see Table 7), based on the evidence discussed in the section on the use of AZA for the management of moderate lupus. It is most often used in women planning pregnancy or pregnant, as it is much safer in pregnancy than CYC or MMF, which are contra-indicated in such situations [239].

Evidence

There was only one open-label controlled trial, with 24 patients with severe (life-threatening) multisystem manifestations of lupus [151], which showed no definite benefit from the addition of AZA compared with 40–60 mg prednisone alone for 6 months, before tapering over the next 18 months, although there was some steroid-sparing benefits seen at 12 months. It has been used as primary treatment at a dose of 2 mg/kg/day as an alternative to MMF or CYC in low-risk renal patients without adverse prognostic factors and when these drugs are contra-indicated, not tolerated or unavailable [24].

AZA has been used more often as maintenance therapy after a course of CYC for severe lupus, based on the evidence from studies undertaken in patients with LN [24, 25]. The rate of major extra-renal flares in the maintenance phase of the Aspreva Lupus Management Study (ALMS) study was low in the AZA group at 6.3% (7/111) and similar to the frequency of 6.9% (8/116) in the MMF group [160]. There is some evidence that AZA may be less effective at preventing renal flare in patients in this LN study than MMF, as discussed in the section on MMF [160]. However in a predominantly Caucasian LN population, in the MAINTAIN study, no difference in number or time of severe systemic flares in the AZA group (4/43) compared with the MMF group (3/53) was observed [161]. There are no trials or controlled studies addressing AZA as a primary treatment for neuropsychiatric lupus or any other specific serious non-renal manifestations of lupus, but it has been used after CYC for the treatment and prevention of recurrence of lupus psychosis in 13 patients [328].

The systematic review of non-biologic immunosuppressants in non-renal SLE by Pego-Reigosa *et al.* [133] only considered the unblinded RCT (showing no benefit) from 1975 [151] and a cohort study (showing a reduced rate of flare [155] in patients on AZA) and concluded that there was little evidence to support the use of AZA in non-renal lupus.

Conclusions

Overall, the LOE for AZA in non-renal severe lupus is 2+ and the GOR is C.

CYC in severe SLE including LN and neuropsychiatric lupus

Summary

CYC, although not licensed for lupus, has been used for the treatment of severe lupus, particularly LN and organ- or life-threatening non-renal disease, since the late 1960s, with the first open-label trial in LN reported in 1971 [364]. Oral CYC is associated with an increased risk of bladder cancer and has been replaced by i.v. CYC pulses in the management of severe lupus. There is most experience with i.v. CYC pulses in LN and NPSLE (Tables 3 and 7). CYC is teratogenic and is contra-indicated in women trying to conceive, or who are pregnant or breast-feeding. It is gonadotoxic and can cause infertility, and men should not father children while on CYC [239].

Evidence

The first controlled trial comparing prednisone with CYC in LN, non-renal lupus and PM was reported in 1973 [365], and a similar design was used to compare oral CYC and AZA in lupus not responsive to 15 mg prednisolone [366], but numbers were small and the aim of matching individual patients and comparing their outcomes was unsuccessful. Since then, studies have used different trial designs and evidence supporting the use of various doses of oral and later i.v. pulse CYC regimens to reduce disease activity and prednisolone dosage and to improve outcomes in patients with LN and non-renal lupus have been reported. The best-known regimens are based on the National Institutes for Health i.v. CYC protocol (monthly i.v. CYC at 500–1000 mg/m^2 body surface area for 6 months, followed by 3 monthly i.v. CYC for 2 years) [367] and the Euro-Lupus protocol, which uses lower doses (500 mg fixed dose i.v. CYC 2-weekly for a total of 6 doses, followed by oral AZA) [368] and appears to be as effective and safer for LN in Europe than high-dose regimens [369]. In recent years, the 3-monthly i.v. CYC maintenance pulses for 2 years in the National Institutes for Health protocol have been replaced by oral MMF or AZA [25, 370].

I.v. CYC pulses were the most widely used regimes for all but the mildest cases of acute proliferative glomerulonephritis until MMF was found to be comparable in efficacy and safer [24, 25]. It should be noted that neither of these drugs is licensed for the treatment of LN, but both are supported as appropriate treatment for the management of LN in the EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24] (Table 3) and the ACR guidelines for screening, treatment and management of LN [25].

Treatment regimens tested in LN have often been applied to severe non-renal lupus disease as there are fewer non-renal studies and they include heterogeneous patient populations. A systematic review [133] evaluated 29 studies, including 4 unblinded RCTs in which 3742 patients with non-renal lupus were treated with a variety of CYC regimens. There are more data on the efficacy and safety of using CYC to treat non-renal lupus than of any other drug treatment; however, there are fewer high-quality studies than for LN, and diverse end points have been used, making it hard to compare the studies.

Data from the ALMS RCT comparing i.v. CYC (0.5–1.0 g/m^2 monthly $\times$ 6) and MMF (target 3.0 g/day) as induction therapy for LN [159] showed that i.v. CYC therapy was associated with almost 95% response in all of the non-renal systems, apart from the haematology, which was confounded by drug-induced cytopenias and anaemia of uncertain cause. There was no difference in response between i.v. CYC or MMF in any of the systems studied, including renal.

Some of the best evidence supports the use of pulse i.v. CYC in NP lupus, with one small RCT favouring an i.v. CYC regimen over i.v. MP alone [186]. That trial used more CSs than we would recommend now and was based on a previous retrospective cohort study that suggested that i.v. CYC was useful in the management of NPSLE [371]. The RCT [186] recruited 32 SLE patients with active severe NP manifestations without thrombosis (such as seizures, optic neuritis, peripheral or cranial neuropathy, coma, brainstem disease or transverse myelitis) that had developed within the previous 15 days. All of the patients received oral prednisolone 1mg/kg/day for up to 3 months and then tapered depending on response and 1 g of i.v. MP daily for 3 days. One group received further 1 g of i.v. MP daily for 3 days repeated monthly for 4 months then bimonthly for 6 months and finally 3 monthly for one year. The other group received i.v. CYC 0.75g/m^2 body surface monthly for 12 months then this dose was repeated every 3 months for another year. The primary end point was at least 20% improvement from baseline using clinical, laboratory or specific neurological criteria and was met in 18/19 (95%) receiving CYC and 6/13 (46%) receiving MP [186]. A Cochrane systematic review of the treatment of NPSLE [372] calculated a relative risk of 2.05 (95% CI: 1.13, 3.73) for 20% response at 24 months with CYC therapy, but most patients responded by 5 months. CYC treatment was also associated with greater improvement in other lupus manifestations, a significant reduction in SLEDAI score at 6 and 12 months, greater reduction in prednisolone dosage and more patients completing the protocol compared with the MP group. There was no difference in adverse events, including infections and deaths. Recruitment to the study was stopped early due to the higher failure rate of the MP arm. Although the RCT is not of high quality [372] due to the small number of patients studied, the heterogeneity of the NP events, the variable outcome measures used for their assessment, and potential confounding by variable oral CS dosing, it is clear that the i.v. MP regimen was not sufficient and that CYC was better at controlling active NPSLE and preventing relapse.

Further evidence for the use of CYC in NPSLE comes from a previous open-label, controlled pilot study on the

use of low-dose i.v. CYC, with a mean dose of 21 mg/day oral prednisone in 37 NPSLE patients, compared with oral prednisone alone in 23 patients (mean dose 21 mg/day) [187], and a cohort study [373] in which a low-dose regimen of i.v. CYC was used in 25 patients with NPSLE with benefit and a low risk of adverse events. A case series [328] found that treating 13 patients with lupus psychosis with oral prednisolone starting at 1 mg/kg/day for 8 weeks and oral CYC (1–2 mg/kg/day) for 6 months followed by oral AZA (1–2 mg/kg/day) led to improvement within a mean of 44 days and only one relapse with psychosis after 2 years; however, 23% developed other NP features and 38% had non-NP flares over the mean follow-up of 7 years. Anti-psychotic agents were used in nine patients for a mean of 6 months. Evidence for CYC and other treatments in neuro-ophthalmic manifestations of lupus have been reviewed in a systematic review [374], but the data on treatment is mostly based on case reports and small case series, for example cases with neuromyelitis optica treated with or without CYC [374].

In contrast to the studies assessing low-dose regimens, high-dose CYC has been studied as well in the hope of achieving better responses in severe lupus. An open-label, uncontrolled study [375] reported the initial safety and efficacy of high-dose CYC (50 mg/kg $\times$ 4 days) without stem cell transplantation in 14 patients with refractory moderate to severe SLE despite CSs and at least one immunosuppressant. A prospective RCT [188] was designed to compare the efficacy and safety of a widely used standard i.v. CYC regimen (monthly i.v. CYC at 750 mg/m^2 body surface area for 6 months, followed by 3 monthly i.v. CYC for 2 years) with this high-dose i.v. CYC regimen. Entry criteria included moderate-to-severe lupus with renal (22 patients), neurologic (14 patients) or other organ system involvement (11 patients). There was no evidence that response differed between the regimens, but non-responders to monthly i.v. CYC could be rescued with high-dose i.v. CYC. There was no difference in serious adverse events, infections, premature ovarian failure or deaths between the two groups. Leuprolide (a gonadotropin-releasing hormone analogue) was not used to protect against ovarian failure [376]. This should be considered with i.v. CYC moderate- and high-dose regimens [188], as amenorrhoea and ovarian failure are dose- and age-related adverse events of CYC [370, 377], but are rare with the European low-dose i.v. CYC regimen (500 mg 2-weekly for 3 months only) recommended for LN [24].

The remaining data [133] supporting the use of CYC for other serious non-renal manifestations of lupus are obtained predominantly from a variety of cohort studies, small case series and case reports, including 5 patients with systemic lupus vasculitis [378], 11 patients with myocarditis [379] and 5 patients with heart failure due to myocarditis [380]. There is one open-label RCT comparing i.v. CYC with enalapril for 6 months in the treatment of pulmonary hypertension, which showed greater benefit from CYC but an increased risk of infection and gastrointestinal side effects [189].

Conclusions

There is considerable evidence supporting the use of i.v. CYC to reduce disease activity and CS usage in severe lupus, for both renal and non-renal disease, including NPSLE. There is no evidence that CYC prevents chronic damage, and all regimens are teratogenic, but there is less risk with the Euro-Lupus regimen of adverse events (such gastrointestinal side effects, alopecia, infection, amenorrhoea and infertility due to ovarian failure) than with higher dose regimens [12, 16, 24, 25, 133, 372]. Overall, the LOE for the use of CYC in non-renal severe lupus, including NPSLE, from 1 systematic review including 29 studies and 1 systematic Cochrane review of NPSLE is 2++, and the GOR is B.

MMF in severe SLE

Summary

There is considerable evidence supporting the use of MMF in the management of LN, and this has been discussed in the Joint EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24] (Table 3) and the ACR guidelines for screening, treatment and management of LN [25]. The mean SOA of all of the authors of this guideline with each of the main EULAR/ERA-EDTA recommendations for the management of LN is shown in Table 3. There is very little evidence for the use of MMF in NPSLE, but it is being used to reduce other types of moderate and severe non-renal lupus disease activity (Table 7), to prevent flare and for its steroid-sparing properties, as an alternative to CYC or AZA, especially in cases where inefficacy, drug intolerance and concerns about toxicity arose. It is not compatible with conception, pregnancy or breast-feeding [239].

Evidence

As mentioned in the section on moderate lupus, there is a systematic review of non-biologic immunosuppressants in non-renal SLE [133] that summarizes the data from 8 papers (covering 768 patients with moderate/severe lupus), which assessed the efficacy and safety of MMF in the treatment of non-renal SLE, including the ALMS RCT comparing the use of MMF with that of CYC as induction therapy for LN [159], and 7 cohort studies including 6 discussed above [162–166, 351] and an abstract that does not meet the criteria for this guideline.

Conclusions

Overall, the LOE for MMF in non-renal lupus from 2 systematic reviews, 2 open-label RCTs in LN and 7 cohort studies is 2++, and the GOR is B.

Rituximab in severe SLE

Summary

According to the NHS England Interim Commissioning Policy Statement for rituximab in SLE [267], rituximab may be considered in patients with severe or moderate SLE (BILAG system category A or $\geqslant$2B system scores, or SLEDAI $>$6) who fail treatment with MMF or CYC, either because of lack of effect or due to adverse events,

providing they have already failed another immunosuppressant or it would be contra-indicated, or who require unacceptably high long-term CS dosing to control their lupus activity (see Fig. 1 flowchart for eligibility and response criteria).

Evidence

Clinical examples of severe lupus are shown in Table 7, and the evidence for rituximab is summarized in Table 2. The systematic reviews by Duxbury *et al.* [201] and Cobo-Ibáñez *et al.* [200] provide evidence supporting the use of rituximab for non-renal severe manifestations of lupus, such as NP involvement (5 cohort studies [381–385]), haematological manifestations (6 cohort studies [383, 385–389]) and at least 10 other cohort studies [382, 383, 385, 387, 390–395]). The data for improvement in NPSLE are still limited and uncontrolled, but showed 73–100% response in small numbers of patients. There is some evidence for improvement (50–100%) in mostly refractory lupus patients and idiopathic autoimmune thrombocytopenia and haemolytic anaemia. There are some specific reports on the use of rituximab in neuro-ophthalmological cases in a systematic review of these conditions [374], and pooled data from European cohorts [396] on the effects of rituximab in LN, as mentioned in the EULAR/ERA-EDTA recommendations for the management of adult and paediatric LN [24]. There are insufficient data to comment on other specific severe lupus manifestations at present, but rituximab is accepted as having steroid-sparing properties (three open-label studies [192, 193, 199]).

Conclusions

Overall, the LOE for rituximab from 3 systematic reviews and 30 studies, including 1RCT and 3 open-label trials for reducing lupus disease activity and for steroid-sparing properties, is 2+, and the GOR is C.

IVIG in severe SLE

Summary

IVIG has been used most in patients with refractory cytopaenias, thrombotic TTP and the catastrophic variant of APS. It can be used in pregnancy (but does not prevent heart block or fetal loss) and in patients with infection. It is rarely indicated as there is not much evidence for its use (Table 2).

Evidence

Much of the initial data are from case reports or small case series reporting treatment of acute events in small numbers of patients [223–226]. A systematic review and meta-analysis covering 3 controlled and 10 observational studies in SLE concluded that IVIG led to a reduction in SLE disease activity scores and a rise in complement levels in 31% of patients ($P = 0.001$, 95% CI: 22.1, 41.3) . There were insufficient data to assess response using other outcome measures, although serious adverse events were rare and mild [227]. The observational studies often did not report concomitant medication and used a variety of outcome measures and treatment regimens, as discussed below.

IVIG at a dose of 400 mg/kg/day for 5 consecutive days was used monthly for 6–24 months with some benefit in an open-label, uncontrolled trial with 12 refractory SLE patients [210]. Another open-label study [213] assessed 13 female SLE patients with a flare who received 0.4 g/kg body weight IVIG daily for 5 days. Short-term benefit was seen irrespective of concomitant therapy. IVIG–related adverse effects were mild and rare, and there was no worsening of renal function [213].

Low-dose IVIG was used to treat histologically confirmed cutaneous lupus in 12 patients starting with doses of 1 g/kg × 2, followed by 400 mg/kg monthly until disease remission or for 6 months [214]. Five patients showed complete or almost complete (>75%) clearing of their skin lesions, two had partial improvement (>50%) and three had poor responses (<50%). There were few side effects in this study, but renal patients were avoided because nephrotoxicity has been reported in other studies [397].

A retrospective chart review of 62 patients treated with low-dose IVIG (~0.5 g/kg) on average every 5 weeks for a mean of 6 courses showed a steady reduction in SLEDAI score over 8 months [215]. Patients with fever, rash, mucosal ulcers, pleurisy, pericarditis, urinary casts and urinary red cells responded in over 50% of cases, but only 30% of arthritis cases responded. Patients with thrombocytopenia, vasculitis and alopecia did not respond. Another group also found a disappointing response to IVIG in thrombocytopenia [216] in a retrospective analysis of 59 patients with immune-mediated severe thrombocytopenia, 44 of whom had definite lupus. A transient response to IVIG was reported in three patients with haemolytic anaemia in another study [217].

The effect of high-dose IVIG (30 g of sulfonated IVIG on days 1–4 and 21–24) in 12 mild to moderate active lupus patients [218] was only temporary in most patients. High-dose IVIG treatment in 17/20 (85%) SLE patients given 1–8 treatment courses consisting of 2 g/kg monthly given over 5 days [219] led to some improvement in arthritis, fever, thrombocytopenia and NP lupus [219]. A retrospective chart review of 17 patients (including 11 with SLE), with a mean follow-up of 30 months and long-term high-dose IVIG treatment monthly for 6 months then every 2–3 months [220], found that there was a significant reduction in the SLEDAI score with significant steroid-sparing effects, and remission was achieved in 12 patients [220].

A case–control study [221] compared 12 pregnant SLE patients with a history of recurrent spontaneous abortions who were on high-dose IVIG (0.5 g/kg every 3–33 weeks) with 12 similar patients treated with prednisolone and NSAIDs. Patients in the IVIG group stopped prednisolone ($n = 4$) and NSAIDs ($n = 9$). Disease activity decreased by the end of pregnancy ($P < 0.0001$) and there was a reduction in autoantibodies and normalization of complement levels in the IVIG group. Such improvements were not seen in the control group, and there were three fetal losses due to spontaneous abortion in this group compared with none in the IVIG group. However, other studies

have not confirmed that IVIG can prevent fetal loss [239], and it is possible that NSAIDs contributed to fetal loss in the control group [240].

A multicentre, prospective, open-label study of pregnant women with anti-SSA/Ro antibodies in the mother and birth of a previous child with CHB/neonatal lupus rash was undertaken to determine whether IVIG (400 mg/kg) given every 3 weeks from weeks 12 to 24 of gestation could prevent the development of CHB [211]. CHB was detected at 19, 20 and 25 weeks in 3 babies at a stage when 20 mothers had completed the IVIG protocol before the trial was stopped. An additional child without CHB developed a transient rash consistent with neonatal lupus [211]. Another European prospective study showed similar results [212].

A large retrospective, single-centre cohort study was published by Camara in 2014 [222], which included 52 SLE patients with predominantly cutaneous, haematological, NP and cardiac manifestations who received at least one cycle of IVIG (400 mg/kg/day for 5 days). IVIG was given to 27 patients with infection and active lupus disease, and 17 (63%) patients showed some response. In 18 (69%) of 26 patients with refractory active disease without infection, some response was seen also. This study was too recent to be included in the comprehensive review on the use of IVIG in rheumatic diseases [228] that covered the case–control study in pregnancy by Perricone *et al.* [221], 4 prospective open-label studies [210, 213, 215, 218, 219], a retrospective cohort study [220] in lupus and a small RCT in LN not discussed here [228].

Conclusions

IVIG, particularly the high-dose regimen, can have some beneficial effects in the short term on disease activity, but has to be continued with intermittent courses for sustained benefit to be seen and only then has steroid-sparing properties. It has a low rate of adverse events in non-renal patients, but can cause nephrotoxicity, especially with pre-existing renal disease. The evidence supporting its use is weak compared with that of other treatments that are cheaper and easier to administer, so it should be reserved for patients in whom other treatments are contra-indicated or have failed. Overall, the LOE for IVIG in non-renal severe lupus from 2 systematic reviews (including a meta-analysis, 3 open-label trials, 10 cohort studies and 4 case series) is 2–, and the GOR is D.

Plasma exchange (plasmapharesis) for severe SLE

Summary

Plasma exchange in SLE has been used in small numbers of patients with conflicting results since the late 1970s. A systematic review was published while this paper was in preparation [238]. It is rarely indicated, because there is inadequate data to support its use except in thrombotic TTP (Table 2).

Evidence

The evidence supporting treatment with plasma exchange, which is expensive and often difficult to organize, remains poor except for thrombotic TTP [229, 398], the catastrophic variant of APS [238] and refractory neuropsychiatric, haematological and renal lupus [238]. Even for rapidly progressive glomerulonephritis, the evidence is limited [399].

Studies have shown that plasmapheresis can reduce immune complexes and anti-dsDNA antibodies, but there is a rapid rebound of complexes and antibodies to pre-treatment levels, as shown originally in 5/8 patients [230]. Marked improvement after plasma exchange was seen in 7/11 (64%) SLE patients in another study [231] lasting up to 3 years, but one (9%) patient with a severe relapse died, and plasma exchange was ineffective in 3 (27%) patients. In another small study of nine patients, 5 (56%) improved, 2 (22%) progressed to end-stage renal failure, and 2 (22%) died due to complications of severe SLE [232].

There was less support for the use of plasma exchange in SLE after a trial comparing plasma exchange in combination with CYC and CSs with standard therapy revealed no benefit from the plasma exchange for 40 patients with severe LN [400]. However, to avoid the rebound increase in autoantibodies after plasma exchange, a synchronized protocol was developed by the Lupus Plasmapharesis Study Group, consisting of plasmapheresis (3 $\times$ 60 ml/kg) followed by high-dose pulse CYC (36 mg/kg) then 6 months of oral immunosuppression. This treatment led to rapid improvement in disease activity in the initial 14 patients with various severe SLE manifestations, sufficient for immunosuppressants including CSs to be withdrawn in 12 (86%) patients at 6 months. Treatment-free clinical remission was sustained in 8 (57%) patients for a mean of 5.6 years [233]. However, there has been concern that improvements seen in this and 2 other uncontrolled studies [234, 235] with 23 patients may have been due to the concomitant immunosuppressants. It is notable that the Lupus Plasmapharesis Study Group never reported on the final disappointing results of a randomized international multicentre trial comparing their synchronized protocol [233] with the administration of pulse CYC alone.

The evidence for treating patients who have diffuse alveolar haemorrhage, thrombotic TTP or catastrophic APS with lupus is predominantly from case reports and small case series [229, 236, 237]. Given the high mortality in TTP in general, but especially with lupus [229, 398], it is essential that patients with TTP are referred early for plasma exchange and specialist care [398, 401]. Further details about the experience with and potential use of plasma exchange and immunoadsorption in lupus and APS, including LN, are covered by the systematic review [238].

Conclusions

There remains a need for further research to better define the patients who are most likely to benefit from plasma exchange, but in general they are considered to be those who have TTP, severe refractory disease or contra-indications to conventional treatment (such as pregnancy). Overall, the LOE for plasma exchange for the treatment of non-renal severe lupus from one systematic review and

Table 8 Research priorities to improve the management of lupus patients

Analysis of the BILAG Biologics Register data is needed to assess the efficacy and safety of using rituximab for treating refractory lupus disease, administered according to the NHS England Interim Clinical Commissioning Policy Statement.
Analysis of the BILAG Biologics Register should also provide some data on the use of MMF in non-renal lupus patients; this is needed to support data from previous renal trials.
More research into stratified and personalised medicine and the cost-effectiveness of immunosuppressive drugs in lupus patients is warranted to help identify which drug will be most suitable for an individual.
Trials of immunosuppressive regimens and biologic therapies that will significantly reduce the need for CSs are needed in renal and non-renal lupus patients.
The cost-effectiveness and value of monitoring drug levels in order to improve adherence/compliance with drug therapy and improve the outcome in terms of reduced disease activity, damage and steroid usage should be investigated (e.g. for HCQ, MMF).
The role of IVIG and plasma exchange in the management of lupus patients requires further evaluation.
More data are required on the long-term outcome for children born to mothers with lupus who were exposed to drugs used pre-conception, while pregnant and/or while breast-feeding.

NHS: National Health Service.

nine studies is weak [3], and the GOR is D, but for TTP it is strongly recommended (grade B), as for non-lupus patients with TTP.

Applicability and utility

Implementation

Diagnosis and assessment of lupus can be difficult due to multisystem involvement and variable laboratory and serological test results. These guidelines will increase knowledge and raise the standard of care for patients with lupus. Only HCQ, CSs and belimumab are licensed treatments for lupus. The evidence for the treatment options discussed in this guideline, which reflect current best practice, has increased considerably in the last 10 years, although there is still relatively little evidence from high-quality RCTs. There should be no barriers to implementation, apart from limitations on the funding for rituximab and belimumab discussed in the relevant sections. The guidelines will be widely presented at local, regional and national meetings for health professionals and patients, carers and supporters of relevant charities.

Key standards of care

Lupus patients should be referred to a physician with experience in managing lupus who can confirm the diagnosis, assess the level of disease activity and provide advice on treatment and monitoring of the disease, its complications and side effects of therapy. Managing immunosuppressive therapies and their potential toxicities in patients with lupus can be a considerable challenge due to the risk of infection, difficulties with attribution of cytopenias to lupus or cytotoxic drugs, and difficulties in distinguishing manifestations of lupus disease activity from damage and co-morbid conditions. Input from a multidisciplinary team including nurse specialists and physiotherapists is usually required, and management may involve a variety of specialists, including rheumatologists, nephrologists, dermatologists, haematologists, cardiologists, chest physicians, neurologists, obstetricians, podiatrists and occupational therapists working as part of collaborative clinical networks involving regional specialist centres, local hospitals and GPs.

It is important to get patients to a low level of disease activity, if not remission, using HCQ, immunosuppressants and the least amount of CSs possible, in order to reduce cumulative damage from the disease and its treatment with CSs [71]. If drug treatment is not working within the expected time frame, it is important to consider adherence to treatment and adjusting the therapy to reduce the accumulation of chronic damage.

Patients need personalized advice, written information and education about the disease and its drug treatment from members of the multidisciplinary team, including specialist nurses and an individual to contact in the event of new symptoms. Additional topics covered should include sun avoidance, adequate vitamin D intake, weight control, exercise, not smoking and other measures to reduce atherosclerotic risk factors, as well as cancer screening, contraception and pregnancy planning when the disease is under good control on appropriate treatment for conception.

Future research agenda

There is a need for more evidence to support decision-making in the management of lupus patients. The guideline development group identified certain priorities for research into lupus to help address this issue, and these are shown in Table 8.

Mechanism for audit of the guideline

To assess compliance with these guidelines, an audit proforma is available on the British Society for Rheumatology website.

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Supplementary data

Supplementary data are available at Rheumatology Online.

References

1 Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008;358:929–39.

2 Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum 2010;39:257–68.

3 Wahren-Herlenius M, Dorner T. Immunopathogenic mechanisms of systemic autoimmune disease. Lancet 2013;382:819–31.

4 Rees F, Doherty M, Grainge M *et al*. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012. Ann Rheum Dis 2016;75:136–41.

5 Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. Arthritis Rheum 1995;38:551–8.

6 Somers EC, Thomas SL, Smeeth L, Schoonen WM, Hall AJ. Incidence of systemic lupus erythematosus in the United Kingdom, 1990–1999. Arthritis Rheum 2007;57:612–8.

7 Lim SS, Bayakly AR, Helmick CG *et al*. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: The Georgia Lupus Registry. Arthritis Rheumatol 2014;66:357–68.

8 Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. Lancet 2014;384:1878–88.

9 Bernatsky S, Boivin JF, Joseph L *et al*. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550–7.

10 Cervera R, Khamashta MA, Hughes GR. The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. Lupus 2009;18:869–74.

11 Lopez R, Davidson JE, Beeby MD, Egger PJ, Isenberg DA. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. Rheumatology 2012;51:491–8.

12 Sutton EJ, Davidson JE, Bruce IN. The systemic lupus international collaborating clinics (SLICC) damage index: a systematic literature review. Semin Arthritis Rheum 2013;43:352–61.

13 Yurkovich M, Vostretsova K, Chen W, Avina-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res 2014;66:608–16.

14 Bruce IN, O'Keeffe AG, Farewell V *et al*. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis 2015;74:1706–13.

15 Chambers SA, Allen E, Rahman A, Isenberg D. Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. Rheumatology 2009;48:673–5.

16 Yee CS, Su L, Toescu V *et al*. Birmingham SLE cohort: outcomes of a large inception cohort followed for up to 21 years. Rheumatology 2015;54:836–43.

17 Patel M, Clarke AM, Bruce IN, Symmons DP. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: evidence of an ethnic gradient. Arthritis Rheum 2006;54:2963–9.

18 Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. Rheumatology 2011;50:1424–30.

19 Hanly JG, O'Keeffe AG, Su L *et al*. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology 2016;55:252–62.

20 Murphy G, Lisnevskaia L, Isenberg D. Systemic lupus erythematosus and other autoimmune rheumatic diseases: challenges to treatment. Lancet 2013;382:809–18.

21 Cervera R, Khamashta MA, Font J *et al*. Morbidity and mortality in systemic lupus erythematosus during a 10-

year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine 2003;82:299–308.

22 Bertsias G, Ioannidis JP, Boletis J *et al*. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008;67:195–205.

23 Bertsias GK, Ioannidis JP, Aringer M *et al*. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010;69:2074–82.

24 Bertsias GK, Tektonidou M, Amoura Z *et al*. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771–82.

25 Hahn BH, McMahon MA, Wilkinson A *et al*. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res 2012;64:797–808.

26 Worrall JG, Snaith ML, Batchelor JR, Isenberg DA. SLE: a rheumatological view. Analysis of the clinical features, serology and immunogenetics of 100 SLE patients during long-term follow-up. Q J Med 1990;74:319–30.

27 Pons-Estel BA, Catoggio LJ, Cardiel MH *et al*. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among ''Hispanics''. Medicine 2004;83:1–17.

28 Font J, Cervera R, Ramos-Casals M *et al*. Clusters of clinical and immunologic features in systemic lupus erythematosus: analysis of 600 patients from a single center. Semin Arthritis Rheum 2004;33:217–30.

29 Isenberg D. Thirty years, five hundred patients: some lessons learned from running a lupus clinic. Lupus 2010;19:667–74.

30 Amaral B, Murphy G, Ioannou Y, Isenberg DA. A comparison of the outcome of adolescent and adult-onset systemic lupus erythematosus. Rheumatology 2014;53:1130–5.

31 Murphy G, Isenberg D. Effect of gender on clinical presentation in systemic lupus erythematosus. Rheumatology 2013;52:2108–15.

32 Bertoli AM, Vila LM, Reveille JD, Alarcon GS. Systemic lupus erythaematosus in a multiethnic US cohort (LUMINA) LIII: disease expression and outcome in acute onset lupus. Ann Rheum Dis 2008;67:500–4.

33 Somers EC, Marder W, Cagnoli P *et al*. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol 2014;66:369–78.

34 Urowitz MB, Gladman DD, Ibanez D *et al*. Evolution of disease burden over five years in a multicenter inception systemic lupus erythematosus cohort. Arthritis Care Res 2012;64:132–7.

35 Urowitz MB, Gladman DD, Ibanez D *et al*. American College of Rheumatology criteria at inception, and accrual over 5 years in the SLICC inception cohort. J Rheumatol 2014;41:875–80.

36 Sherer Y, Gorstein A, Fritzler MJ, Shoenfeld Y. Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients. Semin Arthritis Rheum 2004;34:501–37.

37 Ippolito A, Wallace DJ, Gladman D *et al*. Autoantibodies in systemic lupus erythematosus: comparison of historical and current assessment of seropositivity. Lupus 2011;20:250–5.

38 McHardy KC, Horne CH, Rennie J. Antinuclear antibody-negative systemic lupus erythematosus-how common? J Clin Pathol 1982;35:1118–21.

39 Riboldi P, Gerosa M, Moroni G *et al*. Anti-DNA antibodies: a diagnostic and prognostic tool for systemic lupus erythematosus? Autoimmunity 2005;38:39–45.

40 Jaekell HP, Trabandt A, Grobe N, Werle E. Anti-dsDNA antibody subtypes and anti-C1q antibodies: toward a more reliable diagnosis and monitoring of systemic lupus erythematosus and lupus nephritis. Lupus 2006;15:335–45.

41 Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. Lancet 2013;382:797–808.

42 Mok CC. Investigations and management of gastrointestinal and hepatic manifestations of systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2005;19:741–66.

43 Swaak AJ, Groenwold J, Bronsveld W. Predictive value of complement profiles and anti-dsDNA in systemic lupus erythematosus. Ann Rheum Dis 1986;45:359–66.

44 Ho A, Barr SG, Magder LS, Petri M. A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. Arthritis Rheum 2001;44:2350–7.

45 Illei GG, Takada K, Parkin D *et al*. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. Arthritis Rheum 2002;46:995–1002.

46 Tseng CE, Buyon JP, Kim M *et al*. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:3623–32.

47 Danowski A, de Azevedo MN, de Souza Papi JA, Petri M. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. J Rheumatol 2009;36:1195–9.

48 Nikpour M, Urowitz MB, Ibanez D, Gladman DD. Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. Arthritis Rheum 2009;61:1152–8.

49 Mirzayan MJ, Schmidt RE, Witte T. Prognostic parameters for flare in systemic lupus erythematosus. Rheumatology 2000;39:1316–9.

50 Zecevic RD, Vojvodic D, Ristic B *et al*. Skin lesions—an indicator of disease activity in systemic lupus erythematosus?. Lupus 2001;10:364–7.

51 Birnbaum J, Petri M, Thompson R, Izbudak I, Kerr D. Distinct subtypes of myelitis in systemic lupus erythematosus. Arthritis Rheum 2009;60:3378–87.

52 Ziakas PD, Giannouli S, Zintzaras E, Tzioufas AG, Voulgarelis M. Lupus thrombocytopenia: clinical implications and prognostic significance. Ann Rheum Dis 2005;64:1366–9.

53 Vila LM, Alarcon GS, McGwin G Jr *et al*. Systemic lupus erythematosus in a multiethnic US cohort, XXXVII: association of lymphopenia with clinical manifestations, serologic abnormalities, disease activity, and damage accrual. Arthritis Rheum 2006;55:799–806.

54 Bertoli AM, Vila LM, Apte M *et al*. Systemic lupus erythematosus in a multiethnic US cohort LUMINA LI: anaemia as a predictor of disease activity and damage accrual. Rheumatology 2007;46:1471–6.

55 Laustrup H, Voss A, Green A, Junker P. SLE disease patterns in a Danish population-based lupus cohort: an 8-year prospective study. Lupus 2010;19:239–46.

56 Esdaile J, Abrahamowicz M, Joseph L *et al*. Laboratory tests as predictors of disease exacerbations in systemic lupus erythematosus. Why some tests fail. Arthritis Rheum 1996;39:370–8.

57 Zhao H, Li S, Yang R. Thrombocytopenia in patients with systemic lupus erythematosus: significant in the clinical implication and prognosis. Platelets 2010;21:380–5.

58 Petri M, Singh S, Tesfasyone H, Malik A. Prevalence of flare and influence of demographic and serologic factors on flare risk in systemic lupus erythematosus: a prospective study. J Rheumatol 2009;36:2476–80.

59 ter Borg EJ, Horst G, Hummel EJ, Limburg PC, Kallenberg CG. Measurement of increases in anti-double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus erythematosus. A long-term, prospective study. Arthritis Rheum 1990;33:634–43.

60 Bootsma H, Spronk P, Derksen R *et al*. Prevention of relapses in systemic lupus erythematosus. Lancet 1995;345:1595–9.

61 Walz LeBlanc BA, Gladman DD, Urowitz MB. Serologically active clinically quiescent systemic lupus erythematosus—predictors of clinical flares. J Rheumatol 1994;21:2239–41.

62 Steiman AJ, Gladman DD, Ibanez D, Urowitz MB. Prolonged serologically active clinically quiescent systemic lupus erythematosus: frequency and outcome. J Rheumatol 2010;37:1822–7.

63 Mok CC, Ho LY, Leung HW, Wong LG. Performance of anti-C1q, antinucleosome, and anti-dsDNA antibodies for detecting concurrent disease activity of systemic lupus erythematosus. Transl Res 2010;156:320–5.

64 Cimaz R, Spence DL, Hornberger L, Silverman ED. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. J Pediatr 2003;142:678–83.

65 Brucato A, Cimaz R, Caporali R, Ramoni V, Buyon J. Pregnancy outcomes in patients with autoimmune diseases and anti-Ro/SSA antibodies. Clin Rev Allergy Immunol 2011;40:27–41.

66 Barnes EV, Narain S, Naranjo A *et al*. High sensitivity C-reactive protein in systemic lupus erythematosus: relation to disease activity, clinical presentation and implications for cardiovascular risk. Lupus 2005;14:576–82.

67 O'Neill SG, Giles I, Lambrianides A *et al*. Antibodies to apolipoprotein A-I, high-density lipoprotein, and C-reactive protein are associated with disease activity in patients with systemic lupus erythematosus. Arthritis Rheum 2010;62:845–54.

68 Rezaieyazdi Z, Sahebari M, Hatef MR *et al*. Is there any correlation between high sensitive CRP and disease activity in systemic lupus erythematosus? Lupus 2011;20:1494–500.

69 Firooz N, Albert DA, Wallace DJ *et al*. High-sensitivity C-reactive protein and erythrocyte sedimentation rate in systemic lupus erythematosus. Lupus 2011;20:588–97.

70 Vila LM, Alarcon GS, McGwin G Jr *et al*. Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXIX. Elevation of erythrocyte sedimentation rate is associated with disease activity and damage accrual. J Rheumatol 2005;32:2150–5.

71 van Vollenhoven RF, Mosca M, Bertsias G *et al*. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis 2014;73:958–67.

72 Nossent J, Kiss E, Rozman B *et al*. Disease activity and damage accrual during the early disease course in a multinational inception cohort of patients with systemic lupus erythematosus. Lupus 2010;19:949–56.

73 Stoll T, Sutcliffe N, Mach J, Klaghofer R, Isenberg DA. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus—a 5-yr prospective study. Rheumatology 2004;43:1039–44.

74 Mosca M, Tani C, Aringer M *et al*. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis 2010;69:1269–74.

75 Plazak W, Gryga K, Dziedzic H *et al*. Influence of atorvastatin on coronary calcifications and myocardial perfusion defects in systemic lupus erythematosus patients: a prospective, randomized, double-masked, placebo-controlled study. Arthritis Res Ther 2011;13:R117.

76 Parker B, Urowitz MB, Gladman DD *et al*. Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. Ann Rheum Dis 2013;72:1308–14.

77 Ibanez D, Gladman DD, Touma Z, Nikpour M, Urowitz MB. Optimal frequency of visits for patients with systemic lupus erythematosus to measure disease activity over time. J Rheumatol 2011;38:60–3.

78 Stamp LK, Barclay M. Therapeutic drug monitoring in rheumatic diseases: utile or futile? Rheumatology 2014;53:988–97.

79 Marengo MF, Waimann CA, de Achaval S *et al*. Measuring therapeutic adherence in systemic lupus erythematosus with electronic monitoring. Lupus 2012;21:1158–65.

80 Costedoat-Chalumeau N, Galicier L, Aumaitre O *et al*. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis 2013;72:1786–92.

81 The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing

hydroxychloroquine sulfate in systemic lupus erythematosus. N Engl J Med 1991;324:150–4.

82 Williams HJ, Egger MJ, Singer JZ *et al*. Comparison of hydroxychloroquine and placebo in the treatment of the arthropathy of mild systemic lupus erythematosus. J Rheumatol 1994;21:1457–62.

83 Meinao IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. Lupus 1996;5:237–41.

84 Levy RA, Vilela VS, Cataldo MJ *et al*. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 2001;10:401–4.

85 Ruzicka T, Sommerburg C, Goerz G, Kind P, Mensing H. Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. Br J Dermatol 1992;127:513–8.

86 Bezerra EL, Vilar MJ, da Trindade Neto PB, Sato EI. Double-blind, randomized, controlled clinical trial of clofazimine compared with chloroquine in patients with systemic lupus erythematosus. Arthritis Rheum 2005;52:3073–8.

87 Cortes-Hernandez J, Ordi-Ros J, Paredes F *et al*. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology 2002;41:643–50.

88 Wozniacka A, Lesiak A, Narbutt J, McCauliffe DP, Sysa-Jedrzejowska A. Chloroquine treatment influences proinflammatory cytokine levels in systemic lupus erythematosus patients. Lupus 2006;15:268–75.

89 Costedoat-Chalumeau N, Amoura Z, Hulot JS *et al*. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. Arthritis Rheum 2006;54:3284–90.

90 Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum 2006;54:3640–7.

91 Yokogawa N, Tanikawa A, Amagai M *et al*. Response to hydroxychloroquine in Japanese patients with lupus-related skin disease using the cutaneous lupus erythematosus disease area and severity index (CLASI). Mod Rheumatol 2013;23:318–22.

92 Barber CE, Geldenhuys L, Hanly JG. Sustained remission of lupus nephritis. Lupus 2006;15:94–101.

93 Kasitanon N, Fine DM, Haas M, Magder LS, Petri M. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. Lupus 2006;15:366–70.

94 Wahie S, Daly AK, Cordell HJ *et al*. Clinical and pharmacogenetic influences on response to hydroxychloroquine in discoid lupus erythematosus: a retrospective cohort study. J Invest Dermatol 2011;131:1981–6.

95 Tsakonas E, Joseph L, Esdaile JM *et al*. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. Lupus 1998;7:80–5.

96 Costedoat-Chalumeau N, Amoura Z, Hulot JS *et al*. Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. Ann Rheum Dis 2007;66:821–4.

97 Costedoat-Chalumeau N, Amoura Z, Duhaut P *et al*. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Arthritis Rheum 2003;48:3207–11.

98 Buchanan NM, Khamashta MA, Morton KE *et al*. A study of 100 high risk lupus pregnancies. Am J Reprod Immunol 1992;28:192–4.

99 Abarientos C, Sperber K, Shapiro DL *et al*. Hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis and its safety in pregnancy. Expert Opin Drug Saf 2011;10:705–14.

100 Diav-Citrin O, Blyakhman S, Shechtman S, Ornoy A. Pregnancy outcome following *in utero* exposure to hydroxychloroquine: a prospective comparative observational study. Reprod Toxicol 2013;39:58–62.

101 Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Ann Rheum Dis 2009;68:238–41.

102 Jung H, Bobba R, Su J *et al*. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. Arthritis Rheum 2010;62:863–8.

103 Izmirly PM, Kim MY, Llanos C *et al*. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. Ann Rheum Dis 2010;69:1827–30.

104 Pons-Estel GJ, Alarcon GS, McGwin G Jr *et al*. Protective effect of hydroxychloroquine on renal damage in patients with lupus nephritis: LXV, data from a multiethnic US cohort. Arthritis Rheum 2009;61:830–9.

105 Kasitanon N, Intaniwet T, Wangkaew S *et al*. The clinically quiescent phase in early-diagnosed SLE patients: inception cohort study. Rheumatology 2015;54:868–75.

106 Andrade RM, Alarcon GS, Gonzalez LA *et al*. Seizures in patients with systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA LIV). Ann Rheum Dis 2008;67:829–34.

107 González LA, Pons-Estel GJ, Zhang J, Vilá LM, Reveille JD, Alarcón GS; LUMINA study group. Time to neuropsychiatric damage occurrence in LUMINA (LXVI): a multi-ethnic lupus cohort. Lupus 2009;18:822–30.

108 Pons-Estel GJ, Alarcón GS, Gonzalez LA *et al*. Possible protective effect of hydroxychloroquine on delaying the occurrence of integument damage in lupus: LXXI, data from a multiethnic cohort. Arthritis Care Res 2010;62:393–400.

109 Molad Y, Gorshtein A, Wysenbeek AJ *et al*. Protective effect of hydroxychloroquine in systemic lupus erythematosus. Prospective long-term study of an Israeli cohort. Lupus 2002;11:356–61.

110 Fessler BJ, Alarcón GS, McGwin G Jr *et al*. Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. Arthritis Rheum 2005;52:1473–80.

111 Hernandez-Cruz B, Tapia N, Villa-Romero AR, Reyes E, Cardiel MH. Risk factors associated with mortality in systemic lupus erythematosus. A case–control study in a tertiary care center in Mexico City. Clin Exp Rheumatol 2001;19:395–401.

112 Alarcón GS, McGwin G, Bertoli AM *et al*. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). Ann Rheum Dis 2007;66:1168–72.

113 Petri M. Hydroxychloroquine use in the Baltimore Lupus Cohort: effects on lipids, glucose and thrombosis. Lupus 1996;5 (Suppl 1):S16–22.

114 Zhang CY, Lu LJ, Li FH *et al*. Evaluation of risk factors that contribute to high prevalence of premature atherosclerosis in Chinese premenopausal systemic lupus erythematosus patients. J Clin Rheumatol 2009;15:111–6.

115 Wang C, Fortin PR, Li Y *et al*. Discontinuation of antimalarial drugs in systemic lupus erythematosus. J Rheumatol 1999;26:808–15.

116 Morand EF, McCloud PI, Littlejohn GO. Continuation of long term treatment with hydroxychloroquine in systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis 1992;51:1318–21.

117 Fernandez M, McGwin G Jr, Bertoli AM *et al*. Discontinuation rate and factors predictive of the use of hydroxychloroquine in LUMINA, a multiethnic US cohort (LUMINA XL). Lupus 2006;15:700–4.

118 Tsang ASM, Bultink IE, Voskuyl AE. Long-term evaluation of antimalarials in a Dutch SLE cohort: intolerance and other reasons for non-use. Clin Exp Rheumatol 2014;32:95–100.

119 Wozniacka A, Cygankiewicz I, Chudzik M, Sysa-Jedrzejowska A, Wranicz JK. The cardiac safety of chloroquine phosphate treatment in patients with systemic lupus erythematosus: the influence on arrhythmia, heart rate variability and repolarization parameters. Lupus 2006;15:521–5.

120 Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res 2010;62:775–84.

121 Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis 2010;69:20–8.

122 Chasset F, Frances C, Barete S, Amoura Z, Arnaud L. Influence of smoking on the efficacy of antimalarials in cutaneous lupus: a meta-analysis of the literature. J Am Acad Dermatol 2015;72:634–9.

123 Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol 1999;26:1275–9.

124 Fortin PR, Abrahamowicz M, Ferland D *et al*. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2008;59:1796–804.

125 Islam MN, Hossain M, Haq SA *et al*. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. Int J Rheum Dis 2012;15:62–8.

126 Wilson K, Abeles M. A 2 year, open ended trial of methotrexate in systemic lupus erythematosus. J Rheumatol 1994;21:1674–7.

127 Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M. Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). Ann Rheum Dis 1997;56:382–5.

128 Kipen Y, Littlejohn GO, Morand EF. Methotrexate use in systemic lupus erythematosus. Lupus 1997;6:385–9.

129 Rahman P, Humphrey-Murto S, Gladman DD, Urowitz MB. Efficacy and tolerability of methotrexate in antimalarial resistant lupus arthritis. J Rheumatol 1998;25:243–6.

130 Miyawaki S, Nishiyama S, Aita T, Yoshinaga Y. The effect of methotrexate on improving serological abnormalities of patients with systemic lupus erythematosus. Mod Rheumatol 2013;23:659–66.

131 Wilke WS, Krall PL, Scheetz RJ *et al*. Methotrexate for systemic lupus erythematosus: a retrospective analysis of 17 unselected cases. Clin Exp Rheumatol 1991;9:581–7.

132 Wise CM, Vuyyuru S, Roberts WN. Methotrexate in nonrenal lupus and undifferentiated connective tissue disease—a review of 36 patients. J Rheumatol 1996;23:1005–10.

133 Pego-Reigosa JM, Cobo-Ibáñez T, Calvo-Alén J *et al*. Efficacy and safety of nonbiologic immunosuppressants in the treatment of nonrenal systemic lupus erythematosus: a systematic review. Arthritis Care Res 2013;65:1775–85.

134 Horizon AA, Wallace DJ. Risk:benefit ratio of nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. Expert Opin Drug Saf 2004;3:273–8.

135 Kuhn A, Gensch K, Haust M *et al*. Photoprotective effects of a broad-spectrum sunscreen in ultraviolet-induced cutaneous lupus erythematosus: a randomized, vehicle-controlled, double-blind study. J Am Acad Dermatol 2011;64:37–48.

136 Vila LM, Mayor AM, Valentin AH *et al*. Association of sunlight exposure and photoprotection measures with clinical outcome in systemic lupus erythematosus. P R Health Sci J 1999;18:89–94.

137 Stege H, Budde MA, Grether-Beck S, Krutmann J. Evaluation of the capacity of sunscreens to photoprotect lupus erythematosus patients by employing the photoprovocation test. Photodermatol Photoimmunol Photomed 2000;16:256–9.

138 Patsinakidis N, Wenzel J, Landmann A *et al*. Suppression of UV-induced damage by a liposomal sunscreen: a prospective, open-label study in patients with cutaneous lupus erythematosus and healthy controls. Exp Dermatol 2012;21:958–61.

139 Zahn S, Graef M, Patsinakidis N *et al*. Ultraviolet light protection by a sunscreen prevents interferon-driven skin inflammation in cutaneous lupus erythematosus. Exp Dermatol 2014;23:516–8.

140 Herzinger T, Plewig G, Rocken M. Use of sunscreens to protect against ultraviolet-induced lupus erythematosus. Arthritis Rheum 2004;50:3045–6.

141 Callen JP, Roth DE, McGrath C, Dromgoole SH. Safety and efficacy of a broad-spectrum sunscreen in patients with discoid or subacute cutaneous lupus erythematosus. Cutis 1991;47:130–6.

142 Danowski A, Magder L, Petri M. Flares in lupus: Outcome Assessment Trial (FLOAT), a comparison between oral methylprednisolone and intramuscular triamcinolone. J Rheumatol 2006;33:57–60.

143 Edwards JC, Snaith ML, Isenberg DA. A double blind controlled trial of methylprednisolone infusions in systemic lupus erythematosus using individualised outcome assessment. Ann Rheum Dis 1987;46:773–6.

144 Mackworth-Young CG, David J, Morgan SH, Hughes GR. A double blind, placebo controlled trial of intravenous methylprednisolone in systemic lupus erythematosus. Ann Rheum Dis 1988;47:496–502.

145 Ballou SP, Khan MA, Kushner I. Intravenous pulse methylprednisolone followed by alternate day corticosteroid therapy in lupus erythematosus: a prospective evaluation. J Rheumatol 1985;12:944–8.

146 Isenberg DA, Morrow WJ, Snaith ML. Methyl prednisolone pulse therapy in the treatment of systemic lupus erythematosus. Ann Rheum Dis 1982;41:347–51.

147 Eyanson S, Passo MH, Aldo-Benson MA, Benson MD. Methylprednisolone pulse therapy for nonrenal lupus erythematosus. Ann Rheum Dis 1980;39:377–80.

148 Badsha H, Kong KO, Lian TY *et al*. Low-dose pulse methylprednisolone for systemic lupus erythematosus flares is efficacious and has a decreased risk of infectious complications. Lupus 2002;11:508–13.

149 Sztejnbok M, Stewart A, Diamond H, Kaplan D. Azathioprine in the treatment of systemic lupus erythematosus. A controlled study. Arthritis Rheum 1971;14:639–45.

150 Sharon E, Kaplan D, Diamond HS. Exacerbation of systemic lupus erythematosus after withdrawal of azathioprine therapy. N Engl J Med 1973;288:122–4.

151 Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. Report of a prospective controlled trial in 24 patients. Ann Intern Med 1975;83:597–605.

152 Griffiths B, Emery P, Ryan V *et al*. The BILAG multicentre open randomized controlled trial comparing ciclosporin vs azathioprine in patients with severe SLE. Rheumatology 2010;49:723–32.

153 Schur PH, Christian CL. Controlled study of azathioprine in lupus. N Engl J Med 1968;278:1019–20.

154 Swaak AJ, Statius van Eps LW, Aarden LA, Feltkamp TE. Azathioprine in the treatment of systemic lupus erythematosus. A three-year prospective study. Clin Rheumatol 1984;3:285–91.

155 Oelzner P, Abendroth K, Hein G, Stein G. Predictors of flares and long-term outcome of systemic lupus erythematosus during combined treatment with azathioprine and low-dose prednisolone. Rheumatol Int 1996;16:133–9.

156 Askanase AD, Wallace DJ, Weisman MH *et al*. Use of pharmacogenetics, enzymatic phenotyping, and metabolite monitoring to guide treatment with azathioprine in patients with systemic lupus erythematosus. J Rheumatol 2009;36:89–95.

157 Fox DA, McCune WJ. Immunosuppressive drug therapy of systemic lupus erythematosus. Rheum Dis Clin North Am 1994;20:265–99.

158 Callen JP, Spencer LV, Burruss JB, Holtman J. Azathioprine. An effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. Arch Dermatol 1991;127:515–22.

159 Ginzler EM, Wofsy D, Isenberg D *et al*. Nonrenal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis: findings in a multicenter, prospective, randomized, open-label, parallel-group clinical trial. Arthritis Rheum 2010;62:211–21.

160 Dooley MA, Jayne D, Ginzler EM *et al*. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886–95.

161 Houssiau FA, D'Cruz D, Sangle S *et al*. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis 2010;69:2083–9.

162 Karim MY, Alba P, Cuadrado MJ *et al*. Mycophenolate mofetil for systemic lupus erythematosus refractory to other immunosuppressive agents. Rheumatology 2002;41:876–82.

163 Pisoni CN, Sanchez FJ, Karim Y *et al*. Mycophenolate mofetil in systemic lupus erythematosus: efficacy and tolerability in 86 patients. J Rheumatol 2005;32:1047–52.

164 Bijl M, Horst G, Bootsma H, Limburg PC, Kallenberg CG. Mycophenolate mofetil prevents a clinical relapse in patients with systemic lupus erythematosus at risk. Ann Rheum Dis 2003;62:534–9.

165 Nannini C, Crowson CS, Matteson EL, Moder KG. Mycophenolate mofetil is effective in reducing disease flares in systemic lupus erythematosus patients: a retrospective study. Lupus 2009;18:394–9.

166 Posalski JD, Ishimori M, Wallace DJ, Weisman MH. Does mycophenolate mofetil prevent extra-renal flares in systemic lupus erythematosus? Results from an observational study of patients in a single practice treated for up to 5 years. Lupus 2009;18:516–21.

167 Conti F, Ceccarelli F, Perricone C *et al*. Mycophenolate mofetil in systemic lupus erythematosus: results from a retrospective study in a large monocentric cohort and review of the literature. Immunol Res 2014;60:270–6.

168 Lourdudoss C, Vollenhoven R. Mycophenolate mofetil in the treatment of SLE and systemic vasculitis: experience at a single university center. Lupus 2014;23:299–304.

169 Bandelier C, Guerne PA, Genevay S, Finckh A, Gabay C. Clinical experience with mycophenolate mofetil in systemic autoimmune conditions refractory to common

immunosuppressive therapies. Swiss Med Wkly 2009;139:41–6.

170 Mok CC. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. Scand J Rheumatol 2007;36:329–37.

171 Jones RB, Walsh M, Chaudhry AN, Smith KG, Jayne DR. Randomized trial of enteric-coated mycophenolate sodium versus mycophenolate mofetil in multi-system autoimmune disease. Clin Kidney J 2014;7:562–8.

172 Yahya F, Jasmin R, Ng CT, Cheah TE, Sockalingam S. Open label randomized controlled trial assessing the efficacy of mycophenolate sodium against other conventional immunosuppressive agents in active systemic lupus erythematosus patients without renal involvement. Int J Rheum Dis 2013;16:724–30.

173 Dammacco F, Della Casa AO, Ferraccioli G *et al*. Cyclosporine-A plus steroids versus steroids alone in the 12-month treatment of systemic lupus erythematosus. Int J Clin Lab Res 2000;30:67–73.

174 Manger K, Kalden JR, Manger B. Cyclosporin A in the treatment of systemic lupus erythematosus: results of an open clinical study. Br J Rheumatol 1996;35:669–75.

175 Caccavo D, Lagana B, Mitterhofer AP *et al*. Long-term treatment of systemic lupus erythematosus with cyclosporin A. Arthritis Rheum 1997;40:27–35.

176 Tokuda M, Kurata N, Mizoguchi A *et al*. Effect of low-dose cyclosporin A on systemic lupus erythematosus disease activity. Arthritis Rheum 1994;37:551–8.

177 Morton SJ, Powell RJ. An audit of cyclosporin for systemic lupus erythematosus and related overlap syndromes: limitations of its use. Ann Rheum Dis 2000;59:487–9.

178 Ogawa H, Kameda H, Amano K, Takeuchi T. Efficacy and safety of cyclosporine A in patients with refractory systemic lupus erythematosus in a daily clinical practice. Lupus 2010;19:162–9.

179 Quartuccio L, Sacco S, Franzolini N *et al*. Efficacy of cyclosporin-A in the long-term management of thrombocytopenia associated with systemic lupus erythematosus. Lupus 2006;15:76–9.

180 Germano V, Picchianti DA, Ferlito C *et al*. Cyclosporine A in the long-term management of systemic lupus erythematosus. J Biol Regul Homeost Agents 2011;25:397–403.

181 Conti F, Priori R, Alessandri C *et al*. Safety profile and causes of withdrawal due to adverse events in systemic lupus erythematosus patients treated long-term with cyclosporine A. Lupus 2000;9:676–80.

182 Kusunoki Y, Tanaka N, Kaneko K *et al*. Tacrolimus therapy for systemic lupus erythematosus without renal involvement: a preliminary retrospective study. Mod Rheumatol 2009;19:616–21.

183 Suzuki K, Kameda H, Amano K *et al*. Single center prospective study of tacrolimus efficacy and safety in the treatment of various manifestations in systemic lupus erythematosus. Rheumatol Int 2011;31:757–63.

184 Tam LS, Li EK, Wong CK, Lam CW, Szeto CC. Double-blind, randomized, placebo-controlled pilot study of leflunomide in systemic lupus erythematosus. Lupus 2004;13:601–4.

185 Remer CF, Weisman MH, Wallace DJ. Benefits of leflunomide in systemic lupus erythematosus: a pilot observational study. Lupus 2001;10:480–3.

186 Barile-Fabris L, Ariza-Andraca R, Olguin-Ortega L *et al*. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis 2005;64:620–5.

187 Stojanovich L, Stojanovich R, Kostich V, Dzjolich E. Neuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). Lupus 2003;12:3–7.

188 Petri M, Brodsky RA, Jones RJ *et al*. High-dose cyclophosphamide versus monthly intravenous cyclophosphamide for systemic lupus erythematosus: a prospective randomized trial. Arthritis Rheum 2010;62:1487–93.

189 Gonzalez-Lopez L, Cardona-Munoz EG, Celis A *et al*. Therapy with intermittent pulse cyclophosphamide for pulmonary hypertension associated with systemic lupus erythematosus. Lupus 2004;13:105–12.

190 Merrill JT, Neuwelt CM, Wallace DJ *et al*. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62:222–33.

191 Merrill J, Buyon J, Furie R *et al*. Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). Lupus 2011;20:709–16.

192 Looney RJ, Anolik JH, Campbell D *et al*. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum 2004;50:2580–9.

193 Tanaka Y, Yamamoto K, Takeuchi T *et al*. A multicenter phase I/II trial of rituximab for refractory systemic lupus erythematosus. Mod Rheumatol 2007;17:191–7.

194 Ezeonyeji AN, Isenberg DA. Early treatment with rituximab in newly diagnosed systemic lupus erythematosus patients: a steroid-sparing regimen. Rheumatology 2012;51:476–81.

195 Witt M, Grunke M, Proft F *et al*. Clinical outcomes and safety of rituximab treatment for patients with systemic lupus erythematosus (SLE) – results from a nationwide cohort in Germany (GRAID). Lupus 2013;22:1142–9.

196 Iaccarino L, Bartoloni E, Carli L *et al*. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. Clin Exp Rheumatol 2015;33:449–56.

197 Tanaka Y, Takeuchi T, Miyasaka N *et al*. Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy. Mod Rheumatol 2016;26:80–6.

198 Dias SS, Rodriguez-Garcia V, Nguyen H, Pericleous C, Isenberg D. Longer duration of B cell depletion is associated with better outcome. Rheumatology 2015;54:1876–81.

199 Hickman RA, Hira-Kazal R, Yee CS, Toescu V, Gordon C. The efficacy and safety of rituximab in a chart review

study of 15 patients with systemic lupus erythematosus. Clin Rheumatol 2015;34:263–71.

200 Cobo-Ibáñez T, Loza-Santamaria E, Pego-Reigosa JM *et al*. Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus: a systematic review. Semin Arthritis Rheum 2014;44:175–85.

201 Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. Lupus 2013;22:1489–503.

202 Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA. Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. Lupus 2009;18:767–76.

203 Navarra SV, Guzman RM, Gallacher AE *et al*. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721–31.

204 Furie R, Petri M, Zamani O *et al*. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011;63:3918–30.

205 Wallace DJ, Stohl W, Furie RA *et al*. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum 2009;61:1168–78.

206 van Vollenhoven RF, Petri MA, Cervera R *et al*. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis 2012;71:1343–9.

207 Merrill JT, Ginzler EM, Wallace DJ *et al*. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Arthritis Rheum 2012;64:3364–73.

208 Ginzler EM, Wallace DJ, Merrill JT *et al*. Disease control and safety of belimumab plus standard therapy over 7 years in patients with systemic lupus erythematosus. J Rheumatol 2014;41:300–9.

209 Kandala N-B, Connock M, Grove A *et al*. Belimumab: a technological advance for systemic lupus erythematosus patients? Report of a systematic review and meta-analysis. BMJ Open 2013;3:e002852.

210 Francioni C, Galeazzi M, Fioravanti A *et al*. Long-term i.v. Ig treatment in systemic lupus erythematosus. Clin Exp Rheumatol 1994;12:163–8.

211 Friedman DM, Llanos C, Izmirly PM *et al*. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: results of a multicenter, prospective, open-label clinical trial. Arthritis Rheum 2010;62:1138–46.

212 Pisoni CN, Brucato A, Ruffatti A *et al*. Failure of intravenous immunoglobulin to prevent congenital heart block: findings of a multicenter, prospective, observational study. Arthritis Rheum 2010;62:1147–52.

213 Hundt M, Manger K, Dorner T *et al*. Treatment of acute exacerbation of systemic lupus erythematosus with high-dose intravenous immunoglobulin. Rheumatology 2000;39:1301–2.

214 Goodfield M, Davison K, Bowden K. Intravenous immunoglobulin (IVIg) for therapy-resistant cutaneous lupus erythematosus (LE). J Dermatolog Treat 2004;15:46–50.

215 Sherer Y, Kuechler S, Jose SJ *et al*. Low dose intravenous immunoglobulin in systemic lupus erythematosus: analysis of 62 cases. Isr Med Assoc J 2008;10:55–7.

216 Arnal C, Piette JC, Leone J *et al*. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. J Rheumatol 2002;29:75–83.

217 Gomard-Mennesson E, Ruivard M, Koenig M *et al*. Treatment of isolated severe immune hemolytic anaemia associated with systemic lupus erythematosus: 26 cases. Lupus 2006;15:223–31.

218 Schroeder JO, Zeuner RA, Euler HH, Loffler H. High dose intravenous immunoglobulins in systemic lupus erythematosus: clinical and serological results of a pilot study. J Rheumatol 1996;23:71–5.

219 Levy Y, Sherer Y, Ahmed A *et al*. A study of 20 SLE patients with intravenous immunoglobulin—clinical and serologic response. Lupus 1999;8:705–12.

220 Zandman-Goddard G, Krauthammer A, Levy Y, Langevitz P, Shoenfeld Y. Long-term therapy with intravenous immunoglobulin is beneficial in patients with autoimmune diseases. Clin Rev Allergy Immunol 2012;42:247–55.

221 Perricone R, De CC, Kroegler B *et al*. Intravenous immunoglobulin therapy in pregnant patients affected with systemic lupus erythematosus and recurrent spontaneous abortion. Rheumatology 2008;47:646–51.

222 Camara I, Sciascia S, Simoes J *et al*. Treatment with intravenous immunoglobulins in systemic lupus erythematosus: a series of 52 patients from a single centre. Clin Exp Rheumatol 2014;32:41–7.

223 Sany J. Intravenous immunoglobulin therapy for rheumatic diseases. Curr Opin Rheumatol 1994;6:305–10.

224 De VS, Ferraccioli GF, Di PE, Bartoli E, Bombardieri S. High dose intravenous immunoglobulin therapy for rheumatic diseases: clinical relevance and personal experience. Clin Exp Rheumatol 1996;14 (Suppl 15):S85–92.

225 Engel G, van Vollenhoven RF. Treatment of severe CNS lupus with intravenous immunoglobulin. J Clin Rheumatol 1999;5:228–32.

226 Zandman-Goddard G, Levy Y, Shoenfeld Y. Intravenous immunoglobulin therapy and systemic lupus erythematosus. Clin Rev Allergy Immunol 2005;29:219–28.

227 Sakthiswary R, D'Cruz D. Intravenous immunoglobulin in the therapeutic armamentarium of systemic lupus erythematosus: a systematic review and meta-analysis. Medicine 2014;93:e86.

228 Mulhearn B, Bruce IN. Indications for IVIG in rheumatic diseases. Rheumatology 2015;54:383–91.

229 Jiang H, An X, Li Y *et al*. Clinical features and prognostic factors of thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus: a literature review of 105 cases from 1999 to 2011. Clin Rheumatol 2014;33:419–27.

230 Jones JV, Robinson MF, Parciany RK, Layfer LF, McLeod B. Therapeutic plasmapheresis in systemic lupus erythematosus. Effect on immune complexes and antibodies to DNA. Arthritis Rheum 1981;24:1113–20.

231 Blaszczyk M, Chorzelski T, Daszynski J *et al*. Plasmapheresis in the treatment of systemic lupus erythematosus. Arch Immunol Ther Exp 1981;29:769–72.

232 Habersetzer R, Samtleben W, Blumenstein M, Gurland HJ. Plasma exchange in systemic lupus erythematosus. Int J Artif Organs 1983;6 (Suppl 1):39–41.

233 Euler HH, Schroeder JO, Harten P, Zeuner RA, Gutschmidt HJ. Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide. Arthritis Rheum 1994;37:1784–94.

234 Kimura K, Tsuda H, Kwangseok Y *et al*. Study of plasma levels of soluble CD40 ligand in systemic lupus erythematosus patients who have undergone plasmapheresis. Ther Apher Dial 2005;9:64–8.

235 Bartolucci P, Bréchignac S, Cohen P, Le Guern V, Guillevin L. Adjunctive plasma exchanges to treat neuropsychiatric lupus: a retrospective study on 10 patients. Lupus 2007;16:817–22.

236 Pagnoux C, Korach JM, Guillevin L. Indications for plasma exchange in systemic lupus erythematosus in 2005. Lupus 2005;14:871–7.

237 Letchumanan P, Ng HJ, Lee LH, Thumboo J. A comparison of thrombotic thrombocytopenic purpura in an inception cohort of patients with and without systemic lupus erythematosus. Rheumatology 2009;48:399–403.

238 Kronbichler A, Brezina B, Quintana LF, Jayne DR. Efficacy of plasma exchange and immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome: a systematic review. Autoimmun Rev 2016;15:38–49.

239 Flint J, Panchal S, Hurrell A *et al*. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology 2016;55:1693–7.

240 Flint J, Panchal S, Hurrell A *et al*. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part II: analgesics and other drugs used in rheumatology practice. Rheumatology 2016;55:1698–702.

241 Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I *et al*. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. Lupus 2011;20:206–18.

242 Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. Arthritis Res Ther 2012;14:S4.

243 Smith PP, Gordon C. Systemic lupus erythematosus: clinical presentations. Autoimmun Rev 2010;10:43–5.

244 Kumar K, Chambers S, Gordon C. Challenges of ethnicity in SLE. Best Pract Res Clin Rheumatol 2009;23:549–61.

245 The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599608.

246 Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. Nat Rev Rheumatol 2010;6:358–67.

247 Sultan SM, Ioannou Y, Isenberg DA. A review of gastrointestinal manifestations of systemic lupus erythematosus. Rheumatology 1999;38:917–32.

248 Peponis V, Kyttaris VC, Tyradellis C, Vergados I, Sitaras NM. Ocular manifestations of systemic lupus erythematosus: a clinical review. Lupus 2006;15:3–12.

249 Sivaraj RR, Durrani OM, Denniston AK, Murray PI, Gordon C. Ocular manifestations of systemic lupus erythematosus. Rheumatology 2007;46:1757–62.

250 Papagiannuli E, Rhodes B, Wallace GR *et al*. Systemic lupus erythematosus: an update for ophthalmologists. Surv Ophthalmol 2016;61:65–82.

251 Arroyo AM, Santiago-Casas Y, McGwin G Jr *et al*. Clinical associations of anti-Smith antibodies in PROFILE: a multi-ethnic lupus cohort. Clin Rheumatol 2015;34:1217–23.

252 Pierangeli SS, de Groot PG, Dlott J *et al*. 'Criteria' aPL tests: report of a task force and preconference workshop at the 13th International Congress on Antiphospholipid Antibodies, Galveston, Texas, April 2010. Lupus 2011;20:182–90.

253 Cervera R, Serrano R, Pons-Estel GJ *et al*. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011–8.

254 Pengo V, Ruffatti A, Legnani C *et al*. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood 2011;118:4714–8.

255 Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.

256 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

257 Petri M. Review of classification criteria for systemic lupus erythematosus. Rheum Dis Clin North Am 2005;31:245–54. vi.

258 Petri M, Orbai AM, Alarcon GS *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.

259 Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. J Autoimmun 2014;48–49:10–3.

260 Pons-Estel GJ, Wojdyla D, McGwin G Jr *et al*. The American College of Rheumatology and the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus in two multiethnic cohorts: a commentary. Lupus 2014;23:3–9.

261 Ighe A, Dahlstrom O, Skogh T, Sjowall C. Application of the 2012 Systemic Lupus International Collaborating Clinics classification criteria to patients in a regional Swedish systemic lupus erythematosus register. Arthritis Res Ther 2015;17:3.

262 Ines L, Silva C, Galindo M *et al*. Classification of Systemic Lupus Erythematosus: Systemic Lupus International Collaborating Clinics Versus American College of Rheumatology Criteria. A Comparative Study of 2,055 Patients From a Real-Life, International Systemic Lupus Erythematosus Cohort. Arthritis Care Res 2015;67:1180–5.

263 Amezcua-Guerra LM, Higuera-Ortiz V, Arteaga-Garcia U, Gallegos-Nava S, Hubbe-Tena C. Performance of the 2012 Systemic Lupus International Collaborating Clinics and the 1997 American College of Rheumatology classification criteria for systemic lupus erythematosus in a real-life scenario. Arthritis Care Res 2015;67:437–41.

264 Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. Best Pract Res Clin Rheumatol 2005;19:685–708.

265 Nuttall A, Isenberg DA. Assessment of disease activity, damage and quality of life in systemic lupus erythematosus: new aspects. Best Pract Res Clin Rheumatol 2013;27:309–18.

266 Rao V, Gordon C. Advances in the assessment of lupus disease activity and damage. Curr Opin Rheumatol 2014;26:510–9.

267 NHS England. Interim Clinical Commissioning Policy Statement: rituximab for the treatment of systemic lupus erythematosus in adults (reference NHS England A13/PS/a). https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/10/a13-ps-a.pdf (1 May 2017, date last accessed).

268 Yee CS, Farewell V, Isenberg DA *et al*. The BILAG-2004 index is sensitive to change for assessment of SLE disease activity. Rheumatology 2009;48:691–5.

269 Yee CS, Cresswell L, Farewell V *et al*. Numerical scoring for the BILAG-2004 index. Rheumatology 2010;49:1665–9.

270 Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.

271 Buyon JP, Petri MA, Kim MY *et al*. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005;142(12 Pt 1):953–62.

272 The SELENA-SLEDAI index, (Appendix B). In: Tsokos G, Gordon C, Smolen J, eds. Systemic lupus erythematosus: a companion to rheumatology, 1st edn. Elsevier Science and Technology Journals, 2007: 525.

273 Ruiz-Irastorza G, Khamashta MA. Evaluation of systemic lupus erythematosus activity during pregnancy. Lupus 2004;13:679–82.

274 Yee CS, Akil M, Khamashta M *et al*. The BILAG2004-Pregnancy index is reliable for assessment of disease activity in pregnant SLE patients. Rheumatology 2012;51:1877–80.

275 Gladman DD, Urowitz MB, Goldsmith CH *et al*. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:809–13.

276 Stoll T, Gordon C, Seifert B *et al*. Consistency and validity of patient administered assessment of quality of life by the MOS SF-36; its association with disease activity and damage in patients with systemic lupus erythematosus. J Rheumatol 1997;24:1608–14.

277 McElhone K, Abbott J, Shelmerdine J *et al*. Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. Arthritis Rheum 2007;57:972–9.

278 Mosca M, Tani C, Aringer M *et al*. Development of quality indicators to evaluate the monitoring of SLE patients in routine clinical practice. Autoimmun Rev 2011;10:383–8.

279 Ward MM. Hospital experience and expected mortality in patients with systemic lupus erythematosus: a hospital level analysis. J Rheumatol 2000;27:2146–51.

280 Ward MM. Hospital experience and mortality in patients with systemic lupus erythematosus: which patients benefit most from treatment at highly experienced hospitals? J Rheumatol 2002;29:1198–206.

281 Ward MM. Association between physician volume and in-hospital mortality in patients with systemic lupus erythematosus. Arthritis Rheum 2005;52:1646–54.

282 Ward MM, Odutola JJ. Inter-hospital transfers of patients with systemic lupus erythematosus: characteristics, predictors, and outcomes. J Rheumatol 2006;33:1578–85.

283 Ruperto N, Hanrahan LM, Alarcon GS *et al*. International consensus for a definition of disease flare in lupus. Lupus 2011;20:453–62.

284 Isenberg DA, Allen E, Farewell V *et al*. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Ann Rheum Dis 2011;70:54–9.

285 Moroni G, Radice A, Giammarresi G *et al*. Are laboratory tests useful for monitoring the activity of lupus nephritis? A 6-year prospective study in a cohort of 228 patients with lupus nephritis. Ann Rheum Dis 2009;68:234–7.

286 Gladman D, Ginzler E, Goldsmith C *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.

287 Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options. Part I. J Am Acad Dermatol 2011;65:e179–93.

288 Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options. Part II. J Am Acad Dermatol 2011;65:e195–213.

289 Hebert LA, Dillon JJ, Middendorf DF, Lewis EJ, Peter JB. Relationship between appearance of urinary red blood cell/white blood cell casts and the onset of renal relapse in systemic lupus erythematosus. Am J Kidney Dis 1995;26:432–8.

290 Gordon C, Jayne D, Pusey C *et al*. European consensus statement on the terminology used in the management of lupus glomerulonephritis. Lupus 2009;18:257–63.

291 Boddana P, Webb LH, Unsworth J *et al*. Hypogammaglobulinemia and bronchiectasis in mycophenolate mofetil-treated renal transplant recipients: an emerging clinical phenomenon? Clin Transplant 2011;25:417–9.

292 Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus 2013;22:1286–94.

293 Roberts DM, Jones RB, Smith RM *et al*. Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: a case series. J Autoimmun 2015;57:24–9.

294 Cusack C, Danby C, Fallon JC *et al*. Photoprotective behaviour and sunscreen use: impact on vitamin D levels in cutaneous lupus erythematosus. Photodermatol Photoimmunol Photomed 2008;24:260–7.

295 Jacobs J, Korswagen LA, Schilder AM *et al*. Six-year follow-up study of bone mineral density in patients with systemic lupus erythematosus. Osteoporos Int 2013;24:1827–33.

296 Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. Ann Rheum Dis 2002;61:70–2.

297 Chambers SA, Charman SC, Rahman A, Isenberg DA. Development of additional autoimmune diseases in a multiethnic cohort of patients with systemic lupus erythematosus with reference to damage and mortality. Ann Rheum Dis 2007;66:1173–7.

298 Ong SG, Choy CH. Autoimmune thyroid disease in a cohort of Malaysian SLE patients: frequency, clinical and immunological associations. Lupus 2016;25:67–74.

299 Ho A, Magder LS, Barr SG, Petri M. Decreases in anti-double-stranded DNA levels are associated with concurrent flares in patients with systemic lupus erythematosus. Arthritis Rheum 2001;44:2342–9.

300 Ishizaki J, Saito K, Nawata M *et al*. Low complements and high titre of anti-Sm antibody as predictors of histopathologically proven silent lupus nephritis without abnormal urinalysis in patients with systemic lupus erythematosus. Rheumatology 2015;54:405–12.

301 Bernatsky S, Joseph L, Boivin JF *et al*. The relationship between cancer and medication exposures in systemic lupus erythaematosus: a case–cohort study. Ann Rheum Dis 2008;67:74–9.

302 Bernatsky S, Ramsey-Goldman R, Labrecque J *et al*. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 2013;42:130–5.

303 Tessier-Cloutier B, Clarke AE, Ramsey-Goldman R *et al*. Systemic lupus erythematosus and malignancies: a review article. Rheum Dis Clin North Am 2014;40:497–506, viii.

304 Bernatsky SR, Cooper GS, Mill C *et al*. Cancer screening in patients with systemic lupus erythematosus. J Rheumatol 2006;33:45–9.

305 Croyle L, Morand EF. Optimizing the use of existing therapies in lupus. Int J Rheum Dis 2015;18:129–37.

306 Al Sawah S, Zhang X, Zhu B *et al*. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus—the Hopkins Lupus Cohort. Lupus Sci Med 2015;2:e000066.

307 Toubi E, Rosner I, Rozenbaum M, Kessel A, Golan TD. The benefit of combining hydroxychloroquine with quinacrine in the treatment of SLE patients. Lupus 2000;9:92–5.

308 Cavazzana I, Sala R, Bazzani C *et al*. Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. Lupus 2009;18:735–9.

309 Chang AY, Piette EW, Foering KP *et al*. Response to antimalarial agents in cutaneous lupus erythematosus: a prospective analysis. Arch Dermatol 2011;147:1261–7.

310 Wahie S, Meggitt SJ. Long-term response to hydroxychloroquine in patients with discoid lupus erythematosus. Br J Dermatol 2013;169:653–9.

311 Frances C, Cosnes A, Duhaut P *et al*. Low blood concentration of hydroxychloroquine in patients with refractory cutaneous lupus erythematosus: a French multicenter prospective study. Arch Dermatol 2012;148:479–84.

312 Izmirly PM, Costedoat-Chalumeau N, Pisoni CN *et al*. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody associated cardiac manifestations of neonatal lupus. Circulation 2012;126:76–82.

313 Gleicher N, Elkayam U. Preventing congenital neonatal heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: a review of published literature and registered clinical trials. Autoimmun Rev 2013;12:1039–45.

314 Costedoat-Chalumeau N, Dunogue B, Leroux G *et al*. A critical review of the effects of hydroxychloroquine and chloroquine on the eye. Clin Rev Allergy Immunol 2015;49:317–26.

315 Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011;118:415–22.

316 Ding HJ, Denniston AK, Rao VK, Gordon C. Hydroxychloroquine-related retinal toxicity. Rheumatology 2015;55:957–67.

317 Sato EI. Methotrexate therapy in systemic lupus erythematosus. Lupus 2001;10:162–4.

318 Wong JM, Esdaile JM. Methotrexate in systemic lupus erythematosus. Lupus 2005;14:101–5.

319 Sakthiswary R, Suresh E. Methotrexate in systemic lupus erythematosus: a systematic review of its efficacy. Lupus 2014;23:225–35.

320 Ostensen M, Villiger PM. Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. Lupus 2000;9:566–72.

321 Lander SA, Wallace DJ, Weisman MH. Celecoxib for systemic lupus erythematosus: case series and literature review of the use of NSAIDs in SLE. Lupus 2002;11:340–7.

322 Varas-Lorenzo C, Riera-Guardia N, Calingaert B *et al*. Myocardial infarction and individual nonsteroidal anti-

inflammatory drugs meta-analysis of observational studies. Pharmacoepidemiol Drug Saf 2013;22:559–70.

323 Sanders CJ, van Weelden H, Kazzaz GA *et al*. Photosensitivity in patients with lupus erythematosus: a clinical and photobiological study of 100 patients using a prolonged phototest protocol. Br J Dermatol 2003;149:131–7.

324 NICE. Belimumab for treating active autoantibody-positive systemic lupus erythematosus: Technology Appraisal Guidance [TAG397]. https://www.nice.org.uk/guidance/ta397 (1 May 2017, date last accessed).

325 Badsha H, Edwards CJ. Intravenous pulses of methylprednisolone for systemic lupus erythematosus. Semin Arthritis Rheum 2003;32:370–7.

326 Parker BJ, Bruce IN. High dose methylprednisolone therapy for the treatment of severe systemic lupus erythematosus. Lupus 2007;16:387–93.

327 Rahman P, Humphrey-Murto S, Gladman DD, Urowitz MB. Cytotoxic therapy in systemic lupus erythematosus. Experience from a single center. Medicine 1997;76:432–7.

328 Mok CC, Lau CS, Wong RW. Treatment of lupus psychosis with oral cyclophosphamide followed by azathioprine maintenance: an open-label study. Am J Med 2003;115:59–62.

329 Haque S, Gordon C, Isenberg D *et al*. Risk factors for clinical coronary heart disease in systemic lupus erythematosus: the lupus and atherosclerosis evaluation of risk (LASER) study. J Rheumatol 2010;37:322–9.

330 Azathioprine in connective tissue disorders. Br Med J 1972;1:645–6.

331 Ginzler E, Diamond H, Kaplan D *et al*. Computer analysis of factors influencing frequency of infection in systemic lupus erythematosus. Arthritis Rheum 1978;21:37–44.

332 Jun JB, Cho DY, Kang C, Bae SC. Thiopurine S-methyltransferase polymorphisms and the relationship between the mutant alleles and the adverse effects in systemic lupus erythematosus patients taking azathioprine. Clin Exp Rheumatol 2005;23:873–6.

333 Abu-Shakra M, Shoenfeld Y. Azathioprine therapy for patients with systemic lupus erythematosus. Lupus 2001;10:152–3.

334 Marra CA, Esdaile JM, Anis AH. Practical pharmacogenetics: the cost effectiveness of screening for thiopurine s-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. J Rheumatol 2002;29:2507–12.

335 Schedel J, Godde A, Schutz E *et al*. Impact of thiopurine methyltransferase activity and 6-thioguanine nucleotide concentrations in patients with chronic inflammatory diseases. Ann N Y Acad Sci 2006;1069:477–91.

336 Avina-Zubieta JA, Galindo-Rodriguez G, Robledo I *et al*. Long-term effectiveness of danazol corticosteroids and cytotoxic drugs in the treatment of hematologic manifestations of systemic lupus erythematosus. Lupus 2003;12:52–7.

337 Chakravarty K, McDonald H, Pullar T *et al*. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 2008;47:924–5.

338 Ledingham J, Gullick N, Irving K *et al*. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology 2017;56:865–8.

339 Armenti VT, Radomski JS, Moritz MJ *et al*. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2002;121–30.

340 Saavedra MA, Sanchez A, Morales S, Angeles U, Jara LJ. Azathioprine during pregnancy in systemic lupus erythematosus patients is not associated with poor fetal outcome. Clin Rheumatol 2015;34:1211–6.

341 Lipnick RN, Karsh J, Stahl NI *et al*. Pneumococcal immunization in patients with systemic lupus erythematosus treated with immunosuppressives. J Rheumatol 1985;12:1118–21.

342 Abu-Shakra M, Press J, Varsano N *et al*. Specific antibody response after influenza immunization in systemic lupus erythematosus. J Rheumatol 2002;29:2555–7.

343 Holvast A, van AS, de HA *et al*. Studies of cell-mediated immune responses to influenza vaccination in systemic lupus erythematosus. Arthritis Rheum 2009;60:2438–47.

344 Wallin L, Quintilio W, Locatelli F *et al*. Safety and efficiency of influenza vaccination in systemic lupus erythematosus patients. Acta Reumatol Port 2009;34:498–502.

345 Lofstrom B, Backlin C, Sundstrom C, Ekbom A, Lundberg IE. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case–control study. Ann Rheum Dis 2007;66:1627–32.

346 Nyberg G, Eriksson O, Westberg NG. Increased incidence of cervical atypia in women with systemic lupus erythematosus treated with chemotherapy. Arthritis Rheum 1981;24:648–50.

347 Pisoni CN, Obermoser G, Cuadrado MJ *et al*. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol 2005;23:393–6.

348 Neumann I, Fuhrmann H, Fang IF *et al*. Association between mycophenolic acid 12-h trough levels and clinical endpoints in patients with autoimmune disease on mycophenolate mofetil. Nephrol Dial Transplant 2008;23:3514–20.

349 Appel GB, Contreras G, Dooley MA *et al*. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–12.

350 Isenberg D, Appel GB, Contreras G *et al*. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Rheumatology 2010;49:128–40.

351 Riskalla MM, Somers EC, Fatica RA, McCune WJ. Tolerability of mycophenolate mofetil in patients with systemic lupus erythematosus. J Rheumatol 2003;30:1508–12.

352 Rovin BH, Furie R, Latinis K *et al*. Efficacy and safety of rituximab in patients with active proliferative lupus

nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215–26.

353 Vital EM, Wittmann M, Edward S *et al*. Brief report: responses to rituximab suggest B cell-independent inflammation in cutaneous systemic lupus erythematosus. Arthritis Rheumatol 2015;67:1586–91.

354 Condon MB, Ashby D, Pepper RJ *et al*. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis 2013;72:1280–6.

355 Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy: a national estimate of frequency in systemic lupus erythematosus and other rheumatic diseases. Arthritis Rheum 2009;60:3761–5.

356 Md Yusof MY, Vital EM, Buch MH. B cell therapies, approved and emerging: a review of infectious risk and prevention during use. Curr Rheumatol Rep 2015;17:539.

357 Fredericks CA, Kvam KA, Bear J, Crabtree GS, Josephson SA. A case of progressive multifocal leukoencephalopathy in a lupus patient treated with belimumab. Lupus 2014;23:711–3.

358 Leblanc-Trudeau C, Masetto A, Bocti C. Progressive multifocal leukoencephalopathy associated with belimumab in a patient with systemic lupus erythematosus. J Rheumatol 2015;42:551–2.

359 Manzi S, Sanchez-Guerrero J, Merrill JT *et al*. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis 2012;71:1833–8.

360 Furie R, Petri MA, Strand V *et al*. Clinical, laboratory and health-related quality of life correlates of Systemic Lupus Erythematosus Responder Index response: a post hoc analysis of the phase 3 belimumab trials. Lupus Sci Med 2014;1:e000031.

361 Stohl W, Hiepe F, Latinis KM *et al*. Belimumab reduces autoantibodies, normalizes low complement levels, and reduces select B cell populations in patients with systemic lupus erythematosus. Arthritis Rheum 2012;64:2328–37.

362 European Medicines Agency. Assessment report Benlysta (belimumab): Procedure No. EMEA/H/C/002015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002015/WC500110152.pdf (1 May 2017, date last accessed)

363 Accessdata.FDA.gov. Prescribing information for Benlysta (belimumab).: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125370s053lbl.pdf (8 May 2017, date last accessed).

364 Steinberg AD. An approach to the use of immunosuppressive drugs in nonmalignant diseases. J Allergy Clin Immunol 1973;52:242–50.

365 Fries JF, Sharp GC, McDevitt HO, Holman HR. Cyclophosphamide therapy in systemic lupus erythematosus and polymyositis. Arthritis Rheum 1973;16:154–62.

366 Mackay IR, Mathews JD, Toh BH, Baker HW, Walker I. A sequential trial comparing cyclophosphamide and azathioprine as adjuncts in the treatment of systemic lupus erythematosus. Aust N Z J Med 1974;4:154–8.

367 Gourley MF, Austin HA III, Scott D *et al*. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996;125:549–57.

368 Houssiau FA, Vasconcelos C, D'Cruz D *et al*. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.

369 Houssiau FA, Vasconcelos C, D'Cruz D *et al*. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2010;69:61–4.

370 Contreras G, Pardo V, Leclercq B *et al*. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004;350:971–80.

371 Neuwelt CM, Lacks S, Kaye BR, Ellman JB, Borenstein DG. Role of intravenous cyclophosphamide in the treatment of severe neuropsychiatric systemic lupus erythematosus. Am J Med 1995;98:32–41.

372 Fernandes Moça Trevisani V, Castro AA, Ferreira Neves Neto J, Atallah AN. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. Cochrane Database Syst Rev 2013;2:CD002265.

373 Ramos PC, Mendez MJ, Ames PR, Khamashta MA, Hughes GR. Pulse cyclophosphamide in the treatment of neuropsychiatric systemic lupus erythematosus. Clin Exp Rheumatol 1996;14:295–9.

374 Man BL, Mok CC, Fu YP. Neuro-ophthalmologic manifestations of systemic lupus erythematosus: a systematic review. Int J Rheum Dis 2014;17:494–501.

375 Petri M, Jones RJ, Brodsky RA. High-dose cyclophosphamide without stem cell transplantation in systemic lupus erythematosus. Arthritis Rheum 2003;48:166–73.

376 Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum 2005;52:2761–7.

377 Boumpas DT, Austin HA III, Vaughan EM *et al*. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Intern Med 1993;119:366–9.

378 Martinelli R, Pereira LJ, Santos ES, Rocha H. Clinical effects of intermittent, intravenous cyclophosphamide in severe systemic lupus erythematosus. Nephron 1996;74:313–7.

379 Law WG, Thong BY, Lian TY, Kong KO, Chng HH. Acute lupus myocarditis: clinical features and outcome of an oriental case series. Lupus 2005;14:827–31.

380 van der Laan-Baalbergen NE, Mollema SA, Kritikos H *et al*. Heart failure as presenting manifestation of cardiac involvement in systemic lupus erythematosus. Neth J Med 2009;67:295–301.

381 Tokunaga M, Saito K, Kawabata D *et al*. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. Ann Rheum Dis 2007;66:470–5.

382 Ramos-Casals M, García-Hernández FJ, de Ramón E *et al*. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol 2010;28:468–76.

383 Pinto LF, Velasquez CJ, Prieto C *et al*. Rituximab induces a rapid and sustained remission in Colombian patients with severe and refractory systemic lupus erythematosus. Lupus 2011;20:1219–26.

384 Vital EM, Dass S, Buch MH *et al*. B cell biomarkers of rituximab responses in systemic lupus erythematosus. Arthritis Rheum 2011;63:3038–47.

385 Fernandez-Nebro A, de la Fuente JL, Carreno L *et al*. Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. Lupus 2012;21:1063–76.

386 Lindholm C, Borjesson-Asp K, Zendjanchi K *et al*. Longterm clinical and immunological effects of anti-CD20 treatment in patients with refractory systemic lupus erythematosus. J Rheumatol 2008;35:826–33.

387 Terrier B, Amoura Z, Ravaud P *et al*. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum 2010;62:2458–66.

388 Garcia-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M *et al*. Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. Lupus 2010;19:213–9.

389 Chen H, Zheng W, Su J *et al*. Low-dose rituximab therapy for refractory thrombocytopenia in patients with systemic lupus erythematosus—a prospective pilot study. Rheumatology 2011;50:1640–4.

390 Gottenberg JE, Guillevin L, Lambotte O *et al*. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;64:913–20.

391 Smith KG, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse, and re-treatment. Arthritis Rheum 2006;54:2970–82.

392 Catapano F, Chaudhry AN, Jones RB, Smith KG, Jayne DW. Long-term efficacy and safety of rituximab in refractory and relapsing systemic lupus erythematosus. Nephrol Dial Transplant 2010;25:3586–92.

393 Galarza C, Valencia D, Tobón GJ *et al*. Should rituximab be considered as the first-choice treatment for severe autoimmune rheumatic diseases? Clin Rev Allergy Immunol 2008;34:124–8.

394 Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology 2005;44:1542–5.

395 Reynolds JA, Toescu V, Yee CS *et al*. Effects of rituximab on resistant SLE disease including lung involvement. Lupus 2009;18:67–73.

396 Diaz-Lagares C, Croca S, Sangle S *et al*. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev 2012;11:357–64.

397 Orbach H, Tishler M, Shoenfeld Y. Intravenous immunoglobulin and the kidney—a two-edged sword. Semin Arthritis Rheum 2004;34:593–601.

398 Scully M. Trends in the diagnosis and management of TTP: European perspective. Transfus Apher Sci 2014;51:11–4.

399 Harada T, Ozono Y, Miyazaki M *et al*. Plasmapheresis in the treatment of rapidly progressive glomerulonephritis. Ther Apher 1997;1:366–9.

400 Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. N Engl J Med 1992;326:1373–9.

401 Dutt T, Scully M. A proposal: the need for thrombotic thrombocytopenic purpura Specialist Centres – providing better outcomes. Br J Haematol 2015;170:737–42.

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ORIGINAL RESEARCH

Determining early referral criteria for patients with suspected inflammatory arthritis presenting to primary care physicians: a cross-sectional study

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Objective: Early diagnosis and initiation of treatment for inflammatory arthritis can greatly improve patient outcome. We aimed to provide standardized and validated criteria for use by primary care physicians (PCPs) in the identification of individuals requiring referral to a rheumatologist.

Patients and methods: We analyzed the predictive value of a wide variety of demographic variables, patient-reported complaints, physical examination results, and biomarkers in order to identify the most useful factors for indicating a requirement for referral. Patients for this cross-sectional study were enrolled from various centers of the city of Jeddah, Saudi Arabia, if they were ≥18 years of age and presented to a PCP with small joint pain that had been present for more than 6 weeks. A total of 203 patients were enrolled, as indicated by the sample size calculation. Each patient underwent a standardized physical examination, which was subsequently compared to ultrasound findings. Biomarker analysis and a patient interview were also carried out. Results were then correlated with the final diagnosis made by a rheumatologist.

Results: A total of 9 variables were identified as having high specificity and good predictive value: loss of appetite, swelling of metacarpophalangeal joint 2 or 5, swelling of proximal interphalangeal joint 2 or 3, wrist swelling, wrist tenderness, a positive test for rheumatoid factor, and a positive test for anti-citrullinated protein antibodies.

Conclusion: Nine variables should be the basis of early referral criteria. It should aid PCPs in making appropriate early referrals of patients with suspected inflammatory arthritis, accelerating diagnosis and initiation of treatment.

Keywords: inflammatory arthritis, rheumatoid, diagnosis, primary care, early referral criteria

Introduction

Early diagnosis of inflammatory arthritis is essential for achieving the best possible outcome for patients.[1,2] It is known that initiation of pharmacological treatment at the earliest opportunity can significantly reduce disease progression.[3–5]

A primary care physician (PCP) is usually the first point of contact for a patient experiencing joint pain; however, it is generally a rheumatologist who provides the final diagnosis.[6,7] Therefore, there is a need to optimize the process of transition from the primary care center to the specialist in order to achieve a timely diagnosis.[7,8] Whilst previous studies have outlined potential criteria that could aid a PCP in identifying patients who require early referral to a rheumatology service, these have been based

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on literature searches and discussions among specialists.[2,9] There are currently no criteria that have been identified and validated using a population of arthritis patients.

A further shortcoming of previously established criteria is the lack of standardization of examination techniques. While ultrasound and magnetic resonance imaging is increasingly used to diagnose inflammatory arthritis, these are often not available in the primary care setting.[10] Therefore, the ability of a PCP to carry out an accurate musculoskeletal examination is essential for achieving a prompt referral to a rheumatologist. It has been shown that skills in this area are lacking in physicians, with improvements in training being necessary.[11–13] The introduction of standardized techniques would help in overcoming these issues.

In response to this need, a recent study defined and validated an approach to perform an effective musculoskeletal examination of the hand and wrist joints for diagnosis of inflammatory arthritis.[14] They reported that these standardized techniques could achieve sensitivities in the range of approximately 70–80% for detection of arthritis, with ultrasound used for validation. Building on these results, we here aimed to produce a set of guidelines using these standardized techniques, in addition to blood analysis, which could be the basis of criteria used by PCPs to aid the identification of patients requiring early referral to a rheumatologist.

Patients and methods

Study design

This study was conducted to find out sensitivity and specificity of variables that can be included in early referral criteria for the diagnosis of arthritis, with a hypothesis that training of PCPs regarding the criteria for early diagnosis of arthritis will increase the early referral of patients to rheumatologist; hence, estimation of sample size was essential to apply tools of statistics, given the sensitivity (80%), specificity (70%), and prevalence of the disease as 60%. We consulted a professional biostatistician, who helped us in sample size calculation and data analysis. We considered the value of design effects as 2 to calculate sample size, based on design effects and intraclass correlations.

Potential comprehensive referral criteria were decided upon by a committee consisting of 3 rheumatologists, an expert epidemiologist, and researchers after a thorough search of the literature. The help of biostatistician was sought to calculate sample size and analysis of result to accommodate loss of variability due to sampling technique. These criteria were then used by the PCP when considering a rheumatology referral (Patient Referral Form A) (Figure 1). On attendance at the rheumatology clinic, each patient underwent musculoskeletal examination by a rheumatologist (Patient Referral Form B) and ultrasonography by a trained sonographer (Patient Referral Form C), with each examiner blinded to the findings of the other and to those of the PCP. Patients also underwent blood testing at both a regional laboratory and Fakeeh Hospital. A final diagnosis was made by the rheumatologist after reviewing the findings documented on the referral forms and those of the blood work. The association of each variable in the comprehensive referral criteria with an arthritis diagnosis was then determined using statistical analysis. A final set of variables highly correlated with the final diagnosis of arthritis was then established. These should be the basis of validated referral criteria. The question of how to use these variables by a PCP is not addressed in this paper.

Setting and patients

This cross-sectional study was conducted at primary health care centers (PHC) under the auspices of the Administration of Public Health within the Ministry of Health in Jeddah (Saudi Arabia).

Jeddah is second largest city of KSA and the largest sea port at Red Sea with a population of about 3.4 million. There are total of 39 PHC centers in four regions of Jeddah. At first stage, four PHC centers were selected by adopting simple random sampling technique among the total 39 PHC centers, one from each region, followed by selection of all those patients who met eligibility criteria. There were 3 rheumatologists and 40 PCPs enrolled in the study to find out the sensitivity and specificity of early referral criteria. There was only one ultrasonography (US), who did ultrosonology on all patients. US data were not used for the referral variables but helped in reaching final diagnosis and were part of four categories of variables used to conclude about the state of arthritis, which were as follows:

1. data from ultrasound examination,
2. findings of rheumatologist,
3. laboratory findings
4. findings of PCP.

Patients were enrolled if they were ≥18 years of age and presented to a PCP with small joint pain that had been present for more than 6 weeks. Patients were excluded if they had an established rheumatological diagnosis or had osteoarthritis of the hands, which was either previously diagnosed or presented as bony swellings over the distal inter-phalangeal or

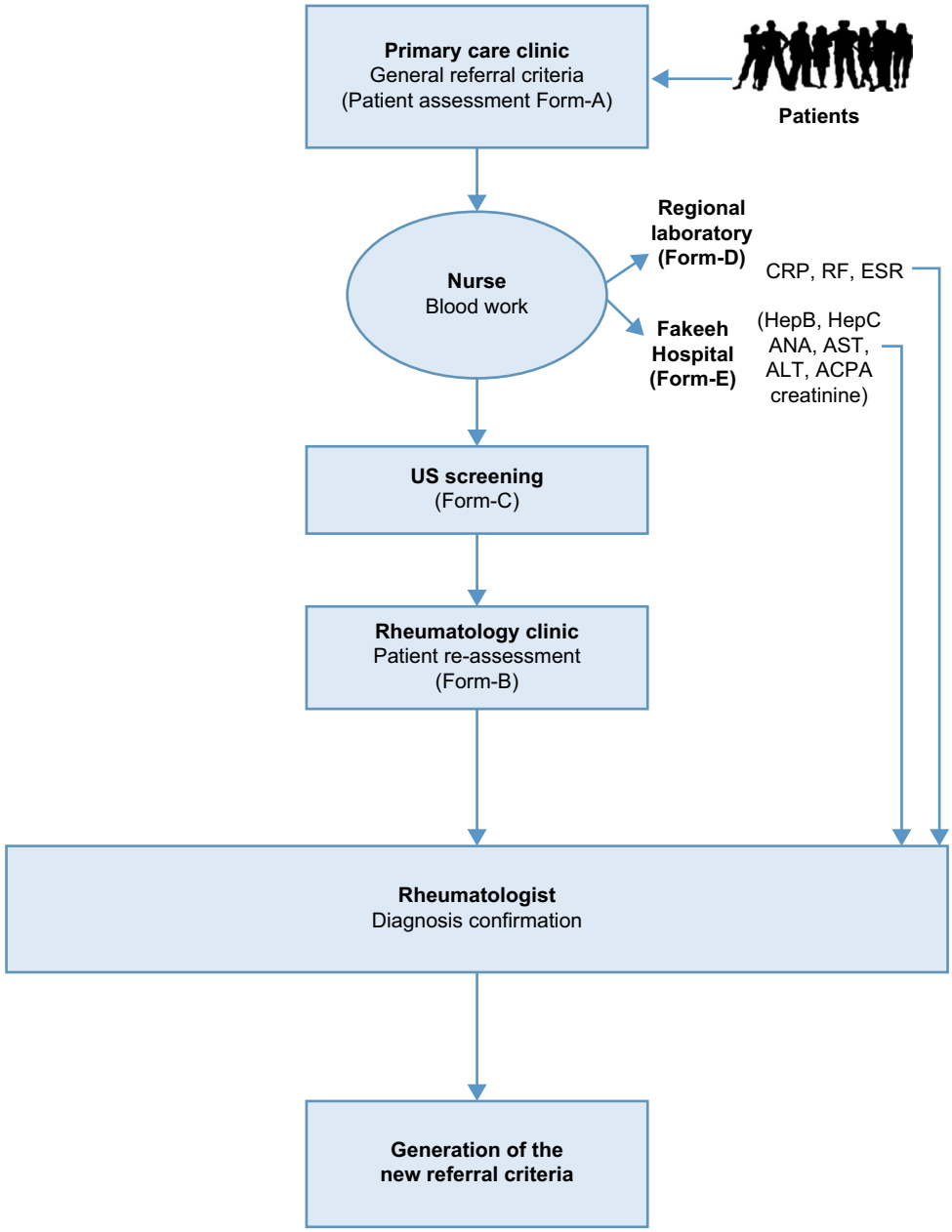


Figure 1 Study design.
Abbreviations: CPR, C-reactive protein; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; Hep, hepatitis; ANA, antinuclear antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACPA, anti-citrullinated protein antibodies; US, ultrasonography.

proximal inter-phalangeal (PIP) joints. A history of hand and/or wrist fracture was a further exclusion criterion.

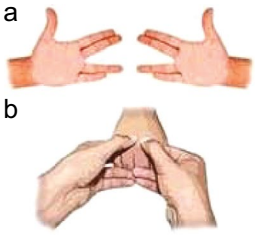
All included patients provided written informed consent, and the study received ethical approval from the institutional review boards of each participating center (Dr. Soliman Fakeeh Hospital and King Abdulaziz University Hospital), as well as the Research Administration of the Directorate of Health Affairs at the Ministry of Health. Furthermore, the study was conducted in accordance with the Declaration of Helsinki and its amendments. Consent for publishing this study was obtained from all the authors.

Examinations performed by PCPs

A standard approach for musculoskeletal examination was used by both the PCP and the rheumatologist (Figure 2). Two-days of training were conducted for every PCP, this was completed 1 week prior to initiation of the study. It was made sure by the rheumatologists, before concluding the training session, that PCPs were applying correct technique to detect musculoskeletal disorders. Ultrasonography was performed on the PIP, metacarpophalangeal (MCP), and wrist joints. Blood analysis performed at the regional laboratory consisted of assessment of levels of C-reactive protein (CRP) and rheumatoid factor

Metacarpophalangeal joint assessment – scissor technique

- A scissor-like shape is made with the fingers (a).
- The patient's hand is held from the sides at the MCP level (b).
- The MCPs are flexed to 90 degrees (b).
- The thumbs are used to palpate the joint – one to apply pressure to the joint, the other to assess for effusion, swelling, and/or tenderness (b).



Proximal inter-phalangeal joint assessment – four-finger technique

- Each PIP is held by the thumb and index finger of one hand of the examiner.
- Pressure is applied until the distal finger becomes whitened due to low blood supply.
- The thumb and index finger of the examiner's other hand are used palpate the joint to identify effusion, swelling, and/or tenderness.

Wrist palpitation – two-thumb technique

- The examiner's thumb should follow the 3rd metacarpal bone on the dorsal aspect of the hand until a dimple is reached at the capitate level.
- Continuous pressure is exerted by the thumb.
- The other thumb is used to intermittently apply pressure approximately half an inch away on the wrist joint in order to identify swelling and/or tenderness.

Figure 2 Standardized musculoskeletal examination procedures.
Note: The described techniques for physical examination should be performed by a trained clinician.
Abbreviations: MCP, metacarpophalangeal; PIP, proximal inter-phalangeal.

(RF), in addition to determination of erythrocyte sedimentation rate. Further tests at Fakeeh Hospital investigated hepatitis B and C, and levels of antinuclear antibody (ANA), aspartate aminotransferase, alanine aminotransferase, creatinine, and anti-citrullinated protein antibodies (ACPA).

A systematic multi-planar grayscale and power Doppler US examination of the PIP, MCP, and two wrist joints were performed. Ultrasonography was performed using LPGIQ 9 scanner (GE Healthcare, Milwaukee, WI, USA) with a high frequency linear array 12-MHz transducer. A standardized acquisition protocol was used in the scanning techniques and definition of pathology. Both dorsal and volar aspects of the joints were scanned. The scanning was done in three positions for each hand. The scanning was done in two positions of each hand and wrist joints. The first position was the wrist MCP and PIP joints in a posterior (dorsal) longitudinal position in relation to the probe of the US. The second position was with the wrist, MCP and PIP joints in an anterior (volar) longitudinal position in relation to the probe of the US. This test helped to reach the final diagnosis in addition to the rheumatologist findings and laboratory results.

Statistical analysis

As the objectives of the study were to find a screening tool for inflammatory arthritis that can be included in early referral criteria, the sample size was calculated based on an expected sensitivity of 80%, specificity of 70%, and prevalence of 60%, with a precision of 10% and a confidence interval of 95%.[15] An adequate sample was essential to have reasonable power of study to determine the association. To minimize the decrease variability due to sampling technique, we increased the design effect (DEFF) (which helps in direct estimation of confidence interval) to 2. This provided a sample size of 203 patients who were referred to the rheumatologist. The association between variables and a positive diagnosis of inflammatory arthritis was evaluated using chi-square test, or Fisher's exact test for the assessment of swelling of the right PIP 5, which did not fulfil chi-square criteria. These analyses were carried out using SPSS v.20 (IBM Corporation, Armonk, NY, USA). Variables that showed a significant association with diagnosis were subjected to further evaluation using the Epi 3 software (Centre of Disease Control, Atlanta, GA, USA) for analysis of data to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value, diagnostic accuracy, and likelihood ratios. The Wilson score was used to give 95% confidence intervals. Finally, the variables that should form the basis of referral criteria were finalized using logistic regression.

Results

Of the 203 patients enrolled in the study, data from 1 were excluded owing to incomplete information. Of the remaining

202 patients, 63.4% were aged 40 years or older, and 81.7% were females. No associations were found between age and sex with a positive inflammatory arthritis diagnosis (Table 1). However, in terms of patient-reported complaints, loss of appetite ($p = 0.04$), stiffness ($p = 0.02$), and a family history of uveitis ($p = 0.01$) were significantly associated (Table 1). A number of the musculoskeletal examination parameters were also found to be linked to diagnosis (Table 2), as were CRP, RF, and ACPA (Table 3).

Subsequent analysis of the variables that showed an association with a positive diagnosis indicated that 13 had a specificity greater than 90% in combination with a good PPV and likelihood ratio (Table 4). We selected a set of variables to form the basis of referral criteria. These variables were defines by applying logistic regression: loss of appetite, swelling of MCP 2 or MCP 5, swelling of PIP 2 or PIP 3, wrist swelling, wrist tenderness, RF positivity, and ACPA positivity (Table 5). We calculated percent agreement for the 6 identified referral criteria, examined by both rheumatologist and PHP, which included; MCP 2, MCP 5, PIP 2, PIP 3, wrist swelling, and wrist tenderness by applying kappa statistics and found the values as 0.229 (p-value = 0.001), 0.261 (p-value = 0.000), 0.38 (p-value = 0.000), 0.187 (p-value = 0.008), 0.425 (p-value = 0.000), and 0.479 (p-value = 0.000), respectively.

Discussion

The progressive nature of inflammatory arthritis means that a delay in diagnosis and initiation of treatment can result in a significantly poorer outcome for patients.[2,4,5,7] The time between symptom onset and diagnosis of rheumatoid arthritis by a rheumatologist in Saudi Arabia has been reported to be as high as 30 months.[16] In comparison, a French study calculated an average of 53 days between PCP visit and rheumatologist assessment.[17] In a multicenter European study, a rheumatologist found that the lag time between symptom

Table 1 Demographic and patient-reported variables with their association to positive diagnosis of inflammatory arthritis

	N	Disease status		*p*-value*
		Yes	No	
Demographics				
Sex				
Male	37	24	13	0.496
Female	165	104	61	
Age				
<40 years	74	52	22	0.081
≥40 years	128	76	52	
Patient-reported				
Loss of appetite				
Yes	31	25	6	0.04
No	171	103	68	
Stiffness				
Yes	93	51	42	0.02
No	109	77	32	
Family history of uveitis				
Yes	7	1	6	0.01
No	195	127	68	

Note: *Chi-square test.

Table 2 Musculoskeletal parameters significantly associated with a positive diagnosis of inflammatory arthritis

	N	Disease status		*p*-value
		Yes	No	
Metacarpophalangeal joints				
Swelling of MCP 2 (right)				
Yes	26	21	5	0.048
No	176	107	69	
Swelling of MCP 2 (left)				
Yes	27	23	4	0.008
No	175	105	70	
Swelling of MCP 5 (right)				
Yes	7	7	0	0.036
No	195	121	74	
Swelling of MCP 3 (left)				
Yes	26	21	5	0.036
No	176	107	69	
Tenderness of MCP 1 (right)				
Yes	57	42	15	0.038
No	145	86	59	
Tenderness of MCP 1 (left)				
Yes	61	47	14	0.006
No	141	81	60	
Tenderness of MCP 2 (left)				
Yes	73	53	20	0.028
No	129	75	54	
Proximal inter-phalangeal joints				
Swelling of PIP 2 (right)				
Yes	29	25	4	0.006
No	173	103	70	
Swelling of PIP 2 (left)				
Yes	29	25	4	0.006
No	173	103	70	
Swelling of PIP 3 (right)				
Yes	34	28	6	0.011
No	168	100	68	
Swelling of PIP 3 (left)				
Yes	32	26	6	0.027
No	170	102	68	
Swelling of PIP 5 (right)				
Yes	12	11	1	0.036*
No	190	117	73	
Wrist				
Swelling of the wrist (right)				
Yes	42	37	5	0.001
No	160	91	69	
Tenderness of the wrist (right)				
Yes	42	36	6	0.001
No	160	92	68	

Note: *p*-values calculated using the chi-square test, except *Fisher's exact test.
Abbreviations: MCP, metacarpophalangeal; PIP, proximal inter-phalangeal.

onset and assessment was approximately 24 weeks, and the time from PCP to specialist was between 2 and 10 weeks.[18]

In this study, we determined several MSK examination findings based on specified and validated techniques to be significantly associated with the early detection and referrals of arthritis by the PCP. This was in particular for techniques that were able to detect swellings not tenderness in the second MCP, fifth MCP, second PIP, third PIP, fifth PIP, and wrist joints. As expected, RF and ACPA positivity in early disease in our cohort of patients were significantly correlated with early detection. We found symptoms associated with arthritis like fatigue and morning stiffness to be not specific and showed poor PPV for early detection of arthritis by a PCP. This is a step towards creating validated early referral criteria for inflammatory arthritis.

Previous attempts to produce a set of guidelines to be used in the primary care setting have been based on literature surveys and discussions among professionals.[2,9] Emery et al specified 3 criteria, each of which indicated that a referral was appropriate for suspected rheumatoid arthritis: ≥3 swollen joints; a positive squeeze test, indicating MCP involvement; and morning stiffness of ≥30 minutes.[2] Suresh et al additionally specified fatigue or weight loss, raised inflammatory markers, and a positive test for RF as indicators for referral.[9] However, there appears to be a distinct lack of studies evalu-

Table 3 Blood parameters significantly associated with a positive diagnosis of inflammatory arthritis

	N	Disease status		*p*-value
		Yes	No	
CRP				
Positive	26	21	5	0.048
Negative	176	107	69	
RF				
Positive	28	24	4	0.008
Negative	166	99	67	
ACPA				
Positive	30	28	2	0.001
Negative	160	91	69	

Abbreviations: CRP, C-reactive protein; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies.

Table 4 Analysis of variables showing an association with a positive diagnosis of inflammatory arthritis

	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	Likelihood ratio (positive)	Likelihood ratio (negative)
Loss of appetite	19.5% (13.6–27.2)	89.47% (80.6–94.6)	75.8% (59.0–87.2)	39.8% (32.7–47.3)	45.6% (39.0–52.4)	1.9 (1.1–3.3)	0.90 (0.88–0.92)
Swelling of MCP 2 (right)	16.4% (11.0–23.8)	93.2% (85.1–97.1)	80.8% (62.1–91.5)	39.2% (32.3–46.6)	44.6% (37.9–51.5)	2.5 (1.0–5.8)	0.9 (0.9–0.9)
Swelling of MCP 2 (left)	18.0% (12.3–25.5)	94.6% (86.9–97.9)	85.2% (67.5–94.1)	40.0% (33.0–47.4)	46.0% (39.3–52.9)	3.3 (1.4–8.0)	0.9 (0.8–0.9)
Swelling of MCP 5 (right)	5.5% (2.7–10.9)	100.0% (95.1–100.0)	100.0% (64.6–100.0)	38.0% (31.4–44.9)	40.1% (33.6–47.0)	undefined	1.0 (0.9–1.0)
Swelling of PIP 2 (right)	19.5% (13.6–27.2)	94.6% (86.9–97.9)	86.2% (69.4–94.5)	40.5% (33.4–47.9)	47.0% (40.3–53.9)	3.6 (1.6–8.1)	0.9 (0.8–0.9)
Swelling of PIP 2 (left)	18.0% (12.3–25.5)	91.9% (83.4–96.2)	79.3% (61.6–90.2)	39.3% (32.3–46.7)	45.1% (38.3–51.9)	2.2 (1.1–4.5)	0.9 (0.9–0.9)
Swelling of PIP 3 (right)	21.9% (15.6–29.8)	91.9% (83.4–96.2)	82.4% (66.5–91.7)	40.5% (33.4–48.0)	47.5% (40.8–54.4)	2.7 (1.5–4.8)	0.9 (0.8–0.9)
Swelling of PIP 3 (left)	20.3% (14.3–28.1)	91.9% (83.4–96.2)	81.3% (64.7–91.1)	40.0% (32.9–47.5)	46.5% (39.8–53.4)	2.5 (1.3–4.7)	0.9 (0.8–0.9)
Swelling of PIP 5 (right)	8.6% (4.9–14.7)	98.7% (92.7–99.8)	91.7% (64.6–98.5)	38.4% (31.8–45.5)	41.6% (35.0–48.5)	6.4 (0.1–300.4)	0.9 (0.9–0.9)
Swelling of wrist (right)	28.9% (21.8–37.3)	93.2% (85.1–97.1)	88.1% (75.0–94.8)	43.1% (35.7–50.9)	52.5% (45.6–59.3)	4.3 (2.5–7.2)	0.8 (0.7–0.8)
Tenderness of wrist (right)	28.1% (21.1–36.5)	91.9% (83.4–96.2)	85.7% (72.2–93.3)	42.5% (35.1–50.3)	51.5% (44.6–58.3)	3.5 (2.2–5.5)	0.8 (0.8–0.8)
RF positive	19.5% (13.5–27.4)	94.4% (86.4–97.8)	85.7% (68.5–94.3)	40.4% (33.2–48.0)	46.9% (40.0–53.9)	3.5 (1.5–7.9)	0.9 (0.8–0.9)
ACPA positive	23.5% (16.8–31.9)	97.2% (90.3–99.2)	93.3% (78.7–98.2)	43.1% (35.7–50.9)	51.1% (44.0–58.1)	8.5 (2.5–27.9)	0.8 (0.8–0.8)

Note: 95% confidence intervals correspond to Wilson's score intervals.
Abbreviations: PPV, positive predictive value; NPV, negative predictive value; MCP, metacarpophalangeal; PIP, proximal inter-phalangeal; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies.

Table 5 Suggested variables that should be included in a referral criteria (based on variables that showed >90% specificity and good positive predictive value and likelihood ratio)

No.	Criteria	How to assess
1	Loss of appetite	History taking
2	MCP 2 swelling either in right and/or left hand	MCP scissor technique: The examiner should make a scissor-like shape with his/her fingers, joining the index and middle fingers together while joining the ring and little finger together, making a space in between. Then, the patient's hand is held from the sides at the MCP level and the MCPs are flexed to 90 degrees. Then, two free thumbs from both hands are used to palpate the joint line for every MCP joint. One thumb is pressed firmly for a power causing whitening of the distal thumb nail, while the other thumb is pushed intermittently in and out to assess for swelling (fluctuation of fluid).
3	MCP 5 swelling either in right and/or left hand	MCP scissor technique: The examiner should make a scissor-like shape with his/her fingers, joining the index and middle fingers together while joining the ring and little finger together, making a space in between. Then, the patient's hand is held from the sides at the MCP level and the MCPs are flexed to 90 degrees. Then, two free thumbs from both hands are used to palpate the joint line for every MCP joint. One thumb is pressed firmly for a power causing whitening of the distal thumb nail, while the other thumb is pushed intermittently in and out to assess for swelling (fluctuation of fluid).
4	PIP 2 swelling either in right and/or left hand	PIP 4-finger: The examiner's thumb and index finger of one hand should hold each PIP from the side and press firmly until the whitening of distal fingers from low blood supply is clear. With the thumb and index finger of the other hand, the examiner should hold the same PIP-joint from anteroposterior direction and push intermittently in and out to look for swelling (fluctuation of fluid).
5	PIP 3 swelling either in right and/or left hand	PIP 4-finger: The examiner's thumb and index finger of one hand should hold each PIP from the side and press firmly until the whitening of distal fingers from low blood supply is clear. With the thumb and index finger of the other hand, the examiner should hold the same PIP-joint from anteroposterior direction and push intermittently in and out to look for swelling (fluctuation of fluid).
6	Wrist swelling either in right and/or left hand	Wrist 2-thumbs: The examiner thumb should follow the third metacarpal bone on the dorsal aspect of the hand until reaching a dimple at the capitate level. This thumb should exert a firm, continuous pressure on this point until the whitening of the distal thumb nail is clear, with the examiner's other thumb pushing intermittently in and out just half an inch away from the other thumb on wrist joint line looking for swelling (fluctuation of fluid).
7	Wrist tenderness either in right and/or left hand	Wrist 2-thumbs: The examiner thumb should follow the third metacarpal bone on the dorsal aspect of the hand until reaching a dimple at the capitate level. This thumb should exert a firm, continuous pressure on this point until the whitening of the distal thumb nail is clear, with the examiner's other thumb pushing intermittently in and out just half an inch away from the other thumb on wrist joint line looking for tenderness (pain felt by the patient).
8	ACPA positivity	Laboratory finding
9	Rheumatoid factor positivity	Laboratory finding

Notes: In adult patients ≥18 years of age who present with small joint pain to PCPs, these variables correlated with the final diagnosis of arthritis. Further research work is needed to determine how to use these variables in clinical practice.
Abbreviations: MCP, metacarpophalangeal; PIP, proximal inter-phalangeal; ACPA, anti-citrullinated protein antibodies; PCPs, primary care physicians.

ating the predictive ability of these referral criteria when used by a PCP. To address this deficiency in information, we assessed a large selection of potential indicators of early inflammatory arthritis, including demographic factors, patient-reported complaints, physical examination results, and blood analysis for patients referred to a rheumatologist by their PCP. While no demographic factors were found to be associated with a positive diagnosis, patient-reported loss of appetite, stiffness, and a family history of uveitis showed a statistically significant relationship. After further analysis, loss of appetite was demonstrated to have high specificity and a good PPV, indicating that it would be a useful indicator when used with other similar variables of a need for a rheumatology referral for a patient with suspected inflammatory arthritis.

Using standardized musculoskeletal examination procedures, the identification of swelling in certain joints was found to be indicative of inflammatory arthritis. Swelling of MCP

2 and 5, and PIP 2 and 3 showed high specificity with high PPVs, while joint tenderness was not found to be a useful factor. A previous study identified MCP 2 and 3, and PIP 3 with the wrist as being the joints most frequently involved in arthritis.[14] Furthermore, the authors reported that swelling resulted in superior sensitivity in comparison to tenderness, albeit with poorer specificity. The wrist joint has been also described as one of the most commonly involved joints.[14] In the present analysis, both swelling and tenderness of the wrist were significantly associated with a diagnosis of inflammatory arthritis, providing the highest sensitivities of all the variables investigated.

Out of the large number of factors investigated using blood analysis, RF and ACPA were identified as having the greatest predictive value. Both of these markers have previously been demonstrated to be indicative of rheumatoid arthritis, and have been linked to disease severity.[19] ACPA has been demonstrated to be the more accurate of the two markers for identifying rheumatoid arthritis, and has been shown to be present much earlier than RF, even before clinical manifestations have become apparent.[20,21] Our data demonstrate that routine testing for RF and ACPA should be carried out for patients suspected of having inflammatory arthritis, with a positive result being strongly predictive when used with other variables of a need for referral to a rheumatologist. ANA testing in this cohort of patients did not correlate with the final diagnosis of arthritis.

Future research work will assess in particular the validity of these 9 highly correlated variables (Table 5) when used by the PCP in routine clinical practice. It should be noted that the individual variables in this current study were evaluated separately. The question of how many of these variables should be present in order to consider referring the patient to a rheumatologist is not answered here. Therefore, the presence of a single variable should alert the PCP to the potential for inflammatory arthritis, with the discovery of more than one variable indicating an even greater need for a rapid rheumatology referral. Loss of appetite by itself in a patient with small joint pain may not justify the early referral to a rheumatologist based on improper application of the findings of this study. These variables then need to be tested collectively in a separate study to determine how many of them should be present to justify early referral. It is then that the definitive criteria can be determined.

A recent systematic literature review identified areas of delay to care for patients with inflammatory arthritis and potential solutions for each.[22] One of these areas was from primary care to rheumatology referral[22] with several suggested solutions including patient self-administered questionnaires[23,24] and use of Gait, Arms, Legs and Spine screening examination by physical therapists to detect RA.[25] Other areas of delay were from rheumatology referral to rheumatology assessment with several solutions including triage of referrals, referral forms, triage clinics, rapid access services, and early arthritis clinics.[22] In a multicenter retrospective cohort of RA patients, only 41% of patients with RA were started on therapy within 6 months of presumed onset of disease, and 78% of the delay was attributable to processes/events that occurred before the patients ever saw a rheumatologist.[26]

Another potential reason for extended referral delays is poor musculoskeletal examination technique in the primary care setting, with improved training during medical school and continuing education programs being advocated.[11] Furthermore, there is a lack of standardized methodology and defined competencies in MSK examination for use in the diagnosis of inflammatory arthritis.[14,27,28]

We think this study is unique in its design as it was based on a strict methodology among group of patients attending primary care centers in Saudi Arabia. All PCPs received training in performing the specified techniques included in this study. The findings of this study can be utilized to create definitive criteria shortening the delay in referrals. Further efforts should be made by whatever approach determined by local health authorities to assure early rheumatology clinic evaluation. It is hoped that the dream of early referral and management of patients with arthritis could become a reality.[29]

There were some limitations in the study. Firstly, the final diagnoses of the patients were not specified; a larger population may have allowed for comparisons to be made between different inflammatory conditions. Secondly, the study was carried out in a single country, which limits the applicability of the data to a global population. This is particularly important when considering the differences in health care systems. In Saudi Arabia, the specialty of the physician first consulted is dependent on patient choice, while in other countries a PCP referral is necessary for a visit to a specialist. As in the former case, many patients choose to initially visit an orthopedic surgeon, the extension of the referral guidelines produced in the present study to clinics of other specialties may therefore be appropriate.[16]

Conclusion

It is widely acknowledged that early diagnosis and initiation of treatment for inflammatory arthritis significantly improve patient outcome. It is therefore essential that the time between symptom onset and rheumatologist assessment is minimized. In the present study, we addressed the lack of available criteria for aiding the PCP in identification of the patients who require early referral to a specialist. Using extensive statistical analysis of data from a cohort of patients referred to a

rheumatology clinic, we have identified 9 variables with high specificity and predictive value for a diagnosis of inflammatory arthritis: loss of appetite, swelling of MCP 2 or MCP 5, swelling of PIP 2 or PIP 3, wrist swelling, wrist tenderness, RF positivity, and ACPA positivity. Furthermore, the inclusion of standardized physical examination techniques should greatly improve their accuracy when used by the PCP. Future research work should determine precisely validated criteria for early referral in a primary care setting.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum*. 2002;46(2):328–346.
2. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. *Ann Rheum Dis*. 2002;61(4):290–297.
3. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis. *Arthritis Rheum*. 2006;55(6):864–872.
4. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)*. 2004;43(7):906–914.
5. van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Ann Rheum Dis*. 2014;73(5):861–870.
6. Gamez-Nava JI, Gonzalez-Lopez L, Davis P, Suarez-Almazor ME. Referral and diagnosis of common rheumatic diseases by primary care physicians. *Br J Rheumatol*. 1998;37(11):1215–1219.
7. van der Linden MP, le Cessie S, Raza K, et al. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis Rheum*. 2010;62(12):3537–3546.
8. Glazier RH, Badley EM, Lineker SC, Wilkins AL, Bell MJ. Getting a grip on arthritis: an educational intervention for the diagnosis and treatment of arthritis in primary care. *J Rheumatol*. 2005;32(1):137–142.
9. Suresh E. Diagnosis of early rheumatoid arthritis: what the non-specialist needs to know. *J R Soc Med*. 2004;97(9):421–424.
10. Tan YK, Østergaard M, Conaghan PG. Imaging tools in rheumatoid arthritis: ultrasound vs magnetic resonance imaging. *Rheumatology (Oxford)*. 2012;51(Suppl 7):vii36–vii42.
11. Akesson K, Dreinhöfer KE, Woolf AD. Improved education in musculoskeletal conditions is necessary for all doctors. *Bull World Health Organ*. 2003;81(9):677–683.
12. Bell MJ, Badley EM, Glazier RH, Poldre P. A pilot study to determine the effect of patient educators on medical students' and residents' skills in joint examination. *Acad Med*. 1997;72(10):919.
13. Altschuler EL, Cruz E, Salim SZ, et al. Efficacy of a checklist as part of a physical medicine and rehabilitation clerkship to teach medical students musculoskeletal physical examination skills: a prospective study. *Am J Phys Med Rehabil*. 2014;93(1):82–89.
14. Almoallim H, Attar S, Jannoudi N, et al. Sensitivity of standardised musculoskeletal examination of the hand and wrist joints in detecting arthritis in comparison to ultrasound findings in patients attending rheumatology clinics. *Clin Rheumatol*. 2012;31(9):1309–1317.
15. Naing L. Sample size for sensitivity and specificity studies. Available from: http://www.kck.usm.my/ppsg/statistical_resources/sample-size_forsensitivity_specificitystudiesLinNaing.xls. Accessed 23 March 2004.
16. Hussain W, Noorwali A, Janoudi N, et al. From symptoms to diagnosis: an observational study of the journey of rheumatoid arthritis patients in Saudi Arabia. *Oman Med J*. 2016;31(1):29–34.
17. Fautrel B, Benhamou M, Foltz V, et al. Early referral to the rheumatologist for early arthritis patients: evidence for suboptimal care. Results from the ESPOIR cohort. *Rheumatology (Oxford)*. 2010;49(1):147–155.
18. Raza K, Stack R, Kumar K, et al. Delays in assessment of patients with rheumatoid arthritis: variations across Europe. *Ann Rheum Dis*. 2011;70(10):1822–1825.
19. Katchamart W, Koolvisoot A, Aromdee E, Chiowchanwesawakit P, Muengchan C. Associations of rheumatoid factor and anti-citrullinated peptide antibody with disease progression and treatment outcomes in patients with rheumatoid arthritis. *Rheumatol Int*. 2015;35(10):1693–1699.
20. Farid SSh, Azizi G, Mirshafiey A. Anti-citrullinated protein antibodies and their clinical utility in rheumatoid arthritis. *Int J Rheum Dis*. 2013;16(4):379–386.
21. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med*. 2007;146(11):797–808.
22. Villeneuve E, Nam JL, Bell MJ, et al. A systematic literature review of strategies promoting early referral and reducing delays in the diagnosis and management of inflammatory arthritis. *Ann Rheum Dis*. 2013;72(1):13–22.
23. Bell MJ, Tavares R, Guillemin F, Bykerk VP, Tugwell P, Wells GA. Development of a self-administered early inflammatory arthritis detection tool. *BMC Musculoskelet Disord*. 2010;11:50.
24. Callahan LF, Pincus T. A clue from a self-report questionnaire to distinguish rheumatoid arthritis from noninflammatory diffuse musculoskeletal pain. The P-VAS:D-ADL ratio. *Arthritis Rheum*. 1990;33(9):1317–1322.
25. Beattie KA, Macintyre NJ, Pierobon J, et al. The sensitivity, specificity and reliability of the GALS (gait, arms, legs and spine) examination when used by physiotherapists and physiotherapy students to detect rheumatoid arthritis. *Physiotherapy*. 2011;97(3):196–202.
26. Tavares R, Pope JE, Tremblay JL, et al. Time to disease-modifying antirheumatic drug treatment in rheumatoid arthritis and its predictors: a national, multicenter, retrospective cohort. *J Rheumatol*. 2012;39(11):2088–2097.
27. Coady DA, Walker DJ, Kay LJ. Teaching medical students musculoskeletal examination skills: identifying barriers to learning and ways of overcoming them. *Scand J Rheumatol*. 2004;33(1):47–51.
28. Dacre J, Haq I. Assessing competencies in rheumatology. *Ann Rheum Dis*. 2005;64(1):3–6.
29. Kovacs D, Torralba KD, Fox DA, Solomon DH, Panush RS. Reflecting on early arthritis. *J Rheumatol*. 2012;39(11):2059–2061.

EXTENDED REPORT

EULAR revised recommendations for the management of fibromyalgia

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ABSTRACT

Objective The original European League Against Rheumatism recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were 'expert opinion'.

Methods A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Results 2979 titles were identified: from these 275 full papers were selected for review and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only 'strong for' therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, the following four main stages are suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as 'weak for' based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability).

Conclusions These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination and organisation of healthcare systems to optimise outcome.

INTRODUCTION

Fibromyalgia is common with a prevalence of 2% in the general population.[1 2] However, its diagnosis and management remain a challenge for patients and healthcare professionals. It often takes >2 years for a diagnosis to be made with an average of 3.7 consultations with different physicians.[3] Referral to specialists and investigations results in high healthcare use, for up to 10 years prior to diagnosis, compared with persons who do not have fibromyalgia.[4] Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common, but not universal, have an important influence on quality of life and emphasise that it is a heterogeneous and complex condition.[5 6]

The original European League Against Rheumatism (EULAR) recommendations for the management of fibromyalgia assessed evidence up to and including 2005.[7] Given the paucity of information and poor quality of the studies available, it was recommended that the guidelines be revised after a period of 4 years. However, no subsequent revision took place and thus a decade later we revisit the recommendations with the aim of making them more evidence based. In the time since the original recommendations, there have been a considerable number of individual trials examining pharmacological and non-pharmacological interventions and, moreover, there have been systematic reviews conducted for nearly all of the commonly used management strategies. Our aim therefore was, using the systematic reviews conducted and taking into account their quality, to make evidence-based recommendations for the use of individual pharmacological and non-pharmacological approaches, and how these could be combined. Further, we aimed to identify priority areas for future research.

METHODS

Working group membership

The working group included 18 members from 12 European countries: clinicians (representing rheumatology, internal medicine, pain medicine and epidemiology), non-clinical scientists (occupational health, epidemiology), patient representatives and the allied health professions (nursing).

Eligibility, search strategy and quality assessment

We focused on systematic reviews (with or without meta-analysis) concerned with the management of fibromyalgia. Details of eligibility, review and quality assessment are provided in online supplementary text.

Evaluating evidence

We retained pain as one of the key outcomes of interest, from the original guidelines, but also included fatigue, sleep and daily functioning. The committee considered the following in making a

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recommendation: number of trials, number of patients, outcomes assessed, quality of reviews and the trials included within the reviews, effect size (and 95% CI), adverse events and cost. We used the Grading of Recommendations Assessment, Development and Evaluation system for making recommendations.[10] This is a four-point scale: strong for/weak for/weak against/strong against; or allowing a recommendation 'use only for research'. The strength of recommendation is based on the balance between desirable and undesirable effects (considering values and preferences), confidence in the magnitude of effects and resource use. A strong recommendation implies that, if presented with the evidence, all or almost all informed persons would make the recommendation for or against the therapy, while a weak recommendation would imply that most people would, although a substantial minority would not.[11]

Two subgroups considered the evidence for pharmacological and non-pharmacological therapies and proposed a recommendation. At a face-to-face meeting, after presentation of the evidence and the preliminary recommendation, discussion resulted in a 'final recommendation'. In addition to the evidence on efficacy/effectiveness, the committee also took into account safety. All participants then voted on their level of agreement with the recommendation on a scale from 0, 'completely disagree', to 10, 'completely agree'. The percentage of the committee scoring at least 7 was taken to indicate level of agreement.

RESULTS

In total, 2979 titles were identified. From these, 571 abstracts and then 275 full papers were selected for review, and 107 reviews evaluated as eligible for consideration in making recommendations for management (figure 1).

Information on the reviews informing these recommendations on pharmacological therapy and on non-pharmacological and complementary and alternative medicines/therapies is collated in online supplementary tables A and B, respectively, while information from one review, for each medicine/therapy, selected based on recency and quality is provided in tables 1 and 2, respectively.

Evaluation of pharmacological medicines

Amitriptyline

Five reviews included up to 13 trials and a maximum of 919 subjects. Häuser *et al*[12] reported that patients receiving amitriptyline were more likely to achieve 30% pain reduction (risk ratio (RR) 1.60, 95% CI 1.15 to 2.24), equivalent to a 'number needed to treat' (NNT) of 3.54, 95% CI 2.74 to 5.01. There was a moderate effect on sleep (standardised mean difference (SMD) −0.56, 95% CI −0.78, to −0.34)[i] and small effect on fatigue (−0.44; −0.71 to −0.16). There was no difference in discontinuation rates compared with patients receiving placebo. Nishishinya *et al*[13] in their high-quality review concluded that 25 mg/day improved pain, sleep and fatigue at 6–8 weeks of treatment but not at 12 weeks while 50 mg/day did not demonstrate efficacy. *Amitriptyline evaluation: weak for, at low dose (100% agreement).*

Anticonvulsants

Nine reviews of pregabalin included up to seven studies and a maximum of 3344 patients. A recent Cochrane review[24] reported patients receiving active treatment were more likely to have 30% pain reduction, RR 1.37, 95% CI 1.22 to 1.53, with a 'number needed to benefit' (NNTB) over placebo of 9, 95% CI 7 to 13. There was a very small effect on fatigue (−0.17; −0.25 to −0.09) and small effect on sleep (−0.35; −0.43 to −0.27) but no effect on disability (−0.01; −0.11 to 0.09). A single, moderate quality, study of gabapentin in 150 subjects (eg, in ref. 104) showed a significant effect on 30% pain reduction (RR 1.65, 95% CI 1.10 to 2.48), a small effect on sleep (−0.71; −1.08 to −0.24) and a large effect on disability (−0.94; −1.32 to −0.56). *Anticonvulsant evaluation: pregabalin—weak for (94% agreement); gabapentin—research only (100% agreement).*

Cyclobenzaprine

A single systematic review of five studies involving 312 patients reported that of those taking cyclobenzaprine 85% experienced side effects and only 71% completed the studies. They were more likely to report themselves as 'improved' (NNT 4.8, 95% CI 3.0 to 11.0). Only two studies reported an 'intention-to-treat' (ITT) analysis. Sleep, but not pain, showed a significant, very small, improvement relative to baseline at the longest outcome considered (12 weeks: SMD 0.34) and patients on placebo showed similar improvement (SMD 0.52).[25] *Cyclobenzaprine evaluation: weak for (75% agreement).*

Growth hormone

A single systematic review of two studies involving 74 patients reported an effect size on pain of 1.36 (0.01 to 1.34).[16] The improvement in functional deficit was not statistically significant (1.24; −0.36 to 2.84). There are concerns on safety (sleep apnoea, carpal tunnel syndrome). The drug is not approved for fibromyalgia (FM) or related disorders in Europe. *Growth hormone evaluation: strong against (94% agreement).*

Monoamine oxidase inhibitors

Four reviews identified up to three studies and 241 patients. Häuser *et al*[26] reported a moderate effect on pain across the studies (−0.54; −1.02, to −0.07), but the single studies that evaluated fatigue and sleep showed no effect. There were no differences in dropouts or adverse events compared with placebo. There was no comparison between compounds. Life-threatening interactions have been documented. *Monoamine oxidase inhibitors (MAOIs) evaluation: weak against (81% agreement).*

NSAIDs

A single review[21] identified two small trials with no evidence of improved outcome compared with placebo. One low-quality review was not considered. *Non-steroidal anti-inflammatory drugs (NSAIDs) evaluation: weak against (100% agreement).*

Serotonin-noradrenalin reuptake inhibitors

Eight systematic reviews were identified, which presented data separately for duloxetine. The largest review of 2249 subjects[32] reported duloxetine, short term (up to 12 weeks) and long term (up to 28 weeks), was more effective than placebo at reducing pain (RR >30% pain, RR 1.38, 95% CI 1.22 to 1.56), although there was no significant effect at 20–30 mg/day and no difference between doses of 60 and 120 mg/day. NNTB, based on 60 mg/day up to 12 weeks, was 6, 95% CI 3 to 12. A previous review reported small effects on sleep (−0.24; −0.37, to −0.12) and disability (−0.33; −0.43, to −0.24) but no effect on fatigue.[30] Seven systematic reviews were identified of milnacipran, a recent one of which evaluated five trials.[30] Patients taking milnacipran were more likely, at the end of treatment, to

[i]All effect sizes are expressed as SMD with 95% CI unless otherwise stated.

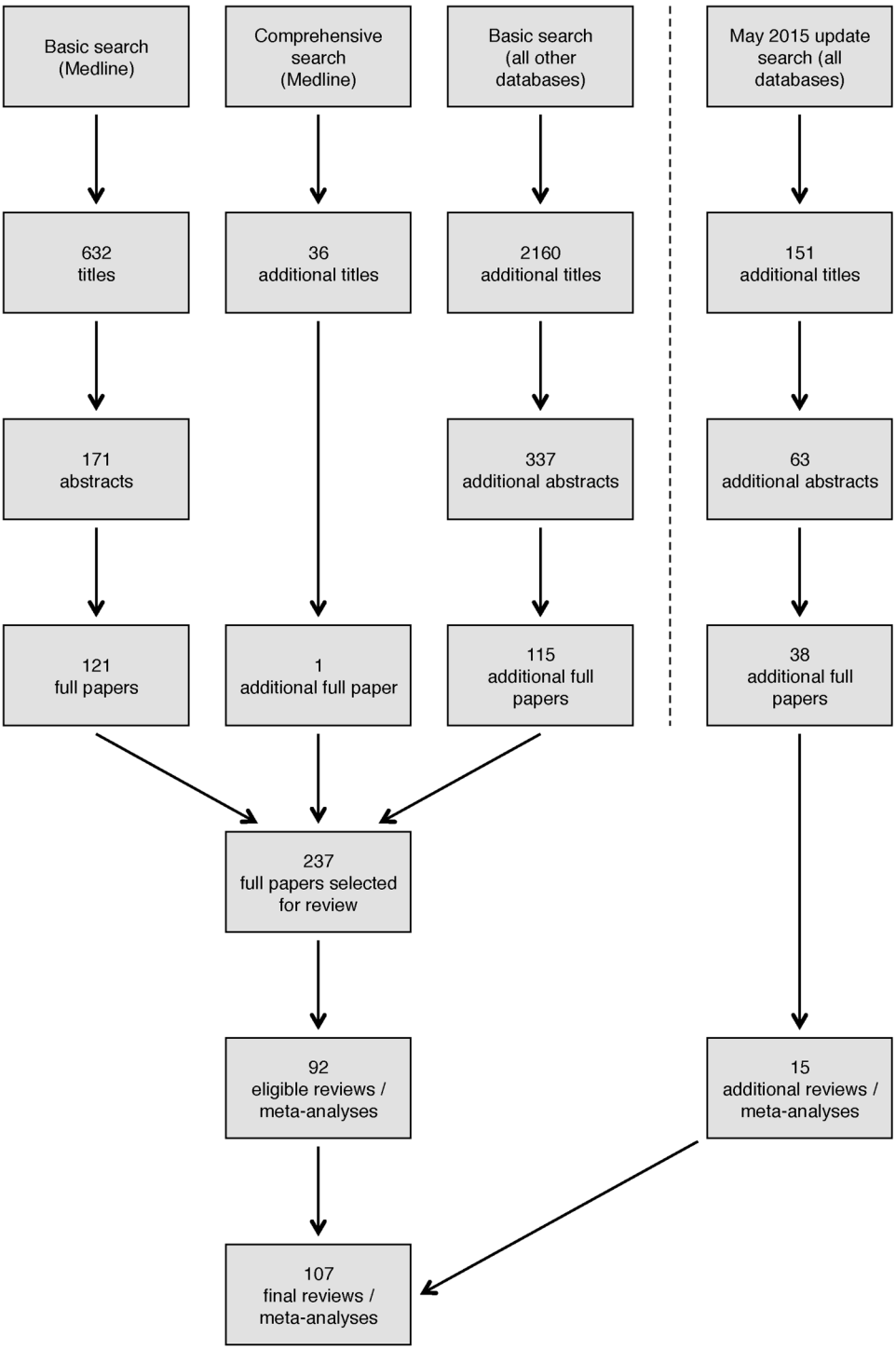

Figure 1 Flow chart identifying eligible reviews.

have 30% pain reduction (RR 1.38, 95% CI 1.25 to 1.51) but there was only a small benefit on fatigue (−0.14; −0.19 to −0.08), disability (−0.16; −0.23 to −0.10) and no effect on sleep. *Duloxetine and milnacipran evaluation: weak for (100% agreement).*

Selective serotonin reuptake inhibitors

Seven systematic reviews included up to 11 trials and a maximum of 521 subjects. Given that reviews have not focused on specific drugs or comparisons, drugs within this class were considered together. A recent review of medium quality included seven trials and reported a moderate effect on pain (−0.40; −0.73, to −0.07), sleep (−0.31; −0.60 to −0.02) and no effect on fatigue (−0.17; −0.46 to 0.11).[36] *Selective serotonin reuptake inhibitor (SSRI) evaluation: weak against (94% agreement).*

Sodium oxybate

A single systematic review of five studies including 1535 patients reported small effects sizes on pain (0.44; 0.31 to 0.58), sleep problems (0.47; 0.28 to 0.66) and fatigue (0.48; 0.35 to 0.60). The European Medicines Agency and the US Food and Drug Administration refused the approval for FM because of safety concerns.[16] The drug is only approved for narcolepsy. *Sodium oxybate evaluation: strong against (94% agreement).*

Table 1 Overview of results from selected systematic reviews of placebo-controlled pharmacological trials

Treatment (review reference)	No. of trials (no. of participants) Review quality	Dosages; durations of treatment	Overall trial quality*	Safety and comments
Amitriptyline[12]	10 (767) AMSTAR=6	10–50 mg/day; 8–24 weeks	Low	There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported.
Anticonvulsants—pregabalin[24]	5 (3256) AMSTAR=10	Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks	High	Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events.
Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT.
Growth hormone[16]	2 (74) AMSTAR=5	0.0125 mg/kg/day; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/day; 9 months to 1 year	NE	Safety concerns include sleep apnoea and carpal tunnel syndrome.
MAOIs[26]	3 (241) AMSTAR=9	Pirlindole 150 mg/day, moclobemide 150–300 mg/day; 4–12 weeks	Low	MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications.
NSAIDs[21]	2 (242) AMSTAR=7	Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6–8 weeks	Low	The adverse event profile, although not considered in this review, is well established for this class of drugs.
SNRIs—duloxetine[31]	6 (2249) AMSTAR=10	20–120 mg/day; 12–28 weeks	Moderate	Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High	Dropout rates due to side effects across studies were double compared with placebo, but there was no difference in serious adverse events.
SSRIs[36]	7 (322) AMSTAR=8	20–40 mg/day citalopram, 20–80 mg/day fluoxetine, 20–60 mg/day paroxetine; 6–16 weeks	Moderate to high	Acceptability and tolerability were similar to placebo NNH 40, 95% CI 19 to 66. Although several studies excluded patients with depression/anxiety, Häuser *et al*[26] showed a small effect of SSRIs in improving depressed mood (SMD −0.37, 95% CI −0.66 to −0.07).
Sodium oxybate[16]	5 (1535) AMSTAR=5	4.5–6 g/day; 8–14 weeks	NE	There is the potential for abuse and central nervous system effects associated with abuse such as seizure, respiratory depression and decreased levels of consciousness.
Tramadol[22]	1 (313) AMSTAR=3	37.5 mg tramadol/325 mg paracetamol 4×/day; 3 months	High	No significant difference in discontinuation due to adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and benefitted from tramadol, demonstrated a lower discontinuation rate in a double-blind phase compared with placebo.[21]

*According to the method of quality evaluation used in the review.
AMSTAR, Assessing the Methodological Quality of Systematic Reviews; FM, fibromyalgia; IGF, insulin growth factor; ITT, intention-to-treat; MAOIs, monoamine oxidase inhibitors; NE, not evaluated; NNH, number needed to harm; NSAIDs, non-steroidal anti-inflammatory drugs; RR, risk ratio; SMD, standardised mean difference; SNRI, serotonin-noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Tramadol, a weak opioid with mild serotonin-noradrenalin reuptake inhibitor (SNRI) activity was considered by two reviews. Roskell *et al*[22] identified a single study of tramadol with paracetamol. Those in the active arm were more likely to have 30% improvement in pain (RR 1.77, 95% CI 1.26 to 2.48). *Tramadol evaluation: weak for (100% agreement)*.

The literature search did not identify any reviews on corticosteroids, strong opioids, cannabinoids and antipsychotics. The committee made a 'strong against' evaluation (100% agreement) regarding the use of strong opioids and corticosteroids in patients with fibromyalgia on the basis of lack of evidence of efficacy and high risk of side effects/addiction reported in individual trials.

Evaluation of non-pharmacological therapies; complementary and alternative medicines and therapies

Acupuncture

Eight reviews included up to 16 trials and 1081 participants. One high-quality review included nine trials, with 395 patients, and demonstrated that acupuncture, added to standard therapy, resulted in a 30% (21%, 39%) improvement in pain.[70] Electric acupuncture was also associated with improvements in pain (22%; 4% to 41%) and fatigue (11%; 2% to 20%). Some adverse events were reported, but these were commonly mild and transient. There is little understanding of the active component of acupuncture, and the evidence supporting the use of real versus sham acupuncture was less consistent. *Acupuncture evaluation: weak for (93% agreement)*.

Table 2 Overview of results from selected systematic reviews of non-pharmacological; complementary and alternative medicine and therapy trials

Treatment (review reference)	No. of trials (no. of participants*) Review quality	Dosages; durations of treatment	Overall trial quality†	Safety and comments
Acupuncture[70]	9 (395) AMSTAR=11	Treatment sessions ranged from 3 to 13 weeks (median=4), with needle retention ranging from 20 to 30 min. Only one study provided journal references for the acupuncture point selection, and the description of the type of needle stimulation/ manipulation was clear in only three studies.	Moderate	One in six people who had acupuncture, and one in three controls, reported adverse events. Such events were minor and lasted less than one day. No serious adverse events were reported in any trials.
Biofeedback[92]	7 (321) AMSTAR=8	EMG biofeedback. Individual sessions varied between 45 and 180 min, and the number of sessions varied between 6 and 16. EEG biofeedback. 20–22 sessions of (where reported) 30 min duration.	Poor	Only two‡ trials reported adverse event data. 4% of patients in one trial receiving EMG biofeedback reported stress. And 74% of patients in another, receiving EEG biofeedback reported a variety of side effects, including: headache, fatigue and sleep problems.
Capsaicin[94]	2 (153) AMSTAR=5	Topical application of *Capsicum annuum L*. cream, either 0.025% capsaicin for 4 weeks or 0.075% for 12 weeks.	Not reported	Patients reported moderate, transient, burning or stinging.
Chiropractic[89]	3 (102) AMSTAR=4	Little detail is given for any trials, but treatment elements included massage, stretching, spinal manipulation, education and resistance training.	Low	Around 50% of patients experience mild-to-moderate transient adverse effects after spinal manipulation.§
CBT[57]	23 (2031) AMSTAR=11	Median duration of therapy=10 weeks, with a median number of 10 sessions, and median total hours=18 hours. All but two studies delivered therapy face to face. Median follow-up (where this was performed 17/23 studies)=6 months.	Low	The assessment of safety in most studies was insufficient. Two studies reported dropout due to worsening of comorbid mental disorders. However, CBT is generally considered safe.
Exercise[41]	34 (2276) AMSTAR=9	Exercise programmes lasting 2.5–24 weeks. Aerobic exercise for ≥20 min, once a day (or twice for ≥10 min), 2–3 days a week. Strength training with ≥8 repetitions per exercise, 2–3 times a week.	Moderate	Although patients may initially notice a deterioration in symptoms, exercise is generally considered safe, especially when practised under supervision.
Hydrotherapy/spa therapy[76]	10 (446) AMSTAR=9	Wide variation in precise treatment strategy between trials. Most consisted of water or mud baths at body temperature 36–37°C, or slightly above (40–45°C), with a median treatment time of 240 min (range 200–300), over several weeks.	Low	Three studies reported no side effects of treatment; one reported slight flashes in 10% of the patients. The remaining trials did not explicitly mention safety.
Hypnotherapy[91]	4 (152) AMSTAR=11	Some variation between trials ranging (where reported) from 300 to 420 min, delivered over 10–26 weeks.	Good	Adverse events were not reported in any of the trials.
Massage[63]	9 (404) AMSTAR=7	Massage therapy time lasted 25–90 min, with between 1 and 20 massage sessions in total.	Low to moderate	No adverse events were reported in any of the trials.
Meditative movement[80]	7 (362) AMSTAR=9	Wide variation in treatments between trials, and included yoga, tai chi, qigong or body awareness therapy. Median (range) duration of treatment=16 (6–24) hours, over 4–12 weeks.	Moderate	Although no serious adverse events were reported, six participants (3.1%) withdrew from the trials because of adverse events (increase of pain; muscle inflammation; chlorine hypersensitivity). The review authors concluded that the acceptance and safety of all types of meditative movement therapies were high.
Mindfulness/mind–body therapy[84]	6 (674) AMSTAR=9	Some variation between trials. Single 2–3.5 hours session per week, for 8–10 weeks. Four out of six programmes also included daily home practice (30–45 min) plus a single all-day retreat.	Low	Safety was assessed and reported in none of the trials.
Multicomponent therapy[60]	9 (1119) AMSTAR=9	Enormous variation in treatment strategies between trials. Most included different combinations of exercise (land and/or water based); education; relaxation; and/or some other specific therapeutic component (eg, Tai Chi; or massage).	Moderate	No adverse events were reported in any of the trials.
SAMe[93]	1 (44) AMSTAR=6	400 mg tablet, twice a day, for 6 weeks.	Moderate	Mild adverse effects such as stomach upset and dizziness were reported.
Other: guided imagery[91]	1 (48) AMSTAR=9	Audiotape-led, individual, guided imagery: 30 min daily for 6 weeks recommended. Median of 44 exercises (range 37–136).	Good	Adverse events were not reported.
Other: homeopathy[98]	4 (163) AMSTAR=7	Variation between trials. Two studied individualised homeopathic treatment, consisting of an initial consultation (and treatment), plus follow-up interviews every 4–8 weeks. Two studied *Arnica montana*, *Bryonia alba* or *Rhus toxicodendron* (potency 6c) daily for between 1 and 3 months.	Low to moderate	No information was provided on safety.

*Total number of persons randomised.
†According to the method of quality evaluation used in the review.
‡Elsewhere in the review, it reports that three studies reported on adverse events. However, in the table where these data are presented, it is only clear for two. However, in a third trial, there were no dropouts due to side effects.
§These data were not contained in this review. The initial recommendation for chiropractic was weak against. However, after discussion, this was downgraded to strong against due to potential safety concerns.
CBT, cognitive behavioural therapy; EMG, electromyographic; SAMe, *S*-adenosyl methionine.

Biofeedback

Two reviews included up to seven trials and 307 participants. Glombiewski *et al*[92] reviewed seven studies, comprising 321 participants. Treatment sessions varied from 6 to 22; with control therapy comprising sham biofeedback, attention control, medication and treatment as usual. Biofeedback was effective in reducing pain intensity (Hedges' g=0.79; 0.22 to 1.36), although all trials were poor quality. There was no evidence of effectiveness in terms of fatigue or sleep and subgroup analysis suggested that any effect was limited to electromyographic (0.86; 0.11 to 1.62) rather than electroencephalographic biofeedback (0.71; −0.37 to 1.8). *Biofeedback evaluation: weak against (100% agreement).*

Capsaicin

Two reviews included two trials and 153 participants. The most recent review, a narrative review of two trials, considered data on 153 patients.[94] Both showed some evidence of positive effect in terms of pain relief, although results were not consistent for other outcomes. Capsaicin gel is generally considered safe, although many users report a mild burning sensation when applied to the skin. However, the number of patients and trials was small and was therefore limited in the extent to which they can provide evidence for toxicity. *Capsaicin evaluation: weak against (86% agreement).*

Chiropractic

Three reviews included up to 13 trials and 102 participants. The most recent review summarised three studies.[89] One study was an open pilot study, one quasi-randomised and in the third no between-group differences were observed in terms of pain. The studies were poor quality and lacked robust interpretable data. *Chiropractic evaluation: strong against (93% agreement).*

Cognitive behavioural therapies

Five reviews included up to 30 trials and at least 2031 participants. One high-quality review included 23 trials, comprising >2000 patients, although the quality of individual trials was reported as generally poor.[58] Cognitive behavioural therapies (CBTs) were effective in reducing pain (−0.29; −0.49 to −0.17) and disability (−0.30; −0.51 to −0.08) at the end of treatment compared with a variety of controls groups, and results were sustained long term. *Behavioural therapy evaluation: weak for (100% agreement).*

Exercise

Twenty reviews included up to 34 trials and at least 2494 participants.[ii] The largest, a Cochrane review, considered 47 different exercise interventions.[41] Aerobic exercise was associated with improvements in pain (0.65; −0.09 to 1.39) and physical function (0.66; 0.41 to 0.92). Busch *et al*[42] reviewed five trials with 219 participants and concluded that resistance training resulted in a significant improvement in pain (−3.3 cm on a 10 cm scale; −6.35 to −0.26) as well as function compared with control. There is some consistency with regard to aerobic and strengthening exercises, although insufficient evidence to suggest superiority of one over the other; land and aquatic exercise appear equally effective.[56] *Exercise therapy evaluation: strong for (100% agreement).*

[ii]It is unclear from some of the reviews how many participants were included. The number of participants represents the minimum about which we can be confident.

Hydrotherapy/spa therapy

Four reviews included up to 21 trials and 1306 participants. One high-quality review included 10 trials, 446 participants and compared a median of 4-hour hydrotherapy (range 200–300 min) against various comparators.[76] There was a significant improvement in pain (−0.78; −1.42 to −0.13) at the end of therapy, maintained in the longer term (median 14 weeks), although the review authors noted that no trials conducted an ITT analysis. There was consistency with regard to the evidence for hydrotherapy and balneotherapy, although little evidence to suggest superiority of one over the other.[77] *Hydrotherapy evaluation: weak for (93% agreement).*

Hypnotherapy

One review included four trials, although the number of participants is unclear.[91] Although six trials of hypnotherapy and/or guided imagery were reviewed, only four examined hypnotherapy in isolation. Median treatment duration (where reported) was 360 min and hypnotherapy was compared with a variety of control therapies: cognitive intervention, active control (physical therapy/massage/relaxation/autogenic training) and treatment as usual. A meta-analysis is presented on all six trials, and isolated data for hypnotherapy are not presented. Two of the four hypnotherapy trials report some significant benefit in terms of pain, the other two demonstrate null, non-significant results. *Hypnotherapy evaluation: weak against (86% agreement).*

Massage

Six reviews have been reported and one meta-analysis with nine trials and 404 patients[63] with sessions lasting 25–90 min, and treatment duration ranging from 1 to 24 weeks (median 5 weeks). Comparator treatments included transcutaneous electrical nerve stimulation (TENS), standard care, guided relaxation and acupuncture. Methodological problems were noted with all of the studies, only four were at low risk of bias in terms of random allocation and only two were analysed as ITT. Overall, massage was not associated with a significant improvement in pain (0.37; −0.19 to 0.93), and of the two ITT analyses, one favoured massage and one favoured control (both significant). A subgroup analysis revealed some evidence of a positive effect with massage of ≥5 weeks duration, although this was based solely on lower-quality trials. *Massage evaluation: weak against (86% agreement).*

Meditative movement

Six reviews, including up to eight trials and 559 participants, focused on qigong, yoga, tai chi or a combination of these therapies. However, there was insufficient evidence to make individual recommendations. One review included seven trials, with 362 participants randomised to tai chi, yoga, qigong or body awareness therapy.[80] Total treatment time ranged from 12 to 24 hours and was compared with a variety of controls, including treatment as usual and active control groups (aerobics, wellness education and stretching). At the end of therapy, improvements were seen in sleep (−0.61; −0.95 to −0.27) and fatigue (−0.66; −0.99 to −0.34) some of which were maintained in the longer term. *Meditative movement evaluation: weak for (71% agreement).*

Mindfulness/mind–body therapy

Six reviews included up to 13 trials and 1209 participants. One recent review, a meta-analysis of six trials, with 674 patients[84] provided evidence that mindfulness-based stress reduction

resulted in improvements in pain (−0.23; −0.46 to −0.01) immediately post treatment compared with usual care and compared with active control interventions (−0.44; −0.73 to −0.16). However, these effects were not robust against bias. *Mindfulness/mind–body therapy evaluation*: *weak for (73% agreement)*.

Multicomponent therapy

Two reviews including up to 27 trials and 2407 participants examined the additional benefit of combining therapies compared with individual therapy. Häuser *et al*[60] conducted a review of management involving both educational or psychological therapies and exercise. In a meta-analysis of nine trials and 1119 patients, multicomponent therapy was effective in reducing pain (−0.37; −0.62 to −0.13), and fatigue, immediately post treatment, compared with waiting list, relaxation, treatment as usual and education. However, effects were short-lived. *Multicomponent therapy evaluation: weak for (93% agreement)*.

S-Adenosyl methionine

Two reviews each included one trial with, in combination, 74 participants. De Silva *et al*[93] reported that, after the end of treatment, significant improvements were observed in pain and fatigue compared with placebo. Sim and Adams[52] reviewed a trial comparing *S*-adenosyl methionine (SAMe) with TENS but data on the main trial comparison are omitted. Side effects are usually mild and infrequent. However, the number of patients and trials was small and therefore cannot provide a robust assessment of toxicity and safety. *SAMe evaluation: weak against (93% agreement)*.

Other complementary and alternative therapies

Three reviews of guided imagery included up to six trials and 357 participants. The highest quality, including only one trial, provided some evidence that guided imagery may be effective in reducing pain (−1.52; −2.17 to −0.87).[90] Two reviews of homeopathy included four trials and 163 participants.[97 98] Both contained a review including only four randomised trials, each of which showed some benefit of homeopathy, on some outcomes. However, none of the individual trials were without serious flaws. *Other complementary and alternative therapies (guided imagery, homeopathy): strong against (93% agreement)*.

Reviews were identified that examined electrothermal and phototherapeutic therapy;[99] phytothermotherapy;[100] music therapy, journaling/storytelling[103] and static magnet therapy,[101] although each was insufficient to allow a recommendation. Marlow *et al*[102] examined the effectiveness of transcranial magnetic and/or direct current stimulation. Eight trials included 244 participants, although not all were analysed by ITT, and appropriate group comparisons were not presented for all studies. Overall, there was little evidence to support either therapy, and several studies reported an unacceptably high rate of adverse events and/or discontinuation due to headache.

EULAR revised recommendations

In terms of overall principles, we recommend, based on unanimous expert opinion, that optimal management requires prompt diagnosis and providing the patient with information (including written material) about the condition. There should be a comprehensive assessment of pain, function and the psychosocial context. Management should take the form of a graduated approach with the aim of improving health-related quality of life. It should focus first on non-pharmacological modalities. This is based on availability, cost, safety issues and patient preference.

We have used the evaluation of individual therapies (above) to make 10 specific recommendations, all based on evidence from systematic reviews and all but one from meta-analysis. The recommendations are given in table 3, and a flow chart of how these therapies may be used in management is shown in figure 2.

We were unanimous in providing a 'strong for' recommendation for the use of exercise, particularly given its effect on pain, physical function and well-being, availability, relatively low cost and lack of safety concerns. The available evidence did not allow us to distinguish between the benefits of aerobic or strengthening. We gave 'weak for' recommendations in relation to meditative movement therapies (which improved sleep, fatigue and quality of life) or mindfulness-based stress reduction (which improved pain and quality of life); the physical therapies acupuncture or hydrotherapy for which there was evidence that they improved pain/fatigue and pain/quality of life, respectively. The effects seen in pragmatic trials of such therapies will include specific and non-specific effects, and it is not possible to disentangle these. There were some non-pharmacological therapies we did not recommend because of lack of effectiveness and/or low study quality: biofeedback, capsaicin, hypnotherapy, massage, SAMe and other complementary and alternative therapies. We provided a 'strong against' evaluation for chiropractic based on safety concerns.

In case of lack of effect of the above therapeutic approaches, we recommend individualised treatment according to patient need. Psychological therapies ('weak for') should be considered for those with mood disorder or unhelpful coping strategies: CBT was effective at producing modest, long-term reductions in pain, disability and improving mood. Pharmacological therapies (all 'weak for') should be considered for those with severe pain (duloxetine, pregabalin, tramadol) or sleep disturbance (amitriptyline, cyclobenzaprine, pregabalin). Multimodal rehabilitation ('weak for') programmes should be considered for those with severe disability—in comparison to individual therapies, those that were multimodal improved a range of short-term outcomes. We did not recommend several pharmacological therapies including NSAIDs, MAOIs and SSRIs because of lack of efficacy and specifically gave a 'strong against' evaluation to growth hormone, sodium oxybate, strong opioids and corticosteroids based on lack of efficacy and high risk of side effects.

DISCUSSION

The previous EULAR recommendations provided an important milestone in the management of fibromyalgia. There were nine recommendations, but only three were supported by strong evidence from the scientific literature; most were based on expert opinion. Since that time, there have been a considerable number of trials published addressing issues in the management of fibromyalgia. The availability of systematic reviews and meta-analysis of randomised controlled trials (RCTs) for all the most common approaches to management allowed us to concentrate on these.

Comparison with 2007 EULAR recommendations

Despite the very large increase in the amount of trial data and summarised in meta-analyses, there are no major changes to the approach of managing patients with fibromyalgia, although we provide new evidence in support for some additional non-pharmacological therapies. In addition, all the recommendations are now firmly evidence based. We now recommend that non-pharmacological therapy should be first-line therapy and then if there is a lack of effect that there should be individualised

Table 3 Recommendations

Recommendation	Level of evidence	Grade	Strength of recommendation	Agreement (%)*
Overarching principles				
Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of FM should take the form of a graduated approach.	IV	D		100
Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment that often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features (such as depression), fatigue, sleep disturbance and patient preferences and comorbidities; by shared decision-making with the patient. Initial management should focus on non-pharmacological therapies.	IV	D		100
Specific recommendations				
Non-pharmacological management				
Aerobic and strengthening exercise	Ia	A	Strong for	100
Cognitive behavioural therapies	Ia	A	Weak for	100
Multicomponent therapies	Ia	A	Weak for	93
Defined physical therapies: acupuncture or hydrotherapy	Ia	A	Weak for	93
Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction	Ia	A	Weak for	71–73
Pharmacological management				
Amitriptyline (at low dose)	Ia	A	Weak for	100
Duloxetine or milnacipran	Ia	A	Weak for	100
Tramadol	Ib	A	Weak for	100
Pregabalin	Ia	A	Weak for	94
Cyclobenzaprine	Ia	A	Weak for	75

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

therapy according to patient need, which may include pharmacological therapy.

Comparison with other recommendation

There are three recent guidelines on the management of FM from Canada, Israel and Germany that have been compared with respect to their recommendations.[105] These guidelines and our EULAR recommendations are in agreement on the principles of approach to management, the need for tailored therapy to the individual and the first-line role of non-pharmacological therapies. There are differences between our guidelines and previous guidelines, which can partly be explained by us using more recently available evidence. There are differences in the strength of recommendations relating to pharmacological therapies: anticonvulsants and SNRIs were strongly recommended by the Canadian and Israeli guidelines while the German and these EULAR guidelines provide a weak recommendation. There are also differences in relation to individual non-pharmacological therapies across guidelines in terms of whether they were assessed. For example, meditative movement is strongly recommended by the German guidelines, but recommended only for a minority of patients in Israel, while these EULAR guidelines provide a 'weak for' recommendation.

The committee recommended that an update is conducted after 5 years in order to determine whether for those therapies with relatively little current evidence further trials have been conducted and, second, whether any new therapies have emerged for the management of fibromyalgia.

Research priorities

In the course of discussion, we identified important questions in terms of guiding management where there was either insufficient (or often no) evidence base to guide decisions, that is, 'research gaps'. We discussed their relatively priority taking into account their potential to guide management, the likelihood that such studies could be conducted and were likely to be funded. We identified five such priority questions:

- Which type of exercise is most effective: strength and/or aerobic training?
- Are combined pharmacological and non-pharmacological approaches to management more effective than single-modality management?
- Are there characteristics of patients with fibromyalgia that predict response to specific therapies?
- How should fibromyalgia be managed when it occurs as a comorbidity to inflammatory arthritis?
- What aspects of a healthcare system optimise outcome for patients (who is best for the management of FM patients)?

Some of these questions are best answered by RCTs. Given, however, the expense of such studies and that they can take almost 10 years from identifying the questions to be answered to results being obtained, alternatives including registers and observational studies should be considered. These can be complemented by qualitative studies to determine the needs of patients.

Dissemination

These recommendations will be disseminated by the international working group through national rheumatology societies. This will include scientific meetings, newsletters and continuing education programmes. We will produce a summary of the recommendations suitable for dissemination through EULAR-affiliated patient groups and through national patient societies. We will investigate assessing agreement with the recommendations in the target population.

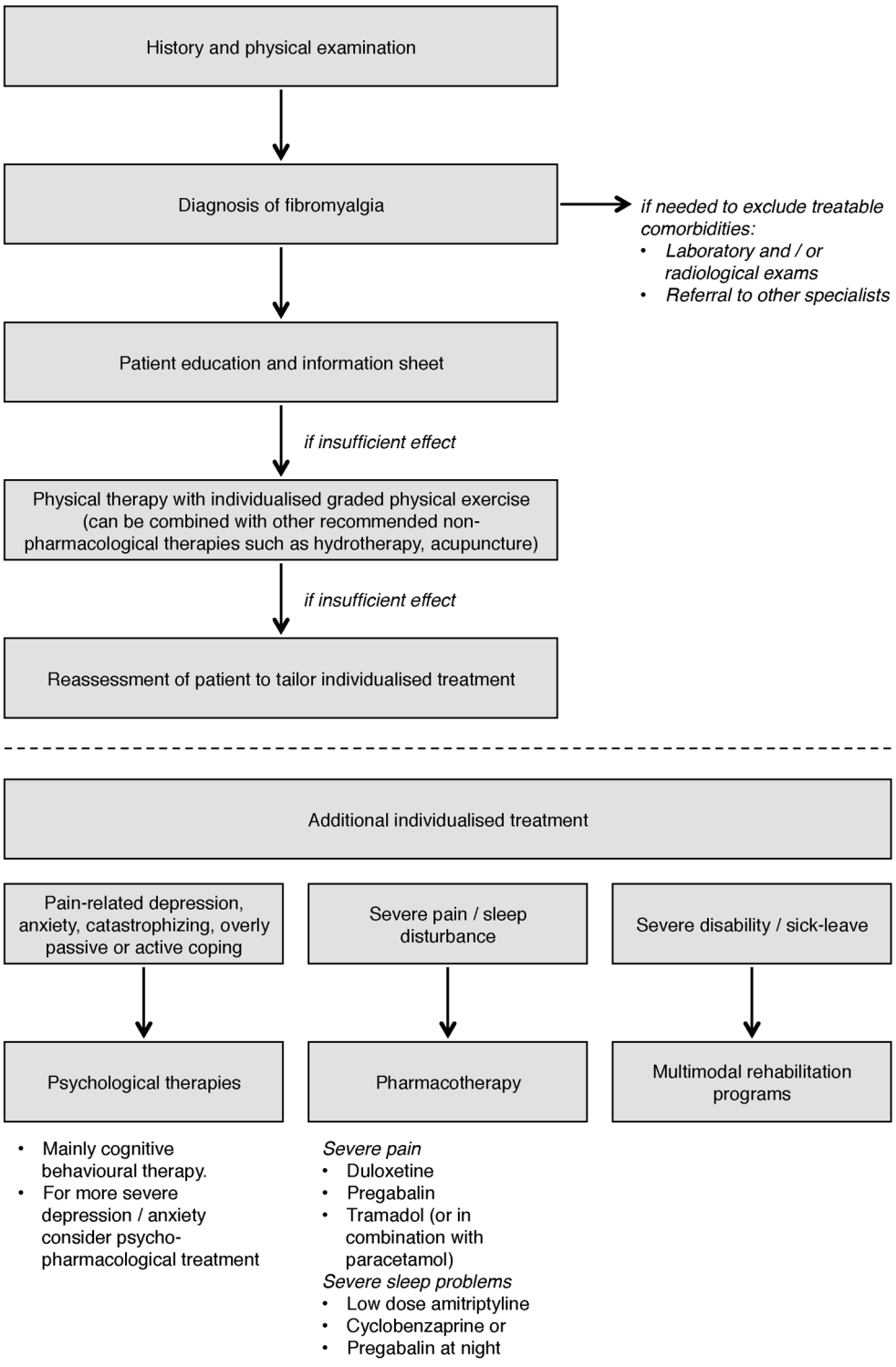

Figure 2 Management recommendations as flow chart.

SUMMARY

In summary, these revised EULAR recommendations newly incorporate a decade of evidence in relation to the pharmacological and non-pharmacological management of fibromyalgia. They allow EULAR to move from recommendations that are predominantly based on expert opinion to ones that are firmly based on scientific evidence from high-quality reviews and meta-analyses. Despite this evidence, however, the size of effect for many treatments is relatively modest. We propose focusing on the research priorities we outline to address issues clarifying to whom certain interventions may best be delivered, their effect in combination, matching patients to therapies and the organisation of healthcare systems to optimise outcome.

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Contributors GJM, FA, PS-P, EC and GTJ were applicants on the grant. EF and LED undertook the literature search and together with FA identified eligible reviews. EF, LED, FA and CK evaluated the quality of each of the eligible reviews. GTJ led the evaluation of non-pharmacological therapies and FA and CK led the evaluation of pharmacological therapies. GJM drafted the manuscript with input from GTJ, WH, EC, CK and EK. All authors (with the exception of FA and EF) participated in a 2-day project meeting, and all authors made important intellectual contributions to the manuscript.

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REFERENCES

1 Queiroz LP. Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep* 2013;17:356.
2 Wolfe F, Ross K, Anderson J, *et al*. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19–28.
3 Choy E, Perrot S, Leon T, *et al*. A patient survey of the impact of fibromyalgia and the journey to diagnosis. *BMC Health Serv Res* 2010;10:102.
4 Boonen A, van den Heuvel R, van Tubergen A, *et al*. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Ann Rheum Dis* 2005;64:396–402.
5 HäuserW, Zimmer C, *et al*. [What are the key symptoms of fibromyalgia? Results of a survey of the German Fibromyalgia Association]. *Schmerz* 2008;22:176–83.
6 Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. *Acta Biomed* 2007;78:88–95.
7 Carville SF, Arendt-Nielsen L, Bliddal H, *et al*. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis* 2008;67:536–41.
8 Shea BJ, Grimshaw JM, Wells GA, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.
9 Abeles M, Solitar BM, Pillinger MH, *et al*. Update on fibromyalgia therapy. *Am J Med* 2008;121:555–61.
10 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
11 Andrews JC, Schünemann HJ, Oxman AD, *et al*. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726–35.
12 Häuser W, Petzke F, Üçeyler N, *et al*. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology* 2011;50:532–43.
13 Nishishinya B, Urrútia G, Walitt B, *et al*. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. *Rheumatology (Oxford)* 2008;47:1741–6.
14 Üçeyler N, Häuser W, Sommer C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. *Arthritis Care Res* 2008;59:1279–98.
15 Moore RA, Derry S, Aldington D, *et al*. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;(12):CD008242.
16 Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. *Eur J Pain* 2014;18:1067–80.
17 Häuser W, Bernardy K, Üçeyler N, *et al*. Treatment of fibromyalgia syndrome with gabapentin and pregabalin–a meta-analysis of randomized controlled trials. *Pain* 2009;145:69–81.
18 Moore RA, Straube S, Wiffen PJ, *et al*. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2009;(3):CD007076.
19 Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. *J Pain* 2010;11:505–21.
20 Tzellos TG, Toulis KA, Goulis DG, *et al*. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. *J Clin Pharm Ther* 2010;35:639–56.
21 Choy E, Marshall D, Gabriel ZL, *et al*. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. *Semin Arthritis Rheum* 2011;41:335–45.
22 Roskell NS, Beard SM, Zhao Y, *et al*. A meta-analysis of pain response in the treatment of fibromyalgia. *Pain Pract* 2011;11:516–27.
23 Siler AC, Gardner H, Yanit K, *et al*. Systematic review of the comparative effectiveness of antiepileptic drugs for fibromyalgia. *J Pain* 2011;12:407–15.
24 Üçeyler N, Sommer C, Walitt B, *et al*. Anticonvulsants for fibromyalgia. *Cochrane Database Syst Rev* 2013;(10):CD010782.
25 Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Care Res* 2004;51:9–13.
26 Häuser W, Bernardy K, Üçeyler N, *et al*. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* 2009;301:198–209.
27 Tort S, Urrútia G, Nishishinya MB, *et al*. Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev* 2012;(4):CD009807.
28 Sultan A, Gaskell H, Derry S, *et al*. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BMC Neurol* 2008;8:29.
29 Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database Syst Rev* 2009;(4):CD007115.
30 Häuser W, Urrútia G, Tort S, *et al*. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev* 2013;(1):CD010292.
31 Ormseth MJ, Eyler AE, Hammonds CL, *et al*. Milnacipran for the management of fibromyalgia syndrome. *J Pain Res* 2010;3:15–24.
32 Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014;(1):CD007115.
33 Derry S, Gill D, Phillips T, *et al*. Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;(3):CD008244.
34 Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997;12:384–9.
35 Arnold LM, Keck PE, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 2000;41:104–13.
36 Häuser W, Wolfe F, Tölle T, *et al*. The role of antidepressants in the management of fibromyalgia syndrome. *Central Nervous System Drugs* 2012;26:297–307.
37 Bednar ML, Soroczynski AC, Groman MJ, *et al*. Effectiveness of land-based and aquatic-based exercises for improving the health status of individuals with fibromyalgia: a systematic review. *J Aquat Phys Ther* 2012;19:26–35.
38 Brosseau L, Wells GA, Tugwell P, *et al*. Ottawa Panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: part 1. *Phys Ther* 2008;88:857–71.
39 Brosseau L, Wells GA, Tugwell P, *et al*. Ottawa Panel evidence-based clinical practice guidelines for strengthening exercises in the management of fibromyalgia: part 2. *Phys Ther* 2008;88:873–86.
40 Busch AJ, Schachter CL, Peloso PM. Fibromyalgia and exercise training: a systematic review of randomized clinical trials. *Phys Ther Rev* 2001;6:287–306.
41 Busch AJ, Barber KA, Overend TJ, *et al*. Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev* 2008;(4):CD003786.
42 Busch AJ, Webber SC, Richards RS. Resistance exercise training for fibromyalgia. *Cochrane Database Syst Rev* 2013;(12):CD010884.
43 Cazzola M, Atzeni F, Salaffi F, *et al*. Which kind of exercise is best in fibromyalgia therapeutic programmes? A practical review. *Clin Exp Rheumatol* 2009;28(Suppl 63):S117–24.
44 Häuser W, Klose P, Langhorst J, *et al*. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther* 2010;12:R79.
45 Kelley GA, Kelley KS, Hootman JM, *et al*. Exercise and global well-being in community-dwelling adults with fibromyalgia: a systematic review with meta-analysis. *BMC Public Health* 2010;10:198.

46 Kelley GA, Kelley KS, Jones DL. Efficacy and effectiveness of exercise on tender points in adults with fibromyalgia: a meta-analysis of randomized controlled trials. *Arthritis* 2011;2011:125485.
47 Lima TB, Dias JM, Mazuquin BF, *et al*. The effectiveness of aquatic physical therapy in the treatment of fibromyalgia: a systematic review with meta-analysis. *Clin Rehabil* 2013;27:892–908.
48 Nüesch E, Häuser W, Bernardy K, *et al*. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. *Ann Rheum Dis* 2013;72:955–62.
49 Perraton L, Machotka Z, Kumar S. Components of effective randomized controlled trials of hydrotherapy programs for fibromyalgia syndrome: a systematic review. *J Pain Res* 2009;2:165–73.
50 Ramel J, Bannuru R, Griffith M, *et al*. Exercise for fibromyalgia pain: a meta-analysis of randomized controlled trials. *Curr Rheumatol Rev* 2009;5:188–93.
51 Reimers N, Reimers CD. Exercise for lower back pain, hip and knee osteoarthritis, and fibromyalgia: effects on pain-a literature review. *Aktuelle Rheumatologie* 2012;37:174–88.
52 Sim J, Adams N. Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia. *Clin J Pain* 2002;18:324–36.
53 Thomas EN, Blotman F. Aerobic exercise in fibromyalgia: a practical review. *Rheumatol Int* 2010;30:1143–50.
54 van Koulil S, Effting M, Kraaimaat FW, *et al*. Cognitive–behavioural therapies and exercise programmes for patients with fibromyalgia: state of the art and future directions. *Ann Rheum Dis* 2007;66:571–81.
55 Mansi S, Milosavljevic S, Baxter GD, *et al*. A systematic review of studies using pedometers as an intervention for musculoskeletal diseases. *BMC Musculoskelet Disord* 2014;15:231.
56 Bidonde J, Busch AJ, Webber SC, *et al*. Aquatic exercise training for fibromyalgia. *Cochrane Database Syst Rev* 2014;(10):CD011336.
57 Bernardy K, Füber N, Köllner V, *et al*. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome—a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol* 2010;37:1991–2005.
58 Bernardy K, Klose P, Busch AJ, *et al*. Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev* 2013;(9):CD009796.
59 Karjalainen KA, Malmivaara A, van Tulder MW, *et al*. Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. *Cochrane Database Syst Rev* 1999;(3):CD001984.
60 Häuser W, Bernardy K, Arnold B, *et al*. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis Care Res* 2009;61:216–24.
61 Scascighini L, Toma V, Dober-Spielmann S, *et al*. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology (Oxford)* 2008;47:670–8.
62 Kalichman L. Massage therapy for fibromyalgia symptoms. *Rheumatol Int* 2010;30:1151–7.
63 Li YH, Wang FY, Feng CQ, *et al*. Massage therapy for fibromyalgia: a systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* 2014;9:e89304.
64 Tsao JC. Effectiveness of massage therapy for chronic, non-malignant pain: a review. *Evid Based Complement Alternat Med* 2007;4:165–79.
65 Yuan SLK, Matsutani LA, Marques AP. Effectiveness of different styles of massage therapy in fibromyalgia: a systematic review and meta-analysis. *Man Ther* 2015;20:257–64.
66 Courtois I, Cools F, Calsius J. Effectiveness of body awareness interventions in fibromyalgia and chronic fatigue syndrome: a systematic review and meta-analysis. *J Bodyw Mov Ther* 2015;19:35–56.
67 Berman BM, Ezzo J, Hadhazy V, *et al*. Is acupuncture effective in the treatment of fibromyalgia? *J Fam Pract* 1999;48:213–18.
68 Cao H, Li X, Han M, *et al*. Acupoint stimulation for fibromyalgia: a systematic review of randomized controlled trials. *Evid Based Complement Alternat Med* 2013;2013:362831.
69 Daya S. The efficacy of acupuncture in the treatment of fibromyalgia syndrome. *Acupunct Assoc Charter Physiother* 2007;3:35–46.
70 Deare JC, Zheng Z, Xue CC. Acupuncture for treating fibromyalgia. *Cochrane Database Syst Rev* 2013;(5):CD007070.
71 Langhorst J, Klose P, Musial F, *et al*. Efficacy of acupuncture in fibromyalgia syndrome—a systematic review with a meta-analysis of controlled clinical trials. *Rheumatology (Oxford)* 2010;49:778–88.
72 Martin-Sanchez E, Torralba E, Díaz-Domínguez E, *et al*. Efficacy of acupuncture for the treatment of fibromyalgia: systematic review and meta-analysis of randomized trials. *Open Rheumatol J* 2009;3:25–9.
73 Mayhew E, Ernst E. Acupuncture for fibromyalgia—a systematic review of randomized clinical trials. *Rheumatology (Oxford)* 2007;46:801–4.
74 Yang B, Yi G, Hong W, *et al*. Efficacy of acupuncture on fibromyalgia syndrome: a meta-analysis. *J Tradit Chin Med* 2014;34:381–91.
75 McVeigh JG, McGaughey H, Hall M, *et al*. The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: a systematic review. *Rheumatol Int* 2008;29:119–30.
76 Langhorst J, Musial F, Klose P, *et al*. Efficacy of hydrotherapy in fibromyalgia syndrome—a meta-analysis of randomized controlled clinical trials. *Rheumatology (Oxford)* 2009;48:1155–9.
77 Naumann J, Sadaghiani C. Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials. *Arthritis Res Ther* 2014;16:R141.
78 Chan CL, Wang CW, Ho RT, *et al*. Qigong exercise for the treatment of fibromyalgia: a systematic review of randomized controlled trials. *J Altern Complement Med* 2012;18:641–6.
79 Cramer H, Lauche R, Langhorst J, *et al*. Yoga for rheumatic diseases: a systematic review. *Rheumatology (Oxford)* 2013;52:2025–30.
80 Langhorst J, Klose P, Dobos GJ, *et al*. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. *Rheumatol Int* 2013;33:193–207.
81 Lauche R, Cramer H, Häuser W, *et al*. A systematic review and meta-analysis of qigong for the fibromyalgia syndrome. *Evid Based Complement Alternat Med* 2013;2013:635182.
82 Peng PW. Tai Chi and chronic pain. *Reg Anesth Pain Med* 2012;37:372–82.
83 Hadhazy VA, Ezzo J, Creamer P, *et al*. Mind-body therapies for the treatment of fibromyalgia. A systematic review. *J Rheumatol* 2000;27:2911–18.
84 Lauche R, Cramer H, Dobos G, *et al*. A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome. *J Psychosom Res* 2013;75:500–10.
85 Niazi AK, Niazi SK. Mindfulness-based stress reduction: a non-pharmacological approach for chronic illnesses. *N Am J Med Sci* 2011;3:20–3.
86 Lakhan SE, Schofield KL. Mindfulness-based therapies in the treatment of somatization disorders: a systematic review and meta-analysis. *PLoS ONE* 2013;8:e71834.
87 Lee C, Crawford C, Hickey A. Mind–body therapies for the self-management of chronic pain symptoms. *Pain Med* 2014;15(Suppl 1):S21–39.
88 Ernst E. Chiropractic manipulation for non-spinal pain—a systematic review. *N Z Med J* 2003;116:U539.
89 Ernst E. Chiropractic treatment for fibromyalgia: a systematic review. *Clin Rheumatol* 2009;28:1175–8.
90 Schneider M, Vernon H, Ko G, *et al*. Chiropractic management of fibromyalgia syndrome: a systematic review of the literature. *J Manipulative Physiol Ther* 2009;32:25–40.
91 Bernardy K, Füber N, Klose P, *et al*. Efficacy of hypnosis/guided imagery in fibromyalgia syndrome-a systematic review and meta-analysis of controlled trials. *BMC Musculoskelet Disord* 2011;12:133.
92 Glombiewski JA, Bernardy K, Häuser W. Efficacy of EMG- and EEG-biofeedback in fibromyalgia syndrome: a meta-analysis and a systematic review of randomized controlled trials. *Evid Based Complement Alternat Med* 2013;2013:962741.
93 De Silva V, El-Metwally A, Ernst E, *et al*. Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review. *Rheumatology (Oxford)* 2010;49:1063–8.
94 de Souza Nascimento S, Desantana JM, Nampo FK, *et al*. Efficacy and safety of medicinal plants or related natural products for fibromyalgia: a systematic review. *Evid Based Complement Alternat Med* 2013;2013:149468.
95 Posadzki P, Ernst E. Guided imagery for musculoskeletal pain: a systematic review. *Clin J Pain* 2011;27:648–53.
96 Meeus M, Nijs J, Vanderheiden T, *et al*. The effect of relaxation therapy on autonomic functioning, symptoms and daily functioning, in patients with chronic fatigue syndrome or fibromyalgia: a systematic review. *Clin Rehabil* 2015;29:221–33.
97 Perry R, Terry R, Ernst E. A systematic review of homoeopathy for the treatment of fibromyalgia. *Clin Rheumatol* 2010;29:457–64.
98 Boehm K, Raak C, Cramer H, *et al*. Homeopathy in the treatment of fibromyalgia—a comprehensive literature-review and meta-analysis. *Complement Ther Med* 2014;22:731–42.
99 Ricci NA, Dias CN, Driusso P. The use of electrothermal and phototherapeutic methods for the treatment of fibromyalgia syndrome: a systematic review. *Rev Bras Fisioter* 2010;14:1–9.
100 Tenti S, Manica P, Galeazzi M, *et al*. Phytothermotherapy in fibromyalgia and osteoarthritis: between tradition and modern medicine. *Eur J Integr Med* 2013;5:248–53.
101 Eccles NK. A critical review of randomized controlled trials of static magnets for pain relief. *J Altern Complement Med* 2005;11:495–509.
102 Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. *Pain Pract* 2013;13:131–45.
103 Crawford C, Lee C, Bingham J. Sensory art therapies for the self-management of chronic pain symptoms. *Pain Med* 2014;15(Suppl 1):S66–75.
104 Moore RA, Wiffen PJ, Derry S. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2014;(4):CD007938.
105 Ablin J, Fitzcharles MA, Buskila D, *et al*. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. *Evid Based Complement Alternat Med* 2013;2013:485272.

EULAR revised recommendations for the management of fibromyalgia

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EXTENDED REPORT

EULAR revised recommendations for the management of fibromyalgia

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ABSTRACT

Objective The original European League Against Rheumatism recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were 'expert opinion'.

Methods A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Results 2979 titles were identified: from these 275 full papers were selected for review and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only 'strong for' therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, the following four main stages are suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as 'weak for' based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability).

Conclusions These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination and organisation of healthcare systems to optimise outcome.

INTRODUCTION

Fibromyalgia is common with a prevalence of 2% in the general population.[1 2] However, its diagnosis and management remain a challenge for patients and healthcare professionals. It often takes >2 years for a diagnosis to be made with an average of 3.7 consultations with different physicians.[3] Referral to specialists and investigations results in high healthcare use, for up to 10 years prior to diagnosis, compared with persons who do not have fibromyalgia.[4] Although pain is the dominant symptom in fibromyalgia, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common, but not universal, have an important influence on quality of life and emphasise that it is a heterogeneous and complex condition.[5 6]

The original European League Against Rheumatism (EULAR) recommendations for the management of fibromyalgia assessed evidence up to and including 2005.[7] Given the paucity of information and poor quality of the studies available, it was recommended that the guidelines be revised after a period of 4 years. However, no subsequent revision took place and thus a decade later we revisit the recommendations with the aim of making them more evidence based. In the time since the original recommendations, there have been a considerable number of individual trials examining pharmacological and non-pharmacological interventions and, moreover, there have been systematic reviews conducted for nearly all of the commonly used management strategies. Our aim therefore was, using the systematic reviews conducted and taking into account their quality, to make evidence-based recommendations for the use of individual pharmacological and non-pharmacological approaches, and how these could be combined. Further, we aimed to identify priority areas for future research.

METHODS

Working group membership

The working group included 18 members from 12 European countries: clinicians (representing rheumatology, internal medicine, pain medicine and epidemiology), non-clinical scientists (occupational health, epidemiology), patient representatives and the allied health professions (nursing).

Eligibility, search strategy and quality assessment

We focused on systematic reviews (with or without meta-analysis) concerned with the management of fibromyalgia. Details of eligibility, review and quality assessment are provided in online supplementary text.

Evaluating evidence

We retained pain as one of the key outcomes of interest, from the original guidelines, but also included fatigue, sleep and daily functioning. The committee considered the following in making a

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recommendation: number of trials, number of patients, outcomes assessed, quality of reviews and the trials included within the reviews, effect size (and 95% CI), adverse events and cost. We used the Grading of Recommendations Assessment, Development and Evaluation system for making recommendations.[10] This is a four-point scale: strong for/weak for/weak against/strong against; or allowing a recommendation 'use only for research'. The strength of recommendation is based on the balance between desirable and undesirable effects (considering values and preferences), confidence in the magnitude of effects and resource use. A strong recommendation implies that, if presented with the evidence, all or almost all informed persons would make the recommendation for or against the therapy, while a weak recommendation would imply that most people would, although a substantial minority would not.[11]

Two subgroups considered the evidence for pharmacological and non-pharmacological therapies and proposed a recommendation. At a face-to-face meeting, after presentation of the evidence and the preliminary recommendation, discussion resulted in a 'final recommendation'. In addition to the evidence on efficacy/effectiveness, the committee also took into account safety. All participants then voted on their level of agreement with the recommendation on a scale from 0, 'completely disagree', to 10, 'completely agree'. The percentage of the committee scoring at least 7 was taken to indicate level of agreement.

RESULTS

In total, 2979 titles were identified. From these, 571 abstracts and then 275 full papers were selected for review, and 107 reviews evaluated as eligible for consideration in making recommendations for management (figure 1).

Information on the reviews informing these recommendations on pharmacological therapy and on non-pharmacological and complementary and alternative medicines/therapies is collated in online supplementary tables A and B, respectively, while information from one review, for each medicine/therapy, selected based on recency and quality is provided in tables 1 and 2, respectively.

Evaluation of pharmacological medicines

Amitriptyline

Five reviews included up to 13 trials and a maximum of 919 subjects. Häuser *et al*[12] reported that patients receiving amitriptyline were more likely to achieve 30% pain reduction (risk ratio (RR) 1.60, 95% CI 1.15 to 2.24), equivalent to a 'number needed to treat' (NNT) of 3.54, 95% CI 2.74 to 5.01. There was a moderate effect on sleep (standardised mean difference (SMD) −0.56, 95% CI −0.78, to −0.34)[i] and small effect on fatigue (−0.44; −0.71 to −0.16). There was no difference in discontinuation rates compared with patients receiving placebo. Nishishinya *et al*[13] in their high-quality review concluded that 25 mg/day improved pain, sleep and fatigue at 6–8 weeks of treatment but not at 12 weeks while 50 mg/day did not demonstrate efficacy. *Amitriptyline evaluation: weak for, at low dose (100% agreement).*

Anticonvulsants

Nine reviews of pregabalin included up to seven studies and a maximum of 3344 patients. A recent Cochrane review[24] reported patients receiving active treatment were more likely to have 30% pain reduction, RR 1.37, 95% CI 1.22 to 1.53, with a 'number needed to benefit' (NNTB) over placebo of 9, 95% CI 7 to 13. There was a very small effect on fatigue (−0.17; −0.25 to −0.09) and small effect on sleep (−0.35; −0.43 to −0.27) but no effect on disability (−0.01; −0.11 to 0.09). A single, moderate quality, study of gabapentin in 150 subjects (eg, in ref. 104) showed a significant effect on 30% pain reduction (RR 1.65, 95% CI 1.10 to 2.48), a small effect on sleep (−0.71; −1.08 to −0.24) and a large effect on disability (−0.94; −1.32 to −0.56). *Anticonvulsant evaluation: pregabalin—weak for (94% agreement); gabapentin—research only (100% agreement).*

Cyclobenzaprine

A single systematic review of five studies involving 312 patients reported that of those taking cyclobenzaprine 85% experienced side effects and only 71% completed the studies. They were more likely to report themselves as 'improved' (NNT 4.8, 95% CI 3.0 to 11.0). Only two studies reported an 'intention-to-treat' (ITT) analysis. Sleep, but not pain, showed a significant, very small, improvement relative to baseline at the longest outcome considered (12 weeks: SMD 0.34) and patients on placebo showed similar improvement (SMD 0.52).[25] *Cyclobenzaprine evaluation: weak for (75% agreement).*

Growth hormone

A single systematic review of two studies involving 74 patients reported an effect size on pain of 1.36 (0.01 to 1.34).[16] The improvement in functional deficit was not statistically significant (1.24; −0.36 to 2.84). There are concerns on safety (sleep apnoea, carpal tunnel syndrome). The drug is not approved for fibromyalgia (FM) or related disorders in Europe. *Growth hormone evaluation: strong against (94% agreement).*

Monoamine oxidase inhibitors

Four reviews identified up to three studies and 241 patients. Häuser *et al*[26] reported a moderate effect on pain across the studies (−0.54; −1.02, to −0.07), but the single studies that evaluated fatigue and sleep showed no effect. There were no differences in dropouts or adverse events compared with placebo. There was no comparison between compounds. Life-threatening interactions have been documented. *Monoamine oxidase inhibitors (MAOIs) evaluation: weak against (81% agreement).*

NSAIDs

A single review[21] identified two small trials with no evidence of improved outcome compared with placebo. One low-quality review was not considered. *Non-steroidal anti-inflammatory drugs (NSAIDs) evaluation: weak against (100% agreement).*

Serotonin-noradrenalin reuptake inhibitors

Eight systematic reviews were identified, which presented data separately for duloxetine. The largest review of 2249 subjects[32] reported duloxetine, short term (up to 12 weeks) and long term (up to 28 weeks), was more effective than placebo at reducing pain (RR >30% pain, RR 1.38, 95% CI 1.22 to 1.56), although there was no significant effect at 20–30 mg/day and no difference between doses of 60 and 120 mg/day. NNTB, based on 60 mg/day up to 12 weeks, was 6, 95% CI 3 to 12. A previous review reported small effects on sleep (−0.24; −0.37, to −0.12) and disability (−0.33; −0.43, to −0.24) but no effect on fatigue.[30] Seven systematic reviews were identified of milnacipran, a recent one of which evaluated five trials.[30] Patients taking milnacipran were more likely, at the end of treatment, to

[i]All effect sizes are expressed as SMD with 95% CI unless otherwise stated.

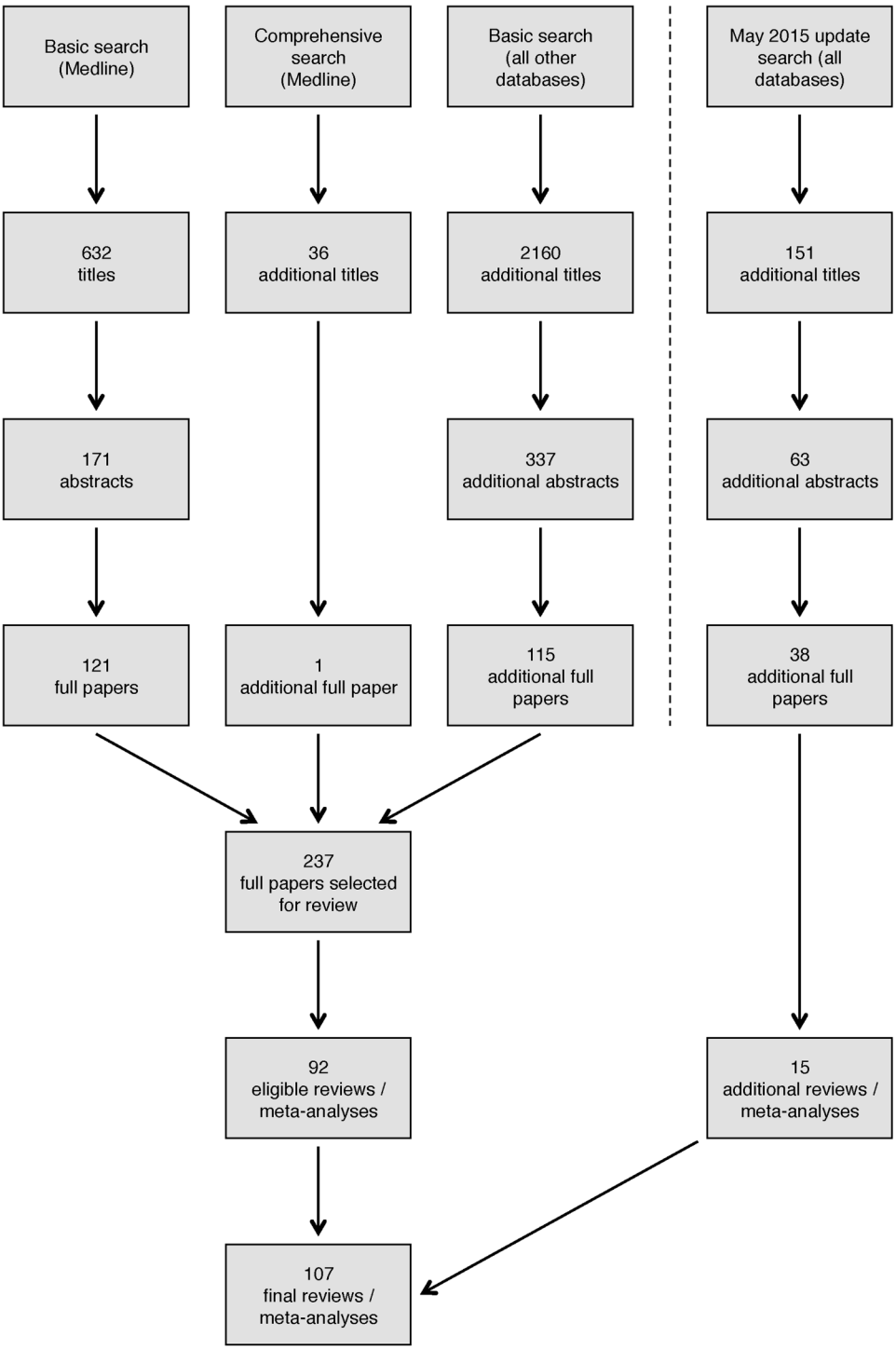

Figure 1 Flow chart identifying eligible reviews.

have 30% pain reduction (RR 1.38, 95% CI 1.25 to 1.51) but there was only a small benefit on fatigue (−0.14; −0.19 to −0.08), disability (−0.16; −0.23 to −0.10) and no effect on sleep. *Duloxetine and milnacipran evaluation: weak for (100% agreement).*

Selective serotonin reuptake inhibitors

Seven systematic reviews included up to 11 trials and a maximum of 521 subjects. Given that reviews have not focused on specific drugs or comparisons, drugs within this class were considered together. A recent review of medium quality included seven trials and reported a moderate effect on pain (−0.40; −0.73, to −0.07), sleep (−0.31; −0.60 to −0.02) and no effect on fatigue (−0.17; −0.46 to 0.11).[36] *Selective serotonin reuptake inhibitor (SSRI) evaluation: weak against (94% agreement).*

Sodium oxybate

A single systematic review of five studies including 1535 patients reported small effects sizes on pain (0.44; 0.31 to 0.58), sleep problems (0.47; 0.28 to 0.66) and fatigue (0.48; 0.35 to 0.60). The European Medicines Agency and the US Food and Drug Administration refused the approval for FM because of safety concerns.[16] The drug is only approved for narcolepsy. *Sodium oxybate evaluation: strong against (94% agreement).*

Table 1 Overview of results from selected systematic reviews of placebo-controlled pharmacological trials

Treatment (review reference)	No. of trials (no. of participants) Review quality	Dosages; durations of treatment	Overall trial quality*	Safety and comments
Amitriptyline[12]	10 (767) AMSTAR=6	10–50 mg/day; 8–24 weeks	Low	There was no analysis of safety but no difference in discontinuation rates compared with patients on placebo was reported.
Anticonvulsants—pregabalin[24]	5 (3256) AMSTAR=10	Three studies with fixed doses of 300, 450 and 600 mg/day; one with fixed doses of 150, 300 or 450 mg/day; one flexible dosing study of 300 or 450 mg/day; 8–14 weeks	High	Increased likelihood of withdrawal due to adverse events, RR 1.68, 95% CI 1.36 to 2.07; NNH 12 95% CI 9 to 17. No difference in likelihood of serious adverse events.
Cyclobenzaprine[25]	5 (312) AMSTAR=7	10–40 mg; 2–24 weeks	Moderate	There was no analysis of adverse outcomes in the trials reviewed although dropout across trials was large (cyclobenzaprine 29%, placebo 43%). Only two studies conducted ITT.
Growth hormone[16]	2 (74) AMSTAR=5	0.0125 mg/kg/day; adjusted to maintain IGF-1 level of 250 ng/mL after first month, 0.0125 mg/kg/day; 9 months to 1 year	NE	Safety concerns include sleep apnoea and carpal tunnel syndrome.
MAOIs[26]	3 (241) AMSTAR=9	Pirlindole 150 mg/day, moclobemide 150–300 mg/day; 4–12 weeks	Low	MAOIs are known to cause potentially fatal hypertensive crises, serotonin syndrome and psychosis when they interact with foods containing tyramine and medications (many of which are commonly used in the treatment of FM), including SSRIs, tricyclic antidepressants and tramadol. The clinical trials had restrictions on concomitant medications.
NSAIDs[21]	2 (242) AMSTAR=7	Ibuprofen 600 mg four times a day, tenoxicam 20 mg/day; 6–8 weeks	Low	The adverse event profile, although not considered in this review, is well established for this class of drugs.
SNRIs—duloxetine[31]	6 (2249) AMSTAR=10	20–120 mg/day; 12–28 weeks	Moderate	Dropout rates due to side effects across studies higher than with placebo. No difference in serious adverse events.
SNRIs—milnacipran[30]	5 (4118) AMSTAR=10	100 or 200 mg/day; 12–27 weeks	High	Dropout rates due to side effects across studies were double compared with placebo, but there was no difference in serious adverse events.
SSRIs[36]	7 (322) AMSTAR=8	20–40 mg/day citalopram, 20–80 mg/day fluoxetine, 20–60 mg/day paroxetine; 6–16 weeks	Moderate to high	Acceptability and tolerability were similar to placebo NNH 40, 95% CI 19 to 66. Although several studies excluded patients with depression/anxiety, Häuser *et al*[26] showed a small effect of SSRIs in improving depressed mood (SMD −0.37, 95% CI −0.66 to −0.07).
Sodium oxybate[16]	5 (1535) AMSTAR=5	4.5–6 g/day; 8–14 weeks	NE	There is the potential for abuse and central nervous system effects associated with abuse such as seizure, respiratory depression and decreased levels of consciousness.
Tramadol[22]	1 (313) AMSTAR=3	37.5 mg tramadol/325 mg paracetamol 4×/day; 3 months	High	No significant difference in discontinuation due to adverse events (RR 1.62, 95% CI 0.94 to 2.80). A high-quality review (AMSTAR score 7) identified a single study, which, among persons who tolerated and benefitted from tramadol, demonstrated a lower discontinuation rate in a double-blind phase compared with placebo.[21]

*According to the method of quality evaluation used in the review.
AMSTAR, Assessing the Methodological Quality of Systematic Reviews; FM, fibromyalgia; IGF, insulin growth factor; ITT, intention-to-treat; MAOIs, monoamine oxidase inhibitors; NE, not evaluated; NNH, number needed to harm; NSAIDs, non-steroidal anti-inflammatory drugs; RR, risk ratio; SMD, standardised mean difference; SNRI, serotonin-noradrenalin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Tramadol, a weak opioid with mild serotonin-noradrenalin reuptake inhibitor (SNRI) activity was considered by two reviews. Roskell *et al*[22] identified a single study of tramadol with paracetamol. Those in the active arm were more likely to have 30% improvement in pain (RR 1.77, 95% CI 1.26 to 2.48). *Tramadol evaluation: weak for (100% agreement)*.

The literature search did not identify any reviews on corticosteroids, strong opioids, cannabinoids and antipsychotics. The committee made a 'strong against' evaluation (100% agreement) regarding the use of strong opioids and corticosteroids in patients with fibromyalgia on the basis of lack of evidence of efficacy and high risk of side effects/addiction reported in individual trials.

Evaluation of non-pharmacological therapies; complementary and alternative medicines and therapies

Acupuncture

Eight reviews included up to 16 trials and 1081 participants. One high-quality review included nine trials, with 395 patients, and demonstrated that acupuncture, added to standard therapy, resulted in a 30% (21%, 39%) improvement in pain.[70] Electric acupuncture was also associated with improvements in pain (22%; 4% to 41%) and fatigue (11%; 2% to 20%). Some adverse events were reported, but these were commonly mild and transient. There is little understanding of the active component of acupuncture, and the evidence supporting the use of real versus sham acupuncture was less consistent. *Acupuncture evaluation: weak for (93% agreement)*.

Table 2 Overview of results from selected systematic reviews of non-pharmacological; complementary and alternative medicine and therapy trials

Treatment (review reference)	No. of trials (no. of participants*) Review quality	Dosages; durations of treatment	Overall trial quality†	Safety and comments
Acupuncture[70]	9 (395) AMSTAR=11	Treatment sessions ranged from 3 to 13 weeks (median=4), with needle retention ranging from 20 to 30 min. Only one study provided journal references for the acupuncture point selection, and the description of the type of needle stimulation/ manipulation was clear in only three studies.	Moderate	One in six people who had acupuncture, and one in three controls, reported adverse events. Such events were minor and lasted less than one day. No serious adverse events were reported in any trials.
Biofeedback[92]	7 (321) AMSTAR=8	EMG biofeedback. Individual sessions varied between 45 and 180 min, and the number of sessions varied between 6 and 16. EEG biofeedback. 20–22 sessions of (where reported) 30 min duration.	Poor	Only two‡ trials reported adverse event data. 4% of patients in one trial receiving EMG biofeedback reported stress. And 74% of patients in another, receiving EEG biofeedback reported a variety of side effects, including: headache, fatigue and sleep problems.
Capsaicin[94]	2 (153) AMSTAR=5	Topical application of *Capsicum annuum L*. cream, either 0.025% capsaicin for 4 weeks or 0.075% for 12 weeks.	Not reported	Patients reported moderate, transient, burning or stinging.
Chiropractic[89]	3 (102) AMSTAR=4	Little detail is given for any trials, but treatment elements included massage, stretching, spinal manipulation, education and resistance training.	Low	Around 50% of patients experience mild-to-moderate transient adverse effects after spinal manipulation.§
CBT[57]	23 (2031) AMSTAR=11	Median duration of therapy=10 weeks, with a median number of 10 sessions, and median total hours=18 hours. All but two studies delivered therapy face to face. Median follow-up (where this was performed 17/23 studies)=6 months.	Low	The assessment of safety in most studies was insufficient. Two studies reported dropout due to worsening of comorbid mental disorders. However, CBT is generally considered safe.
Exercise[41]	34 (2276) AMSTAR=9	Exercise programmes lasting 2.5–24 weeks. Aerobic exercise for ≥20 min, once a day (or twice for ≥10 min), 2–3 days a week. Strength training with ≥8 repetitions per exercise, 2–3 times a week.	Moderate	Although patients may initially notice a deterioration in symptoms, exercise is generally considered safe, especially when practised under supervision.
Hydrotherapy/spa therapy[76]	10 (446) AMSTAR=9	Wide variation in precise treatment strategy between trials. Most consisted of water or mud baths at body temperature 36–37°C, or slightly above (40–45°C), with a median treatment time of 240 min (range 200–300), over several weeks.	Low	Three studies reported no side effects of treatment; one reported slight flashes in 10% of the patients. The remaining trials did not explicitly mention safety.
Hypnotherapy[91]	4 (152) AMSTAR=11	Some variation between trials ranging (where reported) from 300 to 420 min, delivered over 10–26 weeks.	Good	Adverse events were not reported in any of the trials.
Massage[63]	9 (404) AMSTAR=7	Massage therapy time lasted 25–90 min, with between 1 and 20 massage sessions in total.	Low to moderate	No adverse events were reported in any of the trials.
Meditative movement[80]	7 (362) AMSTAR=9	Wide variation in treatments between trials, and included yoga, tai chi, qigong or body awareness therapy. Median (range) duration of treatment=16 (6–24) hours, over 4–12 weeks.	Moderate	Although no serious adverse events were reported, six participants (3.1%) withdrew from the trials because of adverse events (increase of pain; muscle inflammation; chlorine hypersensitivity). The review authors concluded that the acceptance and safety of all types of meditative movement therapies were high.
Mindfulness/mind–body therapy[84]	6 (674) AMSTAR=9	Some variation between trials. Single 2–3.5 hours session per week, for 8–10 weeks. Four out of six programmes also included daily home practice (30–45 min) plus a single all-day retreat.	Low	Safety was assessed and reported in none of the trials.
Multicomponent therapy[60]	9 (1119) AMSTAR=9	Enormous variation in treatment strategies between trials. Most included different combinations of exercise (land and/or water based); education; relaxation; and/or some other specific therapeutic component (eg, Tai Chi; or massage).	Moderate	No adverse events were reported in any of the trials.
SAMe[93]	1 (44) AMSTAR=6	400 mg tablet, twice a day, for 6 weeks.	Moderate	Mild adverse effects such as stomach upset and dizziness were reported.
Other: guided imagery[91]	1 (48) AMSTAR=9	Audiotape-led, individual, guided imagery: 30 min daily for 6 weeks recommended. Median of 44 exercises (range 37–136).	Good	Adverse events were not reported.
Other: homeopathy[98]	4 (163) AMSTAR=7	Variation between trials. Two studied individualised homeopathic treatment, consisting of an initial consultation (and treatment), plus follow-up interviews every 4–8 weeks. Two studied *Arnica montana*, *Bryonia alba* or *Rhus toxicodendron* (potency 6c) daily for between 1 and 3 months.	Low to moderate	No information was provided on safety.

*Total number of persons randomised.
†According to the method of quality evaluation used in the review.
‡Elsewhere in the review, it reports that three studies reported on adverse events. However, in the table where these data are presented, it is only clear for two. However, in a third trial, there were no dropouts due to side effects.
§These data were not contained in this review. The initial recommendation for chiropractic was weak against. However, after discussion, this was downgraded to strong against due to potential safety concerns.
CBT, cognitive behavioural therapy; EMG, electromyographic; SAMe, *S*-adenosyl methionine.

Biofeedback

Two reviews included up to seven trials and 307 participants. Glombiewski *et al*[92] reviewed seven studies, comprising 321 participants. Treatment sessions varied from 6 to 22; with control therapy comprising sham biofeedback, attention control, medication and treatment as usual. Biofeedback was effective in reducing pain intensity (Hedges' g=0.79; 0.22 to 1.36), although all trials were poor quality. There was no evidence of effectiveness in terms of fatigue or sleep and subgroup analysis suggested that any effect was limited to electromyographic (0.86; 0.11 to 1.62) rather than electroencephalographic biofeedback (0.71; −0.37 to 1.8). *Biofeedback evaluation: weak against (100% agreement).*

Capsaicin

Two reviews included two trials and 153 participants. The most recent review, a narrative review of two trials, considered data on 153 patients.[94] Both showed some evidence of positive effect in terms of pain relief, although results were not consistent for other outcomes. Capsaicin gel is generally considered safe, although many users report a mild burning sensation when applied to the skin. However, the number of patients and trials was small and was therefore limited in the extent to which they can provide evidence for toxicity. *Capsaicin evaluation: weak against (86% agreement).*

Chiropractic

Three reviews included up to 13 trials and 102 participants. The most recent review summarised three studies.[89] One study was an open pilot study, one quasi-randomised and in the third no between-group differences were observed in terms of pain. The studies were poor quality and lacked robust interpretable data. *Chiropractic evaluation: strong against (93% agreement).*

Cognitive behavioural therapies

Five reviews included up to 30 trials and at least 2031 participants. One high-quality review included 23 trials, comprising >2000 patients, although the quality of individual trials was reported as generally poor.[58] Cognitive behavioural therapies (CBTs) were effective in reducing pain (−0.29; −0.49 to −0.17) and disability (−0.30; −0.51 to −0.08) at the end of treatment compared with a variety of controls groups, and results were sustained long term. *Behavioural therapy evaluation: weak for (100% agreement).*

Exercise

Twenty reviews included up to 34 trials and at least 2494 participants.[ii] The largest, a Cochrane review, considered 47 different exercise interventions.[41] Aerobic exercise was associated with improvements in pain (0.65; −0.09 to 1.39) and physical function (0.66; 0.41 to 0.92). Busch *et al*[42] reviewed five trials with 219 participants and concluded that resistance training resulted in a significant improvement in pain (−3.3 cm on a 10 cm scale; −6.35 to −0.26) as well as function compared with control. There is some consistency with regard to aerobic and strengthening exercises, although insufficient evidence to suggest superiority of one over the other; land and aquatic exercise appear equally effective.[56] *Exercise therapy evaluation: strong for (100% agreement).*

[ii]It is unclear from some of the reviews how many participants were included. The number of participants represents the minimum about which we can be confident.

Hydrotherapy/spa therapy

Four reviews included up to 21 trials and 1306 participants. One high-quality review included 10 trials, 446 participants and compared a median of 4-hour hydrotherapy (range 200–300 min) against various comparators.[76] There was a significant improvement in pain (−0.78; −1.42 to −0.13) at the end of therapy, maintained in the longer term (median 14 weeks), although the review authors noted that no trials conducted an ITT analysis. There was consistency with regard to the evidence for hydrotherapy and balneotherapy, although little evidence to suggest superiority of one over the other.[77] *Hydrotherapy evaluation: weak for (93% agreement).*

Hypnotherapy

One review included four trials, although the number of participants is unclear.[91] Although six trials of hypnotherapy and/or guided imagery were reviewed, only four examined hypnotherapy in isolation. Median treatment duration (where reported) was 360 min and hypnotherapy was compared with a variety of control therapies: cognitive intervention, active control (physical therapy/massage/relaxation/autogenic training) and treatment as usual. A meta-analysis is presented on all six trials, and isolated data for hypnotherapy are not presented. Two of the four hypnotherapy trials report some significant benefit in terms of pain, the other two demonstrate null, non-significant results. *Hypnotherapy evaluation: weak against (86% agreement).*

Massage

Six reviews have been reported and one meta-analysis with nine trials and 404 patients[63] with sessions lasting 25–90 min, and treatment duration ranging from 1 to 24 weeks (median 5 weeks). Comparator treatments included transcutaneous electrical nerve stimulation (TENS), standard care, guided relaxation and acupuncture. Methodological problems were noted with all of the studies, only four were at low risk of bias in terms of random allocation and only two were analysed as ITT. Overall, massage was not associated with a significant improvement in pain (0.37; −0.19 to 0.93), and of the two ITT analyses, one favoured massage and one favoured control (both significant). A subgroup analysis revealed some evidence of a positive effect with massage of ≥5 weeks duration, although this was based solely on lower-quality trials. *Massage evaluation: weak against (86% agreement).*

Meditative movement

Six reviews, including up to eight trials and 559 participants, focused on qigong, yoga, tai chi or a combination of these therapies. However, there was insufficient evidence to make individual recommendations. One review included seven trials, with 362 participants randomised to tai chi, yoga, qigong or body awareness therapy.[80] Total treatment time ranged from 12 to 24 hours and was compared with a variety of controls, including treatment as usual and active control groups (aerobics, wellness education and stretching). At the end of therapy, improvements were seen in sleep (−0.61; −0.95 to −0.27) and fatigue (−0.66; −0.99 to −0.34) some of which were maintained in the longer term. *Meditative movement evaluation: weak for (71% agreement).*

Mindfulness/mind–body therapy

Six reviews included up to 13 trials and 1209 participants. One recent review, a meta-analysis of six trials, with 674 patients[84] provided evidence that mindfulness-based stress reduction

resulted in improvements in pain (−0.23; −0.46 to −0.01) immediately post treatment compared with usual care and compared with active control interventions (−0.44; −0.73 to −0.16). However, these effects were not robust against bias. *Mindfulness/mind–body therapy evaluation*: *weak for (73% agreement)*.

Multicomponent therapy

Two reviews including up to 27 trials and 2407 participants examined the additional benefit of combining therapies compared with individual therapy. Häuser *et al*[60] conducted a review of management involving both educational or psychological therapies and exercise. In a meta-analysis of nine trials and 1119 patients, multicomponent therapy was effective in reducing pain (−0.37; −0.62 to −0.13), and fatigue, immediately post treatment, compared with waiting list, relaxation, treatment as usual and education. However, effects were short-lived. *Multicomponent therapy evaluation: weak for (93% agreement)*.

S-Adenosyl methionine

Two reviews each included one trial with, in combination, 74 participants. De Silva *et al*[93] reported that, after the end of treatment, significant improvements were observed in pain and fatigue compared with placebo. Sim and Adams[52] reviewed a trial comparing *S*-adenosyl methionine (SAMe) with TENS but data on the main trial comparison are omitted. Side effects are usually mild and infrequent. However, the number of patients and trials was small and therefore cannot provide a robust assessment of toxicity and safety. *SAMe evaluation: weak against (93% agreement)*.

Other complementary and alternative therapies

Three reviews of guided imagery included up to six trials and 357 participants. The highest quality, including only one trial, provided some evidence that guided imagery may be effective in reducing pain (−1.52; −2.17 to −0.87).[90] Two reviews of homeopathy included four trials and 163 participants.[97 98] Both contained a review including only four randomised trials, each of which showed some benefit of homeopathy, on some outcomes. However, none of the individual trials were without serious flaws. *Other complementary and alternative therapies (guided imagery, homeopathy): strong against (93% agreement)*.

Reviews were identified that examined electrothermal and phototherapeutic therapy;[99] phytothermotherapy;[100] music therapy, journaling/storytelling[103] and static magnet therapy,[101] although each was insufficient to allow a recommendation. Marlow *et al*[102] examined the effectiveness of transcranial magnetic and/or direct current stimulation. Eight trials included 244 participants, although not all were analysed by ITT, and appropriate group comparisons were not presented for all studies. Overall, there was little evidence to support either therapy, and several studies reported an unacceptably high rate of adverse events and/or discontinuation due to headache.

EULAR revised recommendations

In terms of overall principles, we recommend, based on unanimous expert opinion, that optimal management requires prompt diagnosis and providing the patient with information (including written material) about the condition. There should be a comprehensive assessment of pain, function and the psychosocial context. Management should take the form of a graduated approach with the aim of improving health-related quality of life. It should focus first on non-pharmacological modalities. This is based on availability, cost, safety issues and patient preference.

We have used the evaluation of individual therapies (above) to make 10 specific recommendations, all based on evidence from systematic reviews and all but one from meta-analysis. The recommendations are given in table 3, and a flow chart of how these therapies may be used in management is shown in figure 2.

We were unanimous in providing a 'strong for' recommendation for the use of exercise, particularly given its effect on pain, physical function and well-being, availability, relatively low cost and lack of safety concerns. The available evidence did not allow us to distinguish between the benefits of aerobic or strengthening. We gave 'weak for' recommendations in relation to meditative movement therapies (which improved sleep, fatigue and quality of life) or mindfulness-based stress reduction (which improved pain and quality of life); the physical therapies acupuncture or hydrotherapy for which there was evidence that they improved pain/fatigue and pain/quality of life, respectively. The effects seen in pragmatic trials of such therapies will include specific and non-specific effects, and it is not possible to disentangle these. There were some non-pharmacological therapies we did not recommend because of lack of effectiveness and/or low study quality: biofeedback, capsaicin, hypnotherapy, massage, SAMe and other complementary and alternative therapies. We provided a 'strong against' evaluation for chiropractic based on safety concerns.

In case of lack of effect of the above therapeutic approaches, we recommend individualised treatment according to patient need. Psychological therapies ('weak for') should be considered for those with mood disorder or unhelpful coping strategies: CBT was effective at producing modest, long-term reductions in pain, disability and improving mood. Pharmacological therapies (all 'weak for') should be considered for those with severe pain (duloxetine, pregabalin, tramadol) or sleep disturbance (amitriptyline, cyclobenzaprine, pregabalin). Multimodal rehabilitation ('weak for') programmes should be considered for those with severe disability—in comparison to individual therapies, those that were multimodal improved a range of short-term outcomes. We did not recommend several pharmacological therapies including NSAIDs, MAOIs and SSRIs because of lack of efficacy and specifically gave a 'strong against' evaluation to growth hormone, sodium oxybate, strong opioids and corticosteroids based on lack of efficacy and high risk of side effects.

DISCUSSION

The previous EULAR recommendations provided an important milestone in the management of fibromyalgia. There were nine recommendations, but only three were supported by strong evidence from the scientific literature; most were based on expert opinion. Since that time, there have been a considerable number of trials published addressing issues in the management of fibromyalgia. The availability of systematic reviews and meta-analysis of randomised controlled trials (RCTs) for all the most common approaches to management allowed us to concentrate on these.

Comparison with 2007 EULAR recommendations

Despite the very large increase in the amount of trial data and summarised in meta-analyses, there are no major changes to the approach of managing patients with fibromyalgia, although we provide new evidence in support for some additional non-pharmacological therapies. In addition, all the recommendations are now firmly evidence based. We now recommend that non-pharmacological therapy should be first-line therapy and then if there is a lack of effect that there should be individualised

Table 3 Recommendations

Recommendation	Level of evidence	Grade	Strength of recommendation	Agreement (%)*
Overarching principles				
Optimal management requires prompt diagnosis. Full understanding of fibromyalgia requires comprehensive assessment of pain, function and psychosocial context. It should be recognised as a complex and heterogeneous condition where there is abnormal pain processing and other secondary features. In general, the management of FM should take the form of a graduated approach.	IV	D		100
Management of fibromyalgia should aim at improving health-related quality of life balancing benefit and risk of treatment that often requires a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function, associated features (such as depression), fatigue, sleep disturbance and patient preferences and comorbidities; by shared decision-making with the patient. Initial management should focus on non-pharmacological therapies.	IV	D		100
Specific recommendations				
Non-pharmacological management				
Aerobic and strengthening exercise	Ia	A	Strong for	100
Cognitive behavioural therapies	Ia	A	Weak for	100
Multicomponent therapies	Ia	A	Weak for	93
Defined physical therapies: acupuncture or hydrotherapy	Ia	A	Weak for	93
Meditative movement therapies (qigong, yoga, tai chi) and mindfulness-based stress reduction	Ia	A	Weak for	71–73
Pharmacological management				
Amitriptyline (at low dose)	Ia	A	Weak for	100
Duloxetine or milnacipran	Ia	A	Weak for	100
Tramadol	Ib	A	Weak for	100
Pregabalin	Ia	A	Weak for	94
Cyclobenzaprine	Ia	A	Weak for	75

*Percentage of working group scoring at least 7 on 0–10 numerical rating scale assessing agreement.

therapy according to patient need, which may include pharmacological therapy.

Comparison with other recommendation

There are three recent guidelines on the management of FM from Canada, Israel and Germany that have been compared with respect to their recommendations.[105] These guidelines and our EULAR recommendations are in agreement on the principles of approach to management, the need for tailored therapy to the individual and the first-line role of non-pharmacological therapies. There are differences between our guidelines and previous guidelines, which can partly be explained by us using more recently available evidence. There are differences in the strength of recommendations relating to pharmacological therapies: anticonvulsants and SNRIs were strongly recommended by the Canadian and Israeli guidelines while the German and these EULAR guidelines provide a weak recommendation. There are also differences in relation to individual non-pharmacological therapies across guidelines in terms of whether they were assessed. For example, meditative movement is strongly recommended by the German guidelines, but recommended only for a minority of patients in Israel, while these EULAR guidelines provide a 'weak for' recommendation.

The committee recommended that an update is conducted after 5 years in order to determine whether for those therapies with relatively little current evidence further trials have been conducted and, second, whether any new therapies have emerged for the management of fibromyalgia.

Research priorities

In the course of discussion, we identified important questions in terms of guiding management where there was either insufficient (or often no) evidence base to guide decisions, that is, 'research gaps'. We discussed their relatively priority taking into account their potential to guide management, the likelihood that such studies could be conducted and were likely to be funded. We identified five such priority questions:

- Which type of exercise is most effective: strength and/or aerobic training?
- Are combined pharmacological and non-pharmacological approaches to management more effective than single-modality management?
- Are there characteristics of patients with fibromyalgia that predict response to specific therapies?
- How should fibromyalgia be managed when it occurs as a comorbidity to inflammatory arthritis?
- What aspects of a healthcare system optimise outcome for patients (who is best for the management of FM patients)?

Some of these questions are best answered by RCTs. Given, however, the expense of such studies and that they can take almost 10 years from identifying the questions to be answered to results being obtained, alternatives including registers and observational studies should be considered. These can be complemented by qualitative studies to determine the needs of patients.

Dissemination

These recommendations will be disseminated by the international working group through national rheumatology societies. This will include scientific meetings, newsletters and continuing education programmes. We will produce a summary of the recommendations suitable for dissemination through EULAR-affiliated patient groups and through national patient societies. We will investigate assessing agreement with the recommendations in the target population.

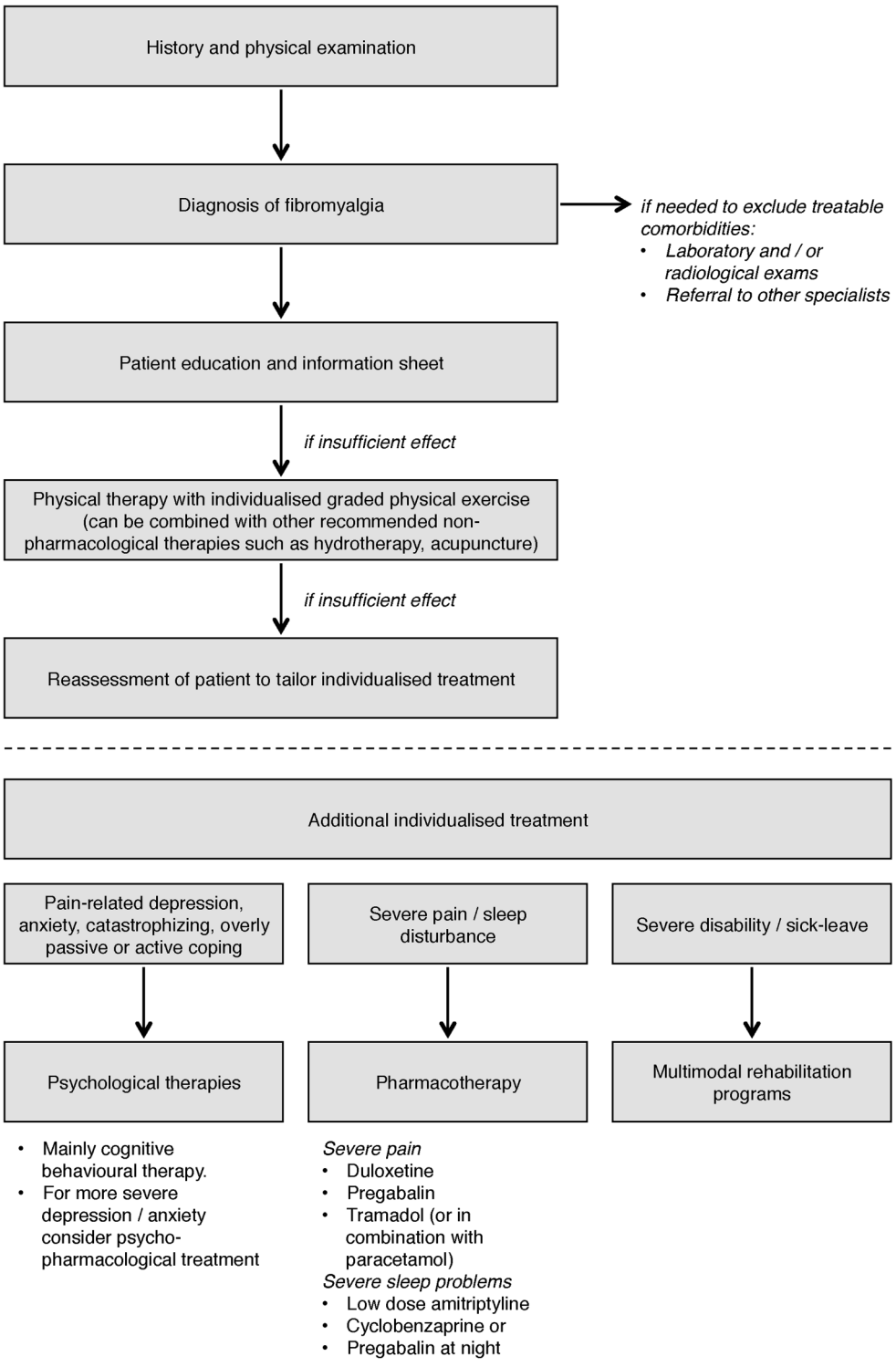

Figure 2 Management recommendations as flow chart.

SUMMARY

In summary, these revised EULAR recommendations newly incorporate a decade of evidence in relation to the pharmacological and non-pharmacological management of fibromyalgia. They allow EULAR to move from recommendations that are predominantly based on expert opinion to ones that are firmly based on scientific evidence from high-quality reviews and meta-analyses. Despite this evidence, however, the size of effect for many treatments is relatively modest. We propose focusing on the research priorities we outline to address issues clarifying to whom certain interventions may best be delivered, their effect in combination, matching patients to therapies and the organisation of healthcare systems to optimise outcome.

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REFERENCES

1 Queiroz LP. Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep* 2013;17:356.
2 Wolfe F, Ross K, Anderson J, *et al*. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19–28.
3 Choy E, Perrot S, Leon T, *et al*. A patient survey of the impact of fibromyalgia and the journey to diagnosis. *BMC Health Serv Res* 2010;10:102.
4 Boonen A, van den Heuvel R, van Tubergen A, *et al*. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. *Ann Rheum Dis* 2005;64:396–402.
5 HäuserW, Zimmer C, *et al*. [What are the key symptoms of fibromyalgia? Results of a survey of the German Fibromyalgia Association]. *Schmerz* 2008;22:176–83.
6 Fietta P, Manganelli P. Fibromyalgia and psychiatric disorders. *Acta Biomed* 2007;78:88–95.
7 Carville SF, Arendt-Nielsen L, Bliddal H, *et al*. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis* 2008;67:536–41.
8 Shea BJ, Grimshaw JM, Wells GA, *et al*. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007;7:10.
9 Abeles M, Solitar BM, Pillinger MH, *et al*. Update on fibromyalgia therapy. *Am J Med* 2008;121:555–61.
10 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
11 Andrews JC, Schünemann HJ, Oxman AD, *et al*. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726–35.
12 Häuser W, Petzke F, Üçeyler N, *et al*. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology* 2011;50:532–43.
13 Nishishinya B, Urrútia G, Walitt B, *et al*. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. *Rheumatology (Oxford)* 2008;47:1741–6.
14 Üçeyler N, Häuser W, Sommer C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. *Arthritis Care Res* 2008;59:1279–98.
15 Moore RA, Derry S, Aldington D, *et al*. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;(12):CD008242.
16 Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. *Eur J Pain* 2014;18:1067–80.
17 Häuser W, Bernardy K, Üçeyler N, *et al*. Treatment of fibromyalgia syndrome with gabapentin and pregabalin–a meta-analysis of randomized controlled trials. *Pain* 2009;145:69–81.
18 Moore RA, Straube S, Wiffen PJ, *et al*. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2009;(3):CD007076.
19 Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. *J Pain* 2010;11:505–21.
20 Tzellos TG, Toulis KA, Goulis DG, *et al*. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. *J Clin Pharm Ther* 2010;35:639–56.
21 Choy E, Marshall D, Gabriel ZL, *et al*. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. *Semin Arthritis Rheum* 2011;41:335–45.
22 Roskell NS, Beard SM, Zhao Y, *et al*. A meta-analysis of pain response in the treatment of fibromyalgia. *Pain Pract* 2011;11:516–27.
23 Siler AC, Gardner H, Yanit K, *et al*. Systematic review of the comparative effectiveness of antiepileptic drugs for fibromyalgia. *J Pain* 2011;12:407–15.
24 Üçeyler N, Sommer C, Walitt B, *et al*. Anticonvulsants for fibromyalgia. *Cochrane Database Syst Rev* 2013;(10):CD010782.
25 Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis. *Arthritis Care Res* 2004;51:9–13.
26 Häuser W, Bernardy K, Üçeyler N, *et al*. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA* 2009;301:198–209.
27 Tort S, Urrútia G, Nishishinya MB, *et al*. Monoamine oxidase inhibitors (MAOIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev* 2012;(4):CD009807.
28 Sultan A, Gaskell H, Derry S, *et al*. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. *BMC Neurol* 2008;8:29.
29 Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database Syst Rev* 2009;(4):CD007115.
30 Häuser W, Urrútia G, Tort S, *et al*. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev* 2013;(1):CD010292.
31 Ormseth MJ, Eyler AE, Hammonds CL, *et al*. Milnacipran for the management of fibromyalgia syndrome. *J Pain Res* 2010;3:15–24.
32 Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014;(1):CD007115.
33 Derry S, Gill D, Phillips T, *et al*. Milnacipran for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;(3):CD008244.
34 Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997;12:384–9.
35 Arnold LM, Keck PE, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 2000;41:104–13.
36 Häuser W, Wolfe F, Tölle T, *et al*. The role of antidepressants in the management of fibromyalgia syndrome. *Central Nervous System Drugs* 2012;26:297–307.
37 Bednar ML, Soroczynski AC, Groman MJ, *et al*. Effectiveness of land-based and aquatic-based exercises for improving the health status of individuals with fibromyalgia: a systematic review. *J Aquat Phys Ther* 2012;19:26–35.
38 Brosseau L, Wells GA, Tugwell P, *et al*. Ottawa Panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: part 1. *Phys Ther* 2008;88:857–71.
39 Brosseau L, Wells GA, Tugwell P, *et al*. Ottawa Panel evidence-based clinical practice guidelines for strengthening exercises in the management of fibromyalgia: part 2. *Phys Ther* 2008;88:873–86.
40 Busch AJ, Schachter CL, Peloso PM. Fibromyalgia and exercise training: a systematic review of randomized clinical trials. *Phys Ther Rev* 2001;6:287–306.
41 Busch AJ, Barber KA, Overend TJ, *et al*. Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev* 2008;(4):CD003786.
42 Busch AJ, Webber SC, Richards RS. Resistance exercise training for fibromyalgia. *Cochrane Database Syst Rev* 2013;(12):CD010884.
43 Cazzola M, Atzeni F, Salaffi F, *et al*. Which kind of exercise is best in fibromyalgia therapeutic programmes? A practical review. *Clin Exp Rheumatol* 2009;28(Suppl 63):S117–24.
44 Häuser W, Klose P, Langhorst J, *et al*. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther* 2010;12:R79.
45 Kelley GA, Kelley KS, Hootman JM, *et al*. Exercise and global well-being in community-dwelling adults with fibromyalgia: a systematic review with meta-analysis. *BMC Public Health* 2010;10:198.

46 Kelley GA, Kelley KS, Jones DL. Efficacy and effectiveness of exercise on tender points in adults with fibromyalgia: a meta-analysis of randomized controlled trials. *Arthritis* 2011;2011:125485.
47 Lima TB, Dias JM, Mazuquin BF, *et al*. The effectiveness of aquatic physical therapy in the treatment of fibromyalgia: a systematic review with meta-analysis. *Clin Rehabil* 2013;27:892–908.
48 Nüesch E, Häuser W, Bernardy K, *et al*. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. *Ann Rheum Dis* 2013;72:955–62.
49 Perraton L, Machotka Z, Kumar S. Components of effective randomized controlled trials of hydrotherapy programs for fibromyalgia syndrome: a systematic review. *J Pain Res* 2009;2:165–73.
50 Ramel J, Bannuru R, Griffith M, *et al*. Exercise for fibromyalgia pain: a meta-analysis of randomized controlled trials. *Curr Rheumatol Rev* 2009;5:188–93.
51 Reimers N, Reimers CD. Exercise for lower back pain, hip and knee osteoarthritis, and fibromyalgia: effects on pain-a literature review. *Aktuelle Rheumatologie* 2012;37:174–88.
52 Sim J, Adams N. Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia. *Clin J Pain* 2002;18:324–36.
53 Thomas EN, Blotman F. Aerobic exercise in fibromyalgia: a practical review. *Rheumatol Int* 2010;30:1143–50.
54 van Koulil S, Effting M, Kraaimaat FW, *et al*. Cognitive–behavioural therapies and exercise programmes for patients with fibromyalgia: state of the art and future directions. *Ann Rheum Dis* 2007;66:571–81.
55 Mansi S, Milosavljevic S, Baxter GD, *et al*. A systematic review of studies using pedometers as an intervention for musculoskeletal diseases. *BMC Musculoskelet Disord* 2014;15:231.
56 Bidonde J, Busch AJ, Webber SC, *et al*. Aquatic exercise training for fibromyalgia. *Cochrane Database Syst Rev* 2014;(10):CD011336.
57 Bernardy K, Füber N, Köllner V, *et al*. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome—a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol* 2010;37:1991–2005.
58 Bernardy K, Klose P, Busch AJ, *et al*. Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev* 2013;(9):CD009796.
59 Karjalainen KA, Malmivaara A, van Tulder MW, *et al*. Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. *Cochrane Database Syst Rev* 1999;(3):CD001984.
60 Häuser W, Bernardy K, Arnold B, *et al*. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis Care Res* 2009;61:216–24.
61 Scascighini L, Toma V, Dober-Spielmann S, *et al*. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology (Oxford)* 2008;47:670–8.
62 Kalichman L. Massage therapy for fibromyalgia symptoms. *Rheumatol Int* 2010;30:1151–7.
63 Li YH, Wang FY, Feng CQ, *et al*. Massage therapy for fibromyalgia: a systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* 2014;9:e89304.
64 Tsao JC. Effectiveness of massage therapy for chronic, non-malignant pain: a review. *Evid Based Complement Alternat Med* 2007;4:165–79.
65 Yuan SLK, Matsutani LA, Marques AP. Effectiveness of different styles of massage therapy in fibromyalgia: a systematic review and meta-analysis. *Man Ther* 2015;20:257–64.
66 Courtois I, Cools F, Calsius J. Effectiveness of body awareness interventions in fibromyalgia and chronic fatigue syndrome: a systematic review and meta-analysis. *J Bodyw Mov Ther* 2015;19:35–56.
67 Berman BM, Ezzo J, Hadhazy V, *et al*. Is acupuncture effective in the treatment of fibromyalgia? *J Fam Pract* 1999;48:213–18.
68 Cao H, Li X, Han M, *et al*. Acupoint stimulation for fibromyalgia: a systematic review of randomized controlled trials. *Evid Based Complement Alternat Med* 2013;2013:362831.
69 Daya S. The efficacy of acupuncture in the treatment of fibromyalgia syndrome. *Acupunct Assoc Charter Physiother* 2007;3:35–46.
70 Deare JC, Zheng Z, Xue CC. Acupuncture for treating fibromyalgia. *Cochrane Database Syst Rev* 2013;(5):CD007070.
71 Langhorst J, Klose P, Musial F, *et al*. Efficacy of acupuncture in fibromyalgia syndrome—a systematic review with a meta-analysis of controlled clinical trials. *Rheumatology (Oxford)* 2010;49:778–88.
72 Martin-Sanchez E, Torralba E, Díaz-Domínguez E, *et al*. Efficacy of acupuncture for the treatment of fibromyalgia: systematic review and meta-analysis of randomized trials. *Open Rheumatol J* 2009;3:25–9.
73 Mayhew E, Ernst E. Acupuncture for fibromyalgia—a systematic review of randomized clinical trials. *Rheumatology (Oxford)* 2007;46:801–4.
74 Yang B, Yi G, Hong W, *et al*. Efficacy of acupuncture on fibromyalgia syndrome: a meta-analysis. *J Tradit Chin Med* 2014;34:381–91.
75 McVeigh JG, McGaughey H, Hall M, *et al*. The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: a systematic review. *Rheumatol Int* 2008;29:119–30.
76 Langhorst J, Musial F, Klose P, *et al*. Efficacy of hydrotherapy in fibromyalgia syndrome—a meta-analysis of randomized controlled clinical trials. *Rheumatology (Oxford)* 2009;48:1155–9.
77 Naumann J, Sadaghiani C. Therapeutic benefit of balneotherapy and hydrotherapy in the management of fibromyalgia syndrome: a qualitative systematic review and meta-analysis of randomized controlled trials. *Arthritis Res Ther* 2014;16:R141.
78 Chan CL, Wang CW, Ho RT, *et al*. Qigong exercise for the treatment of fibromyalgia: a systematic review of randomized controlled trials. *J Altern Complement Med* 2012;18:641–6.
79 Cramer H, Lauche R, Langhorst J, *et al*. Yoga for rheumatic diseases: a systematic review. *Rheumatology (Oxford)* 2013;52:2025–30.
80 Langhorst J, Klose P, Dobos GJ, *et al*. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. *Rheumatol Int* 2013;33:193–207.
81 Lauche R, Cramer H, Häuser W, *et al*. A systematic review and meta-analysis of qigong for the fibromyalgia syndrome. *Evid Based Complement Alternat Med* 2013;2013:635182.
82 Peng PW. Tai Chi and chronic pain. *Reg Anesth Pain Med* 2012;37:372–82.
83 Hadhazy VA, Ezzo J, Creamer P, *et al*. Mind-body therapies for the treatment of fibromyalgia. A systematic review. *J Rheumatol* 2000;27:2911–18.
84 Lauche R, Cramer H, Dobos G, *et al*. A systematic review and meta-analysis of mindfulness-based stress reduction for the fibromyalgia syndrome. *J Psychosom Res* 2013;75:500–10.
85 Niazi AK, Niazi SK. Mindfulness-based stress reduction: a non-pharmacological approach for chronic illnesses. *N Am J Med Sci* 2011;3:20–3.
86 Lakhan SE, Schofield KL. Mindfulness-based therapies in the treatment of somatization disorders: a systematic review and meta-analysis. *PLoS ONE* 2013;8:e71834.
87 Lee C, Crawford C, Hickey A. Mind–body therapies for the self-management of chronic pain symptoms. *Pain Med* 2014;15(Suppl 1):S21–39.
88 Ernst E. Chiropractic manipulation for non-spinal pain—a systematic review. *N Z Med J* 2003;116:U539.
89 Ernst E. Chiropractic treatment for fibromyalgia: a systematic review. *Clin Rheumatol* 2009;28:1175–8.
90 Schneider M, Vernon H, Ko G, *et al*. Chiropractic management of fibromyalgia syndrome: a systematic review of the literature. *J Manipulative Physiol Ther* 2009;32:25–40.
91 Bernardy K, Füber N, Klose P, *et al*. Efficacy of hypnosis/guided imagery in fibromyalgia syndrome-a systematic review and meta-analysis of controlled trials. *BMC Musculoskelet Disord* 2011;12:133.
92 Glombiewski JA, Bernardy K, Häuser W. Efficacy of EMG- and EEG-biofeedback in fibromyalgia syndrome: a meta-analysis and a systematic review of randomized controlled trials. *Evid Based Complement Alternat Med* 2013;2013:962741.
93 De Silva V, El-Metwally A, Ernst E, *et al*. Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review. *Rheumatology (Oxford)* 2010;49:1063–8.
94 de Souza Nascimento S, Desantana JM, Nampo FK, *et al*. Efficacy and safety of medicinal plants or related natural products for fibromyalgia: a systematic review. *Evid Based Complement Alternat Med* 2013;2013:149468.
95 Posadzki P, Ernst E. Guided imagery for musculoskeletal pain: a systematic review. *Clin J Pain* 2011;27:648–53.
96 Meeus M, Nijs J, Vanderheiden T, *et al*. The effect of relaxation therapy on autonomic functioning, symptoms and daily functioning, in patients with chronic fatigue syndrome or fibromyalgia: a systematic review. *Clin Rehabil* 2015;29:221–33.
97 Perry R, Terry R, Ernst E. A systematic review of homoeopathy for the treatment of fibromyalgia. *Clin Rheumatol* 2010;29:457–64.
98 Boehm K, Raak C, Cramer H, *et al*. Homeopathy in the treatment of fibromyalgia—a comprehensive literature-review and meta-analysis. *Complement Ther Med* 2014;22:731–42.
99 Ricci NA, Dias CN, Driusso P. The use of electrothermal and phototherapeutic methods for the treatment of fibromyalgia syndrome: a systematic review. *Rev Bras Fisioter* 2010;14:1–9.
100 Tenti S, Manica P, Galeazzi M, *et al*. Phytothermotherapy in fibromyalgia and osteoarthritis: between tradition and modern medicine. *Eur J Integr Med* 2013;5:248–53.
101 Eccles NK. A critical review of randomized controlled trials of static magnets for pain relief. *J Altern Complement Med* 2005;11:495–509.
102 Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. *Pain Pract* 2013;13:131–45.
103 Crawford C, Lee C, Bingham J. Sensory art therapies for the self-management of chronic pain symptoms. *Pain Med* 2014;15(Suppl 1):S66–75.
104 Moore RA, Wiffen PJ, Derry S. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2014;(4):CD007938.
105 Ablin J, Fitzcharles MA, Buskila D, *et al*. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. *Evid Based Complement Alternat Med* 2013;2013:485272.

EULAR revised recommendations for the management of fibromyalgia

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2016 updated EULAR evidence-based recommendations for the management of gout

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ABSTRACT

Background New drugs and new evidence concerning the use of established treatments have become available since the publication of the first European League Against Rheumatism (EULAR) recommendations for the management of gout, in 2006. This situation has prompted a systematic review and update of the 2006 recommendations.

Methods The EULAR task force consisted of 15 rheumatologists, 1 radiologist, 2 general practitioners, 1 research fellow, 2 patients and 3 experts in epidemiology/methodology from 12 European countries. A systematic review of the literature concerning all aspects of gout treatments was performed. Subsequently, recommendations were formulated by use of a Delphi consensus approach.

Results Three overarching principles and 11 key recommendations were generated. For the treatment of flare, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intra-articular steroids or a combination are recommended. In patients with frequent flare and contraindications to colchicine, NSAIDs and corticosteroids, an interleukin-1 blocker should be considered. In addition to education and a non-pharmacological management approach, urate-lowering therapy (ULT) should be considered from the first presentation of the disease, and serum uric acid (SUA) levels should be maintained at<6 mg/dL (360 μmol/L) and <5 mg/dL (300 μmol/L) in those with severe gout. Allopurinol is recommended as first-line ULT and its dosage should be adjusted according to renal function. If the SUA target cannot be achieved with allopurinol, then febuxostat, a uricosuric or combining a xanthine oxidase inhibitor with a uricosuric should be considered. For patients with refractory gout, pegloticase is recommended.

Conclusions These recommendations aim to inform physicians and patients about the non-pharmacological and pharmacological treatments for gout and to provide the best strategies to achieve the predefined urate target to cure the disease.

INTRODUCTION

Gout is a disabling and common disease in Europe; its prevalence ranges from 0.9% to 2.5% depending on the country.[1–3] The prevalence and incidence of the disease have increased steadily in recent years, particularly in the UK.[4 5] However, despite effective treatments, gout is still often misdiagnosed and its management remains suboptimal.[3 6 7] This situation prompted the elaboration of the first European League Against Rheumatism (EULAR) recommendations for the management of gout, in 2006, which were based on a systematic literature review (SLR) and expert opinion.[8]

Since 2006, our knowledge of the pathophysiology of the disease has improved greatly[9 10] and the field of gout management has advanced quickly. When the first EULAR recommendations were produced, the number of drugs available for gout treatment was limited and the main urate-lowering therapy (ULT) was allopurinol. Since then, a number of new drugs have become available or are in late-stage development (ie, febuxostat, pegloticase, interleukin-1 (IL-1) blockers, lesinurad).[11 12] Moreover, additional data on established drugs such as colchicine[13] and allopurinol[14–16] have been published, and studies have repeatedly identified increased cardiovascular mortality with gout.[17]

Therefore, the indications for old and new drugs need to be clarified and novel therapeutic strategies recommended on the basis of their availability, the patient profile, previous drug failure and benefit/risk ratio as well as the cost of the various drugs now available for the treatment of flare and for lowering urate levels. For this purpose, a task force was convened to update the 2006 EULAR recommendations for the management of gout, with the objective of addressing all overarching principles and individual recommendations by a SLR and expert and patient opinion.

METHODS

With the approval of the EULAR executive committee, the convenor (TB) along with two co-convenors of the 2006 task force (MD and EP), an epidemiologist (FT) and an academic rheumatologist (PR) formed a steering group to update the 2006 EULAR recommendations for the management of gout. The steering group prioritised the research questions, drafted the methodology to be used for these novel set of recommendations and assembled a task force.

This EULAR task force comprised 15 rheumatologists, 1 musculoskeletal radiologist, 2 general practitioners (GPs), 1 research fellow, 2 patients and 3 experts in epidemiology/methodology from 12 European countries. The recommendations were developed according to the standardised operating procedures for the elaboration, evaluation

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dissemination and implementation of recommendations endorsed by the EULAR.[18 19]

The first step was to determine whether the 12 former EULAR recommendations (2006) for the management of gout should be retained, modified or abandoned. For this purpose, members of the task force were sent a questionnaire and were asked to rate each recommendation by using a 9-point numerical rating scale (1, totally disagree; 9, fully agree). For each item, participants indicated whether they would keep the same recommendation (first question). If the answer was scored ≥5, the participants were then asked if they would modify the recommendation (second question). It was explained that the phrasing of the updated recommendations should not be a mere clinical statement—as for most of the 2006 EULAR recommendations—but wherever possible should take the form of a clear active recommendation specific to a particular clinical situation, as advised by the Appraisal of Guidelines for Research & Evaluation (AGREE II).[20] The steering group had predetermined that an item from the 2006 recommendations would be deleted if all scores from the participants for the first question were <5 with a median ≤3.5. Conversely, the item would be unchanged if all scores for to the first question were ≥5 with a median ≥7 and when all scores for the second question were <5 with a median ≤3.5. If not, the items had to be modified. Members of the task force were also invited to indicate topics they would like to address for additional recommendations.

Subsequently, one research fellow (JC-S) with the help of an expert in systematic review methodology (SG) performed an SLR by searching for literature published since 1 January 2005 in MEDLINE, EMBASE and Cochrane Library databases in June 2013. This process included both a general search and a proposition-specific search. The general search strategy consisted of two basic components: (1) gout in whatever possible terms in the databases and (2) types of study design in the forms of systematic review/meta-analysis, randomised controlled trial (RCT)/controlled trial, uncontrolled trial, cohort study, case–control study, cross-sectional study. The two components were combined to search for the current available research evidence on gout. The quality of evidence and grades of recommendation were determined according to the standards of the Oxford Centre for Evidence-Based Medicine.[19] The quality of evidence was assessed by the GRADE method. Criteria for RCTs included adequate randomisation and allocation concealment, prognostic similarity between groups (in terms of the evaluated outcome), equal follow-up of groups, adequate blinding, validation of outcomes, application of intent-to-treat analysis, selective outcome reporting, stopping early for benefit, α-risk control with multiple comparisons or multiple outcomes. Criteria for observational studies included choice of controls, measurement of both exposures and outcomes, confounding factors, completeness of data, magnitude of effect and dose–response gradient. Criteria for meta-analysis included a priori-defined objectives and outcomes of interest, description of the literature search, selection criteria for included studies, assessment of quality of studies, evaluation of publication bias and homogeneity of results.

In the next step, all task force members attended a 2-day meeting during which results of the SLR were presented in an aggregated form. The task force debated and evaluated the evidence presented and formulated a preliminary set of new recommendations. Then, the task force reached consensus regarding the proposed recommendations by using the Delphi sequential voting technique by email after the meeting. Subsequently, the level of agreement for each recommendation was graded. Each participant was asked to rate each recommendation again by using the 9-point numerical rating scale (1, totally disagree; 9, fully agree) and could propose a reformulation of the recommendation.

Subsequently, this set of recommendations was externally evaluated by GPs (n=8) and rheumatologists (n=5) mainly in independent or private practice in Europe (the UK, The Netherlands, Spain, France, Portugal and Italy). Each physician was asked to rate each recommendation by using the abovementioned numerical rating scale. Finally, the task force set up a research agenda to discuss and develop 14 proposals.

Finally, because the delay between the first SLR and the writing of the present manuscript was longer than expected, we conducted an additional SLR from June 2013 to May 2016. Results from this updated SLR can be found in the online supplementary material. The steering group discussed result of this SLR and agreed that it did not impact the overall content of the whole recommendations. Relevant references have been inserted in the body of the manuscript.

RESULTS

The task force voted unanimously for a change in all items of the 2006 recommendations (see online supplementary material). Therefore, all the previous recommendations were amended to reflect newly available evidence from the SLR. In total, 984 references were retrieved form the literature search, among which 51 were analysed (see flow chart, online supplementary material).

At the end of the 2-day meeting, a set of 14 preliminary new recommendations was produced and three Delphi rounds by email were needed to establish the final set of recommendations. Because too many recommendations might result in a loss of focus, the steering committee decided to move the first three recommendations under the umbrella of 'overarching principles', for a final set of 11 novel recommendations that focus more specifically on the treatment of flares and long-term management (tables 1 and 2). The external evaluation is provided as online supplementary material, and the research agenda appears in box 1.

Overarching principles

A. *Every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of SUA below a target level.*

Although gout is a curable disease, its management is still not optimal in a large proportion of patients.[6] Recent studies report that less than half of the patients with gout receive ULT, and that when prescribed, it is often at an insufficient dose to effectively lower the SUA levels to target.[21–24] Since the last 2006 recommendations, barriers to the effective treatment and cure of gout have been identified and the importance of the lack of knowledge of the disease and subsequent non-adherence to treatment have been emphasised.[25–27] Moreover, an observational study showed that full patient education increased adherence to ULT, leading to a high rate (92%) of effectively treated patients at 12 months.[28]

Education of patients was mentioned in the 2006 recommendation (item 2) together with general advice regarding lifestyle as part of a global recommendation. With this first overarching principle dedicated solely to education, the task force emphasises that education is a key aspect of gout management. Also it introduces the approach 'treat to serum urate target,' which has been found effective in alleviating all features of the disease.[28]

Table 1 Overarching principles and final set of 11 recommendations for the treatment of gout

	Overarching principles
A	Every person with gout should be fully informed about the pathophysiology of the disease, the existence of effective treatments, associated comorbidities and the principles of managing acute attacks and eliminating urate crystals through lifelong lowering of SUA level below a target level.
B	Every person with gout should receive advice regarding lifestyle: weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.
C	Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.
	Final set of 11 recommendations
1	Acute flares of gout should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug (s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved.
2	Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus proton pump inhibitors if appropriate), oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin.
3	In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroid (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers. ULT should be adjusted to achieve the uricaemia target following an IL-1 blocker treatment for flare.
4	Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment. In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at low dosage, if not contraindicated, should be considered.
5	ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flares, tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years) or with a very high SUA level (>8.0 mg/dL; 480 μmol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.
6	For patients on ULT, SUA level should be monitored and maintained to <6 mg/dL (360 μmol/L). A lower SUA target (<5 mg/dL; 300 μmol/L) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout. SUA level <3 mg/dL is not recommended in the long term.
7	All ULTs should be started at a low dose and then titrated upwards until the SUA target is reached. SUA <6 mg/dL (360 μmol/L) should be maintained lifelong.
8	In patients with normal kidney function, allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemia target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.
9	In patients with renal impairment, the allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with estimated glomerular filtration rate <30 mL/min.
10	In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life, in whom the SUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.
11	When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension consider losartan or calcium channel blockers; for hyperlipidaemia, consider a statin or fenofibrate.

IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; SUA, serum uric acid; ULT, urate-lowering therapy.

B. *Every person with gout should receive advice regarding lifestyle: weight loss if appropriate and avoidance of alcohol (especially beer and spirits) and sugar-sweetened drinks, heavy meals and excessive intake of meat and seafood. Low-fat dairy products should be encouraged. Regular exercise should be advised.*

Since the previous recommendations (item 2), several studies have confirmed that weight loss, achieved by dietary intervention or bariatric surgery[29–32] is effective in reducing SUA level. Moreover, regular physical activity might decrease the excess mortality associated with chronic hyperuricaemia.[33]

In addition, the association between excessive intake of meat and alcohol with an increased risk of developing gout has been confirmed[29 34 35] as well as increased risk of gout attacks.[36 37]

Importantly, other modifiable risk factors have been identified since 2006, specifically sugar-sweetened drinks, foods rich in fructose and orange or apple juice.[38–41] In contrast, according to epidemiological studies, consumption of coffee,[42–44] and cherries is negatively associated with gout, and eating cherries may reduce the frequency of acute gout flares.[45] Studies found an inverse association between dairy intake and urate levels, particularly with skimmed milk and low-calorie yoghurt.[34 46] This likely results from the uricosuric property of milk, as demonstrated in an RCT.[47] The benefit of dairy products, underlined in the 2006 recommendation, was reported in a RCT, suggesting that skimmed milk powder derivatives have anti-inflammatory effects against acute gout flares.[48] However, impact of lifestyle and dietary modification has little effect on urate concentrations.[49 50] In addition, the task force recognises that the level of evidence to support the effect of lifestyle modification on SUA levels is low, and therefore, this overarching principle was mainly based on expert opinion. However, given the high prevalence of cardiovascular comorbidities in patients with gout, lifestyle modifications should also be implemented as part of cardiovascular prevention.

C. *Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.*

The importance of screening and managing hypertension, hyperglycaemia and obesity in patients with gout was addressed in the previous recommendations (item 3). Since then, a

Table 2 Evidence, grade of recommendation and level of agreement for each recommendation

Item	Category of evidence	Grade of recommendation	Level of agreement (mean±SD)
A	NA	NA	8.9±0.3
B	NA	NA	8.4±1.1
C	NA	NA	8.5±0.9
1	1b*, 4	A, D	8.4±1.1
2	1b, 3†	A, C	8.6±0.7
3	1b‡, 3§	A, C	8.1±0.9
4	2b	B	8.1±0.9
5	1b	A	8.2±0.9
6	3	C	8.8±0.5
7	3	C	8.6±0.7
8	1b¶, 2b**	A, B	8.8±0.4
9	3	C	8.8±0.4
10	1b	A	8.2±1.3
11	3	C	8.2±0.9

Ranking for category of evidence and grade of recommendation is provided in the online supplementary material.
*For the evidence that colchicine should be given as early as possible, within 12 hours of symptom onset.
†There are no randomised controlled trials of intra-articular corticosteroid injections for flares.
‡Level of evidence for canakinumab.
§For ankinra.
¶Level of evidence for febuxostat and allopurinol.
**For uricosurics (probenecid or benzbromarone).
NA, not applicable.

Box 1 Proposals for future research

- Investigating the ability of low-dose NSAIDs or prednisone to prevent ULT-induced flares.
- A head-to-head trial of anakinra versus a conventional anti-inflammatory agent for the treatment of flares.
- A controlled trial of early low-dose colchicine versus early NSAIDs or oral corticosteroids or potential new drugs for flares over 1 week.
- The optimal combined therapy for treatment of an acute attack.
- The optimal duration for prophylaxis of acute attacks when starting ULT.
- Risk factors for flares when initiating ULT.
- The long-term impact of very low urate levels on the central nervous system.
- The possible benefits of XO inhibition and/or lowering serum uric acid levels for cardiovascular diseases.
- The impact of ULT on kidney function.
- The best strategy in patients with tophaceous gout.
- Direct comparison (efficacy, side effects, cost utility) between emerging uricosurics and allopurinol or febuxostat.
- The cost-utility of HLA-B*58:01 determination before initiating allopurinol in patients not of Asian descent.
- Imaging to visualise crystal dissolution during ULT.
- More research should be conducted in primary care.

NSAID, non-steroidal anti-inflammatory drug; ULT, urate-lowering therapy.

number of studies have demonstrated that both hyperuricaemia and gout are associated with chronic kidney disease (CKD).[51 52] In a US population-based study, the prevalence of CKD (stage ≥2) in patients with SUA level ≥10 mg/dL (594.9 µmol/L) and in patients with gout was 86% and 53%, respectively. CKD appears to be a major risk factor for gout and, conversely, gout might cause renal dysfunction.[53 54] The task force agreed that identifying CKD in patients with gout was of major importance because of the therapeutic implications, as discussed in items 1, 2, 4, 5, 8 and 9. Therefore, estimated glomerular filtration rate (eGFR) should be calculated at the time of diagnosis for CKD classification and monitored regularly in parallel with SUA measurement. This item also emphasises the need to search for other important associated comorbidities, especially coronary heart disease, heart failure, stroke, peripheral arterial disease and diabetes because large epidemiological studies have suggested that hyperuricaemia and/or gout are independent risk factors for these conditions[55–63] and for death due to cardiovascular causes.[17 58]

Final set of 11 recommendations on treating patients with gout

1. *Acute flares of gout should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug(s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset and the number and type of joint(s) involved.*

This recommendation was mainly based on expert opinion and derives from the first item of the 2006 recommendations. Because of the recognised high frequency of comorbidities and thus the high frequency of comedications in patients with gout, the task force felt that a global recommendation regarding the choice of drugs for flares based on the presence or absence of contraindications was highly desirable. This item emphasises the importance of searching for contraindications, often present in patients with gout. One study found that more than 90% of patients had at least one contraindication to non-steroidal anti-inflammatory drugs (NSAIDs) and that about one-third of patients who were prescribed colchicine had at least one major contraindication.[64] This item also underlines the importance to treat as early as possible. Colchicine is effective when given within 12 hours of symptoms onset[13] and there was general agreement that early initiation of any treatment for flare leads to better effectiveness. Therefore, the task force recommends the 'pill in the pocket' approach to treat flare in fully informed patients.

2. *Recommended first-line options for acute flare are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus a proton pump inhibitor if appropriate), oral corticosteroids (30–35 mg/day of equivalent prednisolone for 3–5 days) or articular aspiration and injection of corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. Colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin.*

This item amalgamates the 2006 items 4–6, which have been amended in light of novel evidence. The main therapeutic options for flare are colchicine, NSAIDs and corticosteroids. The task force does not prioritise between these options because of no direct comparative evidence, but unlike 2006 item 4, it recommends considering combination therapy, such as colchicine and an NSAID or colchicine and corticosteroids, which can be proposed for patients with particularly severe acute gout (figure 1), for instance, when flares involve multiple

joints. In comparison to 2006 items 4 and 5, more evidence is now available in terms of the effectiveness of colchicine,[65] NSAIDs[66–69] and oral corticosteroids.[70–72] A double-blind, randomised equivalence trial of crystal-proven gout from a primary care source population found that prednisolone (35 mg/day for 5 days) was equivalent to naproxen (500 mg twice a day for 5 days) for treating flare.[71 72] A recent trial also found that oral prednisolone (30 mg/day for 5 days) had analgesic effectiveness equivalent to that of indomethacin.[70] The AGREE trial demonstrated that when taken within 12 hours of flare onset, self-administrated low-dose colchicine (1.8 mg) was as effective as high-dose colchicine (4.8 mg) but with a safety profile comparable to that of a placebo.[65] In Europe, colchicine is available in 1 mg tablets, so the task force recommends the use of 1 mg colchicine followed 1 hour later by 0.5 mg for treating flare. A pharmacokinetic study[73] showed that strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin, clarithromycin, verapamil and ketoconazole when prescribed with colchicine increased colchicine plasma concentration, thereby exposing patients to risk of serious side effects. The safe use of colchicine in patients with severe renal impairment (GFR <30 mL/min) has not been established. Because colchicine clearance is decreased in patients with severe renal impairment,[74 75] the group considered that it should be avoided in these patients, because a reduced dosage[73] might be a source of therapeutic misuse. In addition, it should be noted that colchicine is

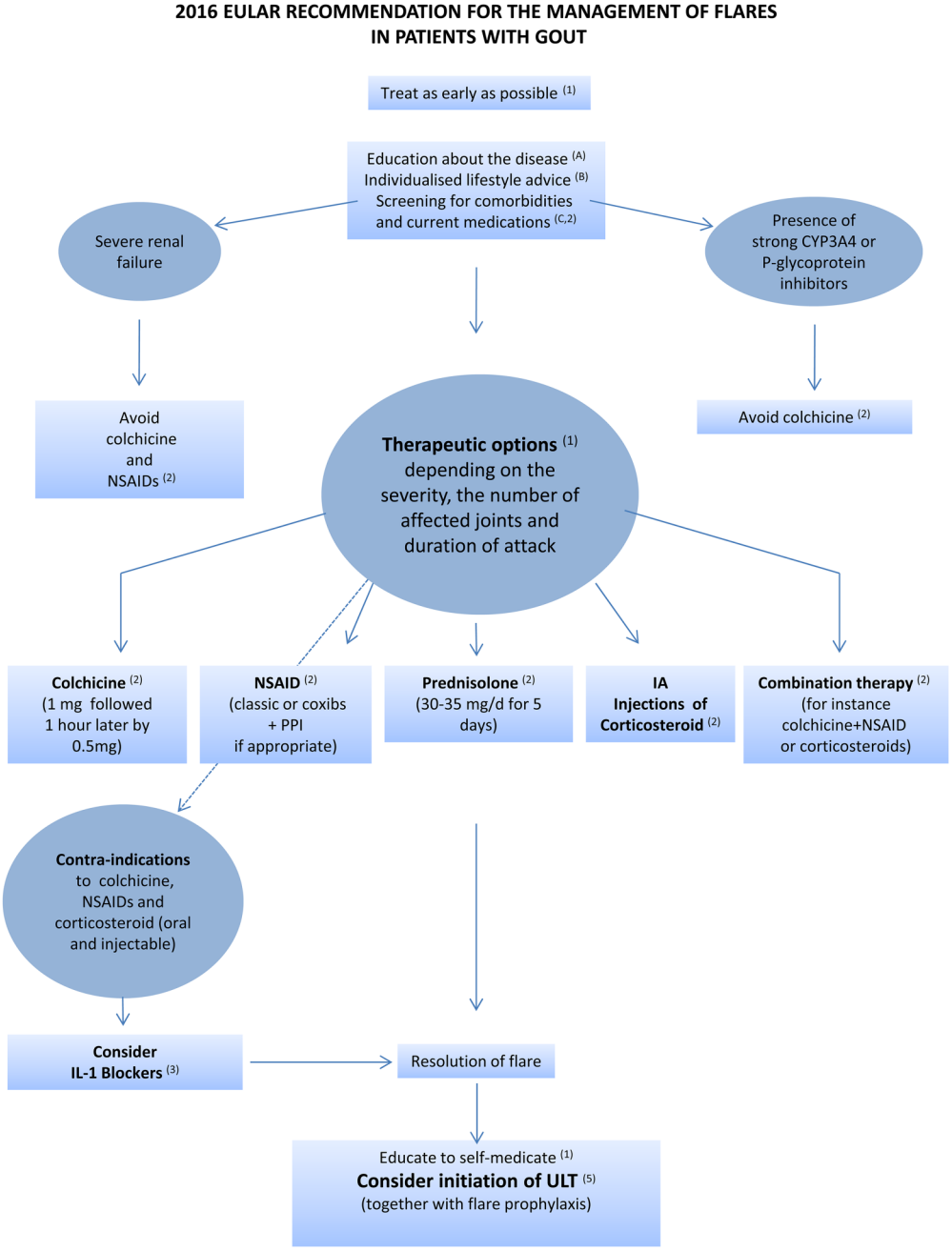

Figure 1 Management of acute flare according to the European League Against Rheumatism recommendations. Letters and numbers in parentheses indicate the items of the recommendations presented in table 1. Strong P-glycoprotein or CYP3A4 inhibitors are cyclosporin, clarithromycin, ketoconazole and ritonavir. IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; ULT, urate-lowering therapy.

contraindicated in some countries in patients with severe renal failure. From data from two RCTs,[71 72] the group also recommends the use of oral prednisolone at 30–35 mg for 5 days for treating flare. Finally, from data from an open trial[76 77] and expert opinion, the group considered that intra-articular injection of corticosteroids, which has a good safety profile, should be considered particularly in patients with monoarthritis of an easily accessible joint, although acknowledging that this may not be practical in many primary care settings.

3. *In patients with frequent flares and contraindications to colchicine, NSAIDs and corticosteroids (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers. ULT should be adjusted to achieve the uricaemia target following IL-1 blocker treatment for flare.*

Since the last 2006 recommendations, IL-1β was found to play a crucial role in monosodium urate (MSU) crystal-induced inflammation.[78] Two RCTs have reported that the anti-IL-1β monoclonal antibody canakinumab (150 mg subcutaneously, one dose) was superior to triamcinolone acetonide (40 mg subcutaneously, one dose) in reducing pain in patients with flare with contraindication, intolerance of or non-response to NSAIDs and/or colchicine.[79] These findings led to approval of the drug in Europe solely in patients with contraindication to colchicine, NSAIDs and steroids. Despite the lack of RCTs of anakinra, a case series also suggest that this IL-1 receptor antagonist, administered subcutaneously at 100 mg for 3 days, could be effective in reducing pain in patients with acute attacks.[80–83] By contrast, an RCT demonstrated that one subcutaneous injection of rilonacept, 320 mg, a soluble receptor fusion protein binding both IL-1α and IL-1β,[84] provided no benefit over indomethacin (oral, 50 mg, three times a day for 3 days).[85] Because of the risk of sepsis in patients receiving IL-1 blockers,[86] the task force considered current infection a contraindication to the use of anti-IL-1 biologics, which implies screening for occult infections. Finally, in accordance with the European Medicines Agency labelling of canakinumab, the group stressed the need to effectively lower SUA level in these patients with severe gout once the flare resolved following IL-1β blockade.

4. *Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment. In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, prophylaxis with NSAIDs at a low dosage, if not contraindicated, should be considered.*

Dispersion of MSU crystals during the initial phase of deposit dissolution may expose the patient to increased rate of acute flare that can contribute to poor treatment adherence.[87] The 2006 recommendations (item 11) mentioned that prophylactic treatment should be given during the first months of ULT. Since then, data from pivotal trials of febuxostat versus a fixed dose of allopurinol (300 mg) found that flare prophylaxis with low-dose colchicine (colchicine, 0.6 mg/day) or low-dose NSAID (naproxen, 250 mg twice daily) for up to 6 months appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in adverse events.[88] However, the task force felt that initiation of prophylaxis should be discussed with every patient. Indeed, a study found that following patient education and with slow upward titration of ULT, mostly allopurinol, many patients chose not to take prophylaxis and did not experience a significantly greater flare rate.[28] This recommendation also explicitly underlines the need to search for renal impairment before prescribing colchicine[75] and co-prescription with statins[89] and P-glycoprotein and/or CYP3A4 inhibitors[73] to avoid serious side effects. Of note, two RCTs found that low-dose colchicine in patients with a history of coronary heart disease could reduce the incidence of major cardiovascular events.[90 91] Reports for several trials described the efficacy of canakinumab and rilonacept,[92–96] two IL-1 inhibitors, for preventing flares during the initiation of allopurinol therapy. However, none of them has been approved for prophylactic treatment.

5. *ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flare (≥2/year), tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years), or with a very high SUA level (>8 mg/dL; 480 µmol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.*

ULT allows for dissolving crystal deposits and the disappearance of gout features, as long as uricaemia is maintained to target. Since 2006, large trials have shown that appropriate ULT reduces the frequency of gout flare and once all crystals have been dissolved, avoids their reoccurrence.[97–99] In addition, effective ULT reduces the size and number of tophi[97 99 100] and facilitates their disappearance, thereby improving the quality of life of patients with gout,[101 102] which can be seriously impaired by the disease.[103–106]

Several studies concur in showing that gout is a risk factor for mortality, in particular from cardiovascular causes,[17 107 108] and a risk factor for kidney impairment[51] as discussed previously (see the third overarching principle).

Unlike the 2006 guideline in which the group of experts recommended starting ULT only for patients with certain severe clinical features, including recurrent acute attacks and tophi (item 7), the current task force recommends possible initiation of ULT close to the first presentation (ie, in most cases, close to the first attack). Indeed, the task force felt that delaying initiation of ULT until the second or third attack would expose patients to a higher crystal load, for difficulties in dissolution and to longstanding hyperuricaemia, which may be deleterious for the cardiovascular system and kidney.[51 56 107–110] Therefore, the recommendation to initiate ULT earlier was mainly based on expert opinion but also took into account studies that suggest a cardiovascular[111 112] and renal benefit[113–116] from xanthine oxidase inhibitors (XOI). XO inhibition improved exercise capacity in patients with chronic stable angina in a randomised cross-over trial.[117] Epidemiological studies suggested that allopurinol might decrease morbidity and mortality in patients with congestive heart failure and a history of gout,[118 119] a benefit not confirmed in a recent randomised trial of patients with heart failure and hyperuricaemia without gout.[120] In addition, pharmaco-epidemiological studies report that allopurinol use is associated with an approximately 20% reduction in myocardial infarction risk.[121 122] However, the task force acknowledged that additional well-conducted trials are warranted in this field, as recent studies yielded conflicting results.[123 124]

Item 5 also underlines the need to start ULT early, particularly in patients with comorbidities and/or SUA level >8 mg/dL. Encouragement to treat patients with high SUA level earlier is based on studies showing an association of high uricaemia with increased flare frequency.[125–127] Similarly, early treatment in patients with comorbidities is supported by a study of a large cohort of gout patients finding hypertension, ischaemic heart disease and CKD all associated with increased risk of recurrence of flare.[128] Young age at gout onset is also a marker of gout severity[129] and should also prompt earlier treatment. This recommendation underlines again the importance of providing full information and involving the patient in the decision-making process, to ensure adherence to ULT and optimal patient-centred outcomes.

Finally, the task force did not give specific guidance on whether urate-lowering drugs should be initiated during a flare or whether a traditional 2 weeks delay from flare termination should be observed. Two small trials have suggested that allopurinol initiation during an acute gout attack did not prolong the duration of flares nor worsen its severity as compared with delayed initiation.[130 131] However, the task force considered that the low number of patients (n=51 and n=31, respectively) in these trials precluded any firm conclusions and that data obtained with allopurinol 200–300 mg could not be generalised to more potent urate-lowering drugs, such as febuxostat or a combination of XOI and an uricosuric.

6. *For patients on ULT, SUA level should be monitored and maintained to <6 mg/dL (360 µmol/L). A lower SUA target (<5 mg/dL; 300 µmol/L) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout. SUA level <3 mg/dL is not recommended in the long term.*

As in 2006 (item 8), the task force recommends a treat-to-target strategy for every patient with gout, to maintain the SUA level <6 mg/dL, which is below the saturation point for MSU[132] to dissolve all crystal deposits.[133] Because the velocity of crystal dissolution depends on the SUA level,[134 135] the task force also recommends reducing the SUA level to <5 mg/dL for severe gout reflecting high crystal load until total crystal dissolution has occurred. The task force also agreed that once dissolution of crystals is achieved, SUA level could be maintained <6 mg/dL by a reduction in the dose of ULT to avoid new formation of urate crystals.

Some studies, but not all,[136–138] have suggested that uric acid might protect against various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease or amyotrophic lateral sclerosis.[139–142] Given these data and the availability of ULT that has the potency to greatly decrease SUA levels, the task force does not recommend lowering continuously the SUA level to <3 mg/dL in the long term that is, for several years.

7. *All ULTs should be started at a low dose and then titrated upward until the SUA target is reached. SUA <6 mg/dL (360 µmol/L) should be maintained lifelong.*

The task force recommends upward titration of ULT in every patient when feasible. This approach, mentioned in 2006 (item 9), might result in fewer episodes of acute flares during treatment initiation[28] and therefore improved adherence to ULT, which is low according to several studies.[27 143 144] Following complete dissolution of MSU crystals, the SUA level should be maintained at <6 mg/dL lifelong. Indeed, a study showed that about 40% of successfully treated patients show recurrence of flare 5 years after withdrawal of ULT.[145] Therefore, determining SUA level on a regular basis is a key aspect of treatment.

8. *In patients with normal kidney function, allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricaemic target. If the SUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric, or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.*

As in 2006 (item 9), the task force recommends the use of allopurinol as first-line therapy in patients with normal kidney function. This recommendation takes into account the efficacy, low cost and safety of this drug. Since 2006, two RCTs have confirmed the superior urate-lowering efficacy of allopurinol (300 mg/day) over placebo.[97 130] Medico-economic studies of ULT reported that a dose-escalation strategy with allopurinol as first-line therapy was cost-effective.[146 147] Allopurinol should be started at a low dose (100 mg/day) to reduce early gout flare[28] and because high starting doses might increase the risk of serious cutaneous adverse reactions (SCARs).[15] The most commonly used allopurinol dose of 300 mg/day does not achieve the SUA target of 6 mg/dL (360 µmol/L) in about 30%–50% of patients with normal kidney function.[28 148 149] For those patients, the task force recommends a dose-escalation strategy to increase the dose in order to reach the predefined uricaemia target. Treatment with allopurinol up to 600–800 mg/day had a 75%–80% success rate of achieving SUA levels of <6 mg/dL (360 µmol/L).[28 150]

Febuxostat is a potent non-purine selective XOI approved at daily doses of 80 and 120 mg in Europe. It is metabolised in the liver and renal excretion is not a major route of elimination, which allows for its use in patients with mild-to-moderate kidney failure. A short-term phase II trial[151] and three large RCTs (see online supplementary material) showed superior urate-lowering efficacy with febuxostat (80 or 120 mg) as compared with the commonly used fixed daily dose of 300 mg allopurinol.[97 98 149] Cutaneous reactions have been described in pivotal trials with febuxostat.[97 149] Despite case reports of SCARs in patients receiving febuxostat,[152 153] recent data do not support any cross-reactivity between the two drugs.[153 154] Therefore, the task force considered that a history of allergic reaction to allopurinol was not a contraindication to febuxostat, but underlined the need to carefully follow these patients.

Uricosurics are recommended, where available, alone or in combination with allopurinol in patients without proper control with allopurinol alone. Benzbromarone (50–200 mg/day) is a more potent uricosuric as compared with probenecid (1–2 g/day).[155] In an RCT of patients without proper control with allopurinol, 300 mg/daily, 92% and 65% of patients reached a SUA target of 300 µmol/L (5 mg/dL) when switched to benzbromarone, 200 mg, or probenecid, 2 g daily, respectively.[148] Finally, the recommendation for combination therapy with allopurinol and a uricosuric, not mentioned in 2006, is based on uncontrolled trials that have suggested that probenecid-allopurinol[156–158] or benzbromarone-allopurinol[135] was more effective than allopurinol alone. Furthermore, emerging uricosuric, such as lesinurad,[159] has shown promising results in a phase II trial when combined with allopurinol.[160]

9. *In patients with renal impairment, the allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with eGFR <30 mL/min.*

This item retained the 2006 recommendation (item 9) to adjust the allopurinol dosage according to the creatinine clearance. The greatest concern with the use of allopurinol in patients with renal failure is the development of SCARs, which includes drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis. Since 2006, several studies have further explored allopurinol-induced SCARs. Allopurinol was found to be the most common drug associated with SJS or toxic epidermal necrolysis in Europe.[161] Allopurinol-induced SCARs are rare, the incidence rate being about 0.7/1000 patient-years in allopurinol initiators in the USA,[162] but the mortality rate is high (25%–30%).[163–165]

Renal failure has been associated with an increased risk of SCARs and poor outcome.[163 164] Decreased renal function results in decreased clearance and higher serum levels of oxypurinol,[164 166] which could induce a cytotoxic T-cell response and trigger hypersensitivity reactions in SCARs.[167] In some studies, dose escalation of allopurinol above the limit allowed by creatinine clearance did not result in SCARs,[14 168] but given the very low incidence of SCARs and the limited number of patients involved in these studies, the task force considered that they probably lacked power to detect a potential association.

Therefore, given the extreme severity of SCARs and the possibility of therapeutic alternatives such as febuxostat, the task force retained the conservative approach to adjust the maximum dose of allopurinol to the creatinine clearance[169] in patients with renal impairment, as required by most regulatory agencies. Because the dose recommendations in renal disease may slightly differ across countries, the task force recommends to follow the local Summary of Product Characteristics.

Febuxostat has been found more effective in patients with CKD than allopurinol given at doses adjusted to creatinine clearance[149 170] and therefore can be used in these patients. Finally, benzbromarone is not recommended for use in patients with eGFR <30 mL/min, but can be used in patients with moderate renal impairment[171 172] because it is predominately metabolised by the liver.

10. *In patients with crystal-proven severe debilitating chronic tophaceous gout and poor quality of life, in whom the SUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.*

Since the last EULAR recommendation, pegloticase has emerged as a powerful ULT for refractory gout. Pegloticase is a pegylated uricase, produced by a genetically modified strain of *Escherichia coli* that catalyses the oxidation of uric acid into allantoin, a more soluble end product.[173] Its efficacy has been assessed in two replicate 6-month, randomised, double-blind, placebo-controlled, phase III trials.[99 100] In this study, the percentage of responders (SUA level <6 mg/dL) was 42%, on average, in patients who received pegloticase, 8 mg, every 2 weeks and 0% in the placebo group. Allergic reactions, possibly related to the occurrence of antibody against pegloticase,[174] were observed in about 25% of patients who received pegloticase biweekly. Given the safety profile of pegloticase and the demonstration of its efficacy in patients with refractory gout, the task force recommends its use in patients with clinically severe crystal-proven gout that cannot be properly treated with conventional ULT, including a combination of an XOI and a uricosuric agent. There was no firm agreement with regards to the duration of treatment with pegloticase. However, there was a consensus to consider a switch, if feasible, toward an oral ULT once all tophi had disappeared.

11. *When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension, consider losartan or calcium channel blockers; for hyperlipidaemia, consider a statin or fenofibrate.*

This recommendation is similar to the 12th 2006 recommendation. However, in addition to losartan, the task force now recommends consideration of calcium blockers in patients with gout. This recommendation is supported by a large epidemiological study finding relative risks of incident gout associated with the current use of calcium channel blockers and losartan of 0.87 (95% CI 0.82 to 0.93) and 0.81 (95% CI 0.70 to 0.94), respectively.[175] Finally, the uricosuric property of fenofibrate[176 177] and statins has been further documented.[178 179]

DISCUSSION

These updated EULAR recommendations aim to provide physicians—rheumatologists, GPs and others—with the best pragmatic strategies to manage hyperuricaemia and flare in patients with gout (figures 1 and 2).

As first-line care providers, GPs have a predominant role in gout treatment. Likewise, the involvement of patients in the management of chronic diseases is crucial. Therefore, in contrast to 2006, the current task force included two GPs and two patients to broaden the involvement of stakeholders involved in the disease. As mentioned previously, gout is mainly managed by GPs, and the task force recognises that we lack trials conducted in primary care; most of the RCTs analysed in this paper were conducted in tertiary care. Overall, this set of recommendations was well graded by external GPs and rheumatologists (see online supplementary material).

Since 2006, the perception of gout has changed. The increase in prevalence of gout in developed countries,[1–3 180] the severity of the arthritis itself,[6] and the increasing evidence for an association between gout with cardiovascular events, kidney failure and mortality have heightened the realisation that gout should never be neglected and should be treated properly.[6] Furthermore, since 2006, the treatment armamentarium has greatly expanded, with the approval of both febuxostat and pegloticase, the demonstration of the efficacy of IL-1 blockers to treat flare and the emergence of novel ULTs.[11 12 181] As expected, the task force modified all the previous 2006 recommendation items to incorporate all these recent developments and altered perspectives that have resulted from recent research evidence.

As compared with 2006, the key differences in terms of the therapeutic strategy for the management of hyperuricaemia are the recommendations to titrate and initiate ULT very early in the course of the disease, to combine an XOI and a uricosuric, and for patients with severe gout to reach a target SUA level of 5 mg/dL (300 μmol/L) to hasten crystal dissolution. The task force was convinced that treatment of hyperuricaemia should be target-oriented and initiated without delay to avoid a further longstanding period of silent urate deposits.[182–184] In addition, a 'start low, go slow' approach is recommended, because it probably results in fewer episodes of acute gout during treatment initiation and therefore might improve ULT adherence.

The task force was aware that not all ULTs mentioned in this paper, especially the uricosurics, are readily available in all European countries. However, it felt that these older drugs, in the absence of available new ULTs, could benefit some patients without adequate control with allopurinol or febuxostat alone. Of note, the recommendation to combine benzbromarone or

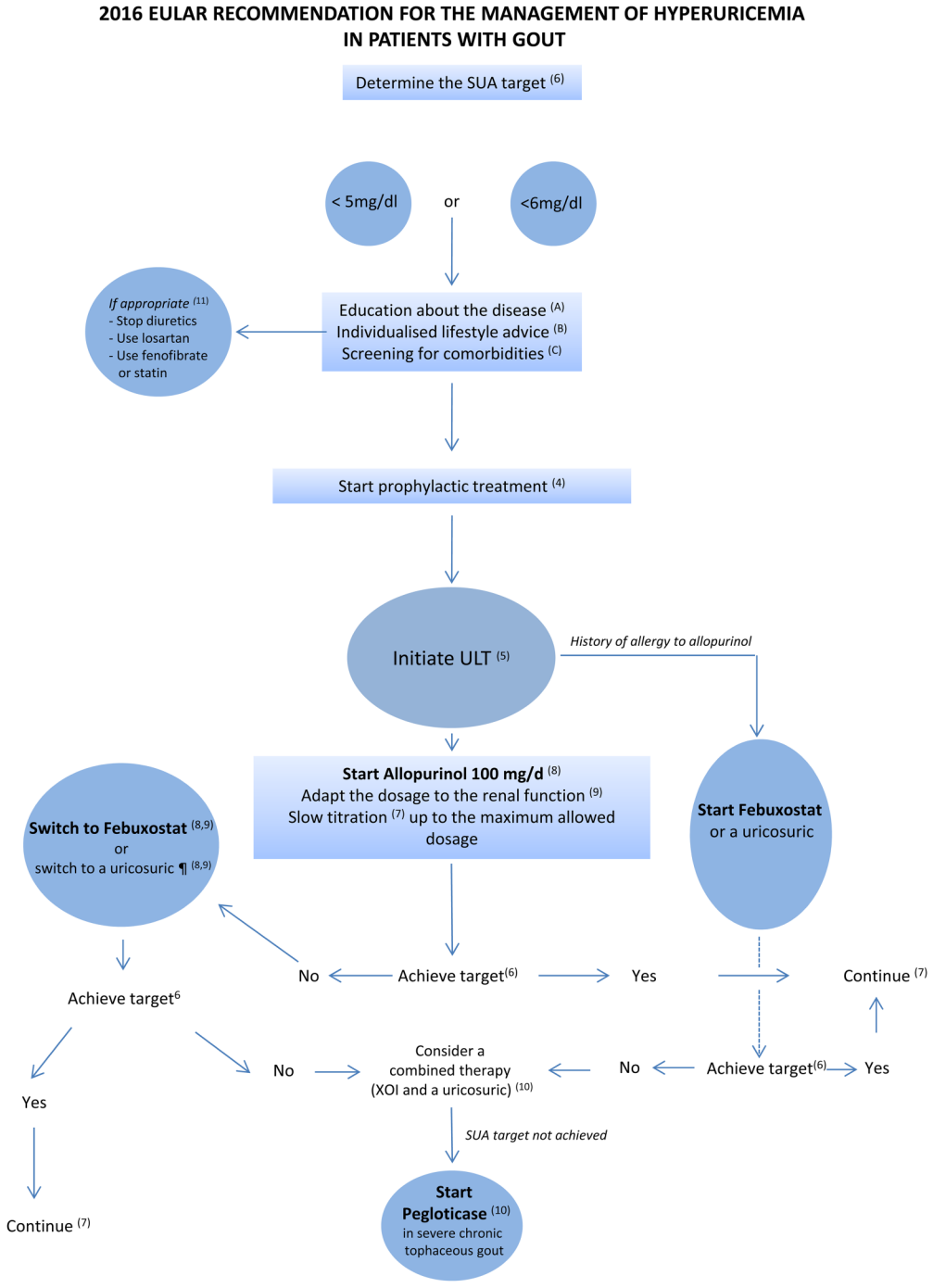

Figure 2 Management of hyperuricaemia in patients with gout according to the European League Against Rheumatism recommendations. Letters and numbers in parentheses refer to the items of the recommendations presented in table 1. SUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor. ¶At this stage, combined allopurinol and a uricosuric is also recommended.

probenecid with an XOI is a novel strategy that should help physicians manage severe gout that is not readily controlled by single agents and not eligible for pegloticase. This recommendation was not strictly evidence-based and relied more on expert opinion and on recent data from phase II trials showing the potency to combine allopurinol or febuxostat with lesinurad, a novel uricosuric targeting URAT1.[11 160]

These revised EULAR recommendations differ in some aspects from the 2012 American College of Rheumatology (ACR) guidelines.[185 186] For instance, ACR recommends allopurinol or febuxostat as first-line therapy, whereas EULAR recommends allopurinol first and then febuxostat with failure to achieve the predetermined SUA target. As indicated previously, this recommendation was not supported by efficacy data, but rather took into account the cost and effectiveness of both drugs at their optimal dosage as well as regulatory rules endorsed in several European countries. Importantly, unlike the ACR, the EULAR recommends adjusting the dosage of allopurinol to the creatinine clearance in patients with renal failure, owing to an increased risk of SCARs in those patients,[164] and febuxostat as an alternative if the SUA target is not reached.

The ACR also recommended that ULT could be started during an acute attack[185] if anti-inflammatory treatment had been introduced, a strategy not recommended in the present paper.

These recommendations also did not mention systematic HLA-B*5801 screening before the initiation of allopurinol. This haplotype is the strongest risk factor for allopurinol-induced SCARs,[187] and oxypurinol, the serum levels of which are increased in patients with renal failure,[164] can preferentially bind to the peptide binding groove of HLA-B*58:01 and dose-dependently activate T cells.[188 189] The association between carriage of this allele and increased risk of SCARs has been mainly observed in certain ethnic populations, including Han Chinese, Thai and Korean patients, showing high allele frequency.[187] By contrast, in Europe, where the allele frequency is much lower, allopurinol-induced SCARs have been reported also in the absence of this haplotype.[190] Although studies conducted in Asia found that screening for HLA-B*58:01 was cost-effective[191 192] and reduced the incidence of allopurinol-induced SCARs,[159] the task force felt that we lack sufficient data to provide firm recommendations for cost-effective screening in populations with low allele frequency, such as Europe. Therefore, screening for this haplotype before initiating allopurinol is left to the discretion of the attending physician, who should however be aware of the genetic risk of severe allergic reaction conferred by HLA-B*58.01 carriage.

Recommendations for the treatment of flares have also markedly evolved since 2006 in that use of colchicine should be tailored according to current medications and comorbidities, oral corticosteroids can be offered and a combination of anti-inflammatory agents is now recommended depending on the severity of flares. Items related to colchicine, NSAIDs and oral corticosteroids are now predominantly evidence-based, whereas those related to combined therapy and intra-articular corticosteroid injections rely on expert and patient opinion, which highlights the need for further trials. The other main novelty for treatment of flares is the recommendation for IL-1 blockade in patients with frequent, poorly controlled flares. Given the price and putative infection risk associated with IL-1 blockers, the task force recommends their use in patients with contraindications to colchicine, NSAIDs and corticosteroids. Finally, the need to educate patients and to promote a 'pill-in-the-pocket' approach is highlighted to provide rapid treatment of flares, because the task force is convinced that patients must play a key role and be fully involved in the management of their disease.

These novel EULAR recommendations will undoubtedly require updating over the next few years. Indeed, we anticipate that new data on existing drugs or emerging drugs, in particular novel uricosurics, will be available soon. In addition, studies of therapeutic strategies are likely to emerge. The task force sincerely hopes that these pragmatic recommendations will improve the current quality of gout care.

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REFERENCES

1 Bardin T, Bouée S, Clerson P, *et al*. Prevalence of gout in the Adult Population of France. *Arthritis Care Res (Hoboken)* 2016;68:261–6.
2 Trifirò G, Morabito P, Cavagna L, *et al*. Epidemiology of gout and hyperuricaemia in Italy during the years 2005–2009: a nationwide population-based study. *Ann Rheum Dis* 2013;72:694–700.
3 Kuo CF, Grainge MJ, Mallen C, *et al*. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74:661–7.
4 Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther* 2010;12:223.
5 Kuo CF, Grainge MJ, Zhang W, *et al*. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol* 2015;11:649–62.
6 Doherty M, Jansen TL, Nuki G, *et al*. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis* 2012;71:1765–70.
7 Richette P, Clerson P, Périssin L, *et al*. Revisiting comorbidities in gout: a cluster analysis. *Ann Rheum Dis* 2015;74:142–7.
8 Zhang W, Doherty M, Bardin T, *et al*. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006;65:1312–24.
9 So A, Thorens B. Uric acid transport and disease. *J Clin Invest* 2010;120:1791–9.
10 Rock KL, Kataoka H, Lai JJ. Uric acid as a danger signal in gout and its comorbidities. *Nat Rev Rheumatol* 2013;9:13–23.

11 Diaz-Torné C, Perez-Herrero N, Perez-Ruiz F. New medications in development for the treatment of hyperuricemia of gout. *Curr Opin Rheumatol* 2015;27:164–9.
12 Edwards NL, So A. Emerging therapies for gout. *Rheum Dis Clin North Am* 2014;40:375–87.
13 Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum* 2009;38:411–19.
14 Stamp LK, O'Donnell JL, Zhang M, *et al*. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arthritis Rheum* 2011;63:412–21.
15 Stamp LK, Taylor WJ, Jones PB, *et al*. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheum* 2012;64:2529–36.
16 Hung SI, Chung WH, Liou LB, *et al*. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005;102:4134–9.
17 Perez-Ruiz F, Martínez-Indart L, Carmona L, *et al*. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. *Ann Rheum Dis* 2014;73:177–82.
18 Dougados M, Betteridge N, Burmester GR, *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;63:1172–6.
19 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
20 Colebatch-Bourn AN, Conaghan PG, Arden NK, *et al*. Raising the quality of rheumatology management recommendations: lessons from the EULAR process 10 years after provision of standard operating procedures. *Rheumatology (Oxford)* 2015;54:1392–6.
21 Annemans L, Spaepen E, Gaskin M, *et al*. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. *Ann Rheum Dis* 2008;67:960–6.
22 Roddy E, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. *Ann Rheum Dis* 2007;66:1311–15.
23 Harrold LR, Mazor KM, Negron A, *et al*. Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire. *Rheumatology (Oxford)* 2013;52:1623–9.
24 Kuo CF, Grainge MJ, Mallen C, *et al*. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. *JAMA* 2015;312:2684–6.
25 Spencer K, Carr A, Doherty M. Patient and provider barriers to effective management of gout in general practice: a qualitative study. *Ann Rheum Dis* 2012;71:1490–5.
26 Reach G. Treatment adherence in patients with gout. *Joint Bone Spine* 2011;78:456–9.
27 Harrold LR, Andrade SE, Briesacher BA, *et al*. Adherence with urate-lowering therapies for the treatment of gout. *Arthritis Res Ther* 2009;11:R46.
28 Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. *Ann Rheum Dis* 2013;72:826–30.
29 Williams PT. Effects of diet, physical activity and performance, and body weight on incident gout in ostensibly healthy, vigorously active men. *Am J Clin Nutr* 2008;87:1480–7.
30 Dalbeth N, Chen P, White M, *et al*. Impact of bariatric surgery on serum urate targets in people with morbid obesity and diabetes: a prospective longitudinal study. *Ann Rheum Dis* 2014;73:797–802.
31 Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial. *Rheumatology (Oxford)* 2010;49:2391–9.
32 Richette P, Poitou C, Manivet P, *et al*. Weight loss, xanthine oxidase and serum urate levels: a prospective, longitudinal study of obese patients. *Arthritis Care Res (Hoboken)* 2016;68:1036–42.
33 Chen JH, Wen CP, Wu SB, *et al*. Attenuating the mortality risk of high serum uric acid: the role of physical activity underused. *Ann Rheum Dis* 2015;74:2034–42.
34 Roddy E, Choi HK. Epidemiology of gout. *Rheum Dis Clin North Am* 2014;40:155–75.
35 Bhole V, de Vera M, Rahman MM, *et al*. Epidemiology of gout in women: fifty-two-year follow-up of a prospective cohort. *Arthritis Rheum* 2010;62:1069–76.
36 Zhang Y, Chen C, Choi H, *et al*. Purine-rich foods intake and recurrent gout attacks. *Ann Rheum Dis* 2012;71:1448–53.
37 Zhang Y, Woods R, Chaisson CE, *et al*. Alcohol consumption as a trigger of recurrent gout attacks. *Am J Med* 2006;119:800.e13–8.
38 Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 2008;336:309–12.
39 Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA* 2010;304:2270–8.
40 Gao X, Qi L, Qiao N, *et al*. Intake of added sugar and sugar-sweetened drink and serum uric acid concentration in US men and women. *Hypertension* 2007;50:306–12.
41 Choi JW, Ford ES, Gao X, *et al*. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum* 2008;59:109–16.
42 Choi HK, Curhan G. Coffee, tea, and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey. *Arthritis Rheum* 2007;57:816–21.
43 Choi HK, Curhan G. Coffee consumption and risk of incident gout in women: the Nurses' Health Study. *Am J Clin Nutr* 2010;92:922–7.
44 Choi HK, Willett W, Curhan G. Coffee consumption and risk of incident gout in men: a prospective study. *Arthritis Rheum* 2007;56:2049–55.
45 Zhang Y, Neogi T, Chen C, *et al*. Cherry consumption and decreased risk of recurrent gout attacks. *Arthritis Rheum* 2012;64:4004–11.
46 Zgaga L, Theodoratou E, Kyle J, *et al*. The association of dietary intake of purine-rich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study. *PLoS ONE* 2012;7:e38123.
47 Dalbeth N, Wong S, Gamble GD, *et al*. Acute effect of milk on serum urate concentrations: a randomised controlled crossover trial. *Ann Rheum Dis* 2010;69:1677–82.
48 Dalbeth N, Ames R, Gamble GD, *et al*. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. *Ann Rheum Dis* 2012;71:929–34.
49 Holland R, McGill NW. Comprehensive dietary education in treated gout patients does not further improve serum urate. *Intern Med J* 2015;45:189–94.
50 Moi JH, Sriranganathan MK, Falzon L, *et al*. Lifestyle interventions for the treatment of gout: a summary of 2 Cochrane systematic reviews. *J Rheumatol Suppl* 2014;92:26–32.
51 Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009-10. *PLoS ONE* 2012;7:e50046.
52 Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med* 2011;125:679–687.e1.
53 Jalal DI, Chonchol M, Chen W, *et al*. Uric acid as a target of therapy in CKD. *Am J Kidney Dis* 2013;61:134–46.
54 Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008;359:1811–21.
55 Liu SC, Xia L, Zhang J, *et al*. Gout and risk of myocardial infarction: a systematic review and meta-analysis of cohort studies. *PLoS ONE* 2015;10:e0134088.
56 Clarson LE, Hider SL, Belcher J, *et al*. Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK clinical practice research datalink. *Ann Rheum Dis* 2015;74:642–7.
57 Krishnan E, Baker JF, Furst DE, *et al*. Gout and the risk of acute myocardial infarction. *Arthritis Rheum* 2006;54:2688–96.
58 Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007;116:894–900.
59 De Vera MA, Rahman MM, Bhole V, *et al*. Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population-based study. *Ann Rheum Dis* 2010;69:1162–4.
60 Baker JF, Schumacher HR, Krishnan E. Serum uric acid level and risk for peripheral arterial disease: analysis of data from the multiple risk factor intervention trial. *Angiology* 2007;58:450–7.
61 Krishnan E. Gout and the risk for incident heart failure and systolic dysfunction. *BMJ Open* 2012;2:e000282.
62 Seminog OO, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. *Rheumatology (Oxford)* 2013;52:2251–9.
63 Krishnan E, Akhras KS, Sharma H, *et al*. Relative and attributable diabetes risk associated with hyperuricemia in US veterans with gout. *QJM* 2013;106:721–9.
64 Keenan RT, O'Brien WR, Lee KH, *et al*. Prevalence of contraindications and prescription of pharmacologic therapies for gout. *Am J Med* 2011;124:155–63.
65 Terkeltaub RA, Furst DE, Bennett K, *et al*. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010;62:1060–8.
66 van Durme CM, Wechalekar MD, Buchbinder R, *et al*. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev* 2014;(9):CD010120.
67 Li T, Chen SL, Dai Q, *et al*. Etoricoxib versus indomethacin in the treatment of Chinese patients with acute gouty arthritis: a randomized double-blind trial. *Chin Med J* 2013;126:1867–71.
68 Schumacher HR, Berger MF, Li-Yu J, *et al*. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. *J Rheumatol* 2012;39:1859–66.
69 Willburger RE, Mysler E, Derbot J, *et al*. Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. *Rheumatology (Oxford)* 2007;46:1126–32.

70 Rainer TH, Cheng CH, Janssens HJ, *et al*. Oral prednisolone in the treatment of acute gout: a pragmatic, multicenter, double-blind, randomized trial. *Ann Intern Med* 2016;164:464–71.
71 Janssens HJ, Janssen M, van de Lisdonk EH, *et al*. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet* 2008;371:1854–60.
72 Man CY, Cheung IT, Cameron PA, *et al*. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute gout-like arthritis: a double-blind, randomized, controlled trial. *Ann Emerg Med* 2007;49:670–7.
73 Terkeltaub RA, Furst DE, Digiacinto JL, *et al*. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. *Arthritis Rheum* 2011;63:2226–37.
74 Richette P, Bardin T. Colchicine for the treatment of gout. *Expert Opin Pharmacother* 2010;11:2933–8.
75 Wason S, Mount D, Faulkner R. Single-dose, open-label study of the differences in pharmacokinetics of colchicine in subjects with renal impairment, including end-stage renal disease. *Clin Drug Investig* 2014;34:845–55.
76 Fernández C, Noguera R, González JA, *et al*. Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. *J Rheumatol* 1999;26:2285–6.
77 Wechalekar MD, Vinik O, Schlesinger N, *et al*. Intra-articular glucocorticoids for acute gout. *Cochrane Database Syst Rev* 2013;(4):CD009920.
78 Martinon F, Pétrilli V, Mayor A, *et al*. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006;440:237–41.
79 Schlesinger N, Alten RE, Bardin T, *et al*. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. *Ann Rheum Dis* 2012;71:1839–48.
80 So A, De Smedt T, Revaz S, *et al*. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther* 2007;9:R28.
81 Chen K, Fields T, Mancuso CA, *et al*. Anakinra's efficacy is variable in refractory gout: report of ten cases. *Semin Arthritis Rheum* 2010;40:210–14.
82 Ottaviani S, Moltó A, Ea HK, *et al*. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. *Arthritis Res Ther* 2013;15:R123.
83 Ghosh P, Cho M, Rawat G, *et al*. Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. *Arthritis Care Res (Hoboken)* 2013;65:1381–4.
84 Terkeltaub R, Sundy JS, Schumacher HR, *et al*. The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. *Ann Rheum Dis* 2009;68:1613–17.
85 Terkeltaub RA, Schumacher HR, Carter JD, *et al*. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. *Arthritis Res Ther* 2013;15:R25.
86 Schlesinger N. Canakinumab in gout. *Expert Opin Biol Ther* 2012;12:1265–75.
87 Becker MA, MacDonald PA, Hunt BJ, *et al*. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. *Nucleosides Nucleotides Nucleic Acids* 2008;27:585–91.
88 Wortmann RL, Macdonald PA, Hunt B, *et al*. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. *Clin Ther* 2010;32:2386–97.
89 Finkelstein Y, Aks SE, Hutson JR, *et al*. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol (Phila)* 2010;48:407–14.
90 Nidorf SM, Eikelboom JW, Budgeon CA, *et al*. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;61:404–10.
91 Deftereos S, Giannopoulos G, Raisakis K, *et al*. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. *J Am Coll Cardiol* 2013;61:1679–85.
92 Schlesinger N, Mysler E, Lin HY, *et al*. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. *Ann Rheum Dis* 2011;70:1264–71.
93 Schumacher HR Jr, Sundy JS, Terkeltaub R, *et al*. Rilonacept (interleukin-1 trap) in the prevention of acute gout flares during initiation of urate-lowering therapy: results of a phase II randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2012;64:876–84.
94 Mitha E, Schumacher HR, Fouche L, *et al*. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. *Rheumatology (Oxford)* 2013;52:1285–92.
95 Schumacher HR Jr, Evans RR, Saag KG, *et al*. Rilonacept (interleukin-1 trap) for prevention of gout flares during initiation of uric acid-lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. *Arthritis Care Res (Hoboken)* 2012;64:1462–70.
96 Sundy JS, Schumacher HR, Kivitz A, *et al*. Rilonacept for gout flare prevention in patients receiving uric acid-lowering therapy: results of RESURGE, a phase III, international safety study. *J Rheumatol* 2014;41:1703–11.
97 Schumacher HR Jr, Becker MA, Wortmann RL, *et al*. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum* 2008;59:1540–8.
98 Becker MA, Schumacher HR Jr, Wortmann RL, *et al*. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;353:2450–61.
99 Sundy JS, Baraf HS, Yood RA, *et al*. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA* 2011;306:711–20.
100 Baraf HS, Becker MA, Gutierrez-Urena SR, *et al*. Tophus burden reduction with pegloticase: results from phase 3 randomized trials and open-label extension in patients with chronic gout refractory to conventional therapy. *Arthritis Res Ther* 2013;15:R137.
101 Strand V, Khanna D, Singh JA, *et al*. Improved health-related quality of life and physical function in patients with refractory chronic gout following treatment with pegloticase: evidence from phase III randomized controlled trials. *J Rheumatol* 2012;39:1450–7.
102 Richette P. Debulking the urate load to feel better. *J Rheumatol* 2012;39:1311–13.
103 Scire CA, Manara M, Cimmino MA, *et al*. Gout impacts on function and health-related quality of life beyond associated risk factors and medical conditions: results from the KING observational study of the Italian Society for Rheumatology (SIR). *Arthritis Res Ther* 2013;15:R101.
104 Becker MA, Schumacher HR, Benjamin KL, *et al*. Quality of life and disability in patients with treatment-failure gout. *J Rheumatol* 2009;36:1041–8.
105 Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. *Ann Rheum Dis* 2008;67:1310–16.
106 Chandratre P, Roddy E, Clarson L, *et al*. Health-related quality of life in gout: a systematic review. *Rheumatology (Oxford)* 2013;52:2031–40.
107 Stack AG, Hanley A, Casserly LF, *et al*. Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. *QJM* 2013;106:647–58.
108 Bhole V, Krishnan E. Gout and the heart. *Rheum Dis Clin North Am* 2014;40:125–43.
109 Richette P, Perez-Ruiz F. Serum uric acid and metabolic risk. *Curr Med Res Opin* 2013;29(Suppl 3):9–15.
110 Krishnan E, Svendsen K, Neaton JD, *et al*. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008;168:1104–10.
111 Higgins P, Dawson J, Lees KR, *et al*. Xanthine oxidase inhibition for the treatment of cardiovascular disease: a systematic review and meta-analysis. *Cardiovasc Ther* 2012;30:217–26.
112 Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich)* 2013;15:435–42.
113 Goicoechea M, Garcia de Vinuesa S, Verdalles U, *et al*. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* 2015;65:543–9.
114 Bose B, Badve SV, Hiremath SS, *et al*. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2014;29:406–13.
115 Kanji T, Gandhi M, Clase CM, *et al*. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrol* 2015;16:58.
116 Sircar D, Chatterjee S, Waikhom R, *et al*. Efficacy of Febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: a 6-month, double-blind, randomized, placebo-controlled trial. *Am J Kidney Dis* 2015;66:945–50.
117 Noman A, Ang DS, Ogston S, *et al*. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010;375:2161–7.
118 Kelkar A, Kuo A, Frishman WH. Allopurinol as a cardiovascular drug. *Cardiol Rev* 2011;19:265–71.
119 Thanassoulis G, Brophy JM, Richard H, *et al*. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med* 2010;170:1358–64.
120 Givertz MM, Anstrom KJ, Redfield MM, *et al*. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study. *Circulation* 2015;131:1763–71.
121 Grimaldi-Bensouda L, Alpérovitch A, Aubrun E, *et al*. Impact of allopurinol on risk of myocardial infarction. *Ann Rheum Dis* 2015;74:836–42.
122 de Abajo FJ, Gil MJ, Rodríguez A, *et al*. Allopurinol use and risk of non-fatal acute myocardial infarction. *Heart* 2015;101:679–85.
123 Kok VC, Horng JT, Chang WS, *et al*. Allopurinol therapy in gout patients does not associate with beneficial cardiovascular outcomes: a population-based matched-cohort study. *PLoS ONE* 2014;9:e99102.

124 Saag KG, Whelton A, Becker MA, *et al*. Impact of febuxostat on renal function in gout subjects with moderate-to-severe renal impairment. *Arthritis Rheumatol* 2016. [Epub ahead of print 19 Feb 2016]. doi:10.1002/art.39654
125 Wu EQ, Patel PA, Mody RR, *et al*. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? *J Rheumatol* 2009;36:1032–40.
126 Abhishek A, Valdes AM, Zhang W, *et al*. Serum uric acid & disease duration associate with frequent gout attacks but are poor at identifying such patients: a case control study. *Arthritis Care Res (Hoboken)* 2016. [Epub ahead of print 11 Feb 2016]. doi:10.1002/acr.22855
127 Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol* 2011;23:192–202.
128 Rothenbacher D, Primatesta P, Ferreira A, *et al*. Frequency and risk factors of gout flares in a large population-based cohort of incident gout. *Rheumatology (Oxford)* 2011;50:973–81.
129 Yamanaka H. Gout and hyperuricemia in young people. *Curr Opin Rheumatol* 2011;23:156–60.
130 Taylor TH, Mecchella JN, Larson RJ, *et al*. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med* 2012;125:1126–1134.e7.
131 Hill EM, Sky K, Sit M, *et al*. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. *J Clin Rheumatol* 2015;21:120–5.
132 Bardin T. Hyperuricemia starts at 360 micromoles (6 mg/dL). *Joint Bone Spine* 2015;82:141–3.
133 Pascual E, Sivera F. Time required for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout. *Ann Rheum Dis* 2007;66:1056–8.
134 Perez-Ruiz F, Lioté F. Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? *Arthritis Rheum* 2007;57:1324–8.
135 Perez-Ruiz F, Calabozo M, Pijoan JI, *et al*. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002;47:356–60.
136 Chamorro A, Amaro S, Castellanos M, *et al*. Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial. *Lancet Neurol* 2014;13:453–60.
137 Peng F, Zhang B, Zhong X, *et al*. Serum uric acid levels of patients with multiple sclerosis and other neurological diseases. *Mult Scler* 2008;14:188–96.
138 Schretlen DJ, Inscore AB, Vannorsdall TD, *et al*. Serum uric acid and brain ischemia in normal elderly adults. *Neurology* 2007;69:1418–23.
139 Chen H, Mosley TH, Alonso A, *et al*. Plasma urate and Parkinson's disease in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol* 2009;169:1064–9.
140 Weisskopf MG, O'Reilly E, Chen H, *et al*. Plasma urate and risk of Parkinson's disease. *Am J Epidemiol* 2007;166:561–7.
141 Kim TS, Pae CU, Yoon SJ, *et al*. Decreased plasma antioxidants in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2006;21:344–8.
142 Abraham A, Drory VE. Influence of serum uric acid levels on prognosis and survival in amyotrophic lateral sclerosis: a meta-analysis. *J Neurol* 2014;261:1133–8.
143 Zandman-Goddard G, Amital H, Shamrayevsky N, *et al*. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. *Rheumatology (Oxford)* 2013;52:1126–31.
144 Solomon DH, Avorn J, Levin R, *et al*. Uric acid lowering therapy: prescribing patterns in a large cohort of older adults. *Ann Rheum Dis* 2008;67:609–13.
145 Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two-stage approach to the treatment of hyperuricemia in gout: the "dirty dish" hypothesis. *Arthritis Rheum* 2011;63:4002–6.
146 Meltzer M, Pizzi LT, Jutkowitz E. Payer decision-making with limited comparative and cost effectiveness data: the case of new pharmacological treatments for gout. *Evid Based Med* 2012;17:105–8.
147 Jutkowitz E, Choi HK, Pizzi LT, *et al*. Cost-effectiveness of allopurinol and febuxostat for the management of gout. *Ann Intern Med* 2014;161:617–26.
148 Reinders MK, van Roon EN, Jansen TL, *et al*. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann Rheum Dis* 2009;68:51–6.
149 Becker MA, Schumacher HR, Espinoza LR, *et al*. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010;12:R63.
150 Reinders MK, Haagsma C, Jansen TL, *et al*. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in patients with gout. *Ann Rheum Dis* 2009;68:892–7.
151 Becker MA, Schumacher HR Jr, Wortmann RL, *et al*. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum* 2005;52:916–23.
152 Abeles AM. Febuxostat hypersensitivity. *J Rheumatol* 2012;39:659.
153 Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. *J Rheumatol* 2011;38:1957–9.
154 Bardin T, Chalès G, Pascart T, *et al*. Risk of cutaneous adverse events with febuxostat treatment in patients with skin reaction to allopurinol. A retrospective, hospital-based study of 101 patients with consecutive allopurinol and febuxostat treatment. *Joint Bone Spine* 2016;83:314–17.
155 Kydd AS, Seth R, Buchbinder R, *et al*. Uricosuric medications for chronic gout. *Cochrane Database Syst Rev* 2014;(11):CD010457.
156 Pui K, Gow PJ, Dalbeth N. Efficacy and tolerability of probenecid as urate-lowering therapy in gout; clinical experience in high-prevalence population. *J Rheumatol* 2013;40:872–6.
157 Reinders MK, van Roon EN, Houtman PM, *et al*. Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients. *Clin Rheumatol* 2007;26:1459–65.
158 Stocker SL, Graham GG, McLachlan AJ, *et al*. Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in patients with gout. *J Rheumatol* 2011;38:904–10.
159 Ko TM, Tsai CY, Chen SY, *et al*. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. *BMJ* 2015;351:h4848.
160 Perez-Ruiz F, Sundy JS, Miner JN, *et al*. Lesinurad in combination with allopurinol: results of a phase 2, randomised, double-blind study in patients with gout with an inadequate response to allopurinol. *Ann Rheum Dis* 2016;75:1074–80.
161 Halevy S, Ghislain PD, Mockenhaupt M, *et al*. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008;58:25–32.
162 Kim SC, Newcomb C, Margolis D, *et al*. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: a population-based cohort study. *Arthritis Care Res (Hoboken)* 2013;65:578–84.
163 Ramasamy SN, Korb-Wells CS, Kannangara DR, *et al*. Allopurinol hypersensitivity: a systematic review of all published cases, 1950-2012. *Drug Saf* 2013;36:953–80.
164 Chung WH, Chang WC, Stocker SL, *et al*. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann Rheum Dis* 2015;74:2157–64.
165 Chao J, Terkeltaub R. A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. *Curr Rheumatol Rep* 2009;11:135–40.
166 Stocker SL, McLachlan AJ, Savic RM, *et al*. The pharmacokinetics of oxypurinol in people with gout. *Br J Clin Pharmacol* 2012;74:477–89.
167 Yun J, Mattsson J, Schnyder K, *et al*. Allopurinol hypersensitivity is primarily mediated by dose-dependent oxypurinol-specific T cell response. *Clin Exp Allergy* 2013;43:1246–55.
168 Dalbeth N, Kumar S, Stamp L, *et al*. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J Rheumatol* 2006;33:1646–50.
169 Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984;76:47–56.
170 Hira D, Chisaki Y, Noda S, *et al*. Population pharmacokinetics and therapeutic efficacy of febuxostat in patients with severe renal impairment. *Pharmacology* 2015;96:90–8.
171 Perez-Ruiz F, Calabozo M, Fernandez-Lopez MJ, *et al*. Treatment of chronic gout in patients with renal function impairment: an open, randomized, actively controlled study. *J Clin Rheumatol* 1999;5:49–55.
172 Fujimori S, Ooyama K, Ooyama H, *et al*. Efficacy of benzbromarone in hyperuricemic patients associated with chronic kidney disease. *Nucleosides Nucleotides Nucleic Acids* 2011;30:1035–8.
173 Sundy JS, Becker MA, Baraf HS, *et al*. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. *Arthritis Rheum* 2008;58:2882–91.
174 Lipsky PE, Calabrese LH, Kavanaugh A, *et al*. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. *Arthritis Res Ther* 2014;16:R60.
175 Choi HK, Soriano LC, Zhang Y, *et al*. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ* 2012;344:d8190.
176 Derosa G, Maffioli P, Sahebkar A. Plasma uric acid concentrations are reduced by fenofibrate: a systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacol Res* 2015;102:63–70.
177 Ansquer JC, Dalton RN, Caussé E, *et al*. Effect of fenofibrate on kidney function: a 6-week randomized crossover trial in healthy people. *Am J Kidney Dis* 2008;51:904–13.
178 Ogata N, Fujimori S, Oka Y, *et al*. Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleosides Nucleotides Nucleic Acids* 2010;29:321–4.
179 Takagi H, Umemoto T. Atorvastatin therapy reduces serum uric acid levels: a meta-analysis of randomized controlled trials. *Int J Cardiol* 2012;157:255–7.

180 Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum* 2011;63:3136–41.
181 Crittenden DB, Pillinger MH. New therapies for gout. *Annu Rev Med* 2013;64:325–37.
182 Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Curr Opin Rheumatol* 2014;26:186–91.
183 Dalbeth N, House ME, Aati O, *et al*. Urate crystal deposition in asymptomatic hyperuricaemia and symptomatic gout: a dual energy CT study. *Ann Rheum Dis* 2015;74:908–11.
184 Dalbeth N, Stamp L. Hyperuricaemia and gout: time for a new staging system? *Ann Rheum Dis* 2014;73:1598–600.
185 Khanna D, Fitzgerald JD, Khanna PP, *et al*. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)* 2012;64:1431–46.
186 Khanna D, Khanna PP, Fitzgerald JD, *et al*. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1447–61.
187 Saito Y, Stamp LK, Caudle KE, *et al*. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin Pharmacol Ther* 2015;99:36–7.
188 Yun J, Marcaida MJ, Eriksson KK, *et al*. Oxypurinol directly and immediately activates the drug-specific T cells via the preferential use of HLA-B*58:01. *J Immunol* 2014;192:2984–93.
189 Lin CH, Chen JK, Ko TM, *et al*. Immunologic basis for allopurinol-induced severe cutaneous adverse reactions: HLA-B*58:01-restricted activation of drug-specific T cells and molecular interaction. *J Allergy Clin Immunol* 2015;135:1063–5.e5.
190 Lonjou C, Borot N, Sekula P, *et al*. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008;18:99–107.
191 Saokaew S, Tassaneeyakul W, Maenthaisong R, *et al*. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. *PLoS ONE* 2014;9:e94294.
192 Park DJ, Kang JH, Lee JW, *et al*. Cost-effectiveness analysis of HLA-B5801 genotyping in the treatment of gout patients with chronic renal insufficiency in Korea. *Arthritis Care Res (Hoboken)* 2015;67:280–7.

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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The application of the recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

Overview

This guideline covers diagnosing and managing spondyloarthritis that is suspected or confirmed in adults who are 16 years or older. It aims to raise awareness of the features of spondyloarthritis and provide clear advice on what action to take when people with signs and symptoms first present in healthcare settings. It also provides advice on the range of treatments available.

In June 2017, we updated recommendation 1.2.7 to clarify the advice on what imaging should be done.

NICE has also produced guidelines on psoriasis and low back pain and sciatica in over 16s.

Who is it for?

- Healthcare professionals
- Commissioners and providers
- People with spondyloarthritis and their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

Spondyloarthritis is a group of inflammatory conditions that have a range of manifestations. Spondyloarthritis may be predominantly:

- axial:
  - radiographic axial spondyloarthritis (ankylosing spondylitis)
  - non-radiographic axial spondyloarthritis **or**
- peripheral:
  - psoriatic arthritis
  - reactive arthritis
  - enteropathic spondyloarthritis.

People with predominantly axial spondyloarthritis may have additional peripheral symptoms, and vice versa.

Axial presentations of spondyloarthritis are often misdiagnosed as mechanical low back pain, leading to delays in access to effective treatments. Peripheral presentations are often seen as unrelated joint or tendon problems, and can be misdiagnosed because problems can move around between joints.

1.1 Recognition and referral in non-specialist care settings

1.1.1 Do not rule out the possibility that a person has spondyloarthritis solely on the presence or absence of any individual sign, symptom or test result.

Suspecting spondyloarthritis

1.1.2 Recognise that spondyloarthritis can have diverse symptoms and be difficult to identify, which can lead to delayed or missed diagnoses. Signs and symptoms may be musculoskeletal (for example, inflammatory back pain, enthesitis and dactylitis) or extra-articular (for example, uveitis and psoriasis [including psoriatic nail symptoms]). Risk factors include recent genitourinary infection and a family history of spondyloarthritis or psoriasis.

1.1.3 Be aware that axial and peripheral spondyloarthritis may be missed, even if the onset is associated with established comorbidities (for example, uveitis, psoriasis, inflammatory bowel disease [Crohn's disease or ulcerative colitis], or a gastrointestinal or genitourinary infection).

1.1.4 Be aware that axial spondyloarthritis:

- affects a similar number of women as men
- can occur in people who are human leukocyte antigen B27 (HLA-B27) negative
- may be present despite no evidence of sacroiliitis on a plain film X-ray.

Referral for suspected axial spondyloarthritis

1.1.5 If a person has low back pain that started before the age of 45 years and has lasted for longer than 3 months, refer the person to a rheumatologist for a spondyloarthritis assessment if **4 or more** of the following additional criteria are also present:

- low back pain that started before the age of 35 years (this further increases the likelihood that back pain is due to spondyloarthritis compared with low back pain that started between 35 and 44 years)
- waking during the second half of the night because of symptoms
- buttock pain
- improvement with movement
- improvement within 48 hours of taking non-steroidal anti-inflammatory drugs (NSAIDs)

- a first-degree relative with spondyloarthritis
- current or past arthritis
- current or past enthesitis
- current or past psoriasis.

If exactly 3 of the additional criteria are present, perform an HLA-B27 test. If the test is positive, refer the person to a rheumatologist for a spondyloarthritis assessment.

1.1.6 If the person does not meet the criteria in recommendation 1.1.5 but clinical suspicion of axial spondyloarthritis remains, advise the person to seek repeat assessment if new signs, symptoms or risk factors listed in recommendation 1.1.5 develop. This may be especially appropriate if the person has current or past inflammatory bowel disease (Crohn's disease or ulcerative colitis), psoriasis or uveitis (see recommendation 1.1.12 for guidance on referral for immediate [same-day] ophthalmological assessment for people with acute anterior uveitis).

Referral for suspected psoriatic arthritis and other peripheral spondyloarthritides

1.1.7 For guidance on identifying spondyloarthritis in people with an existing diagnosis of psoriasis, see assessment and referral for psoriatic arthritis in the NICE guideline on psoriasis.

1.1.8 Urgently refer people with suspected new-onset inflammatory arthritis to a rheumatologist for a spondyloarthritis assessment, unless rheumatoid arthritis, gout or acute calcium pyrophosphate (CPP) arthritis ('pseudogout') is suspected. If rheumatoid arthritis is suspected, see referral for specialist treatment in the NICE guideline on rheumatoid arthritis in adults.

1.1.9 Refer people with dactylitis to a rheumatologist for a spondyloarthritis assessment.

1.1.10 Refer people with enthesitis without apparent mechanical cause to a rheumatologist for a spondyloarthritis assessment if:

- it is persistent **or**

- it is in multiple sites **or**
- any of the following are also present:
  - back pain without apparent mechanical cause
  - current or past uveitis (see recommendation 1.1.12 for guidance on immediate [same-day] ophthalmological assessment for people with acute anterior uveitis)
  - current or past psoriasis
  - gastrointestinal or genitourinary infection
  - inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- a first-degree relative with spondyloarthritis or psoriasis.

Recognising psoriasis

1.1.11 If a person with suspected spondyloarthritis has signs or symptoms of undiagnosed psoriasis, follow the recommendations in the NICE guideline on psoriasis.

Referral for suspected acute anterior uveitis

1.1.12 Refer people for an immediate (same-day) ophthalmological assessment if they have symptoms of acute anterior uveitis (for example, eye pain, eye redness, sensitivity to light or blurred vision).

Case-finding in people with acute anterior uveitis

1.1.13 Ophthalmologists should ask people with acute anterior uveitis whether they have:

- consulted their GP about joint pains **or**
- experienced low back pain that started before the age of 45 years and has lasted for longer than 3 months.

1.1.14 If the person meets either of the criteria in recommendation 1.1.13, establish whether they have psoriasis or skin complaints that appear psoriatic on physical examination.

- If they do, refer the person to a rheumatologist for a spondyloarthritis assessment.
- If they do not, perform an HLA-B27 test. If the test is positive, refer the person to a rheumatologist for a spondyloarthritis assessment.

1.2 Diagnosing spondyloarthritis in specialist care settings

Diagnostic criteria for suspected spondyloarthritis

1.2.1 In specialist care settings, consider using validated spondyloarthritis criteria to guide clinical judgement when diagnosing spondyloarthritis. Examples include:

- general spondyloarthritis criteria:
  - Amor
  - European Spondyloarthropathy Study Group (ESSG)
- axial spondyloarthritis criteria:
  - Assessment of Spondyloarthritis International Society (ASAS; axial)
  - Berlin
  - Rome
  - modified New York
- peripheral spondyloarthritis criteria:
  - ASAS (peripheral)
  - Classification of Psoriatic Arthritis (CASPAR)
- French Society of Rheumatology (reactive arthritis).

1.2.2 Do not rule out a diagnosis of spondyloarthritis solely on the basis of a negative HLA-B27 result.

1.2.3 Do not rule out a diagnosis of spondyloarthritis if a person's C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are normal.

Imaging for suspected axial spondyloarthritis

Initial investigation using X-ray

1.2.4 Offer plain film X-ray of the sacroiliac joints for people with suspected axial spondyloarthritis, unless the person is likely to have an immature skeleton.

1.2.5 Diagnose radiographic axial spondyloarthritis (ankylosing spondylitis) if the plain film X-ray shows sacroiliitis meeting the modified New York criteria (bilateral grade 2–4 or unilateral grade 3–4 sacroiliitis).

1.2.6 If the plain film X-ray does not show sacroiliitis meeting modified New York criteria (bilateral grade 2–4 or unilateral grade 3–4 sacroiliitis), or an X-ray is not appropriate because the person's skeleton is not fully mature, request unenhanced MRI using an inflammatory back pain protocol.

Subsequent investigation using MRI

1.2.7 Radiologists receiving a request for an inflammatory back pain MRI should perform short T1 inversion recovery (STIR) and T1 weighted sequences of the whole spine (sagittal view), and sacroiliac joints (coronal oblique view).

1.2.8 Use the ASAS/Outcome Measures in Rheumatology (OMERACT) MRI criteria to interpret the MRI as follows:

- If the MRI meets the ASAS/OMERACT MRI criteria:
  - diagnose non-radiographic axial spondyloarthritis.
- If the MRI does not meet the ASAS/OMERACT MRI criteria:
  - do not exclude the possibility of axial spondyloarthritis
  - consider specialist musculoskeletal radiology review if there is disparity between the clinical suspicion and imaging findings, particularly in people with an immature skeleton
  - offer an HLA-B27 test if it has not already been done. If positive, base the diagnosis of non-radiographic axial spondyloarthritis on clinical features, for example, using the clinical 'arm' of the ASAS axial classification criteria.

1.2.9 If a diagnosis of axial spondyloarthritis cannot be confirmed and clinical suspicion remains high, consider a follow-up MRI.

Other types of imaging for diagnosing axial spondyloarthritis

1.2.10 Do not offer scintigraphy for people with suspected axial spondyloarthritis.

Imaging for suspected psoriatic arthritis and other peripheral spondyloarthritides

1.2.11 Offer plain film X-ray of symptomatic hands and feet for people with suspected peripheral spondyloarthritis in these areas.

1.2.12 If a diagnosis cannot be made from the plain film X-ray, consider ultrasound of:

- the hands and feet to assess for joint involvement
- suspected enthesitis sites.

1.2.13 Consider plain film X-rays, ultrasound and/or MRI of other peripheral and axial symptomatic sites.

1.2.14 Interpret a positive HLA-B27 result as increasing the likelihood of peripheral spondyloarthritis.

1.2.15 If a diagnosis of peripheral spondyloarthritis is confirmed, offer plain film X-ray of the sacroiliac joints to assess for axial involvement, even if the person does not have any symptoms.

Antibody testing for suspected reactive arthritis

1.2.16 Do not routinely test for infective antibody status to diagnose reactive arthritis in people with a history of gastrointestinal infection.

1.3 Information and support

Information about spondyloarthritis

1.3.1 Provide people with spondyloarthritis, and their family members or carers (as appropriate), with information that is:

- available on an ongoing basis
- relevant to the stage of the person's condition
- tailored to the person's needs.

For more guidance on providing information to people and discussing their preferences with them, see the NICE guideline on patient experience in adult NHS services.

1.3.2 Provide explanations and information about spondyloarthritis, for example:

- what spondyloarthritis is
- diagnosis and prognosis
- treatment options (pharmacological and non-pharmacological), including possible side effects
- likely symptoms and how they can be managed
- flare episodes and extra-articular symptoms
- self-help options
- opportunities for people with spondyloarthritis to be involved in research
- which healthcare professionals will be involved with the person's care and how to get in touch with them
- information about employment rights and ability to work
- local support groups, online forums and national charities, and how to get in touch with them.

Information about disease flares

1.3.3 Advise people with spondyloarthritis about the possibility of experiencing flare episodes and extra-articular symptoms.

1.3.4 Consider developing a flare management plan that is tailored to the person's individual needs, preferences and circumstances.

1.3.5 When discussing any flare management plan, provide information on:

- access to care during flares (including details of a named person to contact [for example, a specialist rheumatology nurse])
- self-care (for example, exercises, stretching and joint protection)
- pain and fatigue management
- potential changes to medicines
- managing the impact on daily life and ability to work.

1.4 Pharmacological management of spondyloarthritis

Axial spondyloarthritis

NSAIDs

1.4.1 Offer NSAIDs at the lowest effective dose to people with pain associated with axial spondyloarthritis, and think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.

1.4.2 If an NSAID taken at the maximum tolerated dose for 2–4 weeks does not provide adequate pain relief, consider switching to another NSAID.

Biological DMARDs – adalimumab, certolizumab pegol, etanercept, golimumab and infliximab for the treatment of ankylosing spondylitis and non-radiographic axial spondyloarthritis

1.4.3 Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorisations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their NHS clinician consider it appropriate to stop.
[This recommendation is from NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.]

1.4.4 Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
[This recommendation is from NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.]

1.4.5 The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.
[This recommendation is from NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.]

1.4.6 The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units **and**
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

[This recommendation is from NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.]

1.4.7 Treatment with another tumour necrosis factor (TNF)-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response.
[This recommendation is from NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.]

1.4.8 When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.
[This recommendation is from NICE's technology appraisal guidance on TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis.]

Biological DMARDs – secukinumab for the treatment of ankylosing spondylitis

1.4.9 Secukinumab is recommended, within its marketing authorisation, as an option for treating active ankylosing spondylitis in adults whose disease has responded inadequately to conventional therapy (NSAIDs or TNF-alpha inhibitors). The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.
[This recommendation is from NICE's technology appraisal guidance on secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors.]

1.4.10 Assess the response to secukinumab after 16 weeks of treatment and only continue if there is clear evidence of response, defined as:

- a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units **and**
- a reduction in the spinal pain VAS by 2 cm or more.

[This recommendation is from NICE's technology appraisal guidance on secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors.]

1.4.11 When using BASDAI and spinal pain VAS scores, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the responses to the questionnaires, and make any adjustments they consider appropriate.
[This recommendation is from NICE's technology appraisal guidance on secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors.]

Psoriatic arthritis and other peripheral spondyloarthritides

Non-biological therapies

1.4.12 Consider local corticosteroid injections as monotherapy for non-progressive monoarthritis.

1.4.13 Offer standard disease-modifying anti-rheumatic drugs (DMARDs) to people with:

- peripheral polyarthritis
- oligoarthritis
- persistent or progressive monoarthritis associated with peripheral spondyloarthritis.

1.4.14 When deciding which standard DMARD to offer, take into account:

- the person's needs, preferences and circumstances (such as pregnancy planning and alcohol consumption)
- comorbidities such as uveitis, psoriasis and inflammatory bowel disease
- disease characteristics
- potential side effects.

1.4.15 If a standard DMARD taken at the maximum tolerated dose for at least 3 months does not provide adequate relief from symptoms, consider switching to or adding another standard DMARD.

1.4.16 Consider NSAIDs as an adjunct to standard DMARDs or biological DMARDs to manage symptoms. Use oral NSAIDs at the lowest effective dose for the shortest possible period of time, and think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.

1.4.17 If NSAIDs do not provide adequate relief from symptoms, consider steroid injections (local or intramuscular) or short-term oral steroid therapy as an adjunct to standard DMARDs or biological DMARDs to manage symptoms.

1.4.18 If extra-articular disease is adequately controlled by an existing standard DMARD but peripheral spondyloarthritis is not, consider adding another standard DMARD.

Targeted synthetic DMARDs – apremilast for the treatment of psoriatic arthritis

1.4.19 For guidance on treating psoriatic arthritis with apremilast, see NICE's technology appraisal guidance on apremilast for treating active psoriatic arthritis.

Biological DMARDs – etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis

1.4.20 Etanercept, infliximab and adalimumab are recommended for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met.

- The person has peripheral arthritis with 3 or more tender joints and 3 or more swollen joints, and
- The psoriatic arthritis has not responded to adequate trials of at least 2 standard DMARDs, administered either individually or in combination.

[This recommendation is from NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.]

1.4.21 Treatment as described in 1.4.20 should normally be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.
[This recommendation is from NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.]

1.4.22 Etanercept, adalimumab or infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as an improvement in at least 2 of the 4 PsARC criteria (1 of which has to be joint tenderness or swelling score) with no worsening in any of

the 4 criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see etanercept and efalizumab for the treatment of adults with psoriasis [NICE technology appraisal guidance 103], infliximab for the treatment of adults with psoriasis [NICE technology appraisal guidance 134] and adalimumab for the treatment of adults with psoriasis [NICE technology appraisal guidance 146] for guidance on the use of TNF inhibitors in psoriasis).
[This recommendation is from NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.]

1.4.23 When using the PsARC healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.
[This recommendation is from NICE's technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.]

Biological DMARDs – golimumab for the treatment of psoriatic arthritis

1.4.24 Golimumab is recommended as an option for the treatment of active and progressive psoriatic arthritis in adults only if:

- it is used as described for other TNF-inhibitor treatments in etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (NICE technology appraisal guidance 199; see recommendations 1.4.20–1.4.23 in this guideline) **and**
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose.

[This recommendation is from NICE's technology appraisal guidance on golimumab for the treatment of psoriatic arthritis.]

1.4.25 When using the PsARC (as set out in NICE technology appraisal guidance 199; see recommendations 1.4.20–1.4.23 in this guideline), healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider

appropriate.
[This recommendation is from NICE's technology appraisal guidance on golimumab for the treatment of psoriatic arthritis.]

Biological DMARDs – ustekinumab for the treatment of psoriatic arthritis

1.4.26 Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:

- treatment with TNF-alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis [NICE technology appraisal guidance 199; see recommendations 1.4.20–1.4.23 in this guideline], and golimumab for the treatment of psoriatic arthritis [NICE technology appraisal guidance 220; see recommendations 1.4.24 and 1.4.25 in this guideline]) **or**
- the person has had treatment with 1 or more TNF-alpha inhibitors.

Ustekinumab is recommended only if the company provides the 90 mg dose of ustekinumab for people who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme.
[This recommendation is from NICE's technology appraisal guidance on ustekinumab for treating active psoriatic arthritis.]

1.4.27 Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the PsARC at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (see recommendations 1.4.20–1.4.23 in this guideline), people whose disease has a PASI 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see NICE technology appraisal guidance on ustekinumab for the treatment of adults with moderate to severe psoriasis).
[This recommendation is from NICE's technology appraisal guidance on ustekinumab for treating active psoriatic arthritis.]

1.4.28 When using the PsARC healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.
[This recommendation is from NICE's technology appraisal guidance on ustekinumab for treating active psoriatic arthritis.]

1.4.29 People whose treatment with ustekinumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue ustekinumab until they and their NHS clinician consider it appropriate to stop.
[This recommendation is from NICE's technology appraisal guidance on ustekinumab for treating active psoriatic arthritis.]

Reactive arthritis

Antibiotics

1.4.30 After treating the initial infection, do not offer long-term (4 weeks or longer) treatment with antibiotics solely to manage reactive arthritis caused by a gastrointestinal or genitourinary infection.

1.5 Non-pharmacological management of spondyloarthritis

1.5.1 Refer people with axial spondyloarthritis to a specialist physiotherapist to start an individualised, structured exercise programme, which should include:

- stretching, strengthening and postural exercises
- deep breathing
- spinal extension
- range of motion exercises for the lumbar, thoracic and cervical sections of the spine
- aerobic exercise.

1.5.2 Consider hydrotherapy as an adjunctive therapy to manage pain and maintain or improve function for people with axial spondyloarthritis.

1.5.3 Consider a referral to a specialist therapist (such as a physiotherapist, occupational therapist, hand therapist, orthotist or podiatrist) for people with spondyloarthritis who have difficulties with any of their everyday activities. The specialist therapist should:

- assess people's needs
- provide advice about physical aids
- arrange periodic reviews to assess people's changing needs.

1.6 Surgery for spondyloarthritis

1.6.1 Do not refer people with axial spondyloarthritis to a complex spinal surgery service to be assessed for spinal deformity correction unless the spinal deformity is:

- significantly affecting their quality of life **and**
- severe or progressing despite optimal non-surgical management (including physiotherapy).

1.6.2 If a person with axial spondyloarthritis presents with a suspected spinal fracture, refer them to a specialist to confirm the spinal fracture and carry out a stability assessment. After the stability assessment, the specialist should refer people with a potentially unstable spinal fracture to a spinal surgeon.

1.7 Managing flares

1.7.1 Manage flares in either specialist care or primary care depending on the person's needs.

1.7.2 When managing flares in primary care, seek advice from specialist care as needed, particularly for people who:

- have recurrent or persistent flares
- are taking biological DMARDs
- have comorbidities that may affect treatment or management of flares.

1.7.3 Be aware that uveitis can occur during flare episodes. See recommendation 1.1.12 for guidance on immediate (same-day) ophthalmological assessment for people with acute anterior uveitis.

1.8 Long-term complications

1.8.1 For guidance on monitoring long-term pharmacological treatments, see the NICE guideline on medicines optimisation.

1.8.2 Take into account the adverse effects associated with NSAIDs, standard DMARDs and biological DMARDs when monitoring spondyloarthritis in primary care.

1.8.3 Advise people that there may be a greater risk of skin cancer in people treated with TNF-alpha inhibitors.

1.8.4 Discuss risk factors for cardiovascular comorbidities with all people with spondyloarthritis.

1.8.5 Consider regular osteoporosis assessments (every 2 years) for people with axial spondyloarthritis. Be aware that bone mineral density measures may be elevated on spinal dual-energy X-ray absorptiometry (DEXA) due to the presence of syndesmophytes and ligamentous calcification, whereas hip measurements may be more reliable.

1.8.6 Advise people with axial spondyloarthritis that they may be prone to fractures, and should consult a healthcare professional following falls or physical trauma, particularly in the event of increased musculoskeletal pain.

1.9 Organisation of care

Coordinating care across settings

1.9.1 Commissioners should ensure that local arrangements are in place to coordinate care for people across primary and secondary (specialist) care. These should cover:

- prescribing NSAIDs and standard DMARDs

- monitoring NSAIDs, standard DMARDs and biological DMARDs
- managing flares
- ensuring prompt access to specialist rheumatology care when needed
- ensuring prompt access to other specialist services to manage comorbidities and extra-articular symptoms.

1.9.2 Ensure that people with spondyloarthritis have access to specialist care in primary or secondary care settings throughout the disease course to ensure optimal long-term spondyloarthritis management (see section 1.7 for arrangements for managing flares).

1.9.3 Ensure that there is effective communication and coordination between all healthcare professionals involved in the person's care, particularly if the person has comorbidities or extra-articular symptoms.

1.9.4 Ensure that there is communication and coordination between rheumatology and other relevant specialities (such as dermatology, gastroenterology and ophthalmology). This is particularly important for people who:

- are already receiving standard DMARDs or biological DMARDs for another condition
- need to start taking standard DMARDs or biological DMARDs for another condition.

1.9.5 For guidance on managing the transition of young people with juvenile idiopathic arthritis to adult services, see the NICE guideline on transition from children's to adults' services for young people using health or social care services.

Putting this guideline into practice

NICE has produced tools and resources to help you put this guideline into practice.

Putting recommendations into practice can take time. How long may vary from guideline to guideline, and depends on how much change in practice or services is needed. Implementing change is most effective when aligned with local priorities.

Changes recommended for clinical practice that can be done quickly – like changes in prescribing practice – should be shared quickly. This is because healthcare professionals should use guidelines to guide their work – as is required by professional regulating bodies such as the General Medical and Nursing and Midwifery Councils.

Changes should be implemented as soon as possible, unless there is a good reason for not doing so (for example, if it would be better value for money if a package of recommendations were all implemented at once).

Different organisations may need different approaches to implementation, depending on their size and function. Sometimes individual practitioners may be able to respond to recommendations to improve their practice more quickly than large organisations.

Here are some pointers to help organisations put NICE guidelines into practice:

1. **Raise awareness** through routine communication channels, such as email or newsletters, regular meetings, internal staff briefings and other communications with all relevant partner organisations. Identify things staff can include in their own practice straight away.

2. **Identify a lead** with an interest in the topic to champion the guideline and motivate others to support its use and make service changes, and to find out any significant issues locally.

3. **Carry out a baseline assessment** against the recommendations to find out whether there are gaps in current service provision.

4. **Think about what data you need to measure improvement** and plan how you will collect it. You may want to work with other health and social care organisations and specialist groups to compare current practice with the recommendations. This may also help identify local issues that will slow or prevent implementation.

5. **Develop an action plan**, with the steps needed to put the guideline into practice, and make sure it is ready as soon as possible. Big, complex changes may take longer to implement, but some may be quick and easy to do. An action plan will help in both cases.

6. **For very big changes** include milestones and a business case, which will set out additional costs, savings and possible areas for disinvestment. A small project group could develop the action plan. The group might include the guideline champion, a senior organisational sponsor, staff involved in the associated services, finance and information professionals.

7. **Implement the action plan** with oversight from the lead and the project group. Big projects may also need project management support.

8. **Review and monitor** how well the guideline is being implemented through the project group. Share progress with those involved in making improvements, as well as relevant boards and local partners.

NICE provides a comprehensive programme of support and resources to maximise uptake and use of evidence and guidance. See our into practice pages for more information.

Also see Leng G, Moore V, Abraham S, editors (2014) Achieving high quality care – practical experience from NICE. Chichester: Wiley.

Context

Spondyloarthritis encompasses a group of inflammatory conditions with some shared features, including extra-articular manifestations. Both peripheral and axial joints can be affected. The spondyloarthritides are distinct from rheumatoid arthritis but are as important to recognise and manage early in their presentation to improve health outcomes.

Most people with these conditions have either psoriatic arthritis or axial spondyloarthritis, which includes ankylosing spondylitis. Ankylosing spondylitis and non-radiographic axial spondyloarthritis primarily affect the spine, in particular the sacroiliac joint. Both conditions present in similar ways; the primary classification difference is whether sacroiliitis is detectable on X-ray.

Psoriatic arthritis may manifest in a number of different patterns. These include predominant involvement of small joints in the hands and feet, predominant large joint involvement, particularly in the knees, or combinations of these. Psoriatic arthritis may also involve the axial joints, and inflammation of the entheses and/or finger and toe joints. Skin and nail involvement may not be present at diagnosis and in its absence, a family history of psoriasis is required to meet the diagnostic criteria.

Less common subgroups are enteropathic spondyloarthritis, which is associated with inflammatory bowel disease (Crohn's disease and ulcerative colitis), and reactive arthritis, which can occur in people after gastrointestinal or genitourinary infections.

The final subgroup is people who have undifferentiated spondyloarthritis. These people generally have an asymmetrical oligoarticular (fewer than 5 involved joints) arthritis, often involving the knees. They do not meet the diagnostic criteria of the other subgroups at presentation but their disease may evolve to do so at a later stage.

This guideline also includes people who are 16 years or older with axial or peripheral symptoms who have previously been diagnosed with juvenile idiopathic arthritis.

Healthcare professionals in non-specialist settings do not always recognise the signs and symptoms of spondyloarthritis, particularly spinal symptoms, which may be mistakenly attributed to other causes of low back pain. This can lead to substantial delays in diagnosis and treatment with consequent disease progression and disability. This guideline seeks to raise awareness of the features of spondyloarthritis and provide clear advice on what action to take when people with signs and symptoms first present in healthcare settings.

This guideline also provides advice on the interventions available to people with spondyloarthritis. These include pharmacological and non-pharmacological treatments, and surgery. The guidance also provides advice on how care for people with spondyloarthritis should be organised across healthcare settings, and what information and support should be provided.

More information

You can also see this guideline in the NICE pathway on spondyloarthritis.

To find out what NICE has said on topics related to this guideline, see our web pages on musculoskeletal conditions and psoriasis.

See also the guideline committee's discussion and the evidence reviews (in the full guideline), and information about how the guideline was developed, including details of the committee.

Recommendations for research

The guideline committee has made the following recommendations for research. The committee's full set of research recommendations is detailed in the full guideline.

1 Referral criteria for people with suspected axial spondyloarthritis

What are the optimal referral criteria for people with suspected axial spondyloarthritis?

Why this is important

The Dutch CaFaSpA study (van Hoeven et al. 2014, 2015) should be repeated in a UK population. This would involve examining GP databases to identify a cohort of people who have a diagnosis of non-specific back pain who first consulted their GP for back symptoms under the age of 45. These people would be invited for a full rheumatological assessment (including identifying signs and symptoms relevant to axial spondyloarthritis, X-ray, MRI and HLA-B27 test). All participants would be given a reference-standard diagnosis of axial spondyloarthritis or not (ideally using expert clinician opinion, or if this is not possible, using the ASAS [Assessment of Spondyloarthritis International Society] classification criteria). The cohort would be split into a development and validation set, to derive and validate optimal rules for case-finding from the available data, with each candidate strategy judged according to expected cost per quality-adjusted life year (QALY) gained (the NICE economic model developed for this guideline could easily be used to estimate these).

As a result of the large number of permutations of possible referral strategies, it is impractical to run separate validation studies for all referral criteria that are developed. Therefore, a single large, representative cohort study would, provided it measured the predictor variables for all reasonable referral strategies, provide the ability to develop and validate any number of possible referral strategies. The study would need to be large enough that sufficient data are available to derive new referral rules and to validate those rules in a separate, independent subset of the data. A UK-specific dataset would provide more relevant data to do this than is currently available from the Dutch CaFaSpA study. For example, that study found an HLA-B27 prevalence of 20% in people with axial spondyloarthritis and 2% in people without; much lower than the estimates found elsewhere (75% and 20% respectively). This lowers the validity of extrapolating any results found to the UK, and reinforces the need for UK-specific data to address this question.

2 Long-term complications of spondyloarthritis

What is the incidence of long-term complications, in particular osteoporosis, cardiovascular disease (CVD) and metabolic syndrome, in people with spondyloarthritis, and how does this compare with the general population? Are any specific spondyloarthritis features or risk factors associated with the incidence and outcomes of these complications?

Why this is important

Spondyloarthritides are a group of systemic inflammatory conditions, and as such it is thought that people with these conditions may have an elevated risk of CVD, particularly if their disease is not adequately controlled. This may have direct vascular effects as well as precluding maintenance of a good level of cardiovascular fitness.

There is also clinical uncertainty around the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs): whether the long-term CVD risks associated with this class of drugs are observed in this population, or whether the suppression of inflammation with these drugs mitigates some of the CVD risks associated with these conditions. In addition, risks of osteoporosis and fracture are known to be higher in people with axial spondyloarthritis than the general population, and the prevalence of axial manifestations in people diagnosed with peripheral disease implies the risks may also be high in peripheral spondyloarthritis.

The longer-term complication rates in the spondyloarthritides need to be established, as well as whether standard biological disease-modifying anti-rheumatic drug (DMARD) therapies and biological DMARDs influence these outcomes. Research that evaluates incidence of osteoporosis, CVD and metabolic syndrome in people with either axial or peripheral spondyloarthritis compared with the general population would therefore be of value. This research should take into account disease stage, personal activity levels and medicine use, and look to address how frequently it is appropriate to monitor people with spondyloarthritis for long-term complications.

3 Educational intervention to improve healthcare professionals' awareness of spondyloarthritis

What is the effectiveness and cost effectiveness of educational interventions for healthcare professionals in order to increase the number of prompt diagnoses of spondyloarthritis?

Why this is important

One of the major reasons for the delays in diagnosing spondyloarthritis is a lack of awareness of the condition by healthcare professionals. This can take many forms, such as a lack of awareness of different spondyloarthritis subtypes, lack of knowledge about associated clinical features (for example, the differences between inflammatory and mechanical back pain) or characteristics of the patient populations (for example, that spondyloarthritis affects similar numbers of men and women, or that a substantial proportion of people with spondyloarthritis are HLA-B27 negative). Educational interventions to improve the level of awareness may therefore lead to reductions in diagnosis delays, but there is a lack of evidence as to the efficacy of these interventions. Randomised controlled trials of structured educational interventions are therefore needed to assess both whether they reduce the length of time it takes for people to be correctly diagnosed, and whether they represent a cost-effective use of NHS resources.

4 Pharmacological management of peripheral spondyloarthritis

What is the comparative effectiveness and cost effectiveness of standard DMARDs for managing peripheral spondyloarthritis, and is this effectiveness affected by differences in dose escalation protocols?

Why this is important

The committee noted that, although there are a number of randomised controlled trials comparing standard DMARDs with placebo for managing peripheral spondyloarthritis, there is a lack of evidence comparing individual standard DMARDs to other standard DMARDs. This lack of evidence makes it difficult to optimise initial therapy, either by specifying specific drugs within the class or optimising dose, administration and monitoring protocols. There is therefore the need for randomised controlled trials looking at alternative drug, dosing and administration route alternatives for the administration of standard DMARDs for managing peripheral spondyloarthritis. These trials should ensure NSAIDs and steroids are available to participants as needed, and should include (as outcome measures) both health-related quality of life (measured using the EQ-5D) and health service resource use, to enable the results to be used to assess the cost effectiveness of the interventions.

5 Biological therapies for peripheral spondyloarthritis

What is the effectiveness and cost effectiveness of biological DMARDs in people with persistent peripheral spondyloarthritis (excluding psoriatic arthritis) or undifferentiated spondyloarthritis?

Why this is important

Although there have been trials conducted of biological therapies for psoriatic arthritis, which have led to positive recommendations in NICE technology appraisals, no such good-quality evidence exists in enteropathic arthritis, reactive arthritis or undifferentiated spondyloarthritis. The substantial side effects possible with biological therapies, and their significant cost, means it is difficult to justify offering them to these groups without good evidence of efficacy. There is therefore the need for randomised controlled trials, with a sufficient sample size to identify possible benefits, in these 3 populations. If trials were to recruit participants from multiple spondyloarthritis subpopulations, results should be clearly stratified by diagnosis to enable any differences in benefits or harms between the groups to be identified. These trials should include (as outcome measures) both health-related quality of life (measured using the EQ-5D) and health service resource use, to enable the results to be used to assess the cost effectiveness of the interventions.

Update information

May 2017: Recommendation 1.2.7 was amended to clarify the advice on what imaging should be done.

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Accreditation

CONSENSO ARGENTINO DE DIAGNÓSTICO Y TRATAMIENTO DE SÍNDROME DE SJÖGREN PRIMARIO

Grupo de estudio Síndrome de Sjögren. Sociedad Argentina de Reumatología

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Revisión final:

-Revisión metodológica: Anastasia Secco.

-Revisión de redacción: Cecilia Asnal.

Índice:

RECOMENDACIONES: DIAGNÓSTICO

Recomendación	NE	GR	GA (%)	*m* (DS)
Para el diagnóstico de queratoconjuntivitis sicca en pacientes con sospecha de Síndrome de Sjögren primario (SSp), se recomienda realizar el test de Schirmer, y/o tinción superficie ocular (más específica que el Schirmer) y /o el ocular staining score.	2	B	94,3	9,4 (1,6)
Dada su baja especificidad, no se recomienda la utilización del break up time para el diagnóstico de queratoconjuntivitis sicca en pacientes con sospecha de SSp.	2	B	70,6	7,7 (3)
Si bien tanto la sialometría no estimulada, la gamagrafía y la sialografía mostraron ser herramientas útiles para evidenciar el compromiso oral en los pacientes con sospecha de SSp; se recomienda el uso de la sialometría no estimulada (técnica sencilla, no invasiva y de bajo costo), siendo esta la única incluida en los criterios clasificatorios ACR/EULAR 2016.	2	B	82,6	9,2 (1,5)
Si bien la ecografía (a) y la RMN (b) de las glándulas salivales podrían ser herramientas diagnósticas útiles, aún necesitan ser normatizadas y validadas para el diagnóstico de SSp, por lo cual no se recomienda su uso sistemático.	(a)2 (b)3	B	82,9	9,1 (1,6)
Para el diagnóstico de SSp se recomienda la determinación de anticuerpos anti La/SSB y, especialmente, anti Ro/SSA (ambos incluidos en los criterios clasificatorios 2002 y 2012, y sólo el anti Ro/SSA en los criterios clasificatorios ACR/EULAR propuestos en 2016).	2	B	100	9,8 (0,5)
Se recomienda la determinación del factor antinuclear (FAN) y del factor reumatoideo (FR) para el diagnóstico de SSp (la positividad del FAN en títulos > o = 1/320 asociado a FR positivo, forma parte de los criterios clasificatorios 2012).	3	B	94,3	9,4 (1,9)
Dado que la biopsia de glándula salival forma parte de los criterios clasificatorios de la enfermedad, se recomienda su realización en pacientes con sospecha de SSp, especialmente en aquellos con anticuerpos específicos negativos.	2	B	91,4	9,5 (1,1)
Se sugiere la realización de biopsia de glándula salival menor con fines diagnósticos, en pacientes con manifestaciones clínicas sugestivas pero no características de la enfermedad (como por ejemplo manifestaciones sistémicas en ausencia de síntomas sicca), especialmente en aquellos con anticuerpos específicos positivos.	5	D	77,2	8,6 (2,6)
En pacientes con SSp y compromiso articular se recomienda el dosaje de anticuerpos anticitrulinas ya que su positividad podría predecir el desarrollo de artritis reumatoidea temprana.	2	B	88,6	8,8 (2,2)
Si bien la ecografía articular podría ser una herramienta útil, no se recomienda su utilización sistemática para el estudio de la artritis en SSp. Deberá valorarse su indicación en cada paciente en particular y considerando la accesibilidad al estudio.	4	C	91,5	9,3 (1,5)
Ante la presencia de compromiso cutáneo como manifestación extraglandular del SSp, se recomienda realizar biopsia de piel, para confirmar el diagnóstico y orientar hacia un mejor manejo del paciente.	4	C	77,2	8,2 (3,2)
Dado que parecería existir una mayor frecuencia de enfermedad celíaca en pacientes con SSp que en la población general, se sugiere solicitar auto anticuerpos específicos y dosaje de IgA total para evaluar presencia de enfermedad subclínica asociada.	4	C	77,2	8,4 (2,2)
Se recomienda el estudio del estado ácido-base venoso e ionograma en pacientes con diagnóstico de SSp, ya que todos los pacientes con acidosis túbulo renal (ATR) tipo 1 (excepto la forma incompleta) tienen acidosis metabólica hiperclorémica.	4	C	85,7	9 (1,9)
Ante sospecha de ATR incompleta (por ejemplo hipokalemia aislada o nefrocalcinosis en ausencia de acidosis metabólica), se recomienda evaluación por nefrología para eventual realización de la prueba de sobrecarga de amonio.	4	C	94,1	9,4 (1,1)

RECOMENDACIONES: TRATAMIENTO

Recomendación	NE	GR	GA (%)	*m* (DS)
Se recomienda el uso de hidratantes bucales para mejorar los síntomas de xerostomía.	3	B	97,1	9,6 (1)
Se recomienda el uso de gotas oftalmológicas con agentes viscosos para el manejo de los síntomas de ojo seco y prevención del daño corneal.	3	B	100	9,9 (0,6)
Se recomienda el uso tópico de ciclosporina A 0,05 % como una opción efectiva para el tratamiento de la queratoconjuntivitis sicca en pacientes con SSp que no responden a agentes viscosos.	2	B	91,5	9,2 (1,4)
Para el tratamiento de la xerosis, especialmente la xerostomía moderada a severa, se recomienda el tratamiento con secretagogos: pilocarpina y cevilemine.	2	B	85,7	9,1 (1,9)
Si bien la evidencia en cuanto al tratamiento con fármacos inmunomoduladores para la artritis como manifestación extraglandular del SSp, es muy escasa; se recomienda el uso de drogas como metotrexate, hidroxicloroquina, sulfasalazina y leflunomida, para el tratamiento de la misma.	4/5	C/D	85,7	9,1 (1,3)
La evidencia respecto al tratamiento de la artritis como manifestación extraglandular del SSp, es muy escasa y desfavorable para algún anti TNF, y nula para la mayoría de los agentes de esta familia, por lo cual no se recomienda su indicación.	4/5	C/D	85,7	9 (1,7)
Dado que no hay evidencia de que el síndrome de Raynaud en el SSp se trate de una manera diferente al de otras enfermedades del tejido conectivo, se sugiere utilizar los mismos fármacos que en otras patologías.	5	D	97	9,8 (0,6)
Para el tratamiento de la vasculitis cutánea se recomienda el uso de esteroides tópicos para alivio de síntomas; corticoides sistémicos en casos severos, o asociados a otras manifestaciones extraglandulares.	4	C	88,6	9,1 (1,9)
Ante vasculitis cutánea crónica o refractaria, se recomienda considerar el uso de azatioprina, metotrexato, mofetil micofenolato, colchicina, dapsona y ciclofosfamida.	4	C	91,4	9,3 (1,7)
Para el tratamiento de la xerosis se sugiere el uso de medidas generales, como por ejemplo, evitar jabón tradicional (contiene detergente) y evitar perfumes que contengan alcohol.	5	D	94,3	9,8 (0,7)
Se recomienda el tratamiento con hidroxicloroquina para el eritema anular. Ante la persistencia del cuadro considerar la combinación de antimaláricos y/o añadir prednisona 0,5-1 mg/día. También se recomienda considerar el uso de tacrolimus tópico.	4	C	91,2	9,4 (1)
Para el eritema anular, se sugiere considerar como otras alternativas, el uso de corticoides tópicos, metotrexate, micofenolato o ciclosporina, a pesar de existir discrepancias respecto a su eficacia.	4	D	80	8,7 (2)
Se recomienda tratamiento inmunosupresor con prednisona 1 mg/kg/día en los pacientes que presenten nefritis intersticial severa y activa (confirmada por biopsia).	4	C	97,2	9,7 (0,8)
Se recomienda considerar el uso de azatioprina en dosis de 1 a 2 mg/kg/día como ahorrador de corticoides, en los pacientes que presenten nefritis intersticial severa y activa (confirmada por biopsia).	4	C	88,6	9,1 (1,8)
En la glomerulonefritis membranoproliferativa puede usarse el esquema de prednisona + ciclofosfamida, con un protocolo símil Lupus; en casos refractarios se recomienda rituximab.	4	C	94,3	9,4 (1,3)

RECOMENDACIONES: TRATAMIENTO

Recomendación	**NE**	**GR**	**GA (%)**	***m* (DS)**
En la glomerulonefritis membranosa podrá optarse por un esquema símil Lupus o utilizarse el esquema de las glomerulonefritis membranosas primarias.	4	C	100	9,5 (0,8)
Existe escasa evidencia con resultados favorables sobre el tratamiento del compromiso neurológico con gammaglobulina, ciclofosfamida asociada a corticoides en pulsos o 1mg/kg/día de meprednisona vía oral, plasmaféresis, interferón α o rituximab, por lo cual se recomienda considerar la posibilidad de estos tratamientos en los casos de compromiso neurológico severo.	4	C	100	9,8 (0,6)
Existe escasa evidencia con resultados favorables acerca del tratamiento del compromiso intersticial pulmonar con corticoides, azatioprina, ciclofosfamida, mofetil micofenolato o rituximab, por lo cual se recomienda considerar dichas opciones ante estos casos.	4	C	94,3	9,4 (1,1)
A pesar que existe escasa evidencia, se recomienda el tratamiento de la anemia hemolítica con dosis de 1 mg/kg/día o con pulsos endovenosos de corticoides. Se sugiere considerar el agregado de azatioprina.	4	C	94,3	9,5 (0,9)
A pesar que existe escasa evidencia, se recomienda el tratamiento de la neutropenia con dosis de 1 mg/kg/día o pulsos endovenosos de corticoides. Se sugiere considerar el agregado de ciclosporina o mofetil micofenolato en esta manifestación.	4	C	74,3	8,5 (2)
A pesar que existe escasa evidencia, se recomienda el tratamiento de la plaquetopenia con dosis de 1 mg/kg/día o pulsos endovenosos de corticoides. Se sugiere considerar el agregado de inmunoglobulinas endovenosas o rituximab en esta manifestación.	4	C	91,5	9,3 (1,2)
Si bien se desconoce la utilidad de la hidroxicloroquina en cuanto a la disminución del riesgo cardiovascular y el daño acumulado en pacientes con SSp; teniendo en cuenta los beneficios encontrados al respecto en otras patologías, se sugiere considerar su uso.	5	D	82,9	8,7 (2)
Si bien existen datos promisorios en cuanto al tratamiento con belimumab y con abatacept de las manifestaciones glandulares y extraglandulares del SSp, medidos por ESSPRI y ESSDAI, al no haber estudios suficientes que avalen su uso, no se recomienda su indicación.	4	C	79,4	8,3 (2,7)
Se han encontrado algunos resultados favorables con el tratamiento con rituximab en manifestaciones extraglandulares, por lo cual se recomienda considerar su indicación en casos seleccionados.	3	B	94,3	9,5 (1,1)

RECOMENDACIONES: CLINIMETRÍA, FACTORES PRONÓSTICOS Y EMBARAZO

Recomendación	**NE**	**GR**	**GA (%)**	***m* (DS)**
Si bien el PROFAD- SSI, el PROFAD-SF y el SSI, son herramientas útiles, dado que el ESSPRI es un cuestionario auto reportado más sencillo y más ampliamente validado, se recomienda este último por sobre los primeros, para la evaluación del compromiso glandular, fatiga y dolor.	2	B	94,3	9,6 (1,1)
Si bien el SSDAI y el SCAI, serían herramientas útiles para medir actividad, dado que el ESSDAI es más exhaustivo que el SSDAI y más simple que el SCAI, detecta los cambios de actividad de forma más exacta y está más ampliamente validado, se recomienda la utilización de este último por sobre los anteriores, para la evaluación de la actividad sistémica.	2	B	94,3	9,4 (1,6)
Para evaluar el daño acumulado se recomienda utilizar el SSDDI (a) y/o SSDI (b).	(a): 2 (b):3	B	97,2	9,7 (1)
Dado que el descenso de C4, la presencia de crioglobulinas, púrpura, agrandamiento parotídeo y linfadenopatías, han mostrado ser predictores de linfoproliferación, se recomienda evaluar la presencia de los mismos para detectar un grupo de pacientes con mayor riesgo de viraje a linfoma.	2	B	97,2	9,8 (0,9)
Adicionalmente, algunos estudios identificaron a la esplenomegalia, descenso de C3, linfopenia, neutropenia, B2 microglobulinemia, gamapatía monoclonal, glomerulonefritis (especialmente crioglobulinémica), presencia de centros germinales o de un score de foco mayor o igual a 3 en la biopsia de glándula salival menor y a la gamagrafía parotídea grado III/IV, como predictores de linfroproliferación, por lo cual se recomienda considerar la evaluación de estos, dentro de los factores de riesgo de desarrollo de linfoma.	2/3	B	96,6	9,5 (1,4)
En los pacientes con SSp y factores de mal pronóstico, se recomienda realizar un monitoreo más estrecho de la enfermedad.	5	D	100	10 (0)
Se recomienda realizar ecocardiograma con doppler a partir de la semana 16 de embarazo en pacientes con SSp y anticuerpos anti Ro+, con o sin anti La+.	4	C	100	10 (0)
Dado los resultados contradictorios en el uso de corticoides para prevenir el bloqueo cardíaco congénito y el bajo nivel de evidencia a favor de sus beneficios para revertirlo, se recomienda valorar la indicación de corticoterapia frente a cada paciente en particular.	4	D	100	9,8 (0,5)
Dado que no se han encontrado anomalías congénitas en fetos de mujeres embarazadas tratadas con hidroxicloroquina (a) y dado que podría prevenir el desarrollo de lupus neonatal (b), se recomienda considerar su uso en pacientes embarazadas con anticuerpos positivos.	(a):3 (b):4	(a):B (b):C	97,1	9,7 (0,8)

NE: nivel de evidencia. GR: grado de recomendación. GA: grado de acuerdo. *m* (DS): media (desvío estándar). PROFAD: *Profile of Fatigue and Discomfort.* PROFAD- SF: *Profile of Fatigue and Discomfort- Short Form.* SSI: *Sicca Symptoms Inventory.* ESSPRI: *European League Against Rheumatism Sjogren's Syndrome Patient Reported Index.* SSDAI: *Sjögren's Syndrome Disease activity index.* SCAI: *Sjögren's Systemic Clinical Activity Index.* ESSDAI: *European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. SSDDI: Sjögren's Syndrome Disease Damage Index.* SSDI: *Sjögren's Syndrome Damage Index*.

En las siguientes recomendaciones no se alcanzó el grado de acuerdo (GA) pre establecido (> o = 70%):

-La realización de ecocardiograma en pacientes asintomáticos con SSp podría detectar la presencia de pericarditis, valvulopatía, disfunción diastólica e hipertensión pulmonar, por lo cual se sugiere considerar su indicación en la práctica diaria (GA: 60,1%).

-Existe evidencia que muestra que puede existir compromiso pulmonar subclínico, así como un aumento de la mortalidad en los pacientes con SSp y compromiso pulmonar, por lo cual se recomienda realizar tomografía de tórax de alta resolución en todos los pacientes con SSp (GA: 40,9%).

-Existe evidencia que muestra que puede existir compromiso pulmonar subclínico, así como un aumento de la mortalidad en los pacientes con SSp y compromiso pulmonar, por lo cual se recomiendarealizar examen funcional respiratorio con difusión de monóxido de carbono en todos los pacientes con SSp (GA: 45,4%).

-Se recomienda realizar biopsia renal a todos los pacientes con SSp y evidencia de compromiso renal, ya sea ATR tipo 1, síndrome de Fanconi, diabetes insípida y glomerulonefritis, para guiar el tratamiento (GA: 65,7%).

-Se recomienda realizar evaluación neurocognitiva de manera sistemática y periódica en los pacientes con SSp (GA: 42,9%).

-La presencia de anticuerpos anti mitocondriales (AMA) podría predecir el desarrollo de cirrosis biliar primaria y la presencia de anticuerpos anti músculo liso (ASMA) podría predecir el desarrollo de hepatitis autoinmune en pacientes con SSp, por lo cual se sugiere considerar el dosaje de ambos anticuerpos en pacientes sin manifestaciones de compromiso hepático (GA: 67,6%).

-En pacientes con deterioro cognitivo vinculable a complicación neuropsicológica de SSp y no justificable por otras causas, podrían utilizarse glucocorticoides como tratamiento farmacológico (GA: 68,6%).

-No se recomienda la hidroxicloroquina para el tratamiento de los síntomas sicca, fatiga, mialgias y artralgias en pacientes con SSp (GA: 45,7%).

INTRODUCCIÓN Y OBJETIVOS

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El Síndrome de Sjögren Primario (SSp), es una enfermedad autoinmune que se caracteriza por un proceso inflamatorio que afecta fundamentalmente a las glándulas de secreción, pero que también puede afectar a otros órganos [1,2].

Es más frecuentemente en las mujeres, con una relación aproximada mujer/ hombre de 10/1 y entre los 40 y 60 años de edad. Un meta análisis de estudios publicados entre 1995 y 2013, con datos heterogéneos, estimó una tasa de incidencia sumaria de siete casos por 100.000 personas- año [3, 4].

Las manifestaciones clínicas características derivan del compromiso glandular y consisten en xeroftalmía, xerostomía, xerodermia, xerovagina, xerotráquea y tumefacción parotídea. La fatiga, de etiología multifactorial, es una manifestación frecuente. Si bien el compromiso glandular puede acarrear complicaciones locales, su mayor importancia radica en el impacto psicosocial y en la calidad de vida que produce en los pacientes [5].

Clásicamente se describe que aproximadamente un 30-40% de los pacientes puede presentar compromiso extraglandular, aunque estudios recientes muestran que hasta el 92% puede presentar actividad sistémica medida por índices validados, en un seguimiento de 75 meses [6,7]. Entre estas manifestaciones se encuentran artritis, artralgias, púrpura, polineuropatía, fenómeno de Raynaud, intersticiopatía pulmonar, acidosis túbulo renal, glomerulonefritis, anemia, leucopenia e hipergamaglobulinemia [1,2].

Determinadas características clínicas y de laboratorio presentes al momento del diagnóstico, permiten identificar a un subgrupo de pacientes que presenta mayor riesgo de linfoproliferación y mortalidad. Entre ellas se destacan la presencia de crioglobulinas, descenso de C4, púrpura, parotidomegalia y linfadenopatías[8].

En los últimos años, con el propósito de avanzar en el diagnóstico, seguimiento y tratamiento de esta patología, han surgido nuevos criterios clasificatorios, métodos diagnósticos, así como índices para medir la actividad y cronicidad de la enfermedad [9, 10].

Por este motivo se realizó una exhaustiva búsqueda bibliográfica con el fin de recomendar conductas, a partir de la mejor evidencia, para optimizar la efectividad en relación al diagnóstico de la enfermedad y sus diferentes manifestaciones, evaluación y seguimiento clínico, pronóstico, tratamiento y manejo en situaciones especiales como el embarazo.

Población blanco:

Pacientes con diagnóstico SSp según criterios de clasificación reconocidos.

Especialidades médicas y grupos a quienes va dirigida:

- Reumatología

- Clínica Médica

-Médicos Generalistas

- Medicina Familiar

- Oftalmólogos

- Odontólogos

- Auditores de obras sociales y prepagas

- Autoridades del Ministerio de Salud de la Nación y Secretarías nacionales, provinciales y municipales de Salud en todo el territorio de nuestro País.

Bibliografía:

1- Sormani de Fonseca M.L, Romanini F.E, Auad C. Síndrome de Sjögren, Maldonado Cocco J.A, Citera G. *Reumatología.* Ediciones Azzurras. Martinez. Buenos Aires. Argentina. 2010.

2-Catalán Pellet A, Secco A, Caeiro F, Encinas L. Síndrome de Sjögren, Ferix R, Munoz Louis R, Espinosa L, Khamashta M, Matucci- Cerinic M, Sanmarti R. Enfermedades Inflamatorias Reumatologicas. 2016.

3-Ramos-Casals M, Brito-Zerón P, Kostov y col. Google-driven search for big data in autoimmune geoepidemiology: analysis of 394,827 patients with systemic autoimmune diseases. Autoimmun Rev. 2015; 14: 670-9.

4- Qin B, Wang J, yang Z y col. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis. 2015; 74: 1983-9.

5- Kassan S.S, Moutsopoulos H.M. Clinical Manifestations and Early Diagnosis of Sjögren Syndrome. *Arch Intern Med.* 2004; 164: 1275-1284.

6- Brito-Zerón P y Ramos-Casals M. Evolución y pronóstico del paciente con síndrome de Sjögren primario. Med Clin (Barc). 2008; 130 (3): 109-115.

7-Ramos-Casals M , Brito-Zerón P , Solans R y col. Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology. 2014; 53: 321- 331.

8-Nishishinya M, Pereda C, Muñoz-Fernández S y col. Identification of lymphoma predictors in patients with primary Sjögren's syndrome: a systematic literature review and meta-analysis. Rheumatol Int. 2015; 35(1): 17-26.

9- Brito-Zerón P, Ramos-Casals M, on behalf of the EULAR-SS task force group. Advances in the understanding and treatment of systemic complications in Sjögren's syndrome. Curr Opin Rheumatol 2014; 26 (5):520–527.

10- Luciano N, Valentini V, Calabrò A y col. One year in review 2015: Sjögren's syndrome. Clin Exp Rheumatol 2015; 33: 259-271.

METODOLOGÍA

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La coordinación general del consenso estuvo a cargo de los coordinadores del grupo de estudio de Síndrome de Sjögren (SS) de la Sociedad Argentina de Reumatología. La coordinación y asesoramiento técnico estuvieron a cargo de un médico reumatólogo y epidemiólogo con amplia trayectoria, asistido por un médico reumatólogo con formación y experiencia en medicina basada en la evidencia, y en el manejo del SSp.

Se discutieron los temas a considerar y se constituyeron varios grupos de trabajo, de acuerdo a la distribución de los mismos:

- Métodos diagnósticos- manifestaciones glandulares.

- Criterios clasificatorios.

-Tratamiento xeroftalmía.

-Tratamiento xerostomía.

- Diagnóstico y tratamiento compromiso músculo esquelético.

- Diagnóstico y tratamiento compromiso cutáneo.

- Diagnóstico y tratamiento compromiso respiratorio.

- Diagnóstico y tratamiento compromiso neurológico.

- Diagnóstico y tratamiento compromiso neurocognitivo.

- Diagnóstico y tratamiento compromiso/enfermedades asociadas gastrointestinales-hepáticas.

- Diagnóstico y tratamiento compromiso renal.

- Diagnóstico y tratamiento compromiso cardiovascular.

- Diagnóstico y tratamiento compromiso hematológico.

- Tratamiento compromiso manifestaciones extrglandulares.

- Clinimetría.

- Factores pronósticos

- Manejo del embarazo.

En abril de 2015 se realizó una primera reunión en la que se dieron las pautas para el planteo de las preguntas según la metodología PICO (P: población, I: intervención, C: comparador, O: outcome), la realización de la búsqueda bibliográfica, la selección de los artículos y la clasificación según su nivel de evidencia [1].

Cada grupo de trabajo planteó las preguntas, las cuales fueron revisadas por los coordinadores técnicos y generales. A partir de estas se generaron las estrategias de búsqueda sistemática de la bibliografía en al menos tres bases (Pub MED, Cochrane Library, LILACS), seleccionando los estudios referentes a cada área que permitieran obtener el nivel de evidencia óptimo para emitir una recomendación adecuada [1-3].

Se estableció como fecha límite de búsqueda julio de 2015. Por considerarse de relevancia, se incluyó como literatura gris y con fecha posterior al límite definido, los nuevos criterios clasificatorios ACR- EULAR, los cuales fueron presentados como comunicación oral en el Congreso Americano de Reumatología (noviembre de 2015).

La selección de estudios respetó una práctica estructurada (NICE-UK), donde la selección de trabajos siguió un orden preestablecido: evaluación del título, resumen, obtención de copia firme del trabajo seleccionado y evaluación del mismo [4].

Para la clasificación de la evidencia se utilizó la clasificación de Oxford 2011 (tabla 1), la cual abarca el espectro de estudios considerados en este consenso: diagnóstico, pronóstico y tratamiento. La misma contempla la posibilidad de disminuir el nivel de evidencia según la calidad del estudio, imprecisión, su carácter indirecto (el estudio PICO no coincide con la pregunta PICO), por inconsistencia entre los estudios o porque el tamaño absoluto del efecto es demasiado pequeño; a su vez, el nivel de evidencia puede aumentar si el tamaño del efecto es grande o muy grande [5].

Se llevaron a cabo reuniones posteriores (agosto y septiembre de 2015), en las que cada grupo expuso las preguntas seleccionadas, la estrategia de búsqueda utilizada para responderlas, el número de artículos encontrados y seleccionados por cada base de datos empleada. En este contexto, se discutieron y bosquejaron las principales recomendaciones, su nivel de evidencia y grado de recomendación (tablas 1 y 2)[5].

Posteriormente, a través de un cuestionario online, los integrantes del consenso evaluaron su grado de acuerdo con cada recomendación con opciones de respuesta desde el cero (totalmente en desacuerdo) al diez (totalmente de acuerdo). Se estableció una mayoría de al menos 70% para su aceptación. Se calculó la media y desvío standard de la puntuación del todal de los votos, para cada una de ellas.

Bibliografía:

1- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50: a guideline developer's handbook. Edinburgh: SIGN; 2014. (SIGN publication no. 50). 2014. Disponible en: http://www.sign.ac.uk

2- Guyatt G, Sinclair J, Cook D, Glasziou P: Users´ guides to the medical literature. XVI how to use a treatment recommendation. JAMA. 1999; 281: 1836-1843.

3- Oxman A, Sackett D, Guyatt G, for the Evidence-Based Medicine Working Group. Users' Guides to the Medical Literature. How to Get Started. JAMA. 1993; 270 (17): 2093- 2095.

4- National Institute for Clinical Excellence. The guidelines manual. London: National Institute for Clinical Excellence. Disponible en: http://www.nice.org.uk/download.aspx?o=422956

5- OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. Disponible en: http://www.cebm.net/index.aspx?o=5653

Tabla 1:

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table
OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

Tabla2:

A	consistent Nivel 1 studies
B	consistent Nivel 2 or 3 studies ***or*** extrapolations from Nivel 1 studies
C	Nivel 4 studies ***or*** extrapolations from Nivel 2 or 3 studies
D	Nivel 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any Nivel

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

SÍNDROME DE SJÖGREN: MÉTODOS DIAGNÓSTICOS
MANIFESTACIONES GLANDULARES

COMPROMISO OCULAR

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Pregunta 1- En pacientes con sospecha de Síndrome de Sjögren primario (SSp), ¿es de utilidad el test de Schirmer para el diagnóstico de queratoconjuntivitis sicca?

Criterios de búsqueda: ((primary sjogren;s syndrome OR sjogren OR sjogren syndrome OR primary sjogren syndrome) AND (test schirmer OR schirmer) AND (diagnosis)).

Pubmed:
Búsqueda: 237 artículos
Seleccionados por título: 27 artículos
Seleccionados por abstract: 10
Seleccionados por artículo: 5
Incluidos manualmente: 1

Cochrane
Búsqueda: 0

LILACS
Búsqueda: 14 artículos
Artículos incluídos: 0

Artículos totales incluídos: 6

Pregunta 2- En pacientes con sospecha de SSp, ¿es de utilidad el test de Rosa de Bengala para el diagnóstico de queratoconjuntivitis sicca?

Criterios de búsqueda: ((primary sjogren;s syndrome OR sjogren OR sjogren syndrome) AND (keratoconjunctivitis sicca) AND (diagnosis) AND (rose Bengal))

Pubmed
Búsqueda: 53 artículos
Seleccionados por título: 13 artículos
Seleccionados por abstract: 8 artículos
Seleccionados por artículo: 6
Incluídos manualmente: 0

Cochrane
Búsqueda: 0

LILACS
Búsqueda: 2 artículos
Artículos incluídos: 0

Artículos totales incluídos: 6

Pregunta 3- En pacientes con sospecha de SS, ¿es de utilidad el BUT para el diagnóstico de queratoconjuntivitis sicca?

Criterios de búsqueda: ((sjogren syndrome OR sjogren) AND (break up time) AND (diagnosis))

Pubmed
Búsqueda: 99 artículos
Seleccionados por título: 24 artículos
Seleccionados por abstract: 5 artículos
Incluídos manualmente: 1

Cochrane
BÚsqueda: 0

LILACS
Búsqueda: 3
Artículos incluídos: 0

Artículos totales incluídos: 6

Dado la superposición de los artículos que responden las preguntas 1,2 y 3, los mismos se describen de manera conjunta.

Markusse y colaboradores publicaron en 1992 un estudio de corte transversal en el cual evaluaron las anormalidades oftalmológicas en Sindrome de Sjögren Primario (SSp) y determinaron el valor diagnóstico de los diferentes tests utilizados en la evaluación del componente ocular. Se enrolaron 44 pacientes con SSp, según criterios modificados de California. Dos grupos de voluntarios sirvieron como control: 21 pacientes con síntomas sicca y 26 sin síntomas sicca. En bajos puntos de corte, el test de Schirmer y el Break up time (BUT) resultaron en una baja sensibilidad (S) y alta especificidad (E). Aplicando un valor de corte de 8 segundos para el BUT la S y E fueron del 80% y 81%, respectivamente. La tinción con Rosa de Bengala (RB) fue altamente especifica (100%) y poco específico (45%) cuando se utilizó un valor de corte con score > o = a 4. El Test de Schirmer mostro una correlación positiva con el BUT (p<0,01), y una correlación negativa con el Rosa de Bengala (p<0,01). El RB tuvo una correlación positiva con la duración de la enfermedad (p<0,05) y una correlación negativa con el BUT (p<0,01) y el Test de Schirmer (p<0,01) [(1)]. NE: 3

Vitali y colaboradores publicaron en 1994 un estudio de corte transversal en el que evaluaron la S y E de varias pruebas como herramientas para el diagnóstico de SS, y formuló criterios diagnósticos en SSp. Participaron 22 centros en 11 países. Se enrolaron 447 pacientes con SS según criterio médico (246 con SSp y 201 con SS secundario) y 246 controles. El RB tuvo un E del 81,7% y una S de 64,3%. El BUT mostró una S de 77,8% y una baja E (38,9%). El test de Schirmer presentó una S y E de76,9% y 72,4%, respectivamente, cuando se consideró un valor de corte de 5mm/5 min. La S se incrementó a 83,6%, pero la E disminuyó a 69,8% al considerar 10 mm / 5 minutos como punto de corte. Sólo el Test de Schirmer y RB mostraron un grado aceptable de concordancia. Los tests oftalmológicos mostraron menor frecuencia y menor compromiso patológico en los pacientes con SS secundario que en aquellos

con SSp. Cuando los valores medios se analizaron para los dos grupos, las diferencias fueron estadísticamente significativas para lactoferrina lagrimal (TFLL) (t de Student = 2,5 p <0 02), BUT (t = 2,75, p <0,01), RB (t = 3,32, p <0,001), pero no para Schirmer (t = 1,86, p = 0,063) [2]. NE: 2

El estudio europeo multicéntrico de corte transversal, de Vitali y colaboradores, publicado en 1996, evaluó los criterios preliminares de SS. Se incluyeron 278 pacientes (157 pacientes con SS según criterio médico y 121 controles). El grupo control estaba conformado por pacientes con otras enfermedades del tejido conectivo, sin SS, y por sujetos sanos. Al menos cuatro de los seis criterios estaban presentes en 79 pacientes de 81 inicialmente clasificados como SSp (S: 97,5%), pero en sólo siete de 121 controles no-SS (E: 94,2%). El test de Schirmer, mostró precisión diagnóstica fue de77% (E 70,7 % y S 86,2 %). El score de RB presentó una S de 52,9% y un E de 91,7%, con una precisión diagnóstico de 75,4% [3]. NE: 2

Versura y colaboradores publicaron en 2006 un estudio de test diagnóstico a fin de evaluar las pruebas oculares incluidas en los criterios de clasificación de SSp.
Se incluyeron 262 pacientes (78 SSp según criterios clasificatorios AECG, 91 con enfermedades autoinmunes no SS y 93 síndrome Sicca). El BUT con resultados menores o iguales a 10 segundos tuvo una E 12.1%, S 91.9%, likehood ratio (LR)+ 1.05, valor predictivo positivo (VPP) de 5.2 y área bajo la curva (ABC) ROC 0.584. El Schirmer I mm ≤ 5 mostró una E 66.7%, S 45.9 %, LR+ 1.38, VPP de 6.8 y ABC de 0.667. La tinción con verde de lisamina con un puntaje mayor a nueve, mostró una E de 75%, una S de 85,1%, LR+ 3,41; un VPP de 15,2 y un ABC de 0,82 [4]. NE: 3

Versura y colaboradores publicaron en 2007 un estudio de test diagnóstico, en el cual se analizó el desempeño de los diferentes test oculares incluidos en los criterios clasificatorios de SSp y se los comparo con otros exámenes relacionados con el status de la superficie ocular. Se enrolaron 177 pacientes .62 con SSp de acuerdo con los criterios clasificatorios AECG, 56 con enfermedades autoinmunes no-SS, y 59 con síndrome Sicca. Los datos mostraron un bajo rendimiento para el diagnóstico de SS del Test de Schirmer I (S: 0,42; E: 0,76; LR+: 1.75, ABC: 0,41) y BUT (S: 0,92, E: 0,17; LR+: 1.11, ABC: 0.59). La tinción con verde de lisamina mostró el mejor rendimiento (S: 0,63, E: 0,89; LR+: 5.72, ABC: 0,68) [5]. NE: 3

Caffery y colaboradores publicaron en 2010 un estudio de corte transversal en el que compararon la presentación clínica de 231 pacientes con SSp con 89 pacientes con ojo seco con deficiencia acuosa (queratoconjuntivitis sicca; KCS), y determinaron los procedimientos que mejor diferenciaban a estos grupos. Se generaron 3 diagramas con las características que mejor distinguían SSp de KCS. La presencia de la tinción con RB de la conjuntiva temporal fue la variable ocular no invasiva más importante que diferenció los grupos. Combinada con la severidad de los síntomas de boca seca de 4,5 / 10, pudo identificar todos menos 3 de los 231 pacientes con SSp. Esta evaluación no invasiva demostró una S del 96,1% con E 56,2% [6]. NE: 3

Knezovi y colaboradores publicaron en 2011 un estudio de corte transversal en el que evaluaron el rendimiento diagnóstico de la prueba RB para el diagnóstico de SS y exploraron las diferencias con otras pruebas diagnósticas. Se incluyeron 66 pacientes: 48 pacientes con diagnóstico de SS según criterios AECG y 18 con síntomas sicca no SS. El BUT presentó una S de 62,50% y E de 83,33%. El AUC fue de 0,71. El test de Schirmer mostró una S 75%, E 83,33% y AUC 0,78 RB exhibió el mejor rendimiento (S: 100%; E: 100%; y AUC: 1,000) [7]. NE: 3

Respecto al rol del test de Schirmer en los criterios clasificatorios ACR- EULAR 2015, revisar el addendum del capítulo de criterios clasificatorios.

Pregunta 4- En pacientes con sospecha de Sjögren, ¿es de utilidad el score de tinción ocular (OSS) para el diagnóstico de queratoconjuntivitis sicca? - Considerando test de Schirmer y OSS, ¿cuál tiene mayor especificidad y sensibilidad para el diagnóstico de queratoconjuntivitis sicca, en pacientes con sospecha de SSp?

Ocular staining score OSS
Criterios de búsqueda: ((primary sjogren;s syndrome OR sjogren OR sjogren syndrome) AND (diagnosis) AND (ocular staining score))

Pubmed
Búsqueda: artículos 36
Seleccionados por título: 8 artículos
Seleccionados por abstract: 3 artículos
Seleccionados por artículo: 3 artículos
Incluídos manualmente: 1 artículo

Cochrane:
Búsqueda: 0

LILACS:
Búsqueda: 0

Artículos totales incluídos: 4

Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups condujo un estudio multicéntrico en 2010 con los objetivos de 1) describir el sistema de clasificación OSS; y 2) analizar la distribución de la OSS entre los participantes en el registro SICCA, y su asociación con otras características fenotípicas del síndrome de Sjögren. Entre los 1.208 participantes, un total de 920 participantes en el Registro SICCA tenía al menos uno de las tres características fenotípicas que se cree están asociadas con el SS: un OSS anormal de 3 o mayor; sialoadenitis linfocítica focal con una puntuación de foco> 1; y / o serología positiva a anticuerpos anti-SS-A o B.
Debido al alto porcentaje de participantes que tuvo un OSS anormal (28%) en ausencia de otras características fenotípicas del SS se consideraron dos subgrupos en el análisis:
1.- puntuación de ≥3 pero ninguno de las otras dos características del síndrome de Sjögren o solo KCS.
2.- puntuación de ≥3 y al menos uno de las otras dos características fenotípicas del síndrome de SS (sialoadenitis linfocítica focal con una puntuación de foco> 1 y / o serología positiva a los anticuerpos anti-SS-A o B) o SS KCS.
Entre los participantes, la mediana OSS fue 5 en el grupo KCS en comparación con 9 del grupo SS-KCS, (p<0,0001). La mediana de BUT de 3.5 entre las personas con KCS- en comparación con 2 en el grupo SS-KCS (P <0,0001). El test de Schirmer, fue lo significativamente menor en el grupo SS-KCS comparado con el grupo KCS. (p<0,001) [8]. NE: 4

En 2012 la American College of Rheumatology (ACR) propone nuevos criterios de clasificación para el SSp. Según los resultados surgidos del análisis de un modelo

estadístico, el OSS ≥3 presentó una S de 89.7 (IC 95%: 86.4–92.7), E 37.8 (34.2–41.2); el BUT <10 segundos una S de 90.5 (87.9–93.0) y E de 21.4 (17.9–24.3); el test de Schirmer < 5 mm/5 minutos una S de 42.7 (37.8–47.6) y E 75.1 (71.7–78.2) [9]. NE: 3

Cornec y colaboradores publicaron en 2014 un estudio de corte transversal en el que evaluaron el grado de acuerdo entre los criterios de clasificación AECG y los nuevos criterios ACR 2012. Se estudiaron 105 pacientes de los cuales 42 (40,0%) cumplieron con los criterios AECG y 35 (33,3%) cumplieron con los criterios ACR. El acuerdo entre la puntuación de tinción ocular ≥3 (ACR) y el test de Schirmer ≤5 mm / 5 min (AECG) fue muy baja (κ = 0,14). La concordancia con la biopsia de glándula salival fue más baja con OSS que el test de Schirmer (k= 0,14 vs 0,35). Ambos test mostraron muy pobre concordancia con anti-SSA/SSB + (coeficiente k= 0,21 OSS y k=0,27, respectivamente) [10]. NE: 4

Rasmussen y colaboradores en 2014, también compararon los criterios de clasificación AECG y los ACR, en un estudio de corte transversal. Se evaluaron 646 participantes. Según criterios AECG y ACR se clasificaron 279 y 268 participantes con SSp, respectivamente. Ambos criterios se encontraron en 244 participantes (81%). Había 24 pacientes AECG- / ACR +, debido principalmente a las diferencias en la puntuación de tinción corneal (n=17). La diferencia más importante en rendimiento de la prueba individual fue en la evaluación de queratoconjuntivitis sicca por OSS. El test de Schirmer I mostró una baja S (rango: 0,49- 0,54) con mayor E (0,71-0,73)
El OSS aumentó la S (0,80-0,90), pero disminuyó la E (0,45-0,51); lo que podría ser parcialmente corregido mediante el aumento su valor de corte de positividad ≥ 3 a ≥ 4/12.
Los dos conjuntos de criterios de clasificación fueron concordantes en la mayoría de casos [11]. NE: 3

Respecto al OSS y los criterios clasificatorios ACR- EULAR 2015, consultar el addendum del capítulo de criterios clasificatorios.

Bibliografía:

1. Markusse M, Hogeweg M, swaak AJG, van Haeringen NJ, Jong PT. Ophalmollogical examinations of patients with primary Sjogren´s syndrome selected from a rheumatological practice. British journal of Rheumatology 1992;31: 473-476
2. Vitali C, Moutsopoulos HM, Bombardieri S. The European Community Study Group on diagnostic criteria for Sjogren's syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjogren's syndrome. Ann Rheum Dis 1994;5310:637-47
3. Vitali C, Bombardieri S, Moutsopoulos HM, Coll J, Gerli R, Hatron PY, Kater L, Konttinen YT, Manthorpe R, Meyer O, Mosca M, Ostuni P, Pellerito RA, Pennec Y, Porter SR, Richards A, Sauvezie B, Schiødt M, Sciuto M, Shoenfeld Y, Skopouli FN, Smolen JS, Soromenho F, Tishler M, Wattiaux MJ, et al. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. The European Study Group on Diagnostic Criteria for Sjögren's Syndrome. Annals of the Rheumatic Diseases 1996; 55: 116-121.
4. Versura P, Frigato M, Mulé R, Malavolta N, Campos EC. A proposal of new ocular items in Sjögren's syndrome classification criteria. Clinical and Experimental Rheumatology 2006; 24: 567-572.
5. Versura P, Frigato M, Cellini M, Mule` R, Malavolta N , Campos EC. Diagnostic performance of tear function tests in Sjogren's syndrome patients. Eye (2007) 21, 229–237.
6. Caffery B1, Simpson T, Wang S, Bailey D, McComb J, Rutka J, Slomovic A, Bookman A. Rose Bengal Staining of the Temporal Conjunctiva Differentiates Sjogren's Syndrome from Keratoconjunctivitis Sicca. Invest Ophthalmol Vis Sci. 2010;51:2381–2387.
7. Knezović I, Alajbeg I, Karlović D, Pavan J, Vrkić N, Bisćan A. Differential Diagnostic Performance of Rose Bengal Score Test in Sjøgren's Syndrome Patients. Coll Antropol. 35 (2011) 4: 1105–1113.
8. Whitcher JP, Shiboski C, Shiboski S, Heidenreich AM, Kitagawa K, Zhang S, Hamann S, Larkin G, McNamara N, Greenspan J, Daniels T. For the Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups. A Simplified Quantitative Method for Assessing Keratoconjunctivitis Sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol. 2010 March; 149(3): 405–415.
9. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, Schiødt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich AM, Helin P, Kirkham B, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Greenspan J, Daniels T; Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups. American College of Rheumatology Classification Criteria for Sjogren's Syndrome: A Data-Driven, Expert Consensus Approach in the Sjogren's International Collaborative Clinical Alliance Cohort. Arthritis Care & Research Vol. 64, No. 4, April 2012, pp 475–487.
10. Cornec D, Jousse-Joulin S, Marhadour T, Pers JO, Boisramé-Gastrin S, Renaudineau Y, Saraux A, Devauchelle-Pensec V. Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome. Rheumatology (Oxford) 2014 Sep;53(9):1604-7.

11. Rasmussen A1, Ice JA, Li H, Grundahl K, Kelly JA, Radfar L, Stone DU, Hefner KS, Anaya JM, Rohrer M, Gopalakrishnan R, Houston GD, Lewis DM, Chodosh J, Harley JB, Hughes P, Maier-Moore JS, Montgomery CG, Rhodus NL, Farris AD, Segal BM, Jonsson R, Lessard CJ, Scofield RH, Sivils KL. Comparison of the American-European Consensus Group Sjögren's syndrome.classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterized sicca cohort. Ann Rheum Dis. 2014 January 1; 73(1):31-8.

SÍNDROME DE SJÖGREN Y MÉTODOS DIAGNÓSTICOS
MANIFESTACIONES GLANDULARES

COMPROMISO ORAL

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Pregunta 1- En los pacientes con sospecha de Síndrome de Sjögren (SSp), ¿es de utilidad la medición de flujo salival para el diagnóstico del compromiso oral?

Criterios de búsqueda: ((primary sjogren;s syndrome OR sjogren OR sjogren syndrome) AND (diagnosis) AND (unstimulated sialometry OR sialometry))

Pubmed:
Resultado Búsqueda: 38 artículos
Por título se seleccionaron: 13 artículos
Por abstract se seleccionaron: 5 artículos
Aporte propio: 2 artículos

Lilacs
Resultado: 7 artículos
Seleccionados: 1

Cochrane
Busqueda: 0

Artículos totales incluídos: 8 artículos

Speight y colaboradores publicaron en 1992, un estudio de corte transversal en el que evaluaron la medición del flujo salival no estimulada en 134 pacientes. 25 pacientes con Síndrome de Sjögren (SS), tanto primario (SSp) como secundario, 69 sujetos controles jóvenes, 20 sujetos sanos de mayor edad que el grupo anterior y 20 pacientes con artritis reumatoide (AR) sin SS. El flujo salival no estimulado fue significativamente superior en los sujetos del grupo control de jóvenes que en todos los demás grupos (p <0,001). Entre los pacientes con SS 52% tenían un flujo de 0-1 ml / min o menos en comparación con sólo el 8% de los controles emparejados por edad. El valor predictivo positivo (VPP) de este bajo flujo fue de 81%, con una sensibilidad (S) del 52% y especificidad (E) del 92% [(1)].NE: 3

Pennec y colaboradores publicaron en 1993 un estudio de corte transversal para establecer la utilidad de las combinaciones de pruebas (tasa de flujo de saliva (FS); lisozima salival (Lys); lactoferrina salival (Lf); Sialografía (SG); gammagrafía de la glándula salival (GGS) y biopsia de las glándulas salivales menores (BGSM)) para evaluar el componente oral del SS. Se incluyeron 40 pacientes con SSp, 16 pacientes con SS secundario, 16 pacientes con enfermedad del tejido conectivo no SS y 14 controles normales. El FS mostró una S del 68%, E 81%, VPP del 90% y VPN del 50%

para SSp. SG presentó una S de 74%, E 87%, VPP 93% y VPN 41%. GGS tuvo una S del 75%, E de 75%, VPP90% y VPN 45%. La BGSM mostró una S del 95%, E 75%, 90% VPP, VPN 14% [(2)]. NE: 3

Vitali y colaboradores publicaron en 1994 un estudio de corte transversal en el evaluaron la sensibilidad y la especificidad de varias pruebas como herramientas diagnósticas para el SS, y formularon criterios clasificatorios preliminares de SS en un estudio multicéntrico. Se incluyeron 447 pacientes con SS (246 con SSp y 201 con SS secundario) y 246 controles (113 de ellos con una enfermedad del tejido conectivo sin SS y 133 controles sanos). Las pruebas orales fueron generalmente más fiables que las pruebas oculares en el diagnóstico SS. En particular, la sialografía parotídea fue la herramientas de diagnóstico más específica (100%)), mientras BGSM (donde la presencia de al menos una foco inflamatorio se consideró como indicativo para el diagnóstico) mostró una buen equilibrio entre sensibilidad y especificidad (82,4% y 86,2%, respectivamente).La medición del flujo salival no estimulado fue mejor en discriminar pacientes de los controles que la medición del flujo salival estimulado. Tuvo una S y una E del 56,1% y 80,7%, respectivamente, con> 1, 5 ml de saliva recogidas en 15 minutos. El flujo salival estimulado mostró una sensibilidad similar (66,4%), pero una especificidad significativamente menor (56,4%), tomando un valor de corte de > 3.5 ml de saliva recogida en 5 minutos. La gammagrafía, mostró una S 87,2% y una E 79% respectivamente [(3)]. NE: 2

Kalk y colaboradores publicaron en 2001 un estudio de corte transversal en el que evaluaron el valor de la sialometría y sialoquímica para el diagnóstico de SS. 100 pacientes (clasificados en 3 grupos: SSp (33), SS secundario (25) y síntomas sicca (42)) fueron evaluados con sialometría, realizándose también la evaluación de una serie de componentes salivares (sodio, potasio, cloruro, calcio, fosfato, urea, amilasa, proteína total). Fueron comparados con un grupo de 36 controles sanos. Los pacientes con SS mostraron menor tasa de flujo salival submandibular / sublingual (SM/SL) y una apreciable diferencia en la composición salival de la parótida y la saliva SM/SL. La velocidad del flujo parótida estimulado se encontró reducida en los pacientes con SS en comparación con el normal (p <0,02). El flujo salival estimulado y no estimulado SL /SM fueron menores en los pacientes con SS que en los controles sanos (p<0,05). En los grupos SSp y SSs la concentración de sodio y cloruro eran seis y dos veces respectivamente más altos que en el grupo sin SS [(4)]. NE: 4

En 2002 Kalk y colaboradores plantearon valores de referencia de los test salivales en un estudio de corte transversal, que ofrecen un posible medio no invasivo de diagnóstico de SS. Incluyeron 120 pacientes: 65 con SS y 55 sin SS. La mayor precisión para el diagnóstico de SS resultó de la combinación de la medición del flujo salival estimulado SM/ SL y la concentración de sodio y cloruro de la saliva de la parótida: sensibilidad de 0,85 y una especificidad de 0,96. La sialometría mostró una S de 0,67 y una E del 0,76 con un VPP 0,78 [(5)]. NE: 3

En 2005 Liquidato y colaboradores publicaron un estudio de corte transversal en el que evaluaron la importancia de la BGSM y de la sialometría, aisladas o asociadas, para la clasificación de SS. Se enrolaron 72 pacientes con xerostomía. De ellos, 26 (36,1%) fueron clasificados como SS, y 46 (63,9%) presentaron diferentes diagnósticos y fueron clasificados como No-SS. El VPP de la biopsia fue mayor que el de la sialometría (p = 0,0036). No hubo diferencias significativas entre VPN (p = 0,0997) y S (p = 0,5237) entre la biopsia y la sialometría. Se observó que la E de la biopsia fue mayor que la de la sialometría (p = 0,0106). Al comparar el VPP de biopsia y biopsia asociados con sialometría, evidenciaron que no hubo diferencias significativas (p = 0,1553). Sin embargo, los VPN de la combinación (p = 0,0129), así

como la S (p = 0,0051) fueron significativamente mayores en comparación con la biopsia sola. La E y el VPP de la biopsia asociada con sialometría fue significativamente mayor (p = 0,035 y p< 0,01, respectivamente), que la biopsia sola [6]. NE: 3

Respecto al rol de la sialometría en los nuevos criterios clasificatorios ACR- EULAR, remitirse al addendum del capítulo de Criterios Clasificatorios.

Pregunta 2- En pacientes con sospecha de SSp, ¿es de utilidad la sialografía para el diagnóstico de disfunción de la glándula salival?

Criterios de búsqueda: ((sjogren OR sjogren syndrome OR primary sjogren syndrome) AND (salivary gland) AND (diagnosis) AND (sialography))

Pubmed
Resultado Búsqueda: 266 artículos
Seleccionados por título: 53 artículos
Seleccionados por abstract se seleccionaron: 10 artículos
Seleccionados por artículo: 7

Lilacs
Resultado: 6 artículos
Seleccionados: 0

Cochrane
Búsqueda:0

Total de artículos incluídos: 7

Markusse y colaboradores publicaron en 1993 un estudio de corte transversal en el que evaluaron la sialografía por sustracción digital de las glándulas parótidas en 34 pacientes con SSp según criterios clasificatorios vigentes (siendo uno de ellos la sialografía) y 78 pacientes en los que se descartó SS (no-SS). Se observó con mayor frecuencia en los pacientes con SSp que en los pacientes no-SS: un patrón de ramificación escasa de los conductos, ampliación progresiva e irregularidad de las paredes del conducto, parénquima no homogéneo y la aparición de dilataciones acinares periféricas. Los hallazgos más discriminativos entre los dos grupos de pacientes fueron la presencia de dilataciones acinares y la pérdida de la homogeneidad del parénquima. La S y E de la presencia de dilataciones acinares fue de 79 y 95%, respectivamente. Tanto la S y E de la presencia de un parénquima irregular o ausente fueron de 91%. El hallazgo concurrente de dilataciones acinares y un parénquima irregular o ausente mostró una S del 77% y una E del 95% [7]. NE: 3

El estudio de Vittali y colaboradores publicado en 1994, fue descripto previamente [3]. NE: 2

Kalk y colaboradores, en 2002, publicaron un estudio de corte transversal en el que evaluaron el valor de la sialografía como herramienta diagnóstica en SS.100 sialogramas parotídeos se interpretaron de forma independiente de una manera ciega por dos médicos entrenados y dos observadores expertos. Los pacientes fueron clasificados como SS y no SS según criterios clasificatorios americano- europeos

(siendo la sialografía uno de estos criterios). Los observadores entrenados alcanzaron una S de 95%y una E del 33% para SS por sialograma, mientras que los observadores expertos llegaron a una S de 87 %y una E del 84%. Sólo había concordancia aceptable entre observadores entrenados y expertos, mientras que ambos observadores expertos mostraron un buen grado de acuerdo entre sí. El acuerdo intra observador fue de bueno a muy bueno, para todos los observadores [5]. NE: 3

Song y colaboradores publicaron en 2014 un meta análisis de estudios heterogéneos, que tuvo como objetivo comparar el rendimiento diagnóstico de la sialografía salival y la ultrasonografía (US) para el diagnóstico de SS. Se incluyeron seis estudios (488 pacientes y 447 controles). Las medidas sumarias de S y E de la sialografía fueron 80,0% (IC 95%: 76,4 a 83,2) y 89,0% (IC 95%: 85,8-91,8), respectivamente. En el caso de la US, la S fue del 77,4% (IC 95%: 73,7-80,9) y la E de 81,5% (IC 95%: 77,6-85,0) [8]. NE: 2

En 2008, Salaffi y colaboradores publicaron un estudio de corte transversal en el que compararon la US de las glándulas salivales con la sialografía y gammagrafía en SSp. Se incluyeron 77 pacientes con SSp y 79 con síntomas sicca pero sin SS. Los hallazgos de la US se clasificaron utilizando un sistema de puntuación ecográfico que varía de 0 a 16, obtenido mediante la suma de las puntuaciones de cada glándula parótida y submandibular. De los 77 pacientes con SSp, 66 tuvieron resultados anormales en la US. El puntaje medio US en los pacientes con SSp fue de 9,0 (rango: 3 a 16), mientras que el los pacientes no SSp fue 3,9 (rango de 0 a 9) (p <0,0001). Los resultados de sialografía mostraron que 59 pacientes con SSp tenían hallazgos anormales, mientras que 58 pacientes tuvieron hallazgos gammagráficos. A través de la comparación de las curvas ROC, la US surgió como la mejor opción ((área bajo la curva (ABC)= 0.863 +/- 0,030), seguido por sialografía (ABC=0.804+/-0,035) y por la gammagrafía de la glándula salival (ABC=0.783+/-0,03). Para la sialografía la S fue 72,7 %, y la E 84,9%, respectivamente [9]. NE: 3

Obinata y colaboradores publicaron en 2010 un estudio de corte transversal en el que evaluaron la precisión de la sialografía, la biopsia de glándula salival, y la US para el diagnóstico de SS. Se incluyeron 73 pacientes (36 sujetos clasificados con SS según tests oculares y serología, y 37 sin SS). La S de la sialografía fue 83,3%, de la US 77,8% y 63,9% para la histopatología. Hubo una diferencia estadísticamente significativa entre los resultados de la sialografía y la histopatología (p< 0,05). La E de la sialografía fue 94,4%, la US 78,8% y 91,4% para la histopatología. Hubo una diferencia estadísticamente significativa entre sialografía y ecografía (p< 0,05). La precisión diagnóstica de la sialografía fue de 89,0%; mientras que, tanto la US como la histopatología, mostraron una precisión de 78,1%. Hubo diferencias estadísticamente significativas entre sialografía, US y la histopatología (p<0,05). La sialografía fue de las tres, la herramienta que mostró mejor desempeño para el diagnóstico de SS [10]. NE: 3

Poul y colaboradores, en 2008, revisaron en forma retrospectiva los datos de 105 sujetos consecutivos investigados simultáneamente por US y sialografía de las glándulas parótidas para SS. De estos, se incluyeron 60 sujetos, 45 con SS (36 SSp, 9 SS secundario) y 15 sujetos sin SS. La US mostró un patrón heterogéneo de la glándula parótida en pacientes con SS, mientras que la sialografía demostró un patrón puntiforme de sialectasia. La S, E y exactitud de la US fueron 84,44%, 73% y 81,6%, respectivamente; y para sialografía convencional fueron 77,77%, 86,66% y 80%, respectivamente. Mediante la combinación de ambas modalidades de imagen, la sensibilidad aumentó a 91% con un 60% de especificidad y el 83,3% de precisión. No

hubo diferencia significativa entre el diagnóstico de SS primario vs SS secundario [11]. NE: 3

Pregunta 3- ¿Qué utilidad tiene en la actualidad la realización de gammagrafía de glándulas salivales para el diagnóstico en pacientes con sospecha de Síndrome de Sjögren?

Criterios de búsqueda:((sjogren OR sjogren syndrome) AND (diagnosis) AND (salivary gland) AND (scintigraphy))

Pubmed
Resultado búsqueda: 229 artículos
Seleccionados por título: 50 artículos
Seleccionados por abstract: 14 artículos
Seleccionados por artículo: 11 artículos
Incluídos manualmente: 0

Cochrane
Busqueda:0

LILACS
Búsqueda: 1 artículo
Artículos incluídos: 1 repetido

Artículos totales incluídos: 11 artículos

En 1987 Arrago y colaboradores evaluaron, en un estudio de corte transversal, la capacidad de la gammagrafía de las glándulas salivares en diferenciar SS, de otras patologías. La gammagrafía de glándulas salivares con pertecnetato de tecnecio-sodio (99mTc) se realizó en 320 pacientes: 145 con sospecha de SSp 165 con SS secundario y 10 con otras enfermedades de las glándulas salivales con sequedad oral o enfermedad del tejido conectivo. La tasa media de excreción fue anormal en 284. De los 145 pacientes derivados por síndrome sicca, se diagnosticó SSp en 131 casos; 14 de ellos tenían gammagrafías normales. Todos los pacientes trasplantados (8) tenían gammagrafías anormales y fueron considerados como SS secundario (n = 59); 84 pacientes con enfermedad autoinmune también fueron clasificados como SS secundario. La correlación entre la tasa media de valor de la excreción y los datos clínicos, biológicos o histológicos fue significativa, especialmente en pacientes con grado III o IV [12]. NE: 3

Markusse y colaboradores publicaron en 1993 un estudio de corte transversal en el que evaluaron la capacidad diagnóstica de la gammagrafía de la glándula salival en pacientes con sospecha de SSp. Se estudiaron 149 pacientes consecutivos con síntomas sicca y 20 sujetos como grupo control. El diagnóstico de SSp se estableció en 26 de estos pacientes, según criterios clasificatorios de California (los cuales incluyen a la sialografía). La gammagrafía de la glándula salival fue anormal en 19 de los 26 pacientes con SSp. Sin embargo, gammagrafías anormales también fueron encontrados en 57 de los 123 pacientes con síntomas sicca y en cinco controles. Esto dio lugar a un VPP de una gammagrafía de la glándula salival anormal de 25% y un VPN de una investigación normal de 90% [7]. NE: 3

El estudio publicado en 1994 por Vittali y colaboradores, fue descripto previamente [3]. NE: 2

En 1999 Hermann y colaboradores publicaron un estudio de corte transversal en el que analizaron cuatro índices numéricos comúnmente citados en estudios de poblaciones con xerostomía y la precisión con que se diferencia SS de otras patologías de las glándulas salivales como sialoadenitis crónica, sialoadenitis por radiación y efectos de drogas a través de la gammagrafía. Se incluyeron 295 pacientes con xerostomía y 31 controles. La fracción de excreción estimulada distinguió SS y sialoadenitis por radiación de los controles sanos con una precisión de 0,78 y 0,90, respectivamente. La precisión máxima de diagnóstico en SS se produjo con un punto de corte de 73%, con S de 73% y E de 73% [13]. NE: 3

Umehara y colaboradores publicaron en 1999 un estudio de corte transversal en el que compararon las características cuantitativas de la gamagrafía de la glándula salival en pacientes con SS con la clasificación histopatológica de la biopsia labial. 39 pacientes con SS y 12 voluntarios normales como grupo control fueron estudiados con gamagrafía salival con estimulación con jugo de limón durante 50 min. La relación de absorción de las glándulas parótidas y submandibulares se encontró disminuida significativamente en el SS en comparación con controles normales (p <0,001). El tiempo entre la estimulación y la mínima captación de las parótidas y glándulas submandibulares estaba aumentado de manera significativa en el SS en comparación con los controles normales (p <0,05).
La máxima acumulación de las glándulas parótidas y submandibulares se encontraba disminuido significativamente en el SS comparado con los controles normales; así como, La máxima secreción de la parótida y submandibular (p <0.01). A mayor grado histopatológico, de uno a cuatro, la velocidad de la secreción de trazador disminuyó en la glándula parótida (p <0,05), y la acumulación del trazador disminuyó en la glándula submandibular (p <0,05) [14]. NE: 4

Aung y colaboradores publicaron en el 2000 un estudio de corte transversal en el que compararon los parámetros cuantitativos de la gammagrafía de las glándulas salivares y las etapas sialográficas en pacientes con SS. 116 pacientes con sospecha de SS se examinaron con gammagrafía de la glándula salival y con sialografía. Cuando la sialografía fue utilizada como el patrón de referencia, el SS fue diagnosticado en 50 de estos 116 pacientes. Con la progresión de las etapas sialográficas de 0 a 4, la cantidad de acumulación de trazador disminuyó en la glándula submandibular (p <0,01), y la cantidad de trazador en la secreción disminuyó en la glándula parótida (p <0,01). Las etapas sialográficas en pacientes con SS se correlacionaron con los parámetros gammagráficos (p <0,0001). La relación de absorción de las glándulas parótidas y submandibulares se encontró significativamente disminuida en el SS en comparación con controles normales; así como, el tiempo al máximo conteo de ambas glándulas (p <0,05). El tiempo entre la estimulación y la mínima captación estaba aumentado de manera significativa en el SS en comparación con los controles normales (p <0,01 y p <0,05 respectivamente). Tanto la máxima acumulación de las glándulas parótidas y submandibulares, como la máxima secreción de las mismas, se hallaron significativamente disminuidas en el SS comparado con los controles normales (p <0,05) [15]. NE: 3

Henriksen y colaboradores publicaron en 2007 un estudio de corte transversal en el que evaluaron el uso de datos cuantitativos de la gammagrafía sobre la absorción, la concentración y la excreción de las cuatro principales glándulas salivales, en la evaluación de pacientes sicca. Se incluyeron 32 sujetos, SS (N: ocho), síndrome sicca aislado (N: 16) y controles sanos (N: ocho). Los pacientes con SS tenían tiempo

máximo al conteo prolongado en ambas glándulas parótidas (18,1 min; p <0,01)) y en las dos glándulas submandibulares (media 13,7 min, p <0,05). La distribución pico del trazador fue significativamente menor en las glándulas parótidas tanto en SS y el grupo sicca en comparación con los controles (p <0,01). La excreción estimulada se encontró disminuída significativamente en los pacientes con SS (16,3% para parótida y 17,4% para las glándulas submandibulares; p <0,01). La excreción (32, 2% para parótida y 26, 9% para las glándulas submandibulares) fue similar en todas las glándulas de los pacientes con SS como en los grupos control (35, 2% para parótida y 27, 8% para las glándulas submandibulares) [16]. NE: 4

Dugonjić y colaboradores publicaron en 2014 un estudio de corte transversal, con el objetivo de validar los parámetros de la gammagrafía y sialometría, como parámetros de diagnóstico en pacientes con SS. Se enrolaron 20 pacientes con SS y 10 controles sanos. Hubo una diferencia significativa en todos los parámetros de secreción de la glándula parótida, mostrando una más lenta y menor secreción en pacientes con SS en relación con el grupo control. La S de la gamagrafía fue del 100%, la E del 80%, el VPN del 100%, y el VPP del 91% [17]. NE: 3

Wu y colaboradores publicaron en 2015) un estudio de corte transversal en el que analizaron el valor diagnóstico de la gamamagrafia con tecnecio 99m de las glándulas salivales en pacientes con ciertas enfermedades de las mismas. Se evaluaron 47 pacientes: 25 con parotiditis obstructiva crónica, 12 con sialolitiasis, y 10 con SS. En los pacientes con parotiditis obstructiva crónica, la gamamagrafia salival con tecnecio 99 mostró una excreción reducida de las glándulas afectadas, mientras que la absorción fue prácticamente normal. Entre los pacientes con sialolitiasis, la gamamagrafia con 99mTc-pertecnetato demostró una reducción de la excreción de las glándulas afectadas y disminución de la absorción en 5 pacientes. En los pacientes con SS la gammagrafía mostró una disminución en la excreción y en la absorción de las 4 glándulas [18]. NE: 4

Pregunta 4- ¿Qué utilidad tiene en la actualidad la realización de ecografía de glándulas salivales para el diagnóstico en pacientes con sospecha de SSp?

Criterios de búsqueda: ((sjogren OR sjogren syndrome) AND (salivary gland) AND (diagnosis) AND (ultrasonography))

Pubmed
Resultado Búsqueda: 118 artículos
Seleccionados por título: 53 artículos
Seleccionados por abstract se seleccionaron: 15 artículos
Seleccionados por artículo: 13 artículos
Incluídos manualmente:

Lilacs:
Resultado: 3 artículos
Seleccionados: 0

Cochrane
Búsqueda:0

Artículos totales incluídos: 3 artículos (3 de los artículos seleccionados se excluyeron por estar incluídos en el meta análisis y otros 3 se excluyeron por analizar la utilidad

de la ecografía al ser incorporada a los criterios clasificatorios de la enfermedad. La descripción de estos últimos, se encuentra en el capítulo correspondiente a criterios clasificatorios.

Delli y colaboradores en 2015, llevaron a cabo una revisión sistemática y meta-análisis de estudios que examinaron las propiedades de la ecografía de las glándulas salivales mayores para el diagnóstico de SS. Se incluyeron 29 estudios, la mayoría de los cuales utilizó los criterios clasificatorios como patrón oro. La S combinada fue de 0, 69 (IC del 95%: 0,67-0,71), la E 0,92 (IC del 95%: 0,91 hasta 0,93), y el OR diagnóstico 33,89 (IC del 95%: 20,75-55,35). Cabe destacar que se observó un alto riesgo de sesgos y se detectó una heterogeneidad significativa entre los estudios [19]. NE: 2

Luciano y colaboradores publicaron en 2015 un estudio de corte transversal en el que evaluaron la utilidad de la US en el diagnóstico de SS. Se enrolaron 109 pacientes diagnosticados con SS según criterios americano- europeos (N: 55), o afectados por una enfermedad del tejido conectivo (ETC) no SS (N: 54). Los pacientes con SS mostraron una puntuación en la US mayor en comparación con aquellos con otras ETC ((media 2,2 (SD 1,8) vs 0,2 (SD 0,5), p <0,0001)). La US mostró una S de 65%, una E de 96%, un VPP del 95% y un VPN del 73%, para el diagnóstico de las SS. Se observó una correlación significativa entre US y el score de foco de la BGSM (r = 0,484; p <0,01) [20]. NE: 3

Baldini y colaboradores publicaron en 2015 un estudio de corte transversal, con el objetivo de evaluar la exactitud de US para la detección temprana de SSp y comparar el rendimiento diagnóstico de US con la BGSM y sialometría. Se enrolaron pacientes con sospecha de SSp y duración de los síntomas ≤ cinco años: 50 pacientes con SS primario según criterios clasificatorios americano- europeos y 57 controles con síntomas sicca sin-SS. La US fue realizada por dos radiólogos sesgados al diagnóstico. Entre los parámetros analizados, la falta de homogeneidad fue el que mejor discriminó pacientes con SSp de sujetos con síndrome sicca. Se encontraron hallazgos patológicos por US en 66% de los pacientes SSp y en menos del 10% de los controles (p <0,01). Se generó un sistema de puntaje, siendo el punto de corte de 2 el que mostró mejor desempeño para el diagnóstico de SSp (S: 66%, E: 98%, VPP: 97% y VPN: 73%). La puntuación US fue significativamente mayor en los pacientes con resultados en sialometría no estimulada <1,5 ml / 15 minutos (2,6 ± 1,7 vs 0,9 ± 1,5, p <0,01) y en pacientes con un score de foco en BGSM ≥1 (2,0 ± 1,8 vs 0,1 ± 0,7, p <0,01) [21]. NE: 3

Pregunta 5- ¿Qué utilidad tiene en la actualidad la realización de RMN de glándulas salivales para el diagnóstico en pacientes con sospecha de SSp?

Criterios de búsqueda: ((salivary gland disease OR salivary gland OR salivary dysfunction OR salivary involvement) AND (primary sjogren OR sjogren syndrome OR primary sjogren syndrome) AND (diagnosis) AND (MRI))

Pubmed
Búsqueda: 319 artículos
Seleccionados por título: 34 artículos
Seleccionados por abstract: 9
Seleccionados por artículo: 6
Incluídos manualmente: 0

Cochrane
Busqueda:0

LILACS:
Artículos encontrados:
Artículos incluídos: 0

Artículos totales incluídos: 6

Izumi y colaboradores publicaron en 1996 un estudio de corte transversal, con el objetivo de evaluar la capacidad de la RMN de la glándula parotídea para diferenciar pacientes con SS. Se incluyeron 40 pacientes con SS, 30 sujetos normales, y 10 pacientes con inflamación de las parótidas por causas diferentes a SS. La glándula parótida en SS se caracterizó por una pérdida de homogeneidad en la intensidad de señal en las imágenes de RMN ponderada-T1, con una apariencia granular. La intensidad de la señal de la glándula parótida fue mayor en los pacientes con SS definido que en los sujetos normales y que en los pacientes con inflamación parotídea (27,8 ± 7,8 versus 12.1 ± 2,9 versus 13,8± 2,4; p <0.01). La RMN en pacientes con SS, mostró una alta correlación con los resultados de la biopsia de glándula salivar (r = 0,834) y sialografía (r = 0,936) [(22)]. NE: 4

Makula y colaboradores publicaron en el 2000, compararon la RMN y la US en un estudio de corte transversal, que incluyó 44 pacientes con SS y 52 controles sanos. La falta de homogeneidad del parénquima se observó con mayor frecuencia en los pacientes con SS que en los controles (RM: 95,4 vs 17,3%; US: 88,6 vs 7,7%; P <0,001). Se encontró una buena concordancia entre RM y la US, tanto en SS (93,2%) como en los controles (86,5%). Cuando se consideraron todos los cambios anormales de la resonancia magnética como resultados positivos, la S de la RM fue alta (100%), pero su E fue baja (40%). Sin embargo, cuando sólo los hallazgos más avanzados, se tomaron como hallazgos positivos, la S de la RM continuó siendo alta (81,8%), mientras que su E aumentó a 100% [(23)]. NE: 3

En el estudio de Niemela y colaboradores publicaron en 2001 un estudio de corte transversal en el que se comparó la RMN y RM sialografía en 26 pacientes con SS y 7 controles sanos. 22/26 pacientes con SS tenían anomalías en la RM. 21 pacientes (81%) tenía un patrón nodular o dendrítico del parénquima, cinco tenían cavidades y seis tuvieron dilataciones de los conductos. En RM sialografía, 25 de los 26 pacientes tenían anomalías de los conductos, y 16 cavitaciones. Las alteraciones en RM tuvieron asociación lineal con los cambios en el sistema ductal (p<0,05) de la RM sialografía. Los cambios en el conducto principal y las ramas en MR sialografía se asociaron uno con el otro (p< 0,01), así como el número y tamaño de las cavidades (p< 0,01). Tanto los cambios del parénquima y las anormalidades sialográficas se asociaron significativamente con la presencia de anticuerpos Ro /SSA (p <0,01) [(24)]. NE: 4

En 2005 Takagi y colaboradores, publicaron un estudio de corte transversal en el que incluyeron 83 pacientes con xerostomía (55 pacientes con SS y 28 pacientes no SS). Las imágenes cuantitativas de la grasa, las áreas de glándula intacta, y el número de focos sialoectásicos mostraron una elevada correlación con la gravedad de la enfermedad. La RM cuantitativa diferenció pacientes con xerostomía con SS, de los no-SS, con ABC de 0,94 para el área de grasa, 0,98 para el área lobular intacta, y 0,91 para el número de focos de sialoectasia. La RM cuantitativa tuvo 96% de S y E del 100% [(25)]. NE: 3

Roberts y colaboradores publicaron en 2008 un estudio de corte transversal en el que evaluaron en uno de 21 pacientes con SS y 11 en voluntarios sanos, las imágenes de RMN con un modelo cinético. En comparación con los voluntarios sanos, los pacientes con SS mostraron un aumento significativamente superior en los parámetros del modelo cinético, incluyendo constante de transferencia transcapilar del agente de contraste y el volumen extracelular extravascular ($p<0,01$). La heterogeneidad de la glándula fue significativamente mayor en los pacientes con SS ($p< 0,01$). Este método tuvo una S del 100% y una E del 64%. El ABC fue 0.96 (IC 95%: 0.89-1.00) [26]. NE: 3

Yan- De Ren y colaboradores publicaron en 2015, un estudio de corte transversal en el que se compararon las imágenes de RMN convencional y RM por sialografía de las glándulas salivales. Incluyó 107 pacientes: grupo SS (93 pacientes) y grupo no-SS (14 pacientes). En el grupo SS, 86/93 RMN mostraron depósitos anormales de grasa en las glándulas parótidas. La RM Sialografía identifico dilatación periférica de los conductos en 86 pacientes. Tanto la RM como RM sialografía, tuvieron una exactitud diagnóstica de 92,5%. La RMN y RM sialografía mostraron una S 92,5 y una E 100% [27]. NE: 3

Bibliografía:

1. Speight PM, Kaul A, Melsom RD. Measurement of whole unstimulated salivary flow in the diagnosis of Sjogren's syndrome. Annals of the Rheumatic Diseases 1992; 51: 499-502.
2. Pennec YL1, Letoux G, Leroy JP, Youinou P. Reappraisal of tests for xerostomia. Clin Exp Rheumatol. 1993 Sep-Oct;11(5):523-8.
3. Vitali C et al. The European Community Study Group on Diagnostic Criteria for Sjogren's Syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjogren's syndrome. Annals of the Rheumatic Diseases 1994; 53: 637-647.
4. Kalk WW, Vissink A, Spijkervet FKL, Bootsma H, Kallenberg CGM, Nieuw Amerongen AV. Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome. Ann Rheum Dis 2001; 60: 1110-1116.
5. Kalk WWI, Vissink A, Stegenga B, Bootsma H, Nieuw Amerongen AV, Kallenberg GM. Sialometry and sialochemistry: a non-invasive approach for diagnosing Sjögren's syndrome. Ann Rheum Dis 2002;61:137–144.
6. Liquidato BM, Bussoloti Filho I. Evaluation of sialometry and minor salivary gland biopsy in classification of Sjögren's Syndrome patients. Rev Bras Otorrinolaringol. V.71, n.3, 346-54, may/jun. 2005.
7. Markusse HM1, van Putten WI, Breedveld FC, Oudkerk M. Digital subtraction sialography of the parotid glands in primary Sjögren's syndrome. J Rheumatol 1993 Feb;20(2):279-83.
8. Song GG1, Lee YH. Diagnostic accuracies of sialography and salivary ultrasonography in Sjögren's syndrome patients: a meta-analysis. Clin Exp rheumatol 2014 Jul-Aug;32(4):516-22.
9. Salaffi F, Carotti M, Iagnocco A, Luccioli F, Ramonda R, Sabatini E, De Nicola M, Maggi M, Priori R, Valesini G, Gerli R, Punzi L, Giuseppetti GM, Salvolini U, Grassi W. Ultrasonography of salivary glands in primary Sjogren's syndrome: a comparison with contrast sialography and scintigraphy. Rheumatology 2008;47:1244–1249.
10. Obinata K, Sato T, Ohmori K, Shindo M, Nakamura M. A comparison of diagnostic tools for Sjögren syndrome, with emphasis on sialography, histopathology, and ultrasonography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010 Jan;109(1):129-34.
11. Poul JH, Brown JE, Davies J. Retrospective study of the effectiveness of high-resolution ultrasound compared with sialography in the diagnosis of Sjogren's syndrome. Dentomaxillofac Radiol 2008 Oct;37(7):392-7.
12. Arrago JP, Rain JD, Brocheriou C, Rocher F. Scintigraphy of the salivary glands in Sjogen's syndrome. J Clin Pathol 1987;40:1463-1467.
13. Hermann GA1, Vivino FB, Shnier D, Krumm RP, Mayrin V. Diagnostic accuracy of salivary scintigraphy indices in xerostomic populations. Clin Nucl Med 1999 Mar;24(3):167-72.
14. Umehara I, Yamada I, Murata Y, Takahashi Y, Okada N, Shibuya H. Quantitative evaluation of salivary gland scintigraphy in Sjögren's syndrome. J Nucl Med 1999;40:64–9.
15. Aung W, Yamada I, Umehara I, Ohbayashi N, Yoshino N, Shibuya H. Sjogren´s Syndrome: Comparison of Assessments with Quantitative Salivary Gland Scintigraphy and Contrast Sialography. J NucIMed2000;41:257-262.
16. Henriksen AM, Nossent HC. Quantitative salivary gland scintigraphy can distinguish patients with primary Sjøgren's syndrome during the evaluation of sicca symptoms. Clin Rheumatol 2007 Nov;26(11):1837-41.

17. Dugonjić S1, Stefanović D, Ethurović B, Spasić-Jokić V, Ajdinović B. Evaluation of diagnostic parameters from parotid and submandibular dynamic salivary glands scintigraphy and unstimulated sialometry in Sjögren's syndrome. Hell J Nucl Med 2014 May-Aug;17(2):116-22.
18. Wu CB, Xi H, Zhou Q, Zhang LM. The Diagnostic Value of Technetium 99m Pertechnetate Salivary Gland Scintigraphy in Patients with Certain Salivary Gland Diseases. J Oral Maxillofac Surg 73:443-450, 2015.
19. Delli K, Dijkstra PU, Stel AJ, Bootsma H, Vissink A, Spijkervet F. Diagnostic properties of ultrasound of major salivary glands in Sjögren's syndrome: a meta-analysis. Oral Dis 2015 May 18.
20. Luciano N, Baldini C, Tarantini G, Ferro F, Sernissi F, Varanini V, Donati V, Martini D, Mosca M, Caramella D, Bombardieri S. Ultrasonography of major salivary glands: a highly specific tool for distinguishing primary Sjögren's syndrome from undifferentiated connective tissue diseases. Rheumatology 2015 Jul 23.
21. Baldini C, Luciano N, Tarantini G, Pascale R, Sernissi F, Mosca M, Caramella D, Bombardieri S. Salivary gland ultrasonography: a highly specific tool for the early diagnosis of primary Sjögren's syndrome. Arthritis Res Ther 2015 May 28;17(1):146
22. Izumi M, Eguchi K, Ohki M, Uetani M, Hayashi K, Kita M, Nagataki S, Nakamura T.
MR Imaging of the Parotid Gland in Sjogren's Syndrome: A Proposal for New Diagnostic Criteria. AJR 1996;166:1483-1487.
23. Makula E, G. Pokorny1, M. Kiss, E. Vörös, L. Kovács1, A. Kovács1, L. Csernay and A. Palkó. The place of magnetic resonance and ultrasonographic examinations of the parotid gland in the diagnosis and follow-up of primary Sjögren's syndrome. Rheumatology (2000) 39 (1): 97-104.
24. Niemelä RK1, Pääkkö E, Suramo I, Takalo R, Hakala M. Magnetic resonance imaging and magnetic resonance sialography of parotid glands in primary Sjogren's syndrome. Arthritis Care & Research 45:512–518, 2001.
25. Takagi Y, Sumi M, Sumi T, Ichikawa Y, Nakamura T. MR Microscopy of the Parotid Glands in Patients with Sjogren's Syndrome: Quantitative MR Diagnostic Criteria. AJNR Am J Neuroradiol 26:1207–1214, May 2005.
26. Roberts C, Parker GJ, Rose CJ, Watson Y, O'Connor JP, Stivaros SM, Jackson A, Rushton VE. Glandular Function in Sjogren Syndrome: Assessment with Dynamic Contrast-enhanced MR Imaging and Tracer Kinetic Modeling—Initial Experience. Radiology. 2008 Mar; 246 (3): 845-53.
27. Yan-De Ren Y, Xiang-Rong Li, Jing Zhang, Li-Ling Long, Wei-Xiong Li, Yao-Qi Han. Conventional MRI techniques combined with MR sialography on T2-3D-DRIVE in Sjögren syndrome. Int J Clin Exp Med 2015;8(3):3974-3982

SÍNDROME DE SJÖGREN Y MÉTODOS DIAGNÓSTICOS
LABORATORIO Y BIOPSIA GLÁNDULAS SALIVALES

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Hospital Alemán

Pregunta 1- En pacientes con sospecha clínica de SSp, ¿es de utilidad el FAN para el diagnóstico, y con qué patrón se asociaría con mayor frecuencia?

Términos utilizados: ((sjogren OR sjoegren OR primary sjogren OR primary sjoegren OR sjogren syndrome OR sjoegren syndrome) AND (ana) OR antinuclear antibodies OR antinuclear antibody))
Artículos encontrados: Pubmed: 1501
Artículos filtrados por ((Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb] OR Review[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp])) de los últimos 10 años: 62
Artículos seleccionados por títulos: 14
Artículos seleccionados: 7

Shiboski y colaboradores publicaron en 2012, los criterios clasificatorios del Colegio Americano de Reumatología (ACR) 2012, en el que incorporan al FAN en títulos de o mayor a 1/320 acompañado con la positividad del factor reumatoideo (FR), como parte del dominio correspondiente al laboratorio inmunológico. El FAN en título de 1/320 o mayor, mostró una sensibilidad de 72.8 (IC 95%: 67.5–77.7) y especificidad de 80.4 (IC 95%: 76.9–84.0) según un modelo de análisis estadístico [(1)]. NE: 3

Cornec y colaboradores publicaron en 2012 un estudio de corte transversal en el que incluyeron 105 pacientes en los que se sospechaba SSp y compararon el grado de acuerdo entre criterios de clasificación para SSp de 2002 y 2012. El ítem serológico en el set de criterios ACR no mostró diferencias en la cuanto a la clasificación de los pacientes en comparación con el item serológico de los criterios Americano- europeos 2002. El FAN positivo se presentó en el 92.6% de los pacientes que cumplían ambos sets de criterios, 62.5% de los pacientes que cumplían solo los criterios 2012 y 53.3% de los que cumplían solo los 2002[(2)]. NE:3

De Nardi y colaboradores publicaron en 2006 una serie de casos consecutivos, que incluyó 335 con SSp, en el que se analizó la prevalencia de auto anticuerpos: el FAN fue encontrado en 278 pacientes (83%) [(3)]. NE: 4

Ter Borg y colaboradores publicaron en 2011, una serie de casos retrospectiva con 65 pacientes con SSp en la que se analizó el perfil inmunológico de pacientes con SSp, encontrándose un porcentaje de positividad del FAN de 77% [(4)]. NE: 4

Locht y colaboradores publicaron en 2005 un estudio de corte transversal que incluyó 321 pacientes con diagnóstico de SSp según los criterios de Copenhagen, en los que aplicaron los criterios AECG 2002. Los patrones de FAN encontrados en este estudio fueron: moteado fino (62%), homogéneo (16%) y anticentrómero (12%) [(5)]. NE: 4

Ramos-Casals y colaboradores publicaron en 2008 una amplia serie de casos multicentrica, que tuvo como objetivo evaluar la expresión clínica e inmunólogica de

1115 pacientes con SSp. Se detectaron 80% de pacientes con FAN positivo dentro de grupo clínico de pacientes con síntomas sicca limitados, y 88% dentro de grupo clínico con compromiso sistémico [6]. NE: 4

Fauchais y colaboradores publicaron en 2010 un estudio de cohorte retrospectivo que incluyó 445 pacientes con SSp según criterios clasificatorios AECG 2002, que tuvo como objetivo evaluar la evolución del perfil inmunológico de esta población de pacientes. Se encontraron 317 pacientes (71%) con FAN positivo; de los cuales 52 (12%) presentaron patrón atípico: anti RNP (N= 12); anticentrómero (N= 14); antiDNA (N= 19); antiscl70 (N= 3); antiJo1 (N= 3); antiSm (N= 3); y antihistona (N= 1). 14 pacientes desarrollaron otra enfermedad reumática autoinmune durante el seguimiento: cinco polimiositis (en un promedio de 78 meses), seis lupus eritematoso sistémico (en un promedio de 77 meses) y dos esclerodermia sistémica (en un promedio de 133 meses). Entre estos 14 pacientes, solo tres presentaron un FAN atípico al diagnóstico de SSp [7]. NE: 3

Pregunta 2- En pacientes con sospecha clínica de SSp, ¿es de utilidad el Ro para el diagnóstico?

Términos utilizados: ((sjogren OR sjoegren OR primary sjogren OR primary sjogren OR sjogren syndrome OR sjoegren syndrome) AND (ro OR ss a OR antibodies ss a))
Artículos encontrados: Pubmed: 3868
Artículos filtrados por ((Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb] OR Review[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp])) de los últimos 10 años: 314
Artículos seleccionados por títulos: 35
Full text seleccionados por abstract: 9 artículos
Artículos agregados manualmente: 5 artículos
Total: 14 artículos

En la publicación de Shiboski y colaboradores acerca de los criterios ACR 2012, comentada previamente, la positividad del anti Ro y o anti La mostró una sensibilidad del 83.7% y una especificidad del 91.5%, en un modelo estadístico [1]. NE: 3
En el estudio de Cornec y colaboradores de 2014 que comparó el grado de acuerdo entre criterios de clasificación para SSp de 2002 y 2012, el SSA (+) se observó en el 66.7% de los pacientes que cumplían ambos sets de criterios, en el 50% de los pacientes que cumplían solo los criterios 2012 y en 26.7% de los que cumplían solo los criterios 2002 [2]. NE: 3

Vitali y colaboradores publicaron en 2002 un estudio de test diagnóstico, en el que se propusieron los criterios americano- europeos 2002. Para clasificar un paciente con diagnóstico de SSp se requiere la presencia de anticuerpos anti Ro y/ o anti La, o la presencia de uno o más focos de infiltrado linfocitario en la biopsia de glándula salival menor (BGSM) [8]. NE: 2

En el estudio publicado por Ramos Casals y colaboradores en 2008, comentado con anterioridad, que incluyo 1115 pacientes con SSp, se detectaron 40% de pacientes Ro (+) dentro del grupo clínico con síntomas sicca limitados, y 50% dentro del grupo clínico con compromiso sistémico [6]. NE: 4

Retamozo y colaboradores publicaron en 2012 un estudio de corte transversal que tuvo como objetivo evaluar si la determinación de anticuerpos anti Ro52 influenciaría en la clasificación y caracterización clínica de los pacientes con sospecha de SSp. Se

incluyeron 187 pacientes que cumplían con al menos cuatro de los seis criterios clasificatorios 1993, incluyendo la positividad de anticuerpos (FAN, FR, anti-Ro/SSA y/ o anti-La/SS-B) como criterio obligatorio. Se utilizó ELISA cualitativo para la detección de Anti-Ro/SSA y ELISA semicuantitativo para la detección de Anti-Ro52. Se detectó la presencia de Anti-Ro52 en 70/187 (37%) de los pacientes. Un porcentaje significativo de pacientes con anti-Ro/SSA presentaban negatividad para anti-Ro52 (22%), mientras que 13 pacientes (12%) fueron negativos para anti-Ro/SSA pero positivos para anti-Ro52, cumpliendo los criterios 2002 sin necesidad de realizar una BGSM. Los títulos elevados de anti-Ro52 se asociaron con compromiso severo en la cintigrafía, BGSM positiva, parotidomegalia, anemia, leucopenia y FR. También se encontró correlación entre dicho anticuerpo y la edad, los niveles de gammaglobulinas, los títulos de FR y niveles séricos de IgA y de IgG [(9)]. NE: 4

Respecto al papel que ocupa este anticuerpo en los nuevos criterios clasificatorios propuestos, ACR- EULAR, se sugiere al lector consultar el addendum del capítulo de criterios clasificatorios.

Pregunta 3- En pacientes con sospecha clínica de SSp, ¿es de utilidad el La/SSB para el diagnóstico?

Términos utilizados: ((sjogren OR sjoegren OR primary sjogren OR prymary sjoegren OR sjogren syndrome OR sjoegren syndrome) AND (anti ssb OR ssb OR la antibodies))
Artículos encontrados: Pubmed: 1062
Artículos filtrados por((Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb] OR Review[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp]))de los últimos 10 años: 67
Artículos seleccionados por título: 15
Artículos seleccionados por abstracts: 7 artículos
Artículos agregados manualmente: 3 artículos
Total de artículos: 10

En la publicación del Colegio Americano de 2012 el Ro/SSA y La/SSB se encontraron en SSp con una sensibilidad del 83.7% y una especificidad del 91.5% [(1)]. NE: 3

En el estudio de Cornec y colaboradores de 2014, que comparó el grado de acuerdo entre criterios de clasificación para SSp de 2002 y 2012, el LA/ SSB positivo se observó en el 66.7% de los pacientes que cumplían ambos sets de criterios, 50% en el grupo de pacientes que cumplían solo los criterios 2012 y 26.7% en los que cumplían solo los criterios 2002 [(2)]. NE: 3

En el estudio publicado por Fauchais y colaboradores, que incluyo 445 pacientes con SSp, realizado para evaluar la evolución del perfil inmunológico se encontraron176 pacientes (39%) con La/SSB (+) [(7)]. NE: 3

En el estudio publicado por Vitali y colaboradores, descripto con anterioridad, se determinó que se requiere la presencia de anticuerpos anti Ro o anti La, para cumplir con el dominio de laboratorio inmunológico del set de criterios americano- europeos 2002 [(8)]. NE: 2

Pregunta 4- En pacientes con sospecha clínica de SSp, ¿es de utilidad el FR para el diagnóstico de SSp?

Términos utilizados: ((sjogren OR sjoegren OR primary sjogren OR primary sjogren OR sjogren syndrome OR sjoegren syndrome) AND (rheumatoid factor))
Artículos encontrados: Pubmed: 902
Cochran : 0
Lilacs: 0
Artículos filtrados por((Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb] OR Review[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp]))): 79
Artículos seleccionados por título: 17
Artículos seleccionados por abstracts: 5 artículos
Artículos agregados manualmente: 3 artículos
Total: 8

En la publicación del Colegio Americano de 2012, el FR positivo mostró una sensibilidad del 72.3% y una especificidad del 86.4% para el diagnóstico de SSp [(1)] NE: 3

En el estudio de Cornec y colaboradores ya comentado, se observó el FR positivo en el 51.9% de los pacientes que cumplían ambos sets de criterios, 50% en el grupo de pacientes que cumplían solo criterios 2012 y 6.7% en los que cumplían solo criterios 2002 [(2)]. NE: 3

En la serie de 65 pacientes con SSp publicada por Ter Borg y colaboradores en 2011, comentada previamente, se observó un porcentaje de pacientes con IgM FR positivo de 68% [(7)]. NE: 4

Santiago y colaboradores publicaron en 2015 un estudio de corte transversal, que incluyo 218 pacientes con sospecha de SSp y que consideró a la histología de glándula salival menor como patrón oro. Se encontró que el 31% de los pacientes presentaron FR positivo, con una sensibilidad del 47% (IC 95%: 33- 61%) y especificidad de 78% (69- 87%) [(10)]. NE: 3

En la serie de 1115 pacientes con SSp publicada por Ramos-Casals y colaboradores, comentada previamente, se detectaron 40% de pacientes FR positivo dentro del grupo clínico de pacientes con síntomas sicca limitados, y 50% dentro del grupo clínico con compromiso sistémico [(6)]. NE: 4

Pregunta 5- ¿Cuáles son las indicaciones para incluir la biopsia de glándula salival menor (BGSM) dentro de los métodos diagnósticos en pacientes con sospecha diagnostica de SSp?

Términos utilizados: ((salivary gland biopsy indication OR minor salivary gland biopsy indication) AND (sjogren syndrome OR primary sjogren))
Artículos encontrados: Pubmed: 929
Artículos filtrados por ((Controlled Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb] OR Review[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp])) de los últimos 10 años e idioma ingles: 920 (artículos eliminados por idioma: 2 (alemán y japonés) y 1 artículo eliminado por NO ser en humanos)
Artículos seleccionados por título: 9
Artículos seleccionados por abstracts: 5

Artículos agregados manualmente: 2
Total: 7

En la publicación del Colegio Americano de 2012 la BGSM con Foco score (FS) mayor o igual a 1 mostró una sensibilidad del 83.5% y una especificidad del 82.3% para el diagnóstico de SSp [1]. NE: 3

En el estudio publicado por Vitali y colaboradores, descripto previamente, se determinó que se requiere la presencia de anticuerpos anti Ro o anti La o de BGSM positiva, para poder clasificar a un paciente con SSp según los criterios clasificatorios americano- europeos 2002 [8]. NE: 2

Guellec y colaboradores publicaron en 2013 una revisión sistemática de estudios heterogéneos entre ellos, en la que se reportó una sensibilidad del 63.5 al 93.7%; y una especificidad de 61.2 a 100% de la BGSM [11]. NE: 2

El estudio de 2015 de Santiago y colaboradores, comentado con anterioridad; que incluyó 218 pacientes; encontró que 78 (36%) de ellos presentaban BGSM positiva; determinando este método como especialmente útil para el diagnóstico de SSp en pacientes seronegativos [10]. NE: 3

Pereira y colaboradores publicaron en 2014 una serie de casos retrospectiva; que incluyo el estudio de 38 pacientes con BGSM; 42% de las mismas fueron positivas para diagnóstico de SSp [12]. NE: 4

Daniels y colaboradores publicaron en 2011 un estudio de corte transversal, multicéntrico, que incluyo 1787 pacientes con sospecha de SSp: 1093 (61%) presentaron BGSM positiva para SSp; 66% con un FS > 1, 3% FS = 1, 31% un FS < 1 [13]. NE: 4

Salomonsson y colaboradores publicaron en 2009 un estudio de corte transversal, que incluyó 210 pacientes con BGSM, 67 pacientes presentaron FS > 1 (30) [14]. NE: 4

Respecto al papel de la BGSM en los nuevos criterios clasificatorios ACR- EULAR, consultar el addendum del capítulo de criterios clasificatorios.

BIBLIOGRAFIA:

1. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, Schiødt M, Umehara H, Vivino F, Zhao Y, Dong Y, Greenspan D, Heidenreich AM, Helin P, Kirkham B, Kitagawa K, Larkin G, Li M, Lietman T, Lindegaard J, McNamara N, Sack K, Shirlaw P, Sugai S, Vollenweider C, Whitcher J, Wu A, Zhang S, Zhang W, Greenspan J, Daniels T; Sjögren's International Collaborative Clinical Alliance (SICCA) Research Groups. American College of Rheumatology Classification Criteria for Sjögren's Syndrome: A Data-Driven, Expert Consensus Approach in the Sjögren's International Collaborative Clinical Alliance Cohort. Arthritis Care & Research Vol. 64, No. 4, April 2012, pp 475–487.

2. Cornec D, Saraux A, Cochener B, Pers JO, Jousse-Joulin S, Renaudineau Y, Marhadour T, Devauchelle-Pensec V. Level of agreement between 2002 American–European Consensus Group and 2012 American College of Rheumatology classification criteria for Sjögren's syndrome and reasons for discrepancies. Arthritis Research & Therapy 2014, 16:R74discrepancies.

3. Nardi N, Brito-Zeron P, Ramos-Casals M, Aguilo S, Cervera R, Ingelmo M, et al. Circulating auto-antibodies against nuclear and non-nuclear antigens in primary Sjögren's syndrome: prevalence and clinical significance in 335 patients. Clin Rheumatol 2006;25:341e6.

4. Ter Borg E-J, Risselada AP, Kelder JC. Relation of systemic autoantibodies to the number of extraglandular manifestations in primary Sjögren's syndrome: a retrospective analysis of 65 patients in the Netherlands. Semin Arthritis Rheum 2011;40:547e51.

5. Locht H, Pelck R, Manthorpe R. Clinical manifestations correlated to the prevalence of autoantibodies in a large (n= 321) cohort of patients with primary Sjögren's syndrome: a comparison of patients initially diagnosed according to the Copenhagen classification criteria with the american-european consensus criteria. Autoimmun Rev 2005;4:276e81.

6. Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, Del Pino-Montes J, Calvo-Alen J, Jiménez-Alonso J, Micó ML, Beltrán J, Belenguer R, Pallarés L; GEMESS Study Group. Primary Sjögren syndrome in spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore). 2008 Jul;87(4):210-9.

7. Fauchais AL, Martel C, Gondran G, Lambert M, Launay D, Jauberteau MO, Hachulla E, Vidal E, Hatron PY. Immunological profile in primary Sjögren's syndrome: clinical significance, prognosis and long-term evolution to other auto-immune disease. Autoimmun Rev. 2010 Jul;9(9):595-9.

8. Vitali C1, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH; European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002 Jun;61(6):554-8.

9. Retamozo S1, Akasbi M, Brito-Zerón P, Bosch X, Bove A, Perez-de-Lis M, Jimenez I, Soto-Cardenas MJ, Gandia M, Diaz-Lagares C, Viñas O, Siso A, Perez-Alvarez R, Yague J, Ramos-Casals M. Anti-Ro52 antibody testing influences the classification and clinical characterisation of primary Sjögren's syndrome. Clin Exp Rheumatol. 2012 Sep-Oct;30(5):686-92.

10. Santiago ML, Seisdedos MR, Garcia Salinas RN, Catalán Pellet A, Villalón L, Secco A. Usefulness of antibodies and minor salivary gland biopsy in the study of sicca syndrome in daily clinical practice. Reumatol Clin. 2015 May-Jun;11(3):156-60

11. Guellec D, Cornec D, Jousse-Joulin S, Marhadour T, Marcorelles P, Pers JO, Saraux A, Devauchelle-Pensec V. Diagnostic value of labial minor salivary gland biopsy for Sjögren's syndrome: a systematic review. Autoimmun Rev. 2013 Jan; 12(3):416-20.

12. Pereira DL, Vilela VS, Dos Santos TC, Pires FR. Clinical and laboratorial profile and histological features on minor salivary glands from patients under investigation for Sjögren's syndrome. Med Oral Patol Oral Cir Bucal. 2014 May 1;19(3):e237-41.

13. Daniels TE, Cox D, Shiboski CH, Schiødt M, Wu A, Lanfranchi H, Umehara H, Zhao Y, Challacombe S, Lam MY, De Souza Y, Schiødt J, Holm H, Bisio PA,Gandolfo MS, Sawaki T, Li M, Zhang W, Varghese-Jacob B, Ibsen P, Keszler A, Kurose N, Nojima T, Odell E, Criswell LA, Jordan R, Greenspan JS; Sjögren's International Collaborative Clinical Alliance Research Groups. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. Arthritis Rheum. 2011 Jul;63(7):2021-30.

14. Salomonsson S, Rozell BL, Heimburger M, Wahren-Herlenius M. J. Minor salivary gland immunohistology in the diagnosis of primary Sjögren's syndrome. Oral Pathol Med. 2009 Mar;38(3):282-8.

CRITERIOS CLASIFICATORIOS DEL SINDROME DE SJÖGREN

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Pregunta 1- En pacientes con sospecha de Síndrome de Sjögren Primario (SSp), ¿cuál es la especificidad y sensibilidad de los criterios 2002 para el diagnóstico de SSp?

Búsqueda:

"Search ((sicca syndrome) AND (classification criteria) AND (sjögren syndrome diagnoses))

Se encontraron 241 artículos

"Search ((sicca síndrome AND classification criteria) AND (sjögren syndrome diagnoses) AND (classification criteria 2002))

Se encontraron 35 artículos

Se seleccionaron por título y por abstract 5 artículos.

Locht y colaboradores publicaron en el año 2005 una serie de casos retrospectiva, que incluyó 321 pacientes consecutivos desde 1984 en un registro sueco de SSp según criterios de Copenhagen y se analizó con qué frecuencia cumplían los criterios americano-europeos 2002 (AECG 2002). Se observó que 205/321 cumplían los criterios AECG 2002. A su vez se observó que la mayor razón de esta discrepancia se debía al requisito de la positividad de anticuerpos anti-Ro/La o a la presencia del infiltrado característico en la biopsia de glándula salival menor [(1)]. NE: 4

Vitali y colaboradores publicaron en 2002 un estudio de diagnóstico que tuvo como objetivo definir y evaluar la utilidad de el set de criterios clasificatorios AECG 2002. Participaron 22 centros de 11 países, incluyéndose 693 casos, subdivididos en pacientes con SSp, SS secundario y controles, según opinión de expertos, que fue considerado como el patrón oro. Se analizaron los puntos de corte de las curvas ROC derivadas de la combinación de los diferentes tests diagnósticos y manifestaciones glandulares, tomándose como el mejor punto de corte el que mostraba una sensibilidad de 89.5 % y especificidad 95.2%. A su vez se definieron los criterios de exclusión [(2)]. NE: 2

Brun y colaboradores publicaron en 2002, una serie de casos retrospectiva, que incluyó 203 pacientes registrados en una base de datos con diagnóstico de SSp usando ICD-10 de enero 1999 a noviembre 2000. Se evaluó cuántos cumplían los criterios europeos *preliminares* y los propuestos criterios europeos *modificados* (actuales AECG 2002). 116/203 cumplieron los *preliminares* y 83/ 203 los *modificados.* Un solo paciente que no cumplía los criterios *preliminares,* cumplió los *modificados*. En conclusión los *modificados* resultaron más específicos en esta cohorte [(3)]. NE: 4

Plešivčnik Novljan y colaboradores publicaron en 2014, una serie de casos que incluyó 63 pacientes que cumplían criterios clasificatorios de Copenhagen que tuvo como objetivo comparar el desempeño de diferentes criterios clasificatorios aplicados en esta población de pacientes. Nueve de los 63 pacientes desarrollaron una segunda enfermedad del tejido conectivo, por lo que se excluyeron. En 34 pacientes se realizaron nuevamente todos los tests, siendo el rédito de retención estadísticamente significativo para todos los criterios, excepto para los europeos 1993. 25/34 (73%) cumplieron los mismos criterios iniciales, seis (18%) cumplieron diferentes criterios a los iniciales y tres de 32 pacientes con diagnóstico inicial de SSp utilizando los criterios europeos, no pudieron ser clasificados como SSp por ninguno de los otros sets de criterios. No hubo diferencia estadísticamente significativa entre ACR 2012 y AECG tanto inicialmente como en el seguimiento. Todos los pacientes que cumplían inicialmente los criterios ACR, también cumplían los AECG [(4)]. NE: 4

Galvez y colaboradores publicaron en 2009, un estudio de test diagnóstico que tuvo como objetivo evaluar el desempeño de los criterios clasificatorios preliminares europeos y los propuestos AECG 2002. Se incluyeron 88 pacientes a quienes se les había realizado biopsia de labio por sospecha de SS, los cuales fueron evaluados por dos reumatólogos independientes. Dos anátomo- patólogos independientes que no conocían el diagnóstico, revisaron las biopsias. El diagnóstico médico se consideró el patrón oro para clasificar a los pacientes en SSp y SS secundario. Según el criterio médico, los pacientes se dividieron en 35 SSp y 17 pacientes con SS secundario. La sensibilidad y especificidad de los AECG 2002 para SSp 97.2% y 48.6%, respectivamente. Para SS secundario, la especificidad fue de 97.2% y la sensibilidad de 64.7%. Los criterios preliminares mostraron menor especificidad (75%) y mayor sensibilidad (65.7%). En SS secundario la especificidad de los criterios preliminares fue de 97.2% y la sensibilidad de 70.6% [(5)]. NE: 3

Pregunta 2- En pacientes con sospecha de SSp, ¿cuál es la sensibilidad y especificidad de los criterios del 2012?

"Search ((sicca syndrome) AND (classification criteria) AND (sjögren syndrome diagnoses)) AND (classification criteria 2012))

"Search ((sicca syndrome) AND (classification criteria) AND (sjögren syndrome diagnoses) AND (classification criteria 2012) AND (validation classification criteria 2012))

Se encontraron 23 artículos se seleccionaron por título y abstract 4 artículos.

Shiboski y colaboradores publicaron en 2012, un nuevo sets de criterios: criterios clasificatorios ACR 2012. Un panel de expertos compuesto por reumatólogos, oftalmólogos y estomatólogos, se reunió en el 2004 para definir la población blanco y la lista de variables a considerar. En una segunda etapa (abril 2006) se realizó la reducción de variables y establecieron valores de corte de los tests. En una tercera fase (mayo 2009) se definieron los criterios de clasificación preliminares. La cohorte

incluyó pacientes mayores a 21 años, con al menos una de las siguientes características positivas: síntomas de ojo o boca seca, sospecha previa de diagnóstico de SS, positividad FAN, FR o anti Ro, aumento parotídeo bilateral en contexto de clínica compatible con SS, aumento de caries dentales, diagnóstico de AR o LES y alguna de las manifestaciones previamente mencionadas. Se excluyeron los pacientes con diagnóstico de HCV, HIV, sarcoidosis, amiloidosis, TBC activa, enfermedad injerto vs huésped, otras enfermedades del tejido conectivo (no AR ni LES), radiación cefálica o cuello, tratamiento con gotas oftálmicas por glaucoma, cirugía de córnea o de párpados en los últimos cinco años y condiciones físicas o mentales que interfieran con la participación en el estudio. Para el análisis se excluyeron los pacientes con AR y LES dado el bajo número de pacientes incluidos. Para la validación se realizó una comparación con versiones alternativas de los criterios preliminares, comparación con un modelo construido a partir de un rango de tests diagnósticos y tomados como patrón oro, comparación con los AECG 2002 y medición de la estabilidad de los criterios en el tiempo. El set final de criterios propuestos incluyó: Ro+ y/o La+ o FAN+≥1/320 y FR+, ocular staining score ≥ 3, biopsia con al menos un foco linfocitario/4mm2. Al tomar los criterios 2002 como patrón oro se encontró una sensibilidad de 94.7% (95%CI: 92.6, 96.3) y especificidad de 93.3% (95%CI: 91.3, 95.0) [(6)]. NE: 3.

Hernández- Molina y colaboradores publicaron en 2014 un estudio de test diagnóstico, que tuvo como objetivo evaluar el desempeño de los AECG 2002 y los ACR 2012 para SS en pacientes con enfermedades autoinmunes. Se incluyeron 100 pacientes con AR, 100 con LES, 100 con esclerodermia y 50 con SSp, de forma aleatorizada. Dos reumatólogos independientes clasificaron a los pacientes en: SS (probable o definitivo) y no SS. El diagnóstico clínico se consideró como el patrón oro. Se aplicaron a cada paciente los criterios ACR 2012 y AECG 2002. En 154 pacientes se realizó diagnóstico clínico de SS. La sensibilidad de los criterios AECG 2002 fue de 61.6 versus 62.3 de los ACR 2012, mientras que la especificidad fue de 94.3 para los primeros y 91.3 para los segundos, 31/154 no cumplieron ninguno de los criterios [(7)]. NE: 3

Rasmussen y colaboradores publicaron en 2014 un estudio de corte transversal, en el que se compararon los criterios AECG y los nuevos criterios ACR 2012 para SSp en una población de 646 pacientes con complejo sicca. La utilización de los criterios AECG y ACR resultaron en la clasificación de 279 y 268 pacientes con SSp, respectivamente. 244 (81%) pacientes cumplieron ambos criterios [(8)]. NE: 4

También responde a esta pregunta el artículo de Plešivčnik Novljan M [(4)].

Pregunta 3- En pacientes con sospecha de SSp, ¿cuál es el desempeño de los criterios del 2012 en comparación con los del 2002, para el diagnóstico de SSp?

"Search ((sicca syndrome) AND (classification criteria) AND (sjögren syndrome diagnoses) AND (classification criteria 2012) AND (sicca syndrome) AND (classification criteria) AND (sjögren syndrome diagnoses) AND classification criteria 2002))

Responden a esta pregunta los artículos de Plešivčnik Novljan M [4], de Hernández-Molina G [7], y de Rasmussen [8], comentados anteriormente.

Pregunta 4- En pacientes con sospecha de SSp, agregar la ecografía parotídea, ¿mejora el desempeño de los criterios 2012 para el diagnóstico de SSp?

-"Search ((sicca syndrome) AND (classification criteria) AND (sjogren syndrome diagnoses) AND (salivary gland ultrasonography))
"Search ((sicca syndrome) AND (classification criteria) AND (sjogren syndrome diagnoses) AND (ultrasonography))

Se encontraron 28 artículos se seleccionaron por título y abstract 4 artículos.

Cornec y colaboradores publicaron en 2012 un estudio de test diagnóstico, que tuvo como objetivo determinar el desempeño de la ultrasonografía (USG) de las glándulas salivales para el diagnóstico de SSp y sugerir modificaciones en los criterios AECG 2002. Se incluyeron 158 pacientes de los cuales 78 tenían diagnóstico de SSp según criterio de un grupo de expertos ciego a los resultados de la USG y 61 pacientes cumplían criterios clasificatorios 2002. La ecografía fue llevada a cabo por un evaluador ciego a los datos clínicos de los pacientes. Los resultados de las curvas ROC mostraron que un grado cuatro de USG representaba el mejor valor diagnóstico (0,82). A partir del peso de las variables obtenidos del análisis de regresión logística, se construyó un score formado por cinco variables: flujo salival: 1,5; Schirmer's test: 1,5; biopsia de glándula salival: 3; SSA/SSB: 4,5; SGUS: 2. De acuerdo al resultado de las curvas ROC, un score mayor o igual a cinco de un total de 12 mostró una sensibilidad de 85,7% y especificidad de 94,9%, comparado con 77,9% de sensibilidad y 98.7% de especificidad para los criterios clasificatorios 2002 [9]. NE: 3

Takagi y colaboradores publicaron en 2014, un estudio de test diagnóstico, que tuvo como objetivo evaluar la utilidad de la USG como un ítem adicional en los criterios clasificatorios americanos 2012. Se incluyeron 581 pacientes a los que dividieron en 364 SS (243 SSp y 121 SS secundario) y 217 no SS, según criterios clasificatorios AECG 2002, seleccionándose a 184 de ellos (102 SS y 82 no SS), que presentaban dos o más criterios positivos y dos o más criterios negativos, respectivamente, según criterios americanos 2012. Se tomó como estudio de referencia o gold standard a los criterios AECG 2002. Los criterios 2012 mostraron una sensibilidad de 91%, especificidad de 90%. Al incorporar la USG como alternativa a uno de los tres criterios 2012, se logró una sensibilidad de 89- 91%, especificidad 87- 96% y precisión entre 89- 92%, comparable a los criterios 2012 originales [10]. NE: 3

Cornec y colaboradores publicaron en 2013 un estudio de test diagnóstico, que incluyó 101 pacientes con sospecha de SS, que tuvo como objetivo evaluar la utilidad de la incorporación de la USG a los criterios clasificatorios 2012. Se utilizó como patrón oro el diagnostico de SSp según opinión de expertos. Cuarenta y cinco pacientes fueron diagnosticados con SS y 56 con complejo sicca no SS (se incluyeron en este grupo a

pacientes con complejo sicca no SS (se incluyeron en este grupo a pacientes con complejo sicca idiopático, asociado a enfermedades del tejido conectivo y secundario a drogas). Los criterios ACR 2012 aplicados a los 101 pacientes con sospecha de SS tuvieron moderada sensibilidad (64,4%) y buena especificidad (91,1%). Agregar la ecografía a los criterios ACR 2012 aumentó la sensibilidad de un 64% a un 84,4% y disminuyó levemente la especificidad, de 91% a 89% [(11)]. NE: 3

Milic y colaboradores publicaron en 2011 un estudio de test diagnóstico en el que evaluaron la utilidad de la USG al para suplantar a la centellografía glandular en los criterios americano AECG 2002. Se incluyeron 190 pacientes; 140 de ellos con diagnóstico de SSp según criterios 2002 y 50 pacientes con complejo sicca no SSp. Según los resultaos de las curvas ROC se estableció un valor de corte del score USG de siete. El score USG fue positivo en 129 (92%), la centellografía en 123 (88%) y la biopsia de glándula salival menor en 93 (66%). De los 140 pacientes con SSp, 88 (63%) cumplían los criterios clasificatorios que utilizaban USG, 85 (61%) pacientes los criterios que utilizaban la centellografía y 71 (51%) los que usaban la biopsia. Ningún paciente del grupo no SSp cumplió ninguno de los tres sets de criterios. La precisión diagnóstica de cada set de criterios fue alta y similar (criterios con USG: ROC 0.99, criterios con centellografía 0.98 y criterios con biopsia 0.97) [(12)]. NE: 3

Bibliografía

1) “Clinical manifestations correlated to the prevalence of autoantibodies in a large (n=321) cohort of patients with primary Sjögren's syndrome: a comparison of patients initially diagnosed according to the Copenhagen classification criteria with the American-European consensus criteria” Locht H y col. Autoimmun Rev. 2005 Jun;4(5):276-81.

2) “Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group” Vitali C y col. Ann Rheum Dis. 2002 Jun;61(6):554-8.

3) “Sjögren´s sindrome in an out-patient clinic: classification of patients according to the preliminary European criteria and the proposed modified European criteria” J.G. Brun y col. Rheumatology 2002;41: 301-304

4) “Comparison of the performance of the different classification criteria for primary Sjögren's syndrome: a prospective cohort study” Plešivčnik Novljan M y col. Clin Rheumatol. 2014 Nov;33(11):1657-64.

5) “Diagnostic evaluation and classification criteria in Sjögren's Syndrome” Gálvez J y col. Joint Bone Spine. 2009 Jan;76(1):44-9

6) “American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort.” Shiboski SC y col. Arthritis Care Res (Hoboken). 2012 Apr;64(4):475-87.

7) “Utility of the American-European Consensus Group and American College of Rheumatology Classification Criteria for Sjögren's syndrome in patients with systemic autoimmune diseases in the clinical setting.” Hernández-Molina G y col. Rheumatology (Oxford). 2015 Mar;54(3):441-8.

8) “Comparison of the American-European Consensus Group Sjogren's syndrome classification criteria to newly proposed American College of Rheumatology criteria in a large, carefully characterised sicca cohort.” Rasmussen A y col. Ann Rheum Dis. 2014 Jan;73(1):31-8

9) “Contribution of salivary gland ultrasonography to the diagnosis of Sjögren's syndrome: toward new diagnostic criteria?” Cornec D y col. Arthritis Rheum. 2013 Jan;65(1):216-25.

10) “Ultrasonography as an additional item in the American College of Rheumatology classification of Sjögren's syndrome.” Takagi Y y col. Rheumatology (Oxford). 2014 Nov;53(11):1977-83

11) “Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome.”Cornec D y col. Rheumatology (Oxford). 2014 Sep;53(9):1604-7.

12) “Ultrasonography of major salivary glands could be an alternative tool to sialoscintigraphy in the American-European classification criteria for primary Sjogren's syndrome.” Milic V y col. Rheumatology (Oxford). 2012 Jun;51(6):1081-5

Addendum

En el Congreso Americano de Reumatología (ACR) noviembre de 2015, fueron presentados, como comunicación oral, los nuevos criterios clasificatorios propuestos por ACR- EULAR. Los mismos se describen brevemente en este apartado, como resultado de búsqueda manual y con fecha posterior a la establecida como límite (julio 2015), por considerarse de relevancia.

A partir de un estudio de corte transversal, se definieron cinco criterios a ser aplicados en pacientes con sospecha de Síndrome de Sjögren primario (SSp) ya sea por presentar al menos un síntoma de sequedad oral u ocular o un dominio positivo del ESSDAI (por sus siglas en inglés *European League Against Rheumatism Sjögren's Syndrome Disease Activity Index*). Los criterios incluyen: mayor o igual a un foco de infiltrado linfocitario en la biopsia de glándula salival (tres puntos), anti- Ro positivo (tres puntos), ocular staining score mayor o igual a cinco (un punto), test de Schirmer menor o igual a 5 mm/ 5 min (un punto), sialometría no estimulada menor o igual a 0.1 ml/ min (un punto). El puntaje total es de nueve y se requiere un puntaje mayor o igual a cuatro para clasificar un paciente con SSp. Los criterios de exclusión serían similares a los americano- europeos 2002.

TRATAMIENTO DE OJO SECO EN SÍNDROME DE SJÖGREN PRIMARIO

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Pregunta 1- ¿Los lubricantes artificiales y/o el suero autólogo previenen el daño corneal en pacientes con *queratoconjuntivits* sicca en pacientes con Síndrome de Sjögren Primario (SSp)?

PubMed Search ((Primary Sjögren's syndrome OR Primary syndrome, Sjogrens OR Primary sicca syndrome) AND (keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (prevent corneal damage) AND (autologous serum OR artificial lubricants))

Total de artículos encontrados: 618
Artículos Seleccionados: 6

Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Tears, Artificial" AND "serum" AND "Corneal Damage"

Total de artículos encontrados: 62
Artículos Seleccionados: 1

Se encontró un solo artículo que evalúa estos tratamientos en pacientes con SSp. El resto de la bibliografía evalúa los mismos en pacientes con ojo seco.

Cömez y colaboradores[i] publicaron en 2013, un estudio que evaluó la osmolaridad de las lágrimas y test funcionales (Ocular Surface Disease Index (OSDI), test de Schirmer y break-up time (BUT)) en pacientes con ojo seco utilizando lubricantes con diferentes osmolaridades. Fue un estudio de 12 semanas, aleatorizado, simple ciego (pacientes), 22 pacientes recibieron Polietileglicol (ojo derecho) y Ácido Hialurónico (ojo izquierdo) y 21 pacientes recibieron Dextran 70 más Hidroxipropilmetilcelulosa (ojo derecho) y Carboximetilcelulosa (ojo izquierdo). Trece pacientes tuvieron pérdida de seguimiento a las 12 semanas. En todas las visitas se demostró mejoría sintomática y en los test objetivos: Los primeros dos compuestos mencionados tuvieron mayor mejoría numérica en el Test de Schirmer (6.7 a 3.4 y 6.4 a 2.9 mm, respectivamente) en comparación con los dos últimos (4.7 a 2.4 y 4.7 a 2.8 mm, respectivamente), aunque sin alcanzar la significancia estadística (p = 0.14). Resultados similares se obtuvieron en el resto de los test objetivos [(1)]. **NE: 3**

Lee y colaboradores publicaron en 2011 un estudio aleatorizado, simple ciego (observador), que comparó la eficacia y seguridad de Hialuronato de Sodio (HS) y Carboximetilcelulosa (CMC). Se incluyeron 67 sujetos con ojo seco y se aleatorizaron a recibir seis veces al día HS 0.1% (n:32) o CMC 0.5% (n:33) por ocho semanas. Se encontró una mejoría significativa respecto al basal en los test de tinción conjuntival y corneal a las cuatro semanas: cambio respecto al basal con HS 22.00 ± 1.27 vs. CMC

22.60 ± 1.41; *p:* 0.05 y en semana ocho: cambio respecto al basal con HS 22.70 ± 1.33 vs. CMC 22.60 ± 1.45; *p:* 0.05). En BUT el cambio respecto al basal a las cuatro semanas fue: HS 1.10 ± 1.83 vs. CMC 1.50 ± 1.68; *p:* 0.05) y en semana ocho, respecto al basal, HS 1.80 ± 1.95 vs. CMC 2.50 ± 2.14; *p:* 0.05. La mejoría también se evidenció en los síntomas de sequedad ocular, no encontrándose diferencias significativas entre ambos grupos[ii]. **NE: 3**

Troiano y colaboradores publicaron en 2008 un estudio aleatorizado, simple ciego, en el que evaluaron dos grupos de tratamiento: 14 pacientes recibieron Ácido Hialurónico 0.4% oftálmico 300mOsm/Lt y otros 14 Ácido Hialurónico 0.4% gotas oftálmicas con 150 mOsm/Lt. Debían colocarse una gota en cada ojo cuatro veces al día por siete días, luego de un día de lavado del tratamiento se invertían los grupos. Se encontró una mejoría estadísticamente significativa respecto al basal en ambos grupos, el compuesto hipotónico fue significativamente superior al compuesto isotónico en mejorar los síntomas de ojo seco y el epitelio de la córnea y conjuntiva. Al finalizar el estudio el 60.7% prefirió utilizar lágrimas hipotónicas, el 10.7% isotónicas y el 28.6% refirió no tener preferencias[iii]. **NE: 3.**

Wegener y colaboradores publicaron en 2015 un estudio aleatorizado, en el que investigaron el efecto de agentes viscosos (Hydroxypropyl methylcellulose (HPMC), Carbomer, Povidone y la combinación de HPMC más Povidone) utilizados tres veces al día durante cuatro semanas, en la densidad corneal en pacientes con ojo seco. La morfología corneal fue documentada con una fotografía con método Scheimpflug y la densidad corneal fue analizada en cinco sitios anatómicos (epitelio, membrana de Bowman, estroma, membrana de Descemet y endotelio). Se incluyeron 98 ojos de 49 pacientes con ojo seco y 65 ojos de 33 controles sanos agrupados por edad, quienes no recibían tratamiento. La densidad corneal se redujo en las cinco capas anatómicas de los pacientes con ojo seco en comparación con los controles[iv]. **NE: 3**

Aragona y colaboradores publicaron en 2002 un estudio aleatorizado, doble ciego, que evaluó el efecto de hialuronato de sodio en pacientes con ojo seco. Se incluyeron 86 pacientes con ojo seco definido como: Test Rosa de Bengala o Fluoresceína de tres, BUT <10 segundos o Test de Schirmer <5.5mm; fueron aleatorizados a recibir lágrimas con hialuronato de sodio o Solución Salina por tres meses con una gota cuatro- ocho veces al día. Objetivamente se comparó: citología de impresión, lámpara de hendidura y síntomas subjetivos al mes, dos y tres meses de tratamiento. Después de tres meses los pacientes que recibieron tratamiento con hialuronato de sodio, mejoraron el score de impresión citológica respecto al inicial (p= 0.024 v inicio) y al placebo (p = 0.036). No se encontraron diferencias estadísticamente significativas en el resto de las evaluaciones[v]. **NE: 3.**

Ostuni y colaboradores publicaron en 2005 una serie de casos que tuvo como objetivo determinar la seguridad y eficacia Carbopol 974P en pacientes con SSp con keratoconjuntivitis Sicca no respondedores a tratamiento con lágrimas artificiales. Incluyeron 60 pacientes (57 F, 3 M). Se midió test de Schirmer, B.U.T., Rosa de Bengala y examen clínico oftalmológicos (fluoresceína, infiltrados corneales, presencia de úlceras) y un cuestionario de ojo seco (0-30) realizados en la visita basal, a las dos

y 12 semanas. Los test objetivos de ojo seco mostraron una mejoría estadísticamente significativa a la semana dos, la cual fue aún más marcada en la semana 12 Schirmer: *p*=0,006, B.U.T. *p*=0,000, Rosa Bengala *p*<0,001. La adición de Carbopol 974P al tratamiento tradicional es una opción válida y segura[vi]. **NE:4.**

Pregunta 2- Lubricantes artificiales vs. ciclosporina tópica. Ventajas de uso concomitante vs aislado.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (topical cyclosporine))

Artículos encontrados: 58.
Artículos Seleccionados: 3.

Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Topical Administration" AND "ciclosporin"

Artículos encontrados: 62.
Artículos Seleccionados: 1.

No se encontraron artículos en LILACs.

Schrell y colaboradores publicaron en 2012 un estudio aleatorizado, con el objetivo de evaluar el uso de ciclosporina 0.05% tópica en pacientes con ojo seco severo, estudiaron 62 pacientes con queratoconjuntivitis sicca que fueron aleatorizados a recibir una gota en cada ojo de ciclosporina 0.05% dos veces al día (n:31) o lágrimas artificiales con ácido hialurónico una gota en cada ojo cinco veces al día. Como test objetivos se utilizaron LIPCOF (Lid-parallel Conjunctival Folds), BUT, fluoresceina y Rosa de Bengala además se midió la presión intraocular y el score de OSDI (cuestionario autorreportado). El grupo de tratamiento tuvo mejoría significativa en todos los parámetros, pero esta fue evidente recién después del tercer mes de tratamiento[vii]. **NE: 3**

Stonecipher K y colaboradores reportaron en el 2005, los resultados de una amplia serie de casos respecto al uso de Ciclosporina A 0.05% emulsión oftálmica para el tratamiento de queratoconjuntivitis sicca en la vida real. Participaron 4504 oftalmólogos, optometristas y médicos generales, quienes identificaban a los pacientes, los invitaban a participar, entregaban la medicación y recolectaban las mediciones a través de cuestionarios autorreportados (basal, 30 y 60 días). Se incluyeron 5884 pacientes, 84% mujeres con una media de edad de 63 años. Se observó una significativa disminución en el 30% de la severidad de los síntomas. Más del 60% disminuyó significativamente el uso de lágrimas artificiales[viii]. **NE: 4.**

Devecı H. publicaron en 2014, un estudio de cohorte en el que evaluaron la eficacia de Ciclosporina A 0.05% tópica en pacientes con ojo seco debido a SSp o SS secundario. Incluyeron 26 pacientes a quienes le indicaron Ciclosporina 0.05% tópica y 20 quienes recibieron solución salina. Como test objetivos utilizaron Schirmer y BUT y como subjetivos dolor, fotosensibilidad, sensación que quemazón o arenilla. A la semana se

objetivo mejoría significativa en Test de Schirmer aumentando de 4.5 ± 1.2 mm en la primera evaluación a 12.1 ± 8.8 mm a la semana y BUT (5.7 ± 1.0s aumentó a 7.0 ± 1.8s en una semana *p*= 0.0001). Esta mejoría se mantuvo al repetir las evaluaciones al mes de tratamiento, demostrando eficacia en el grupo de tratamiento[ix]. **NE: 3.**

Pregunta 3- Lubricantes artificiales vs. suero autólogo vs ciclosporina tópica. Ventajas de uso en conjunto vs aislado.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (autologous serum) AND ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (topical cyclosporine))

Artículos encontrados: 30
Artículos Seleccionados: 2

No se encontraron artículos en las búsquedas en Cochrane ni LILACs.

Noble BA y colaboradores publicaron en 2004 un estudio aleatorizado en el que compararon el uso de lágrimas al 50% de suero autólogo versus tratamiento convencional. Los pacientes debían tener test de Schirmer menor a cinco, Rosa de Bengala y Fluoresceína positivos y debían tener oclusión lagrimal. Se incluyeron 16 pacientes con ojo seco (seis de ellos con SS), se analizaron los resultados en 31 ojos. Ocho pacientes recibieron tres meses de suero autólogo 50% y tres meses de tratamiento convencional y ocho pacientes viceversa. Se observó mejoría en los pacientes que utilizaron suero autólogo, aunque no significativa en test objetivos. Posteriormente se evidenció empeoramiento al pasar a tratamiento convencional[x]. **NE: 3.**

Fox RI y colaboradores evaluaron 15 pacientes con ojo seco, seis recibieron solución salina (placebo) y nueve lágrimas oftálmicas con suero autólogo. Se evaluaron previo al inicio y a los tres meses. Se encontró mejora significativa en las evaluaciones subjetivas aunque no en las objetivas. Ningún paciente tuvo mejora completa de los síntomas ni de los test objetivos[xi]. **NE: 4.**

Pregunta 4- Uso de AINES tópicos. AINES vs Ciclosporina Tópica.

Pub Med Search

((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary primary sicca syndrome OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome) AND (topical cyclosporine) AND (keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome OR keratoconjunctivitis sicca) AND (topical NSAID))

Artículos encontrados: 2.

Artículos Seleccionados: 0.

Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Topical Administration" AND "ciclosporin" OR "NSAIDs"

Artículos encontrados: 110.
Artículos Seleccionados: 0.

No se encontraron artículos en LILACs.

Pregunta 5- Corticoides tópicos.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (topical corticosteroids))

Artículos encontrados: 24.
Artículos Seleccionados: 2.

Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Topical Administration" AND "Corticosteroids"

Artículos encontrados: 62.
Artículos Seleccionados: 1.

Sin datos en LILACs.

Hong S y colaboradores[xii], publicaron en 2007 una serie de casos en la que evaluaron la recurrencia a largo plazo de los síntomas subjetivos y parámetros objetivos (BUT, Schirmer, Fluoresceína y Citología de Impresión) de keratoconjuntivitis sicca en pacientes con SS. Evaluaron 106 ojos de 53 pacientes que fueron tratados con solución de metilprednisolona al 1% sin conservantes, una gota en cada ojo, cuatro veces al día por dos semanas. Fueron revaluaron cada dos semanas y se hizo descenso escalonado antes de la discontinuación. Luego de iniciado el tratamiento se observó mejora significativa en BUT: previo 2.51 (+/-1.47+, post tratamiento 3.96 (+/-1.94) *p:* <0.001; Test de Schirmer previo al tratamiento 2.7 (+/-2) y posterior 3.92 (+/-2.2) *p:* <0.001 y en la percepción subjetivas de síntomas de ojo seco: previo al tratamiento media 77.6 (+/-15.7) y posterior 40.28 (+/_15.7) *p:* <0.001. Luego del primer ciclo de tratamiento, 11 pacientes (20.8%) recayeron, con un media de

sobrevida de 56.6 semanas. Después de un segundo ciclo de corticoides, solo un paciente recayó, con una media de sobrevida de 72.4 semanas. No se reportaron eventos adversos serios [12]. **NE: 4**

Sainz De La Maza Serra M y colaboradores publicaron en 2000 un estudio observacional, prospectivo, con grupo control, que incluyó 15 pacientes, 30 ojos, tratados con esteroides tópicos (una gota de metilprednisolona al 1% tres veces al día en ambos ojos durante dos semanas) tras las cuales fueron sometidos a la oclusión de los puntos lagrimales, y 15 pacientes, 30 ojos, sometidos directamente a la oclusión de los puntos lagrimales. La gravedad de la sintomatología (0-3+) y la tinción corneal con fluoresceína (0-9+) fueron evaluados a la semana y a los 2 meses. La sintomatología fue negativa en el 67% de los pacientes tratados con corticoides previos y en el 27% del grupo 2 (p=0,0001) a la semana, y en el 80% y en el 33% (0,0003) a los dos meses. La tinción corneal con fluoresceína fue negativa en el 67% (OD) y 73% (OI) de los pacientes tratados con corticoides previos y en el 33% (AO) sin tratamiento previo (p=0,0001, AO) a la semana, y en el 80% (AO) pacientes y 60% (AO) (p=0,0001, AO) a los dos meses. No hubieron efectos secundarios o complicaciones en ningún paciente. El uso de esteroides tópicos sin conservantes durante dos semanas como paso previo a la oclusión de los puntos lagrimales fue eficaz en controlar la sintomatología y la tinción corneal con fluoresceína en los pacientes con keratoconjuntivitis sicca grave asociada al SS[xiii]. **NE: 4**

Marsh P publicaron en 1999 un estudio retrospectivo de serie de casos en el que estudiaron la eficacia y seguridad de los corticoides tópicos en keratoconjuntivitis Sicca en pacientes con SS. Informan los beneficios de gotas de Metilprednisolona previo a la oclusión lagrimal. En 43% de los pacientes se observó un alivio moderado y 57% un alivio completo de los síntomas. Los eventos adversos encontrados en el uso prolongado fueron: aumento de presión intraocular en un paciente a los tres meses de tratamiento, empeoramiento de una catarata preexistente en un paciente a los seis meses y formación de una catarata en otro paciente, a los seis meses[xiv]. **NE: 4**

Pregunta 6- Corticoides Tópicos vs AINES Tópicos.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND topical NSAID) AND (keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (topical corticosteroids))

Artículos encontrados: 2
Artículos Seleccionados: 1
Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Topical Administration" AND "Corticosteroids" OR "NSAIDs"

Artículos encontrados: 65
Artículos Seleccionados: 1

Avunduk y colaboradores publicaron en 2003 un estudio en el cual 32 pacientes con keratoconjuntivitis Sicca con o sin SS, fueron aleatorizados en tres grupos: 1- Lagrimas Artificiales 2- Lagrimas Artificiales más Lagrimas con AINE´s y 3- Lagrimas Artificiales más Gotas con Corticoides. Se evaluaron síntomas subjetivos y objetivos con: Test de Schirmer Rosa de Bengala y Fluoresceina antes del tratamiento al día 15 y 30. También se utilizó citología de impresión. No hubo diferencias significativas en los grupos que adicionaron AINE´s y Corticoides[xv]. **NE: 4.**

Aragona y colaboradores publicaron en 2013[xvi], un estudio doble ciego, placebo controlado, aleatorizado, que incluyó 40 pacientes, que tuvo como objetivo evaluar la utilidad de clobetasona 0.1% en gotas para el tratamiento del ojo seco con pacientes con SS. El tratamiento fue por 30 días. Si bien se evaluo un cuestionario acerca de los sintomas, BUT, tincion conjuntival, citologia de impresion conjuntival para expresion de HLA-DR, solo se encontró una mejoría significativa respecto al basal respecto a los sintomas y de expresión de HLA- DR a los 30 dias de tratamiento. **NE: 3**

Pregunta 7- AINES Tópicos.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (topical NSAID)).

Artículos encontrados: 9

Artículos seleccionados: 3

Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Topical Administration" AND "NSAIDs"

Artículos encontrados: 60

Artículos seleccionados: 0

Aragona, y colaboradores publicaron en 2005 un estudio observacional, prospectivo, que tuvo como objetivo evaluar el efecto de dos AINES en la sensibilidad y superficie corneal (BUT, Fluoresceína y disconfort). un grupo de 10 mujeres (35-63 años) fueron tratadas con indometacina 0.1%, una gota en cada ojo, tres veces al día y otro grupo (nueve mujeres y un hombre de 38-65 años) fueron tratados con diclofecnac 0.1% con el mismo régimen. No se permitieron AINES sistémicos. Las evaluaciones se realizaron día cero, 15 y 30 de tratamiento y a los siete días de la discontinuación. Ambos grupos tuvieron reducción significativa de la sensibilidad corneal ($P<0.05$) al día 30 y el grupo que recibió diclofenac tuvo menor sensibilidad que indometacina ($P<0.05$). El Test de Fluoresceína empeoró significativamente en ambos grupos luego de la discontinuación. Desde el día 15 hubo mejoría significativa respecto al basal en ambos grupos respecto al discomfort ($P<0.05$)[xvii]. **NE: 4**

Avisar, R y colaboradores publicaron en 2000[xviii], un estudio aleatorizado en el que compararon la eficacia y seguridad a corto plazo de diclofecnac sódico 0.1% y solución cloruro de sodio 5% (hipertónica) en el tratamiento de la queratitis filamentaria en pacientes con ojo seco secundario a SS. Incluyeron 32 pacientes, 16 en cada grupo, el régimen de tratamiento fue una gota cuatro veces al día por 28 días. Al mes de evaluación los filamentos habían desaparecido en ambos grupos. No se reportaron eventos adversos. **NE: 4.**

Guidera y colaboradores publicaron en 2001[xix] una serie de casos retrospectiva en el que informaron la complicaciones en 18 ojos de 16 pacientes tratados con AINES tópicos (ketorolac y dos formulaciones de diclofenac). Reportan que tres pacientes tuvieron úlceras, seis queratitis y cinco perforación. Once pacientes tenían como antecedente cirugía de cataratas reciente, nueve de ellos además recibieron corticoides y antibióticos. Los potenciales riesgos que predisponen a la queratitis inducida por AINES parecen ser el uso concomitante de corticoides, cirugía reciente y la queratitis previa al inicio del tratamiento. **NE: 4.**

Pregunta 8- Ciclosporina tópica. Ciclosporina tópica vs Corticoesteroides tópicos. Ventajas uso concomitante vs aislado.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND topical cyclosporine) AND (keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (topical corticosteroids))

Artículos enocontrados: 8.
Artículos seleccionados: 3.

Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Topical Administration" AND "ciclosporin" OR "Topical Administration" AND "corticoisteroids"

Artículos enocontrados: 10.
Artículos seleccionados: 0.

Sall K. y colaboradores en el año 2000 publicaron un estudio randomizado multicéntrico para evaluar la eficacia y seguridad de emulsión oftálmica en ojo seco moderado/severo. El objetivo fue comparar eficacia y seguridad de ciclosporina A en dos dosis 0.05% y 0.1% en pacientes con ojo seco moderado/severo. Incluyeron un total de 877 pacientes en dos estudio multicéntricos, randomizados, doble ciego, comparado con placebo, de seis meses de duración. El 31% de los pacientes tenían SSp. En ambos grupos de tratamiento se observó una mejora significativa en el test de Schirmer comparado con placebo. En el resto de los test objetivos solo se vio mejoría

significativa en el grupo de Ciclosporina 0.05%, quienes además mostraron mejora en parámetros subjetivos como el discomfort y uso de lágrimas artificiales. Sólo el 0.8% (7/877) discontinuaron por falta de eficacia. No se reportaron eventos adversos serios, las dos infecciones oculares correspondían a pacientes en el grupo placebo[xx]. **NE: 2.**

En la revisión bibliográfica se encontraron además estudios observaciones como el de Dastjerdi M y colaboradores[xxi] y Barber LD y colaboradores[xxii] en los cuales continúan afirmando que la ciclosporina A tópica es un tratamiento eficaz y seguro para el ojo seco.

El resto de los artículos ya fueron citados.

Pregunta 9- Cevemeline.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (cevimeline))

Artículos encontrados: 8

Artículos seleccionados: 1

No se encontraron artículos en las búsquedas en Cochrane ni LILACs.

Petrone y colaboradores publicaron en 2002 un estudio aleatorizado, doble ciego, placebo controlado, de 12 semanas de duración, que tuvo como objetivo evaluar eficacia y seguridad de dos dosis de cevimeline (15 y 30mg tres veces al día vía oral) para el tratamiento de xerostomía y keratoconjuntivitis sicca en pacientes con SS. Se incluyeron 197 pacientes, los que recibieron la dosis de 30 mg tres veces al día tuvieron mejorías estadísticamente significativas en las mediciones subjetivas de ojo seco (p= 0.0453), boca seca (p=0.0004) y en mediciones objetivas, incremento del flujo salival (p=0.007), flujo lacrimal medido por Test de Schirmer. Los eventos adversos más frecuentemente reportados fueron: cefalea, dolor abdominal, transpiración y náuseas[xxiii]. **NE: 2**

Pregunta 10- N acetil cisteína tópica vs bromehexina sistémica en filamentos corneales. Ventajas uso concomitante vs aislado.

Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (N acetyl Cysteine topical OR corneal filaments Bromehexin))

No hay datos

Pregunta 11- Pilocarpina.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (lacrimal secretory stimulus) AND (systemic secretagogues OR systemic pilocarpine))

Artículos encontrados: 371

Artículos seleccionados: 2

Cochrane Search "Sjogren Syndrome" OR "Keratoconjunctivitis Sicca" AND "Pilocarpine"

Artículos encontrados: 64

Artículos seleccionados: 0

Aragona P y colaboradores publicaron en 2006 evaluaron el efecto de la pilocarpina oral sobre el epitelio conjuntival en pacientes con SSp. Incluyeron 15 pacientes en este estudio prospectivo, comparativo. Fueron evaluados previo al inicio, al mes, dos meses y 15 días de terminado el tratamiento. Se midieron síntomas subjetivos y objetivos oculares (BUT, Schirmer, Fluoresceína, Impronta conjuntival y test de secreción lagrimal basal). En sus resultados informaron que hubo un aumento en el número de la impronta celular, mejora en los síntomas subjetivos de ojo seco y el BUT a los dos meses de tratamiento[xxiv]. **NE: 4**

Papas y colaboradores realizaron un estudio multicéntrico, randomizado, doble ciego, placebo controlado para evaluar la seguridad y eficacia de pilocarpina en ojo y boca seca de pacientes con SSp. Incluyeron 256 pacientes que se aleatorizaron a recibir pilocarpina (dosis titulable 20-30mg/día) vs placebo. Se objetivo desde el día uno, un aumento en la secreción de saliva, mejoría en la evaluación global en el grupo tratamiento (*p:* <0.0001) que se mantuvo durante las 12 semanas de tratamiento. Respecto a la sequedad ocular, en el grupo de tratamiento se observó mejoría en tres de los ocho síntomas evaluados a partir de la semana seis y a la semana 12 se objetivo una mejoría significativa tanto en la evaluación global (*p:* <0.0001) como en seis de los ocho síntomas evaluados (*p:* 0.04). Los eventos adversos más frecuentemente observados son los comúnmente descriptos[xxv]. **NE: 3.**

El resto de los artículos no tienen como desenlace los test oculares.

Pregunta 12- Obstrucción canalicular con punctum plugs vs implantes intracanaliculares. 14 Oclusión canalicular vs gotas oftálmicas.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (intracanalicular implants OR obstruction with punctum plugs OR Canalicular obstruction with punctum plugs))

Artículos encontrados: 19.

Pub Med Search ((keratoconjunctivitis sicca OR keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND (intracanalicular implants OR obstruction with punctum plugs OR Canalicular obstruction with punctum plugs OR artificial lubricants))

Artículos encontrados: 170.

Artículos seleccionados: 7.

En las búsquedas realizadas en Cochrane y LILACs no se seleccionaron artículos.

Holzchuh R y colaboradores publicaron en 2011 una serie de casos en la cual evaluaron la influencia de la oclusión lagrimal parcial en la superficie del ojo seco en SSp. En este estudio evaluaron 37 ojos de 19 pacientes con keratoconjuntivitis sicca (16 mujeres, con una media de 49.1 años DS 14.2). Con anestesia local realizaron la cauterización térmica de los conductos lagrimales, obteniendo una oclusión parcial de menos de 0.5mm. Midieron Schirmer, BUT, diámetro lagrimal, Fluoresceína y Rosa de Bengala, previo, a las 24 semanas y a los 24 meses del procedimiento. La media de diámetro lagrimal previo al procedimiento fue de 0.65 ± 0.134 mm. Todos fueron satisfactoriamente reducidos a menos de 0.05mm. El Test de Schirmer tuvo una mejora estadísticamente significativa a las 24 semanas y se mantuvo estable a los 24 meses. BUT, Rosa de Bengala y Fluoresceína mejoraron después de las 24 semanas y esta fue mayor a los 24 meses[xxvi]. **NE: 4**

Mansour Ky colaboradores[xxvii] publicaron en 2007 un estudio observacional en el que evaluaron la eficacia a corto plazo de la oclusión lagrimal con tapón en pacientes con ojo seco por SSp. Incluyeron 20 pacientes con keratoconjuntivistis sicca severa causada por SSp y les realizaron la oclusión de los conductos lagrimales (superior e inferior) con tapón de un ojo, utilizando el otro ojo como control. Los pacientes continuaron utilizando su medicación habitual para ojo seco. Realizaron evaluaciones objetivas (como Test de Schirmer, Rosa de Bengala test) y subjetivos (discomfort) al inicio y a las seis semanas. Abandonaron el estudio siete pacientes, se analizaron 13. Se encontraron diferencias significativas a favor de la oclusión en el Test de Schirmer y Rosa de Bengala aunque no mejoró el componente mucoso de las lágrimas. Hubo mejoría en los síntomas subjetivos de discomfort[27]. **NE: 4.**

Egrilmez Sy colaboradores[xxviii] publicaron en 2003 una serie de casos en la que estudiaron la eficacia de del tapón SmartPlug™ en ojo seco de pacientes con SSp, en quienes persistían los síntomas a pesar del uso de lágrimas artificiales. Incluyeron 22 pacientes con diagnóstico de SSp con Test de Schirmer <5 mm sin anestesia. . Se realizaron mediciones objetivas (Schirmer, Verde de Lisamina y BUT) en la evaluación basal, al mes 1, 6 y 12 de la colocación del tapón SmartPlug™ en el canalículo lagrimal inferior de ambos ojos. Se encontraron diferencias significativas desde el mes de tratamiento en los test objetivos[28]. **NE: 4**

Dursun y colabaoradores[xxix], publicaron en 2003 una serie de casos con el objetivo de evaluar los cambios en la superficie ocular en pacientes con keratoconjuntivitis sicca luego de la oclusión lagrimal con tapones de silicona. Incluyeron 32 ojos de 18 pacientes quienes persistían con ojo seco a pesar del tratamiento médico y que presentaban resultados de test de Schirmer menor a 5mm. Realizaron evaluaciones previo al implante, a las seis semanas y al año. Objetivamente midieron citología de impresión de cuadrante temporal e inferior (graduadas por el método de Nelson), Schirmer, BUT, Fluoresceína, Rosa de Bengala y cuestionarios para mediciones subjetivas. Los síntomas subjetivos mejoraron a las seis semanas. Se encontró mejora significativa ya a las seis semanas post tratamiento. Se observó además un incremento global en la densidad celular estadísticamente significativa a las seis semanas y al año post tratamiento. La oclusión lagrimal mejora la estabilidad del film lagrimal[29]. **NE: 4.**

Sakamoto A y colaboradores[xxx] publicaron en 2004 un estudio observacional, comparativo, en el que evaluaron la eficacia y tiempo de retención de dos tipos de implantes de siliconas para oclusión lagrimal en pacientes con ojo seco con y sin SSp. Estudiaron 36 pacientes (17 SSp y 19 sin SSp) con keratoconjuntivitis sicca a quienes le colocaron dos tipos de tapones de silicona (Eagle Plugs o FCI Punctal Plugs). El 29% de los pacientes perdieron el tapón siendo más frecuente en Eagle Plus. Ambos tipos mejoraron el Test de Fluoresceína y Rosa de Bengala, aunque con una clara diferencia en la tasa de retención en el grupo de Punctal Plugs[30]. **NE: 4**

En el resto de los artículos se comentan las complicaciones de estos tratamientos. El SmartPlug Study Group publicó en 2006 una revisión de las complicaciones y su manejo[xxxi].

En un estudio publicado en 2010, Chen y colaboradores[xxxii], publicaron un estudio observacional, comparativo en el que evaluaron la oclusión lagrimal superior versus inferior en pacientes con ojo seco. Incluyeron 20 pacientes con ojo seco a quienes le ocluían el lagrimal superior de un ojo e inferior del otro con un tapón colágeno. Como comparador utilizaron 20 pacientes sin ojo seco a quienes le realizaron el mismo procedimiento. Realizaron mediciones objetivas y subjetivas. En los pacientes con ojo seco se observó una mejora significativa en ambos ojos, no encontrándose diferencias entre la oclusión superior o inferior[32]. **NE: 4.**

Qin W, Liu Z publicaron en 2013[xxxiii] un estudio observacional, comparativo, en el que evaluaron el efecto de la oclusión lagrimal versus el uso de lágrimas artificiales en 42 pacientes con SSp. Ambos tratamientos mejoraron el ojo seco[33]. **NE: 4.**

Pregunta 13- ¿El tratamiento con hidroxicloroquina mejora la keratoconjuntivitis sicca en pacientes con SSp?

((keratoconjunctivitis sicca secondary Primary Sjögren's syndrome) AND (hydroxycloroquine) AND (treatment))

Articulos encontrados: 0

((Primary Sjögren's syndrome) AND (hydroxycloroquine) AND (treatment))

Articulos encontrados: 45

Articulos seleccionados: 2

En las búsquedas realizadas en Cochrane y LILACs no se seleccionaron artículos.

Gottenberg y colaboradores[xxxiv] publicaron en 2014 un ensayo clínico multicéntrico, aleatorizado, placebo, controlado, que incluyó 120 pacientes, en el que evaluaron la eficacia de la hidroxicloroquina en el tratamiento de la sequedad, fatiga y dolor de los pacientes con SSp. Respecto a la sequedad, entre la semana cero y 24 el promedio de la escala análoga visual de sequedad (EVA) se modificó de 6.38 (2.14) a 5.85 (2.57) en el grupo placebo y 6.53 (1.97) a 6.22 (1.87) en el grupo de hidroxichoroquina. Las escalas de sequedad no se modificaron entre la semana 24 y 48 en los pacientes que se les prescribió hidroxicloroquina (fase abierta del estudio) y que previamente habían recibido placebo (N+ 64)[34]. **NE: 2**

Yavuz y colaboradores[xxxv] publicaron en 2011 una serie de casos que incluyó 32 pacientes, y que tuvo como objetivo evaluar la acción del tratamiento por 48 semanas con hidroxicloroquina en parámetros de medición subjetivos y objetivos de sequedad ocular. Se evaluaron los mismos parámetros luego de tres meses de suspensión del fármaco. A las 48 semanas de tratamiento no se observó mejoría del test de Schirmer. Hubo empeoramiento algunos de los parámetros de medición a los tres meses de suspensión del tratamiento[35]. **NE: 4**

Pregunta 14- ¿El tratamiento con agentes biológicos mejora la keratoconjuntivitos sicca en pacientes con SSp?

((keratoconjunctivitis sicca secondary Primary Sjögren's syndrome OR keratoconjunctivitis sicca secondary primary sicca syndrome) AND ((biologic agents))

Articulos encontrados: 11

Seleccionados: 0

((Primary Sjögren's syndrome) AND (biological agents) AND (treatment))

Articulos encontrados: 298.

Articulos seleccionados:

En las búsquedas realizadas en Cochrane y LILACs no se seleccionaron artículos.

Mariette y colaboradores[xxxvi] publicaron en 2015 una serie de 30 casos con SSp a quienes se les administró tratamiento con belimumab. Respecto a la sequedad, a la semana 28 de tratamiento el promedio de EVA disminuyo de 7.8 (1.8) a 6.2 (2.9) (p=0.0021). El flujo salival y el test de Schirmer no se modificaron con el tratamiento[36]. **NE: 4**

Meiners y colaboradores[xxxvii] publicaron en 2014 una serie de 15 pacientes con SSp quienes recibieron tratamiento con abatacept durante 24 semanas. Se observó mejoría significativa del ESSPRI, no así del test de Schirmer, ni del BUT[37]. **NE: 4**

Devauchelle-Pensec y colaboradores[xxxviii] publicaron en 2014 un estudio aleatorizado, placebo controlado, paciente e investigador ciego, farmacéutico no ciego, para evaluar la eficacia y seguridad de rituximab. Se incluyeron 120 pacientes con puntuaciones de 50 mm o superior en al menos dos de cuatro EVAs (actividad global, dolor, fatiga y sequedad), no encontrándose mejorías a las 24 semanas del tratamiento, en el EVA de sequedad, ni en el resto de las escalas mencionadas[38]. **NE: 2**

Meijer y colaboradores[xxxix] publicaron en 2010 un estudio doble ciego en el que 30 pacientes fueron aleatorizadas a recibir rituximab o placebo, respecto a la sequedad, se observó una mejoría estadísticamente significativa en comparación con el placebo. A su vez, en el grupo tratado con rituximab, se encontró en comparación con la medición basal, mejoría en la tinción ocular con verde de lisamina[39]. **NE: 3**

Bibliografía

[i] Cömez AT, Tufan HA, Kocabıyık O. Effects of lubricating agents with different osmolalities on tear osmolarity and other tear function tests in patients with dry eye. Curr Eye Res. 2013 Nov;38(11):1095-103.

[ii] Lee JH, Ahn HS, Kim EK. Efficacy of sodium hyaluronate and carboxymethylcellulose in treating mild to moderate dry eye disease. Cornea. 2011 Feb;30(2):175-9.

[iii] Troiano P y Monaco G. Effect of hypotonic 0.4% hyaluronic acid drops in dry eye patients: a cross-over study. Cornea. 2008 Dec;27(10):1126-30.

[iv] Wegener AR, Meyer LM, Schönfeld CL. Effect of Viscous Agents on Corneal Density in Dry Eye Disease. J Ocul Pharmacol Ther. 2015 Jun 23.

[v] Aragona P, Papa V, Micali A. Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. Br J Ophthalmol 2002;86:181–184.

[vi] Ostuni P, Battista A, Furlan A. Efficacy of Carbopol 974P (Siccafluid) in the treatment of severe to moderate

keratoconjunctivitis sicca (KCS) in patients with primary Sjögren's syndrome (SS) not responding to standard treatment with artificial tears. Reumatismo. 2005 Apr-Jun;57(2):119-24.

[vii] Schrell C, Cursiefen C, Kruse F. Topical cyclosporine a 0.05% in the treatment of keratoconjunctivitis sicca. Klin Monbl Augenheilkd. 2012 May;229(5):548-53.

[viii] Stonecipher K, Perry HD, Gross RH. The impact of topical cyclosporine A emulsion 0.05% on the outcomes of patients with keratoconjunctivitis sicca. Curr Med Res Opin. 2005 Jul;21(7):1057-63.

[ix] Devecı H y Kobak S. The efficacy of topical 0.05 % cyclosporine A in patients with dry eye disease associated with Sjögren'ssyndrome. Int Ophthalmol. 2014 Oct;34(5):1043-8.

[x] Comparison of autologous serum eye drops with conventional therapy in a randomised controlled crossover trial for ocular surface disease. Br J Ophthalmol. 2004 May;88(5):647-52.

[xi] Fox RI, Chan R, Michelson JB. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. Arthritis Rheum. 1984 Apr;27(4):459-61.

[xii] Hong S, Kim T, Chung SH. Recurrence after topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren's syndrome. J Ocul Pharmacol Ther. 2007 Feb;23(1):78-82.

[xiii] Sainz de la Maza Serra M, Castellvi C, Kabbani O. Nonpreserved topical steroids

and lacrimal punctal occlusion for severe keratoconjunctivitis sicca. Arch Soc Esp Oftalmol. 2000 Nov;75(11):751-756.

[xiv] Marsh P y Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren syndrome. Ophthalmology. 1999 Apr;106(4):811-6.

[xv] Avunduk AM, Avunduk MC, Varnell ED. The comparison of efficacies of topical corticosteroids and nonsteroidal anti-inflammatory drops on dry eye patients: a clinical and immunocytochemical study. Am J Ophthalmol. 2003 Oct;136(4):593-602.

[xvi] Pasquale Aragona, Rosaria Spinella, Laura Rania, et al. Safety and efficacy of 0.1% clobetasone butyrate eyedrops in the treatment of dry eye in Sjögren syndrome. Eur J Ophthalmol 2013; 23(3): 368 – 376.

[xvii] Aragona P, Stilo A, Ferreri F. Effects of the topical treatment with NSAIDs on corneal sensitivity and ocular surface of Sjögren's syndrome patients. Eye (Lond.) 19, 535–539 (2005).

[xviii] Avisar R, Robinson A, Appel I. Diclofenac Sodium, 0.1% (Voltaren Ophtha), Versus Sodium Chloride, 5%, in the Treatment of Filamentary Keratitis. Cornea 19, 145–147 (2000).

[xix] Guidera AC, Luchs JI, Udell IJ. Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs.Ophthalmology 108, 936–944 (2001).

[xx] Sall K, Stevenson DO, Mundorf TK. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. Ophthalmology Volume 107, Issue 4, Pages 631–639, April 2000.

[xxi] Dastjerdi M, Hamrah P, Reza D. High-frequency Topical Cyclosporine 0.05% in the Treatment of Severe Dry Eye Refractory to Twice-daily Regimen. Cornea. 2009 Dec; 28(10): 1091–1096.

[xxii] Barber LD, Pflugfelder SC, Tauber J. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years.Ophthalmology. 2005 Oct;112(10):1790-4

[xxiii] Petrone D, Condemi JJ, Fife R. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum. 2002 Mar;46(3):748-54.

[xxiv] Aragona P, Spinella R. Conjunctival epithelium improvement after systemic pilocarpine in patients with Sjogren's syndrome. Br J Ophthalmol. 2006 Feb;90(2):166-70.

[xxv] Papas A, Sherrer YS, Charney M. Successful Treatment of Dry Mouth and Dry Eye Symptoms in Sjögren's Syndrome Patients With Oral Pilocarpine: A Randomized, Placebo-Controlled, Dose-Adjustment Study. J. Clin. Rheumatol. 10, 169–177 (2004).

[xxvi] Holzchuh R, Villa Albers MB, Osaki TH. Two-year outcome of partial lacrimal punctal occlusion in the management of dry eye related to Sjögren syndrome. Curr Eye Res. 2011 Jun;36(6):507-12.

[xxvii] , Leonhardt CJ, Kalk WW. Lacrimal punctum occlusion in the treatment of severe keratoconjunctivitis Sicca caused by Sjögren syndrome: a uniocular evaluation. Cornea. 2007 Feb;26(2):147-50.

[xxviii] Egrilmez S, Aslan F, Karabulut G.Clinical efficacy of the SmartPlug™ in the treatment of primary Sjogren's syndrome with keratoconjunctivitis sicca: one-year follow-up study. Rheumatol Int. 2011 Dec;31(12):1567-70. Epub 2010 May 21.
[xxix] Dursun D, Ertan A, Bilezikçi B.Ocular surface changes in keratoconjunctivitis sicca with silicone punctum plug occlusion. Curr Eye Res. 2003 May;26(5):263-9.
[xxx] Sakamoto A, Kitagawa K, Tatami A. Efficacy and retention rate of two types of silicone punctal plugs in patients with and without Sjögren syndrome. Cornea. 2004 Apr;23(3):249-54.
[xxxi] SmartPlug Study Group. Management of complications after insertion of the SmartPlug punctal plug: a study of 28 patients.Ophthalmology. 2006 Oct;113(10):1859 22.
[xxxii] Chen F, Wang J, Chen W. Upper punctal occlusion versus lower punctal occlusion in dry eye. Invest Ophthalmol Vis Sci. 2010 Nov;51(11):5571-7. Epub 2010.
[xxxiii] Qiu W, Liu Z, Ao M. Punctal plugs versus artificial tears for treating primary Sjögren síndrome with keratoconjunctivitis SICCA: a comparative observation of their effects on visual function. Rheumatol Int. 2013 Oct;33(10):2543-8. Epub 2013 May 7.
[xxxiv] Gottenberg JE, Ravaud P, Puéchal X. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA. 2014 Jul 16;312(3):249-58.

[xxxv] Yavuz S, Asfuroğlu E, Bicakcigil M. Hydroxychloroquine improves dry eye symptoms of patients with primary Sjogren's syndrome. Rheumatol Int. 2011 Aug;31(8):1045-9.

[xxxvi] Mariette, Raphaèle Seror, Luca Quartuccio. Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis 2015;74:526-531
[xxxvii] Meiners PM, Vissink A, Kroese FG. Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis. 2014 Jul;73(7):1393-6.

[xxxviii] Devauchelle-Pensec V, Mariette X, Jousse-Joulin S. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med. 2014 Feb 18; 160 (4): 233-42.

[xxxix] Meijer JM, Meiners PM, Vissink A. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010 Apr;62(4):960-8.

XEROSTOMÍA - TRATAMIENTO

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Pregunta 1- Los Sustitutos de la saliva, Anetholetrithione, bromhexina, cevimeline, pilocarpina, xilitol, ¿mejoran la xerostomía en Síndrome de Sjögren primario (SSp)?

Términos: Sjogren's syndrome, xerostomia, treatment, drugs, Hyposalivation, salivary substitutes, sicca syndrome

RESULTADOS

- *Pilocarpina*

Resultados

PudMed: 28

Cocharane:4

Lilac: 3

Seleccionado 2 (PudMed)

Vivino y colaboradores publicaron en 1999 un ensayo clínico aleatorizado, multicéntrico, placebo controlado, doble ciego, que tuvo como objetivo evaluar la seguridad y eficacia de la pilocarpina en comprimidos como tratamiento sintomático para la boca seca y ojo seco causados por el SS. Se incluyeron 373 pacientes con SSp o SS secundario, que fueron aleatorizados a recibir 2,5 mg de pilocarpina, 5 mg de pilocarpina, o comprimidos de placebo 4 veces al día durante 12 semanas. Los síntomas se evaluaron en escalas visual análoga (EVA) y cuestionarios. Se midió la tasa de flujo salival. Como resultado, una proporción significativamente mayor de pacientes en el grupo de pilocarpina 5 mg mostró una mejoría en comparación con el grupo placebo (P <0,01) en las evaluaciones globales de xerostomía, xeroftalmia y otros síntomas de sequedad (P <0.05). El flujo salival aumentó significativamente de 2 a 3 veces (P <0,001) después de la administración de la primera dosis y se mantuvo durante todo el estudio de 12 semanas. El efecto adverso más común fue la sudoración, y no se reportaron eventos adversos graves relacionados con las drogas [(1)]. NE: 2

- *Cevimeline*

Resultados

PudMed: 4

Cocharane:o

Lilac: 0

Seleccionado 4

Noaiseh y colaboradores publicaron en 2014 un estudio de cohorte retrospectiva que tuvo como objetivo comparar el perfil de tolerabilidad y efectos secundarios de la pilocarpina y cevimeline en pacientes con SSp. Se definió falla al tratamiento a la decisión de suspensión de la medicación por el médico o el paciente, ya sea por falta de mejoría clínica como por efectos adversos. Se incluyeron 118 pacientes con SSp que cumplían los criterios Americano europeos 2002, 59 recibieron como terapia inicial pilocarpina y 59 cevimeline. Cevimeline se asoció con menores tasas de fracaso en comparación con pilocarpina como primera droga utilizada (27% versus 47%, *p*: 0.02), al igual que al considerar la utilización de la droga ya sea como primera indicación o al ser indicada posterior a la falla de la otra (32% versus 61%,p <0.001). La sudoración severa fue la causa más frecuente de suspensión de ambos tratamientos y ocurrió más frecuentemente en el grupo de pilocarpina (25%versus11%, p: 0.02). Fue menos frecuente la discontinuación de un segundo secretagogos, cuando hubo falla al primero (52% versus 27%, p: 0.004) [(2)]. NE: 3

Leung y colaboradores publicaron en 2008 un estudio doble ciego, controlado con placebo, en el cual los pacientes fueron aleatorizados, a recibir cevimeline 30 mg o placebo, tres veces al día durante diez semanas, seguido de un período de lavado de cuatro semanas antes del cruce de rama de tratamiento. Los participantes completaron los siguientes cuestionarios: Inventario La xerostomía (XI), el Índice General de Evaluación de Salud Oral (GOHAI), Índice de Enfermedades de la superficie ocular (IESO) y el Cuestionario de calidad de vida (SF-36). Las evaluaciones clínicas incluyeron sialometría, el examen de la cavidad oral para evaluar la xerostomía y complicaciones dentales de la xerostomía. Se incluyeron cincuenta pacientes (22 SSp y 28 SS secundario) de los cuales 44 completaron el estudio. Hubo una mejora significativa en XI y GOHAI así como los signos xerostómicos de la cavidad oral después del tratamiento con cevimeline. Sin embargo, no hubo una mejora en las tasas de flujo salival y síntomas de ojo seco. La calidad de vida evaluada por SF-36, no mejoró después del tratamiento con cevimeline.[(3)]. NE: 3

Fife y colaboradores publicaron en el 2002 un estudio multicéntrico, doble ciego, placebo controlado y aleatorizado. El objetivo fue evaluar la eficacia y seguridad de cevilemine en el tratamiento de la xerostomía en pacientes con SSp y SS secundario. Se incluyeron 75 pacientes y completaron el estudio 61 de ellos. Los pacientes fueron aleatorizados a recibir 30 mg de cevimeline tres veces al día, 60 mg tres veces al día, o placebo por seis semanas. Se evaluó EVA del paciente para evaluar la xerostomía y medición de flujo salival. Los pacientes en ambas ramas de tratamiento con cevilemine, presentaron mejoría significativa de la sequedad oral, tanto en la

evaluación por EVA como de flujo salival y disminución en el uso de saliva artificial. Los eventos adversos más frecuentes fueron los gastrointestinales, especialmente nauseas, y fueron más frecuentes en la rama de 60 mg tres veces al día. Se plantea a la dosis de 30 mg tres veces al día como la mejor opción terapéutica.[4]. NE: 3

Petrone y colaboradores publicaron en 2002 un estudio doble ciego, aleatorizado, placebo controlado de 12 semanas de duración, que incluyo 197 pacientes con SSp o SS secundario, para evaluar la eficacia y seguridad de cevilemine para el tratamiento de la xerostomía y la keratoconjuntivitis sicca. Los pacientes fueron aleatorizados a recibir 15 mg de cevilemine tres veces al día, 30 mg tres veces al día o placebo. Se evaluó EVA global de sequedad por el paciente, así como EVA especifico de xerostomía y xeroftalmia, así como medición de flujo de secreción salival y lagrimal. Los pacientes en la rama de tratamiento con dosis de 30 mg tres veces al día presentaron mejoría significativa en los tres EVAs, en el flujo salival y lagrimal [5]. NE: 2

- *Bromhexina*

Resultados

Pudmed 4

Lilac 0

Cochrane :0

Seleccionado 1-

Fossaluzza y colaboradores publicaron en 1984 una serie de 11 pacientes con SS tratados con bromhexina, en el cual se observó mejoría en la secreción lagrimal en siete casos y en la secreción de saliva en cuatro.[6]. NE: 4

Anetholetrithione

Resultados

Pud med: 1

Cochrane:0

Lilac: 0

NE: 4

Malmstron y colaboradores publicaron en 1988 una serie de casos que incluyó 25 pacientes con sospecha de SS. 11 de dichos pacientes (diez de ellos con SS confirmado) recibieron tratamiento con Sulfarlem (trithioparamethoxyphenylpropene), además de cuatro pacientes con xerostomía de etiología no aclarada y dos pacientes con xerostomía. Un solo paciente con SS refirió mejoría de los síntomas [7]. NE: 4

- *Xilitol*

Resultados

PudMed: 3

Cocharane:1

Lilac: 3

Seleccionado 1(PudMed)

Alpoz y colaboradores publicaron en 2008 un estudio simple ciego, que tuvo como objetivo estudiar la respuesta al tratamiento con xialine versus placebo. Se incluyeron veintinueve pacientes con SS. Durante los 14 dias de tratamiento, no se encontraron diferencias significativas entre el placebo y el tratamiento con xialine respecto a la sensación de ardor en lengua, disminución de gusto e ingesta nocturna de líquido. Sin embargo, los pacientes prefirieron el tratamiento con xialine versus placebo (p: 0.011) [8]. NE: 3

Pregunta 2- Los hidratantes bucales, ¿mejoran la xerostomía y sus consecuencias como caries enfermedad periodontal y perdida de elementos dentarios, en pacientes con Síndrome de Sjögren?

Se realizó busqueda bibliografica en
1. PubMed
2. Cochrane
3.lilacs
Términos: Sjogren's syndrome, xerostomia, treatment, hydrating mouth

Resultados
Pud med: 5
Cochrane 2
Lilac: 0
Seleccinado 1

Furness y colaboradores publicaron en 2011 una revisión sistemática que incluyo 36 estudios, aleatorizados y controlados, incluyendo 1597 pacientes con xerostomía, que evaluaron diferentes terapias tópicas para el tratamiento de la xerostomía. De ellos, nueve de los estudios compararon sustitutos salivales con placebo, cinco estudios compararon directamente a los sustitutos salivales con estimulantes de la producción de saliva. Solo un estudio presentaba bajo riesgo de sesgo y 17 tenian un alto riesgo. Dada la heterogeneidad de los estudios, fue posible realizar meta análisis solo con pocas intervenciones. El sustituto salival de glicerol oxigenado en spray mostro ser efectivo en comparación con un spray de electrolitos (diferencia de medias standarizada: 0.77. IC 95%: 0.38- 1.15). La goma de mascar se asoció con un aumento en la producción de saliva, pero no se encontró evidencia que muestre mayor o menor efectividad que los sustitutos salivales.[9] NE: 2

Pregunta 3- Las dietas hidratantes, ¿están indicadas para aliviar la xerostomía en pacientes con Síndrome de Sjögren?

Resultados

Se realizó búsqueda bibliográfica en
1. PubMed
2. Cochrane
3.lilacs

Términos: Sjögren's syndrome, xerostomia, treatment, Hyposalivation, hydrating diet.
Pud med: 2
Cochrane 0
Lilac: 0
Seleccionado 1

De Rossi y colaboradores publicaron en 2014 un estudio aleatorizado, placebo controlado, doble ciego, que tuvo como objetivo evaluar una formulación natural que contiene catequinas del té (Camellia sinensis) en 60 pacientes con xerostomía, incluyendo pacientes con SS.El placebo contenía todos los ingredientes de la formulación natural y 500 mg xilitol, pero sin los extractos principales de la planta. Luego de ocho semanas de tratamiento, el placebo no mejoro la producción de saliva, mientras que la formulación con catequinas mostro un aumento estadísticamente significativo en el flujo salival no estimulado (3, 8 veces) y estimulados (2,1 veces) La puntuación de calidad de vida mostró una mejora significativa en ambos grupos, pero no hubo diferencia significativa entre ellos.[10]. NE: 3

Pregunta 4- Los fármacos inmunomoduladores o inmunosupresores, ¿recuperan la xerostomía en el SSp? Corticoides, hidroxicloroquina, talidomida, ciclosporina, metotrexato, azatioprina, micofenolato, leflunomida.

Se realizó una búsqueda bibliográfica en

Resultados
1. PubMed

2. Cochrane

3. Lilacs

Términos: Sjogren's syndrome, xerostomia, treatment, drugs, immunosuppressants, sicca syndrome.

Pud med: 1

Cochrane 0

Lilac: 0

Gottenberg y colaboradores publicaron en 2014 un ensayo clínico multicentrico, aleatorizado, placebo, controlado, que incluyo 120 pacientes, en el que evaluaron la eficacia de la hidroxicloroquina en el tratamiento de la sequedad, fatiga y dolor de los pacientes con SSp. Respecto a la sequedad, entre la semana 0 y 24 el promedio de la

escala analogo visual de sequedad (EVA) se modificó de 6.38 (2.14) a 5.85 (2.57) en el grupo placebo y 6.53 (1.97) a 6.22 (1.87) en el grupo de hidroxichoroquina. Las escalas de sequedad no se modificaron entre la semana 24 y 48 en los pacientes que se les prescribió hidroxicloroquina (fase abierta del estudio) y que previamente habían recibido placebo (N+ 64) [11]. NE: 2

Pregunta 5- Los fármacos biológicos, ¿recuperan la xerostomía en el SSp? anti TNF, rituximab, anti BLISS, anti CD 20, abatacept.

Se realizó una búsqueda bibliográfica en
1. PubMed

2. Cochrane

3.Lilacs

Términos: Sjogren's syndrome, xerostomia, treatment, drugs, biological.

RESULTADOS

Pud med: 4

Cochrane 0

Lilac: 0

Devauchelle-Pensec y colaboradores publicaron en 2014 un estudio aleatorizado, placebo controlado, paciente e investigador ciegos (farmacéutico no ciego), para evaluar la eficacia y seguridad de rituximab. Se incluyeron 120 pacientes con puntuaciones de 50 mm o superior en al menos dos de cuatro EVAs (actividad global, dolor, fatiga y sequedad), no encontrándose mejorías a las 24 semanas del tratamiento, en el EVA de sequedad, ni en el resto de las escalas mencionadas.[12]. NE: 2

Meijer y colaboradores publicaron en 2010 un estudio doble ciego en el que 30 pacientes fueron aleatorizadas a recibir rituximab o placebo, respecto a la sequedad, se observó una mejoría estadísticamente significativa en comparación con el placebo. A su vez, en el grupo tratado con rituximab, se encontró en comparación con la medición basal, mejoría en la tinción ocular con verde de lisamina.[13]. NE: 3

Adler y colaboradores publicaron en 2013 una serie de casos que tuvo como objetivo evaluar prospectivamente los cambios histopatológicos, serológicos y clínicos en respuesta al tratamiento con abatacept en pacientes con SSp. La sangre, la saliva y muestras de biopsia de las glándulas salivares menores se obtuvieron antes y después de ocho dosis de abatacept en 11 pacientes con SSp. Se evaluaron el número de focos linfocítica y células B y subtipos T (CD20, CD3, CD4 y CD8) en la histología. Estos datos se compararon con los resultados en sangre periférica y con los cambios en la secreción de saliva. El número de focos linfocíticos disminuyeron significativamente con el tratamiento (P: 0,041). Las células T disminuyeron de manera significativa en el porcentaje de infiltrado linfocitario totales (p 0,037). En la sangre

periférica, las células B aumentaron (P 0,038). También se observó un aumento de los linfocitos totales (p 0,044) y las células CD4 (P 0,009) al ajustar por el tiempo de evolución de la enfermedad. Las gammaglobulinas disminuyeron significativamente (P 0,005), pero la reducción de IgG no alcanzó significación. Ajustado a la duración de la enfermedad, la producción de saliva aumento significativamente con el tratamiento (P 0,029) [(14)]. NE: 4

Meiners y colaboradores publicaron en 2014 una serie de 15 pacientes con SSp a quienes recibieron tratamiento con abatacept durante 24 semanas. Se observó mejoría significativa del ESSPRI, no así del test de Schirmer, ni del BUT [(15)].NE: 4

Mariette y colaboradores publicaron en 2015 una serie de 30 casos con SSp a quienes se les administro tratamiento con belimumab. Respecto a la sequedad, a la semana 28 de tratamiento, el promedio de EVA disminuyo de 7.8 (1.8) a 6.2 (2.9) (p=0.0021). El flujo salival y el test de Schirmer no se modificaron con el tratamiento [(16)]. NE: 4

BIBLIOGRAFÍA

1 -Vivino FB[1], Al-Hashimi I, Khan Z, LeVeque FG, Salisbury PL 3rd, Tran-Johnson TK, Muscoplat CC, Trivedi M, Goldlust B, Gallagher SC. "Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group." Arch Intern Med. 1999 Jan 25;159(2):174-81.

2. Noaiseh G1, Baker JF, Vivino FB "Comparison of the discontinuation rates and side-effect profiles of pilocarpine and cevimeline for xerostomia in primary Sjögren's syndrome." Clin Exp Rheumatol. 2014 Jul-Aug;32(4):575-7.

3- Leung KC1, McMillan AS, Wong MC, Leung WK, Mok MY, Lau CS. "The efficacy of cevimeline hydrochloride in the treatment of xerostomia in Sjögren's syndrome in southern Chinese patients: a randomised double-blind, placebo-controlled crossover study." Clin Rheumatol. 2008 Apr;27(4):429-36.

4. Fife RS[1], Chase WF, Dore RK, Wiesenhutter CW, Lockhart PB, Tindall E, Suen JY "Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial.". Arch Intern Med. 2002 Jun 10;162(11):1293-300.

5. Dianne Petrone, John J. Condemi, Rose Fife, Oscar Gluck, Stanley Cohen,and Paul Dalgin. "A Double-Blind, Randomized, Placebo-Controlled Study of Cevimeline in Sjo¨gren's Syndrome Patients With Xerostomia and Keratoconjunctivitis Sicca." ARTHRITIS & RHEUMATISM. Vol. 46, No. 3, March 2002, pp 748–754

6. Fossaluzza V. Klin Monbl Augenheilkd. Bromhexine in symptomatic treatment of Sjögren syndrome.[Article in German] . 1984 Oct;185(4):292-5.

7. Malmström MJ1, Segerberg-Konttinen M, Tuominen TS, Hietanen JH, Wolf JE, Sane JI, Konttinen YT. “Xerostomia due to Sjögren's syndrome. Diagnostic criteria, treatment and outlines for a continuous dental care programme and an open trial with Sulfarlem.” Scand J Rheumatol. 1988;17(2):77-86.

8. Alpöz E1, Güneri P, Onder G, Cankaya H, Kabasakal Y, Köse T. “The efficacy of Xialine in patients with Sjögren's syndrome: a single-blind, cross-over study.” Clin Oral Investig. 2008 Jun;12(2):165-72.

9.Intervenciones para el tratamiento de la sequedad en la boca: terapias tópicas. Furness S, Worthington HV, Bryan G, Birchenough S, Base de Datos Cochrane R. McMillan Syst Rev. 2011

10. De Rossi SS1, Thoppay J2, Dickinson DP3, Looney S1, Stuart M4, Ogbureke KU5, Hsu S6. “A phase II clinical trial of a natural formulation containing tea catechins for xerostomia.” Oral Surg Oral Med Oral Pathol Oral Radiol. 2014 Oct;118(4):447-454.

11. Jacques-Eric Gottenberg, MD, PhD; Philippe Ravaud, MD, PhD; Xavier Puéchal, MD, PhD; Véronique Le Guern “Effects of Hydroxychloroquine on Symptomatic Improvement in Primary Sjögren Syndrome The JOQUER Randomized Clinical Trial” JAMA. 2014;312(3):249-258.

12. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Puéchal X, Le Guern V, Sibilia J, Gottenberg JE, Chiche L, Hachulla E, Hatron PY, Goeb V, Hayem G, Morel J, Zarnitsky C, Dubost JJ, Pers JO, Nowak E, Saraux A. “Treatment of primary Sjögren syndrome with rituximab: a randomized trial.” Ann Intern Med. 2014 Feb 18;160(4):233-42.

13. Meijer JM1, Meiners PM, Vissink A, Spijkervet FK, Abdulahad W, Kamminga N, Brouwer E, Kallenberg CG, Bootsma H. “Effectiveness of rituximab treatment in

primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial." Arthritis Rheum. 2010 Apr;62(4):960-8.

14. Adler S, Körner M, Förger F, Huscher D, Caversaccio MD, Villiger PM "Evaluation of histologic, serologic, and clinical changes in response to abatacept treatment of primary Sjögren's syndrome: a pilot study." Arthritis Care Res (Hoboken). 2013 Nov;65(11):1862-8.

15. Meiners PM, Vissink A, Kroese FG, Spijkervet FK, Smitt-Kamminga NS, Abdulahad WH, Bulthuis-Kuiper J, Brouwer E, Arends S, Bootsma H. "Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study)."Ann Rheum Dis. 2014 Jul;73(7):1393-6.

16. Mariette X, Seror R, Quartuccio L, Baron G, Salvin S, Fabris M, Desmoulins F, Nocturne G, Ravaud P, De Vita S." Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study."Ann Rheum Dis. 2015 Mar;74(3):526-31

DIAGNÓSTICO Y TRATAMIENTO DE LAS MANIFESTACIONES MÚSCULO-ESQUELÉTICAS DEL SÍNDROME DE SJÖGREN PRIMARIO

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Pregunta 1- ¿En pacientes con Síndrome de Sjögren Primario (SSp) y artritis, es de utilidad el dosaje de anticuerpos anticitrulinas (anti-CCP) para el diagnóstico diferencial con artritis reumatoidea?

Se utilizaron los términos ((Primary Sjogren Syndrome) AND (arthritis) AND (anti-cyclic citrullinated peptide antibod))

Se encontraron 20 artículos a través de búsqueda en Pubmed. Se excluyeron 15 artículos por título/ abstract/review. Se seleccionaron 5 artículos.

Se realizó otra búsqueda con los términos ((Primary Sjogren Syndrome) AND (arthritis) AND (no anti-cyclic citrullinated peptide antibod))

Esta búsqueda arrojó 25 artículos de los cuales se descartaron 20 por título/ abstract/review. Cuatro estaban duplicados. Se incluyó 1 artículo más en el análisis

La misma búsqueda por LILCS identificó 12 artículos, 6 se descartaron por título/abstract/review los otros 6 estaban duplicados.

A través de Cochrane se identificaron 6 artículos que fueron descartados por título/abstract/review.

Kim y colaboradores publicaron en 2012 un estudio de corte transversal, cuyo objetivo fue determinar la prevalencia de anti-CCP en SSp y su significado clínico. Se analizaron 95 pacientes con SSp. Se analizaron las características clínicas y de laboratorio de los pacientes anti-CCP positivos. Veintiún pacientes fueron anti-CCP positivos (22,1%) y 40 pacientes fueron factor reumatoideo (FR) positivos (42,1%). Setenta y nueve pacientes tenían artralgias (83,1%) y 31 (32,6%) artritis no erosiva en el examen físico y estudios por imágenes. Los pacientes anti-CCP positivos tuvieron con más frecuencia positividad para FR y anti-Ro (p: 0.01 y 0.03 respectivamente), así como artritis no erosiva con mayor frecuencia que los anti-CCP negativos (76,1% vs 21,6% p<0,01) [(1)] **NE: 4**

Atzeni y colaboradores publicaron en 2008 un estudio de corte transversal, que tuvo como objetivo investigar la prevalencia de anti- CCP en pacientes con SSp y su relación con datos clínicos y de laboratorio. Se analizaron datos clínicos y de laboratorio de 141 pacientes con SSp. Se evaluó la presencia de sinovitis y compromiso extraglandular. Catorce pacientes (9,9%) tenían niveles elevados de anti-CCP y 94 (66,7%) fueron positivos para FR. Ochenta y uno tenían compromiso extraglandular (57,4%) y 44 (31,2%) tuvo sinovitis sin signos radiográficos de erosión. Hubo asociación entre la presencia de anti-CCP y sinovitis (p<0,001) pero no asociación entre anti-CCP y compromiso extraglandular (p=0,77). En el análisis multivariado se confirmó esta asociación. En conclusión sólo una minoría de pacientes con SSp fueron anti-CCP positivos, éstos se vieron significativamente asociados a presencia de sinovitis [(2)]**. NE: 4**

Gottenberg y colaboradores publicaron en 2005 un estudio de corte transversal, cuyo objetivo fue investigar la prevalencia de anti-CCP y anticuerpos anti-keratina (AKA) en pacientes con SSp. Se investigó la presencia de anti CCP y AKA en 149 pacientes con diagnóstico de SSp. Además se evaluaron al mismo tiempo las radiografías de manos y pies. Quince pacientes tenían AR y 134 tenían SSp. De éstos; 80 (59%) fueron FR positivos, diez (7,5%) anti-CCP, y siete (5,2%) AKA positivos. Cinco (3,7%) fueron anti-CCP y AKA positivos. No hubo diferencias clínicas ni de laboratorio entre los pacientes anti-CCP positivos y negativos [(3)]**. NE: 4**

Ryu y colaboradores publicaron en 2013 un estudio que tuvo como objetivo evaluar las características y el significado clínico de los anti CCP en pacientes. A su vez se analizó la progresión a artritis reumatoidea (AR). Mientras que el diseño que respondió al objetivo principal del estudio fue de corte transversal; el diseño que respondió a este último análisis fue de cohorte retrospectiva. Se evaluaron las características clínicas de 405 pacientes en los que se diagnosticó SSp en la primera visita. De éstos, 171 presentaron artralgias en el período de seguimiento. Se realizó dosaje de anti CCP en 128 pacientes, en 38 el resultado fue positivo y en 190 negativo. Comparando los pacientes seropositivos con los negativos, 32 (84,2 %) versus 98 (51,5 %) (p<0,01) presentaban artralgias, y 28 (73,6 %) versus 33 (17,3 %) (p< 0,01) artritis. Después de 60 meses (rango 7-98), 23 pacientes anti CCP positivos (52,6 %) versus cero paciente anti CCP negativo (0 %) (p< 0,01) progresaron a AR según criterios ACR 2010. En el análisis multivariado, ajustado por edad, FR, eritrosedimentación y proteína C reactiva, la presencia de anti CCP se asoció independiente y significativamente con el desarrollo de AR (OR: 2,5. IC 95 %: 1,7–3,7) [(4)]. **NE: 2**

Barcelos y colaboradores publicaron en 2009 un estudio de corte transversal, que tuvo como objetivo evaluar la prevalencia y significado clínico de los anticuerpos anti- CCP, FR IgM e IgA en SSp. Se compararon las características clínicas y serológicas de 31

pacientes con SSp y 31 con AR. Nueve (29%) pacientes con SSp tenían artritis, y diez (32,3%) de los pacientes con AR tenían SS secundario. La prevalencia de FR fue similar en SSp y AR, sin embargo los pacientes con AR con FR positivos fueron principalmente los que tenían SS secundario. Los anti-CCP se detectaron en el 64,5% de los pacientes con AR y en 6,9% con SSp (p<0,0005). Los anti-CCP fueron principalmente positivos en pacientes con AR y SS secundario (8 pacientes 80%) y menos frecuentes en pacientes con AR sin SS secundario (18 pacientes 58,1%). No hubo pacientes con SS primario con artritis con anti-CCP positivo [(5)]. **NE: 4**

Mohammed y colaboradores publicaron en 2009 un estudio de casos y controles que tuvo como objetivo evaluar las características clínicas, serológicas, y los antígenos clase II MHC en un grupo de pacientes con SSp y artritis severa. Se incluyeron 35 pacientes con SSp, y se compararon aquellos pacientes con SSp que presentaban artritis inflamatoria (casos. N: 17) con aquellos sin artritis (controles. N: 18). Todos los pacientes cumplían con los criterios de SSp. No hubo diferencias en las características demográficas o clínicas entre ambos grupos. Todos los pacientes tenían anticuerpos anti-Ro/SSA, la mayoría tenía anticuerpos anti-La / SSB, y un alto porcentaje de estos pacientes presentaban anticuerpos anti-CCP, los cuales estaban ausentes en aquellos sin artritis inflamatoria. La tipificación del HLA reveló que la mayoría de los pacientes con anticuerpos anti-CCP expresaron moléculas de clase II MHC con el epítope compartido (SE) [(6)]**. NE: 4**

Pregunta 2- ¿Los pacientes con SSp y artritis, tienen anticuerpos anti Ro y anti La con mayor frecuencia que aquellos que no tienen compromiso articular?

Se realizó una búsqueda en PUBMED con los términos ((Primary Sjogren síndrome) AND (arthritis) AND (Ro) AND (La))

Se encontraron 70 artículos, 68 se excluyeron por título /abstract/review, 1 artículo fue no recuperable. Se incluyó sólo 1 artículo.

Se realizó otra búsqueda con los términos ((Primary Sjogren síndrome) AND (arthritis) AND (SSA) AND (SSB))

Se encontraron 218 artículos, se excluyeron 217 por título/abstract/review; el artículo revisado en su totalidad carecía de datos suficientes para ser incluido.

Borg y colaboradores publicaron en 2011 un estudio retrospectivo, longitudinal, cuyo objetivo fue investigar la prevalencia de manifestaciones extraglandulares en pacientes con SSp atendidos en un hospital de los Países Bajos, y definir si estas manifestaciones se correlacionaban con la presencia de anticuerpos. Se incluyeron 65 pacientes con SSp. El 80% tuvieron Anti Ro y/o Anti La positivos. Sólo un paciente de esta serie tuvo artritis. El anti Ro se asoció independiente y significativamente con la presencia de enfermedad extraglandular [7]. **NE: 4**

Pregunta 3- ¿Los pacientes con SSp y artritis, tienen FR positivo con mayor frecuencia que aquellos que no tienen compromiso articular?

Se realizó la búsqueda por Pubmed con los términos ((Primary Sjogren Syndrome) AND (arthritis) AND (rheumatoid factor))

Se encontraron 375 artículos, se excluyeron 371 por título /abstract/review, 2 estaban duplicados en valoración anti-CCP, 2 fueron no recuperables. No se incluyó ningún artículo.

Se realizó la misma búsqueda por LILACS, se encontraron 127 resultados ninguno relevante.

Ocurrió lo mismo con la búsqueda en Cochrane, 47 resultados ninguno relevante.

Pregunta 4- ¿Hay evidencia que la hidroxicloroquina es efectiva para controlar la artritis en el SSp?

Se realizó la búsqueda por Pubmed con los términos ((Primary Sjogren Syndrome) AND (arthritis) AND (hydroxychloroquine))

Se encontraron 41 artículos, se excluyeron 37 por título/abstract/review, 2 fueron irrelevantes. Se incluyeron 3 artículos.

Se realizó la misma búsqueda por LILACS, se encontraron 5, se descartaron todos.

Ocurrió lo mismo con la búsqueda en Cochrane, 4 resultados, ninguno relevante.

Gottenberg y colaboradores publicaron en 2014 un ensayo aleatorizado, doble ciego, controlado con placebo, multicéntrico, que tuvo como objetivo primario evaluar la eficacia de la hidroxicloroquina para el tratamiento de los síntomas principales del SSp: sequedad, dolor y fatiga, en la semana 24. Se incluyeron 120 pacientes con SSp, que fueron aleatorizados 1: 1 a recibir hidroxicloroquina o placebo hasta la semana 24.

Todos los pacientes recibieron hidroxicloroquina en la fase abierta del estudio, que culminó en la semana 48. Se realizó un análisis post- hoc del mismo objetivo a la semana 48. No se encontraron diferencias significativas entre ambos grupos en cuanto al objetivo primario. En el análisis post hoc en la semana 48, aunque hubo una diferencia numérica a favor del grupo que recibió hidroxicloroqina de inicio, tampoco las diferencias fueron estadísticamente significativas. Veintisiete (42.2) pacientes del grupo placebo y 18 (32.1) del grupo de tratamiento con hidroxicloroquina presentaron compromiso articular y el uso de HCQ no mejoró los síntomas de artralgias y/o artritis durante las 24 semanas de tratamiento en comparación con el grupo placebo [8]. **NE: dado que los resultados respecto al compromiso articular provienen de un sub análisis, se considera NE 4.**

Fox y colaboradores publicaron en 1996 una serie de casos retrospectiva que incluyó 50 pacientes con SSp (Criterios San Diego). Cuarenta de ellos completaron dos años de tratamiento. Se encontró: (a) mejoría sostenida de los síntomas locales (dolor en los ojos, boca dolorosa) y mejoría de las manifestaciones sistémicas (artralgias y mialgias) después del tratamiento con HCQ 6-7 mg / kg / día, durante tres años de seguimiento; (b) mostró una mejora significativa en los niveles de VSG y de IgG; (c) No hubo toxicidad tardía [9]. **NE: 4**

Kruize y colaboradores publicaron en 1993 un estudio aleatorizado, controlado con placebo, doble ciego, que incluyó 19 pacientes, con diagnóstico de SSp (criterios de Daniels y Talal), cuyo objetivo fue evaluar el efecto del tratamiento con hidroxicloroquina en la clínica y laboratorio de pacientes con SSp. Los pacientes fueron aleatorizados en dos grupos. Uno de los grupos recibió hidroxicloroquina 400 mg/ día en el primer año del estudio y placebo en el segundo año. El otro grupo recibió placebo en el primer año e hidroxicloroquina en el segundo. La respuesta clínica se midió con un cuestionario estandarizado y exámen físico en visitas trimestrales. Completaron el estudio ocho pacientes del primer grupo y seis del segundo. El uso de hidroxicloroquina a una dosis de 400 mg al día tomadas durante un período de 12 meses no tuvo beneficios clínicos relevantes a pesar de una mejoría de la hiperglobulinemia y ligeros cambios en la eritrosedimentación (VSG) y IgM [10]. **NE: 4**

Pregunta 5- ¿Los pacientes con SSp y artritis cursan durante su enfermedad con reactantes de fase aguda elevados con mayor frecuencia que aquellos sin artritis?

Pregunta 6- ¿Los pacientes con SSp y artritis, deben recibir tratamiento inmunosupresor?

Por superposición en los resultados de la búsqueda, ambas preguntas se describen en forma conjunta.

Se realizó una búsqueda por Pubmed con los términos Primary Sjogren Syndrome AND Arthritis AND C-reactive protein AND treatment response AND disease activity.

Se identificaron 188 artículos. Se excluyeron 170 por título/abstract/review. De los 18 identificados utilizando los criterios de inclusión se seleccionaron 3.

La búsqueda en Cochrane aportó 10 artículos, se seleccionó 1.

La búsqueda en Lilacs aportó 99 artículos, se seleccionaron 6. De éstos dos estaban duplicados en la búsqueda de Pubmed, 1 en Cochrane y 2 eran irrelevantes

En el artículo de Kruize y colaboradores descripto previamente, se observó una mejoría ligera en los valores de VSG con el tratamiento con hidroxicloroquina [(10)]. NE: 4

Mariette y colaboradores publicaron en 2004, un estudio aleatorizado, doble ciego, controlado con placebo para evaluar la eficacia de infliximab en el SSp. El objetivo primario fue evaluado por la respuesta global al tratamiento definida por una mejoría en el 30%, entre las semanas cero y diez, en los valores de dos de tres escalas análogo visual (EVA) que median dolor articular, fatiga y sequedad. Se incluyeron 103 pacientes aleatorizados a recibir la droga versus placebo en la semana cero, dos y seis y fueron seguidos por 22 semanas. Dentro de los objetivos secundarios se encontraba la mejoría en el número de articulaciones tumefactas y dolorosas. El estudio no alcanzó el objetivo primario. Respecto al compromiso articular, la media de conteo de articulaciones tumefactas en la visita basal fue solo de 0,7 (DS 2) en el grupo placebo y de 1,3 (DS 3,5) en la rama de infliximab. La media de articulaciones dolorosas fue de 7.8 (DS 8,2) y 8.8 (DS: 8.0), respectivamente. No hubo mejoría en el número de articulaciones dolorosas y tumefactas; así como tampoco en la tasa de flujo salival basal, en los resultados del test de Schirmer, en el foco de la biopsia de glándula salival labial, ni en los niveles de proteína C-reactiva (PCR) y de VSG, evaluados en las semanas cero, diez, y 22, como así también en la calidad de la vida evaluada por SF-36 en las semanas cero, diez, y 22 [(11)]. **NE: dado que la mejoría en el compromiso articular, es un objetivo secundario del estudio y que la media de articulaciones tumefactas fue muy baja, se considera NE: 4.**

El artículo de Moutsopoulus y colaboradores seleccionado no está disponible. Sólo se obtuvo el abstract. Once de los 50 pacientes con SSp incluidos en el estudio, tenían aumentos mínimos o moderadas en los niveles de PCR. Los pacientes con niveles elevados de PCR no tuvieron diferencias clínicas respecto de aquellos con niveles de PCR normales. Por lo tanto, el síndrome de SSp sería uno de los trastornos inflamatorios caracterizados por una respuesta relativamente baja de PCR [(12)]. **NE: 4**

Sankar y colaboradores publicaron en 2004, un estudio piloto de 12 semanas, aleatorizado, doble ciego, controlado con placebo que tuvo como objetivo evaluar la potencial eficacia y seguridad de etanercept en el SSp. Este desenlace se midió a través de una mejoría de un mínimo del 20% respecto al basal de al menos dos de los siguientes tres dominios: medición objetiva o subjetiva de sequedad bucal, oral y de

los niveles de IgG o VSG. Se incluyeron 14 pacientes en cada grupo. De los 14 pacientes que recibieron etanercept, 11 tenían SSp y tres SS secundario a AR. Tres pacientes de esta rama no completaron el estudio. A las 12 semanas, la VSG había disminuido en el grupo de etanercept en comparación con la línea base ($p < 0,004$); sin embargo, la reducción media fue sólo en el 18,6%. Respecto al compromiso articular, no se encontraron diferencias entre ambos grupos, respecto al dolor articular medido por EVA [13]. **NE: 4**

He y colaboradores publicaron en 2013 un **e**studio retrospectivo, de corte transversal, donde se identificaron 64 casos de AR con superposición con SS (AR/SS) entre 509 casos de AR. Los casos de SSp (n = 187) detectados durante el mismo período actuaron como controles. En comparación con los pacientes con AR sin SS, los pacientes AR/SS tenían artritis más grave; una mayor incidencia de anomalías hematológicas y fiebre; y una mayor frecuencia de FR, ANA y anti-SSA y anti-SSB ($p <0,05$). En comparación con el SSp, los pacientes AR/SS eran mayores, tenían una artritis más grave, anemia y compromiso pulmonar; una menor incidencia de fiebre, leucopenia, trombocitopenia; y una mayor frecuencia de FR y anti CCP ($p <0,05$). En comparación con AR y SSp, los pacientes AR/SS tuvieron puntajes más altos de actividad de la enfermedad tanto de la AR como del SS [14]. **NE: 4**

Pregunta 7- ¿En los pacientes con SSp y dolor articular se debe realizar de rutina radiografía de ambas manos y pies para evaluar el compromiso óseo?

Se realizó una búsqueda en Pubmed ((Primary Sjogren Syndrome) AND (Arthritis) AND (arthralgia) AND (radiography) AND (hand) AND (foot) AND (joint involvement))

Se identificaron 37 artículos. Se excluyeron 27 por título/abstract/review, 8 por texto completo, se seleccionaron 2.

En la búsqueda en Lilacs no se seleccionó ningún artículo.

Pease y colaboradores publicaron en 1993, una serie de casos que incluyó 48 pacientes con SSp, 54 % de los cuales desarrollaron artralgias o artritis. Las radiografías (Rx) de manos revelaron erosiones articulares en el 33% de las articulaciones en las interfalángicas proximales, en el 27% de las articulaciones metacarpofalángicas y en el 12% de articulaciones de la muñeca [15]. **NE: 4**

Tsampoulas y colaboradores publicaron en 1986, un estudio de corte transversal en el cual se evaluaron las Rx de manos en 37 pacientes con SSp, 19 pacientes con AR/SS secundario y 29 con AR solamente. A su vez, se analizaron los antecedentes de artralgias y/ o artritis esporádicas o persistente. Veinte de 37 pacientes con SSp presentaron una historia de artralgias o artritis de las articulaciones de las manos, en ninguno de los casos la artritis fue crónica. En contraste, los otros dos grupos presentaron artritis crónica. La evaluación de las Rx de la mano demostró que los pacientes con SSp presentaban estrechamiento del espacio articular leve, pero sin

erosiones, mientras que los otros dos grupos de pacientes presentaron estrechamiento del espacio articular más grave y diversos grados de erosiones, con diferencias estadísticamente significativas en comparación con los otros dos grupos [16]. **NE: 4**

Pregunta 8- ¿Es la ecografía un método diagnóstico eficaz para la evaluación de artritis en el SSp?

Se realize una búsqueda en Pubmed ((primary sjogren syndrome) AND (arthritis) AND (joint ultrasound) AND (diagnosis of rheumatoid arthritis))

Se identificaron 13 artículos, se seleccionaron 8 para evaluación de texto completo, incluyéndose 4 para el análisis.

Amezcua- Guerra y colaboradores publicaron en 2013, un estudio de corte transversal, que tuvo como objetivo caracterizar los hallazgos ultrasonográficos (US) del compromiso articular en los pacientes con SSp. También se analizó la capacidad de la US para discriminar entre SSp y AR con SS asociado. La evaluación de los pacientes incluyó la realización de laboratorio inmunológico, evaluación de antecedentes, estado clínico y la US. Se incluyeron 17 pacientes con SSp, 18 con SS secundario, y 17 controles sanos que fueron sometidos a exámenes de diversas regiones articulares. En los pacientes con SSp, se observó sinovitis en las articulaciones metacarpofalángicas (76%), muñecas (76%), y rodillas (76%). La presencia de power doppler fue poco frecuente. Se encontraron erosiones en los carpos de tres (18%) pacientes con SSp, uno de ellos, con anti-CCP positivos. La presencia de erosiones en la segunda metacarpofalángica mostró una sensibilidad del 28,8% y una especificidad del 100% para el diagnóstico de AR con SS secundario [17]. **NE: 4**

Iagnocco y colaboradores publicaron en 2010, una serie de casos, que tuvo como objetivo evaluar el compromiso articular en SSp a través de la US y a su vez, relacionarlo con el laboratorio y la clínica. Se evaluaron 32 pacientes con SSp mediante US. Se encontraron signos ecográficos de sinovitis de la articulación radio-ulno-carpiana en 17 (26,5%) de 64 muñecas. Se encontró una correlación estadísticamente significativa entre la puntuación del SSDDI (por sus siglas en inglés *SS Disease Activity Index*) y el grado de signos ecográficos de proliferación sinovial en la muñeca (p = 0,04). Los pacientes con sinovitis tenían una mayor edad y una puntuación superior del SSDDI (p = 0,004) [18]. **NE: 4**

Riente y colaboradores publicaron en 2009, un estudio de corte transversal que tuvo como objetivo evaluar la frecuencia de compromiso articular y tendinoso de manos en pacientes con SSp. Se incluyeron 48 pacientes con SSp (criterios americano-europeos 2002). Como controles se incluyó a 40 voluntarios sanos. Se observó clara evidencia de artritis inflamatoria en nueve (18,7%) pacientes, erosiones en metacarpofalángicas e interfalángicas proximales en seis pacientes (12,5%). En diez (20,8%) pacientes se observó tenosinovitis de flexores por US, la cual si bien fue más frecuente que en los controles, no se fue estadísticamente significativa [19]. **NE: 4**

Iagnocco y colaboradores publicaron en 2002, un estudio de corte transversal, que tuvo como objetivo evaluar la presencia de sinovitis en pacientes con SSp. Se incluyeron 60 pacientes con SSp, 31 pacientes con AR y SS secundario, 17 pacientes con SS secundario y otras enfermedades del tejido conectivo (diferentes a AR), 14 pacientes con AR y 32 controles sanos. El derrame articular fue significativamente más frecuente en el SS secundario con AR y en la AR. Los resultados demostraron signos de leve sinovitis en SSp. La sinovitis más grave se encontró tanto en el SS secundario con AR como en la AR [20]. **NE: 4**

Pregunta 10- ¿Se justifica hacer una evaluación de laboratorio (enzimas musculares) y electromiograma (EMG) en pacientes con SSp que presenten mialgias?

Se realizó una búsqueda en Pubmed ((Primary Sjogren Syndrome) AND (myalgia) AND (electromyogram) AND (creatin-fosfocinasa) AND (myopathy))

Se encontraron 164 artículos se excluyeron por título y abstract 155, se incluyeron 3, luego de revisar los seleccionados.

Colafracesco y colaboradores publicaron en 2015, una serie de casos retrospectiva (1.320 pacientes con SSp), cuyo objetivo fue describir la frecuencia de miositis, así como los hallazgos clínicos, histológicos y las estrategias de tratamiento. Diecisiete pacientes (1,28%) presentaron debilidad muscular [mialgias (07/17, 41,1%)], acompañados por un aumento de CPK [13/17, (76,4%)] y/o EMG anormal [13/14, (92,8%)]. Diez de 17 (58,8%) cumplieron al menos tres criterios clasificatorios para miositis inflamatoria. Los hallazgos histológicos confirmaron la posible presencia de una miositis por cuerpos de inclusión o de una miopatía más similar a la polimiositis (PM) [21]. **NE: 4**

Lindvall y colaboradores publicaron en 2002, una serie de casos en la que se incluyeron 48 pacientes con SSp. El dolor muscular y, especialmente la fibromialgia, fueron muy común en el SS. Se observaron signos de inflamación en 26 de 36 biopsias (72%), e inflamación combinada con degeneración/regeneración en 17 biopsias (47%). Si bien, los signos histopatológicos de miositis fueron muy comunes en el SS, los síntomas musculares no estuvieron relacionados con los signos histológicos de inflamación muscular [22]. **NE 4**

Vrethem y colaboradores publicaron en 1990 una serie de casos en la que se incluyeron 17 pacientes consecutivos con SSp, a los cuales se les realizó EMG y biopsia muscular. Estas últimas fueron realizadas en 15 pacientes con SSp, 11 de las cuales mostraron mositis o infiltrados inflamatorios perivasculares y tres mostraron signos de denervación. Una combinación de la inflamación y de los signos

morfológicos de miopatía, compatible con el diagnóstico histológico de PM, se observó en cuatro casos, uno de los cuales mostró signos clínicos de PM [23]. **NE: 4**

Pregunta 11- ¿Los pacientes con SSp y miopatía deben recibir tratamiento inmunosupresor?

Se realizó una búsqueda ((Primary Sjogren Syndrome) AND (myopathy) AND (ïmmunosuppressive therapy) AND (myopathy remission))

Se identificaron 19 artículos en búsqueda por Pubmed. Se excluyeron 13 por título, abstract y review, 3 fueron irrelevantes, otros 3, reportes de casos. No se incluyó ningún artículo.

Pregunta 12- ¿En pacientes con SSp y fatiga hay evidencia que la hidroxicloroquina controle este síntoma?

Se realize una búsqueda ((Primary Sjogren Syndrome) AND (fatigue) AND (hydroxychloroquine) AND (clinical improvement))

Se identificaron 7 artículos en Pubmed. Se excluyó 1 por título. Se seleccionaron 6 de los cuales 5 fueron irrelevantes. Se incluyó 1 para análisis. La búsqueda en Cochrane no aportó artículos adicionales.

El estudio publicado por Gottenberg y colaboradores, comentado previamente, no mostró diferencias estadísticamente significativas entre el grupo tratado con hidroxicloroquina y el grupo placebo, respecto a la mejoría de la fatiga [24]. **NE: 2**

1- Kim SM, Park E, Lee JH, Lee SH, Kim HR. The clinical significance of anti-cyclic citrullinated peptide antibody in primary Sjögren syndrome. Rheumatol Int. 2012; 32:3963-7.
2- Atzeni F, Sarzi-Puttini P, Lama N, Bonacci E, Bobbio-Pallavicini F, Montecucco C, Caporali R. Anti-cyclic citrullinated peptide antibodies in primary Sjögren syndrome may be associated with non-erosive synovitis. Arthritis Res Ther. 2008;10:R51.
3- Gottenberg JE, Mignot S, Nicaise-Rolland P, Cohen-Solal J, Aucouturier F, Goetz J, Labarre C, Meyer O, Sibilia J, Mariette X. Prevalence of anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with primary Sjögren's syndrome. Ann Rheum Dis. 2005; 64:114-7.
4- Ryu YS, Park SH, Lee J, Kwok SK, Ju JH, Kim HY, Jeon CH. Follow-up of primary Sjogren's syndrome patients presenting positive anti-cyclic citrullinated peptides antibody. Rheumatol Int. 2013; 33:1443-6.
5- Barcelos F, Abreu I, Patto JV, Trindade H, Teixeira A. Anti-cyclic citrullinated peptide antibodies and rheumatoid factor in Sjögren's syndrome. Acta Reumatol Port. 2009; 34:608-12.
6- Mohammed K, Pope J, Le Riche N, Brintnell W, Cairns E, Coles R, Bell DA. Association of severe inflammatory polyarthritis in primary Sjögren's syndrome: clinical, serologic, and HLA analysis. J Rheumatol. 2009; 36:1937-42.
7- ter Borg EJ, Risselada AP, Kelder JC. Relation of systemic autoantibodies to the number of extraglandular manifestations in primary Sjögren's Syndrome: a retrospective analysis of 65 patients in the Netherlands. Semin Arthritis Rheum. 2011; 40:547-51.
8- Gottenberg JE, Ravaud P, Puéchal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA. 2014 16;312:249-58.
9- Fox RI, Dixon R, Guarrasi V, Krubel S. Treatment of primary Sjögren's syndrome with hydroxychloroquine: a retrospective, open-label study. Lupus. 1996:S31-6.
10- Kruize AA, Hené RJ, Kallenberg CG, van Bijsterveld OP, van der Heide A, Kater L, Bijlsma JW. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. Ann Rheum Dis. 1993; 52:360-4.
11- Mariette X, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, Combe B, Puéchal X, Pennec Y, Sauvezie B, Perdriger A, Hayem G, Janin A, Sibilia J. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). Arthritis Rheum. 2004; 50:1270-6.
12- Moutsopoulos HM, Elkon KB, Mavridis AK, Acritidis NC, Hughes GR, Pepys MB. Serum C-reactive protein in primary Sjögren's syndrome. Clin Exp Rheumatol.1983;1:57-8.
13- Sankar V, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, Baum BJ, Pillemer SR. Etanercept in Sjögren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum. 2004; 50:2240-5.

14- He J, Ding Y, Feng M, Guo J, Sun X, Zhao J, Yu D, Li Z. Characteristics of Sjögren's syndrome in rheumatoid arthritis. Rheumatology (Oxford). 2013; 52:1084-9.
15- Pease CT, Shattles W, Barrett NK, Maini RN. The arthropathy of Sjögren's syndrome. Br J Rheumatol. 1993; 32:609-13.
16- Tsampoulas CG, Skopouli FN, Sartoris DJ, Kaplan P, Kursunoglu S, Pineda C, Resnick D, Moutsopoulos HM. Hand radiographic changes in patients with primary and secondary Sjögren's syndrome. Scand J Rheumatol. 1986;15:333-9.
17- Amezcua-Guerra LM1, Hofmann F, Vargas A, Rodriguez-Henriquez P, Solano C, Hernández-Díaz C, Castillo-Martinez D, Ventura-Ríos L, Gutiérrez M, Pineda C. Joint involvement in primary Sjögren's syndrome: an ultrasound "target area approach to arthritis". Biomed Res Int. 2013;2013:640265.
18- Iagnocco A, Modesti M, Priori R, Alessandri C, Perella C, Takanen S, Valesini G. Subclinical synovitis in primary Sjögren's syndrome: an ultrasonographic study. Rheumatology (Oxford). 2010; 49:1153-7.
19- Riente L, Scirè CA, Delle Sedie A, Baldini C, Filippucci E, Meenagh G, Iagnocco A, Montecucco C, Grassi W, Valesini G, Bombardieri S. Ultrasound imaging for the rheumatologist. XXIII. Sonographic evaluation of hand joint involvement in primary Sjögren's syndrome. Clin Exp Rheumatol. 2009; 27:747-50.
20- Iagnocco A, Coari G, Palombi G, Valesini G. Knee joint synovitis in Sjögren's syndrome. Sonographic study. Scand J Rheumatol. 2002;31:291-5.
21- Colafrancesco S, Priori R, Gattamelata A, et al. Myositis in primary Sjögren's syndrome: data from a multicentre cohort. Clin Exp Rheumatol. 2015; 33:457-64.
22- Lindvall B, Bengtsson A, Ernerudh J, Eriksson P. Subclinical myositis is common in primary Sjögren's syndrome and is not related to muscle pain. J Rheumatol. 2002; 29:717-25.
23- Vrethem M, Lindvall B, Holmgren H, Henriksson KG, Lindström F, Ernerudh J. Neuropathy and myopathy in primary Sjögren's syndrome: neurophysiological, immunological and muscle biopsy results. Acta Neurol Scand. 1990; 82:126-31.
24- Gottenberg JE, Ravaud P, Puéchal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA. 2014 16;312: 249-58.

SINDROME DE SJÖGREN Y COMPROMISO CUTÁNEO

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Pregunta 1- ¿Es necesaria la biopsia cutánea ante la sospecha de vasculitis cutánea en un paciente con Síndrome Sjögren primario (SSp), para iniciar tratamiento?

Líneas de Búsqueda

1) primary Sjögren's syndrome OR sjögren syndrome AND

2) Cutaneous vasculitis AND

3) Cutaneous biopsy OR skin biopsy AND

4) treatment OR therapeutic

((cutaneous biopsy OR skin biopsy) AND (cutaneous vasculitis) AND (primary Sjogren's syndrome OR sjogren syndrome OR sjogren s syndrome OR sjogren syndrome OR sjogren mikulicz syndrome) AND (treatment OR therapeutic))

RESULTADO DE BÚSQUEDA:

- PUBMED: se encontraron 30 artículos. Se descartaron por título y abstract 2, se seleccionaron 5.
- COCHRANE: 3 artículos, pero evaluaban otros desenlaces
- LILACS: 0 artículo

Tsai y colaboradores publicaron en 2008 un reporte de un caso de SSp con vasculitis leucocitoclástica y nefropatía IgA. La clínica de la paciente era compatible con síntomas de sequedad ocular y oral, presencia de anti SSA y además se contaba con biopsia de glándula salival menor. Se obtuvo muestra de la lesión purpúrica, y se pudo obtener el diagnóstico de vasculitis leucocitoclástica, al igual que con la afectación renal [(1)]. NE: 4

Roguedas y colaboradores publicaron en 2010 un estudio de corte transversal, que tuvo como objetivo evaluar la frecuencia de xerosis en pacientes con SSp, y comparar la histopatología de las glándulas sudoríparas con las glándulas salivales menores,

con respecto a su contribución al diagnóstico. Se evaluaron 22 pacientes con SSp y 22 controles sanos emparejados. Se les solicitó que evalúen su sequedad cutánea de acuerdo a una escala análoga visual. La xerosis fue más frecuente en los pacientes con SSp que en los controles sanos (9 de 22 en comparación con 2 de 22, P <0,02). En las muestras de axila (punch de 6mm) se halló infiltración linfocítica en la piel de 8 de los 12 pacientes con SSp biopsiados. Concomitantemente se encontró infiltrados de células B en infiltrados de la piel de los pacientes, de manera que su presencia podría ser una clave para el diagnóstico de la enfermedad [(2)]. NE: 4

Zazzetti y colaboradores publicaron en 2010 una serie de casos retrospectiva que tuvo como objetivo evaluar las características clínicas y serológicas, así como la frecuencia de manifestaciones sistémicas en pacientes con SSp. Se incluyeron 41 pacientes que cumplían criterios de clasificación americano- europeo 2002 (AECG), todos de sexo femenino. El 80,49% presentaron manifestaciones sistémicas, dentro de las cuales las más frecuentes fueron artritis, vasculitis cutánea y polineuropatía. Respecto a la vasculitis cutánea se observó en diez pacientes, en nueve de ellos la histología fue de tipo leucocitoclástica y en una linfocítica [(3)]. NE: 4.

Alexander y colaboradores publicaron en 1983 una serie de casos en la que se estudiaron 22 pacientes con SSp y afectación cutánea. Las manifestaciones cutáneas más frecuentemente halladas fueron púrpura y urticaria. La mayoría de las lesiones se asociaron a histología compatible con angeítis leucocitoclástica y en menor medida a vasculitis mononuclear. El 84% de los pacientes que tenían vasculitis presentaban Ro positivo [(4)]. NE: 4.

Guggisberg y colaboradores publicaron en 1997 el caso de una mujer de 75 años que al examen físico presentaba lesiones cutáneas en miembros inferiores hiperpigmentadas, observándose además eritema, lesiones ulceradas y necróticas; síndrome sicca, hipergammaglobulinemia, ANA, Ro y La positivos. Se realizó biopsia de las lesiones y el estudio histopatológico demostró una vasculitis leucitoclástica [(5)]. NE: 4.

Pregunta 2- Ante el diagnóstico de vasculitis cutánea en paciente con SSp, ¿es necesario solicitar estudios complementarios para evaluación de afectación sistémica?

Líneas de Búsqueda:

1) primary Sjögren's syndrome OR sjögren syndrome (Sinónimos) AND
2) systemic disease OR systemic involvement AND
3) test OR management

RESULTADO DE BÚSQUEDA:

- PUBMED: Se encontraron 448 artículos, se seleccionaron 7 artículos por título y abstract, se seleccionaron 2 por lectura crítica.
- COCHRANE: 1 artículo, que se descartó por lectura
- LILACS: 0

Ramos- Casals y colaboradores publicaron en 2004 una serie de casos que tuvo como objetivo investigar las características clínicas y serológicas de 558 pacientes consecutivos con SSp, y seleccionar aquellos con evidencia clínica de lesiones cutáneas, excluyendo reacciones alérgicas y xerodermia. Todos cumplían cuatro o más criterios para SSp propuestos por el Grupo de Estudio de la Comunidad Europea en 1993. Un total de 89 (16%) pacientes presentaban compromiso cutáneo, estando la vasculitis cutánea presente en 52 (58%) pacientes. De ellas, 14 fueron vasculitis crioglobulinémicas, 11 vasculitis urticarianas y las restantes 26, púrpura cutánea no asociada a crioglobulinas. Se obtuvieron biopsias de piel en 38 pacientes (73%). Las principales características asociadas a la vasculitis fue el predominio de la afectación de los pequeños vasos versus los de mediano calibre. Los pacientes con vasculitis cutánea presentaron una mayor prevalencia de compromiso articular (50% vs 29%, p = 0.044), neuropatía periférica (31% vs 4%, p < 0.001), fenómeno de Raynaud (40% vs 15%, p = 0.008), compromiso renal (10% vs 0%, p = 0.028), anticuerpos antinucleares (88% vs 60%, p = 0.002), factor reumatoideo (78% vs 48%, p = 0.004), anticuerpos anti Ro/SS-A (70% vs 43%, p = 0.011) y hospitalizaciones (25% vs 4%, p = 0.005) comparados con el grupo sin vasculitis. Seis (12%) pacientes murieron, todos con crioglobulinemia sistémica [(6)]. NE: 4.

Malladi y colaboradores publicaron en el 2012 un estudio de corte transversal que tuvo como objetivo evaluar las manifestaciones extraglandulares en SSp entre los pacientes enrolados en el registro the Sjögren's International Collaborative Clinical Alliance (SICCA). Se incluyeron 1927 pacientes del registro SICCA, incluyendo 886 participantes que cumplían con los criterios AECG del año 2002, 830 casos "intermedios" que tenían hallazgos objetivos de SSp pero no cumplían con los criterios AECG, y 211 controles individuales. Se estudiaron la prevalencia de anormalidades en los laboratorios hematológico e inmunológico, hallazgos específicos reumatológicos y el compromiso de impacto de órganos, así como presencia de linfoma. Se encontraron, como hallazgos frecuentes, hipergammaglobulinemia e hipocomplementemia, vasculitis cutánea ((34 (4%) versus 5 (1%) versus 3 (1%), respectivamente)) y linfadenopatías ((66 (8%) versus 37 (5%) versus 9 (4%), respectivamente)). Entre los otros hallazgos clínicos solo la cirrosis biliar primaria se asoció a SSp en mayor frecuencia [(7)]. NE: 4

Pregunta 3- En pacientes con SSp y vasculitis cutánea, ¿es necesario utilizar corticoides para mejoría o remisión de ésta última?

Líneas de Búsqueda:

1) Sjögren's syndrome (sinónimos) AND
2) Steroid OR glucocorticoid OR corticosteroid AND
3) Cutaneous vasculitis AND
4) Treatment

(((((((primary Sjogren's syndrome) OR sjogren syndrome) OR sjogren s syndrome) OR sjogren syndrome) OR sjogren mikulicz syndrome)) AND cutaneous vasculitis) AND (((Steroid) OR glucocorticoid) OR corticosteroid)

RESULTADOS:

- PUBMED: se encontraron 22 artículos, de los cuales sólo 2 responden la pregunta
- COCHRANE: 133 Artículos, se descartan por título y abstract 128, 3 repetidos (de búsqueda en PUBMED), 1 sin abstract, 1 con abstract en inglés pero artículo original en otro idioma.
- LILACS: 0 artículo

En la serie de 558 casos descripta previamente, publicada por Ramos-Casals y colaboradores, 38 de los 52 pacientes (73%) que presentaban vasculitis cutánea, fueron tratados con corticoides orales, siete de los cuales requirieron dosis mayores a 30 mg/día. Siete pacientes recibieron agentes inmunosupresores y dos plasmaféresis. 27 pacientes presentaron recaídas del cuadro [6]. NE: 4

Pregunta 4- ¿DAPSONA y COLCHICINA podrían ser consideradas como opciones terapéuticas para remisión de un cuadro de vasculitis cutánea asociada a SSp?

Líneas de Búsqueda:

1) Sjögren's syndrome (sinónimos) AND

2) Cutaneous vasculitis AND

3) Dapsone OR colchicine AND

4) remission

((primary Sjogren's syndrome OR sjogren syndrome OR sjogren s syndrome OR sjogren syndrome OR sjogren mikulicz syndrome) AND (cutaneous vasculitis) AND (dapsone OR colchicine) AND (remission))

RESULTADO:

- PUBMED: No se encontraron artículos
- COCHRANE: No se encontraron artículos
- LILACS: No se encontraron artículos

Si bien no se encontraron artículos que respondan la pregunta, se seleccionaron dos artículos que proveen información indirecta.

Holtman y colaboradores reportaron en 19990 un caso de una paciente de 35 años, con diagnóstico presuntivo de Síndrome de Sjögren (SS), con antecedente de síntomas de sequedad ocular y oral, agrandamiento parotídeo, y episodio de epistaxis, que presento un cuadro de lesiones compatibles con vasculitis urticariana en miembros superiores y tronco. Con los hallazgos de laboratorio, más la asociación de síntomas que se adicionaron posteriormente se realizó el diagnóstico de Lupus

eritematoso sistémico y SS secundario. Realizó tratamiento con corticoide tópico, hidroxicloroquina (400 mg/día), difenhidramina (50 mg 4 veces/día) y factor protector solar. Intercurrió con eritema multiforme que se asumió por efecto de la hidroxicloroquina, y se instauró tratamiento con corticoides vía oral a dosis de 60 mg/día. A pesar de esto, continuó con el rash urticariano y fotosensibilidad, por lo cual se decidió instaurar dapsona a dosis de 100 mg/día, presentando rápida mejoría de las lesiones, descendiendo la dosis posteriormente [8]. NE: 4

Wiles y colaboradores reportaron en 1985 dos casos de vasculitis urticariana, una de ellas una vasculitis leucocitoclástica y la otra una vasculitis mononuclear. Ambos casos se dieron en pacientes de sexo femenino, y antes de realizar tratamiento con colchicina, recibieron antihistamínicos (como difenhidramina), corticoides vía oral e hidroxicloroquina, entre otros, los cuales fueron inefectivos. Luego de la instauración de colchicina a dosis de 0,6 mg (2 o 3 veces por día), hubo una rápida mejoría de las placas urticarianas, presentando una de las pacientes un cuadro de diarrea que se asumió como efecto adverso de la droga instaurada, por lo cual se suspendió transitoriamente y luego de la resolución del cuadro, se reinstauró el tratamiento [9]. NE: 4

Pregunta 5- ¿Cuál sería la mejoría clínica ante la indicación de medidas locales en el tratamiento de la XEROSIS en pacientes con SSp?

Líneas de Búsqueda:

1) Sjögren’s síndrome (sinónimos) AND

2) Xerosis OR skin xerosis OR cutaneous xerosis AND

3) treatment

((primary Sjogren's syndrome OR sjogren syndrome OR sjogren s syndrome OR sjogren syndrome OR sjogren mikulicz syndrome) AND (xerosis OR skin xerosis OR cutaneous xerosis))

RESULTADO DE BÚSQUEDA:

- PUBMED: 24 artículos, se seleccionan por título 5, se descartan todos.
- COCHRANE: 0
- LILACS: 0

Pregunta 6- Ante la presencia de manifestaciones cutáneas no vasculíticas (eritema anular, vitiligo, liquen plano, etc) en un paciente con diagnóstico de SSp, ¿es necesario adoptar conductas terapéuticas diferentes a las adoptadas para las mismas entidades en otro contexto patológico?

Líneas de Búsqueda:

1) Sjögren's syndrome (con todos los sinónimos) AND
2) Annular erythema OR Vitiligo OR Livedo reticularis OR Lichen planus AND
3) treatment

((primary Sjogren's syndrome) AND [Title/Abstract] OR sjogren syndrome) AND Title/Abstract OR sjogren s syndrome) AND [Title/Abstract] OR sjogren syndrome) AND [Title/Abstract] OR sjogren mikulicz syndrome) AND [Title/Abstract] AND (Annular erythema) AND [Title/Abstract] OR Livedo reticularis) AND [Title/Abstract] OR Raynaud's phenomenon) AND [Title/Abstract] OR Vitiligo) AND [Title/Abstract] OR Lichen planus) AND [Title/Abstract] AND (treatment))

RESULTADO DE BÚSQUEDA:

- PUBMED: se seleccionan 162 artículos, se seleccionan 11 manualmente según título y abstract
- COCHRANE: 0
- LILACS: 0

Yokota y colaboradores publicaron en 2005 el caso de una mujer japonesa de 36 años de edad, con diagnóstico de SSp, con clínica, pruebas objetivas de sequedad ocular, perfil inmunológico y biopsia de glándula salival menor compatibles. Intercurrió con lesiones cutáneas compatibles con eritema anular. Se obtuvo notable mejoría con dos aplicaciones tópicas de tacrolimus 0,1%, y desaparición completa de las lesiones al día 35 de tratamiento [(10)]. NE: 4

Katayama y colaboradores publicaron en 2010 un estudio retrospectivo, en el cual se enrolaron 28 casos de eritema anular, 23 en pacientes con SSp y cinco con SS secundario de un único centro, y 92 casos obtenidos en la literatura, con el objetivo de evaluar las características clínicas y el manejo terapéutico de esta manifestación cutánea. El 75% de los casos con EA asociado a SSp tenían positividad para anticuerpos anti-SSA y anti-SSB. Entre las opciones terapéuticas se incluyen corticoides tópicos y orales, drogas antimaláricas y tacrolimus [(11)]. NE: 4

De Winter y colaboradores reportaron en 2006 un caso de una mujer de 23 años, con antecedente de enfermedad de Graves que intercurrió con eritema anular. Presentó además síntomas sicca, agrandamiento parotídeo, positividad para anticuerpos anti-Ro (SS-A) y anti-La (SS-B), test de Schirmer positivo, y biopsia cutánea con infiltrado linfocítico perivascular y periapendicular. Se realizó el diagnóstico de eritema anular asociado a SS. Luego de dos meses de tratamiento con hidroxicloroquina, mejoraron las manifestaciones cutáneas, así como el componente sicca [(12)]. NE: 4.

Haimowitz y colaboradores reportan en el 2000, el caso de una mujer caucásica de 75 años, que presentó eritema anular, descartándose tanto clínica como serológicamente Lupus eritematoso cutáneo subagudo. La paciente presentaba síntomas sicca, anticuerpos anti SSA y anti SSB y evaluación de biopsia de piel y glándula salival menor. Tanto el componente cutáneo como lo síntomas sicca mejoraron con la terapia antimalárica (hidroxicloroquina y quinacrina) [(13)]. NE: 4.

Nobeyama y colaboradores exponen el caso de una paciente de sexo femenino, asiática, de 26 años de edad, con diagnóstico clínico y serológico de SS y presencia

de eritema anular. Realizó tratamiento con corticoides vía oral (betametasona) siendo refractaria, por lo cual se añadió ciclosporina a dosis de 1,8 mg/kg/día con posterior mejoría de las lesiones cutáneas, manteniéndose inactivas inclusive luego del descenso de dosis del corticoide [14]. NE: 4.

Tanioko y colaboradores reportan en 2009 el caso de una paciente de origen japonés de 54 años de edad con diagnóstico de SS. Presentaba lesiones compatibles con vitíligo en espalda y cuello. Se instauró tratamiento con corticoides tópicos y calcipotriol tópico, sin respuesta favorable. Luego de diez sesiones con fototerapia con rayos UV B se obtuvo mejoría, quedando sólo lesiones maculares de tipo residual. Se consideró que dado el origen autoinmune de ambas enfermedades, estarían claramente relacionadas [15]. NE: 4.

Pregunta 7- ¿Sería útil indicar drogas inmunomoduladoras / inmunosupresoras en pacientes con SSp y compromiso cutáneo, para mejoría de las manifestaciones vasculíticas?

Líneas de Búsqueda:

1) Sjögren's síndrome (sinónimos) AND
2) Cutaneous vasculitis AND
3) Immunomodulatory drugs OR DMARD/DMARDS OR Hydroxychloroquine OR Methotrexate OR Cyclophosphamide OR Azathioprine OR Mycophenolate mofetil OR Cyclosporine OR Thalidomide

((primary Sjogren's syndrome OR sjogren syndrome OR sjogren s syndrome OR sjogren syndrome OR sjogren mikulicz syndrome) AND (cutaneous vasculitis) AND (Immunomodulatory drugs OR Azathioprine OR DMARD OR DMARDS OR Hydroxychloroquine OR Methotrexate OR Cyclophosphamide OR Mycophenolate mofetil) OR Cyclosporine OR Thalidomide))

RESULTADO DE BÚSQUEDA:

- PUBMED: Se encontraron 15 artículos, se descartaron todos por lectura crítica
- COCHRANE: 0
- LILACS: 0

En el reporte de caso de SSp y eritema anular, publicado por Nobeyama y colaboradores, comentado previamente, se indicó tratamiento con corticoides vía oral (betametasona) siendo refractario, por lo cual se añadió ciclosporina a dosis de 1,8 mg/kg/día con posterior mejoría de las lesiones cutáneas, manteniéndose inactivas inclusive luego del descenso de dosis del corticoide [14]. NE: 4

En la serie de 558 casos descripta previamente, publicada por Ramos- Casals y colaboradores, 38 de los 52 pacientes (73%) que presentaban vasculitis cutánea,

fueron tratados con corticoides orales, siete de los cuales requirieron dosis mayores a 30 mg/d. Siete pacientes recibieron agentes inmunosupresores (cuatro ciclofosfamida y tres azatioprina), y dos plasmaféresis. 27 pacientes presentaron recaídas del cuadro. Otros tratamientos incluyeron antiinflamatorios no esteroideos en diez casos, antihistamínicos en cinco, cloroquina en cuatro y dapsona en un paciente [6]. NE: 4.

Pregunta 8- ¿Qué inmunomodulador/ inmunosupresor ha demostrado ser más útil como tratamiento para mejoría y/o remisión de la afectación cutánea (vasculítica/no vasculítica) en SSp?

-Se incluyen las siguientes drogas: Hidroxicloroquina (HCQ) – Metotrexato (MTX) – Ciclofosfamida (CFM) – Azatioprina (AZA) – Micofenolato Mofetil (MMF) – Ciclosporina (CYS) - Talidomida

Las Líneas de Búsqueda eran similares a la de pregunta 7, por lo cual se unificaron. Siendo los resultados los mismos.

Pregunta 9- El uso de biológicos en pacientes con SSp y afectación cutánea, ¿queda reservado sólo si hay compromiso de la vida o afectación de órganos internos?

Líneas de Búsqueda:

1) Sjögren's síndrome
2) Skin involvement
3) Biologic therapy/therapies OR usa como sinónimos el nombre de los biológicos, como Rituximab OR antiCD20 OR Rituxan)
((primary Sjogren's syndrome OR sjogren syndrome OR sjogren s syndrome OR sjogren syndrome OR sjogren mikulicz syndrome) AND (Biologic therapy OR Biologic therapies OR Rituximab OR anti CD20))

((primary Sjogren's syndrome OR sjogren syndrome OR sjogren s syndrome OR sjogren syndrome OR sjogren mikulicz syndrome) AND ((Biologic therapy OR Biologic therapies OR Rituximab OR anti CD20) AND (cutaneous involvement OR skin involvement))

RESULTADOS DE BÚSQUEDA:

- PUBMED: la búsqueda arrojó 12 artículos. Se seleccionan por título y abstract 7
- COCHRANE: 0
- LILACS: 0

Se seleccionan 4 artículos más por búsqueda manual.

Logvinenko y colaboradores publicaron en 2012 una serie de casos que incluye 13 pacientes con SSp y vasculitis crioglobulinémica y 17 pacientes con SSp y linfoma MALT en glándula parótida. Se comparó el tratamiento con rituximab (RTX) monoterapia y RTX combinado con ciclofosfamida. La respuesta clínica, serológica e histológica fue mayor en pacientes con terapia combinada que en pacientes tratados con RTX monoterapia, y el número de recaídas fue mayor en este último grupo. Respecto a las manifestaciones cutáneas de vasculitis desaparecieron en el 75% de los casos luego de la monoterapia con rituximab y en el 100% de los casos luego de combinarlo con ciclofosfamida. Luego de seis meses de seguimiento se observó una respuesta completa al tratamiento en 25% de los pacientes luego de un curso de monoterapia y en el 83% de los casos posterior a la terapia combinada [16]. NE: 4.

Gottenberg y colaboradores publicaron en 2013 una serie de casos retrospectiva del registro francés de pacientes tratados con RTX. Incluye 78 pacientes con SSp, cinco con vasculitis crioglobulinémica, solo detalla que en dos casos pudo descenderse la dosis de corticoides [17]. NE: 4.

Meijer y colaboradores publicaron en 2010, un ensayo doble ciego, aleatorizado, controlado con placebo. El objetivo del estudio fue evaluar la eficacia y seguridad del Rituximab (RTX) en pacientes con SSp. Se incluyeron 30 pacientes que fueron asignados al azar a un grupo de tratamiento, en una relación 2: 1 (RTX: placebo), quienes recibieron RTX a una dosis de 1g en infusiones los días 1 y 15. El seguimiento se llevó a cabo a las 5, 12, 24, 36, y 48 semanas. Respecto a manifestaciones extraglandulares relacionadas con compromiso cutáneo, 30% de pacientes en cada grupo (seis en el grupo tratado y tres en la rama placebo) presentaban vasculitis al ingresar al estudio, observándose diferencias significativas a favor del RTX a las 24 semanas de tratamiento (p: 0,03) [18]. NE: 3.

Ramos- Casals y colaboradores publicaron en 2010 una serie de casos proveniente del registro español de enfermedades refractarias tratadas con RTX, los datos fueron retrospectivos y el cálculo del ESSDAI fue retrospectivo.15 pacientes con SSp recibieron recibieron tratamiento con RTX: seis casos con linfoma (tuvieron compromiso cutáneo- púrpura-). El compromiso cutáneo no fue uno de los motivos de indicación de RTX: lo fue el compromiso neurológico (cuatro casos), hematológico (dos), glomerulonefritis (uno), artritis (uno) y la enteropatía perdedora de proteínas (uno) [19]. NE: 4.

Pregunta 10- En pacientes con SSp y afectación cutánea severa, en quienes hay compromiso de la vida, ¿la realización de plasmaféresis podría ser una conducta terapéutica?

Líneas de Búsqueda:

1) Sjögren's syndrome

2) Skin involvement

3) Apheresis OR plasmapheresis OR plasma Exchange

((primary Sjogren's syndrome OR sjogren syndrome OR sjogren s syndrome OR sjogren syndrome OR sjogren mikulicz syndrome) AND (cutaneous involvement OR skin involvement) AND (Apheresis OR plasmapheresis OR plasma Exchange))

RESULTADOS DE BÚSQUEDA:

- PUBMED: 2 artículos
- COCHRANE: 0
- LILACS: 0

Ting- Yun y colaboradores reportaron en 2012 un caso de una paciente con antecedentes de ojo y boca seca que comenzó con deterioro cognitivo agregando anemia, plaquetopenia y falla renal con aumento de LDH. Se inició plasmaféresis con sospecha de SS, luego a los tres días se agregó metilprednisolona y ciclofosfamida endovenosa (600 mg), continuando con ciclofosfamida vía oral. En la revisión de la bibliografía, se encontraron seis casos de PTT asociado a SSp, en tres de ellos la plasmaféresis fue eficaz, no siempre asociada a corticoides [20]. NE: 4.

Gubin y colaboradores publicaron en 1996 una serie de siete casos de pacientes con SSp con GNF crioglobulinemica y vasculitis necrotizante ulcerativa a los cuales se les realizó aféresis combinado con pulsos de corticoides. Presentaron mejoria de los parámetros de laboratorio y los síntomas sicca [21]. NE: 4.

Bibliografía

1. Tsai TC, Chen CY, Lin WT, Lee WJ, Chen HC. Sjogren's syndrome complicated with IgA nephropathy and leukocytoclastic vasculitis. Ren Fail. 2008;30(7):755-8.
2. Roguedas AM, Pers JO, Lemasson G, Devauchelle V, Tobón GJ, Saraux A, Misery L, Youinou P.Memory B-cell aggregates in skin biopsy are diagnostic for primary Sjögren's syndrome. J Autoimmun. 2010 Nov;35(3):241-7.
3. Zazzetti F, Rivero MA, Duartes Noé DE, Gallacher A, Schiel A, Khoury MC, Laborde HA, Barreira JC. Frequency of systemic manifestations in patients with primary Sjögren's syndrome in Argentina. Reumatol Clin. 2010 Nov-Dec;6(6):299-302. Alexander EL, Provost TT. Cutaneous manifestations of primary Sjögren's syndrome: a reflection of vasculitis and association with anti-Ro (SSA) antibodies. J Invest Dermatol. 1983 May; 80 (5):386-91.
4. Guggisberg D, Perrenoud D, Frenk E. Severe, chronic anorexia and extensive leg ulcerations as presenting signs of primary Sjögren'ssyndrome. Dermatology. 1997;195(1):93-5.
5. Ramos-Casals M, Anaya JM, García-Carrasco M, Rosas J, Bové A, Claver G, Diaz LA, Herrero C, Font J. Cutaneous vasculitis in primary Sjögren syndrome: classification and clinical significance of 52 patients. Medicine (Baltimore). 2004 Mar;83(2):96-106.
6. Malladi AS, et al. Primary Sjögren's syndrome as a systemic disease: a study of participants enrolled in an international Sjögren's syndrome registry. Arthritis Care Res (Hoboken). 2012 Jun;64(6):911-8.
7. Holtman J et al. Dapsone is an effective therapy for the skin lesions of subacute cutaneous Lupus Erythematosus and urticarial vasculitis in a patient with C2 deficiency. J Rheumatol 1990;17:1222-5
8. Wiles J et al. Urticarial Vasculitis treated with colchicine. Arch Dermatol. 1985 june. Vol 121
9. Yokota K, Shichinohe R, Hayasaka T. Topical tacrolimus in the treatment of annular erythema associated with Sjögren's syndrome. Clin Exp Dermatol. 2005 Jul;30(4):450-1.
10. Katayama I, Kotobuki Y, Kiyohara E, Murota H. Annular erythema associated with Sjögren's syndrome: review of the literature on the management and clinical analysis of skin lesions. Mod Rheumatol. 2010 Apr;20(2):123-9.
11. de Winter S, van Buchem MA, Vermeer MH. Annular erythema of Sjögren's syndrome. Lancet. 2006 May 13;367(9522):1604.
12. Haimowitz JE, McCauliffe DP, Seykora J, Werth VP. Annular erythema of Sjögren's syndrome in a white woman. J Am Acad Dermatol. 2000 Jun;42(6):1069-72.

13. Nobeyama Y, Matsuzaki H, Nakagawa H. Annular erythema of Sjögren's syndrome treated successfully with low-dose cyclosporine. J Dermatol. 2014 May;41(5):463-4.
14. Tanioka M, Takahashi K, Miyachi YI. Narrowband ultraviolet B phototherapy for inflammatory vitiligo with raised borders associated with Sjögren's syndrome. Clin Exp Dermatol. 2009 Apr;34(3):418-20.
15. Logvinenko OA, et al. Rituximab therapy for systemic manifestations and MALT lymphomas of the parotid gland in Sjögren's disease: preliminary data. Ter Arkh. 2012;84(12):88-96.
16. Gottenberg JE, Cinquetti G, Larroche C,et al., Club Rhumatismes et Inflammations and the French Society of Rheumatology. Efficacy of rituximab in systemic manifestations of primary Sjogren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. Ann Rheum Dis 2013; 72:1026– 1031.
17. Meijer JM, Meiners PM, Vissink Aet al. Effectiveness of rituximab treatment in primary Sjogren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960-8
18. Ramos Casals M, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol 2010;28:468–76.
19. Ting-Yun Lin et al. Cyclophsphamide-rescued plsmapheresis-unresponsive secondary thrombotic thrombocytopenic purpura caused by Sjögren's syndrome. Arch Med Sci 2012;8,5: 934-938
20. Gubin MA, Shcherbachenko OI, Lobodov BV. The use of plasmapheresis in treating Sjögren's disease (syndrome). Stomatologiia (Mosk) 1996;75(3):24-6

SÍNDROME DE SJÖGREN PRIMARIO Y COMPROMISO RESPIRATORIO

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Pregunta 1- En pacientes con Síndrome de Sjögren primario (SSp), ¿con qué frecuencia se diagnostica la presencia de compromiso pulmonar?

Estrategia/combinación de términos:

((sjogren[All Fields]) AND (involvement[All Fields]) AND (upper[All Fields]) AND (respiratory[All Fields]) AND (airway[All Fields] sjogren[All Fields]) AND (involvement[All Fields]) AND (upper[All Fields]) AND (airway[All Fields]

sjogren[All Fields]) AND (xerotrachea[All Fields]))

Resultados de la búsqueda: pubmed= 56 artículos, Lilacs= 18, Cochrane= 0
Total: 62
Excluídos: 60
Total: 7

Yazisiz y colaboradores publicaron en 2010 una serie de casos retrospectiva que tuvo como objetivo investigar la prevalencia, los predictores y los hallazgos radiológicos del SSp asociado a afectación pulmonar. Se incluyeron 123 pacientes sin compromiso pulmonar pre-existente que fueron seguidos durante cinco años. El diagnóstico de afectación pulmonar se basó en la presencia de signos / síntomas pulmonares y / o alteración de las pruebas de función pulmonar, junto con alteraciones en la tomografía computarizada de alta resolución (TACAR). 14 pacientes (11,4%) presentaron signos/ síntomas de compromiso pulmonar con alteraciones en la TACAR y/o en pruebas de función pulmonar (PFR). La tasa de fumadores, la razón hombre / mujer y la edad media fueron mayores en los pacientes con compromiso de pulmón ($p < 0,05$). El patrón más frecuente en la TACAR fue vidrio esmerilado (64.3%). Otros hallazgos comunes fueron las bronquiectasias, patrón reticular y panal de abeja, la localización predominantemente en los lóbulos inferiores [(1)]. NE: 4

Palm y colaboradores publicaron en 2013 una serie de casos de pacientes consecutivos que tuvo como objetivo describir la prevalencia de manifestaciones clínicas pulmonares en el SSp, y en base a los datos de un registro, evaluar la calidad de vida y la mortalidad en estos pacientes. La afectación pulmonar se definió como anomalías típicas identificadas con TACAR y / o PFR. En nuestra cohorte total (216 pacientes), 59 (27%) presentaron compromiso pulmonar. Las anormalidades por TACAR se encontraron en 50 pacientes (23%) y de las PFT en 34 pacientes (16%). Se observó un deterioro significativo e independiente en el dominio de función física del SF 36, en el análisis ajustado. En un periodo de 8 años de seguimiento, 17 pacientes murieron, 10 de ellos con compromiso pulmonar (4.5% versus 17%, $p < 0.01$) [(2)]. NE: 4

Strimlan y colaboradores publicaron en 1976 una serie de 343 pacientes, observándose afectación pulmonar en 31 de ellos (9%). Tos, disnea, neumonitis recurrente y dolor pleural fueron las principales manifestaciones. Las características radiográficas incluyeron los patrones intersticial y alveolar difuso, y el derrame pleural [3]. NE: 4

Constantopoulos y colaboradores publicaron en 1985 una serie de 36 pacientes con SSp que fueron evaluados por manifestaciones respiratorias utilizando clínica, radiología, PFR y en cinco casos biopsia. 27 pacientes (75%) tenían evidencia de compromiso respiratorio, el cual ocurrió, por lo general, a principios del curso de la enfermedad. La enfermedad pulmonar intersticial difusa fue la más común (25%), seguida de las enfermedades de la pequeña v**ía** aérea (22%) y la sequedad de las vías respiratorias superiores (17%) [4] .NE: 4

Gardiner y colaboradores publicaron en 1993 una serie de 16 pacientes con SSp que presentaban disnea, en los que se realizó investigados con la TACAR, lavado broncoalveolar y biopsia transbronquial. Seis pacientes presentaban evidencia de fibrosis intersticial, cinco infiltración linfocítica peribronquial y tres engrosamiento pleural [5]. NE: 4

Uffmann y colaboradores publicaron en el 2001 una serie de 37 pacientes consecutivos con SSp y radiografía de tórax normal. En 34 pacientes, la TACAR se correlacionó con las PFR. Se observó TACAR anormal en 24 de 37 pacientes (65%): engrosamiento septal interlobular, patrón reticulonodular; vidrio esmerilado, quistes parenquimatosos, opacidades intralobulillares, panalización, engrosamiento de la pared bronquial, bronquiectasias, e irregularidades pleurales. La TACTAR fue normal en cuatro pacientes con PFR que indicaba presencia de enfermedad de las pequeñas vías aéreas. Se encontraron anormalidades en TACAR en siete pacientes con PFR normal. La correlación general entre la TACAR y PFR era pobre [6]. NE: 4

Garcia- Carrasco y colaboradores publicaron en el 2002 una serie de 373 casos consecutivos con SSp en la que se describen las características clínicas y de laboratorio de los pacientes incluidos en un registro de cuatro hospitales. En lo que respecta al compromiso pulmonar, el mismo se observó en 37 (9%) pacientes, manifestado por tos y/ o disnea, con anormalidades intersticiales en las radiografías de tórax, las PFR y/o alveolitis y/ o fibrosis en la TACAR [7]. NE: 4

Pregunta 2- ¿Los pacientes con SSp y enfermedad intersticial pulmonar tienen peor pronóstico que los pacientes con SSp sin compromiso pulmonar?

Estrategia/combinación de términos:
((sjogren[All Fields]) AND (nsip[All Fields] OR uip[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields]))

Resultados de la búsqueda:
Pubmed= 9 artículos, lilacs= 3, cochrane= 0
Total: 175

Excluidos: 173
Total: 2

Enomoto y colaboradores publicaron en 2013 un estudio de cohorte retrospectivo, que tuvo como objetivo evaluar el valor pronóstico de la neumonía intersticial usual (NIU), e identificar los factores pronósticos en pacientes con SSp y enfermedad pulmonar intersticial (EPI). Se incluyeron 33 pacientes con SSp y EPI: 22 con neumonía intersticial no específica (NINE) y 11 con UIP. El tiempo promedio de seguimiento fue de 110 meses, y la tasa de supervivencia a los cinco años de 87,3%, en la población total de pacientes. El pronóstico de los pacientes con NIU no fue significativamente diferente al de los pacientes con NINE. El análisis multivariado identificó a la presión arterial de monóxido de carbono (HR: 1.68. IC 95%: 1.24–2.28, *P* < 0.01) la extensión del patrón reticular en la TACTAR (HR: 4.17. IC 95%: 1.18–14.73, *P* = 0.03), y la severidad de los focos de fibroblastos por anatomía patológica (HR: 9.26. IC 95%: 1.74–49.35, *P* <0.01) como factores independientes asociados a mayor mortalidad [8]. NE: 3

Parambil y colaboradores publicaron en 2006 una serie de casos retrospectiva, que incluyó 18 pacientes con SSp y sospecha de EPI, a quienes se les realizó biopsia de pulmón. La histopatología fue compatible con NINE en cinco pacientes, neumonía organizada en cuatro, NIU en tres, neumonía intersticial linfocítica en tres, linfoma en dos y amiloidosis en un paciente. El tratamiento incluyó prednisona con o sin inmunosupresores. En un promedio de 38 meses de seguimiento, la mayoría de los pacientes mejoraron o permanecieron estables, excepto tres pacientes con NIU, uno con NINE y uno con amiloidosis [9]. NE: 4.

Pregunta 3- ¿Aumenta la mortalidad el compromiso respiratorio en SSp?

Estrategia/combinación de términos:

((lund[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) AND ("sjogren's syndrome"[MeSH Terms] OR "sjogren's"[All Fields]) AND ("syndrome"[All Fields] OR "sjogren's syndrome"[All Fields] OR "syndrome"[All Fields]) AND ("sjogren"[All Fields]) OR "syndrome sjogren"[All Fields]) AND primary[All Fields])
(("lung"[MeSH Terms] OR "lung"[All Fields]) AND sjogren[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]))

Resultados de la búsqueda: pubmed= 9 artículos, lilacs= 1, cochrane= 0
Total: 26
Excluidos: 24
Total: 1

Chen y colaboradores publicaron en 2014 una serie de casos retrospectiva, que incluyó 44 pacientes con SSp y compromiso pulmonar, que tuvo como objetivo demostrar la correlación entre la TACAR y las PFR con el pronóstico de estos

pacientes. 12 de los 44 pacientes murieron en un promedio de tiempo de seguimiento de 3. 7 años, en 11 de ellos la causa de muerte fue la falla respiratoria. Los pacientes que fallecieron presentaron menor FEV1 (63.1 +/-19.4% vs. 79.0+/- 22.7%, p: 0.017), FVC (58.7 +/- 20.4% vs. 77.1 +/- 17.5%, p: 0.005) y PEF (54.3+/- 20.5% vs. 72.0 +/- 24.8%, p: 0.035) y puntajes más altos de score tomográfico (9.2+/-5.7 vs. 5.2+/- 3.5, p: 0.033) comparado con los pacientes que sobrevivieron. Un puntaje en el score tomográfico mayor o igual a 13, se mostró como un factor de riesgo independiente para mortalidad, en el análisis multivariado (OR: 40.15. IC 95%: 2.75- 586.99) [(10)]. NE: 4

Pregunta 4- ¿La evaluación de la actividad de la enfermedad pulmonar intersticial en el SSp requiere realización de DLCO y TACAR?

Estrategia/combinación de términos:

((sjogren[All Fields]) AND ("activity"[All Fields]) AND ("lung diseases, interstitial"[MeSH Terms] OR "lung"[All Fields]) AND ("diseases"[All Fields]) AND ("interstitial"[All Fields] OR "interstitial lung diseases"[All Fields] OR ("interstitial"[All Fields]) AND ("lung"[All Fields]) AND ("disease"[All Fields]) OR "interstitial lung disease"[All Fields]) AND (dlco[All Fields])

(primary[All Fields]) AND ("sjogren's syndrome"[MeSH Terms] OR "sjogren's"[All Fields]) AND ("syndrome"[All Fields] OR "sjogren's syndrome"[All Fields] OR ("sjogren"[All Fields]) AND ("syndrome"[All Fields] OR "sjogren syndrome"[All Fields]) AND ("motor activity"["activity"[All Fields]) AND ("lung diseases, interstitial"[MeSH Terms] OR "lung"[All Fields]) AND ("diseases"[All Fields]) AND ("interstitial"[All Fields] OR "interstitial lung diseases"[All Fields] OR "interstitial"[All Fields] AND "lung"[All Fields]) AND ("disease"[All Fields]) OR "interstitial lung disease"[All Fields]) AND dlco[All Fields]

sjogren[All Fields]) AND (interstitial[All Fields]) AND (involvement[All Fields]) AND (hrct[All Fields]

sjogren[All Fields]) AND ("lung diseases, interstitial"[MeSH Terms] OR ("lung"[All Fields]) AND ("diseases"[All Fields]) AND ("interstitial"[All Fields] OR "interstitial lung diseases"[All Fields] OR "interstitial"[All Fields]) AND ("lung"[All Fields]) AND ("disease"[All Fields]) OR "interstitial lung disease"[All Fields]) AND (hrct[All Fields]))

Resultados de la búsqueda: pubmed= 8 artículos, lilacs= 3, cochrane= 0
Total: 9
Excluidos: 5
Total: 3

Lohrmann y colaboradores publicaron en 2004 una serie de casos retrospectiva, que incluyó 24 pacientes, que tuvo como objetivo evaluar las anomalías pulmonares observadas en la TACTAR en pacientes con SSp. De los 24 pacientes incluidos, 19 (79,2%) mostraron hallazgos patológicos y cinco (21,8%) presentaron TACTAR normal. Se encontró enfermedad de las vías respiratorias sola o en asociación con la presencia de diversos grados de enfermedad intersticial [(11)]. NE: 4

En el estudio de Chen y colaboradores, descripto previamente, el grado de compromiso por TACTAR se asoció significativamente con mayor mortalidad [10]. NE: 4

En el estudio de Uffman y colaboradores publicado en 2001, comentado con anterioridad, que incluyó a 37 pacientes con SSp y radiografías de tórax normales. 24 (64%) de 37 presentaron TACTAR alterada y 32 pacientes alterados la PFR. La correlación entre TACTAR y PFR fue pobre. TACTAR y PFR parecen ser sensibles tanto para la detección temprana en anormalidades del parénquima y disminución de la función pulmonar en pacientes asintomáticos con SSp [6]. NE: 4

Pregunta 5- ¿Se debería indicar la biopsia de glándula salival en pacientes con EPI y sospecha de SSp?

Estrategia/combinación de términos:
((("lung diseases"[MeSH Terms] OR "lung"[All Fields]) AND ("diseases"[All Fields] OR "lung diseases"[All Fields] OR "lung"[All Fields] AND "disease"[All Fields] OR "lung disease"[All Fields]) AND (gland [All Fields]) AND (salivary [All Fields]) AND ("pathology"[Subheading] OR "pathology"[All Fields] OR "biopsy"[All Fields] OR "biopsy"[MeSH Terms]) AND (sjogren[All Fields]))

Resultados de la búsqueda: pubmed= 15 artículos, lilacs= 8, cochrane= 0
Total: 18
Excluidos: 17
Total: 1

Fischer y colaboradores publicaron en 2009 una serie de casos, que tuvo como objetivo describir las características de pacientes con EPI de causa desconocida, con manifestaciones compatibles con de SSp y una biopsia de glándula salival positiva. Se incluyeron 38 pacientes con EPI, en quienes se realizó evaluación pulmonar, serológica y clínica. Todos los pacientes fueron sometidos a biopsia de glándula salival menor. En 13 pacientes, la biopsia fue positiva, lo que confirmó el diagnóstico de SSp, según criterios clasificatorios 2002. De ellos siete pacientes eran mujeres; 8 tenían historia de tabaquismo y 10 presentaban xeroftalmía o xerostomía. Cuatro pacientes fueron negativos para anticuerpos antinucleares y factor reumatoideo y tres de ellos también eran negativos para anti Ro y anti La [12]. NE: 4

Pregunta 6- El diagnóstico de la enfermedad pulmonar en SSp, ¿requiere la realización de lavado broncoalveolar/biopsia?

Estrategia/combinación de términos:

((Involvement [All Fields]) AND ("lung"[MeSH Terms] OR "lung"[All Fields]) AND (sjogren[All Fields]) AND (BAL[All Fields]

("disease"[MeSH Terms] OR "disease"[All Fields]) AND "lung"[MeSH Terms] OR "lung"[All Fields]) AND sjogren[All Fields]) AND (BAL[All Fields]

"disease"[MeSH Terms] OR "disease"[All Fields]) AND ("lung"[MeSH Terms] OR "lung"[All Fields]) AND (sjogren[All Fields]) AND ("lung"[MeSH Terms] OR "lung"[All Fields]) AND ("pathology"[Subheading] OR "pathology"[All Fields] OR "biopsy"[All Fields] OR "biopsy"[MeSH Terms])

Involvement [All Fields]) AND ("lung"[MeSH Terms] OR "lung"[All Fields]) AND (sjogren[All Fields]) AND ("lung"[MeSH Terms] OR "lung"[All Fields]) AND ("pathology"[Subheading] OR "pathology"[All Fields] OR "biopsy"[All Fields] OR "biopsy"[MeSH Terms]))

Resultados de la búsqueda: pubmed= 86 artículos, lilacs= 18, cochrane= 1
Total: 89
Excluidos: 88
Total: 0

Pregunta 7- ¿El compromiso respiratorio en el SSp debe ser tratado con esteroides?

Estrategia/combinación de términos:

((sjogren[All Fields]) AND (interstitial[All Fields]) AND (involvement[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("steroids"[MeSH Terms] OR "steroids"[All Fields]))

Resultados de la búsqueda: pubmed= 7 artículos, lilacs= 2, cochrane= 0
Total: 8
Excluidos: 7
Total: 1

En la serie de 18 casos, publicada por Parambil y colaboradores y descripta previamente, los pacientes fueron tratados con prednisona, generalmente en dosis de 1 mg/ kg/ dia. Otras drogas fueron agregadas con posterioridad, en los casos en los que no se encontraba mejoría, e incluyeron hidroxichloroquina (cinco pacientes), azatioprina (dos pacientes) y ciclofosfamida (dos pacientes). La mitad de los pacientes presentaron 10% de aumento de la FVC o 15% en la difusión de monóxido de carbono, mientras que el 28% mostro deterioro de estos parámetros. Siete pacientes murieron en un periodo de seguimiento promedio de 38 meses, en tres de ellos debido a exacerbación de EPI [(9)]. NE: 4

Pregunta 8- ¿El compromiso intersticial en el SSp debe ser tratado con inmunosupresores?

Estrategia/combinación de términos:

((sjogren[All Fields]) AND (interstitial[All Fields]) AND (involvement[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]

sjogren[All Fields]) AND (interstitial[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("immunosuppressive agents"[Pharmacological Action] OR "immunosuppressive agents"[MeSH Terms] OR "immunosuppressive"[All Fields] AND ("agents"[All Fields] OR "immunosuppressive agents"[All Fields] OR "immunosuppressants"[All Fields]))

Resultados de la búsqueda: pubmed= 9 artículos, lilacs= 2, cochrane= 0
Total: 9
Excluidos: 7
Total: 3

Schnabel y colaboradores publicaron en 1998 una serie de seis casos de pacientes con rápida progresión de EPI asociada a enfermedades del colágeno, (dos PM, dos ES, un LES y un SSp) recibieron 6-9 ciclos de de cilofosfamida en pulsos endovenosos (0,5 g / m2 de superficie corporal, junto con un curso inicial de 50 mg de prednisolona, que se disminuyó gradualmente asociada a un mantenimiento con hidroxicloroquina y azatioprina.Todos los pacientes mostraron una mejoría significativa en la tolerancia al ejercicio y la función pulmonar [13]. NE: 4

Dalvi y colaboradores publicaron en 2007 un reporte de caso en el cual se observó mejoría clínica y radiológica en un paciente con SSp y neumonía intersticial linfocítica que fue tratado con corticoides, azatioprina e hidroxichloroquina [14]. NE: 4

En la serie de 18 casos publicada por Parambil y colaboradores, descripta previamente, los pacientes recibieron tratamiento con prednisona y, en los casos de en los que no se encontraba mejoría, se agregó hidroxichloroquina (cinco pacientes), azatioprina (dos pacientes) y ciclofosfamida (dos pacientes). La mitad de los pacientes presentaron 10% de aumento de la FVC o 15% en la difusión de monóxido de carbono, mientras que el 28% mostro deterioro de estos parámetros. Siete pacientes murieron en un periodo de seguimiento promedio de 38 meses, en tres de ellos debido a exacerbación de EPI [9]. NE: 4

Deheinzelin y colaboradores publicaron en 1996 una serie de casos que incluyo 20 pacientes con SSp y EPI, 11 de los cuales fueron tratados con azatioprina, seis de ellos recibió concomitantemente prednisona. La FVC aumentó un 10% en siete de los pacientes que recibieron tratamiento [15]. NE: 4

Pregunta 9- ¿El compromiso intersticial en el SSp debe ser tratado con terapias biológicas?

Estrategia/combinación de términos:
(("biological therapy"[MeSH Terms] OR "biological"[All Fields]) AND ("therapy"[All Fields] OR "biological therapy"[All Fields] OR ("biologic"[All Fields] AND "therapies"[All Fields]) OR "biologic therapies"[All Fields]) AND (sjogren[All Fields]) AND ("lung diseases"[MeSH Terms] OR ("lung"[All Fields]) AND ("diseases"[All Fields] OR "lung diseases"[All Fields] OR ("lung"[All Fields]) AND ("disease"[All Fields]) OR "lung disease"[All Fields]))

Resultados de la búsqueda: pubmed= 9 artículos, lilacs= 2, cochrane= 0
Total: 10
Excluidos: 8
Total: 1

Seror y colaboradores publicaron en 2007 una serie de casos retrospectiva, que tuvo como objetivo investigar la eficacia y seguridad del rituximab en las manifestaciones sistémicas del SSp y los cambios en biomarcadores de las células B. Se incluyeron 16 pacientes que cumplían los criterios clasificatorios 2002. En cinco pacientes la indicación fue por linfoma, en dos por EPI refractaria asociada a poliartritis, en otros dos por poliartritis severa, en cinco por crioglobulinemia mixta, en uno por trombocitopenia y en uno por mononeuritis multiple. Se observó respuesta favorable en cuatro de los cinco pacientes con linfoma y en nueve de los 11 pacientes con compromiso sistémico, incluyendo una buena respuesta respecto al compromiso pulmonar [16]. NE: 4

BIBLIOGRAFIA:

1- Yazisiz V, Arslan G, Ozbudak IH, Turker S, Erbasan F, Avci AB, Ozbudak O, Terzioglu E. Lung involvement in patients with primary Sjögren's syndrome: what are the predictors? Rheumatol Int (2010) 30:1317–1324

2- Palm O, Garen T, Berge Enger T, Jensen JL, Lund MB, Aaløkken TM, Gran JT. Clinical pulmonary involvement in primary Sjogren's syndrome: prevalence, quality of life and mortality—a retrospective study based on registry data. Rheumatology 2013;52:173-179

3- Strimlan CV, Rosenow EC 3rd, Divertie MB, Harrison EG Jr. Pulmonary Manifestations of Sjögren's syndrome. Chest. 1976 Sep;70(03):354-61

4- Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM. Respiratory manifestations in primary Sjögren's syndrome. A clinical, functional, and histologic study. Chest. 1985 Aug;88(2):226-9.

5- Gardiner P, Ward C, Allison A, Ashcroft T, Simpson W, Walters H, Kelly C. Pleuropulmonary abnormalities in primary Sjögren's syndrome. J Rheumatol. 1993 May;20(5):831-7.

6- Uffmann M, Kiener HP, Bankier AA, Baldt MM, Zontsich T, Herold CJ. Lung manifestation in asymptomatic patients with primary Sjögren syndrome: assessment with high resolution CT and pulmonary function tests. J Thorac Imaging. 2001 Oct;16(4):282-9.

7- García-Carrasco M, Ramos-Casals M, Rosas J, Pallarés L, Calvo-Alen J, Cervera R, Font J, Ingelmo M. Primary Sjögren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore). 2002 Jul;81(4):270-80.

8- Enomoto Y, Takemura T, Hagiwara E, Iwasawa T, Fukuda Y, Yanagawa N, Sakai F, Baba T, Nagaoka S, Ogura T. Prognostic factors in intersticial lung disease associated with primary sjogren syndrome a retrospective analisys of 33 pathologically proven cases. Plos one 2013 sep 9;8 (9) e:73774

9- Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. Chest. 2006 Nov;130(5):1489-95.

10- Chen MH, Chou HP, Lai CC, Chen YD, Chen MH, Lin HY, Huang DF. Lung involvement in primary Sjögren's syndrome: Correlation between high-resolution computed tomography score and mortality. J Chin Med Assoc. 2014 Feb;77(2):75-82.

11- Lohrmann C, Uhl M, Warnatz K, Ghanem N, Kotter E, Schaefer O, Langer M. High-resolution CT imaging of the lung for patients with primary Sjogren's syndrome. Eur J Radiol. 2004 Nov;52(2):137-43.

12- Fischer A, Swigris JJ, du Bois RM, Groshong SD, Cool CD, Sahin H, Lynch DA, Gillis JZ, Cohen MD, Meehan RT, Brown. Minor salivary gland biopsy to detect

primary Sjogren syndrome in patients with interstitial lung disease. Chest. 2009 Oct;136(4):1072-8.
13- Schnabel A, Reuter M, Gross WL. Intravenous pulse cyclophosphamide in the treatment of interstitial lung disease due to collagen vascular diseases. Arthritis Rheum. 1998 Jul;41(7):1215-20.
14- Dalvi V, Gonzalez EB, Lovett L. Lymphocytic interstitial pneumonitis (LIP) in Sjögren's syndrome: a case report and a review of the literature. Clin Rheumatol. 2007 Aug;26(8):1339-43.
15- Deheinzelin D , Capelozzi VL , Kairalla RA , Barbas Filho JV , Saldiva PH , de Carvalho CR . Interstitial lung disease in primary Sjögren's syndrome. Clinical-pathological evaluation and response to treatment. Am J Respir Crit Care Med. 1996; 154 (3 pt 1): 794 - 799 .
16- Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis 2007;66(3):351- 7.

SÍNDROME DE SJÖGREN PRIMARIO Y COMPROMISO NEUROLÓGICO

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Pregunta 1- ¿El compromiso neurológico en Sindrome de Sjögren primario (SSp) se asocia a positividad de antiRo/La?

Se utilizaron los siguientes términos de búsqueda: neurology affection - neurologic compromise -neurology - neurologic AND Sjögren - Sjögren Syndrome - Sjogren disease AND La-SSB - La/SSB - Ro/SSA autoantigen - Ro/SSA autoantibodies - Ro-SSA autoantibodies - Ro autoantibodies - Ro antibodies - Ro-SSA antigen - Ro autoantigen - Ro autoantibody - Ro/La - SSA antigen - Ro SSA/antigen

Se encontraron en Pubmed 2754 artículos, 2716 se descartaron por título, 17 se descartaron por abstract, 12 se descartaron por contenido; se seleccionaron 9 artículos para análisis. Las búsquedas por LILACS y por Cochrane no arrojaron resultados.

Kvarnström y colaboradores publicaron en 2015 una serie de casos de pacientes consecutivos que tuvo como objetivo determinar la incidencia de SSp y la frecuencia de manifestaciones extraglandulares (MEG) al diagnóstico. Se evaluaron pacientes derivados por diferentes especialistas y se determinó el número de casos incidentes desde enero 2007 hasta diciembre 2011. De los 781 pacientes derivados, 199 (25,5%) cumplieron criterios para SSp. En un sub análisis del estudio en el que se compararon los pacientes con anticuerpos positivos (FAN, anti Ro y/o anti La) versus aquellos con anticuerpos negativos, no se encontraron diferencias significativas respecto a la presencia de neuropatía (NPT) periférica entre ambos grupos ((6/105 (5.7%) versus 4/88 (4.5%), *p*: 0.15) [(1)]. NE: 4

Morreale y colaboradores publicaron en 2014 un estudio de corte transversal, que tuvo como objetivo evaluar la prevalencia del compromiso del sistema nerviosos central (SNC) en SSp y los posibles marcadores de daño del sistema nervioso. Se incluyeron 120 pacientes de un centro de Italia. En 81 pacientes (67,5%) se observó compromiso del SNC, siendo la cefalea la manifestación más frecuente (46,9%), seguidos de los trastornos cognitivos (44.4%) y del estado de ánimo (38.3%). Los anticuerpos anti Ro/SSA se encontraron en 68 (84%) y anti La/SSB en 22 (27.2%) de los sujetos con compromiso del SNC. La presencia de anticuerpos anti Ro/SSA se encontró significativa e independientemente asociada a un aumento de riesgo de cefalea (OR: 2.85, IC 90%: 1.43–9.6; p< 0.01) y alteraciones del estado de ánimo (OR: 2.72, IC 90%: 2.95–13; p <,0.01) [(2)]. NE: 4

Hsu y colaboradores publicaron en 2014 un estudio de corte transversal, con recolección retrospectiva de los datos, cuyo objetivo fue analizar las características

clínicas y los marcadores serológicos asociados a la presencia de NPT periférica en pacientes con SSp. Se incluyeron 250 pacientes con SSp que habían sido hospitalizados en el período comprendido entre junio de 2005 y junio de 2011, en un Hospital de Taiwan. Tanto el dosaje de anticuerpos como el electromiograma fueron realizados durante la internación. Dieciocho pacientes presentaron compromiso del sistema nervioso periférico (SNP), seis neuropatía craneal y 12 neuropatía sensitivo motora versus 232 sin compromiso del SNP. De estos últimos, 33 tenían compromiso SNC, 16 accidente cerebrovascular o vasculitis, nueve movimientos anormales, cinco meningoencefalitis, tres epilepsia. No se encontró asociación estadísticamente significativa entre la presencia de neuropatía y la positividad de anticuerpos anti Ro, ni anti La [(3)]. NE: 4

Jamilloux y colaboradores publicaron en 2014, un estudio retrospectivo, longitudinal, que tuvo como objetivo evaluar si el perfil inmunológico y la presencia de manifestaciones sistémicas se asociaban a la presencia de manifestaciones neurológicas. Se incluyeron 420 pacientes de dos centros de Francia con una media de seguimiento de 73 (+/- 68) meses. Noventa y cinco pacientes (22%) desarrollaron compromiso neurológico, excluyéndose dos por diagnóstico de linfoma. Sesenta y dos pacientes presentaron compromiso del SNP, 41 del SNC y diez de ambos. En el análisis multivariado se encontró asociación negativa entre la presencia de compromiso neurológico y la presencia de anti Ro (OR 0.42, IC 0.25-0.71 $p<0.05$) [(4)]. NE: 4

Séne y colaboradores publicaron en 2011 un estudio de casos de pacientes con NPT periférica y controles (pacientes sin NPT periférica) que tuvo como objetivo evaluar la relación entre la presencia de NPT periférica en pacientes con SSp y los marcadores de proliferación monoclonal de células B y de activación crónica. Se incluyeron 120 pacientes, de un único centro de Paris evaluados en el período correspondiente a 1985-2009. Treinta pacientes (25%) presentaban NPT periférica. En el análisis multivariado, no se encontró asociación estadísticamente significativa entre el anti Ro, ni anti La con la presencia de NPT [(5)]. NE: 4

Delande y colaboradores publicaron en 2004 una serie de casos que tuvo como objetivo describir las manifestaciones clínicas, de laboratorio, e imágenes en pacientes con SSp y compromiso neurológico referidos a un departamento de neurología o medicina interna en un Hospital de Francia (enero 1993-dic 2001). Se incluyeron 82 pacientes con compromiso neurológico (31 SNC, 26 SNP y 25 ambos). En un sub análisis se evaluaron las diferencias entre pacientes con compromiso del SNC y SNP. Los pacientes con Ro+ (medido por inmunodifusión) tuvieron significativamente mayor compromiso del SNP que SNC. En los 39 pacientes en los que también se utilizó Western blot para la detección de los anticuerpos anti Ro, está diferencia no se observó [(6)]. NE: 4

Scofield y colaboradores publicaron en 2012 un estudio de corte transversal cuyo objetivo fue determinar el porcentaje de pacientes con SSp (según criterios clasificatorios americano- europeos 2002) con NPT sensitiva y su asociación con la

presencia de anticuerpos anti Ro/La. Se incluyeron 88 pacientes, en los que se realizó dosaje de anticuerpos y evaluación neurológica. En 27 pacientes se encontró NPT periférica (alta sensibilidad fina, vibratoria o propiocepción detectados por electromiografía); por técnica de doble inmunodifusión se encontraron 12 pacientes con anticuerpos anti Ro y anti La positivos. El 66,7% de ellos presentaba NPT versus 25% de NPT en los pacientes con dichos anticuerpos negativos. Utilizando métodos más sensibles como Inno-Lia assay, se encontraron 32 pacientes con ambos anticuerpos positivos; en 13 de ellos, se observó NPT [7]. NE: 4

Ramos- Casals y colaboradores publicaron en 2008 una serie de casos que tuvo como objetivo evaluar la presentación clínica de pacientes con SSp atendidos en 12 centros de España y determinar cómo las características epidemiológicas, clínicas y analíticas modulan la expresión de la enfermedad. Se incluyeron 1010 pacientes con SSp (según criterios europeos 1993), tanto casos prevalentes como incidentes. 110 (11%) presentó compromiso SNP, 21 (2%) SNC. 518/1002 (52%) anti Ro positivo. 19/233 (8%) de casos incidentes tuvieron NPT periférica versus 58/238 (34%) de los pacientes con enfermedad mayor a 10 años evolución (p<0.001). En un sub análisis los pacientes anti Ro y/o anti La positivos tuvieron mayor frecuencia de NPT periférica (74 de 534 pacientes seropositivos (14%) p=0.001), tanto en el análisis univariado como multivariado (ajustado por tiempo de evolución, sexo y edad) [8]. NE: 4
Alexander y colaboradores publicaron en 1994 un estudio de corte transversal que tuvo como objetivo determinar la relación entre la presencia de anticuerpos anti Ro y los diferentes tipos de compromiso del SNC (por ejemplo focal o difuso), así como con las imágenes cerebrales y la angiografía. Se incluyeron cuatro grupos: I: SS y compromiso activo del SNC (N: 52, 45 SSp y 7 SS secundario), en los que se determinó la presencia de anti Ro por doble difusión en gel; II: SS y compromiso activo del SNC (N:49, 43 con SSp y seis con SS secundario) con determinación de Ro60kD por ELISA; III y IV: sin compromiso del SNC (N grupo III=38, 33 con SSp y cinco con SS secundario y N grupo IV=1diez, nueve con SSp y uno con SS secundario) con dosaje de anti Ro por doble difusión en gel y ELISA, respectivamente, y 20 controles sanos. El anti Ro se encontró presente en 28/52 (54%) pacientes del grupo I versus 9/38 (24%) del grupo III (p=0.005). Diez pacientes murieron por compromiso del SNC (19%), ocho presentaban anti Ro positivo (29%) versus 2/24 (8%) Ro negativo (p=0.085). En el grupo I, 39 pacientes (75%) tuvieron alteración en la TAC y/o RM de los cuales 25/28(89%) presentaban Ro positivos versus 14/24(58%) Ro negativos (p=0.022; OR 6; IC 95%: 1.4-25.3). Lesiones extensas se observaron en 19/28(68%) Ro positivos versus 4/24(17%) Ro negativos (p<0.0003; OR 10.6; IC 95%: 2.8-40.1). Se realizaron 44 angiografías: 16/21 (76%) pacientes anti Ro positivos mostraron alteraciones versus 4/23 (17%) de los anti Ro negativos (p<0.0002; OR 15.2; IC 95%: 3.5-66.3) [9]. NE: 4

Pregunta 2- ¿El compromiso neurológico en el SSp se asocia a hipergammaglobulinemia?

Se utilizaron los siguientes términos de búsqueda: neurology affection - neurologic compromise - neurology - neurologic AND Sjögren - Sjögren Syndrome- Sjogren disease AND hypergamma - hypergammaglobulinaemia – gammapathy

Sjögren - Sjögren Syndrome - Sjogren disease AND hypergamma - hypergammaglobulinaemia – gammapathy

Se encontraron 4 artículos por LILACS no se seleccionó ninguno. En Cochrane se encontraron 70, tampoco se seleccionó ningún artículo. En Pubmed: se encontraron 175 Artículos, 164 se descartaron por título, 1 se descartó por abstract y 6 se descartaron por contenido. Se analizaron 4 artículos.

Martel y colaboradores publicaron en 2011 un estudio de cohorte retrospectiva que tuvo como objetivo evaluar el perfil inmunológico y su impacto en la actividad de la enfermedad y evolución a largo plazo en pacientes con SSp y compromiso sistémico. Se incluyeron 445 pacientes de dos centros de Francia desde 1985-2009. Setenta pacientes (16%) presentaron compromiso del SNP. Doscientos veinticinco pacientes tuvieron hipergammaglobulinemia (201 de ellos al momento del diagnóstico), no encontrándose asociación estadísticamente significativa e independiente de la misma con el desarrollo de compromiso del SNP, en el análisis multivariado [(10)]. NE: 3

En el estudio de Sène D y colaboradores, que fue comentado previamente, se observó que los pacientes con NPT sensitiva no atáxica presentaban hipergammaglobulinemia con una frecuencia significativamente mayor que los pacientes sin NPT (35% vs. 64%; p = 0.023); esta asociación no se observó en el análisis multivariado. En el caso de la NPT sensoriomotora se observó una menor frecuencia de hipergammaglobulinemia (14% versus 64%; p = 0.01) y una mayor frecuencia de gamapatía monoclonal (71% vs. 17%; p = 0.004), comparado con los pacientes sin NPT. Dichas asociaciones no se observaron en el análisis multivariado [(5)]. NE: 4

Brito Zerón y colaboradores publicaron en 2012 un estudio retrospectivo, longitudinal, que tuvo como objetivo evaluar las características clínicas y la evolución de los pacientes con gammapatía monoclonal (GM). Se incluyeron 408 pacientes consecutivos en el período comprendido entre enero 1990 y julio 2011, divididos en tres grupos: I- pacientes que cumplían criterios Americano-Europeos (n=221); II- pacientes que cumplían exclusivamente criterios 1993 (n=122) y III- pacientes con SS asociado a HCV (n=65). 48/221 (22%) de los pacientes del grupo I tuvieron GM; mientras que en los grupos control, la prevalencia fue de 16% en el grupo II ($p > 0.05$) y 52% en el grupo III ($p < 0.001$). En un sub análisis del estudio, los pacientes del grupo I con GM tuvieron mayor compromiso neurológico ((20/48 (48%) versus los pacientes del mismo grupo, sin GM ((40/173 (23%), p=0.016)). De los 48 pacientes 27 fueron seguidos al menos 3 años, 15 con GM intermitente y 12 GM persistente. 5/15 tuvieron compromiso SNC versus ningún paciente con GM persistente (p=0.047) [(11)]. NE: 4

Terrier y colaboradores publicaron en 2007 una serie de casos que tuvo como objetivo evaluar los resultados de la biopsia neuromuscular en pacientes con NPT periférica y SSp. Se incluyeron 40 pacientes. El diagnóstico de SSp fue posterior al desarrollo de NPT en25 casos, simultáneo en dos y posterior en 13. Al diagnóstico de la NPT, 27 pacientes (68%) presentaban otras manifestaciones extraglandulares. Se realizaron 34 biopsias neuromusculares. En 18 de ellas se observó atrofia neurogénica en

ausencia de vasculitis, en ocho vasculitis linfocítica y en 14 vasculitis necrotizante. En un sub análisis se observó que 1/18 (6%) pacientes sin vasculitis en la biopsia versus 8/22 (36%) con hallazgos de vasculitis en la biopsia, presentaban GM (p=0.03) [12]. NE: 4

Pregunta 3- ¿El compromiso neurológico en el SSp se asocia a hipocomplementemia?

Se utilizaron los siguientes términos de búsqueda: neurology affection - neurologic compromise - neurology - neurologic AND Sjögren - Sjögren Syndrome - Sjogren disease AND hypocomplementemia - complement C3 - complement C4 Sjögren - Sjögren Syndrome - Sjogren disease AND hypocomplementemia - complement C3 - complement C4

Se encontraron en Pubmed 143 artículos (132 se descartaron por título, 2 se descartaron por abstract y 6 por contenido). Se seleccionaron 3 artículos para análisis. En LILACS no se encontró ninguno. En Cochrane 3 pero no se seleccionó ninguno para análisis.

En el estudio descripto previamente de Terrier y colaboradores, 3/16 (19%) pacientes sin vasculitis versus 10/18 (56%) con vasculitis en la biopsia, presentaron hipocomplementemia (p=0.04) [12]. NE: 4

En el estudio de Delalande y colaboradores descripto con anterioridad, los pacientes con hipocomplementemia tuvieron mayor frecuencia de compromiso del SNP ((11(42,3%) versus dos con compromiso del SNC ((6,4%) versus 8 (32%) SNC + SNP, p <0, 01)) [6]. NE: 4

Ramos- Casals y colaboradores publicaron en 2005, un estudio observacional, retrospectivo y longitudinal, que tuvo como objetivo analizar la prevalencia e implicancias clínicas de la hipocomplementemia en pacientes con SSp. Dos centros, en Francia y España, reclutaron desde 1993 al 2003, 336 pacientes. Además, analizaron 46 pacientes con SS asociado a HCV y 184 con HCV y crioglobulinemia. Se realizó dosaje de complemento en la visita basal y, al menos, anualmente y se registraron las manifestaciones clínicas en forma acumulativa y retrospectiva. Los pacientes con bajos niveles de C4 tuvieron mayor prevalencia de NPT periférica ((8/39 (20%) versus 16/297 (5%), p<0.003)). En el análisis multivariado, la NPT mostró una asociación significativa e independiente con el descenso de C4 [13]. NE: 4

Pregunta 4- ¿El compromiso neurológico en el SSp se asocia a la presencia de crioglobulinas?

Se utilizaron los siguientes términos de búsqueda: neurology affection - neurologic compromise - neurology - neurologic AND Sjögren - Sjögren Syndrome - Sjogren disease AND Cryoglobulins- cryoglobulinemia - cryoglobulinemia/complications - cryoglobulinaemia - cryoglobulin Sjögren - Sjögren Syndrome - Sjogren disease AND cryoglobulins - cryoglobulinemia - cryoglobulinaemia - cryoglobulin cryoglobulinemia/complications“ -

La búsqueda por Cochrane encontró 1 artículo que no fue seleccionado y por LILACS 9 que fueron descartados. Por Pubmed se encontraron 267 Artículos, 253 se descartaron por título, 4 por abstract y 5 por contenido. Se seleccionaron 5 para su análisis.

En el estudio de Sène y colaboradores, la NPT sensitivomotora se encontró asociada a la presencia de crioglobulinemia mixta ((4/7 (57.1%) versus 10/90 (11.1%); p=0.008)). Sin embargo, no se observó asociación en el análisis multivariado [11]. NE: 4

En el trabajo de Delalande y colaboradores, los pacientes con crioglobulinas positivas tuvieron significativamente mayor compromiso del SNP: 14 (53,8%), versus seis (19,3%) con compromiso del SNC versus diiez (40%) con compromiso SNC+SNP [6]. NE: 4

En un sub análisis del estudio de Jamiloux y colaboradores, se encontró CN en 29/93 (31%), compromiso del SNC en 11/41 (27%) y del SNP en 22/62 (36%). A su vez, en el análisis multivariado, se observó asociación entre positividad de crioglobulinas y presencia de CN (OR 2.96, IC 1.57-5.58 p<0.05). El modelo de Cox mostró a las crioglobulinas como el único factor predictivo para el CN, especialmente NPT sensitivomotora y mononeuritis múltiple. Cuatro pacientes murieron, tres por encefalitis aguda y uno por vasculitis cerebral (presentaban crioglobulinas positivas) [4]. NE: 4

Quatuccio y colaboradores publicaron en 2015 un estudio de casos y controles, que tuvo como objetivo determinar diferencias entre pacientes con SSp con vasculitis crioglobulinémica (VC) y vasculitis hipergammaglobulinémica (VHG) en cinco centros italianos. Se incluyeron 652 pacientes: grupo I, N=23 (VC con púrpura y crioglobulinas positivas); grupo II, N=40 (VHGV) y grupo III, N=589 (controles: pacientes sin púrpura). 26 (4%) tuvieron NPT periférica. De ellos, nueve (39%) con VC y 16 (2,7%) de los controles (p<0.0001; RR: 23; IC 95%: 8,7-60,9). Un sólo paciente (2,5%) del grupo de VHG, presentó NPT [14]. NE: 4

En el estudio de Martel y colaboradores publicado en 2011, descripto previamente, se identificaron 68 de 445 pacientes, con crioglobulinas positivas (tipo II, N=24; tipo III, N=44), las cuales estuvieron presentes al momento del diagnóstico en 41 casos (9%). 26 de estos pacientes desarrollaron CN. Las crioglobulinas se encontraron asociadas a mayor frecuencia de compromiso del SPN ((23/68 (34%) versus 47/347 (13%) p=0.0003)). En el análisis multivariado se observó asociación significativa e independiente entre la presencia de crioglobulinas y NPT (OR 2.18, CI 1.09–4.37, p=0.02) [10]. NE: 3

Pregunta 5- ¿El compromiso neurológico en el SSp se asocia a la presencia de anticuerpos antifosfolípidos?

Se utilizaron los siguientes términos de búsqueda: neurology affection - neurologic compromise - neurology - neurologic AND Sjögren - Sjögren Syndrome - Sjogren disease AND antiphospholipid antibody - glycoprotein - anticardiolipin - lupus anticoagulant

Se encontraron 8 artículos por LILACS, ninguno seleccionado. Por Cochrane 3, ninguno seleccionado. Por Pubmed: 167 Artículos, 4 seleccionados por título abstract y contenido.

Pasoto y colaboradores publicaron en 2012 un estudio de corte transversal, que tuvo como objetivo evaluar la frecuencia de anticuerpos antifosfolipídicos (APLs) en SSp y su asociación con las manifestaciones clínicas. Se incluyeron 100 pacientes consecutivos del Hospital de Clínicas de San Pablo desde el 2010 al 2011, y 89 controles sanos. En todos los sujetos se realizó dosaje de anti coagulante lúpico (AL), anti cardiolipinas (ACL) y anti B2 glicoproteinas. Se realizó una exhaustiva evaluación clínica para recabar datos de historia de manifestaciones trombóticas y no trombóticas de SAF, factores de riesgo cardiovascular y manifestaciones sistémicas de SSp. Cinco pacientes tuvieron eventos trombóticos, dos accidentes cerebrovasculares (ACV), cuatro TVP y uno IAM, mientras que no hubo ninguno en los controles (p=0.061). 16/100 tuvieron alguno de los anticuerpos positivos. No hubo diferencias respecto a la presencia de migraña, ni compromiso SNP entre pacientes con o sin APLs. Respecto a los ACV, la frecuencia fue 2/16 (12,5%) versus 0/84 (p=0.024) [15]. NE: 4.

En este estudio descripto previamente, en el que se incluyeron 250 pacientes con SSp, 18 de los cuales presentaban compromiso SNP, seis NPT craneal, 12 NPT sensitivomotora, se observaron mayores títulos y positividad de AFL en estos 18 pacientes, en comparación con el resto: β2 glicoproteína 13,6 versus 1,35 (p=0.001); ACL IgG 6,8 vs 0 (p=0.001); ACL IgM 1,7 vs 0 (p=0.028). La anti B2 glicoproteina I se encontró significativa e independientemente asociada a dicha manifestación en el análisis multivariado [3]. NE: 4

Fauchais y colaboradores publicaron en 2004 un estudio de corte transversal que tuvo como objetivo determinar la prevalencia y significado clínico de los AFLs en una cohorte de pacientes con SSp. Los datos fueron recolectados en forma retrospectiva en un servicio de Medicina Interna de Francia; se incluyeron 108 pacientes, con una mediana de seguimiento de 60±47 meses. 74 pacientes tuvieron al menos dos determinaciones de AFL. 28 pacientes (38%) presentaron anticuerpos positivos. 5/28 (18%) de los pacientes con anticuerpos positivos versus 7/46 (15%) de los pacientes con anticuerpos negativos tuvieron compromiso del SNP, mientras que 1/28 (4%) versus 9/46 (20%) presentaron compromiso del SNC, respectivamente. Las diferencias no fueron estadísticamente significativas en ninguno de los dos casos [16]. NE: 4

Cervera y colaboradores publicaron en 1997 un estudio de corte transversal, cuyo objetivo fue determinar la prevalencia y significado clínico de los AFLs en pacientes con SSp. Se incluyeron 80 pacientes con SSp, los cuales se compararon con 50 pacientes con SS asociado a LES, 100 pacientes con LES y 100 controles sanos. En todos se realizó dosaje de anticuerpos para SAF y una evaluación clínica y de laboratorio. De los 80 pacientes, 11 (14%) tuvieron AFL+. Ningún paciente con anticuerpos positivos tuvo NPT periférica versus 9/69 del subgrupo con anticuerpos negativos [17]. NE: 4

Pregunta 6- ¿El compromiso neurológico en el SSp se asocia a otras manifestaciones extraglandulares?

Se incluyeron los siguientes términos de búsqueda: Sjögren - Sjögren Syndrome - Sjogren disease ANDneurology affection - neurologic compromise - neurology - neurologic AND Lung - heart - articular - arthritis - cutaneous - kidney - renal - extraglandular

Se encontraron cuatro artículos en Cochrane (ninguno seleccionado). En LILACS diez, uno artículo seleccionado (Anaya col). En Pubmed: 326 artículos, dos seleccionados por título, abstract y contenido.

Anaya y colaboradores publicaron en el año 2000 un estudio de corte transversal, que tuvo como objetivo determinar la prevalencia y las características clínicas e inmunogenéticas de los pacientes con SSp y compromiso neurológico. De los 95 pacientes incluidos, 11 (11,6%) presentaron compromiso neurológico. Ocho afección SNP (cinco con síndrome de túnel carpiano y tres con polineuropatia sensitiva distal) y tres SNC (migraña complicada, esclerosis múltiple c/ vasculitis y neuritis óptica c/ epilepsia). El compromiso del SNP se observó en pacientes con mayor compromiso extraglandular: vasculitis cutánea (OR: 6, IC 1,3-27, p=0.02) y fenómeno de Raynaud (OR: 10,3; IC 2-55; p = 0.004) [18]. NE: 4

En el trabajo de Jamilloux y colaboradores, descripto previamente, se encontró asociación significativa e independiente entre CN y el fenómeno de Raynaud (OR 1.84, IC 1.11-3.04 p<0.05), así como con el compromiso renal (OR 2.39, IC 1.07-5.32 p<0.05) [4]. NE: 4

En el estudio de Delalande, comentada con anterioridad, los pacientes con compromiso del SNP tuvieron una frecuencia significativamente mayor de Fenómeno de Raynaud, compromiso pulmonar, compromiso dermatológico y hematológico respecto de los pacientes con compromiso del SNC [6]. NE: 4

Pregunta 7- ¿La presencia de vasculitis en la biopsia neuromuscular o cerebral en SSp se asocia a positividad de crioglobulinas?

Se utilizaron los siguientes términos de búsqueda: nerve biopsy - brain biopsy AND Sjögren - Sjögren Syndrome - Sjogren disease AND Cryoglobulins-cryoglobulinemia - cryoglobulinemia/complications - cryoglobulinaemia - cryoglobulin AND Vasculitis

Se encontraron 137 artículos en Pubmed, se seleccionó uno para análisis (136 se descartaron por título, abstract y por contenido)

En el estudio de Terrier y colaboradores, 4/18 (22%) pacientes sin vasculitis en la biopsia versus 11/22 (50%) tuvieron crioglobulinas positivas [12]. NE: 4

Pregunta 8- ¿Cúales son los métodos diagnósticos apropiados para el diagnóstico de compromiso neurológico en SSp?

Los términos de búsqueda utilizados fueron: Sjögren - Sjögren Syndrome - Sjogren disease AND neurology affection - neurologic compromise - neurology - neurologic AND Diagnosis - diagnostic

Se encontraron en Pubmed 374 artículos, se seleccionaron para su análisis siete. El resto se descartó por título, abstract o contenido. No se encontraron artículos en las búsquedas de Lilacs ni Cochrane.

Mori y colaboradores publicaron en 2001 una serie de casos, cuyo objetivo fue evaluar los hallazgos en EMG, RM y biopsia de nervio sural de pacientes con NPT y SSp. Se incluyeron 14 pacientes, 12 de los cuales mostraron hiperintensidad en T2, en el cordón posterior de columna cervical. Los dos pacientes restantes mostraron pérdida axonal [19]. NE: 4

Mori y colaboradores publicaron en 2005 una serie de casos, cuyo objetivo fue describir las características clínicas de pacientes con NPT asociada a SSp. Se incluyeron 92 pacientes. En el 93% de los casos el diagnóstico de SSp fue posterior al compromiso neurológico. NPT sensitivo atáxica (n = 36), NPT sensitivo dolorosa sin ataxia (n = 18), MNM (n = 11), y polirradiculopatía (n = cuatro). En la NPT sensitiva atáxica, dolorosa y autonómica, se observaron anormalidades en RM y potenciales evocados. Se realizaron 55 biopsias de nervio sural. Se observó pérdida de fibras axonales pequeñas en los casos de NPT dolorosa y fibras de mayor tamaño en NPT atáxica. En las biopsias se encontró angeítis e infiltrados perivasculares en los casos de mononeuritis múltiple y NPT sensitivo atáxica [20]. NE: 4

Alexander y colaboradores publicaron en 1988 un estudio de corte transversal, que tuvo como finalidad evaluar los posibles hallazgos en RMN de cerebro en pacientes con SSp y manifestaciones neurológicas. Se incluyeron 38 pacientes, 16 de los cuales presentaron manifestaciones neuropsiquiátricas. 8/16 además tuvieron déficit neurológico focal. Doce/16 (75%) tuvieron lesiones en RM versus 2/22 (9%) de los pacientes sin compromiso neurológico ($p<0.0001$). 7/8 pacientes con déficit focales y 5/8 con disfunción cognitiva o síntomas psiquiátricos también presentaron lesiones en RM [21]. NE: 4

Tzarouchi y colaboradores publicaron en 2014 un estudio de corte transversal que tuvo como objetivo evaluar la presencia de lesiones en sustancia blanca y la presencia de cambios micro estructurales en pacientes con SSp. Se incluyeron 19 pacientes versus 16 controles macheados por edad. No hubo diferencias significativas entre pacientes y controles. 13/19 (68,4%) versus 6/16(37,5%) tuvieron áreas de aumento de intensidad en sustancia blanca [22]. NE: 4

En un estudio que incluyó de 82 pacientes, descripto con anterioridad, se realizó RM de cerebro en 58 paciente (71%). Se observaron lesiones en sustancia blanca, gris y cuerpo calloso, con una mayor frecuencia de lesiones en pacientes con compromiso del SNC que del SNP (80 vs 25%; $p=0.008$). En 39 (47,5%) de los casos se realizó RM de médula espinal con presencia de lesiones hiperintensas en el 49% de los pacientes, todos ellos con manifestaciones clínicas de compromiso del cordón espinal. Se observaron lesiones hiperintensas en T2 en el 75% de los 29 pacientes con mielopatía[6]. NE: 4

En el estudio de Alexander y colaboradores, se observaron alteraciones en la TAC y/o RM en 39 pacientes (75%) del grupo con SSp y compromiso de SNC. En 19 de ellos las lesiones fueron extensas. A su vez, de las 44 angiografías realizadas, 20 fueron patológicas [9]. NE: 4

En el estudio de Morreale y colaboradores, comentado previamente, que incluyó 120 pacientes, 81 (67,5%) tuvieron compromiso del SNC. 64 pacientes (79%) de los pacientes mostraron síntomas focales del SNC, siendo la cefalea la manifestación más común, seguidos de trastornos neurocognitivos. LaRM con espectroscopia reveló alteraciones en la sustancia blanca frontal subcortical y en los ganglios de la base, mientras que la ultrasonografía mostró deterioro en la microvasculatura [2]. NE: 4

Pregunta 9- ¿Cúal es el tratamiento y evolución de las manifestaciones neurológicas?

Los términos de búsqueda fueron Sjögren Sjögren Syndrome - Sjogren disease AND treatment neurology affection - neurologic compromise - neurology - neurologic AND Hydroxychloroquine / azathioprine / corticosteroid – glucocorticoid - steroid - methylprednisolone - methylprednisone – prednisone / Cyclophosphamide / Rituximab / Immunoglobulin - gammaglobulin

Por Cochrane y Lilacs no se seleccionó ningún artículo. Por Pubmed tampoco se seleccionó ningún artículo para hidroxicloroquina, azatioprina, corticoides, ciclofosfamida, rituximab, gammaglobulinas.

Por búsqueda manual:

Morozumi y colaboradores publicaron en 2009 una serie de cinco casos con NPT sensitiva dolorosa asociada a SSp. Los cinco tuvieron alteración en EMG y biopsia de nervio sural con reducción leve de pequeñas fibras mielínicas y amielínicas. Ninguno tuvo vasculitis. Todos recibieron IG IV 0,4 g/kg x 5 días. Todos mejoraron. Dos pacientes tuvieron recaídas que respondieron exitosamente al re tratamiento con IVIG [23]. NE: 4

Chen y colaboradores describen una serie de casos de cuatro pacientes con SSp entre 1994-1999 con polineuropatía sensitivo atáxica. El tratamiento temprano con plasmaféresis (1-2 semanas de evolución) implicó respuesta favorable; mientras que en los otros dos casos, en los cuales el inicio de tratamiento fue más tardío (3-4 semanas) el cuadro neurológico permaneció estable. Todos los casos recibieron corticoides en pulsos o en dosis de 1mg/K [24]. NE: 4

Santosa y colaboradores publicaron en 2012, una serie de ocho casos que tuvo como objetivo reportar las características de los pacientes con SSp y compromiso neurológico evaluados en un hospital terciario de Singapore. En seis pacientes se realizó el diagnóstico de SSp simultáneamente con el diagnóstico del compromiso neurológico. Cuatro pacientes presentaron compromiso del SNP, dos del SNC y dos de ambos. Tres de los casos correspondieron a mielitis transversa. Todos los pacientes recibieron pulsos de metilprednisona; tres pacientes recibieron además,

ciclofosfamida + IG IV y tres ciclofosfamida (sin IG IV). El tratamiento de mantenimiento fue variable (mofetil micofenolato, azatioprina, hidroxicloroquina y metotrexate). En todos los casos se observó una respuesta favorable al tratamiento, y en un período de seguimiento de 19 meses, cinco pacientes presentaron recuperación completa [25]. NE: 4

De Seze y colaboradores reportaron los resultados de 14 pacientes con SSp y mielitis. Seis pacientes tuvieron mielitis aguda y ocho crónica. Ninguno tuvo hipocomplementemia o AFL. Seis tuvieron crioglobulinas. Todos recibieron tratamiento con ciclofosfamida, sin mayores eventos adversos. Nueve mejoraron (cuatro con respuesta tardía), tres se estabilizaron y dos empeoraron. Dos pacientes al suspender el tratamiento recayeron, uno falleció por IAM; la terapia de mantenimiento fue azatioprina en seis y micofenolato en cinco pacientes [26]. NE: 4

Yamada y colaboradores publican en 2005 una serie de tres casos.

Paciente 1: paciente de sexo masculino, de 46 años, con ganglionopatía sensitiva atáxica y diagnóstico de SSp en forma simultánea. Recibió tratamiento inicial con meprednisona 0,5mg/K, ciclosporina y plasmaféresis sin respuesta. Luego recibió inmunoglobulinas endovenosas con mejoría transitoria y requerimiento de tratamiento cada tres o cuatro semanas). Al iniciar interferón α tuvo mejoría clínica y en el EMG.

Paciente 2: paciente de sexo femenino, de 67 años, con diagnóstico de SSp 14 años previos al compromiso neurológico, que consistió en ganglionopatía sensitiva atáxica refractaria al tratamiento combinado con glucocorticoides, ciclofosfamida y plasmaféresis. Por respuesta insuficiente recibió tratamiento con inmunoglobulinas endovenosas con respuesta. Luego del tratamiento con interferón mejoró en forma sostenida.

Paciente 3: paciente de sexo femenino de 45 años, con polineuropatía sensitivo motora y diagnóstico simultáneo de SSp. No presentó respuesta adecuada al tratamiento con glucocorticoides, ciclosporina y ciclofosfamida. La respuesta a la plasmaféresis fue parcial. Luego de inmunoglobulinas endovenosas tuvo una mejoría marcada pero con recaídas frecuentes. A los tres años del inicio del cuadro, recibió interferón con mejoría sostenida, descenso en las cifras de anticuerpos y menor número de focos en biopsia de glándula salival [27]. NE: 4

Delalande y colaboradores, respecto al tratamiento, de los 73 paciente que recibieron glucocorticoides, 29 (45%) mejoraron o se estabilizaron, mientras que 13 no respondieron. La mayoría de los casos eran pacientes con NPT. 34 pacientes recibieron terapia inmunosupresora: 11 pacientes con mielitis y nueve con mononeuritis múltiple recibieron ciclofosfamida, con respuesta favorable en 11/12 casos de mielopatía y en todos los casos de mononeuritis múltiple [6]. NE: 4

Bibliografía

1- Kvarnström M, Ottosson V, Nordmark B, Wahren-Herlenius M. "Incident cases of primary Sjögren's syndrome during a 5-year period in Stockholm County: a descriptive study of the patients and their characteristics." Scand J Rheumatol 2015;44:135–142

2- Morreale M, Marchione P, Giacomini P, Pontecorvo S, Marianetti M, Vento C, Tinelli E, Francia A. "Neurological involvement in primary Sjögren syndrome: a focus on central nervous system." PLoS One. 2014; 9(1): e84605

3- Hsu CW, Su YJ, Chang WN, Tsai NW, Chiu WC, Cheng BC, Su CM, Huang CR, Chang YT, Lu CH. "The association between serological biomarkers and primary Sjogren's syndrome associated with peripheral polyneuropathy." Biomed Res Int. 2014;2014:902492

4- Jamilloux Y, Magy L, Hurtevent JF, Gondran G, de Seze J, Launay D, Ly KH, Lambert M, Hachulla E, Hatron PY, Vidal E, Fauchais AL. "Immunological profiles determine neurological involvement in Sjögren's syndrome." European Journal of Internal Medicine 25 (2014) 177–181.

5- Sène D, Jallouli M, Lefaucheur JP, Saadoun D, Costedoat-Chalumeau N, Maisonobe T, Diemert MC, Musset L, Haroche J, Piette JC, Amoura Z, Cacoub P. "Peripheral neuropathies associated with primary Sjögren syndrome: immunologic profiles of nonataxic sensory neuropathy and sensorimotor neuropathy." Medicine (Baltimore). 2011 Mar;90(2):133-8.

6- Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, Dubucquoi S, Pruvo JP, Vermersch P, Hatron PY. "Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients.". Medicine (Baltimore). 2004 Sep;83(5):280-91

7- Scofield AK, Radfar L, Ice JA, Vista E, Anaya JM, Houston G, Lewis D, Stone DU, Chodosh J, Hefner K, Lessard, CJ, Moser KL, Scofield RH. "Relation of sensory peripheral neuropathy in Sjögren syndrome to anti-Ro/SSA." J Clin Rheumatol. 2012 September; 18(6): 290–293.

8- Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, Del Pino-Montes J, Calvo-Alen J, Jiménez-Alonso J, Micó ML, Beltrán J, Belenguer R, Pallarés L; GEMESS Study Group "Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients". Medicine (Baltimore). 2008 Jul;87(4):210-9

9- Alexander EL, Ranzenbach MR, Kumar AJ, Kozachuk WE, Rosenbaum AE, Patronas N, Harley JB, Reichlin M. "Anti-Ro(SS-A) autoantibodies in central nervous system disease associated with Sjögren's syndrome (CNS-SS): clinical, neuroimaging, and angiographic correlates". Neurology. 1994 May;44(5):899-908

10- Martel C, Gondran G, Launay D, Lalloué F, Palat S, Lambert M, Ly K, Loustaud-Ratti V, Bezanahary H, Hachulla E, Jauberteau MO, Vidal E, Hatron PY, Fauchais AL. "Active immunological profile is associated with systemic Sjögren's syndrome." J Clin Immunol (2011) 1:840– 847.

11- Brito-Zerón P, Retamozo S, Gandía M, Akasbi M, Pérez-De-Lis M, Diaz-Lagares C, Bosch X, Bové A, Pérez- Alvarez R, Soto-Cárdenas MJ, Sisó A, Ramos-

Casals M. J. "Monoclonal gammopathy related to Sjögren syndrome: a key marker of disease prognosis and outcomes." Journal of Autoimmunity 39 (2012) 43e48

12- Terrier B, Lacroix C, Guillevin L, Hatron PY, Dhote R, Maillot F, Diot E, Sarrot-Reynauld F, Sordet C, Dubourg O, Meyer L, Mariette X, Gottenberg JE. "Diagnostic and prognostic relevance of neuromuscular biopsy in primary Sjögren's syndrome-related neuropathy." Arthritis & Rheumatism (Arthritis Care & Research)Vol. 57, No. 8, December 15, 2007, pp 1520–1529

13- Ramos-Casals M, Brito-Zerón P, Yagüe J, Akasbi M, Bautista R, Ruano M, Claver G, Gil V, Font J."Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjogren's syndrome" Rheumatology 2005;44:89–94

14- Quartuccio L, Isola M, Baldini C, Priori R, Bartoloni E, Carubbi F, Gregoraci G, Gandolfo S, Salvin S, Luciano N, Minniti A, Alunno A, Giacomelli R, Gerli R, Valesini G, Bombardieri S, De Vita S. "Clinical and biological differences between cryoglobulinaemic and hypergammaglobulinaemic purpura in primary Sjögren's syndrome: results of a large multicentre study." Scand J Rheumatol. 2015;44(1):36-41

15- Pasoto SG, Chakkour HP, Natalino RR, Viana VS, Bueno C, Lianza AC, de Andrade JL, Neto ML, Fuller R, BonfaE. "Lupus anticoagulant: a marker for stroke and venous thrombosis in primary Sjögren's syndrome." Clin Rheumatol (2012) 31:1331–1338

16- Fauchais AL, Lambert M, Launay D, Michon-Pasturel U, Queyrel V, Nguyen N, Hebbar M, Hachulla E, Devulder B, Hatron PY.

17- "Antiphospholipid antibodies in primary Sjögren's syndrome: prevalence and clinical significance in a series of 74 patients" Lupus (2004) 13, 245 -248

17- Cervera R, García-Carrasco M, Font J, Ramos M, Reverter JC, Muñoz FJ, Miret C, Espinosa G, Ingelmo M. "Antiphospholipid antibodies in primary Sjögren's syndrome: prevalence and clinical significance in a series of 80 patients." Clin Exp Rheumatol. 1997 Jul-Aug;15(4):361-5.

18- Anaya, Juan Manuel; Villa, Luis Alfredo; Vargas, Sergio; Restrepo, Carlos; Mantilla, Ruben D; Restrepo, Lucas. "Compromiso neurológico asociado al sindrome de Sjögren / Nervous system involvement in patients with Sjögren's syndrome Acta Med Colomb; (2000) Acta Médica Colombiana Vol. 25 N° 4 Julio-Agosto 2000.

19- Mori K, Koike H, Misu K, Hattori N, Ichimura M, Sobue G. "Spinal cord magnetic resonance imaging demonstrates sensory neuronal involvement and clinical severity in neuronopathy associated with Sjögren's syndrome." J Neurol Neurosurg Psychiatry 2001;71:488–492

20- Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, Katsuno M, Fujita A, Aiba I, Ogata A, Saito T, Asakura K, Yoshida M, Hirayama M, Sobue G. "The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy." Brain (2005), 128, 2518–2534

21- Alexander EL, Beall SS, Gordon B, Selnes OA, Yannakakis GD, Patronas N, Provost TT, McFarland HF. "Magnetic resonance imaging of cerebral lesions in patients with the Sjögren syndrome." Ann Intern Med. 1988 Jun;108(6):815-23

22- Tzarouchi LC, Zikou AK, Tsifetaki N, Astrakas LG, Konitsiotis S, Voulgari P, Drosos A, Argyropoulou MI. "White matter water diffusion changes in primary Sjögren syndrome." (AJNR Am J Neuroradiol 35:680–85 Apr 2014

23- Morozumi S, Kawagashira Y, Iijima M, Koike H, Hattori N, Katsuno M, Tanaka F, Sobue G. "Intravenousimmunoglobulin treatment for painful sensory neuropathy associated with Sjögren's syndrome." Journal of the Neurologica Sciences 279 (2009) 57–61

24- Chen WH, Yeh JH, Chiu HC. Plasmapheresis inthe treatment of ataxic sensory neuropathy associated with Sjögren's syndrome. Eur Neurol 2001. 45: 270-274

25- Santosa A, Lim AY, Vasoo S, Lau TC, Teng GG. "Neurosjögren: early therapy is associated with successful outcomes." Journal of Clinical Rheumatology & Volume 18, Number 8, December 2012

26- de Seze J, Delalande S, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, Hatron PY, Vermersch P "Myelopathies secondary to Sjögren's syndrome: treatment with monthly intravenous cyclophosphamide associated with corticosteroids." J Rheumatol. 2006 Apr;33(4):709-11

27- Yamada S, Mori K, Matsuo K, Inukai A, Kawagashira Y, Sobue G. "Interferon alfa treatment for Sjogren's syndrome associated neuropathy." J Neurol Neurosurg Psychiatry. 2005;76:576–578

COMPROMISO NEUROCOGNITIVO EN SÍNDROME DE SJÖGREN PRIMARIO

Damian Duartes Noé, Federico Zazzetti, Juan Carlos Barreira. Hospital Británico

Pregunta 1- ¿Cuál es la prevalencia del compromiso neurocognitivo en Síndrome de Sjögren primario (SSp)?
Búsqueda
(("Neurobehavioral Manifestations"[Mesh] OR "Memory Disorders"[Mesh] OR "Executive Function"[Mesh] OR "psychology" [Subheading] OR "Dyslexia"[Mesh] OR "Conscience"[Mesh] OR "Concept Formation"[Mesh] OR "Apraxias"[Mesh] OR "Aphasia"[Mesh]) AND ("Sjogren's Syndrome"[Mesh]) AND ("Prevalence"[Mesh] OR "Epidemiology"[Mesh]))
Resultado de búsqueda: 9
Seleccionados por título y abstract: 3

Van Leeuwen y colaboradores publicaron en 2015, un estudio de corte transversal que incluyo 300 pacientes con SSp y que tuvo como objetivo identificar los perfiles psicológicos niveles de fatiga asociados. Los pacientes completaron cuestionarios sobre fatiga (inventario de fatiga multidimensional), cognición de actividad física (Tampa-SK), enfermedad cognitiva, regulación cognitiva, procesamiento y regulación de las emociones [Escala de alexitimia de Toronto 20, Cuestionario de regulación de la emoción (ERQ), Cuestionario de Expresividad Berkeley], estrategias de copia (COPE) y apoyo social. El principal eje de análisis factorial produjo seis factores psicológicos: el apoyo social, el pensamiento negativo, pensamiento positivo, expresividad emocional, la evitación y la alexitimia. Al realizar el análisis por cluster, estos factores se agruparon en cuatro perfiles psicológicos: funcional (39%), alexitimia (27%), autosuficientes (23%) y disfuncional (11%). Independientemente del perfil psicológico, el nivel de fatiga fue sustancialmente mayor en los pacientes que en la población general. Los pacientes con una disfunción o un perfil alexitímico reportaron más fatiga que aquellos con un perfil autosuficiente [(1)]. NE: 4

Yoshikawa y colaboradores publicaron en 2012 un estudio de corte transversal que tuvo como objetivo evaluar la prevalencia y el impacto de SS en los pacientes en una clínica de función cognitiva. Se reclutaron pacientes con disfunción cognitiva, desde 2007 a 2010. Además de los exámenes de demencia, se midieron los niveles de anticuerpos anti-SSA y SSB de los pacientes. Se añadieron la prueba de Schirmer y/o una biopsia de labio si se consideraba necesario. El diagnostico de SSp se basó en los criterios de consenso americano- europeos. De los 276 casos que completaron los exámenes, 265 (97varones y 168 mujeres, edad media: 77,9, puntuación - mini-mental state examination – MMSE- mediana: 23) no demostraron deterioro cognitivo. 16 pacientes (6,3%) y siete pacientes (2,7%) fueron positivos para anticuerpos SS-B y anti-SS-A, respectivamente. 20 pacientes (7,5%) fueron diagnosticados con SSp (edad media: 77,2 años de edad, MMSE mediana: 21). Siete de estos pacientes habían sido diagnosticados con deterioro congnitivo mínimo, y 13 con demencia. Todos tenían

hipoperfusión focal asimétrica en el SPECT, y 18 tenían lesiones subcorticales en la RM. 12 fueron tratados por demencia (tiempo medio: 2,1 años), y su MMSE mejoró significativamente (mediana MMSE: 26, p = 0,0019), mientras que el MMSE de los sujetos sin diagnóstico de SS empeoró (n = 126, mediana: 22) [(2)]. NE: 4

Harboe y colaboradores publicaron en 2009, un estudio de corte transversal que tuvo como objetivo comparar la prevalencia y el patrón de los síndromes neuropsiquiátricos (NP) observados en el lupus eritematoso sistémico (LES) con aquellos observados en pacientes con SSp utilizando los criterios del Colegio Americano de Reumatología (ACR) para los 19 síndromes NP de LES. Se incluyeron 68 pacientes con LES ((media (DE) de edad de 43,8 (13,6) años)) y 72 con SSp (edad 57,8 (13,0) años). Especialistas en medicina interna, neurología y neuropsicología realizaron exámenes estandarizados. En todos los pacientes se realizaron imágenes por resonancia magnética cerebral y estudios neurofisiológicos. Se observaron similar prevalencia en LES y SSp de cefalea (87% vs. 78%, p = 0,165), disfunción cognitiva (46% vs 50%, p = 0,273), trastornos del humor (26% vs 33%, p = 0,376), trastornos de ansiedad (12% frente al 4%, p = 0,095), neuropatía craneal (1% frente al 4%, p = 0,339) y trastornos convulsivos (7% vs 3%, p = 0,208).La enfermedad cerebrovascular fue más frecuente en LES que en SSp (12% frente al 3%, p = 0,049); pero la mononeuropatía (0% frente al 8%, p = 0,015) y la polineuropatía (18% vs 56%, p <0,001) fueron menos comunes en LES que en SSp. Otros síndromes fueron raros o ausentes en ambos grupos de pacientes[(3)]. NE: 4

Pregunta 2- ¿El compromiso neurocognitivo en SSp es subclínico?

(("Neurobehavioral Manifestations"[Mesh] OR "Memory Disorders"[Mesh] OR "Executive Function"[Mesh] OR "psychology"[Subheading] OR "Dyslexia"[Mesh] OR "Conscience"[Mesh] OR "Concept Formation"[Mesh] OR "Apraxias"[Mesh] OR "Aphasia"[Mesh]) AND ("Sjogren's Syndrome"[Mesh] AND subclinical [All Fields]))

Resultado de búsqueda: 2

Le Guern y colaboradores publicaron en 2010 un estudio de corte transversal que tuvo como objetivo evaluar el compromiso subclínico del sistema nervioso central (SNC) en el SSp, mediante la comparación de resonancia magnética de cerebro, pruebas neuropsicológicas y tomografía de cerebro con emisión de fotón simple ((99m) Tc-ECD (SPECT)) de los pacientes con SSp con controles emparejados. Se investigaron de forma prospectiva 10 mujeres (<55 años) con SSp definido por criterios americano-europeos, sin antecedentes de afectación neurológica, y se compararon con 10 controles emparejados por edad y sexo. En todos los sujetos se realizó resonancia magnética de cerebro, pruebas neuropsicológicas, incluyendo la evaluación general y el estudio de la función cognitiva focal, y (99m) Tc-ECD (SPECT) cerebral.
Las anomalías en SPECT (99m) Tc-ECD cerebrales fueron significativamente más frecuentes en pacientes con SSp (10/10) que en los controles (2/10; p <0,05). También fueron significativamente más común en pacientes con SSp (8/10) las disfunciones cognitivas, expresadas principalmente como trastornos ejecutivos y visuoespaciales, que en los controles (0/10; p <0,01). Notablemente, entre los grupos, las comparaciones mostraron una correlación significativa entre la evaluación neuropsicológica y anomalías cerebrales en la (99m) Tc-ECD (SPECT) en pacientes

con SSP (r (s) = 0,49, p <0,01). Las anomalías en resonancia magnética en pacientes y controles no difirieron significativamente [4]. NE: 4

Hietaharju y colaboradores publicaron en 1990 una serie de casos en la que describieron las manifestaciones centrales y periféricas del sistema nervioso en 48 pacientes con SS. 56% de los pacientes tenía alteraciones neurológicas. Las manifestaciones más frecuentes fueron neuropatías por atrapamiento (19%) y la polineuropatía (15%). Las pruebas electrofisiológicas mostraron compromiso del sistema nervioso subclínico en el SS: la electroencefalografía (EEG) fue anormal en el 48%, y los potenciales evocados visuales (VEP) en el 12% de los pacientes evaluados. Para encontrar posibles anomalías neuropsiquiátricas se aplicó el Inventario de Personalidad Multifásico de Minnesota, y en 33/43 pacientes se encontró que tenían síntomas psiquiátricos. Los más frecuentes fueron síntomas depresivos. En el 44% de los pacientes hubo evidencia adicional de compromiso extraglandular o trastornos autoinmunes. Ninguna correlación se pudo encontrar entre los grupos de pacientes con o sin trastornos neurológicos en relación con la ocurrencia simultánea de trastornos asociados [5]. NE: 4

Pregunta 3- ¿Cómo se realiza la evaluación de compromiso neurocognitivo en SSp?

(("Sjogren's Syndrome"[Mesh]) AND (cognitive symptoms inventory (CSI) OR beck depression OR minimental test (mmse) OR trail-making test a OR digit span OR rey auditory-verbal learning test OR wms-iii OR semantic and phonological vf tests OR clock s test OR trail-making test b OR rey osterrieth complex figure))

Resultado de búsqueda: 2

Rodrigues y colaboradores publicaron en 2014 un estudio de corte transversal que tuvo como objetivo investigar el déficit cognitivo en pacientes con SSp. Se incluyeron 18 pacientes con SSp, con edades comprendidas entre los 25 y los 61 años, que fueron sometidos a una batería neuropsicológica breve y se compararon con 18 pacientes con esclerosis múltiple y 18 controles sanos. Se observó que tanto los pacientes con SSp como los pacientes con esclerosis multiple tuvieron un rendimiento significativamente peor que el grupo control en el test de Aprendizaje Auditivo Verbal de Rey 3. Ambos grupos de pacientes mostraron niveles significativamente más elevados de depresión en el Inventario de Depresión de Beck (BDI); (p = 0,003). El análisis de los datos del test Trail Making B-A reveló una diferencia significativa entre los grupos de pacientes y el grupo control sano (P = 0,023). Al ajustar el análisis utilizando el BDI como covariable, los resultados no se modificaron [6]. NE: 4.

Martinez y colaboradores publicaron en 2010, un estudio de cohorte que tuvo como objetivo determinar la progresión de la disfunción cognitiva en el SSp.12 sujetos con SSp se compararon con diez sujetos con migraña y diez controles sanos con pruebas neuropsicológicas, de estado de ánimo y de fatiga, en el momento basal y ocho años

más tarde. Durante el seguimiento, los sujetos SSp tuvieron un rendimiento inferior al de los sujetos con migraña en el Ensayo de Performance Continua (CPT), pero no difirieron en otras tareas. Comparado con los controles, los dos grupos de pacientes obtuvieron puntuaciones más bajas en el tiempo de reacción simple, los pacientes con SSp obtuvieron puntuaciones más bajas en el "Wisconsin Card Sorting Test" (WCST) y los pacientes con migraña mostraron un rendimiento inferior al de los controles en la prueba de orientación temporal "JOLO" (Benton's Judgment of Line Orientation Test). Tanto los pacientes con SSp, como el grupo con migraña, no mostraron diferencias significativas en los cambios cognitivos con el tiempo, excepto que los sujetos con migraña mejoraron la fluidez verbal. En comparación con el momento basal, tanto SSp como los pacientes con migraña tuvieron menor rendimiento en el tiempo de reacción simple, en la prueba "Trail Making Test" (TMT) parte B, en el test de Stroop y en el test "JOLO". Sin embargo, mostraron puntuaciones más altas en la memoria verbal y visual, en el WCST y en la prueba CPT. Los pacientes con SSp mostraron también niveles más altos de depresión y fatiga que los otros dos grupos, con cambios no significativos en el tiempo [(7)]. NE: 3

Pregunta 4- ¿Cuál es el tratamiento del compromiso neurocognitivo en SSp?

(("Neurobehavioral Manifestations"[Mesh] OR "Memory Disorders"[Mesh] OR "Executive Function"[Mesh] OR "psychology"[Subheading] OR "Dyslexia"[Mesh] OR "Conscience"[Mesh] OR "Concept Formation"[Mesh] OR "Apraxias"[Mesh] OR "Aphasia"[Mesh]) AND ("Sjogren's Syndrome"[Mesh]) AND (Treatment))

Resultado de búsqueda: 16

Artículos seleccionados: 3

Wong y colaboradores publicaron en 2014 un caso clínico de una mujer de 54 años de edad con diagnóstico de SSpque presentó una historia de 1 año de alucinaciones visuales que requirió su ingreso a una unidad psiquiátrica. Si bien las alucinaciones resolvieron con olanzapina y hidroxicloroquina, recurrieron cuando fueron suspendidas. A pesar de reiniciar olanzapina, sus alucinaciones visuales persistieron. Cuando ella comenzó a recibir una dosis decreciente de prednisolona todas sus alucinaciones resolvieron. Este informe se suma a la pequeña literatura sobre manifestaciones psiquiátricas del SS y proporciona evidencia de que dosis bajas de corticosteroides pueden ser un tratamiento eficaz para esta manifestación [(8)]. NE: 4

Hirohata y colaboradores presentaron en 2005 un reporte de un caso de una mujer de 50 años de edad que inicialmente mostró falta de memoria, y más tarde desarrolló una alteración de la conciencia. Además de presentar una meningoencefalitis aséptica revelada por el examen del líquido cefalorraquídeo y las imágenes de la resonancia magnética, la presencia en el suero de anticuerpos anti-SS-A y anti-SS-B y hallazgos inflamatorios en la biopsia de labio indicaron SSp. La resonancia magnética con (FLAIR) reveló áreas pequeñas bien definidas de alta intensidad de señal en la corteza con compromiso de la sustancia blanca subcortical. La terapia con corticosteroides dio lugar a una rápida y casi completa resolución de las lesiones corticales con una marcada mejoría de las manifestaciones clínicas. La alteración de la memoria es una manifestación inicial rara en la meningoencefalitis asociada con SSp. Nuestro paciente con SSp mostró lesiones corticales inflamatorias en la resonancia, que fueron revertidas con el tratamiento con corticosteroides [(9)]. NE: 4

Caselli y colaboradores publicaron en 1991 el reporte de un caso de una mujer de 56 años con diagnóstico de SSp serológica y clínicamente documentado y una demencia progresiva desarrollada durante un período de 15 meses. La resonancia magnética y angiografía fueron normales, pero una biopsia cerebral dió a conocer una inflamación linfocítica perivascular en leptomeníngeas y de vasos de parénquima. El tratamiento con dosis altas de corticoides produjo una rápida y casi completa resolución de la demencia [10]. NE: 4

Bibliografía

1-van Leeuwen N, Bossema ER, Knoop H, Kruize AA, Bootsma H, Bijlsma JW, Geenen R. Psychological profiles in patients with Sjögren's syndrome related to fatigue: a cluster analysis. Rheumatology (Oxford). 2015 May;54(5):776-83.

2-Yoshikawa K, Hatate J, Toratani N, Sugiura S, Shimizu Y, Takahash T, Ito T, Fukunaga R. Prevalence of Sjögren's syndrome with dementia in a memory clinic. J Neurol Sci. 2012 Nov 15;322(1-2):217-21.

3-Harboe E, Tjensvoll AB, Maroni S, Gøransson LG, Greve OJ, Beyer MK, Herigstad A, Kvaløy JT, Omdal R.
Neuropsychiatric syndromes in patients with systemic lupus erythematosus and primary Sjögren syndrome: a comparative population-based study.Ann Rheum Dis. 2009 Oct;68(10):1541-6.

4-Le Guern V, Belin C, Henegar C, Moroni C, Maillet D, Lacau C, Dumas JL, Vigneron N, Guillevin L. Cognitive function and 99mTc-ECD brain SPECT are significantly correlated in patients with primary Sjogren syndrome: a case-control study. Ann Rheum Dis. 2010 Jan;69(1):132-7.

5-Hietaharju A, Yli-Kerttula U, Häkkinen V, Frey H. Nervous system manifestations in Sjögren's syndrome.
Acta Neurol Scand. 1990 Feb;81(2):144-52.

6-Rodrigues DN, Hora JS, Salgado MC, Paes RA, Vasconcelos CC, Landeira-Fernandez J, Alvarenga RM.
A short neuropsychological evaluation of patients with primary Sjögren's syndrome. Arq Neuropsiquiatr. 2014 Jan;72(1):38-43.

7-Martínez S, Cáceres C, Mataró M, Escudero D, Latorre P, Dávalos A. Is there progressive cognitive dysfunction in Sjögren Syndrome? A preliminary study. Acta Neurol Scand. 2010 Sep;122(3):182-8.

8- Wong JK, Nortley R, Andrews T, D'Cruz D. Psychiatric manifestations of primary Sjögren's syndrome: a case report and literature review. BMJ Case Rep. 2014 May 23;2014.

9- Hirohata M, Yasukawa Y, Ishida C, Komai K, Yamada M. Reversible cortical lesions in primary Sjögren's syndrome presenting with meningoencephalitis as an initial manifestation. J Neurol Sci. 2005 May 15;232(1-2):111-3.

10-Caselli RJ, Scheithauer BW, Bowles CA, Trenerry MR, Meyer FB, Smigielski JS, Rodriguez M. The treatable dementia of Sjögren's syndrome. Ann Neurol. 1991 Jul;30(1):98-101.

MANIFESTACIONES Y ENFERMEDADES GASTROINTESTINALES- HEPÁTICAS ASOCIADAS AL SÍNDROME DE SJÖGREN PRIMARIO

M. Paula Girard Bosch, Rodrigo Garcia Salinas, Alfredo Arturi. Htal. Italiano de La Plata

Pregunta 1- En pacientes con síndrome de Sjögren primario (SSp), ¿es de utilidad realizar manometría esofágica para evaluar los trastornos de motilidad (aperistalsis, ondas terciarias, disminución de la contractilidad, contracciones no peristálticas) y la presión del esfínter esofágico inferior como posibles causas de disfagia?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(disfagia))

(tw:(sjogren)) AND (tw:(trastornos de la motilidad esofágica))

COCHRANE: Sjogren AND dysphagia

Sjogren AND esophageal motility disorder

Sjogren AND lower esophageal sphincter

PUBMED: ((sjogren OR sjogren syndrome OR sjogren s syndrome OR sjogren´s syndrome) AND (esophageal motility disorder OR esophageal motility disorders) AND (lower esophageal sphincter) AND (dysphagia))

La búsqueda en Cochrane arrojó 7 artículos, se desecharon los 7 por título. La búsqueda en Lilacs, 56. Se desecharon 50 artículos por título, 5 por abstract, se incluyó 1 artículo. La búsqueda en Pubmed encontró 4, se descartaron 2 por título, se incluyeron 2.

Türy y colaboradores publicaron en 2005 un estudio de corte transversal que tuvo como objetivo evaluar la motilidad esofágica por manometría en pacientes con SSp. Se llevó a cabo manometría esofágica en 40 pacientes con SSp, 15 con artritis reumatoidea (AR), 15 con AR y SS secundario y 21 voluntarios sanos. Diversos parámetros de la motilidad esofágica (presión del esfínter esofágico inferior EEI, velocidad y duración de la contracción peristáltica) se encontraron alterados en pacientes con SSp los cuales podrían estar relacionados con un aumento de la presión del EEI. No se halló correlación entre trastornos esofágicos y otros factores estudiados (duración de la enfermedad, sintomatología, manifestaciones extraglandulares, marcadores serológicos e histología de biopsia de glándula salival menor) lo cual sugiere que la causa de la disfagia es multifactorial [(1)]. NE: 4

Rosztóczy y colaboradores publicaron en 2001, un estudio de corte transversal en el que evaluaron por manometría los cambios de la motilidad esofágica en pacientes con SSp. La manometría esofágica se llevó a cabo en 25 pacientes con SSp con manifestaciones sistémicas y en 42 controles. Los pacientes con SSp también completaron un cuestionario de disfagia y se sometieron a mediciones de flujo salival. Como la disminución de la velocidad peristáltica era la anomalía motora más frecuente en los pacientes con SSp (11/25 casos), se dividieron en dos grupos para su posterior análisis: los pacientes con una disminución de la velocidad peristáltica (2,7 cm/s) mostraron una disminución de la presión (p <0,01) y prolongación del tiempo de relajación en el EEI (p <0,05), con mayores tasas de contracciones simultáneas (p=0,05) en el cuerpo esofágico, en comparación con los que tenían una velocidad peristáltica normal. De los parámetros clínicos, la disminución de la velocidad peristáltica en el cuerpo esofágico se asoció con una disminución en la producción de saliva, tanto en estado basal como después de la estimulación. Por otra parte, este grupo de pacientes tenía requerimientos de líquido significativamente mayor para tragar que los que tenían velocidades peristálticas normales (p = 0,05). No se hallaron diferencias significativas con parámetros de laboratorio o con manifestaciones sistémicas de la enfermedad [(2)]. NE: 4

Manterola y colaboradores publicaron en 1994, un estudio observacional que tuvo como objetivo evaluar la función motora esofágica en pacientes con síndrome de Sjögren (SS) y su relación con el síntoma disfagia. Se estudiaron, mediante manometría esofágica, 20 pacientes con SS. Además contestaron un cuestionario acerca de la existencia de sintomatología esofágica. Se utilizaron 20 individuos como grupo control, ninguno de los cuales refería sintomatología esofágica ni ingería medicamentos que pudiesen influir en la motilidad digestiva. En el estudio de parámetros motores esofágicos se constató un incremento significativo de la presión del EEI y un enlentecimiento de la progresión de las ondas peristálticas tras las degluciones líquidas en pacientes con SS al compararlos con el grupo control. De acuerdo al resultado de la encuesta, 15 pacientes (75%) presentaban disfagia de mayor o menor intensidad. Al comparar los parámetros de motilidad entre el grupo con y sin disfagia, no se constataron alteraciones ni diferencias significativas entre ellos [(3)]. NE: 4

Pregunta 2- En pacientes con SSp y sospecha de gastritis crónica atrófica, ¿es de utilidad realizar fibroendoscopía digestiva alta y eventual biopsia para descartar la presencia de alteraciones en la mucosa (gastritis atrófica o infiltrado linfocítico)?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(gastritis atrófica))

COCHRANE: Sjogren AND atrophic gastritis

PUBMED: ((sjogren OR sjogren syndrome OR sjogren s syndrome OR sjogren´s syndrome) AND (atrophic gastritis))

Se encontró 1 artículo por Cochrane que se descartó por título. Por Lilacs 8, se descartaron 4 por título, el resto por abstract. Por Pubmed se encontraron 19, se descartaron 13 por título, 3 por abstract, se incluyeron 3.

Ostuni y colaboradores, publicaron en 1993 una serie de 20 pacientes italianos con SSp y complicaciones gástricas. Se observaron síntomas gástricos en 11 casos (55%) y anormalidades endoscópicas en diez (50%), incluyendo dos casos con úlcera duodenal activa. Sólo dos pacientes (10%) mostraron moderada gastritis atrófica crónica (AG), mientras que la mayoría (85%) tenían gastritis superficial (SG). No se encontró correlación entre la endoscopia, histología y síntomas gástricos. Los niveles en suero de pepsinógeno (PGI) fueron significativamente mayores ($p < 0,01$) y las concentraciones de PGI en el fondo del estómago fueron significativamente menores ($p < 0,05$) en los pacientes con SSp que en un grupo control de sujetos con dispepsia. Los niveles de gastrina antral y en suero fueron elevados en tres casos con SSp (15%) que incluye los dos con AG, aunque los niveles medios no fueron diferentes de los controles. Se detectaron anticuerpos frente a células parietales gástricas (PCA) en dos casos (10%), de los cuales uno presentaba AG [4]. NE: 4

Pokorny y colaboradores publicaron en 1991 un estudio de corte transversal en el que realizaron examen histológico de la mucosa gástrica de 44 pacientes con SSp con compromiso extraglandular y en un grupo control. Las muestras de biopsia se tomaron de tres regiones separadas: el antro, el corpus, y la zona de transición entre el antro y el cuerpo. La incidencia de gastritis atrófica crónica fue considerablemente mayor en los pacientes con SSp que en los controles. En los pacientes jóvenes las lesiones atróficas fueron más comunes tanto en el antro y en el corpus que en el grupo control. En pacientes de mediana edad sólo el antro, y en los ancianos sólo el corpus, se vieron afectados con más frecuencia que en los controles. Los tres tipos de gastritis atrófica fueron observados en los pacientes con SSp. La disminución de la secreción de ácido gástrico principalmente se asoció a gastritis atrófica de los tipos A y AB, mientras que la hipergastrinemia se observó casi exclusivamente en la gastritis de tipo A [5]. NE: 4

Collin y colaboradores publicada en 1997 un estudio de corte transversal que evaluó la aparición de gastritis de acuerdo con la clasificación de Sydney en pacientes con SSp. Treinta y dos pacientes consecutivos (27 mujeres y cinco hombres) con SSp y 64 sujetos control con dispepsia se sometieron a gastroscopia y toma de biopsia de la mucosa del antro y cuerpo gástricos. La gastritis atrófica del cuerpo se encontró con mayor frecuencia en los sujetos control, pero la diferencia no fue estadísticamente significativa. Ninguno de los sujetos tenía una atrofia severa (grado 3). Se encontró inflamación de la mucosa gástrica, ya sea en el corpus o antro, en 85% de los pacientes con SSp y en el 61% de los sujetos control ($p= 0,02$). El Helicobacter pylori estaba presente en el 31% del SSp y en el 39% de los controles, sin diferencias significativas entre los grupos [6]. NE: 4

Pregunta 3- En pacientes con SSp, ¿es de utilidad controlar los niveles de pepsinógeno y gastrina séricos para descartar gastritis corporal atrófica crónica?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(gastritis atrófica))

(tw:(sjogren)) AND (tw:(pepsinogeno)) AND (tw:(gastrina))

COCHRANE: Sjogren AND atrophic gastritis

Sjogren AND pepsinogen

Sjogren AND gastrin

PUBMED: ((sjogren OR sjogren syndrome OR sjogren s syndrome OR sjogren´s syndrome) AND (atrophic gastritis))

((sjogren OR sjogren syndrome OR sjogren s syndrome OR sjogren´s syndrome) AND (atrophic gastritis) AND (gastrin) AND (pepsinogen))

En la búsqueda en Cochrane se encontró 1 artículo que fue descartado por título. Por Lilacs 10, se descartaron 4 por título y el resto por abstract. Por Pubmed se encontraron 19, se descartaron 13 por título, 4 por abstract, se seleccionaron 2.

Los artículos seleccionados, ya fueron descriptos en preguntas previas. Se destacan los siguientes datos:
En la publicación de Otsuni y colaboradores, los niveles séricos de PG I fueron mayores (p <0.01) y las concentraciones de PG I en el fondo del estómago fueron menores (p <0,05) en los pacientes con SSp que en un grupo control de sujetos dispépticos. Los niveles séricos y antrales de gastrina fueron elevados en tres casos con SSp (15%), incluyendo los dos con GA, aunque los niveles medios no fueron diferentes de los controles. El SSp se asoció a menudo con la presencia de gastritis superficial y altos niveles séricos de PG I [(4)]. NE: 4
En la publicación de Pokorny y colaboradores, los tres tipos de gastritis crónica atrófica se observaron en pacientes con SSp. La disminución de la secreción ácida gástrica se asoció principalmente con la gastritis atrófica de los tipos A y AB, mientras que hipergastrinemia se produjo casi exclusivamente en la gastritis de tipo A [(5)]. NE: 4

Pregunta 4- En pacientes con SSp, ¿es de utilidad controlar los niveles de vitamina B 12 séricos y la presencia de anticuerpos anticélulas parietales y antifactor intrínseco para descartar gastritis corporal atrófica crónica?

ESTRATEGIA DE BÚSQUEDA:

LILACS:

(tw:(sjogren)) AND (tw:(vitamina b12)) AND (tw:(factor intrinseco)) AND (tw:(células parietales))

(tw:(sjogren)) AND (tw:(vitamina b12))

(tw:(sjogren)) AND (tw:(células parietales))

(tw:(sjogren)) AND (tw:(factor intrinseco))

COCHRANE: Sjogren AND vitamin b12 AND intrinsic factor AND gastric parietal cells

PUBMED: ((sjogren OR sjogren syndrome OR sjogren s syndrome OR sjogren´s syndrome) AND atrophic gastritis) AND (vitamin b12) AND (intrinsic factor) AND ((gastric parietal cell OR gastric parietal cells))

(vitamin b12) AND (sjogren OR sjogren syndrome OR sjogren s syndrome sjogren OR sjogren syndrome OR sjogren s syndrome) AND (intrinsic factor (sjogren OR sjogren syndrome OR sjogren s syndrome) AND (parietal cell OR parietal cells))

En la búsqueda por Cochrane no se encontraron artículos; por Lilacs se encontraron 21 que se descartaron por título. De los 58 artículos encontrados por Pubmed se seleccionó 1.

En el artículo de Ostuni y colaboradores, descripto previamente, se detectaron anticuerpos contra las células parietales gástricas (PCA) en dos casos (10%) de los cuales uno presentaba gastritis atrófica [(4)]. NE: 4

Pregunta 5- En pacientes con SSp, ¿debemos solicitar autoanticuerpos específicos y dosaje de IgA para descartar enfermedad celíaca subclínica asociada?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(enfermedad celiaca))

COCHRANE: Sjogren AND celiac disease

PUBMED: ((sjogren OR sjogren syndrome OR sjogren s syndrome OR sjogren´s syndrome) AND (celiac disease))

Se encontraron por Cochrane 3 artículos que se descartaron por título. Por Lilacs 67, se descartaron 63 por título, se incluyeron 4. Por Pubmed se encontraron 110 artículos, se descartaron 104 por título, 2 por abstract, se seleccionaron 4.

Luft y colaboradores publicaron en 2003 un estudio de corte transversal en el que se evaluó la prevalencia de anticuerpos transglutaminasa IgA tisular (anti-tTG) por ELISA en una cohorte de pacientes con SSp y otras enfermedades reumatológicas sistémicas. Se estudió el suero de 50 pacientes con SSp, 50 con lupus eritematoso sistémico (LES), 50 con artritis reumatoidea (RA), 30 con esclerosis sistémica (SSc) y 50 controles sanos. También se incluyó un grupo de 40 pacientes con enfermedad celíaca (EC) confirmada por biopsia. Seis de los 50 (12%) pacientes con SSp presentaban anti-tTG comparado con dos (4%) de los sueros normales, tres (6%) con LES, dos (7%) con SSc y uno con (2%) AR. Al comparar con el grupo de pacientes con EC confirmada, 33 (83%) presentaban anti-tTG. Cinco de los seis pacientes con SSp y anti-tTG positivos presentaban síntomas, signos, o biopsia compatible con EC [(7)]. NE: 4

Frente a la hipótesis de que los pacientes con SSp presentan EC concomitante más frecuentemente que en la población sana (con predominio de la forma latente), Szodoray y colaboradores publicaron en 2004 un estudio de corte transversal, en el que se evaluaron 111 pacientes húngaros con diagnóstico de SSp observando que la

frecuencia de EC en la población con SSp fue significativamente mayor que en la población europea sin SSp (4,5: 100 vs 4.5-5.5: 1000). Los hallazgos de laboratorio en estos pacientes mostraron significativamente más altas tasas de eritrosedimentación y niveles de IgG, IgA, IgM [8]. NE: 4

Iltanen y colaboradores publicaron en 1999 un estudio de corte transversal en el que evaluaron la presencia de EC e inflamación de la mucosa del intestino delgado en pacientes con SSp. Un total de 34 pacientes con SSp y 28 controles fueron sometidos a biopsia de intestino delgado, se evaluaron: morfología de las vellosidades, linfocitos intraepiteliales del yeyuno, HLA-DR, DQA y DQB y anticuerpos antigliadina y antiendomisio en suero. En cinco (14,7%) de 34 pacientes con SSp se encontró EC. La densidad de las células T yeyunales intraepiteliales se encontró incrementada en todos los pacientes celíacos y en cuatro pacientes no celíacos. Todos los pacientes celíacos, el 69% de no celíacos con SSp y el 11% de los sujetos control mostraron un aumento en la expresión de HLA-DR (p: 0,001). HLA DQ2 estaba presente en 19 (56%) pacientes con SSp, incluyendo los cinco pacientes celíacos [9]. NE: 4

Pregunta 6- En pacientes con SSp, ¿debemos descartar por endoscopía y biopsia enfermedad inflamatoria intestinal subclínica asociada?

ESTRATEGIA DE BÚSQUEDA:

LILACS:

(tw:(sjogren)) AND (tw:(enfermedad inflamatoria intestinal))

COCHRANE: Sjogren AND inflammatory bowel disease

PUBMED: ((sjogren OR sjogren syndrome OR sjogren s syndrome OR sjogren´s syndrome) AND (inflammatory bowel disease OR inflammatory bowel diseases))

En la búsqueda bibliográfica por Cochrane se encontraron 12 artículos, se descartaron 9 por título y 1 por abstract; se seleccionaron 2. En la búsqueda por Lilacs se encontró sólo 1 que se descartó por abstract. En la búsqueda por Pubmed se encontraron 58, se descartaron por título 57, se incluyó 1.

Palm y colaboradores publicaron en 2002, un estudio de corte transversal en el que evaluaron la prevalencia de SSp, la producción de saliva y lágrimas, y de síntomas sicca en pacientes con enfermedad inflamatoria intestinal (EII). Se evaluaron 521 pacientes con EII y un grupo control formado por 68 sujetos sanos. SSp fue diagnosticada de acuerdo con los criterios europeos propuestos por el Grupo de Consenso americano- europeo y los criterios europeos. Observaron que tanto el SSp, los síntomas sicca y la producción de saliva y lágrimas no presentaban mayor prevalencia en los pacientes con EII en comparación con los controles, lo que indica una falta de asociación entre el SSp y la EII [10]. NE: 4

Pregunta 7- Los pacientes con SSp y crioglobulinemia asociada, ¿requieren controles más estrictos para descartar compromiso intestinal vasculítico?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(crioglobulinemia)) AND (tw:(vasculitis))

COCHRANE: Sjogren AND cryoglobulinemia AND vasculitis

PUBMED: ((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (cryoglobulinemia) AND (vasculitis))

La búsqueda en Cochrane encontró 1 artículo que se descartó por título. La búsqueda de Lilacs, 51 que se descartaron también por título. La búsqueda por Pubmed encontró 112, se descartaron por título 109, por abstract 1, se descartaron 2 por texto completo. No se seleccionó ningún artículo.

Pregunta 8- En pacientes con SSp, ¿es de utilidad solicitar enzimas pancreáticas séricas para el monitoreo de la función pancreática exócrina?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(insuficiencia pancreatica exocrina))

COCHRANE: Sjogren AND exocrine pancreatic insufficiency

PUBMED: ((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (exocrine pancreatic insufficiency))

No se encontraron artículos por Cochrane. Por Lilacs 6, 3 se descararon por título, 1 por abstract, se seleccionaron 2. Por Pubmed se encontraron 9, se descartaron por título 4, por abstract 2, se seleccionó un artículo.

Afzelius y colaboradores, en una serie de casos publicada en 2010 examinaron la morfología, las funciones endocrina y exocrina del páncreas en 12 pacientes con SSp incluidos de manera consecutiva, sin enfermedad pancreática conocida. Se utilizaron: colangiopancreatografía por resonancia magnética estimulada por secretina (CPRM), prueba de Lundh, prueba de tolerancia oral a la glucosa y toma de muestras de sangre. El 25% de los pacientes tenían cambios morfológicos del páncreas y dos pacientes tuvieron cambios similares a pancreatitis crónica. Cuatro pacientes presentaban función exócrina del páncreas reducida, ya sea por reducción significativa de amilasa y/o lipasa en el jugo pancreático [(11)]. NE: 4

Pregunta 9- En pacientes con SSp, ¿es de utilidad la colangeopancreatografía por resonancia magnética estimulada con secretina para descartar insuficiencia pancreática exócrina y pancreatitis crónica?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(pancreatitis cronica))

COCHRANE: Sjogren AND chronic pancreatitis

PUBMED: ((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (chronic pancreatitis))

En la búsqueda para pancreatitis crónica no se encontraron artículos por Cochrane. Por Lilacs 6, se descartaron por título 3, por abstract 1, se incluyeron 2 para el análisis. Por Pubmed se encontraron 9, se descartaron por título 4, por abstract 2, se incluyeron

3.

LILACS:

(tw:(sjogren)) AND (tw:(insuficiencia pancreatica exocrina))

PUBMED: ((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (exocrine pancreatic insufficiency))

En la búsqueda para insuficiencia pancreática exócrina se encontró 1 artículo por Cochrane que se descartó por título. Por Lilacs se encontraron 47 que fueron descartados por título. Por Pubmed 86, se descartaron por título 83, por abstract 2, se seleccionó 1 para su análisis.

En el estudio descripto previamente de Afzelius y colaboradores, al estudiar a 12 pacientes con SSp se encontró que el 25% presentaba anormalidades en la morfología pancreática por colangiorresonancia magnética, y dos pacientes cambios semejantes a los descritos en casos de pancreatitis crónica. El 80% de los pacientes presentaron función exocrina normal y el 100% llenados duodenales normales [(11)]. NE: 4

Pregunta 10- En pacientes con SSp y afección pancreática, ¿cuál es el tratamiento de primera línea?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(insuficiencia pancreatica exocrina)) AND (tw:(tratamiento))

(tw:(sjogren)) AND (tw:(pancreatitis cronica)) AND (tw:(tratamiento))

COCHRANE: Sjogren AND chronic pancreatitis AND treatment

Sjogren AND exocrine pancreatic insufficiency AND treatment

PUBMED:((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (chronic pancreatitis) AND (treatment sjogren OR sjogren s syndrome OR sjogren syndrome) AND (exocrine pancreatic insufficiency) AND (treatment))

No se encontraron artículos por Cochrane, por Lilacs se encontraron 4, se descartaron 3 por título y 1 por abstract. Por Pubmed se encontraron 33, se descartaron 32 por título y 1 por abstract. Ningún artículo arrojo resultados que respondan a la pregunta pico.

Pregunta 11- En pacientes con SSp, ¿es de utilidad monitorear los niveles séricos de fosfatasa alcalina para evaluar la asociación con cirrosis biliar primaria?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(cirrosis biliar primaria))

COCHRANE: Sjogren AND primary biliary cirrhosis

PUBMED:

((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (primary biliary cirrhosis))

Se encontraron 11 artículos por Cochrane que se descartaron por título. Por Lilacs 206, se descartaron por título 196, 5 por abstract y se seleccionó 1. Por Pubmed se encontraron 386 artículos, se descartaron por título 365 y 16 por abstract. Se seleccionaron 2 artículos.

Hatzis y colaboradores publicaron en 2008 un estudio de corte transversal que tuvo como objetivo evaluar la prevalencia de cirrosis biliar primaria (CBP) en pacientes con SSp. Se evaluaron 410 pacientes con SSp, encontrándose una bioquímica compatible con colestasis en 36 de ellos (8.8%). Veintiuno de los 36 pacientes (5.1%) presentaron anticuerpos antimitocondriales positivos (AMA); a diez de ellos y a siete de los 15 pacientes AMA negativos, se les realizó biopsia de hígado. El resultado de la anatomía patológica fue compatible con CBP en todos, menos un caso (AMA negativo). En la mayoría se encontró un estadio 1 [12]. NE: 4

Skoupoli y colaboradores publicaron en 1994 un estudio de corte transversal, que incluyo 300 pacientes con SSp, en quienes se investigó la frecuencia de compromiso hepático. En 7% de los pacientes se observó compromiso subclínico, con elevación de enzimas hepáticas. En 6.6% se detectaron AMA positivos por inmunofluorescencia, 92% de los cuales presentaron biopsia compatible con estadio 1 de CBP [13]. NE: 4

Pregunta 12- En pacientes con SSp, ¿es de utilidad monitorear la presencia de AMA para descartar cirrosis biliar primaria?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(cirrosis biliar primaria))

COCHRANE: Sjogren AND primary biliary cirrhosis

PUBMED: ((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (primary biliary cirrhosis))

Se encontraron 11 artículos por Cochrane que se descartaron por título. 206 por Lilacs de los cuales 196 se descartaron por título y cinco por abstract. Se encontraron 386 por Pubmed, se descartaron 365 por título y 16 por abstract. Se seleccionaron 3

Tanto el estudiode Hatzis y colaboradores [12], como el de Skoupoli y colaboradores [13] fueron descriptos previamente. NE: 4

Csepregi y colaboradores publicaron en 2002 un estudio de cohorte que tuvo como objetivo evaluar la utilidad de los anticuerpos AMA y anti músculo liso (ASMA) en predecir el desarrollo de enfermedad hepática autoinmune en pacientes con SSp. Se incluyeron 180 pacientes, sin antecedentes de compromiso hepático, en quienes se realizó el dosaje de ambos anticuerpos y se los siguió durante cinco años. Nueve (5%) pacientes presentaron hepatopatía de causa autoinmune (cinco CBP, dos hepatitis autoinmune tipo 1, uno superposición de hepatits autoinmune y hepatitis C y otro diagnosticado como una colangiopatía autoinmune). En tres pacientes se encontraron AMA positivos en el momento basal y dos de ellos desarrollaron CBP, mientras que el tercero (en el cual no se realizó biopsia) permaneció asintomático en los cinco años de seguimiento. 27 pacientes (39%) presentaron ASMA positivos, la mayoría en títulos de 1:80, sólo tres en títulos igual o mayor a 1:160 y estos últimos fueron los que se encontraron asociados al desarrollo de hepatitis autoinmune [14]. NE: 3

Pregunta 13- En pacientes con SSp, ¿es de utilidad monitorear la presencia de ASMA para descartar la asociación con hepatitis autoinmune?

ESTRATEGIA DE BÚSQUEDA:

LILACS: (tw:(sjogren)) AND (tw:(hepatitis autoinmune))

COCHRANE: Sjogren AND autoimmune hepatitis

PUBMED: ((sjogren OR sjogren s syndrome OR sjogren syndrome) AND (autoimmune hepatitis))
En la búsqueda por Cochrane se encontrron 14 artículos que fueron todos descartados por título. Por Lilacs se encontraron 78; se descartaron por título74 y 3 por abstract. Por Pubmed se encontraron 290, se descartaron 278 por título, 10 por abstract, se seleccionó 1 artículo

El artículo seleccionado es el de Csepregi y colaboradores, descripto previamente [14]. NE: 3

Bibliografía

1 . Türk T, Pirildar T, Tunc E, Bor S, Doğanavsargil E. Manometric assessment of esophageal motility in patients with primary Sjögren´s syndrome. Rheumatol Int. 2005 May; 25 (4): 246-9.

2 . Rosztóczy A1, Kovács L, Wittmann T, Lonovics J, Pokorny G. Manometric assessment of impaired esophageal motor function in primary Sjögren's syndrome. Clin Exp Rheumatol. 2001 Mar-Apr; 19 (2): 147-52.

3. Manterola Delgado C, Grande L, Toledo Pimentel V, Ros E, Barroso MS. Esophagic motility in Sjögren's syndrome. Cuad. cir. 1994; 8(1): 11-5.

4. Ostuni PA, Germana B, Di Mario F, Rugge M, Plebani M, et al. Gastric involvement in primary Sjögren's syndrome. Clin Exp Rheumatol 1993; 11(1): 21-5.

5. Pokorny G; Karácsony G; Lonovics J; Hudák J; Németh J; Varró V. Types of atrophic gastritis in patients with primary Sjögren's syndrome. Ann Rheum Dis 1991; 50(2): 97-100.

6. Collin P1, Karvonen AL, Korpela M, Laippala P, Helin H. Gastritis classified in accordance with the Sydney system in patients with primary Sjögren's syndrome. Scand J Gastroenterol. 1997 Feb; 32 (2): 108-11.

7. Luft LM1, Barr SG, Martin LO, Chan EK, Fritzler MJ. Autoantibodies to tissue transglutaminase in Sjögren's syndrome and related rheumatic diseases. J Rheumatol. 2003 Dec;30 (12): 2613-9.

8. Szodoray P1, Barta Z, Lakos G, Szakáll S, Zeher M. Coeliac disease in Sjögren's syndrome-a study of 111 Hungarian patients. Rheumatol Int. 2004 Sep; 24 (5): 278-82.

9. Iltanen S, Collin P, Korpela M, Holm K, Partanen J, et al. Celiac disease and markers of celiac disease latency in patients with primary Sjögren's syndrome. Am J Gastroenterol. 1999 Apr; 94 (4): 1042-6.

10. Palm Ø, Moum B, Gran JT. Estimation of Sjögren's syndrome among IBD patients. A six year post-diagnostic prevalence study. Scand J Rheumatol. 2002; 31 (3): 140-5.

11. Afzelius P, Fallentin EM, Larsen S, Møller S, Schiødt M. Pancreatic function and morphology in Sjögren's syndrome. Scand J Gastroenterol. 2010 Jun;45(6):752-8

12. Hatzis GS, Fragoulis GE, Karatzaferis A, Delladetsima I, Barbatis C, et al. Prevalence and longterm course of primary biliary cirrhosis in primary Sjögren's syndrome. J Rheumatol. 2008 Oct; 35 (10): 2012-6.

13. Skopouli FN, Barbatis C, Moutsopoulos HM. Liver involvement in primary Sjögren's syndrome. Br J Rheumatol. 1994 Aug; 33 (8): 745-8

14. Csepregi A, Szodoray P, Zeher M. Do autoantibodies predict autoimmune liver disease in primary Sjögren's syndrome? Data of 180 patients upon a 5 years follow-up. Scand J Immunol. 2002 Dec; 56 (6): 623-9.

SÍNDROME DE SJÖGREN PRIMARIO Y COMPROMISO RENAL

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Pregunta 1- En los pacientes con Síndrome de Sjögren Primario (SSp) y acidosis tubular (ATR) distal, ¿es necesario realizar biopsia renal para el diagnóstico?

Estrategia/combinación de términos:

((primary sjogren syndrome) AND (renal tubular acidosis) AND (renal biopsy) AND (diagnosis))

Resultados de la búsqueda: pubmed= 41 artículos, lilacs= 23, cochrane= 0

Total: 64

Artículos Duplicados: 22

Total: 42

Excluídos: 38

Total: 5

Ren y colaboradores publicaron en 2008 una serie de casos que tuvo como objetivo identificar las características clínicas, alteraciones en la anatomía patológica y evolución de los pacientes con SSp. Se incluyeron todos los pacientes con SSp y compromiso renal que fueron admitidos en el Hospital Ruijin desde abril de 1993 a diciembre de 2006. Se analizaron retrospectivamente todos los datos de las características clínicas y cambios patológicos, habiéndose realizado biospia renal en 41 pacientes. Este estudio incluyó 130 pacientes con SSp: 122 mujeres y ocho hombres. Las edades oscilaron entre 16 y 68 años (media 44,1 +-11.52). Noventa y cinco pacientes (73.1%) desarrollaron ATR (acidosis tubular renal) de los cuales 91 tuvieron ATR distal. Nueve pacientes presentaron parálisis hipopotasémica. Cuatro pacientes desarrollaron síndrome de Fanconi y tres diabetes insípida nefrogénica. Veintisiete de los 130 pacientes (20,8%) desarrollaron proteinuria tubular y 18/130 (13,8%) presentaron compromiso glomerular, 35 (27,7%) desarrollaron insuficiencia renal (creatininemia > 115 micromol/l). La mayoría (70,8%) presentó aumento de los niveles de IgG en el suero. La incidencia de nefritis intersticial crónica en la biopsia fue de 80,5%. La inmunofluorescencia fue negativa en la mayoría de los casos. Noventa y seis pacientes fueron tratados con corticoIdes o inmunosupresores de los cuales 18 recuperaron la función renal (1). NE: 4.

Bridoux y colaboradores publicaron en 2004 una serie de dos casos en la que se describieron los hallazgos clínico- patológicos en la disfunción tubular proximal en pacientes con SSp. El cuadro clínico de ambos pacientes se caracterizó por xerostomía, xeroftalmía, extenso infiltrado linfocítico en la biopsia de glándula salival, pruebas positivas para anticuerpos anti-SSA/SSB y anticuerpos antinucleares, insuficiencia renal con proteinuria, hematuria microscópica y ATR tipo 1. Estudios posteriores revelaron que un paciente padecía de ATR proximal (tipo 2). Ninguno de estos pacientes tuvo proteinuria de Bence Jones o gamapatía monoclonal. La biopsia renal demostró tubulitis proximal focal asociada a diferenciación y atrofia de células tubulares proximales y nefritis intersticial difusa con fibrosis. No se observaron depósitos glomerulares o peritubulares considerables de inmunoglobulina de cadena ligera ni pesada. Estos resultados demuestran que la disfunción tubular difusa, distal y proximal, puede ocurrir en pacientes con SSp y nefritis intersticial y que la Infiltración linfocítica de las células tubulares proximales probablemente está implicada en la patogenia del síndrome de Fanconi en el SSp (2). NE: 4

Bossini y colaboradores publicaron en 2001 una serie de casos para estudiar la prevalencia y naturaleza del compromiso renal en pacientes con SSp. Se incluyeron 60 pacientes italianos con SSp, diagnosticado según los criterios de clasificación europeos. En todos los pacientes se realizaron los siguientes exámenes: electrolitos y creatinina en suero y en orina de 24 h, pH venoso con bicarbonato, análisis de orina, cultivo de orina, osmolaridad urinaria y pH urinario. En los pacientes que presentaron una osmolaridad en la primera orina de la mañana por debajo de los valores de referencia ajustados para la edad, se realizó una prueba de privación de agua. Se efectuó, además, una prueba de carga oral con cloruro de amonio a los pacientes con pH urinario por encima de 5.5 en las muestras de la mañana. Se practicó biopsia renal a los pacientes que tuvieron alteración de la función. Dieciséis pacientes (27%) tuvieron evidencia de laboratorio de disfunción tubular y glomerular. Un grado variable de disminución del clearence de creatinina fue encontrado en ocho pacientes (13%); acidosis tubular distal en tres (5%); hipokalemia en cuatro (7%); y proteinuria patológica en 12 (20%). La capacidad de concentrar la orina fue defectuosa en diez pacientes. Sólo cuatro pacientes presentaron manifestaciones clínicas, incluyendo cuadriparesia hipokalémica (uno), síndrome nefrótico (dos), litiasis renal con cólicos recurrentes con dolor en el flanco y hematuria (uno). En dos pacientes el compromiso renal precedió el inicio del síndrome sicca. Las biopsias renales de nueve pacientes demostraron nefritis túbulo intersticial en seis y enfermedad glomerular en tres. Los pacientes con afectación renal tuvieron una duración de la enfermedad significativamente más corta en comparación con los pacientes sin anormalidades renales (3). NE: 4

Maripuri y colaboradores publicaron en 2009, una serie de casos cuyo objetivo fue reportar los hallazgos clínicos y los resultados de las biopsias renales en pacientes con SSp y compromiso de la función renal. Se les practicó biopsia renal a 24 pacientes de los 7276 con SSp a lo largo de 40 años. Todos los casos fueron revisados por un patólogo renal, nefrólogo y reumatólogo. Se presentaron los hallazgos de laboratorio, anatomía patológica, tratamiento inicial y la respuesta terapéutica. Diecisiete de 24 pacientes (71%) tuvieron nefritis túbulo intersticial aguda o crónica como lesión

primaria, siendo la forma crónica la más frecuente (11 de 17; 65%). Dos tuvieron glomerulonefritis (GN) crioglobulinémica, dos glomeruloesclerosis focal y segmentaria. Veinte pacientes (83%) fueron tratados inicialmente con corticoides. Además, tres recibieron rituximab durante el seguimiento. Dieciséis fueron seguidos después de la biopsia por más de 12 meses (media de 76 meses; rango 17 a 192), y 14 de 16 mantuvieron la mejoría de la función renal a través del seguimiento. De los 7 pacientes que presentaron insuficiencia renal crónica estadío IV, ninguno progresó a etapa V con el tratamiento (4). NE: 4

Goules y colaboradores publicaron en el año 2000, una amplia serie de casos, en la que evaluaron la frecuencia y significado de la nefritis intersticial (NI) y la GN. Se incluyeron 471 pacientes con SSp que fueron seguidos durante una media de 10 años. Veinte pacientes (4.2%) desarrollaron enfermedad renal. A 18 pacientes se le realizó biopsia renal percutánea; dos pacientes se negaron. Diez pacientes tuvieron nefritis intersticial, ocho pacientes GN y dos pacientes presentaron ambas entidades combinadas. La histología glomerular mostró cambios compatibles con GN membranoproliferativa en cinco pacientes y mesangial proliferativa en cuatro. Los pacientes con NI fueron más jóvenes al inicio de la enfermedad en comparación con los pacientes con GN (36.8 en comparación con 46,0 años, p= 0,063). Los pacientes con GN tenían más larga duración de la enfermedad en comparación con los pacientes con NI (media de 8 años vs 2.2 años respectivamente, p=0,001). La mayoría de los pacientes con GN (80%) tuvo crioglobulinemia monoclonal IgMk (tipo II) y bajos niveles de complemento C4. Dos pacientes (ambos con GN) desarrollaron insuficiencia renal crónica que requirió hemodiálisis (5). NE: 4

Pregunta 2- En los pacientes con SS p y ATR distal, ¿es mandatorio el uso de inmunosupresión para lograr la remisión?

Estrategia/combinación de términos:

((primary sjogren syndrome) AND (renal tubular acidosis) AND (steroids) AND (remission))

((primary sjogren syndrome) AND (renal tubular acidosis)) AND (treatment) AND (remission))

((primary sjogren syndrome) AND (renal tubular acidosis)) AND (steroids) AND (azathioprine) AND (remission))

((primary sjogren syndrome) AND (renal tubular acidosis) AND (treatment))

Resultados de la búsqueda: pubmed= 36, lilacs= 20, cochrane= 1

Total: 57

Artículos Duplicados: 19

Total: 38

Excluídos: 33

Total: 4

Saeki y colaboradores en 2001 reportaron el caso de una paciente joven con SSp, insuficiencia renal progresiva y ATR. Fue tratada con tres infusiones de altas dosis de corticoesteroides (en pulsos) seguido de la administración posterior de dosis bajas por vía oral. Se evaluó la eficacia a los seis meses después del comienzo de la terapia, observándose una mejoría significativa sin la aparición de efectos adversos. Esto se objetivó no sólo en pruebas de laboratorio sino también en la anatomía patológica de una nueva biopsia renal (6). NE: 4

Ring y colaboradores reportaron en 2006 el caso de una mujer de 55 años de edad, el primer paciente con SSp y ATR distal pero sin linfoma tratado con depleción de células B, rituximab. Rápidamente después de la depleción de las células B mejoró notablemente la xerostomía, mientras que los resultados serológicos y la ATR permanecieron sin cambios. En la biopsia de glándulas salivares labiales la infiltración de linfocitos y particularmente las células CD20 disminuyeron notablemente. La expresión de Acuaporina1 (AQP-1) en células mioepiteliales era muy baja antes del tratamiento y aumentó notablemente después del mismo. La AQP-5 apical en el acino celular también aumentó después del rituximab. Por el contrario, la NKCC1 basolateral no expresó cambios ni antes ni después del rituximab. La mejoría fue sostenida y permaneció durante diez meses después del tratamiento (7). NE: 4

El estudio de Ren, descripto al comienzo, incluyó 130 pacientes con SSp, 95 (73.1%) con ATR, 27 (20,8%) con proteinuria tubular y 18 (13,8%) con compromiso glomerular. Noventa y seis fueron tratados con corticoides o inmunosupresores de los cuales 18 recuperaron la función renal (1). NE: 4

Kaufman y colaboradores publicaron en 2008 un caso de nefritis intersticial severa con proteinuria en un paciente con SSp, realizaron una revisión de la literatura con respecto a la enfermedad renal en SSp y su manejo para sugerir recomendaciones acerca del tratamiento. Se describió un caso raro de SSp que se presentó con tetraparesia hipokalémica y proteinuria debido a una severa NI. Fue tratado con éxito con altas dosis de esteroides y azatioprina. Revisando la literatura, se identificaron 180 casos reportados de compromiso renal en SSp (que cumplían criterios europeos para SSp), 89 de los cuales tuvieron biopsias renales que revelaron NI en 49 casos, GN en 33 muestras y ambas entidades en siete. Dieciocho estudios reportaron experiencias de tratamiento de la enfermedad renal en 32 casos de SSp. Diecisiete pacientes fueron tratados con corticosteroides y ciclofosfamida, y 15 pacientes recibieron sólo esteroides con mejoría en la mayoría de los casos (8). NE: 4

Pregunta 3- a. ¿Son la potasemia y el estado ácido los mejores indicadores para el diagnóstico de ATR distal?

3- b. En pacientes con SSp y sospecha de ATR distal incompleta, ¿debe realizarse prueba de sobrecarga de amonio para el diagnóstico?

Estrategia/combinación de términos:

((primary sjogren syndrome) AND (renal tubular acidosis) AND (metabolic acidosis) AND (hypokalemia) AND (diagnosis))

((primary sjogren syndrome) AND (renal tubular acidosis) AND (incomplete renal tubular acidosis) AND (diagnosis))

(((primary sjogren syndrome) AND renal tubular acidosis)) AND diagnosis

Resultados de la búsqueda: pubmed= 77, lilacs= 67, cochrane= 0

Total: 144

Artículos Duplicados: 65

Total: 79

Excluídos: 74

Total: 5

Both y colaboradores publicaron en 2015, un estudio de corte transversal, que tuvo como objetivos analizar la prevalencia de la ATR distal en SSp y comparar una prueba de acidificación urinaria con furosemida y fludrocortisona (FF) con el patrón oro, cloruro de amonio (NH4Cl), para detectar la ATR distal. Se evaluó la acidificación urinaria en 57 pacientes con SSp con NH4Cl y FF. Un defecto de acidificación urinaria se definió como una incapacidad para alcanzar un pH urinario < 5.3 después de NH4Cl. La prevalencia de ATR distal completa (defecto de acidificación urinaria con acidosis) fue del 5% (tres/57). Los tres pacientes tuvieron autoanticuerpos SSA/RO y SSB/LA positivos y deterioro de la función renal. La prevalencia de la forma incompleta (defecto de acidificación urinaria sin acidosis) fue del 25% (14/57). En comparación con pacientes sin ATR distal, los pacientes con ATR distal incompleta presentaron un PH venoso significativamente menor, y bicarbonatemia y PH urinario mayor. Los anticuerpos SSB/LA fueron más prevalentes en los grupos ATR distal ($p < 0.05$). En comparación con NH4CL, los valores predictivos positivos y negativos de FF fueron 46% y 82%, respectivamente. Durante la prueba de acidificación urinaria con NH4CL los pacientes presentaron vómitos más frecuentemente que con la prueba con FF (9 vs 0, $p < 0.05$) (9). NE: 4.

Duffles y colaboradores publicaron en 2014 un estudio de corte transversal en el cual evaluaron la disfunción tubular (principalmente ATR distal tipo 1 y defectos en la concentración) en pacientes con SSp. Se valoró la función tubular renal de pacientes con SSp mediante la detección de la lesión tubular proximal (a través de mediciones de urinaria β2microglobulina y albúmina), de ATR tipo 1 (a través de un protocolo de acidificación con furosemida y fludrocortisona) y defectos en la con concentración (a través de la prueba de privación de agua). Se evaluaron un total de 25 pacientes con SSp, con una función renal conservada (eGFR 92,5 ± 26,3 mL/min/1.73 m^2). Se

encontró ATR tipo 1 en el 24%. Por otro lado, los defectos en la concentración fueron diagnosticados en el 28% de los pacientes, los que presentaron una peor función renal (FGe 68.6 ± 27,7 mL/min/1.73 m^2). Un aumento de β2microglobulina fue encontrado en un 16% de los pacientes, los que asimismo, tuvieron alteraciones de la función renal (FG 39,5 ± 11,9 mL/min/1.73 m (2). Estos datos mostraron una alta prevalencia de disfunción tubular (10). NE: 4

Pertoovara y colaboradores publicaron en 2001 un estudio de casos y controles con el objeto de identificar factores de riesgo clínicos e inmunológicos subyacentes al desarrollo de compromiso renal en el SSp. Setenta y ocho pacientes (75 mujeres, tres hombres) con SSp fueron cuidadosamente entrevistados obteniéndose además datos clínicos y de laboratorio desde el momento del diagnóstico. Los datos de referencia de una latente o evidente ATR distal (casos) fueron proteinuria leve o mayor excreción urinaria de alfa-1 microglobulina (alpha1m) después de un tiempo de enfermedad promedio de nueve +/- cuatro años. Se compararon con los datos de referencia basales de los pacientes que no tuvieron manifestaciones de ATR distal en el seguimiento (controles). Los pacientes con ATR distal latente o manifiesta presentaron niveles más altos de gamaglobulina en suero total (24 +-7 vs 19 +/-6 g/l, p = 0.011) y proteinemia (84 +-7 vs 79 +/-7 g/l, p = 0.024) comparado con aquellos con capacidad de acidificación renal normal. Los niveles de referencia de suero de beta-2 microglobulina (beta2m) fueron mayores en pacientes con un defecto de acidificación que en aquellos con capacidad de acidificación normal (3.1 +-1.1 vs 2.6 +/-0,8 mg/l, p = 0.072). En aquellos que desarrollaron proteinuria con posterioridad los niveles séricos de beta2m fueron significativamente mayores al inicio del estudio en comparación con aquellos con excreción urinaria de proteínas normal (3.1 +-1.4 vs 2.5 +/-0,8 mg/l, p = 0.052). El subgrupo de pacientes con SSp que había aumentado la excreción urinaria de alpha1m como un signo de proteinuria tubular, tuvo niveles más altos de eritrosedimentación (55 +/-27 mm/h vs 40 +/-23 mm/h, p = 0.076) y significativamente mayores niveles de beta2m (4.6 + /-1.8 vs 2.6 +/-0,8 mg/l, p = 0,029) comparado con aquellos que tuvieron una excreción normal. Por lo tanto, altos niveles de gamma-globulina en suero total, proteínas en suero y beta2m fueron las variables más fuertemente asociadas al desarrollo de ATR distal en pacientes de SSp. Niveles basales altos en suero de beta2m también se asociaron con la posterior aparición de proteinuria leve y aumento de la excreción urinaria de alpha1m en pacientes con SSp (11). NE: 4

Aasarod y colaboradores publicaron en el 2000, un estudio de corte transversal en el que analizaron la utilidad del cociente citrato/creatinina para identificar pacientes con ATR distal en pacientes con SSp. Se evaluó el compromiso renal en 62 pacientes con SSp, clasificados según criterios propuestos por el Grupo Europeo. La capacidad de concentración de la orina se evaluó mediante la aplicación de 1-desamino-8-D-arginine-vasopressina intranasal. En los pacientes con pH urinario > 5.5 sin acidosis metabólica (n = 28), se realizó una prueba de acidificación con cloruro amónico. Se midieron el citrato urinario, albúmina, NAG, ALP y beta2m y se calculó el aclaramiento de creatinina. La capacidad de concentración máxima de la orina y la creatinina se redujeron en 13 casos (21%). La excreción de albúmina fue > 30 µg/min en solamente un paciente (1,6%). Siete pacientes (11,3%) tuvieron ATR distal completa o

incompleta, cuatro tuvieron disminución del clearence de creatinina y cinco disminución de la capacidad de concentración máxima de orina. La relación de citrato/creatinina en orina fue por debajo del percentilo 2.5 en todos los pacientes con ATR distal completa o incompleta. La prevalencia de ATR distal fue menor que en estudios anteriores. Hubo también algunos pacientes con signos de enfermedad glomerular (1.6%) (12). NE: 4

Pertovaara y colaboradores publicaron en 1999 un estudio de corte transversal, que tuvo como objetivo determinar la presencia de compromiso renal en pacientes con SSp. Se evaluó la excreción urinaria de proteínas totales en orina de 24 h, así como las tasas de excreción urinaria de albúmina, alfa-1 microglobulina (alpha1m) y de IgG de recolecciones de ocho hs durante la noche, en 78 pacientes con SSp (75 mujeres, tres hombres). La capacidad de acidificación de orina después de una carga oral de cloruro de amonio fue evaluada en 55 de estos pacientes. Se observó proteinuria leve (0.42 0.15 g/24 h) en 34 pacientes (44%). Aumento de las tasas de excreción urinaria de albúmina (> = 20 microgramos/min), alpha1m (> = 7,0 µg/min) o IgG (> = 5.0 µg/min) fueron detectados en nueve (12%), nueve (12%) y 11 pacientes (14%), respectivamente. ATR distal latente o evidente se observó en 18 de los 55 pacientes con SSp (33%). Estos pacientes tuvieron una duración más larga de la enfermedad (10 +-4 vs 8 +-4 años; p</=0.05); también presentaron proteinuria (67 vs 27%; p</=0.025) e hipertensión arterial (44 vs 14%; p</=0.05), una creatininemia mayor (92+/-39 vs 78+/-13 µmol/l; p</=0.025) y una concentración de β2m elevada (3.3+/-1.6 g/l vs 2.6+/-0. 6 g/l; p</=0.025) comparados con pacientes con una acidificación urinaria normal. Por lo tanto, los que presentaron ATR distal tuvieron una más larga duración de la enfermedad, un mayor nivel sérico de β2m, hipertensión y proteinuria, comparados con aquellos con capacidad de acidificación renal normal (13). NE: 4

Pregunta 4- En pacientes con SSp y glomerulonefritis (GN), ¿debe el tratamiento ser el mismo que el de la GN lúpica para lograr la remisión?

Estrategia/combinación de términos:

((primary sjogren syndrome) AND (glomerulonephritis) AND (renal biopsy) AND (diagnosis))

((primary sjogren syndrome) AND (glomerulonephritis) AND (steroids) AND (remission))

((primary sjogren syndrome) AND (glomerulonephritis) AND (steroids) AND (azathioprine))

((primary sjogren syndrome) AND (glomerulonephritis) AND (treatment))

((primary sjogren syndrome) AND (glomerulonephritis) AND (treatment) AND (remission))

Resultados de la búsqueda: pubmed= 46, lilacs= 25, cochrane= 1

Total: 72

Artículos Duplicados: 24

Total: 48

Excluídos: 41

Total: 4

Goules y colaboradores publicaron en 2013 un estudio de cohorte para estimar la prevalencia e investigar los hallazgos clínicos y resultados del compromiso renal clínicamente significativo en una cohorte de 715 pacientes con SSp según criterios del consenso americano-europeo. Se identificaron los casos con compromiso renal clínicamente significativo y se registraron los hallazgos clínicos e inmunológicos. El pronóstico en estos pacientes fue evaluado por la presencia de cualquiera de los siguientes eventos: muerte, hemodiálisis, fallo renal crónico y linfoma. La mortalidad entre pacientes con y sin compromiso renal se evaluó mediante curvas de Kaplan-Meier. Treinta y cinco pacientes con SSp (4.9%) tuvieron compromiso renal clínicamente significativo, representando un tiempo de seguimiento luego del diagnóstico de compromiso renal de 252.2 personas-año. Trece pacientes (37.1%) tuvieron nefritis intersticial sola, 17 pacientes (48.6%) tuvieron GN sola, y cinco pacientes (14.3%) tuvieron ambas entidades. Nueve pacientes murieron (25.7%), 11 (31.4%) desarrollaron fallo renal crónico (incluidos cuatro pacientes con hemodiálisis crónica) y nueve desarrollaron linfoma (25.7%). La tasa global de sobrevida a cinco años fue del 85%. El análisis de Kaplan-Meier mostró una reducción de la sobrevida estadísticamente significativa en los pacientes con compromiso renal comparados con los que no lo tenían (P<0.0001), con mayor aumento de la mortalidad entre los pacientes con GN ((ocho de nueve muertes reportadas (89%) y ocho de nueve linfomas (89%) se observaron entre los pacientes con GN)). Respecto al tratamiento de la GN, el mismo fue instaurado según criterio médico. Para la inducción se utilizaron diferentes opciones: ciclofosfamida endovenosa mensual en dosis de 1 gm/m2 sumado a 1 gramo de metilprednisolona; metilprednisolona oral como monoterapia (0.5–0.75 mg/kg día) o en combinación con otro inmunosupresor (2 mg/kg/día de azatioprina o 2–3 mg/kg/ día de ciclosporina); terapia de depleción de células B (3 ciclos de dos infusiones cada uno de rituximab, con un intervalo entre ciclos de seis meses). La mayoría de los pacientes presentó una respuesta favorable con los diferentes esquemas de tratamiento instaurados (14). NE como estudio pronóstico de compromiso renal: 2. NE para responder la pregunta: 4.

En la serie de casos publicada por Maripuri y colaboradores en 2009, comentada previamente, 20 pacientes (83%) fueron tratados inicialmente con corticoides, tres recibieron rituximab durante el seguimiento. La mediana de dosis inicial de prednisona fue 40 mg (rango 30 a 60 mg) con una mediana de duración de 30 semanas (rango cuatro a 52 semanas). Dieciséis pacientes fueron seguidos por más de 12 meses luego de la biopsia renal (mediana de 76 meses, rango de 17 a 192) y 14 de 16 mantuvieron o mejoraron la función renal durante el seguimiento. De los siete

pacientes con insuficiencia renal estadio IV ninguno progreso a estadio V con tratamiento (15). NE: 4

En el reporte de caso y revisión de la literatura publicada por Kaufman y colaboradores en 2008, un paciente con nefritis tubulointersticial severa fue tratado exitosamente con dosis altas de corticoides y azatioprina. Revisando la literatura se identificaron 180 reportes de casos de compromiso renal en SSp, a 89 de los cuales se les realizó biopsia renal la cual revelo nefritis intersticial en 49 casos, GN en 33 casos y ambos hallazgos en siete. Diecisiete pacientes fueron tratados con corticoides y ciclofosfamida y 15 pacientes recibieron solo corticoides con mejoría en la mayoría de los casos (16). NE: 4

Tatsumi y colaboradores publicaron en 1998 un caso de GN crescéntica asociada a nefropatía membranosa en un paciente con SSp. El paciente desarrolló insuficiencia renal, la cual resolvió con el tratamiento con corticoides y plasmaféresis. Varios reportes han descripto el efecto beneficioso del uso de corticoides con o sin otros agentes citotóxicos en la GN asociada al SSp. Las drogas utilizadas, dosis y tiempo de tratamiento no están protocolizadas y con frecuencia son extrapoladas de su uso en otras patologías (17). NE: 4

Pregunta 5- ¿Existen biomarcadores que puedan predecir el compromiso renal en pacientes con SSp?

Estrategia/combinación de términos:

((primary sjogren syndrome) AND (renal disease) AND (predictive factors))

Resultados de la búsqueda: pubmed= 4, lilacs= 2, cochrane= 0

Total: 6

Artículos Duplicados: 2

Total: 4

Excluídos: 3

Total: 1

El estudio de Goules descripto con anterioridad, tuvo como objetivo identificar factores de riesgo clínicos e inmunológicos relacionados con el desarrollo de compromiso renal en SSp. Incluyó 78 pacientes. Se observó que los pacientes con ATR distal latente o establecida presentaron niveles basales significativamente más altos de

gammaglobulina total 24 +/- 7 vs 19 +/- 6 g/l, p= 0.011) y de proteínas séricas (84 +/- 7 vs 79 +/- 7 g/l, p= 0.024) comparados con aquellos con capacidad de acidificación renal normal. Los niveles basales de β2m fueron más altos en pacientes con defectos de la acidificación comparados con aquellos con capacidad de acidificación normal (3.3 +/- 1.1 vs 2.6 +/- 0.8 mg/l, p=0.072). En aquellos con proteinuria subsecuente los niveles séricos basales de β2m fueron más altos comparados con aquellos con excreción de proteínas urinarias normal (3.1 +/- 1.4 vs 2.5 +/- 0.8 mg/l, p= 0.052). El subgrupo de pacientes con SSp que tuvo aumentada la excreción de la alfa1m urinaria tuvo signos de proteinuria tubular, mayores niveles basales de eritrosedimentación (55 +/- 27 vs 40 +/- 23 mm/h, p= 0.076) y valores basales significativamente más altos de β2m (4.6 +/- 1.8 vs 2.6 +/- 0.8 mg/l, p= 0.029) comparado con los pacientes con excreción urinaria normal de alfa-1m (11). NE: 4

Bibliografía:

1-Ren H1, Wang WM, Chen XN, Zhang W, Pan XX, Wang XL, Lin Y, Zhang S, Chen N. Renal involvement and follow up of 130 patients with primary Sjögren's syndrome. J Rheumatol. 2008 Feb; 35(2):278-84.

2- Bridoux F1, Kyndt X, Abou-Ayache R, Mougenot B, Baillet S, Bauwens M, Lemaitre V, Goujon JM, Touchard G, Vanhille P. Proximal tubular dysfunction in primary Sjögren's syndrome: a clinicopathological study of 2 cases. Clin Nephrol. 2004 Jun; 61(6):434-9.

3-Bossini N1, Savoldi S, Franceschini F, Mombelloni S, Baronio M, Cavazzana I, Viola BF, Valzorio B, Mazzucchelli C, Cattaneo R, Scolari F, Maiorca R. Clinical and morphological features of kidney involvement in primary Sjögren's syndrome. Nephrol Dial Transplant. 2001 Dec; 16(12):2328-36.

4- Maripuri S1, Grande JP, Osborn TG, Fervenza FC, Matteson EL, Donadio JV, Hogan MC. Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009 Sep; 4(9):1423-31. doi: 10.2215/CJN.00980209.

5- Goules A1, Masouridi S, Tzioufas AG, Ioannidis JP, Skopouli FN, Moutsopoulos HM. Clinically significant and biopsy-documented renal involvement in primary Sjögren syndrome. Medicine (Baltimore). 2000 Jul; 79 (4):241-9.

6- Saeki Y1, Ohshima S, Ishida T, Shima Y, Umeshita-Sasai M, Nishioka K, Yamaguchi N, Suemura M. Remission of the renal involvement in a patient with primary Sjögren's syndrome (SS) after pulse high-dose corticosteroid infusion therapy. Clin Rheumatol. 2001;20(3):225-8.

7- Ring T1, Kallenbach M, Praetorius J, Nielsen S, Melgaard B. Successful treatment of a patient with primary Sjögren's syndrome with Rituximab. Clin Rheumatol. 2006 Nov;25(6):891-4.

8- Kaufman I1, Schwartz D, Caspi D, Paran D. Sjögren's syndrome - not just Sicca: renal involvement in Sjögren's syndrome Scand J Rheumatol. 2008 May-Jun;37(3):213-8.

9- Both T1, Hoorn EJ2, Zietse R2, van Laar JA3, Dalm VA3, Brkic Z2, Versnel MA2, van Hagen PM3, van Daele PL3. Prevalence of distal renal tubular acidosis in primary Sjögren's syndrome. Rheumatology (Oxford). 2015 May;54(5):933-9.

10- Duffles Amarante GB, Zotin MC, Rocha E, Delgado AG, Leite M Jr, Gomes CP. Renal tubular dysfunction in patients with primary Sjögren syndrome. Clin Nephrol. 2014 Mar;81(3):185-91.

11- Pertovaara M1, Korpela M, Pasternack A. Factors predictive of renal involvement in patients with primary Sjögren's syndrome. Clin Nephrol. 2001 Jul;56(1):10-8.

12- Aasarød K1, Haga HJ, Berg KJ, Hammerstrøm J, Jørstad S. Renal involvement in primary Sjögren's syndrome. QJM. 2000 May;93(5):297-304.

13- Pertovaara M1, Korpela M, Kouri T, Pasternack A. The occurrence of renal involvement in primary Sjögren's syndrome: a study of 78 patients. Rheumatology (Oxford). 1999 Nov;38(11):1113-20.

14- Goules AV1, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjögren's syndrome: clinical presentation and outcome. Arthritis Rheum. 2013 Nov;65(11):2945-53.

15- Maripuri S1, Grande JP, Osborn TG, Fervenza FC, Matteson EL, Donadio JV, Hogan MC.

Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009 Sep;4(9):1423-31.

16- Kaufman I1, Schwartz D, Caspi D, Paran D. Sjögren's syndrome - not just Sicca: renal involvement in Sjögren's syndrome. Scand J Rheumatol. 2008 May-Jun;37(3):213-8.

17- Tatsumi H1, Tateno S, Hiki Y, Shigematsu H, Kobayashi Y. Crescentic glomerulonephritis associated with membranous nephropathy in a case with primary Sjögren'ssyndrome. Nephrol Dial Transplant. 1998 Oct;13(10):2624-7.

COMPROMISO CARDIOVASCULAR EN EL SÍNDROME DE SJÖGREN

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Pregunta 1- ¿Qué consejo de prevención cardiovascular primaria deben darse en el Síndrome de Sjögren primario (SSp)?

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome AND cardiovascular diseases AND prophylaxis; prevention

Pub Med: 58 artículos: 1 seleccionado

Lilacs: 0

Cochrane: 8 descartados.

Cruz y colaboradores publicaron en 2010 un estudio de corte transversal, en el que se incluyeron73 pacientes y 65 controles. El objetivo fue investigar el perfil lípidico en SSp y su asociación con test de laboratorio incluyendo marcadores de inflamación. Las características demográficas eran similares entre ambos grupos. Los resultados de colesterol total (204.0±43.39 versus 206.5±42.76 mg/ml, p= 0.73), LDL (131.6±37.38 versus 130.62±38.24 mg/dl, p = 0.88), HDL (49.7±13.5 versus 51±11.5 mg/dl, p = 0.56) y triglicéridos (129.3±81.0 versus 116.8±53.5 mg/dl, p = 0.29) fueron similares en ambos grupos. Al categorizar a los sujetos en dislipémicos y no dislipémicos, se observó una mayor frecuencia de dislipemia en los pacientes con SSp (76.7% versus 61.5% en los controles, p= 0.06).A su vez, los pacientes con SSp con dislipemia presentaron valores de eritrosedimentación significativamente mayores que los pacientes con SSp sin dislipemia (44.05±28.07 versus 28.28±18.00; p= 0.03). La dislipemia se asoció con aumento de la VSG. Los pacientes con SSp tuvieron una fuerte tendencia a presentar dislipemia cuando se los comparó con sujetos sanos [(1)]. NE: 4

Pregunta 2- ¿Tiene utilidad el ecocardiograma en pacientes con SSp asintomáticos para detectar pericarditis?

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): echocardiography - pericarditis- Sjögren syndrome - asymptomatic pericarditis – asymptomatic condition

Pub Med: 3 artículos, los 3 descartados

Manual: 1 seleccionado (Pub Med)

Lilacs: 9 descartados por título

Cochrane: 0

Vassiliou y colaboradores publicaron en 2008 un estudio de corte transversal que tuvo como objetivo describir las alteraciones ecocardiográficas en los pacientes con SSp y su relación con los parámetros clínicos y de laboratorio. Se incluyeron 107 pacientes con SSp (casos) y 112 controles sanos (controles). 32 de 107 pacientes con SSp versus 12 de 112 controles presentaron regurgitación de la válvula mitral ($p < 0.001$). La regurgitación se encontró en 25 casos en comparación con 11 controles ($p = 0.007$); mientras que la regurgitación tricuspídea se observó en 11 versus tres sujetos ($p = 0.022$). En nueve pacientes con SSp se observó derrame pericárdico leve y en un sujeto del grupo control ($p= 0.008$). También el índice de masa del ventrículo fue significativamente superior en los casos que en los controles (108.9± 17.21 gm-2 *vs*. 85.8 ± 6.73 gm-2; $p <0.001$). Las principales manifestaciones clínicas que se encontraron asociadas con los diferentes hallazgos ecocardiográficos fueron la púrpura palpable, los anticuerpos reactivos y la disminución de C4 [(2)]. NE: 4

Pregunta 3- ¿Tiene utilidad la realización de ecocardiograma en pacientes asintomáticos con SSp como método de rastreo para detectar pericarditis, valvulopatías o hipertensión pulmonar?

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome - valvular heart disease – echocardiography - asymptomatic disease – pulmonary hypertension

Echocardiography and Sjögren síndrome Pub Med: 52. 6 seleccionados.

Lilacs: 9 descartados por título

Cochrane: 1 descartado

Cicek y colaboradores publicaron en 2014 un estudio de corte transversal en el que se incluyeron 50 pacientes y 47 voluntarios sanos, que tuvo como objetivo evaluar la función ventricular izquierda en pacientes con SSp usando ecocardiograma con doppler, el índice de performance miocárdico y métodos ecocardiográficos convencionales. Los grupos eran similares en cuanto a edad, sexo, niveles de tensión arterial, niveles de glucemia, perfil lipídico y antecedentes de tabaquismo. Se observó que la relajación isovolumétrica y la desaceleración eran significativamente más prolongadas; mientras que, la onda diastólica temprana (ODT) era significativamente menor en los pacientes con SSp. Al comparar los hallazgos del ecocardiograma con doppler tisular, se encontró que la onda sistólica (OS), la ODT eran significativamente menores; mientras que el tiempo de relajación isovolumétrica y el índice de

performance miocárdico eran significativamente superiores en lo pacientes con SSp. A su vez, aunque estadísticamente significativos, los niveles de correlación entre la elasticidad de la aorta y la OS fueron bajos (r = 0.35, p < 0.001), ODT (r = 0.42, p < 0.001) [3]. NE: 4

Bayram y colaboradores publicaron en 2013 un estudio de corte transversal en el que se evaluaron 50 pacientes con SSp y 48 voluntarios sanos con características demográficas similares. Se excluyeron a los pacientes menores de 18 años, mayores de 60 años, con enfermedad cardíaca estructural, hipertensión, diabetes, enfermedad pulmonar y otras enfermedades sistémicas crónicas. Como resultados se observó que la onda sistólica miocárdica, la onda diastólica temprana y la onda diastólica tardía fueron significativamente menores, mientras que el tiempo de relajación isovolumétrico y el índice de performance miocárdico fueron significativamente superiores en los pacientes con SSp [4]. NE: 4

Akyel y colaboradores publicaron en 2012 un estudio de corte transversal en el que se estudiaron 40 pacientes con SSp y 25 controles. Cualquier otra enfermedad diferente a SSp se consideró criterio de exclusión (incluídas la hipertensión arterial y diabetes). Las características basales de ambos grupos fueron similares. El índice de performance miocárdica se encontró significativamente alterado en los pacientes con SSp (0.41 vs. 0.32, p<0.01). Se encontró un significativo retardo electromecánico intra atrial (16.4±6.4, 5.0±4.5, p<0.01) e inter atrial (30.6±10.1,15.4 ± 5.9, p<0.01) en los pacientes, en comparación con los controles sanos [5]. NE: 4

El estudio publicado por Vassiliou y colaboradores en 2008, fue descripto previamente [2].

Kobak y colaboradores publicaron en 2014 un estudio de corte transversal que tuvo como objetivo describir la frecuencia de la hipertensión pulmonar en el SSp y analizar su relación con el laboratorio y la clínica. Se incluyeron 47 pacientes con SSp. Una presión sistólica mayor a 30 mmHg medida por ecocardiograma con doppler se consideró como hipertensión pulmonar. En 23.4% (11 pacientes) se detectó hipertensión pulmonar, en cinco de estos pacientes el valor fue superior 35mmHg. La misma fue más frecuente en los pacientes más jóvenes (promedio de edad 41.6 versus 56.2 años; *p*: 0,04) y menor tiempo de evolución de la enfermedad (promedio 4.3 versus 9.5 años; p: 0,04), sin encontrarse asociaciones con las manifestaciones clínicas, ni de laboratorio [6]. NE: 4

Ye y colaboradores publicaron en 2008 una serie de casos retrospectiva que tuvo como objetivo analizar las manifestaciones de pacientes con SSp y SS secundario. Se analizaron datos clínicos, serológicos y ecocardiograma de 124 pacientes incluídos. Se excluyeron los pacientes con enfermedad cardíaca congénita, reumática y coronaria, los pacientes hipertensos y los diabéticos. Los pacientes eran asintomáticos, en los que presentaron derrame pericárdico se asoció a disminución del complemento, aumento de la PCR y Ro+. La hipertensión pulmonar se asoció a aumentos de la gammaglobulina. Los hallazgos más frecuente fueron el derrame pericárdico (20%), la disfunción ventricular diastólica (13.7%) y la hipertensión pulmonar (12.9%) [7]. NE: 4

Pregunta 4- ¿Los pacientes con SSp que van a ser sometidos a procedimientos odontológicos que son portadores de valvulopatía, deben recibir profilaxis antibiótica?

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): antibiotic prophylaxis – dental instrumentation – Sjögren syndrome – heart valvular disease

Pub Med: 0

Lilacs: 0

Cochrane: 0

Pregunta 5- ¿Qué tratamientos farmacológicos han demostrado utilidad en los pacientes con SSp y fenómeno de Raynaud para disminuir la intensidad o la frecuencia de los episodios? Antagonistas cálcicos

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome – Raynaud – Raynaud syndrome – decrease intensity - decrease frecuency – calcium channel blockers

Pub Med: 5 artículos todos descartados

Lilacs: 0

Cochrane: 0

Pregunta 6- ¿Qué tratamientos farmacológicos han demostrado utilidad en los pacientes con SSp y fenómeno de Raynaud para disminuir la intensidad o la frecuencia de los episodios? bosentán

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome – Raynaud – Raynaud syndrome – decrease intensity - decrease frecuency – **bosentan – digital ulcers**

Pub Med: 1 artículos descartado

Lilacs: 0

Cochrane: 1 descartado

Pregunta 7- ¿Qué tratamientos farmacológicos han demostrado utilidad en los pacientes con SSp y fenómeno de Raynaud para disminuir la intensidad o la frecuencia de los episodios? Anticoagulación

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome – Raynaud – Raynaud syndrome – decrease intensity - decrease frecuency – **anticoagulation**

Pub Med: 0

Lilacs: 0

Cochrane: 0

Pregunta 8- ¿Qué tratamientos farmacológicos han demostrado utilidad en los pacientes con SSp y fenómeno de Raynaud para disminuir la intensidad o la frecuencia de los episodios? Corticoides

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome – Raynaud – Raynaud syndrome – decrease intensity - decrease frecuency – **corticosteroids**

Pub Med: 9 descartados

Lilacs: 0

Cochrane: 0

Pregunta 9- ¿Qué tratamientos farmacológicos han demostrado utilidad en los pacientes con SSp y fenómeno de Raynaud para disminuir la intensidad o la frecuencia de los episodios? Prostaglandinas.

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome – Raynaud – Raynaud syndrome – decrease intensity - decrease frecuency – prostaglandins

Pub Med: 0

Lilacs: 0

Cochrane: 0

Pregunta 10- ¿Qué tratamientos han demostrado disminuír la mortalidad y la morbilidad en el tratamiento de las vasculitis sistémicas graves? Corticoides, rituximab, recambio plasmático, micofenolato, azatioprina?

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome – Systemic vasculitis – treatment - decrease mortality – mycophenolic acid – mofetil mycofenolate – corticosteroids – rituximab – azathioprine – plasmapheresis exchage

Pub Med: 1 descartado (habla sobre transplante de stem cells pero no Sjögren), mico 0, corticoides 0, rituximab 24, descartados, azatioprina 6, descartados, plasmaferesis: 0

Lilacs: 0

Cochrane: 1 descartado

Pregunta 11- ¿Qué utilidad clínica tienen los nuevos métodos complementarios de diagnóstico como angio resonancia en el paciente con SSp y evidencia de cardiopatía isquémica y miocarditis? ¿Es igual que en la población general?

Límites: Publicación 01/1999-06/2015. Humanos, ambos sexos, >18 años. Core clinical journal, clinical trial, meta-analysis, practice guidelines, randomized controlled trial, review, comparative study, serie de casos.

Términos de la búsqueda (MeSH): Sjögren syndrome – Myocarditis

Pub Med: 31, todos descartados, 2 hablaban del diagnóstico pero en 1999 cuando no existían las nuevas tecnologías.

Lilacs: 10 todos descartados, mismas razones

Cochrane: 0

BIBLIOGRAFÍA:

1.Cruz W[1], Fialho S, Morato E, Castro G, Zimmermann A, Ribeiro G, Neves F, Pereira I. Is there a link between inflammation and abnormal lipoprotein profile in Sjögren's syndrome? Joint Bone Spine. 2010 May;77(3):229-31. doi: 10.1016/j.jbspin.2010.02.011. Epub 2010 Apr

2.Vassiliou VA, Moyssakis I, Boki KA, Moutsopoulos HM. Is the heart affected in primary Sjögren's syndrome? An echocardiographic study. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):109-12.

3. Ciçek OF, Bayram NA, Ayhan H, Erten S, Aslan AN, Sarı C, Ozen MB, Bİlen E, Bastuğ S, Durmaz T, Keleş T, Bozkurt E. Assessment of the relationship between aortic stiffness and left ventricular functions withechocardiography in patients with Sjögren's syndrome. Int J Rheum Dis. 2014 Jul;17(6):658-63. doi: 10.1111/1756-185X.12258. Epub 2013 Dec 14.

4. Bayram NA, Cicek OF, Erten S, Keles T, Durmaz T, Bilen E, Sarı C, Bozkurt E.Assessment of left ventricular functions in patients with Sjögren's syndrome using tissue Dopplerechocardiography. Int J Rheum Dis. 2013 Aug;16(4):425-9. doi: 10.1111/1756-185X.12049. Epub 2013 Apr 4.

5. Akyel A, Tavil Y, Tufan A, Yayla C, Kaya A, Tezcan ME, Ozturk MA, Boyaci B.Atrial electromechanical delay and diastolic dysfunction in primary Sjögren syndrome. Clin Invest Med. 2012 Oct 6;35(5):E303.

6. Kobak S1, Kalkan S2, Kirilmaz B3, Orman M4, Ercan E3. Autoimmune Dis. 2014; 2014:710401. doi: 10.1155/2014/710401. Epub 2014 Jan 9. Pulmonary Arterial Hypertension in Patients with Primary Sjögren's Syndrome.

7. Ye YC[1], Zeng Y, Zhu WL, Zhao Y, Zeng XF, Zhang SY, Fang Q, Li XM. Cardiac manifestations in Sjogren syndrome. Zhonghua Xin Xue Guan Bing Za Zhi. 2008 Apr;36(4):327-31.

MANIFESTACIONES HEMATOLÓGICAS DEL SINDROME DE SJÖGREN PRIMARIO

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Pregunta 1- En pacientes con Síndrome de Sjögren primario (SSp), ¿con qué frecuencia se diagnostica la presencia de anemia?

- **Search ((Primary Sjögren's syndrome OR Primary syndrome, Sjogrens OR Primary sicca syndrome) AND (Anemia) AND (diagnosis OR assessment))**
- **29 RESULTADOS; SELECCIONADOS POR TÍTULO Y ABSTRACT**

Zhou y colaboradores publicaron en 2010 un estudio de corte transversal que tuvo como objetivo evaluar la prevalencia y causas de anemia en pacientes con SSp. Se incluyeron 132 pacientes consecutivos. Se realizaron determinaciones habituales de índices hematológicos, inmunológicos y examen de médula ósea. Se observó una frecuencia de 34% (45 pacientes). Las causas fueron anemia de trastornos crónicos (69%), anemia hemolítica autoinmune ((AHA) 18%)), anemia ferropénica (9%) y por otras causas (4%). La prevalencia de anticuerpos FAN, anti-Ro/SSA y anti-La/SSB fue mayor en el grupo de pacientes con anemia. Los pacientes con AHA presentaron una mayor frecuencia de anticardiolipinas y a su vez, la frecuencia de hipocomplementemia fue mayor en los pacientes con AHA comparado con los pacientes sin anemia. Se observaron anormalidades en la médula ósea en dos pacientes con anemia [(1)]. NE: 4

Baimpa y colaboradores en una serie de casos retrospectiva publicada en el 2009, que incluyó 536 pacientes con SSp, reportaron una frecuencia de anemia del 29% (IC 95%, 28,5%-32,6%) [(2)]. NE: 4

Ramos-Casals y colaboradores, en una serie de 1010 pacientes con SSp publicada en 2008, encontraron mayor frecuencia de anemia de trastornos crónicos en pacientes con hipocomplementemia y crioglobulinas positivas [(3)]. NE: 4

Pregunta 2- En pacientes con SSp, ¿con qué frecuencia se diagnostica leucopenia?

- **Search ((Primary Sjögren's syndrome OR Primary syndrome, Sjogrens OR Primary sicca syndrome) AND (diagnosis) OR assessment) AND (Leukopenia))**
- **35 RESULTADOS; 4 SELECCIONADOS POR TÍTULO Y ABSTRACT**

La leucopenia está descripta como la manifestación más frecuente junto con la anemia y su prevalencia varía del 14% al 33% dependiendo las series [2,3,5].

Baimpa y colaboradores en su trabajo de 536 pacientes, reportan una frecuencia de leucopenia del 14% (IC 95%, 4,2%-17,2%) [2]; mientras que Ramos-Casals y colaboradores, en la publicación de la serie de 1010 pacientes, encontraron que la presencia de leucopenia es más frecuente en pacientes seropositivos para FAN/Ro/La y en aquellos que presentan hipocomplementemia y positividad para crioglobulinas [3]. NE: 4

Con respecto a la linfopenia, Baimpa y colaboradores describieron una frecuencia del 6,5% y asociación con parótidomegalia [2]. NE: 4

Mandl y colaboraodres publicaron en 2004, un estudio de corte transversal en el que incluyeron 80 pacientes con SSp según criterios clasificatorios americano-europeos 2002 y 37 pacientes con síntomas sicca que no cumplían dichos criterios. Informan una frecuencia del 16% en pacientes Ro+, encontrando diferencia significativa frente a los Ro negativos y frente a los pacientes que no cumplían criterios de SSp [5]. NE: 4

La agranulocitosis es una manifestación infrecuente. Friedman colaboradores publicaron una serie de 13 pacientes con agranulocitosis y SSp y observaron que en 11 de estos pacientes la misma había sido la primera manifestación de la enfermedad [7]. NE: 4

Pregunta 3- En pacientes con SSp, ¿con qué frecuencia se diagnostica hipergammaglobulinemia?

- **Search ((Primary Sjögren's syndrome) OR Primary syndrome, Sjogrens OR Primary sicca syndrome) AND (diagnosis OR assessment) AND (Hypergammaglobulinemia))**

- **87 RESULTADOS; 2 SELECCIONADOS POR TÍTULO Y ABSTRACT**

La Hipergamaglobulinemia es una manifestación frecuente en estos pacientes y se la asocia a mayor incidencia de manifestaciones extraglandulares. Baimpa colaboradores observaron una frecuencia de 26,3% (IC 95%, 22,6%-30,3%) y asociación estadísticamente significativa con manifestaciones del sistema nervioso periférico, (p=0,0045), púrpura palpable (p<0.001) y linfadenopatía (p=0,003). En su serie de casos también se describe una frecuencia de gammapatía monoclonal de 3,9% (IC 95%, 2,4%-5,9%) y asociación estadísticamente significativa con compromiso pulmonar (p=0,0035), púrpura palpable (p<0,001), linfadenopatía (p=0,004), esplenomegalia (p=0,001) y vasculitis confirmada por biopsia (p<0,001) [2]. NE: 4

Pregunta 4- En pacientes con Síndrome de Sjögren primario, ¿con qué frecuencia se diagnostica trombocitopenia?

Search ((Primary Sjögren's syndrome) OR Primary syndrome, Sjogrens) OR Primary sicca syndrome)) AND ((diagnosis) OR assessment)) AND Thrombotic thrombocytopenic purpura

- **4 RESULTADOS, 2 SELECCIONADOS POR TÍTULO Y ABSTRACT.**

La trombocitopenia autoinmune es una manifestación infrecuente. Baimpa y colaboradores reportaron una frecuencia de 3,7% (IC 95%, 2,3%-5,7%) [(2)]; mientras que Ramos-Casals y colaboradores observaron una frecuencia de 16% en pacientes Ro/La +, 20% en pacientes con hipocomplementemia y un 30% en pacientes con crioglobulinas positivas [(3)]. NE: 4

Pregunta 5- En pacientes con SSp y anemia hemolítica asociada, ¿el tratamiento con inmunosupresores revierte la hemólisis?

ANEMIA HEMOLÍTICA: Search ((Primary Sjögren's syndrome OR Primary syndrome, Sjogrens OR Primary sicca syndrome) AND (treatment OR management) AND (hemolytic anemia) AND (immunosuppressive))

- **15 RESULTADOS, 3 SELECCIONADOS POR TÍTULO Y ABSTRACT**

Pregunta 6- En pacientes con SSP y Neutropenia asociada, ¿el tratamiento con inmunosupresores revierte la misma?

NEUTROPENIA: Search ((Primary Sjögren's syndrome OR Primary syndrome, Sjogrens OR Primary sicca syndrome) AND (treatment OR management) AND (neutropenia OR leukopenia OR lymphopenia) AND (immunosuppressive))

- **10 RESULTADOS; 1 SELECCIONADO POR TÍTULO Y ABSTRACT**

Pregunta 7- En pacientes con SSp y Trombocitopenia autoinmune asociada, ¿el tratamiento con inmunosupresores revierte la lisis plaquetaria?

TROMBOCITOPENIA AUTOINMUNE: Search (((((((Primary Sjögren's syndrome) OR Primary syndrome, Sjogrens) OR Primary sicca syndrome))) AND ((treatment) OR management)) AND ((thrombotic thrombocytopenic purpura) OR autoimmune thrombocytopenia) AND immunosuppressive.

- **11 RESULTADOS, 1 SELECCIONADO POR TÍTULO Y ABSTRACT**

Pregunta 8- En pacientes con SSp e hipergammaglobulinemia asociada, ¿el tratamiento con inmunosupresores la disminuye?

HIPERGAMMAGLOBULINEMIA: ((Primary Sjögren's syndrome OR Primary syndrome, Sjogrens) OR Primary sicca syndrome) AND (treatment OR management) AND (hypergammaglobulinemia))

- **13 RESULTADOS, 0 SELECCIONADOS**

((Sjogren's syndrome) AND (treatment OR management) AND (immunosuppressive) AND ("last 10 years"[PDat]))

328 RESULTADOS, 6 SELECCIONADOS

Resultados:

Se analizarán las preguntas 5, 6, 7 y 8 en conjunto debido a la superposición de artículos hallados en las búsquedas respectivas.

La evidencia del rol de los inmunosupresores para el tratamiento del SSp que podemos encontrar en la literatura es muy limitada. Los principales datos provienen de reportes o de series de casos de pacientes con manifestaciones hematológicas severas. Los pocos estudios clínicos que se encuentran no tienen por objetivo evaluar dichos tratamientos para las manifestaciones hematológicas secundarias a la enfermedad.Fialho y colaboradores reportaron en 2012 un paciente con posterior diagnóstico de SSp, que debutó con pancitopenia a predominio de leucopenia, asociado a hipergammaglobulinemia, con punción de médula ósea normal. Fue tratado con prednisona 1mg/kg/día asociado a factor estimulante de colonias de granulocitos y posteriormente con ciclosporina, con pobre respuesta. Se indicó tratamiento con con Mofetil Micofenolato 2 gr/día con mejoría de las tres series y seguimiento al año sin recaídas [8]. NE: 4

De la misma manera, Willeke y coloboradores publicaron en 2007 una serie de casos prospectiva, en la que se incluyeron 11 pacientes con SSp y manifestaciones sistémicas refractarias a terapias convencionales. Los pacientes recibieron tratamiento con micofenolato sódico 1,440 mg/día durante seis meses, con resultados favorables. Dentro de los criterios de inclusión se describió la presencia de hipergammaglobulinemia y reportaron que siete de los 11 pacientes presentaban leucopenia. Luego de 12 semanas de tratamiento se observó una disminución significativa de las gammaglobulinas (únicamente Ig M) ($p<0,05$) y un aumento significativo en el recuento de la serie blanca ($p<0,05$) [9]. NE: 4

Choung colaboradores reportaron en 2012 un caso de un paciente con posterior diagnóstico de SSp que debutó con pancitopenia a predominio de trombocitopenia severa, con biopsia de médula ósea normal, que inicialmente fue tratado con prednisona 1 mg/kg/día por dos semanas y ante la falta de respuesta se rotó el tratamiento a inmunoglobulinas endovenosas 1,200 mg/día por tres días y posterior mantenimiento con prednisona 10 mg/día asociada a ciclosporina 100 mg/día con recuperación de las tres series, y seguimiento por cinco meses sin recaídas [10]. NE: 4

Chen y colaboradores publicaron en 2013, un estudio de casos y controles en el que incluyeron 35 pacientes con SSp asociado a trombocitopenia y 15 controles sanos. En el grupo de pacientes con SSp encontraron menor porcentaje de linfocitos B de memoria (CD19+ y 27+) y a su vez, estos presentaban menor expresión del receptor FcγRIIb. Por otro lado observaron una asociación negativa con la positividad del auto-anticuerpo Ro. Luego de tres pulsos de 1 g de metilprednisolona reportaron un up-regulation de estos receptores en el subgrupo de linfocitos B CD19+ y CD27+ y aumento del recuento de plaquetas [11]. NE: 4

Respecto al rituximab, los estudios en pacientes con SSp en general tienen como objetivo evaluar su eficacia para mejorar la función lagrimal, el flujo salival, las medidas subjetivas de severidad y las manifestaciones sistémicas en forma global. Toumeh A y colaboradores, publicaron en 2014 el caso de un paciente con púrpura trombótica trombocitopénica refractaria a plasmaféresis y corticoides, el cual fue tratado con rituximab con buena respuesta [12]. NE: 4

Bibliografía:

1) Zhou JG, Qing YF, Jiang L, et al. Clinical analysis of primary Sjögren's syndrome complicating anemia. Clin Rheumatol. 2010 May;29(5):525-9.

2) Baimpa E, Dahabreh IJ, et al. Hematologic manifestations and predictors of lymphoma development in primary Sjögren syndrome: clinical and pathophysiologic aspects. Medicine (Baltimore). 2009 Sep;88(5):284-93.

3) Ramos-Casals M1, Solans R, et al. GEMESS Study Group. Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore). 2008 Jul;87(4):210-9.

4) He J, Ding Y, et all. Analysis of the clinical features at onset of primary Sjögren's syndrome. Beijing Da Xue Xue Bao. 2012 Apr 18;44(2):225-8

5) Mandl T, Bredberg, et all. CD4+ T-lymphocytopenia a frequent finding in anti-SSA antibody seropositive patients with primary Sjögren's syndrome. J Rheumatol. 2004 Apr;31(4):726-8.

6) Okada J. Autoimmune hemolytic anemia in primary Sjögrens syndrome. Intern Med. 2006;45(10):669-70.

7) Friedman J, Klepfish A, Miller EB, Ognenovski V, Ike RW, Schattner A. Agranulocytosis in Sjögren's syndrome: two case reports and analysis of 11 additional reported cases. Semin Arthritis Rheum. 2002 Apr;31(5):338-45. Review.

8) Fialho SC, Bergamaschi S, et al. Mycophenolate mofetil in primary Sjögren's syndrome: a treatment option for agranulocytosis. Rev Bras Reumatol. 2012 Mar-Apr;52(2):297-9.

9) Willeke P, Schlüter B, et al. Mycophenolate sodium treatment in patients with primary Sjögren syndrome: a pilot trial. Arthritis Res Ther. 2007;9(6):R115

10) Choung BS, Yoo WH. Successful treatment with intravenous immunoglobulin of severe thrombocytopenia complicated in primary Sjögren's syndrome. Rheumatol Int. 2012 May;32(5):1353-5. doi: 10.1007/s00296-010-1395-4.

11) Chen H, Zhou S, et al. High-dose methylprednisolone pulse therapy upregulated FcγRIIb expression on B cells in primary Sjögren's syndrome patients with thrombocytopenia. Clin Rheumatol. 2013 Dec; 32(12):1783-90.

12) Toumeh A[1], Josh N. Refractory thrombotic thrombocytopenic purpura associated with primary Sjogren syndrome treated with rituximab: a case report. Am J Ther. 2014 Mar-Apr;21(2): e56-60.

SÍNDROME DE SJÖGREN PRIMARIO: COMPROMISO EXTRAGLANDULAR

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Se realizó una extensa búsqueda bibliográfica en Pubmed, Cochrane y Lilacs. Se resume la búsqueda de Pubmed. Las otras búsquedas no aportaron información adicional.

Pregunta 1- ¿Es eficaz / seguro el uso de **corticoides** en el tratamiento del Síndrome de Sjögren primario (SSp) extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatmen)) AND (corticosteroids))

Se encontraron 13 referencias en pubmed, que se descartaron por título y resumen, no se seleccionó ninguno por lectura crítica

Pregunta 2- ¿Es eficaz / seguro el uso de **antipalúdicos** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (hydroxychloroquine OR chloroquine OR antimalarial))

Se encontraron 129 referencias, se descartaron por título y resumen 126, se seleccionaron por lectura crítica 3

Gottenberg y colaboradores publicaron en 2014 un ensayo clínico aleatorizado, placebo controlado. Se evaluaron 120 pacientes aleatorizados (1:1) a recibir tratamiento con hidroxicloroquina 400mg/d vía oral versus placebo. El objetivo del estudio fue evaluar la eficacia de la hidroxicloroquina medidos en la reducción de 30% o más en dos de tres EVAs de sequedad, dolor y fatiga entre la semana 0 y 24. Todos los pacientes recibieron hidroxicloroquina en la fase abierta del estudio, que culminó en la semana 48. Se realizó un análisis post- hoc del mismo objetivo a la semana 48. No se encontraron diferencias significativas entre ambos grupos en cuanto al objetivo primario. (17.9% versus 17.2%; P = .98). . En el análisis post hoc en la semana 48, aunque hubo una diferencia numérica a favor del grupo que recibió hidroxicloroqina de inicio, tampoco las diferencias fueron estadísticamente significativas. Dentro de los objetivos secundarios se encontraban, el ESSPRI (por sus siglas en *inglés EULAR Sjogren's Syndrome Patient Reported Index*) y el ESSDAI (por sus siglas en inglés *EULAR Sjogren's Syndrome Disease Activity Index*), no encontrándose diferencias significativas entre ambos grupos a la semana 24 No hubo eventos adversos significativos [(1)]. NE: 2.

Fox y colaboradores publicaron en 1996 una serie de casos en la que incluyeron 50 pacientes tratados con hidroxicloroquina 400 mg/d, de los cuales 40 completaron dos años de tratamiento. Se definió mejoría con el tratamiento a una mejoría mayor o igual al 20% en el test de Schirmer o Rosa de Bengala, en el flujo saliva y, en al menos dos de las siguientes mediciones: EVA global del médico, EVA del dolor y de fatiga del paciente, y del 20% o más de la eritrosedimentación. Se encontró una mejoría significativa en los síntomas de sequedad y en el Rosa de Bengala, test de Schirmer, de la xerostomía, flujo salival y la eritrosedimentación. En aproximadamente el 60% de los pacientes se encontró mejoría en todos los parámetros evaluados por EVAs. Se evaluaron sicca, dolor, fatiga. Hubo mejoría leve, no hubo eventos adversos [(2)] .NE: 4

Kruize y colaboradores publicaron en 1993 un estudio doble ciego, controlado, que incluyó 19 pacientes que recibieron hidroxicloroquina 400 mg/día vía oral versus placebo, durante dos años. Se observó un descenso significativo de IgG e IgM en comparación con el placebo. No se observaron diferencias significativas respecto a las manifestaciones extraglandulares evaluadas (fatiga, mialgias y artralgias). Tampoco se observó mejoría en los síntomas sicca [(3)]. NE: 3

Pregunta 3- ¿Es eficaz / seguro el uso de **metotrexate** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (methotrexate))

Se encontraron 85 referencias, se descartaron por título y resumen 84, se seleccionó por lectura crítica 1 artículo

Skopouli y colaboradores publicaron en 1996 una serie de casos que incluyó 17 pacientes, que tuvo como objetivo evaluar la utilidad del metotrexate en el tratamiento del SSp. Los pacientes recibieron 0.2 mg/ kg peso por semana durante un año. Se observó mejoría en los síntomas sicca. En siete pacientes se redujo la dosis de metotrexate por elevación de transaminasas [4]. NE: 4

Pregunta 4- ¿Es eficaz / seguro el uso de **leflunomida** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (leflunomide))

Se encontraron 17 referencias, se descartaron por título y resumen todos, no se seleccionó ninguno por lectura crítica

Pregunta 5- ¿Es eficaz / seguro el uso de **azatioprina** en el tratamiento del SSp extraglandular ?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (azathioprine))

Se encontraron 20 referencias, se descartaron por título y abstract 19, se seleccionó por lectura crítica 1

Prince y colaboradores publicaron en 1998, un estudio doble ciego, controlado con placebo, que incluyo 25 pacientes y tuvo como objetivo establecer el lugar de bajas dosis de azatioprina (1 mg/kg/d) como droga modificadora de la enfermedad en

pacientes con SSp, no complicado. Seis pacientes suspendieron el tratamiento por efectos adversos. No se encontraron cambios significativos en las variables clínicas, serológicas e histológicas medidas luego de seis meses de tratamiento [5]. NE: 3

Pregunta 6- ¿Es eficaz / seguro el uso de **ciclofosfamida** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (cyclophosphamide))

Se encontraron 220 referencias, se descartaron todas por título y resumen.

Pregunta 7. ¿Es eficaz / seguro el uso de **micofenolato** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (mycophenolate))

Se encontraron 18 referencias, se descartaron por título y abstract 17 y se seleccionó 1 por lectura crítica

Willeke y colaboradores publicaron en 2007, una serie de casos (11 pacientes), que tuvo como objetivo evaluar la eficacia y seguridad de micofenolato sódico en pacientes con SSp refractarios a otros agentes inmunosupresores. Se evaluó el estado clínico, pruebas de función glandular, diferentes parámetros de laboratorio y parámetros subjetivos, a través de diferentes cuestionarios. Se observó mejoría en el EVA de sequedad ocular y disminución en los requerimientos de lágrimas artificiales. Sin embargo, no se encontró mejoría significativa en los parámetros objetivos de

xeroftalmía ni xerostomía. Se observó un descenso significativo de la hipergamaglobulinemia, el factor reumatoideo, aumento de los niveles de complemento y glóbulos blancos [6]. NE: 4

Pregunta 8- ¿Es eficaz/seguro el uso de la **sulfasalazina** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (Sulfasalazine))

Se encontraron 14 referencias, se descartaron por título y resumen todos, no se seleccionó ninguno por lectura crítica

Pregunta 9. ¿Es eficaz / seguro el uso de **rituximab** en el tratamiento del SSp extraglandular ?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (rituximab))

Se encontraron 198 referencias, se descartaron por título y resumen 193, se seleccionaron por lectura crítica 5. Un estudio se encontraba en etapa de desarrollo al momento de realizarse la búsqueda ("The TRACTISS protocol: a randomised double blind placebo controlled clinical trial of anti-B-cell therapy in patients with primary Sjögren's Syndrome", Brown S et al. BMC MusculoskeletDisord. 2014 Jan 17;15:21, 110 pacientes, ongoing).

Meijer y colaboradores publicaron en 2010 un estudio doble ciego, aleatorizado (2:1, rituximab versus placebo) que tuvo como objetivo primario evaluar la respuesta al rituximab en el flujo salival. Dentro de los objetivos secundarios se evaluaron variables

funcionales, de laboratorio y subjetivas. Se incluyeron 30 pacientes con una secreción de saliva estimulada mayor a 0,15 ml/minuto, que recibieron rituximab versus placebo en día 1 y 15. El seguimiento fue por 48 semanas. Se encontró mejoría significativa en el flujo de saliva en el grupo tratado con rituximab (el cual comenzó a decrecer en la semana 12), mientras que en el grupo que recibió placebo se observó un descenso significativo del mismo desde el momento basal, las diferencias entre ambos grupos fueron significativas en la semana 12. También se encontraron diferencias significativas en comparación con el placebo en el recuento de células B, niveles de factor reumatoideo, escala de fatiga, EVA de síntomas sicca y algunas manifestaciones extraglandulares, como vasculitis [(7)]. NE: 3

Devauchelle-Pensec y colaboradores publicaron en 2014, un estudio aleatorizado (1:1), placebo controlado, multicéntrico, paciente e investigador ciegos (farmacéutico no ciego). El objetivo fue evaluar la respuesta al tratamiento con rituximab (1 gramo semana 0 y 2), medido por la mejoría en al menos 30 mm en dos de cuatro EVAs (actividad global, dolor, fatiga y sequedad) en la semana 24. Se incluyeron 120 pacientes con al menos 50 mm en dos de los cuatro EVAs mencionados, con una enfermedad de menos de 10 años de evolución. El promedio de actividad basal medida por ESSDAI de los pacientes incluidos fue 10, 1 (DS 6,8). No se encontraron diferencias significativas entre los grupos en cuanto al objetivo primario (diferencia: 1.0%. IC 95%: -16.7% a 18.7%). La proporción de pacientes que alcanzó dicho objetivo fue mayor en la semana 6 en el grupo tratado con rituximab (22.4% versus 9.1%; *p*: 0.036). También se encontró una mejoría significativa de al menos 30 mm en el EVA de fatiga en las semanas seis y 16 [(8)]. NE: 2

Carubbi y colaboradores publicaron en 2013 un estudio de cohorte que tuvo como objetivo evaluar los beneficios del rituximab en comparación con drogas convencionales, medidos por ESSDAI cada 12 semanas, hasta la semana 120. El rituximab se administró en semana cero y dos; este esquema se repitió cada 24 semanas. Se incluyeron 41 pacientes de dos centros con una enfermedad de menos de dos años de evolución desde el inicio de los síntomas, con ESSDAI igual o mayor a seis y dos de cuatro EVAs mayor a 50 mm (actividad global, sequedad, fatiga, dolor). Los pacientes de un centro recibieron tratamiento con rituximab y los del otro centro drogas convencionales. El ESSDAI basal en cada grupo fue 19.8 (6 a 41) en grupo de tratamiento convencional y 20.3 (6 a 41) en el grupo de rituximab. A partir del segundo curso de tratamiento, se observaron diferencias significativas a favor de rituximab, la cual se mantuvo a lo largo de todo el período de seguimiento [(9)] .NE: 3

Clair y colaboradores publicaron en 2013 una serie de casos que incluyó 12 pacientes y tuvo como objetivo evaluar la seguridad y respuesta al tratamiento con rituximab, administrado en dosis de 1 gramo en el día 1 y 15, con un seguimiento de 52 semanas. No se observó toxicidad, observándose una mejoría significativa entre la semana 0 y 26 en la actividad global de la enfermedad, medida por EVA del médico (mediana de disminución 26 mm; P: 0.012) y del paciente (mediana de disminución: 8.5 mm; P: 0.009). también se observó una mejoría significativa en la xerotráquea, sed, discomfort oral y en la fatiga. No se observaron mejorías significativas en los test objetivos de función glandular [(10)]. NE: 4

Gottenberg y colaboradores publicaron en 2013, una serie de casos, que evaluó la utilidad del rituximab en 78 pacientes. La indicación del tratamiento fue el compromiso sistémico en 74 casos y el compromiso glandular severo en los cuatro restantes. 17 pacientes recibían concomitantemente otro agente inmunosupresor. La mediana de

seguimiento fue de 34.9 meses (6–81.4) (226 pacientes/año). La mediana de ESSDAI disminuyó significativamente desde el basal ((11 (2–31) a 7.5 (0–26)). La mediana de dosis de corticosteroides se disminuyó de 17.6 mg/d (3–60) a 10.8 mg/d (p: 0.1). 41 pacientes recibieron re tratamiento con rituximab [11]. NE: 4

Pregunta 10- ¿Es eficaz / seguro el uso de **infliximab** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (infliximab))

Se encontraron 9 referencias, se descartaron por título y resumen 8. Se seleccionó para lectura crítica 1 artículo

Mariette y colaboradores publicaron en 2004 un ensayo clínico aleatorizado, doble ciego, placebo controlado, que incluyó 103 pacientes aleatorizados a recibir infusiones de infliximab (5 mg/kg) o placebo en las semanas cero, dos y seis, y fueron seguidos por 22 semanas. Los pacientes tenían una enfermedad activa definida por EVA mayor a 50 mm en dos de tres EVAs que evaluaban dolor articular, fatiga y sequedad. Se definió respuesta favorable a una mejoría mayor o igual al 30% en dos de tres EVAs, entre las semanas cero y diez. En la semana 10, 26.5% del grupo placebo y 27.8% del grupo tratado con infliximab, tuvo una respuesta favorable (P: 0.89). En la semana 22, tampoco se encontraron diferencias significativas entre los grupos (20.4% versus 16.7%, respectivamente; P: 0.62) [12]. NE: 3

Pregunta 11. ¿Es eficaz / seguro el uso de etanercept en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (etanercept))

Se encontraron 7 referencias, se descartaron por título y resumen 6 artículos. Se seleccionó para lectura crítica 1.

Sankar y colaboradores publicaron en 2004, un estudio aleatorizado, doble ciego, placebo controlado de 12 semanas de duración para evaluar la utilidad del etanercept. Se incluyeron 14 pacientes en cada grupo. El objetivo primario fue evaluado mediante al menos 20% de mejoría desde el basal de dos de tres variables: medición subjetiva u objetiva de sequedad oral, medición subjetiva u objetiva de sequedad ocular, y niveles de IgG o eritrosedimentación (ESR). De los 14 pacientes que recibieron etanercept, tres tenían SS secundario. Tres pacientes en el grupo de etanercept y uno en el grupo placebo, no completaron el estudio. Cinco pacientes en el grupo tratado y tres en el no tratado mostraron mejoría en la semana 12, sin diferencias significativas entre ambas ramas [13]. NE: 3

Pregunta 12. ¿Es eficaz / seguro el uso de **adalimumab** en el tratamiento del SS extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (adalimumab))

Se encontraron 3 referencias, se descartaron las 3, por lo tanto no se seleccionó ningún artículo para lectura.

Pregunta 13. ¿Es eficaz / seguro el uso de **abatacept** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (abatacept))

Se seleccionaron 9 artículos, se descartaron por título y resumen 8. Se seleccionó 1 artículo para lectura crítica.

Meiners y colaboradores publicaron en 2014 una serie de casos que evaluó la respuesta al tratamiento con abatacept, medidos por ESSDAI y ESSPRI. Se incluyeron 15 pacientes vírgenes de tratamiento biológico. Los pacientes recibieron tratamiento hasta la semana 24 y fueron controlados hasta la semana 48. Los pacientes mostraron una mejoría significativa del ESSDAI desde el basal, tanto en la semana cuatro, como en la 12 y en la 24 ((media (DS): 11±5 (11), 6±4 (6), 6±8 (3) y 3±3 (2), respectivamente)). Lo mismo sucedió con el ESSPRI ((7.0±1.5 (7.5), 6.0±1.7 (6.0), 5.6±1.6 (6.0), 5.8±2.3 (5.8), respectivamente [14]. NE: 4

Pregunta 14. ¿Es eficaz / seguro el uso de **belimumab** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome)

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (belimumab))

Se seleccionaron 14 artículos, se descartaron por título y resumen 13. Se seleccionó 1

artículo para lectura crítica

Mariette y colaboradores publicaron en 2015 una serie de casos para evaluar la respuesta al tratamiento con belimumab. Se incluyeron 30 pacientes, con manifestaciones sistémicas, o enfermedad menor a cinco años de evolución o marcadores de activación de células B. Recibieron tratamiento durante 24 semanas y el objetivo primario fue la mejoría en dos de cinco ítems, medidos en la semana 28: reducción de al menos 30% en el EVA de sequedad, en el de fatiga, en el de dolor, actividad global por el médico y mayor a 25% de mejoría en los marcadores de activación de células B. El objetivo primario fue alcanzado en 18 (60%) del total de pacientes. El promedio de ESSDAI disminuyó de 8.8 (7.4) a 6.3 (6.6), (p=0.0015) y; el ESSPRI disminuyó de 6.4 (1.1) a 5.6 (2.0), (p=0.0174)[15]. NE: 4

Pregunta 15. ¿Es eficaz / seguro el uso de **plasmaféresis** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (plasmapheresis))

Se encontraron 16 referencias, se descartaron por título y resumen todas. Sin embargo existen muchos reportes de casos en los que se utilizó plasmaféresis con otros inmunosupresores a criterio del médico tratante en cada caso con resultados variables.

Pregunta 16. ¿Es eficaz / seguro el uso de **gammaglobulinas** en el tratamiento del SSp extraglandular?

Estrategias/combinación de términos para la búsqueda

((multiorganic OR non-sicca OR non sicca OR nonsicca features

OR nonsicca OR systemic OR multiorgan

OR multiple organ OR extra-glandular OR extraglandular OR primary Sjögren syndrome

OR Sjögren syndrome OR Sjögren) AND (Sjögren OR Sjögren syndrome

OR primary Sjögren syndrome) AND (therapy OR treatment) AND (gammaglobulinas))

Se encontraron 15 referencias, se descartaron por título y resumen14. Se seleccionó para lectura crítica 1 artículo.

En el artículo de Gheitasi y colaboradores, del total de 1120 pacientes con SSp, recibieron IVIG 25 pacientes, todos con diferentes combinaciones de drogas inmunosupresoras por lo que no se pueden obtener conclusiones [16]. NE: 4

Bibliografía

1. Gottenberg et al. “Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial”. JAMA 2014 Jul 16;312(3):249-58
2. Fox et al. “Treatment of primary Sjögren's syndrome with hydroxychloroquine: a retrospective, open-label study” Lupus. 1996 Jun; 5 Suppl 1:S31-6.
3. Kruize et al. “Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial” Ann Rheum Dis. 1993 May;52(5):360-4.
4. Skopouli FN et al. “Methotrexate in primary Sjögren's syndrome”, Clin Exp Rheumatol. 1996 Sep-Oct;14(5):555-8.
5. Prince EJ, Rigby SP, Clancy U, Venables PJ. A doble blind placebo controlled trial of azathioprine in the treatment of primary Sjogrens syndrome. J Rheumatol. 1998; 25(5): 896-899.
6. Willeke P et al. “Mycophenolate sodium treatment in patients with primary Sjögren syndrome: a pilot trial”, Arthritis Res Ther. 2007;9(6):R115
7. Meijer JM et al. “Effectiveness of Rituximab treatment in primary Sjögren’s syndrome: a randomised, double-blind, placebo-controlled trial” Arthritis Rheum 2010; 62:960-8, 30
8. Devauchelle-Pensec V et al “Treatment of primary Sjögren syndrome with rituximab: a randomized trial”. Ann Intern Med. 2014 Feb 18; 160(4): 233-42
9. Carubbi et al. “Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study” Arthritis Res Ther. 2013 Oct 30;15(5):R172.
10. St Clair et al. “Rituximab therapy for primary Sjögren's syndrome: an open-label clinical trial and mechanistic analysis” Arthritis Rheum. 2013 Apr;65(4): 1097-106; 12
11. Gottenberg et al. “Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry” Ann Rheum Dis. 2013 Jun;72(6):1026-31.
12. Mariette X.et al. “Inefficacy of infliximab in primary Sjögren Syndrome: TRIPSS”. Arthritis Rheum 2004; 50(4): 1270-1276.
13. Sankar V et al. “Etanercept in Sjögren Syndrome: a twelve week random doble blind placebo controlled pilot clinical trial.” Arthritis and Rheum 2004; 50(7): 2240-2245.
14. Meiners PM et al. “Abatacept treatment reduces disease activity in early Sjögren Syndrome. Open label proof of concept ASAP Study”. Annals Rheum dis 2014. 73: 1393-1396. Meiners PM et al. “Abatacept treatment reduces disease activity in early Sjögren Syndrome. Open label proof of concept ASAP Study”. Annals Rheum dis 2014. 73: 1393-1396.
15. Mariette X et al. “Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study”. Annals Rheum Dis 2015 (3) 526-31. N: 30 pacientes. Estudio prospectivo en fase II, open label.
16. Gheitasi H et al. “How are we treating our Systemic patients with Primary SS? Analysis of 1120 patients.” Int inmmunopharmacology 2015. 27(2) 194-9.

CLINIMETRÍA EN SÍNDROME DE SJÖGREN

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Pregunta 1- ¿Existe algún instrumento que permita evaluar respuesta a tratamiento en SINTOMAS SICCA en pacientes con Síndrome de Sjögren primario (SSp)?

Términos utilizados: ((Sjögren syndrome) AND (dry mouth) AND (treatment response, Sjögren syndrome) AND (dry mouth) AND (measure Sjögren syndrome) AND (xerostomia) AND (treatment response Sjögren syndrome) AND (xerostomia) AND (measure sicca symptoms) AND (Sjögren syndrome) AND (treatment response sicca symptoms) AND (Sjögren syndrome) AND (measure response laboratory parameters) AND (correlation) AND (xerostomia) AND (Sjögren syndrome laboratory parameters) AND (correlation) AND (dry mouth) AND (Sjögren syndrome) AND (dry eye) AND (measure, Sjögren syndrome) AND (xerophthalmia) AND (measure, Sjögren syndrome) AND (xerophthalmia) AND (treatment response, Sjögren syndrome) AND (dry eye) AND (treatment response, laboratory parameters) AND (correlation) AND (sicca symptoms, laboratory parameters) AND (correlation) AND (sicca symptoms) AND (Sjögren syndrome, laboratory parameters) AND (correlation) AND (dry eye) AND (Sjögren syndrome, laboratory parameters) AND (correlation) AND (xerophthalmia) AND (Sjögren syndrome))

Artículos encontrados: Pubmed: 1255; Cochrane: 0; Lilacs: 5
Artículos seleccionados por título: Pubmed: 52; Cochrane: 0; Lilacs: 0
Artículos seleccionados por abstract y texto completo: Pubmed: 6; Cochrane: 0; Lilacs: 0
Artículos seleccionados por referencia: 2

Bowman colaboradores publicaron en 2003 un estudio de corte transversal que tuvo como objetivo evaluar la utilidad de un cuestionario construído para evaluar los síntomas SICCA en pacientes con SSp: el SICCA Symptom Inventory (SSI). Se incluyeron 130 pacientes con SSp, 93 con Artritis Rematoidea (AR), 83 con Lupus Eritematoso Sistémico (LES), y 103 controles sanos, de diferentes centros en Inglaterra. Como grupo control alternativo se incluyeron 26 pacientes con síntomas orales u oculares sin enfermedad autoinmune de base. Los resultados arrojaron que los cuatro grupos (SSp, AR, LES y SICCA sin enfermedad autoinmune) coincidían en siete componentes de sequedad y discomfort: sequedad ocular, oral, vaginal, cutánea, manos frías, fatiga y artralgias. Sobre esta base se construyó el SSI que incluía cuatro de estos dominios SICCA: oral, ocular, vaginal y cutáneo; la primera versión incluía 42 síntomas, mientras que la versión corta incluyó diez síntomas con la misma cantidad de dominios [(1)].
NE: 2

Seror y colaboradores publicaron en 2011 un estudio de corte transversal que tuvo como objetivo evaluar el desempeño del ESSPRI (por su sigla en inglés *European League Against Rheumatism Sjogren's Syndrome Patient Reported Index*). El mismo consiste en tres escalas análogo visuales (EVAs) de sequedad, fatiga y dolor músculo esquelético. Se incluyeron 230 pacientes, de 12 países, los cuales completaron el ESSPRI, el SSI, el PROFAD (por sus siglas en inglés *Profile of Fatigue and Discomfort*) y un EVA global por el paciente. El ESSPRI mostró una muy buena

correlación con el EVA global por el paciente (r=0.70), el PROFAD (r=0.73) y el SSI (r=0.66) [2]. NE: 2

Seror y colaboradores publicaron en 2015 un estudio multicéntrico, que tuvo por objetivo validar el ESSDAI (por sus siglas en inglés *European League Against Rheumatism Sjögren's Syndrome Disease Activity Index*) y el ESSPRI en diferentes países. Se incluyeron 395 pacientes y en cada visita el médico completó el ESSDAI, el Índice de Actividad de la Enfermedad (SSDAI), el Índice de Actividad Sistémica en Sjögren (SCAI) y el EVA global del médico; los pacientes completaron el ESSPRI, el SSI, el PROFAD y el EVA global del paciente. La correlación del ESSDAI con el EVA global del médico fue de r=0.59 y la del ESSRPI con el EVA global del paciente de r=0.70. La correlación entre los índices realizados por los pacientes y los índices de actividad sistémica fueron baja o muy baja (rango: 0.07- 0.29). La confiabilidad fue muy buena en todos los casos. La sensibilidad al cambio fue muy buena en los índices de actividad sistémica y baja en los índices autoreportados siendo significativamente mejor en el caso del ESSPRI que el SSI y el PROFAD [3]. NE: 2

Pregunta 2- ¿Existe algún instrumento para evaluar FATIGA en pacientes con SSp?

Términos utilizados: ((Sjögren syndrome, mesaure fatigue, assessment fatigue, establishment fatigue, fatigue index, fatigue self report, fatigue and correlation activity, fatigue and Sjögren syndrome) AND (treatment response))

Artículos encontrados: Pubmed: 150; Cochrane: 6; Lilacs: 1
Artículos seleccionados por título: Pubmed: 22; Cochrane: 0; Lilacs: 0
Artículos seleccionados por abstract y texto completo: Pubmed: 2; Cochrane: 0; Lilacs: 0
Artículos seleccionados por referencia: 2

Bowman y colaboradores, publicaron en el 2004, un estudio de corte transversal, multicéntrico, para evaluar la validez de un cuestionario creado exclusivamente para medir fatiga en SSp, el Profile of Fatigue and Discomfort - Sicca Symptoms Inventory (ProFAD-SSI). El estudio incluyó 380 pacientes, de los cuales 137 presentaban diagnóstico de SSp, 74 de AR, 66 de LES y 103 controles sanos. Dicho cuestionario comprende 64 preguntas divididas en 8 dominios (fatiga somática, fatiga mental, artralgias, disfunción vascular, y sequedad ocular, oral, cutánea y vaginal). Cada pregunta tiene un valor de 0 a 7 en una escala de Likert. Este nuevo cuestionario se comparó con otros ya existentes no específicos para SSp como el Medical Outcome Study Short-Form 36 (SF-36), el World Health Organization's cross cultural quality of life questionnaire (WHOQOL-BREF) y el Hospital Anxiety and Depression Scale (HAD) que consta de 14 preguntas auto-reportadas para identificar depresión o ansiedad clínicamente significativas. El ProFAD-SSI demostró ser una herramienta útil y sensible para medir FATIGA en pacientes con SSp, y también en AR y LES [4]. NE: 2

Bowman y colaboradores publicaron en 2009 un estudio de corte transversal que validó la versión abreviada del primer cuestionario, el ProFAD-SSI-SF. Se incluyeron 43 pacientes con SSp (casos) y 50 controles AR. Esta última versión consta de 19 preguntas, cada una de las cuales refleja las distintas facetas de los 8 dominios de la versión extendida. Se encontró una fuerte correlación entre el ProFAD-SSI y el ProFAD-SSI-SF (r= 0,8) [5]. NE: 2

En el estudio de Seror y colaboradores publicado en 2011 y mencionado previamente, el ProFAD-SSI-SF se correlacionó con el EVA de fatiga reportado por el paciente, siendo útil para identificar fatiga somática no así para fatiga mental [(2)]. Este último dato sirvió de base para desarrollar el ESSPRI el cual incluye, como fue mencionado anteriormente, un EVA de fatiga [(3)]. NE: 2.

Pregunta 3- ¿Existe algún instrumento para evaluar el COMPROMISO ARTICULAR en pacientes con SSp?

Términos utilizados: ((("Sjögren syndrome") AND ("arthritis evaluation" OR "arthritis impact" OR "arthritis impact measure" OR "arthritis impact measurement"OR "arthritis impact measurement scale" OR "arthritis impact measurement scale 2" OR "arthritis impact measurement scale aims" OR "arthritis impact measurement scales questionnaire" OR "arthritis impact measurement scales, 2" OR "arthritis impact measurement scales 2 pain" OR "arthritis impact measurement scale score" OR "arthritis impact measurement scale short" OR "arthritis impact measurement scales aims" OR "arthritis impact measurement scales aims questionnaire" OR "arthritis impact scale" OR "arthritis implications") OR "arthritis improvement" OR "arthritis index" OR "arthritis index pain" OR "arthritis index questionnaires" OR "arthritis index score" OR "arthritis measurement" OR "arthritis pain scale" OR "arthritis pain scales" OR "arthritis questionnaire" OR "arthritis remission criteria" OR "arthritis remission criteria Sjögren syndrome and arthritis evaluation, Sjögren syndrome and arthritis index, Sjögren syndrome and arthritis impact measurement, Sjögren syndrome and arthritis impact scale))

Artículos encontrados: Pubmed: 779; Cochrane: 1; Lilacs: 9
Artículos seleccionados por título: Pubmed: 0; Cochrane: 0; Lilacs: 0

No se encontró evidencia de cómo evaluar el compromiso articular en pacientes con SSp.

Pregunta 4- ¿Existen instrumentos para medir ACTIVIDAD y DAÑO en SSp?

Términos utilizados: ((Sjögren Syndrome) AND (Disease activity) AND (Outcome measures , Sjögren syndrome) AND (instruments disease activity, Sjögren Syndrome AND damage index) AND (outcome measures, Sjögren syndrome) AND (damage index, Sjögren syndrome) AND (disease activity) AND (weights and measures, Sjögren Syndrome) AND (damage index) AND (outcome measures, Sjögren syndrome) AND (structural damage) AND (disease activity, Sjögren Syndrome) AND (Disease activity) AND (outcome measure ,Sjögren Syndrome) AND (damage index) AND (outcome measures, Sjögren syndrome) AND (damage index, Sjögren syndrome) AND (instruments disease activity, Sjögren syndrome) AND (damage index , Sjögren Syndrome) AND (Disease activity) AND (Outcome measures)).

Artículos encontrados: Pubmed: 150; Cochrane: 139; Lilacs: 59
Artículos seleccionados por título: Pubmed: 40; Cochrane: 0; Lilacs: 0
Artículos seleccionados por abstract y texto completo: Pubmed: 6; Cochrane: 0; Lilacs: 0
Artículos seleccionados por referencia: 4

El ESSPRI es un cuestionario auto-reportado, comentado previamente, diseñado para medir actividad en los tres principales síntomas referidos por los pacientes con SSp (sequedad, dolor y fatiga). El ESSPRI, ha demostrado ser un índice simple, con buena sensibilidad al cambio, siendo útil también para valorar la actividad de la enfermedad, tanto en los ensayos clínicos como en la práctica diaria [3]. NE: 2

Vitali y colaboradores publicaron en 2007 un estudio multicéntrico, de corte transversal, en el que se incluyeron 206 pacientes con SSp. Un modelo con 11 variables (SSDAI) fue el mejor en predecir la actividad sistémica de los pacientes. El mismo mostró una alta correlación con el EVA global del médico en la evaluación basal y a los tres meses (r: 0.87 y 0.82, respectivamente). El análisis de las curvas ROC mostró que los pacientes con una alta actividad de la enfermedad podían identificarse con un score mayor o igual a cinco [6]. NE: 2

Bowman y colaboradores publicaron en 2007 un estudio de corte transversal que incluyó 104 pacientes con SSp, 65 de los cuales fueron controlados cada tres meses, durante 12 meses. Un grupo de expertos propuso los dominios a considerar en el índice de actividad sistémica en SS (SCAI) el cual fue testeado por análisis de factores. Se encontró una alta correlación entre los dominios de fatiga, músculo esquelético y Raynaud del SCAI, con los dominios de fatiga, artralgias y vascular del PROFAD. Se encontró una asociación significativa entre las modificaciones de tratamiento y la aparición de brotes, definida por SCAI. La correlación entre el SCAI y la escala de evaluación por el médico para evaluar brotes fue alta (r: 0.71), mostrando ser un índice reproducible y sensible al cambio [7]. NE: 2

Seror y colaboradores publicaron en 2010 un estudio multicéntrico, de corte transversal, que tuvo como objetivo desarrollar un nuevo índice de actividad sistémica de la enfermedad: el ESSDAI. 39 expertos identificaron 12 dominios órgano específicos, cada uno de los cuales estaba conformado por tres o cuatro ítems. Se tomaron los datos de 96 pacientes con complicaciones sistémicas y se generaron 702 viñetas. A su vez, los expertos evaluaron la actividad de la enfermedad de cinco pacientes con un EVA global. Utilizando el EVA como variable dependiente, se estimó el peso de cada dominio en un modelo de regresión logística múltiple. Los 12 dominios se encontraron significativamente asociados con el EVA global del médico, con un peso de cada uno de ellos entre 1 y 6. El ESSDAI mostró una buena correlación con el EVA global del médico tanto de los pacientes reales como con las 702 viñetas (r=0.61 y r=0.58, respectivamente). En la actualidad, este es el índice con más repercusión [8]. NE: 2

En el estudio publicado por Seror y colaboradores en el 2015, se compararon todos los índices específicos para evaluar a los pacientes con SSp y se encontró una baja correlación entre los índices de actividad sistémica y los índices auto-reportados, implicando que estos dos componentes evalúan diferentes facetas de la enfermedad. Debido a la baja correlación entre ambos, se recomienda utilizar ambos índices para evaluar la actividad de la enfermedad en los pacientes con SSp [3]. NE: 2

Dentro de los índices de daño se encuentran: el Sjögren's Syndrome Disease Damage Index (SSDDI) que es un Índice desarrollado en el mismo estudio y con la misma metodología que el SSDAI [6], y el Sjögren's Syndrome Damage Index (SSDI) que correspondería a una versión modificada del SLICC [9].

En el primer caso se observó que un modelo compuesto por nueve variables, era el mejor predictor de daño. El puntaje obtenido con el SSDDI mostró una alta correlación con el EVA global de daño por el médico (r= 0.760) [6]. NE: 2

Barry y colaboradores publicaron en 2008 un estudio de corte transversal que incluyó 114 pacientes con SSp que fueron evaluados en visita basal y a los 12 meses. Basados en la validación por expertos (reumatólogos, oftalmólogos y odontólogos) se generó un índice de daño formado por 29 items incorporados en los dominios ocular, oral y de compromiso sistémico (SSDI). El SSDI mostró una baja correlación con la duración de la enfermedad (r = 0.436), la función física medida por SF-36 (r = 0.250, T = 0; r = 0.261 T = 12 meses) y la actividad de la enfermedad (r = 0.213, T = 0; r = 0.215, T =12 meses). El índice de daño ocular mostró una baja correlación con el dominio de sequedad ocular del PROFAD-SSI (r = 0.228, T = 0; r = 0.365, T = 12 meses). El índice fue sensible al cambio a los 12 meses (z = -3.262; P < 0.01). El SSDI posee como ventaja por sobre el SSDDI en que reconoce daño en los aparatos cardiovascular, gastrointestinal y osteomuscular [9]. NE: 2

Pregunta 5- ¿Existe algún instrumento para evaluar CALIDAD de vida en SSp?

Términos utilizados: ((quality of life) AND (measure) AND (Sjögren syndrome, quality of life) AND (assessment) AND (Sjögren syndrome, quality of life) AND (Sjögren syndrome)).

Artículos encontrados: Pubmed: 252; Cochrane: 1; Lilacs: 2
Artículos seleccionados por título: Pubmed: 34; Cochrane: 0; Lilacs: 0
Artículos seleccionados por abstract y texto completo: Pubmed: 13; Cochrane: 0; Lilacs: 0
Artículos seleccionados por referencia: 3
Artículos seleccionados: 0

Varios trabajos han demostrado una disminución de la calidad de vida en los pacientes con SSp, y esto se ve asociado en su mayoría a la intensidad de los síntomas SICCA y mioarticulares. La mayoría de estos trabajos han elegido para medir calidad de vida el cuestionario Short Form-36, pero no existe en la actualidad instrumento específico de SSp para medir calidad de vida [10-12].

Pregunta 6- ¿Existe algún instrumento para evaluar CAPACIDAD FUNCIONAL en SSp?

Términos utilizados: ((Sjögren syndrome) AND ("physical function" OR "physical function/disability" OR "physical function assessment" OR "physical function assessments" OR "physical function capacity" OR "physical function categories" OR "physical function category" OR "physical function component" OR "physical function components" OR "physical function data" OR "physical function domain scale" OR "physical function domain scores" OR "physical function domains" OR "physical function evaluation" OR "physical function exams" OR "physical function impairment" OR "physical function impairments" OR "physical function improvement" OR "physical function improvements" OR "physical function index" OR "physical function indicators" OR "physical function instrument" OR "physical function item" OR "physical function level" OR "physical function levels" OR "physical function limitation" OR "physical

function limitations" OR "physical function loss" OR "physical function measure" OR "physical function measurements" OR "physical function measures" OR "physical function outcome" OR "physical function outcomes" OR "physical function parameters" OR "physical function questionnaire" OR "physical function questionnaires" OR "physical function questions" OR "physical function scale" OR "physical function scales" OR "physical function score" OR "physical function scores" OR "physical function sf 36" OR "physical function short" OR "physical function short form" OR "physical function status" OR "physical function sub scale" OR "physical function subscale" OR "physical function subscale s ability" OR "physical function subscale score" OR "physical function subscale scores" OR "physical function subscale's ability" OR "physical function subscales" OR "physical function variables" OR "physical function, disability" OR "physical function, loss" OR "physical functional" OR "physical functional abilities" OR "physical functional ability" OR "physical functional activities" OR "physical functional aspects" OR "physical functional outcome" OR "physical functional outcomes" OR "physical functional performance" OR "physical functional performance test" Sjögren syndrome) AND (HAQ Sjögren syndrome and physical function capacity Sjögren syndrome and physical function, Sjögren syndrome and functional impairment, Sjögren syndrome and functional assessment, Sjögren syndrome and HAQ, Sjögren syndrome and physical function involvement, Sjögren syndrome and physical function capacity))

Artículos encontrados: Pubmed: 1446; Cochrane: 5; Lilacs: 12
Artículos seleccionados por título: Pubmed: 2; Cochrane: 0; Lilacs: 0
Artículos seleccionados por abstract y texto completo: Pubmed: 2; Cochrane: 0; Lilacs: 0
Artículos seleccionados por referencia: 0
Artículos seleccionados: 2

No hay un instrumento validado para evaluar la capacidad funcional en pacientes con SSp. El más empleado es el HAQ.

Hackett y colaboradores publicaron en 2012 un estudio de corte transversal en la que se incluyeron 69 pacientes con SSp y 69 voluntarios sanos. El deterioro funcional evaluado por una versión de dicho cuestionario, denominada “HAQ improved”, se asoció con reducción en la calidad de vida, dolor, fatiga, depresión y actividad de la enfermedad [13]. NE: 4

George y colaboradores publicaron en 2011 una serie de 40 pacientes en la que determinaron que la diferencia mínimamente importante para el HAQ fue, en promedio, -0.18 (±0.23) para mejoría y 0.14 (±0.30) para deterioro, comparado con un reporte del estado general por el paciente [14]. NE: 4

BIBLIOGRAFÍA

1- Bowman SJ, et al. Validation of the Sicca Symptoms Inventory for clinical studies of Sjögren's syndrome.
J. Rheumatol 2003 Jun;30(6):1259-66
Seror R, et al. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome.Ann Rheum dis 2011;70(6):968-72

2- Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T, Bootsma H, Tzioufas A, Solans-Laqué R, Mandl T, Gottenberg JE, Hachulla E, Sivils KL, Ng WF, Fauchais AL, Bombardieri S, Valesini G, Bartoloni E, Saraux A, Tomsic M, Sumida T, Nishiyama S, Caporali R, Kruize AA, Vollenweider C, Ravaud P, Vitali C, Mariette X, Bowman SJ; EULAR Sjögren's Task Force. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis. 2015 May;74(5):859-66

3- Bowman SJ, et al. Measurement of fatigue and discomfort in primary Sjogren's syndrome using a new questionnaire tool. Rheumatology (Oxford) 2004 Jun; 43(6):758-64.

4- Bowman SJ, et al. Patient-reported outcomes in primary Sjogren's syndrome: comparison of the long and short versions of the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory. Rheumatology (Oxford) 2009 Feb; 48(2):140-3.

5- Vitali C, et al. Sjögren's syndrome disease damage index and disease activity index: Scoring systems for the assessment of disease damage and disease activity in Sjögren's syndrome, derived from an analysis of a cohort of Italian patients. Arthritis Rheum 2007; 56: 2223-31.

6- Bowman SJ, et al. Sjögren's Systemic Clinical Activity Index (SCAI) a systemic disease activity measure for use in clinical trial in primary Sjögren's syndrome. Rheumatology (Oxford) 2007; 46 (12): 1845-51

7- Seror R, et al. EULAR Sjögren's syndrome disease activity index: Development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010; 69:1103-9

8- Barry R, et al. The Sjögren's Syndrome Damage Index - a damage index for use in clinical trials and observational studies in primary Sjögren's syndrome. Rheumatology 2008;(47):1193-8

9- Cho HJ et al. The EULAR Sjogren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjogren's syndrome patients: in comparison with non-Sjogren's sicca patients. Rheumatology 2013; 52(12):2208-17.

10- Baturone R et al. Health-related quality of life in patients with primary Sjögren's syndrome: relationship with serum levels of proinflammatory cytokines. Scand J Rheumatol 2009; 38(5):386-9.

11- Meijer JM et al.Health-related quality of life, employment and disability in patients with Sjogren's syndrome. Rheumatology 2009;48(9):1077-82.

12- Hackett K, Newton J, Frith J, Elliott C, Lendrem D, Foggo H, et al. Impaired Functional Status in Primary Sjögren's Syndrome. Arthritis Care Res 2012;64(11):1760-4.

13- George A and Pope J. The minimally important difference (MID) for patient-reported outcomes including pain, fatigue, sleep and the Health Assessment Questionnaire Disability Index (HAQ-DI) in primary Sjögren's syndrome. Clin Exp Rheumatol 2011; 29(2):248-53.

SÍNDROME DE SJÖGREN PRIMARIO: FACTORES PRONÓSTICOS

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1) En pacientes con Síndrome de Sjögren primario (SSp)**,** la presencia de anticuerpos Ro/SSA, La/SSB y factor reumatoideo, ¿se asocian a un mayor riesgo de linfoma?

2) En pacientes con SSp, las crioglobulinas positivas ¿se asocian a mayor riesgo de linfoma/ mortalidad?

3) En pacientes con SSp, la hipocomplementemia, ¿se asocia a un mayor riesgo de linfoma/mortalidad?

4) En pacientes con SSp, la presencia de parótidomegalia, ¿se asocia a un mayor riesgo de linfoma/mortalidad?

5) En pacientes con SSp, la vasculitis cutánea, ¿se asocia a mayor riesgo de linfoma/mortalidad?

6) En pacientes con SSp, la linfadenopatías y la esplenomegalia, ¿se asocian a mayor riesgo de viraje a linfoma/mortalidad?

7) En pacientes con SSp, la biopsia de glándula salival menor grado III/IV de la clasificación de Chisholm, ¿se asocia a un mayor riesgo de desarrolla linfoma?

8) En pacientes con SSp, la leucopenia, ¿se asocia a mayor riesgo de desarrollar linfoma?

9) En pacientes con SSp, la gamapatia monoclonal, ¿se asocia a mayor riesgo de desarrollo de linfoma?

10) En pacientes con SSp la presencia de compromiso pulmonar, ¿se asocia a mayor mortalidad?

11) En pacientes con SSp, la glomérulonefritis crioglobulinémica, ¿se asocia a un mayor riesgo de linfoma?

12) La presencia de centros germinales en la biopsia de glándula salival menor, ¿se asocia a mayor riesgo de desarrollo de linfoma?

13) En pacientes con SSp, la elevación de los niveles séricos de beta 2 microglobulina, ¿se asocia a mayor actividad de la enfermedad, con aumento de riesgo de desarrollo de linfoma?

Estrategias de búsqueda:

1) ((sjogren syndrome) AND (anti ro) AND (anti la OR rheumatoid factor) AND (lymphoma))

2) ((sjogren syndrome) AND (cryoglobulin) AND (mortality/lymphoma))

3) ((sjogren syndrome) AND (hypocomplementemia) AND (lymphoma /mortality))

4) ((sjogren syndrome) AND (parotid enlargement) AND (lymphoma))

5) ((sjogren syndrome) AND (lymphadenopathy) AND (splenomegaly) AND (lymphoma/mortality))

6) ((sjogren syndrome) AND (vasculitis OR palpable purpura) AND (mortality/lymphoma))

7) ((sjogren syndrome) AND (biopsy) AND (gland salivary minor) AND (chisholm) AND (lymphoma))

8) ((sjogren syndrome) AND (leucopenia OR lymphopenia OR neutropenia OR anemia) AND (lymphoma))

9) ((sjogren syndrome) AND (monoclonal gammapathy) AND (lymphoma))

10) ((sjogren syndrome) AND (lung disease) AND (mortality))

11) ((sjogren syndrome) AND (glomerulonephritis) AND (lymphoma))

12) ((sjogren syndrome) AND (centers germinal) AND (lymphoma))

13) ((sjogren syndrome)) AND (B_2microglobulia) AND (mortality/lymphoma)).

Artículos encontrados:

Pubmed: 522

Cochrane: 22

Lilacs: 3

Se seleccionaron 37 artículos por título y abstract, todos ellos de la base de Pubmed. Se agregaron 4 artículos por búsqueda manual.

En este capítulo los artículos se describen de manera conjunta, dado que la mayoría de los mismos responden a varias de las preguntas PICO seleccionadas.

La asociación de SSp y linfoma, en su mayoría linfoma no Hodgkin (LNH), ha sido documentada en los últimos 40 años[1-6]. Acorde a distintos reportes, el riesgo de

desarrollar linfoma o enfermedad linfoproliferativa (ELP), se encuentra alrededor del 4% durante los primeros 5 años, 10% a los 15 años y 18% después de 20 años de realizado el diagnóstico[7-14].

Zintzaras y colaboradores publicaron un meta análisis de estudios de cohorte, heterogéneos entre ellos, donde reportaron que los pacientes con SSp son más susceptibles a desarrollar linfoma (tasa de incidencia estandarizada: 18,8. IC 95%: 9,5-37,3) en comparación con pacientes con otras enfermedades autoinmunes como el lupus eritematoso sistémico ((LES) (7.4. IC 95%: 3,3-17,0)) y la artritis reumatoide (AR). En el caso de SSp la tasa de incidencia estandarizada fue de 18,8 (95%: 9.5-37.3); seguidos por LES, y un menor riesgo para AR (3.9; 95% CI, 2.5-5.9)[15]. NE: 2

Nishishinya, y colaboradores publicaron en el año 2014 una revisión sistemática que incluyó 18 artículos en la cual resumen la evidencia existente respecto a los factores predictivos de linfoma en pacientes con SSp. Dichos estudios incluyen pacientes que cumplen criterios clasificatorios diferentes para la enfermedad, con eventual desarrollo de diferentes tipos de linfoma[16].

Dado la heterogeneidad de los estudios incluídos, los mismos se describirán en el transcurso de este texto:

Skopouli y colaboradores publicaron en el año 2000 un estudio de cohorte prospectiva en el que evaluaron 261 pacientes con SSp, según criterios clasificatorios 1993, con una mediana de seguimiento de tres años ((rango intercuartilo (RIQ): 2- 5)). El desarrollo de linfoma se encontró asociado con bajos niveles de C4 (RR: 7.5; IC 95%: 2.1- 26; p = .0016), presencia de crioglobulinas (RR: 7.9; IC 95%: 2.3-27.4; p= .0012),y púrpura (RR: 3.9; IC 95%: 1.1-14.2; p =.037). El principal predictor de mortalidad fue el descenso del complemento (RR: 6.5; p= .0041) [8]. NE: 2.

Ioannidis y colaboradores publicaron en 2002 un estudio de cohorte retrospectiva que incluyó 723 pacientes griegos con SSp, según criterios europeos 1993, en un seguimiento promedio de 6,06 años, donde evaluaron el riesgo de mortalidad y desarrollo de ELP. Durante un seguimiento de 4384 personas- año, se hallaron 39 muertes, de las cuales siete se debieron a linfoma, 38 pacientes desarrollaron ELP. La razón de mortalidad estandarizada fue 1,15 (IC 95%: 0,86-1,73) en comparación con la población general de Grecia. En los casos incidentes, la probabilidad de desarrollo de ELP fue de 2, 6% a los cinco años y 3,9% a los diez años. La tasa de mortalidad fue significativamente mayor en pacientes con niveles bajos de C4 en la primera visita del estudio HR: 4,39; IC del 95%: 2,18 a 8,83). En el análisis multivariado se encontraron como predictores independientes del desarrollo de ELP parótidomegalia (HR 5,21; IC del 95%: 1,76 a 15,4), la púrpura palpable (HR 4.16, IC 95%: 1,65 a 10,5), y bajos niveles de C4 (HR 2.40, IC 95%: 0,99 a 5,83), en la primera visita del estudio[4]. NE: 2.

Baimpa y colaboradores publicaron en el año 2009 un estudio de cohorte retrospectiva que incluyó 536 pacientes con SSp, según criterios 2002, con una media de segumiento de 31 meses (rango: 0- 317 meses). Anemia, linfopenia, trombocitopenia, hipergammaglobulinemia, gammapatía monoclonal, y crioglobulinemia mostraron una correlación significativa con la presencia de síntomas extraglandulares tales como

púrpura palpable, linfadenopatía y esplenomegalia[7]. El linfoma se diagnosticó en 7,5% (IC del 95% 5,4% -10%) de los pacientes. En el modelo multivariado, se encontró que el desarrollo de LNH en pacientes con SSp se podría predecir por la presencia de neutropenia (HR: 8,97. IC 95%: 1, 10- 73; p = 0,041), crioglobulinemia (HR: 2,91. IC 95%: 1,15- 6,94; P = 0,008), esplenomegalia (HR: 3,97. IC 95%: 1,49- 10, 62; p = 0,006), linfadenopatía (HR: 2, 62. IC 95%: 1,15- 5 ,94; p = 0,021), y bajos niveles de C4 (HR: 3,31. IC 95%: 1,35- 8,12; p = 0,009) [7]. NE: 2.

Solans- Laque y colaboradores describieron en el año 2011 una cohorte prospectiva, que incluyó 244 pacientes con SSp, según criterios 1993, con una mediana de seguimiento de 8, 6 años (1- 20 años) y encontraron que la púrpura (HR 8.04, 95% [IC] 2.33-27.67), parotidomegalia (HR 6.75, 95%IC 1.89-23.99), anemia (HR 3.43, 95%IC 1.04-11.35), leucopenia (HR 8.70, 95%IC 2.38-31.82), linfocitopenia (HR 16.47, 95%IC 3.45-78.67), hipergammaglobulinemia (HR 4.06, 95%IC 1.06-15.58), disminución de C3 (HR 36.65, 95%IC 10.65-126.18), y descenso de C4 (HR 39.70, 95%IC 8.85-126.18) fueron predictores de desarrollo de LNH, pero solo la hipocomplementemia y la linfocitopenia fueron factores de riesgo independientes en el análisis multivariado ajustado por edad [10]. NE: 2.

Kassan y Colaboradores reportaron en el año 1978, en 142 pacientes con síndrome sicca, con un seguimiento promedio de ocho años, que la presencia de linfopenia, espleno y parótidomegalia se asociaban a un mayor riesgo de desarrollo de linfoma [2]. NE: 3.

A su vez Risselada y colaboradores publicaron en el año 2013 un estudio de cohorte retrospectiva, que incluyó 195 pacientes con SSp, según criterios 2002, con un promedio de seguimiento de 7, 6 años de los cuales 21 pacientes (11%) desarrollaron LNH. La parotidomegalia (OR 2.84) y los bajos niveles de C4 (OR 7.71) se encontraron asociados con el desarrollo de LNH [13] .NE: 2.

Quartuccio y Colaboradores en el año 2013 publicaron un estudio de corte transversal que incluyó 661 pacientes con SSp, según criterios clasificatorios 2002, observándose asociación independiente tanto de las crioglobulinas (RRR) 6.8; IC 95: 2.1- 22.1], los bajos niveles de C4 (RRR 8.3, IC95%: 3.6- 19.2), como de la leucopenia (RRR 3.3; IC95%: 1.5- 7.05) con el desarrollo de linfoma [14].NE: 4

Theander y colaboradores publicaron en el año 2006 un estudio de cohorte prospectiva, que incluyó 506 pacientes con SSp, que cumplían criterios de Copenague, o 1993, o 2002, con una mediana de seguimiento de ocho años (rango: 1-19 años). En este estudio no se consideraron las crioglobulinas. Dentro de los factores evaluados, se encontraron como fuerte predictores de malignidad a la púrpura palpable (HR) = 4.64; IC 95%: 1.13- 16.45), descenso de C3 (HR = 6.18; IC 95%: 1.57-24.22), descenso de C4 (HR = 9.49; IC 95%: 1.94- 46.54), linfocitopenia T CD4+ (HR = 8.14; IC95%: 2.10- 31.53) [18]. NE: 4

Brito-Zeron publicaron en 2007 un estudio de cohorte prospectiva que incluyó 247 pacientes, con diagnóstico de SSp según criterios 1993 (167 de ellos cumplían criterios 2002) llegaron a la conclusión de que tanto las crioglobulinas (HR 4.58,

p=0.013) y los bajos niveles séricos de C4 (HR 5.47, p= 0.027), se correlacionaron sustancialmente con progresión a linfoma, ya sea de forma independiente o combinados [19]. NE: 2

Aunque la púrpura palpable se encuentra relacionada con el desarrollo de desórdenes linfoproliferativos, pocos estudios mostraron una asociación independiente[4,8,11]. En el estudio de cohorte publicado por Ioannidis y colaboradores en 2002 (723 pacientes), la presencia de púrpura al diagnóstico se asoció en forma independiente al desarrollo de linfoma [4]. NE: 2

Seis estudios evaluaron anti-Ro / anti-La,[4,14,17-19,21] pero sólo un estudio mostró una asociación significativa con el desarrollo de enfermedad linfoproliferativa en el análisis univariado, la cual no se mantuvo en el análisis multivariado [4]. NE: 2

La linfopenia se mostró como un factor de riesgo independiente en la mitad de los trabajos que evaluaban este resultado.[11] Es así que Theander y colaboradores destacaron como fuerte predictor de malignidad a la linfocitopenia T CD4+ (HR = 8.14, 95% CI 2.10 to 31.53) [18]. En particular, hubo una asociación estadísticamente significativa entre la linfopenia T CD4 + y LNH (p = 0,001) [9]. La neutropenia también se identificó como un factor predictor importante en un estudio[9], pero no alcanzó asociación estadísticamente significativa en otros tres[2,15,22]. Por último, la anemia, la presencia de ANA o factor reumatoideo e hipergammaglobulinemia no se asociaron con linfoma o ELP en los análisis ajustados[2,4,9,12,15,17,18-22]. NE: 2

Partiendo de otros artículos no incluidos en la revisión previamente mencionada y con respecto a la gammapatía monoclonal, en la década de 1980, Moutsopoulos y colaboradores informaron la presencia de inmunoglobulinas monoclonales en pacientes con SSp y su asociación con manifestaciones extraglandulares y trastornos linfoproliferativos; estudios posteriores han informado que hasta el 20% de los pacientes con SSp pueden tener gammapatía monoclonal de significado indeterminado [23-27]. NE: 4.

A su vez Brito-Zeron y colaboradores, presentaron en el año 2012 un estudio de cohorte que incluyó a 221 pacientes con SSp de los cuales 48 (22%) presentaron esta manifestación. Los pacientes con gammapatía tuvieron una mayor prevalencia de parotidomegalia (38% vs 20%, p= 0.021), vasculitis (21% vs 6%, p= 0.003), compromiso neurológico (42% vs 23%, p= 0.016), bajos niveles de C3 (24% vs 11%, p = 0.028), descenso de C4 (24% vs 7%, p = 0.003), y crioglobulinas (23% vs 8%, p=0.012) comparados con aquellos pacientes sin gammapatía. De 48 pacientes con SSp y gammapatía, ocho desarrollaron neoplasias hematológicas después de una media de seguimiento de diez años (17% vs 5%, p= 0.009). La tasa de supervivencia acorde a la presencia o ausencia de gammapatía fue de 83% y 97%, respectivamente (log rank 0.004)[28]. NE: 3

El valor pronóstico del análisis de la histología de la glándula salival ha sido recientemente destacado debido a que la organización de focos de linfocitos dentro de los centros germinales se mostró asociado a mayor riesgo de linfoma no hodgkin (LNH) y enfermedad sistémica. Theander y colaboradores publicaron en el 2011 un

estudio de cohorte retrsopectiva en el cual la presencia de centros germinales (CG) se asoció con el desarrollo de linfoma; dada las características del estudio, el análisis no pudo ajustarse por el resto de los factores predictores [29]. N: 3. El número de focos en las glándulas salivales ha demostrado estar asociado positivamente con la formación de centros germinales[30]. Estas observaciones subrayan la importancia de la biopsia de glándula salival menor, cuyo análisis histológico incluye la evaluación del número de focos linfocitarios. NE: 2.

Risselada y colaboradores publicaron un estudio de cohorte retrospectiva, en el año 2014, que incluyó 174 pacientes con SSp. La media de focus score (FS número de focos linfocitarios en 4 mm^2) fue significativamente mayor en pacientes que desarrollan LNH (3,0 ± 0,894 vs 2,25 ± 1,086; p = 0,021). El umbral de ≥ tres focos mostró un valor predictivo positivo del 16% para linfoma, y un valor predictivo negativo de 98%. Un FS ≥ tres contribuyó de forma significativa e independiente con el desarrollo de la LNH en un modelo de regresión múltiple [31]. NE: 2

Así mismo Carubbi y colaboradores en un estudio multicéntrico, retrospectivo, de corte transversal, realizado en Italia y publicado en el año 2014, también demostraron el valor pronóstico de la biopsia de glándula salival [32]. NE: 4

Risselada y colaboradores en una revisión sistemática de la literatura, estudiaron el rol de los CG ectópicos en la inmunopatología de pacientes con SSp. Seleccionaron 16 estudios, heterogéneos entre ellos, en donde encontraron presencia de CG en 25.1 +/- 5,0% de los pacientes con SSp. La media de FS era 1,25 puntos mayor en pacientes con CG en comparación con aquellos sin CG. La producción de saliva fue menor en pacientes con CG, aunque esto no alcanzó significancia estadística. Los porcentajes de pacientes positivos para el factor reumatoide, anti RO y anti LA, fueron significativamente mayores en pacientes con CG (aumento, 15%, 18% y 18%, respectivamente). Además, los pacientes con CG se caracterizaron por niveles aumentados de mediadores proinflamatorios locales y sistémicos. Es importante destacar que estos pacientes tuvieron un mayor riesgo de desarrollo de linfoma (14% frente a 1%) [30]. NE: 2

Los pacientes con SSp con afectación renal presentan una reducción de la supervivencia y este hecho estaría estrechamente relacionado con el tipo de enfermedad renal y la propensión a desarrollar linfoma. Si bien, los pacientes con nefritis intersticial tienen un mejor pronóstico, la glomerulonefritis se asocia con el desarrollo de linfoma, como parte de las manifestaciones extraepiteliales mediada por complejos inmunes crioprecipitables, posiblemente debido a crioglobulinemia, que se considera un factor de riesgo independiente de mortalidad y morbilidad en SSp. Goules y colaboradores publicaron en 2013 un estudio de cohorte; en el cual, en 715 pacientes con SSp encontraron 35 pacientes (4,9%) con afectación renal clínicamente significativa. Trece (37,1%) tenían solo nefritis intersticial, 17 pacientes (48,6%) tuvieron solo glomerulonefritis (GN), y cinco pacientes (14,3%) tenían ambas entidades. Nueve pacientes fallecieron (25,7%), 11 desarrollaron insuficiencia renal crónica (incluyendo 4 que requirieron hemodiálisis crónica) (31,4%), y nueve linfoma (25,7%). En general la tasa de supervivencia a los cinco años fue del 85%. El análisis de sobrevida mostró reducción estadísticamente significativa de la supervivencia de

pacientes con SSp con afectación renal en comparación a los que no tenían afectación renal (p <0,0001 por log rank test). Ocho de nueve muertes (89%) y ocho de nueve linfomas (89%) se observaron entre los pacientes con GN [33]. NE: 2

La frecuencia de compromiso pulmonar en pacientes con SSp varía de un 8 a un 75% en diferentes series, dependiendo del método de diagnóstico empleado[34]. Nannini y colaboradores, en un estudio de cohorte prospectiva publicado en 2013, encontraron que el desarrollo de enfermedad pulmonar en SSp se asociaba con pobre supervivencia (HR 2,16; IC del 95%: 0,99 a 4,74).[35]NE: 2 Similares hallazgos encontraron Palm y colaboradores en un estudio retrospectivo donde estudiaron a 216 pacientes con SSp, de los cuales 59 presentaron compromiso pulmonar. Detectaron un aumento del riesgo cuatro veces mayor de morir a los diez años de la enfermedad entre los pacientes con afectación pulmonar (n = 10, 17%) en comparación con los que no tenían afectación pulmonar (n = 7, 4,5%) (p = 0,002) [36]. NE: 4

En estudios previos la B_2 microglobulina fue encontrada en el suero, saliva y líquido sinovial de pacientes con SSp[37-40]. Gottenberg y Colaboradores publicaron en 2005, un estudio de corte transversal, en el que estudiaron la asociación existente entre B_2 microglobulina con la producción de autoanticuerpos y el compromiso extraglandular en el momento basal, en 177 pacientes con SSp. Encontraron que la secreción de anticuerpos (anti Ro y anti La) se relacionó con un aumento de la B_2 microglobulina en suero. Así mismo, su concentración se asoció con compromiso extraglandular en el análisis univariado ($p<10^{-4}$). Entre los 25 pacientes que tuvieron determinaciones seriadas de B_2 microglobulina, la concentración se incrementó en todos aquellos con exacerbación de la enfermedad [41] .NE: 4

Bibliografía:

1. Jordan RC, Speight PM (1996) Lymphoma in Sjogren's syndrome. From histopathology to molecular pathology. Oral Surg Oral Med O 81(3):308–320

2. Kassan SS, Thomas TL, Moutsopoulos HM, Hoover R, Kimberly RP, Budman DR et al (1978) Increased risk of lymphoma in sicca syndrome. Ann Intern Med 89(6):888–892

3. Pariente D, Anaya JM, Combe B, Jorgensen C, Emberger JM, Rossi JF et al (1992) Non-Hodgkin's lymphoma associated with primary Sjogren's syndrome. Eur J Med 1:337–342

4. Ioannidis JPA, Vassiliou VA, Moutsopoulos HM (2002) Longterm risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome. Arthritis Rheum 46:741–747

5. Smedby KE, Baecklund E, Askling J (2006) Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors, and lymphoma characteristics. Cancer Epidemiol Biomarkers Prev 15:2069–2077

6. Smedby KE, Hjalgrim H, Askling J, Chang ET, Gregersen H, Porwit-MacDonald A et al (2006) Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst 98:51–60

7. Baimpa E, Dahabreh IJ, Voulgarelis M, Moutsopoulos HM (2009) Hematologic manifestations and predictors of lymphoma development in primary Sjogren syndrome: clinical and pathophysiologic aspects. Medicine (Baltimore) 88:284–293

8. Skopouli FN, Dafni U, Ioannidis JPA, Moutsopoulos HM (2000) Clinical evolution, and morbidity and mortality of primary Sjogren's syndrome. Semin Arthritis Rheum 29:296–304

9. Smedby KE, Vajdic CM, Falster M et al (2008) Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood 111:4029–4038

10. Solans-Laque R, Lopez-Hernandez A, Angel Bosch-Gil J, Palacios A, Campillo M, Vilardell-Tarres M (2011) Risk, predictors, and clinical characteristics of lymphoma development in primary Sjogren's syndrome. Semin Arthritis Rheum 41:415–423

11. Liang Y, Yang Z, Qin B, Zhong R (2013) Primary Sjögren´s syndrome and malignancy risk: a systematic review and meta-analysis. Ann Rheum Dis. 2014 Jun;73(6):1151-6

12. Johnsen SJBJG, Goransson LG, Smastuen MC, Johannesen TB, Haldorsen K et al (2013) Risk of non-Hodgkin´s lymphoma in primary Sjögren`s syndrome: a population-based study. Arthritis Care Res 65:816–821

13. Risselada AP, Kruize AA, Bijlsma JW (2013) Clinical features distinguishing lymphoma development in primary Sjögren´s syndrome—a retrospective cohort study. Semin Arthritis Rheum. 2013 Oct;43(2):171-7

14. Quartuccio L, Isola M, Baldini C, Priori R, Bartoloni Bocci E, Carubbi F et al (2013) Biomarkers of Lymphoma in Sjögren`s syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. J Autoimmun 2014 Jun;51:75-80

15. Zintzaras E, Voulgarelis M, Moutsopoulos HM (2005) The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med 165:2337–2344

16. Nishishinya M, Pereda C, Muñoz-Fernandez S et al(2014) Identification of lymphoma predictors in patients with primary Sjögren's Syndrome: a systematic literature review and meta-analysis. Rheumatol Int. 2015 Jan;35(1):17-26

17. Sutcliffe N, Inanc M, Speight P, Isenberg D (1998) Predictors of lymphoma development in primary Sjogren's syndrome. Semin Arthritis Rheum 28:80–87

18. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT (2006) Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 65:796–803

19. Brito-Zeron P, Ramos-Casals M, Bove A, Sentis J, Font J (2007) Predicting adverse outcomes in primary Sjogren's syndrome: identification of prognostic factors. Rheumatology 46:1359–1362

20. Lazarus M, Robinson D, MakV et al. (2006) Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. Rheumatology 2006;45:1012–1015.

21. Martel C, Gondran G, Launay D, Lalloué F, Palat S, Lambert Met al (2011) Active immunological profile is associated with systemic Sjogren's syndrome. J Clin Immunol 31:1–8

22. Pertovaara M, Pukkala E, Laippala P, Miettinen A, Pasternack A (2001) A longitudinal cohort study of Finnish patients with primary Sjogren's syndrome: clinical, immunological, and epidemiological aspects. Ann Rheum Dis 60:467–472

23. Brito-Zerón P, Ramos-Casals M, Nardi N, Cervera R, Yagüe J, Ingelmo M, et al. Circulating monoclonal immunoglobulins in Sjögren syndrome: prevalence and clinical significance in 237 patients. Medicine (Baltimore) 2005;84:90e7.

24. Moutsopoulos HM, Steinberg AD, Fauci AS, Lane HC, Papadopoulos NM. High incidence of free monoclonal lambda light chains in the sera of patients with Sjogren's syndrome. J Immunol 1983;130:2663e5

25. Moutsopoulos HM, Costello R, Drosos AA, Mavridis AK, Papadopoulos NM. Demonstration and identification of monoclonal proteins in the urine of patients with Sjögren's syndrome. Ann Rheum Dis 1985;44:109e12

26. Tzioufas AG, Costello R, Manoussakis MN, Papadopoulos NM, Moutsopoulos HM. Cryoglobulinemia in primary Sjögren's syndrome: a monoclonal process. Scand J Rheumatol Suppl 1986;61:111e3

27. Tzioufas AG, Manoussakis MN, Costello R, Silis M, Papadopoulos NM, Moutsopoulos HM. Cryoglobulinemia in autoimmune rheumatic diseases. Evidence of circulating monoclonal cryoglobulins in patients with primary Sjögren's syndrome. Arthritis Rheum 1986;29:1098e104

28. Brito-Zerón P, Retamozo S, Gandía M, Akasbi M, Pérez-De-Lis M, Diaz-Lagares C, Bosch X, Bové A, Pérez-Alvarez R, Soto-Cárdenas MJ, Sisó A, Ramos-Casals Monoclonal gammopathy related to Sjogren syndrome: a key marker of disease prognosis and outcomes. M.J Autoimmun. 2012 Aug;39(1-2):43-8.

29. Theander E, Vasaitis L, Baecklund E, et al. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. Ann Rheum Dis 2011;70:1363–8.

30. Risselada AP, Looije MF, Kruize AA, et al. The role of ectopic germinal centers in the immunopathology of Primary Sjögren's syndrome: a systematic review. Semin Arthritis Rheum 2012;42:368–76.

31. Risselada AP, Kruize AA, Goldschmeding R, Lafeber FP, Bijlsma JW, van Roon. The prognostic value of routinely minor salivary gland assessments in primary Sjögren syndrome. Ann Rheum Dis. 2014 Aug;73(8):1537-40.

32. Carubbi F, Alunno A, Cipriani P, Bartoloni E, Baldini C, Quartuccio L, Priori R, Valesini G, De Vita S, Bombardieri S, Gerli R, Giacomelli. A retrospecive, multicenter study evaluating the prognostic value of minor salivary gland histology in a large cohort of patients with primary Sjögren syndrome. R.Lupus. Mar;24(3):315-20.

33. Goules AV, Tatouli IP, Moutsopoulos HM, Tzioufas AG. Clinically significant renal involvement in primary Sjogren's syndrome: clinical presentation and outcome Arthritis Rheum. 2013 Nov;65(11):2945-53.

34. Parambil JG, Myers JL, Lindell RM, et al. Interstitial lung disease in primary Sjögren syndrome. Chest 2006;130:1489–95

35. Nannini C, Jebakumar AJ, Crowson CS, Ryu JH, Matteson EL. Primary Sjogre's syndrome and asociated interstitial lung disease: a population-based study of incidence and mortality. BMJ Open. 2013 Nov 25;3(11):e003569.

36. Palm O, Garen T, Berge Enger T, Jensen JL, Lund MB, Aaløkken TM, Gran JT. Clinical pulmonary involvement in primary Sjogre's syndrome: prevalence, quality of life and mortality- a retrospective study based on registry data. Rheumatology (Oxford). 2013 Jan;52(1):173-9.

37. Michalski JP, Daniels TE, Talal N, Grey HM. Beta2 microglobulin and lymphocytic infiltration in Sjogren's syndrome. N Engl J Med 1975;293:1228–31

38. Talal N, Grey HM, Zvaifler N, Michalski JP, Daniels TE. Elevated salivary and synovial fluid beta2-microglobulin in Sjogren's syndrome and rheumatoid arthritis. Science 1975;187:1196–8

39. Maddali Bongi S, Campana G, D'Agata A, Palermo C, Bianucci G. The diagnosis value of beta 2-microglobulin and immunoglobulins in primary Sjogren's syndrome. Clin Rheumatol 1995;14:151–6

40. Castro J, Jimenez-Alonso J, Sabio JM, Rivera-Civico F, Martin-Armada M, Rodriguez MA, et al. Salivary and serum beta$_2$-microglobulin and gammaglutamyl-transferase in patients with primary Sjogren syndrome and Sjogren syndrome secondary to systemic lupus erythematosus. Clin Chim A

41. J-E Gottenberg, M Busson, J Cohen-Solal, F Lavie, K Abbed, R P Kimberly, J Sibilia, X Mariette. Correlation of serum B lymphocyte stimulator and b$_2$ microglobulin with autoantibody secretion and systemic involvement in primary Sjogren's syndrome. Ann Rheum Dis 2005;64:1050–1055.

SÍNDROME DE SJÖGREN PRIMARIO Y EMBARAZO

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Pregunta 1- Complicaciones en el embarazo:

1a. ¿Las pacientes con Síndrome de Sjögren Primario (SSp), requieren controles más estrictos durante su embarazo para evitar abortos?

1b. ¿Las pacientes con SSp, requieren controles más estrictos durante su embarazo para evitar partos pre término?

1c. ¿Las pacientes con SSp, requieren controles más estrictos durante su embarazo para evitar el bajo peso al nacer?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome) AND (pregnancy complication OR abortion OR Pre-Eclampsia OR Fetal growth restriction OR intra-uterine growth restriction OR pre term delivery OR Low Birth Weight))

(tw:("Sjogren's Syndrome" OR Sjogren OR "Sjögren's Syndrome" OR "sjogren syndrome" OR "síndrome de sjogren")) AND (tw:("pregnancy complication" OR abortion OR "Pre-Eclampsia" OR "Fetal growth restriction" OR "intra-uterine growth restriction" OR "pre term delivery" OR "Low Birth Weight" OR "bajo peso al nacer" OR abortos OR "retraso crecimiento intrauterino"))

Se hallaron 240 artículos de los cuales 228 fueron eliminados por título, 5 por abstracts y 1 por el contenido del texto completo; quedando seleccionados 6 artículos.

De Carolis y colaboradores publicaron en 2014 un estudio retrospectivo que tuvo como objetivo evaluar los resultados del embarazo en mujeres con SSp. Se compararon 34 mujeres con SSp con 136 controles. Se observó un aumento estadísticamente significativo de la tasa de abortos espontáneos, partos prematuros y cesáreas en los embarazos en los pacientes con SSp. La media de peso al nacer y el percentil de peso medio al nacer fueron significativamente menores en los hijos de mujeres con SSp en comparación con los controles. El resultado del embarazo fue similar en las mujeres con diagnóstico previo y post embarazo analizado. Es importante resaltar que las mujeres con SSp experimentaron embarazos complicados con más frecuencia que los controles aún antes de la aparición de los síntomas [(1)]. NE: 4

Hussein y colaboradores publicaron en 2011 un estudio de casos y controles anidado, que tuvo como objetivo analizar los resultados del embarazo y del feto en pacientes con SSp en comparación con la población general. Se encontró que el peso al nacer fue significativamente diferente entre los casos y los controles (p = 0,025). Los recién

nacidos de las mujeres con SSp se caracterizaron por presentar menor peso al nacer (p = 0,007). El 25% de estos bebés eran pequeños para la edad gestacional en comparación con sólo el 7,5% de los controles (p = 0,04). Las cesáreas fueros más frecuentes en las mujeres con SSp (p=0.020). En este estudio todos los bebés nacidos prematuramente y con bajo peso al nacer entre los casos se encontraron en el grupo de pacientes con SSp diagnosticado antes del embarazo [(2)]. NE: 4

Siamopoulou-Mavridou y colaboradores publicaron en 1988, un estudio retrospectivo, que tuvo como objetivo evaluar los resultados de los embarazos en mujeres que posteriormente desarrollaron manifestaciones clínicas de enfermedades autoinmunes. Se evaluaron 419 embarazos en 154 mujeres con enfermedades autoinmunes, observándose que los embarazos en mujeres que posteriormente desarrollaron SSp (N: 21), tuvieron una mayor incidencia de abortos espontáneos que los controles sanos (p < 0,05) [(3)]. NE: 4

En otros tres estudios no se encontraron diferencias estadísticamente significativas [(4-6)]. NE: 4

En conclusión, si bien no se encontró evidencia en cuanto a la frecuencia en la que deben realizarse los controles del embarazo en estas pacientes, se observó mayor prevalencia de abortos espontáneos, partos prematuros y cesáreas en pacientes con SSp. El peso al nacer fue significativamente menor en los hijos de mujeres con SSp en comparación con los controles.

Pregunta 2- Control de Complicaciones cardiológicas:

¿En pacientes con SSp con anticuerpo anti Ro y/o La positivo, es de utilidad el doppler fetal para el diagnóstico de bloqueo cardíaco congénito?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome OR RO ANTIBODIES OR LA ANTIBODIES) AND (atrioventricular block OR congenital heart block) AND (diagnosis) AND (DOPPLER COLOR OR ULTRASOUND OR cardiac monitoring))

(tw:("Sjogren's Syndrome" OR Sjogren OR "Sjögren's Syndrome" OR "sjogren syndrome" OR "síndrome de sjogren")) AND (tw:("lupus neonatal" OR "neonatal lupus")) AND (tw:("doppler color" OR ultrasound OR “echocardiographic screening” OR “cardiac monitoring” OR “echocardiography” OR “doppler color echocardiography” OR ecocardiograma))

Se hallaron 155 artículos de los cuales 153 fueron eliminados por título, 1 por abstract, quedando seleccionado 1 artículo.

Friedman y colaboradores, publicaron en 2010 una serie de casos (estudio PRIDE) en la que evaluaron 127 mujeres embarazadas con anti-SSA / Ro de las cuales se analizaron 98 embarazos. El protocolo incluyó ecocardiogramas fetales semanales entre las 16 y 26 semanas de gestación y estudios quincenales en las semanas 26 a 34. Los intervalos PR de 150 ms o mayores eran considerados prolongados (bloqueo

de primer grado). La prolongación del intervalo PR fue poco común (tres casos) y no precedió al bloqueo más avanzado. El BCC de tercer grado ocurrió en tres pacientes. En este estudio se observó que el bloqueo avanzado y la miocardiopatía pueden ocurrir dentro de la primera semana posterior a un ecocardiograma normal [(7)]. NE: 4

Pregunta 3- Utilidad de la Hidroxicloroquina (HCQ)

¿En pacientes con SSp, es de utilidad el tratamiento profiláctico con HCQ para prevenir el lupus neonatal/bloqueo cardiaco congénito (BCC)?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome SS-A antibodies OR ro antibodies OR la antibodies OR SS-B antibodies) AND (hydroxychloroquine OR antimalarial drug) AND (Neonatal Systemic lupus erythematosus OR neonatal lupus OR Congenital heart block OR congenital heart defect OR congenital complete heart block))

(tw:("Sjogren's Syndrome" OR Sjogren OR "Sjögren's Syndrome" OR "sjogren syndrome" OR "SINDROME DE SJOGREN")) AND (tw:(hydroxychloroquine OR "antimalarial drug" OR"antimaláricos" OR hidroxicloroquina)) AND (tw:("Neonatal Systemic lupus erythematosus" OR "neonatal lupus" OR "Congenital heart block" OR "congenital heart defect" OR "congenital complete heart block"))

Se hallaron 80 artículos de los cuales se eliminaron 75 por título, 1 por abstract y 3 por texto completo, 1 artículo fue seleccionado.

Izmirly y colaboradores publicaron en 2012 un estudio de cohorte histórica en el que se incluyeron 257 embarazos de madres con anticuerpos anti SSA / Ro positivos posteriores al nacimiento de un niño con lupus neonatal (LN). De las madres evaluadas, 40 habían recibido HCQ y 217 no habían sido expuestos a la misma. La tasa de recurrencia de LN con compromiso cardíaco en los fetos expuestos a HCQ fue 7,5 % (3/40) en comparación con 21,2 % (46/217) en el grupo no expuesto (p = 0,050). En el análisis multivariado el uso de HCQ resultó significativamente asociado a un menor riesgo de LN cardíaco (OR = 0,2; IC95 %: 0,06- 0,92 ; p = 0,037) [(8)]. NE: 4

Pregunta 4- Utilidad de las inmunoglobulinas en el LN:

¿En pacientes con SSp embarazadas la utilización de inmunoglobulinas cambia el pronóstico del LN?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome SS-A antibodies OR ro antibodies OR la antibodies OR SS-B antibodies) AND (Neonatal Systemic lupus erythematosus OR neonatal lupus OR Congenital heart block OR congenital heart defect OR congenital complete heart block) AND (intravenous immunoglobulin OR immunoglobulin OR IVIG))

(tw:(("Sjogren's Syndrome" OR Sjogren ORS "sjögren's Syndrome" OR "sjogren syndrome" OR "SS-A antibodies" OR "ro antibodies" OR "la antibodies" OR "SS-B antibodies" OR “Síndrome de Sjogren”) AND (tw:("Neonatal Systemic lupus erythematosus" OR "neonatal lupus" OR "Congenital heart block" OR "congenital heart defect" OR "congenital complete heart block" OR “bloqueo cardíaco congénito” OR “bloqueo cardíaco”)) AND (tw:("intravenous immunoglobulin" OR immunoglobulin OR IVIG OR inmunoglobulinas))

Se encontraron 455 artículos. De los mismos, 439 fueron eliminados por título, 14 por abstract, quedando 2 seleccionados.

Pisoni y colaboradores publicaron en 2010 un estudio multicéntrico, observacional, de cohorte prospectiva. Se evaluaron 24 embarazos en 22 mujeres en las que en un embarazo anterior los fetos habían desarrollaron BCC. Quince pacientes recibieron infusiones de inmunoglobulinas endovenosas (IVIG). Los nueve embarazos en las siete pacientes restantes se utilizaron como controles. Las IVIG se administraron a una dosis de 400 mg / kg en las semanas 12, 15, 18, 21, y 24 de embarazo. Tres fetos de madres con diagnóstico de SSp desarrollaron BCC entre los 15 embarazos en el grupo de tratamiento (20%) y en los nueve embarazos del grupo control (11%). La utilización de IVIG a la dosis y la frecuencia utilizada en este estudio no fue eficaz como terapia profiláctica para evitar el BCC en madres de alto riesgo [(9)]. NE: 4

Friedman y colaboradores publicaron en 2010 una serie de casos, multicéntrica. Se evaluaron 20 madres las cuales recibieron IVIG en las mismas dosis que en el estudio previo, cada tres semanas, desde la semana 12 hasta la semana 24 de gestación. Tres fetos desarrollaron bloqueo cardíaco a pesar de las infusiones de IVIG [(10)].NE: 4

Pregunta 5- Utilidad de los corticoides en el LN:

¿En pacientes con SSp es útil el uso de corticoides para evitar o tratar el lupus neonatal ?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome SS-A antibodies OR ro antibodies OR la antibodies OR SS-B antibodies) AND (Neonatal Systemic lupus erythematosus OR neonatal lupus OR Congenital heart block OR congenital heart defect OR congenital complete heart block) AND (dexamethasone OR betamethasone OR glucocorticoid OR corticosteroids))

(tw:(“Sjogren's Syndrome” OR Sjogren OR “Sjögren's Syndrome” OR “sjogren syndrome” OR “síndrome de sjogren” OR “SS-A antibodies” OR “ro antibodies” OR “la antibodies” OR “SS-B antibodies") AND (tw:(“Neonatal Systemic lupus erythematosus” OR “neonatal lupus” OR “lupus neonatal” OR “Congenital heart block” OR “congenital heart defect” OR “congenital complete heart block” OR “bloqueo cardíaco congénito" OR "lupus neonatal") AND (tw:(dexamethasone OR glucocorticoid OR corticosteroids OR corticoides OR dexametasona OR betametasona))

Se hallaron 92 artículos, 73 fueron eliminados por título, y 15 por abstract. Quedaron seleccionados 4 artículos que se presentan a continuación.

Costedoat-Chalumeau y colaboradores publicaron en 2003 una serie de casos restrospectiva en la que se evaluaro siete madres consideras "pacientes de alto riesgo" con historia pasada de BCC y anti Ro positivo. Se produjeron 13 embarazos posteriores en los cuales no se observó BCC. De los cuatro embarazos en mujeres tratadas con 10 mg / día de prednisona, en ninguno se produjeron complicaciones. En los tres embarazos en mujeres que no recibieron esteroides se reportaron dos abortos espontáneos tempranos y un hijo nacido vivo. Al evaluar los seis embarazos en mujeres tratadas con dexametasona (4-5 mg / día), se encontró: un aborto temprano espontáneo y otro tardío, dos mortinatos, y dos nacidos vivos con restricción del crecimiento intrauterino e insuficiencia suprarrenal leve [(11)]. NE: 4

Shinohara y colaboradores publicaron en 1999 un estudio de cohorte retrospectiva, en el que se evaluaron 87 hijos de 40 madres con Anticuerpos anti-Ro / SSA positivo. Ninguno de los 26 recién nacidos cuyas madres recibieron la terapia de mantenimiento con corticoesteroides antes de la semana 16 de gestación mostró BCC. En 15 de los 61 recién nacidos cuyas madres no recibieron corticoesteroides durante el embarazo o comenzaron a recibirlos después de las 16 semanas de gestación se desarrolló BCC. El BCC completo, una vez desarrollado, no respondió al tratamiento con corticoesteroides [(12)]. NE: 4

En el estudio PRIDE comentado previamente (estudio prospectivo, observacional, multicéntrico, serie de casos), se evaluaron 98 embarazos. El LN se desarrolló en diez casos (cuatro sólo se manifestaron como compromiso cutáneo). Tres fetos presentaron bloqueo de tercer grado los cuales no revirtieron con el uso de dexamentasona. Dos fetos presentaron prolongación del intervalo PR mayor a 150 ms y ambos revirtieron con la utilización de 4 mg de dexametasona [(7)]. NE: 4

Saleeb y colaboradores publicaron en 1999 un estudio de cohorte retrospectivo en el que se evaluaron 47 madres con Anticuerpos anti-SSA / Ro o anticuerpos anti-SSB/La positivos e hijos con BCC. En 28 embarazos las madres recibieron dexametasona 4-9 mg / día durante tres a 19 semanas o betametasona 12-24 mg / semana (grupo A). En 22 embarazos no se utilizaron esteroides (grupo B). Se desarrolló bloqueo de tercer grado en 21 fetos en el grupo A y 18 fetos del grupo B y ninguno fue reversible a pesar del tratamiento con esteroides. La terapia con esteroides fue más eficaz en la resolución de los derrames pleurales, ascitis y la hidropesía fetal. Aunque los fetos del grupo A tenían más complicaciones en la presentación que los del grupo B, no hubo diferencias significativas en la duración del embarazo, el número de muertes, el grado final del bloqueo cardiaco, o la necesidad implantación de marcapasos [(13)]. NE: 4

Pregunta 6- Utilidad de la plasmaféresis en el LN:

¿En pacientes con SSp, es de utilidad el uso de plasmaféresis para el tratamiento del BCC?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome SS-A antibodies OR ro antibodies OR la antibodies OR SS-B antibodies) AND (Neonatal Systemic lupus erythematosus OR neonatal lupus OR Congenital heart block OR congenital heart defect OR congenital complete heart block) AND (Plasmapheresis OR plasma exchange OR plasma exchanges))

(tw:("Sjogren's Syndrome" OR Sjogren OR "Sjögren's Syndrome" OR "sjogren syndrome" OR "síndrome de sjogren" OR "síndrome de Sjögren") AND (tw:("Neonatal Systemic lupus erythematosus" OR "neonatal lupus" OR "Congenital heart block" OR "congenital heart defect" OR "congenital complete heart block") AND (tw:(Plasmapheresis OR "plasma exchange" OR plasmaféresis))

Se hallaron 27 artículos de los cuales 13 fueron eliminados por el título, 12 por el contenido del abstract, 1 por el texto, quedando seleccionado 1 artículo.

Martínez-Sánchez y colaboradores publicaron en 2015 una serie de tres casos que tuvo como objetivo evaluar la eficacia y seguridad de la combinación de esteroides, plasmaféresis y la admisnsitración de IGIV sobre los niveles de Ro / SS-A maternos en casos de afectación cardíaca fetal. Los tres casos fueron fetos con afectación cardíaca leve los cuales fueron tratados con la triple terapia. La disminución más significativa de anticuerpos se produjo después del primer ciclo. La evolución natural de la enfermedad fue detenida y ninguno de los recién nacidos necesitó marcapasos [(14)]. NE: 4

Pregunta 7- Utilidad de los niveles de Vitamina D:

¿Es de utilidad lograr niveles adecuados de vitamina D para evitar el desarrollo de LN en pacientes con SSp?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome SS-A antibodies OR ro antibodies OR la antibodies OR SS-B antibodies) AND (Neonatal Systemic lupus erythematosus OR neonatal lupus OR Congenital heart block OR congenital heart defect OR congenital complete heart block) AND (VITAMIN D 2 OR VITAMIN D 3 OR vitamin d))

(tw:(“Sjogren's Syndrome” OR Sjogren OR “Sjögren's Syndrome” OR “sjogren syndrome” OR “síndrome de sjogren” OR “SS-A antibodies” OR “ro antibodies” OR “la antibodies” OR “SS-B antibodies”) AND (tw:(“Neonatal Systemic lupus erythematosus” OR “neonatal lupus” OR “lupus neonatal” OR “Congenital heart block” OR “congenital heart defect” OR “congenital complete heart block” OR “bloqueo cardíaco conegénito" OR "lupus neonatal") AND (tw:(“VITAMIN D” 2 OR “VITAMIN D 3” OR “vitamin d” OR “vitamina D”))

Se hallaron 3 artículos, todos fueron eliminados por título.

Pregunta 8- Síndrome Antifosfolipídico en pacientes con SSp:

En pacientes embarazadas con SSp, ¿es necesaria la búsqueda de anticuerpos anti fosfolipídicos (aFL)?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome) AND (antiphospholipid antibody syndromes OR antiphospholipid syndrome OR Antibodies, Antiphospholipid))

(tw:("Sjogren's Syndrome" OR Sjogren OR "Sjögren's Syndrome" OR "sjogren syndrome" OR "síndrome de sjogren" OR "síndrome de Sjögren") AND (tw:("antiphospholipid antibody syndromes" OR "antiphospholipid syndrome" OR "Antibodies, Antiphospholipid" OR "síndrome antifosfolipídico" OR SAF))

Se hallaron 382 artículos, de los cuales 377 fueron eliminados por el título, 4 por abstracts, 1 artículo fue seleccionado.

Cervera y colaboradores publicaron en 1997 un estudio de corte transversal que tuvo como objetivo determinar la prevalencia y la importancia clínica de los aFL en una cohorte de pacientes con SSp. Se evaluaron 87 pacientes de manera prospectiva. Se compararon con los siguientes grupos de pacientes: 50 pacientes con SS asociado con lupus eritematoso sistémico (LES), 100 pacientes con LES sin SS; y 100 donantes de sangre sanos. Sólo 11 (14%) de los pacientes con SSp presentaron anticuerpos anticardiolipinas o anticoagulante lúpico, o ambos en el suero, pero ninguno contra la beta 2-glicoproteína I. En los pacientes con SSp, los aFL estuvieron presentes en un porcentaje menor que en los pacientes con SS secundario a LES o en pacientes con LES sin SS. La presencia de aFL en estos pacientes con SSp no se asoció con eventos clínicos de SAF [(15)]. NE: 4.

Pregunta 9- Suspensión de drogas en pacientes embarazadas con SSp:

¿En pacientes con SSp embarazadas es necesario suspender el uso de pilocarpina para evitar efectos teratógenos?

Se realizó la siguiente búsqueda:

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome) AND (pilocarpine) AND (Teratogenesis OR CONGENITAL ABNORMALITIES OR Abnormalities, Drug-Induced))

(tw:("Sjogren's Syndrome" OR Sjogren OR "Sjögren's Syndrome" OR "sjogren syndrome" OR "síndrome de sjogren" OR "síndrome de Sjögren")) AND (tw:(pilocarpine OR pilocarpina) AND (tw:(Teratogenesis OR "CONGENITAL ABNORMALITIES" OR "Abnormalities, Drug-Induced" OR teratogénesis OR "anormalidades congénitas"))

Se hallaron 2 artículos, ambos fueron eliminados por el título.

Pregunta10-¿En pacientes con SSp embarazadas es necesario suspender el uso de hidroxicloroquina para evitar efectos teratógenos?

((Sjogren's Syndrome OR Sjogren OR Sjögren's Syndrome OR sjogren syndrome) AND (hydroxychloroquine) AND (Teratogenesis OR CONGENITAL ABNORMALITIES OR Abnormalities, Drug-Induced))

(tw:("Sjogren's Syndrome" OR Sjogren OR "Sjögren's Syndrome" OR "sjogren syndrome" OR "síndrome de sjogren" OR "síndrome de Sjögren")) AND (tw:(Teratogenesis OR "CONGENITAL ABNORMALITIES" OR "Abnormalities, Drug-Induced" OR teratogénesis OR "anormalidades congénitas")) AND (tw:(hydroxychloroquine OR HIDROXICLOROQUINA))

Se hallaron 5 artículos, todos eliminados por el título.

Se realizó una nueva búsqueda sin especificar la población de estudio (SSp): (hydroxychloroquine) AND (Teratogenesis OR CONGENITAL ABNORMALITIES OR Abnormalities, Drug-Induced)

(tw:(hydroxychloroquine OR HIDROXICLOROQUINA)) AND (tw:(Teratogenesis OR "CONGENITAL ABNORMALITIES" OR "Abnormalities, Drug-Induced"))

Se hallaron 64 artículos de los cuales 60 fueron eliminados por el título, 2 por el contenido del abstract, quedando 2 artículos seleccionados.

En el primer estudio, publicado por Diav-Citrin y colaboradores en 2013, se evaluó la seguridad de la HCQ durante el embarazo en enfermedades reumatológicas. Consistió en un estudio observacional, de cohorte prospectiva. Se evaluaron114 embarazos de madres expuestas a HCQ que se compararon con 455 embarazos de mujeres no expuestas. La diferencia en la tasa de anomalías congénitas no fue estadísticamente significativa (p = 0,094). El presente estudio sugiere que el tratamiento con HCQ en el embarazo no es un teratógeno [16]. NE: 3

Levy y colaboradores publicaron en 2001 un estudio aleatorizado y controlado para evaluar la seguridad del uso de la HCQ durante el embarazo. Se incluyeron 20 pacientes embarazadas de manera consecutiva. El grupo que recibió HCQ incluyó ocho pacientes con LES y dos con lupus eritematoso discoide. El grupo de placebo incluyó a nueve pacientes con LES. No se encontraron anormalidades congénitas, ni en la evaluación neuro-oftalmológica y auditiva que se realizó a los 1,5 y a los tres años de edad [17]. NE: 3

Bibiliografía:

1. The impact of primary Sjogren's syndrome on pregnancy outcome: our series and review of the literature. De Carolis S et. al. Autoimmun Rev. 2014 Feb;13(2):103-7.
2. Pregnancy and fetal outcome in women with primary Sjogren's syndrome compared with women in the general population: a nested case-control study. Hussein SZ et. al. Rheumatology (Oxford). 2011 Sep;50(9):1612-7.
3. Outcome of pregnancy in patients with autoimmune rheumatic disease before the disease onset. Siamopoulou-Mavridou A et. al. Ann Rheum Dis. 1988 Dec;47(12):982-7.
4. Outcome of pregnancy in Italian patients with primary Sjögren syndrome. Priori R, et. al. J Rheumatol. 2013 Jul;40(7):1143-7
5. Pregnancy outcome in patients with primary Sjögren's syndrome. a case-control study. Haga HJ, et. al. J Rheumatol. 2005 Sep;32(9):1734-6)
6. Obstetric and gynaecological profile in patients with primary Sjögren's syndrome. Skopouli FN, et. al. Ann Rheum Dis. 1994 Sep;53(9):569-73.)
7. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. Friedman DM, et. al. 2008 Jan 29;117(4):485-93.
8. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Izmirly PM, et. al. Circulation. 2012 Jul 3;126 (1):76-82.
9. Failure of intravenous immunoglobulin to prevent congenital heart block: Findings of a multicenter, prospective, observational study. Pisoni CN, et. al. Arthritis Rheum. 2010 Apr;62(4):1147-52.
10. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Friedman DM, et. al. Arthritis Rheum. 2010 Apr;62(4):1138-46.
11. Questions about dexamethasone use for the prevention of anti-SSA related congenital heart block. Costedoat-Chalumeau N, et. al. Ann Rheum Dis. 2003 Oct;62(10):1010-2.
12. Neonatal lupus erythematosus: results of maternal corticosteroid therapy. Shinohara K, et al. Obstet Gynecol. 1999 Jun;93(6):952-7.
13. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the research registry for neonatal lupus. Saleeb S, et.al. Arthritis Rheum. 1999 Nov;42(11):2335-45.
14. The effect of a triple therapy on maternal anti-Ro/SS-A levels associated to fetal cardiac manifestations. Martínez-Sánchez N, et. al. Autoimmun Rev. 2015 May;14(5):423-8.
15. Antiphospholipid antibodies in primary Sjögren's syndrome: prevalence and clinical significance in a series of 80 patients. Cervera R,et. al. Clin Exp Rheumatol. 1997 Jul-Aug;15(4):361-5.

16. Pregnancy outcome following in utero exposure to hydroxychloroquine: a prospective comparative observational study. Diav-Citrin O, et. al. Reprod Toxicol. 2013 Aug;39:58-62.
17. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Levy RA, et. al. Lupus. 2001;10(6):401-4.

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Guidelines

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BSR and BHPR guideline for the treatment of systemic sclerosis

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Key words: scleroderma, systemic sclerosis, management, Raynaud's phenomenon, lung fibrosis, pulmonary hypertension, digital ulcers

Executive Summary

Scope and purpose

SSc is a complex, multi-organ disease that requires a comprehensive multidisciplinary guideline. This is a short summary of the guideline, which is available in full as supplementary material at *Rheumatology* Online. Each recommendation is graded for level of evidence (I-IV) and strength (A-D).

Eligibility and exclusion criteria

Patients are classified as having SSc based on current classification criteria (ACR/EULAR 2013 [1]). Other scleroderma spectrum diseases are not included in this document.

NICE has accredited the process used by the BSR to produce its treatment of systemic sclerosis guidance. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

Part A: general approach to SSc management

Figure 1 summarizes a general approach to management of SSc.

Importance of early diffuse SSc: current priorities and approach

Management of early diffuse cutaneous SSc (dcSSc) should occur within the framework of a multidisciplinary team.

Recommendations in management of early SSc

(i) Early recognition and diagnosis of dcSSc is a priority, with referral to a specialist SSc centre (III, C).

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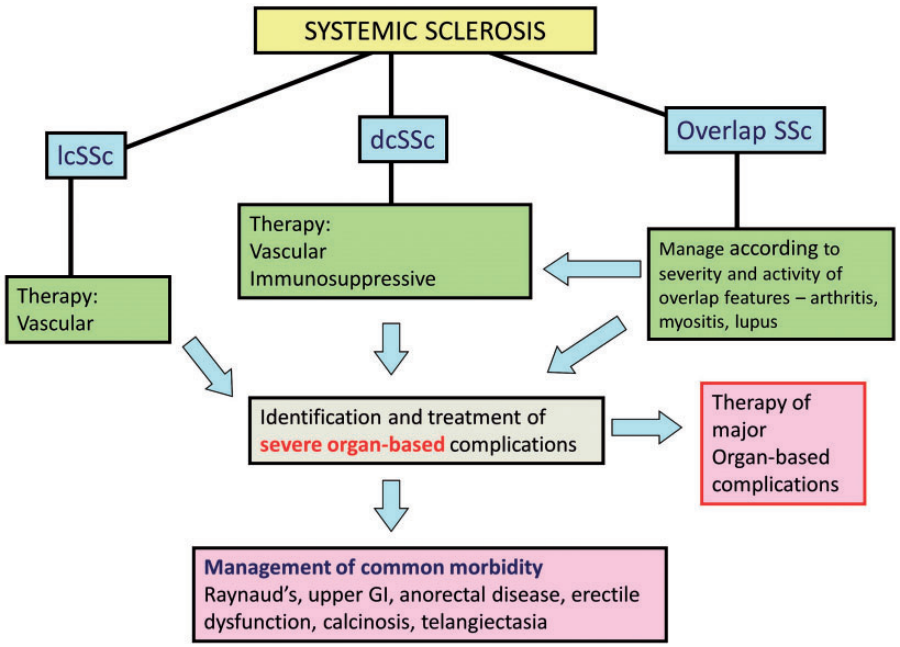
Fig. 1 Overview of management of SSc



The principles of current management of SSc are summarized. Once a confirmed diagnosis is established, all patients can be designated as either lcSSc or dcSSc subset based upon the extent of skin thickening. Proximal skin involvement, involving skin of trunk or proximal limbs, is designated diffuse. Cases with overlap disease should be identified so that overlap features may be treated concurrently with SSc. All patients require symptomatic treatment, and both limited and diffuse cases should be treated for vascular manifestations. Active, early dcSSc requires immunosuppressive treatment. In all cases of SSc, vigilant follow-up to determine significant organ-based complications is mandatory. dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; GI: gastrointestinal.

(ii) Patients with early dcSSc should be offered an immunosuppressive agent: MTX, MMF or i.v. CYC (III/C), although the evidence base is weak. Some patients might later be candidates for autologous haemopoietic stem cell transplant (ASCT; see below).
(iii) D-Pen is not recommended (IIa/C).
(iv) ASCT may be considered in some cases, particularly where there is risk of severe organ involvement, balancing concerns about treatment toxicity (IIa/C).
(v) Skin involvement may be treated with either MTX (II, B) or MMF (III, C). Other options include CYC (III, C), oral steroid therapy (in as low a dose as possible to suppress symptoms, and with close monitoring of renal function; III, C) and possibly rituximab (III, C).
(vi) AZA or MMF should be considered after CYC to maintain improvement in skin sclerosis and/or lung function (III, C).

Part B: key therapies and treatment of organ-based disease

RP and digital ulcers

RP is almost universal and can be treated by vasodilators, but benefit must be balanced against side-effects. Around half of patients with SSc report a history of digital ulceration that reflects more structural vasculopathy. Severe digital ulcers (DUs) are those causing or threatening tissue destruction or when three or more occur in 1 year. These should be considered for advanced therapy, such as sildenafil, iloprost or bosentan [2].

Recommendations for RP in SSc

(i) First-line treatments are calcium channel blockers (Ia, A) and angiotensin II receptor antagonists (Ib, C).
(ii) Other treatments that may be considered are: selective serotonin reuptake inhibitors, α-blockers and statin therapy (III, C).
(iii) Phosphodiesterase type 5 inhibitors are being used increasingly for SSc-related RP (IIa, C).
(iv) Intravenous prostanoid (e.g. iloprost; Ia, B) and digital (palmar) sympathectomy (with or without botulinum toxin injection) should be considered in severe and/or refractory cases (III, D).

Recommendations for DUs in SSc

(i) DUs require integrated management by a multidisciplinary team; management includes local and systemic treatment (III, C).
(ii) Oral vasodilator treatment should be optimized, analgesia optimized and any infection promptly treated (III, C).

(iii) Sildenafil should now be used before considering i.v. prostanoids and bosentan, in line with the current National Health Service (NHS) England Clinical Commissioning policy [3] (I, A).
(iv) In severe active digital ulceration, patients should receive i.v. prostanoid (Ia, B). In patients with recurrent, refractory DUs, a phosphodiesterase type 5 inhibitor (IIa, B) or i.v. prostanoid (Ia, B) and an endothelin receptor antagonist (including bosentan; Ia, B) should be considered.
(v) Digital (palmar) sympathectomy (with or without botulinum toxin injection) may also be considered in severe and/or refractory cases (III, D).

Lung fibrosis

Up to 80% of SSc patients will develop interstitial lung disease, but this may be mild and stable. Immunosuppression should be considered when extensive or progressive disease is confirmed.

Recommendations for lung fibrosis in SSc

(i) All SSc cases should be evaluated for lung fibrosis. Treatment is determined by the extent and severity and the likelihood of progression to severe disease (I, A).
(ii) CYC by i.v. infusion is recommended (I, A/B), and MMF may also be used as an alternative or after CYC (II, B).

Pulmonary arterial hypertension

For patients living in England, treatments are initiated through a designated Pulmonary Hypertension Centre (see NHS England A11/S/a) according to the national commissioning policy for treatment of pulmonary arterial hypertension (PAH; NHS England/A11/P/b and NHS Commissioning Board (NHSCB)/A11/P/a), reflecting expert recommendations [4].

Recommendations for PAH in SSc

(i) Diagnosis should be based upon results of full evaluation of PAH, including right heart catheterization and evaluation of concomitant SSc-related cardiac or lung disease (I, A).
(ii) Therapies licensed for PAH should be used in the UK Pulmonary Hypertension Centres, taking account of the agreed commissioning policies (I, A/B).

Gut disease

Gastro-oesophageal reflux is near universal and needs treatment. Other gastrointestinal (GI) manifestations include constipation, bloating, small intestinal bacterial overgrowth, altered bowel habit and anorectal incontinence (overall management covered elsewhere [5]).

Recommendations for GI manifestations in SSc

The following therapeutic approaches and drugs are considered by experts to be of value in treatment of GI tract complications of SSc.

(i) Proton pump inhibitors and histamine H2 receptor antagonists are recommended for treatment of gastro-oesophageal reflux and dysphagia and may require long-term administration (III, C).
(ii) Prokinetic dopamine agonists may be used for dysphagia and reflux (III, C).
(iii) Parenteral nutrition should be considered for patients with severe weight loss refractory to enteral supplementation (III, C).
(iv) Intermittent broad-spectrum oral antibiotics (e.g. ciprofloxacin) are recommended for intestinal overgrowth, and rotational regimes may be helpful (III, C).
(v) Anti-diarrhoeal agents (e.g. loperamide) or laxatives may be used for symptomatic management of diarrhoea or constipation that often alternate as clinical problems (III, C).

Renal complications

SSc renal crisis (SRC) causes severe hypertension and acute kidney injury and without treatment is often lethal. It affects 5–10% of SSc patients, predominantly the diffuse subset.

Recommendations for treatment of SRC

(i) Patients at risk of SRC should be followed closely and their blood pressure monitored at least weekly (III, C).
(ii) Prompt recognition of SRC and initiation of therapy with an angiotensin-converting enzyme inhibitor offers the best opportunity for a good outcome (III, C).
(iii) Other anti-hypertensive agents may be considered for management of refractory hypertension in conjunction with an angiotensin-converting enzyme inhibitor in SRC (III, C).

Cardiac disease

Clinically evident cardiac involvement includes diastolic or systolic heart failure, arrhythmia and conduction disturbances and has a significant mortality.

Recommendations for treatment of cardiac manifestations of SSc

Although the published evidence base is limited, experts have recommended the following treatment approach for cardiac complications of SSc.

Systolic heart failure

(i) Consider immunosuppression with or without a pacemaker (IV, D).
(ii) Consider the potential benefit of an implantable cardioverter defibrillator (III, D).
(iii) Angiotensin-converting enzyme inhibitors and carvedilol. Selective β-blockers may be considered, but consider aggravation of RP (IV, D).

Diastolic heart failure with preserved left ventricular ejection fraction

(i) Diuretics, including spironolactone and furosemide (IV, D).

(ii) Calcium channel blockers have been shown to reduce the frequency of systolic heart failure in SSc with investigational evidence of cardiac abnormalities (III, D).

Skin manifestations

Treatment of skin thickening, assessed by modified Rodnan skin score, is central to management of dcSSc treatment, and pruritus is common and troublesome in early stage disease.

Recommendations for skin manifestations in SSc

(i) Practical approaches to ensure adequately moisturized skin are essential, especially moisturizers that are lanolin based (III, C).
(ii) Antihistamines are often used for itch (III, C).
(iii) Current treatment options for telangiectasia include skin camouflage and laser or intense pulsed light therapy (III, C).

Calcinosis in SSc

There is a very limited evidence base (mainly case reports and small series) to guide clinicians on the management of calcinosis in patients with SSc.

Recommendations for treatment of calcinosis in SSc

(i) Calcinosis complicated by infection should be recognized early and treated with appropriate antibiotic therapy (III, D).
(ii) Surgical intervention should be considered for severe, refractory calcinosis, which is severely impacting upon functional ability and quality of life (III, D).

Musculoskeletal manifestations

Musculoskeletal involvement includes tendinopathy, joint contractures and, in some cases, overlap arthritis.

Recommendations for musculoskeletal manifestations in SSc

(i) Musculoskeletal manifestations of SSc may benefit from immunomodulatory treatments given for other complications, such as skin disease (III, C).
(ii) When arthritis or myositis is more severe, generally in the context of an overlap SSc syndrome, management is in line with similar clinical conditions occurring outside the context of SSc (III, C).

ASCT as a treatment for poor prognosis early dcSSc

Haematopoietic stem cell transplant registry data, several case reports and pilot studies in the USA and Europe in dcSSc demonstrated a rapid clinical improvement, but with important treatment-related mortality [6].

Recommendation for ASCT in SSc

(i) Current evidence supports use of ASCT in poor-prognosis diffuse SSc where patients do not have severe internal organ manifestations that render this treatment option highly toxic (Ib, B).

Non-drug interventions

Although the evidence base is limited, non-drug interventions may have merit and are well tolerated.

Recommendation for non-drug interventions in SSc

(i) Specialist experience of SSc cases is likely to make non-drug interventions more effective, and these approaches are popular with patients and can be expected to impact positively on the disease. More research is needed in this area (III, D).

Part C: service organization and delivery within NHS England

SSc should be diagnosed promptly, investigated appropriately and managed within an integrated system of primary, secondary and tertiary level care.

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Supplementary data

The full guideline is available as supplementary data at *Rheumatology* Online.

References

1 van den Hoogen F, Khanna D, Fransen J *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.

2 Hughes M, Ong VH, Anderson ME *et al*. Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis. Rheumatology 2015;54:2015–24. PubMed PMID: 26116156.

3 Engage.england.nhs.uk. Specialised Services - Policy and Specification Consultation - NHS England - Citizen Space [Internet]. https://www.engage.england.nhs.uk/consultation/specialised-services-policies/user_uploads/bosntn-sildnfl-syst-sclerosis-pol.pdf. Accessed 2 March 2016.

4 Galiè N, Humbert M, Vachiery JL *et al*. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119. PubMed PMID: 26320113.

5 Hansi N, Thoua N, Carulli M *et al*. Consensus best practice pathway of the UK scleroderma study group: gastrointestinal manifestations of systemic sclerosis. Clin Exp Rheumatol 2014;32 (6 Suppl 86): S214–21.

6 van Laar JM, Farge D, Sont JK *et al*. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA 2014;311:2490–8.

NICE National Institute for Health and Care Excellence

NICE quality standard

Low back pain and sciatica in over 16s

Quality standard

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Contents

This standard is based on NG59.

This standard should be read in conjunction with NG12, CG75, NG41 and NG65.

Quality statements

Statement 1 Primary care services have an approach to risk stratification for young people and adults presenting with a new episode of low back pain with or without sciatica.

Statement 2 Young people and adults with low back pain with or without sciatica do not have imaging requested by a non-specialist service unless serious underlying pathology is suspected.

Statement 3 Young people and adults with low back pain with or without sciatica are given advice and information to self-manage their condition.

Statement 4 Young people and adults are not given paracetamol alone, anticonvulsants or antidepressants to treat low back pain without sciatica.

Statement 5 Young people and adults are not given opioids to treat chronic low back pain without sciatica.

Statement 6 Young people and adults do not have spinal injections for low back pain without sciatica with the exception of radiofrequency denervation for people who meet the criteria.

NICE has developed guidance and a quality standard on patient experience in adult NHS services (see the NICE pathway on patient experience in adult NHS services), which should be considered alongside these quality statements.

A full list of NICE quality standards is available from the quality standards topic library.

Quality statement 1: Risk stratification

Quality statement

Primary care services have an approach to risk stratification for young people and adults presenting with a new episode of low back pain with or without sciatica.

Rationale

Risk stratification can be used to identify a person's risk of poor functional outcome or long-term problems from low back pain with or without sciatica. Risk stratification tools can help to determine the complexity and intensity of support that a person may need.

Quality measures

Structure

Evidence of a locally defined approach to risk stratification and of systems in place to make staff aware of the approach.

Data source: Local data collection, for example, service specifications and written communications to staff.

What the quality statement means for different audiences

Service providers (primary care services) have an approach to risk stratification that they communicate to staff who undertake consultations for young people and adults presenting with a new episode of low back pain with or without sciatica. This can help support decisions about whether risk stratification is used with individual patients and, if so, which risk stratification tool is selected.

Healthcare professionals (such as GPs and nurses) are aware of their service's approach to risk stratification for use at the first consultation with young people and adults presenting with low back pain with or without sciatica. This can determine whether risk stratification is used and, if so, which risk stratification tool is selected.

Commissioners (such as clinical commissioning groups and NHS England) ensure that the services they commission have an approach to risk stratification for people presenting with a new episode

of low back pain with or without sciatica and systems in place to make staff aware of their local approach.

Young people and adults presenting with a new episode oflow back pain with or without sciatica are assessed in a way that is consistent with a local approach to risk stratification. Their treatment and support is then chosen in line with the results of the assessment.

Source guidance

Low back pain and sciatica in over 16s (2016) NICE guideline NG59, recommendation 1.1.2.

Definition of terms used in this quality statement

Risk stratification

Stratification aims to improve the outcome by selecting treatments that may be more likely to work in certain groups of people. There are several methods of stratification which are all similar in outcome. The STarT Back risk assessment tool is an example of a validated tool for stratification by risk of ongoing functional impairment.

[Adapted from NICE's guideline on low back pain and sciatica in over 16s, recommendation 1.1.2 with expert opinion]

Quality statement 2: Referrals for imaging

Quality statement

Young people and adults with low back pain with or without sciatica do not have imaging requested by a non-specialist service unless serious underlying pathology is suspected.

Rationale

Imaging does not often change the initial management and outcomes of someone with back pain. This is because the reported imaging findings are usually common and not necessarily related to the person's symptoms. Many of the imaging findings (for example, disc and joint degeneration) are frequently found in asymptomatic people. Requests for imaging by non-specialist clinicians, where there is no suspicion of serious underlying pathology, can cause unnecessary distress and lead to further referrals for findings that are not clinically relevant.

Quality measures

Structure

a) Evidence of local arrangements for young people and adults with low back pain with or without sciatica to be referred for specialist opinion.

Data source: Local data collection, for example, service protocols.

b) Evidence of local protocols outlining serious underlying pathology in relation to presentations of low back pain with or without sciatica.

Data source: Local data collection, for example, service protocols.

Process

Proportion of young people and adults with low back pain with or without sciatica who have imaging requested by a non-specialist service when no serious underlying pathology is suspected.

Numerator – the number in the denominator who have imaging requested by a non-specialist service.

Denominator – the number of young people and adults with low back pain with or without sciatica for whom there is no suspicion of serious underlying pathology.

Data source: Local data collection, for example, patient notes.

What the quality statement means for different audiences

Service providers (non-specialist services) ensure that staff are aware of and use local referral pathways to specialist services and do not request imaging for young people and adults with low back pain with or without sciatica unless serious underlying pathology is suspected.

Healthcare professionals (such as GPs and nurses) do not request imaging within a non-specialist service for young people and adults with low back pain with or without sciatica unless serious underlying pathology is suspected. Healthcare professionals should explain to young people and adults who are referred for a specialist opinion that they may not need imaging.

Commissioners (such as clinical commissioning groups and NHS England) ensure that they commission specialist services with clinicians who have the expertise to make a decision about whether young people and adults with low back pain with or without sciatica should have imaging and that these services accept referrals from non-specialist services.

Young people and adults withlow back pain with or without sciatica do not have imaging requested by a non-specialist service (such as a GP practice) unless serious underlying disease is suspected.

Source guidance

Low back pain and sciatica in over 16s (2016) NICE guideline NG59, recommendations 1.1.1 and 1.1.4.

Definitions of terms used in this quality statement

Non-specialist service

Services such as a GP practice in primary care.

[Expert opinion]

Serious underlying pathology

Example of serious underlying pathology include but are not limited to: cancer, infection, trauma or inflammatory disease such as spondyloarthritis. If serious underlying pathology is suspected, refer to relevant NICE guidance on:

- metastatic spinal cord compression in adults
- spinal injury
- spondyloarthritis in over 16s
- suspected cancer.

[Adapted from NICE's guideline on low back pain and sciatica in over 16s, recommendation 1.1.1]

Quality statement 3: Self-management

Quality statement

Young people and adults with low back pain with or without sciatica are given advice and information to self-manage their condition.

Rationale

Low back pain and sciatica are common and recurrent conditions that can be long term. It is therefore important that the person learns how to manage their symptoms to reduce their pain and distress and improve their functioning and quality of life. Healthcare professionals can support the person's ability to self-manage their condition by giving reassuring advice about the benign nature of the condition, the high probability of a rapid improvement in symptoms and the importance of early return to normal life activities. These include returning to work where applicable, physical activity and exercise.

Quality measures

Structure

Evidence of local arrangements to ensure that staff have access to information and the knowledge needed to signpost to other services for young people and adults with low back pain with or without sciatica.

Data source: Local data collection, for example, service protocols.

Process

Proportion of young people and adults with low back pain with or without sciatica who are given advice and information to self-manage their condition.

Numerator – the number in the denominator who are given advice and information to self-manage their condition.

Denominator – the number of young people and adults with low back pain with or without sciatica.

Data source: Local data collection, for example, audit of patient notes.

Outcome

a) Number of repeat GP appointments for young people and adults with low back pain with or without sciatica.

*Data source:*Local data collection, for example, audit of patient notes.

b) Levels of satisfaction amongst young people and adults with the management of their low back pain with or without sciatica.

*Data source:*National Pain Audit 2012 and local data collection.

What the quality statement means for different audiences

Service providers (such as GP practices) ensure that staff have the knowledge and information needed to support young people and adults with low back pain with or without sciatica to self-manage their condition. This can include having the expertise to give verbal information, providing leaflets or giving information about access to exercise schemes such as walking support groups.

Healthcare professionals (such as GPs, nurses and physiotherapists) advise and provide information to young people and adults with low back pain with or without sciatica to help them self-manage their condition. This can include verbal information provided by a healthcare professional, leaflets, or information about access to exercise schemes such as walking support groups.

Commissioners (such as clinical commissioning groups and NHS England) ensure that the services they commission employ healthcare professionals with the expertise to give verbal information, provide leaflets or give information about access to exercise schemes such as walking support groups for young people and adults with low back pain with or without sciatica to self-manage their condition.

Young people and adults withlow back pain with or without sciatica are given advice and information to manage their condition themselves. The information can cover the importance of continuing with normal activities and, where applicable, returning to work and access to exercise schemes such as walking support groups.

Source guidance

Low back pain and sciatica in over 16s (2016) NICE guideline NG59, recommendation 1.2.1.

Definition of terms used in this quality statement

Advice and information to self-manage their condition

People are provided with advice and information, tailored to their needs and capabilities, to help them self-manage their low back pain with or without sciatica, at all steps of the treatment pathway. It includes:

- information on the nature of low back pain and sciatica
- encouragement to continue with normal activities and access to exercise schemes.

[Adapted from NICE's guideline on low back pain and sciatica in over 16s, recommendation 1.2.1 with expert opinion]

Quality statement 4: Anticonvulsants, antidepressants and paracetamol for low back pain without sciatica

Quality statement

Young people and adults are not given paracetamol alone, anticonvulsants or antidepressants to treat low back pain without sciatica.

Rationale

The use of medicines without a significant clinical benefit in managing low back pain with or without sciatica can lead to unnecessary side effects for the person, risk of dependency and inappropriate use of resources.

Quality measures

Structure

Evidence of local arrangements to ensure that no GP prescriptions include paracetamol alone, anticonvulsants or antidepressants to treat young people and adults with low back pain without sciatica unless the young person or adult has other indications for those medicines.

Data source: Local data collection, for example, service protocols.

Process

a) Proportion of young people and adults with low back pain without sciatica, who are given anticonvulsants and have no other indications for them.

Numerator – the number in the denominator who are given anticonvulsants.

Denominator – the number of young people and adults with low back pain without sciatica and no other indications for anticonvulsants.

Data source: Local data collection, for example, GP prescribing audits.

b) Proportion of young people and adults with low back pain without sciatica, who are given antidepressants and have no other indications for them.

Numerator – the number in the denominator who are given antidepressants.

Denominator – the number of young people and adults with low back pain without sciatica and no other indications for antidepressants.

Data source: Local data collection, for example, GP prescribing audits.

c) Proportion of young people and adults with low back pain without sciatica, who are given paracetamol alone and have no other indications for it.

Numerator – the number in the denominator who are given paracetamol alone.

Denominator – the number of young people and adults with low back pain without sciatica and no other indications for paracetamol.

Data source: Local data collection, for example, GP prescribing audits.

Outcome

Number of medicines-related adverse events for young people and adults with low back pain without sciatica.

*Data source:*Local data collection, for example, GP prescribing audits.

What the quality statement means for different audiences

Service providers (such as GP practices) have systems in place to make staff aware that they should not give paracetamol alone, anticonvulsants or antidepressants to treat low back pain without sciatica. Young people and adults should only be given these medicines if they have other indications for them.

Healthcare professionals (such as GPs and nurses) do not treat low back pain without sciatica with paracetamol alone, anticonvulsants or antidepressants. They should only offer these medicines if there are other indications for them.

Commissioners (such as clinical commissioning groups and NHS England) ensure that they have agreed service specifications which state that services do not treat low back pain without sciatica with paracetamol alone, anticonvulsants or antidepressants.

Young people and adults withlow back painwithout sciatica are not given paracetamol alone, anticonvulsants or antidepressants unless they need them for other conditions. This is because these medicines are not effective in either easing back pain or restoring function such as walking and doing daily tasks.

Source guidance

Low back pain and sciatica in over 16s (2016) NICE guideline NG59, recommendations 1.2.21 and 1.2.24–25.

Quality statement 5: Opioids for chronic low back pain without sciatica

Quality statement

Young people and adults are not given opioids to treat chronic low back pain without sciatica.

Rationale

The use of opioids does not have a significant clinical benefit in the management of chronic low back pain without sciatica. It can therefore lead to unnecessary side effects for the person, risk of dependency and inappropriate use of resources.

Quality measures

Structure

Evidence of local arrangements to ensure that no GP prescriptions include opioids to treat young people and adults with chronic low back pain without sciatica unless they have other indications for those medicines.

Data source: Local data collection, for example, service protocols.

Process

Proportion of young people and adults who are given opioids to treat chronic low back pain without sciatica and have no other indications for them.

Numerator – the number in the denominator who are given opioids.

Denominator – the number of young people and adults with chronic low back pain without sciatica and no other indications for opioids.

Data source: Local data collection, for example, GP prescribing audits.

Outcome

Number of opioids-related adverse events for young people and adults with chronic low back pain without sciatica.

Data source:Local data collection, for example, GP prescribing audits.

What the quality statement means for different audiences

Service providers (such as GP practices) have systems in place to make staff aware that they should not give opioids to treat chronic low back pain without sciatica. Young people and adults should only be offered opioids when there are other indications for those medicines.

Healthcare professionals (such as GPs and nurses) do not give opioids to young people and adults to treat chronic low back pain without sciatica. They should only offer opioids when there are other indications for those medicines.

Commissioners (such as clinical commissioning groups and NHS England) ensure that they have agreed service specifications which state that services do not treat chronic low back pain without sciatica using opioids.

Young people and adults withlow back painwithout sciatica are not given opioids to treat their condition unless they need them for other conditions. This is because these medicines are not effective in either easing pain or restoring function such as walking and doing daily tasks.

Source guidance

Low back pain and sciatica in over 16s (2016) NICE guideline NG59, recommendation 1.2.23.

Definition of terms used in this quality statement

Chronic low back pain

Having symptoms for more than 3 months.

[Adapted from NICE's full guideline on low back pain and sciatica in over 16s]

Quality statement 6: Spinal injections

Quality statement

Young people and adults do not have spinal injections for low back pain without sciatica with the exception of radiofrequency denervation for people who meet the criteria.

Rationale

Spinal injections for treating low back pain without sciatica are not clinically or cost effective, except for people who meet the criteria for a procedure called 'radiofrequency denervation'. To determine whether these people will benefit from this procedure, they may be offered a diagnostic block of the nerves that supply the joints between the vertebrae. If they experience significant pain relief they may then be offered radiofrequency denervation in an attempt to achieve longer-term relief.

Quality measures

Structure

Evidence of local arrangements to ensure that spinal injections are not given to young people and adults to treat low back pain without sciatica, with the exception of radiofrequency denervation for people who meet the criteria.

Data source: Local data collection, for example, service protocols.

Process

Proportion of young people and adults who have spinal injections for low back pain without sciatica who meet the criteria for radiofrequency denervation.

Numerator – the number in the denominator who meet the criteria for radiofrequency denervation.

Denominator – the number of young people and adults who have spinal injections for low back pain without sciatica.

Data source: Local data collection, for example, patient notes.

What the quality statement means for different audiences

Service providers (such as hospitals) have systems in place to make staff aware that spinal injections for low back pain without sciatica should not be performed, with the exception of radiofrequency denervation for people who meet the criteria.

Healthcare professionals (such as physicians, surgeons and radiologists) do not give young people and adults spinal injections for low back pain without sciatica, with the exception of radiofrequency denervation for people who meet the criteria.

Commissioners (such as clinical commissioning groups and NHS England) specify in contracts that services that treat young people and adults with low back pain without sciatica do not perform spinal injections, with the exception of radiofrequency denervation for people who meet the criteria.

Young people and adults withlow back painwithout sciatica do not have spinal injections with the exception of the procedure of 'radiofrequency denervation' for people who meet the criteria. To check whether the procedure is suitable for the person, an anaesthetic is injected to temporarily block some of the nerves in the spine. If the pain is significantly reduced, the nerves are permanently sealed off using heat (radiofrequency ablation). This stops them from transmitting pain signals.

Source guidance

Low back pain and sciatica in over 16s (2016) NICE guideline NG59, recommendations 1.3.1, 1.3.2 and 1.3.3.

Definitions of terms used in this quality statement

Spinal injections

These are injected agents which aim to either reduce inflammation in tissues (for example, steroid injections), induce inflammation to stimulate healthy tissue regrowth (for example, prolotherapy) or reduce firing of nerve fibres that may be contributing to pain (for example, local anaesthetic). However, medial branch block injections can be used as a diagnostic tool to establish whether the person is likely to respond to radiofrequency denervation.

[Adapted from NICE's guideline on Low back pain and sciatica in over 16s with expert opinion]

Radiofrequency denervation

The procedure called 'radiofrequency denervation' involves sealing off some of the nerves to the joints of the spine to stop the nerves transmitting pain signals. It aims to achieve longer-term pain relief in people with low back pain who experience significant but short-term relief after a diagnostic block by injection of local anaesthetic.

[Adapted from NICE's guideline on Low back pain and sciatica in over 16s with expert opinion]

Criteria

Referral for assessment for radiofrequency denervation for people with chronic low back pain should be considered using the following criteria:

- non-surgical treatment has not worked for them **and**
- the main source of pain is thought to come from structures supplied by the medial branch nerve **and**
- they have moderate or severe levels of localised back pain (rated as 5 or more on a visual analogue scale, or equivalent) at the time of referral.

Only perform radiofrequency denervation in people with chronic low back pain after a positive response to a diagnostic medial branch block.

[Adapted from NICE's guideline on low back pain and sciatica in over 16s, recommendations 1.3.2 and 1.3.3 with expert opinion]

About this quality standard

NICE quality standards describe high-priority areas for quality improvement in a defined care or service area. Each standard consists of a prioritised set of specific, concise and measurable statements. NICE quality standards draw on existing NICE or NICE-accredited guidance that provides an underpinning, comprehensive set of recommendations, and are designed to support the measurement of improvement.

Expected levels of achievement for quality measures are not specified. Quality standards are intended to drive up the quality of care, and so achievement levels of 100% should be aspired to (or 0% if the quality statement states that something should not be done). However, this may not always be appropriate in practice. Taking account of safety, shared decision making, choice, and professional judgement, desired levels of achievement should be defined locally.

Information about how NICE quality standards are developed is available from the NICE website.

See quality standard advisory committees on the website for details of standing committee 4 members who advised on this quality standard. Information about the topic experts invited to join the standing members is available on the quality standard's webpage.

This quality standard has been incorporated into the NICE pathway on Low back pain and sciatica in over 16s.

NICE has produced a quality standard service improvement template to help providers make an initial assessment of their service compared with a selection of quality statements. This tool is updated monthly to include new quality standards.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Improving outcomes

This quality standard is expected to contribute to improvements in the following outcomes:

- functional improvement
- avoidance of harm
- return to work.

It is also expected to support delivery of the Department of Health's outcome frameworks:

- Adult social care outcomes framework 2015–16
- NHS outcomes framework 2016–17
- Public health outcomes framework for England, 2016–19.

Resource impact

NICE quality standards should be achievable by local services. The potential resource impact is considered by the quality standards advisory committee, drawing on resource impact work for the source guidance.

Diversity, equality and language

During the development of this quality standard, equality issues were considered and equality assessments are available. Any specific issues identified during development of the quality statements are highlighted in each statement.

Commissioners and providers should aim to achieve the quality standard in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this quality standard should be interpreted in a way that would be inconsistent with compliance with those duties.

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Endorsing organisation

This quality standard has been endorsed by NHS England, as required by the Health and Social Care Act (2012)

Supporting organisation

Many organisations share NICE's commitment to quality improvement using evidence-based guidance. The following supporting organisations have recognised the benefit of the quality standard in improving care for patients, carers, service users and members of the public. They have agreed to work with NICE to ensure that those commissioning or providing services are made aware of and encouraged to use the quality standard.

- Public Health England

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SPECIAL ARTICLE

2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

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Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions. These recommendations cannot adequately convey all uncertainties and nuances of patient care.

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Dr. Cannon has received honoraria from Takeda (less than $10,000). Dr. Hansen has received research grants from Takeda and Merck Sharpe & Dohme. Dr. Lane has received consulting fees from Merck (less than $10,000) and has served as an expert witness on behalf of Novartis. Dr. Saha has received consulting fees from UCB Biosciences (more than $10,000). Dr. McAlindon has received consulting fees from Pfizer (less than $10,000).

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Objective. **To develop recommendations for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP).**

Methods. **We conducted a systematic review to synthesize the evidence for the benefits and harms of GIOP prevention and treatment options. The Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of evidence. We used a group consensus process to determine the final recommendations and grade their strength. The guideline addresses initial assessment and reassessment in patients beginning or continuing long-term (≥3 months) glucocorticoid (GC) treatment, as well as the relative benefits and harms of lifestyle modification and of calcium, vitamin D, bisphosphonate, raloxifene, teriparatide, and denosumab treatment in the general adult population receiving long-term GC treatment, as well as in special populations of long-term GC users.**

Results. **Because of limited evidence regarding the benefits and harms of interventions in GC users, most recommendations in this guideline are conditional (uncertain balance between benefits and harms). Recommendations include treating only with calcium and vitamin D in adults at low fracture risk, treating with calcium and vitamin D plus an additional osteoporosis medication (oral bisphosphonate preferred) in adults at moderate-to-high fracture risk, continuing calcium plus vitamin D but switching from an oral bisphosphonate to another antifracture medication in adults in whom oral bisphosphonate treatment is not appropriate, and continuing oral bisphosphonate treatment or switching to another antifracture medication in adults who complete a planned oral bisphosphonate regimen but continue to receive GC treatment. Recommendations for special populations, including children, people with organ transplants, women of childbearing potential, and people receiving very high-dose GC treatment, are also made.**

Conclusion. **This guideline provides direction for clinicians and patients making treatment decisions. Clinicians and patients should use a shared decision-making process that accounts for patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.**

INTRODUCTION

Glucocorticoids (GCs) play an important role in the treatment of many inflammatory conditions. It is estimated that 1% of the US population is treated long-term with GCs (1). However, GC use causes significant toxicity, including bone loss and fractures (2,3). More than 10% of patients who receive long-term GC treatment are diagnosed with a fracture, and 30–40% have radiographic evidence of vertebral fractures (4,5). The highest rate of bone loss occurs within the first 3–6 months of GC treatment, and a slower decline continues with persistent use (6). Both high daily and high cumulative GC doses increase risk of fracture, particularly vertebral fracture, due to the greater effects of GCs on trabecular bone than on cortical bone. Risk factors for GC-induced fracture include low bone strength at the beginning of GC treatment and the rate of decline in bone mass during treatment, which is largely determined by the dose and duration of GC use. In children, GC treatment also affects bone strength, growth, and total adult skeletal mass, with a similar profile of risk factors (7–10).

However, GC treatment is a potentially reversible risk factor for glucocorticoid-induced osteoporosis (GIOP); if GC treatment is terminated, bone mineral density (BMD) increases and fracture risk declines (6,11,12). In addition, the absolute risk of future fracture in an individual is substantially influenced by demographic and other characteristics (age, race, sex, and concomitant OP risk factors). For these reasons, it is important to identify those patients taking GCs for whom the benefits of preventive therapy sufficiently outweigh potential harms.

Numerous risk calculators can be applied in clinical practice to provide estimates of risk of major OP fracture and hip fracture clinically diagnosed, with adjustment for GC dose in some but not all calculators (13–15). Most stratify GC use into 2 categories: low (prednisone ≤7.5 mg/day) or high (>7.5 mg/day), based on data from clinical trials and epidemiologic studies (15,16) demonstrating increasing fracture risk with higher daily doses. However, these calculators may underestimate the fracture risk in patients with prolonged treatment with very high doses of GCs for conditions such as giant cell arteritis, vasculitis, lupus, and dermatomyositis (16,17). Van Staa et al reported a marked increase in relative risk of vertebral and hip fractures in patients who had received treatment with prednisolone ≥30 mg/day with a cumulative dose of >5 gm (15).

There are insufficient data to develop individual prediction tools for children and for adults <40 years of age. Nevertheless, observational data indicate a substantial risk of clinically diagnosed vertebral fracture among premenopausal women ≥30 years of age receiving very high doses of GCs (10-year risk 5–20%) (18–25).

Despite increasing information about risk factors for fracture in GC users and the availability of effective therapies to prevent fracture, many long-term GC users never receive therapy to prevent bone loss or are treated

only after a fracture has occurred (26,27). The American College of Rheumatology (ACR) identified GIOP as an important public health issue and first published recommendations for its prevention and treatment in 1996 (28). The ACR updated these guidelines in 2001 and 2010, as new techniques for assessing fracture risk and new information about risk factors and therapies became available (28–30). The present ACR guideline outlines the treatment recommendations for GIOP. The guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (see below) and included therapies for the treatment of OP approved by the US Food and Drug Administration before 2015. No other therapies have been approved as of the time of publication of these guidelines.

METHODS

Methodology overview. We developed this guideline according to the ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes the GRADE methodology (www.gradeworkinggroup.org) (31–33). Conflicts of interest and disclosures were determined and managed according to ACR policy (https://www.rheumatology.org/Portals/0/Files/GIOP-Guidelines-Disclosure-Summary.pdf). The full methods are described in detail in Supplementary Appendix 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). This work involved 4 teams: 1) a Core Leadership Team (4 members), which supervised and coordinated the project and drafted the clinical questions and manuscript; 2) a Literature Review Team, which completed the literature search and abstraction; 3) an Expert Panel, which developed the clinical questions (PICO [population/intervention/comparator/outcomes] questions) and the scope of the guideline project; and 4) a Voting Panel, which included adult and pediatric rheumatologists, internists, a nephrologist, a pulmonologist, a gastroenterologist, medical specialists with clinical expertise in treating GIOP, and a patient who provided input from the patient perspective and voted on the recommendations. Rosters of the team and panel members are shown in Supplementary Appendix 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract).

Framework for the GIOP guideline development. The Panel ranked fracture (hip, vertebral, nonvertebral) as the *critically important outcome measure* for treatment evaluation. *Important outcome measures* included adverse effects of treatments, in particular the incidence of serious and total adverse events (see Supplementary Appendix 3 [http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract] for a list of adverse events).

At the initial meeting, the Voting Panel and Expert Panel agreed that the scope of the project should be the assessment, prevention, and treatment of OP and fractures in children and adults taking glucocorticoids (prednisone at >2.5 mg/day for ≥3 months), including patients with organ transplants, women of childbearing potential, and people receiving very high-dose GCs. Treatment of people using inhaled GCs and those with a glomerular filtration rate of <30 ml/minute were not addressed in these guidelines.

Adult men and women were divided into 2 groups based on age (≥40 years or <40 years). After population risk groups were defined, interventions and comparators for each clinical scenario were specified using a PICO question (see list of PICO questions in Supplementary Appendix 3). PICO questions included assessment and reassessment of fracture risks, treatment comparisons, and questions about duration and reassessment of treatment. When it was necessary to use BMD to support a recommendation (which was the case in only 4 PICO questions, all addressing pediatric patients with GIOP), the Voting Panel downgraded the quality of evidence for indirectness, since BMD provides only indirect evidence of the impact on fracture.

Systematic synthesis of the literature. We performed systematic searches of the published English-language literature including OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the beginning of each database through October 6, 2015 (Supplementary Appendix 4, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract), and update searches were conducted on April 23, 2016. We performed duplicate screening of literature search results using DistillerSR software (https://distillercer.com/products/distillersr-systematic-review-software/) (Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). Data were extracted into RevMan software (http://tech.cochrane.org/revman), and the quality of each study was evaluated using the Cochrane risk of bias tool (http://handbook.cochrane.org/). We exported RevMan files into GRADEpro software to formulate a GRADE summary of findings table (Supplementary Appendix 3) for each PICO question (34). The overall quality of evidence was evaluated using GRADE quality assessment criteria (31).

In clinical scenarios not addressed by data from randomized clinical trials, data from observational cohort studies were used to estimate relative effects. In situations in which the question had not been tested in a sample of patients taking GCs but had been tested in a non-GIOP population, we applied the relative risk values from that study, making the assumption that the effect was generalizable, but we downgraded the quality of evidence for indirectness.

We projected absolute risk reduction within each risk stratum according to hypothetical baseline fracture risk ranging from 1% to 20%. The following cut points were used to stratify levels of risk: <5% incidence of vertebral fractures over 5 years, between 5% and <10%, and ≥10%. The Voting Panel then made recommendations based on absolute fracture reduction with treatment in each of these strata. We focused on vertebral fracture rates because this outcome was more consistently reported in the literature and because of the greater effects of GCs on trabecular bone.

Moving from evidence to recommendations. GRADE methodology specifies that panels make recommendations based on the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences. Key to the recommendation is the

Table 1. Fracture risk categories in GC-treated patients

	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤−2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥20% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z score <−3 **or** rapid bone loss (≥10% at the hip or spine over 1 year) **and** Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ <10% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment

* https//www.shef.ac.uk/FRAX/tool.jsp.
† Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is >7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
‡ Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus.

tradeoff between desirable and undesirable outcomes and cost; recommendations require estimating the relative value patients place on the outcomes. We are unaware of published literature exploring patient values and preferences regarding these issues. Our judgments were based on the experience of the Panel members (which included a patient) in shared decision-making with their patients. Below we outline the Voting Panel's assessment of these tradeoffs that informed the final recommendations.

Consensus building. The Voting Panel voted on the direction and strength of the recommendation related to each PICO question. An 80% level of agreement was used as the threshold for a recommendation; if 80% agreement was not achieved during an initial vote, the Panel members held additional discussions before re-voting. Consistent with GRADE guidance, in some instances the Voting Panel chose to provide a strong recommendation despite a low quality rating of evidence (33). In such cases, a written explanation is provided, describing the reasons for this decision.

Moving from recommendations to practice. When applying these risk-stratified recommendations in clinical settings, adults ≥40 years of age receiving long-term GCs should be designated as being at moderate-to-high risk or low risk of fracture (Table 1) based on BMD, history of fracture, and 10-year risk of major OP fracture and hip fracture calculated using a tool that combines risk factors with GC dose. Although many tools that incorporate GC use are available, the Voting Panel suggested using FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) for fracture risk assessment. When GC use is included as a risk factor in FRAX, the fracture risk generated is the risk associated with a prednisolone dose of 2.5–7.5 mg/day (prednisolone and prednisone doses are nearly equivalent). For people receiving doses of >7.5 mg/day, the fracture risk generated with FRAX should be increased by a relative 15% for major osteoporotic fracture and 20% for hip fracture risk (13). For example, if the 10-year hip fracture risk is 2.0% with GC use entered in FRAX, the risk estimate should be increased to 2.4% if the prednisone dose is >7.5 mg.

There are no tools available to estimate absolute fracture risk in children or in adults <40 years of age. These groups were considered to be at high fracture risk if they have previously sustained an OP fracture. The Voting Panel designated men and women <40 years of age to be at moderate risk if they were expected to continue GC treatment at >7.5 mg/day for 6 months and had either 1) a hip or spine BMD Z score of <−3 or 2) a rapid decline in hip or spine BMD (equivalent to ≥10% in 1 year) during GC treatment.

RESULTS/RECOMMENDATIONS

How to interpret the recommendations

1. The Voting Panel's assessment was that patients would be willing to take calcium and vitamin D with only a very small absolute risk reduction, that all or virtually all would be willing to take bisphosphonates to achieve a 5-year absolute reduction in vertebral fracture risk of 5%, and that most would choose to take oral bisphosphonates if the fracture

reduction were ≥3% to <5% (leading to a conditional recommendation in favor). The 5-year time period was chosen because few clinical trials have data on fracture risk reduction past 3–5 years. Further, the Panel members thought that most patients would decline oral bisphosphonates with an absolute reduction in 5-year risk of vertebral fractures of 1.6–2.9% (leading to a conditional recommendation against), and all or virtually all would decline if the risk reduction were <1.5% (leading, in the presence of high- or moderate-quality evidence, to a strong recommendation against).

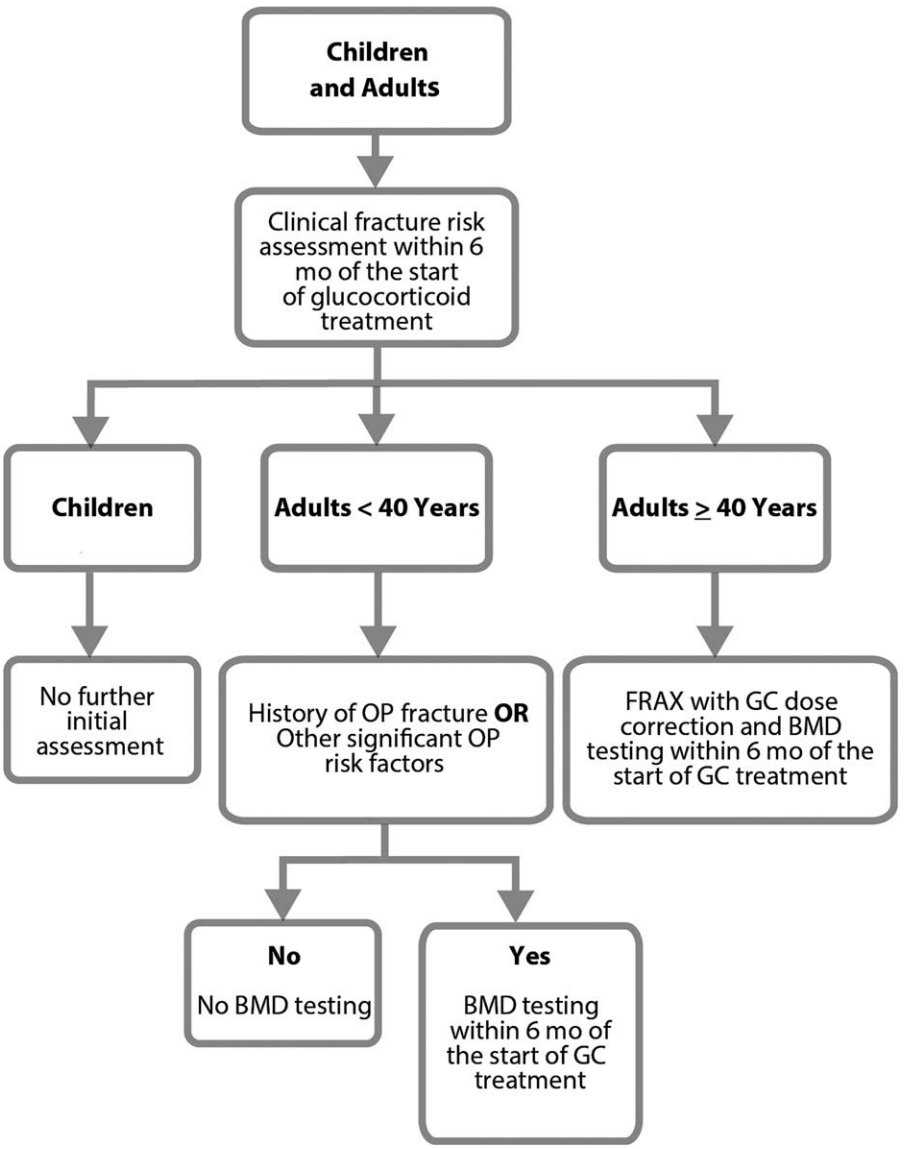

Figure 1. Initial fracture risk assessment. A clinical fracture risk assessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age. The risk of major osteoporotic fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available.

For intravenous (IV) bisphosphonates, denosumab, raloxifene, and teriparatide, which have greater harms or burden of treatment, the threshold was higher, although the Panel did not specify a threshold value. Because raloxifene may increase the risk of death due to stroke in postmenopausal women with documented coronary heart disease or at increased risk of major coronary events and/or may increase the risk of deep vein thrombosis and pulmonary embolism (35), and there is no evidence of its benefit in fracture reduction in GC-treated patients, the Voting Panel considered the drug as a treatment option only for postmenopausal women with contraindications to all other treatments. We are unaware of published literature exploring patient values and preferences regarding these issues. The judgments are based on the experience of the Panel members (which included a patient) in shared decision-making with their patients.

2a. A *strong recommendation* means that the Panel was *confident* that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation.

2b. A *conditional recommendation* means that the Panel believed the desirable effects of following the recommendation *probably* outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach.

2c. A *good practice recommendation* (36) means that although the Panel believed the benefits of proceeding according to the guidance far outweigh the harms, the supporting evidence is indirect, and the Panel did not formally assess the relevant evidence. The logic for the good practice statements is as follows: Appropriate management regarding bone health is based on an initial assessment and reassessment of fracture risk. However, there are inadequate data directly addressing outcomes in patients whose cases were managed with, versus those without, initial and follow-up fracture risk assessments. The chain of evidence—limited antifracture treatment with limited adverse effects in those at low risk; more aggressive antifracture treatment with resultant decrease in fractures in those at high risk—is nevertheless compelling, though without a structured review of the evidence for the benefits and harms, the statement in question does not warrant a formal GRADE recommendation.

3. For each recommendation, details regarding the PICO questions and the GRADE evidence tables are listed in Supplementary Appendices 1 and 3 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract).

4. Recommendations for BMD testing are based on the assumption that it is available in the region where the patient receives treatment and that there are no significant barriers, including the patient's functional status or financial barriers, that preclude testing, and that the results are likely to have an impact on clinical decision-making.

Recommendations for fracture risk assessment and reassessment

Initial fracture risk assessment. All of the fracture risk assessment and reassessment recommendations are made as good practice recommendations. In all adults and children, an *initial clinical fracture risk assessment should be performed as soon as possible, but at least within 6 months of the initiation of long-term GC treatment* (Figure 1). This assessment should include a history with the details of GC use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other risk factors for fracture (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age.

In addition, for adults ≥40 years of age, the initial absolute fracture risk should be estimated using FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) with the adjustment for GC dose and BMD testing (if available, or without BMD if it is not available) as soon as possible, but at least within 6 months of the initiation of GC treatment.

For adults <40 years of age, BMD testing should be done as soon as possible but at least within 6 months of the initiation of GC treatment if the patient is at high fracture risk because of a history of previous OP fracture(s) or if the patient has other significant OP risk factors (malnutrition, significant

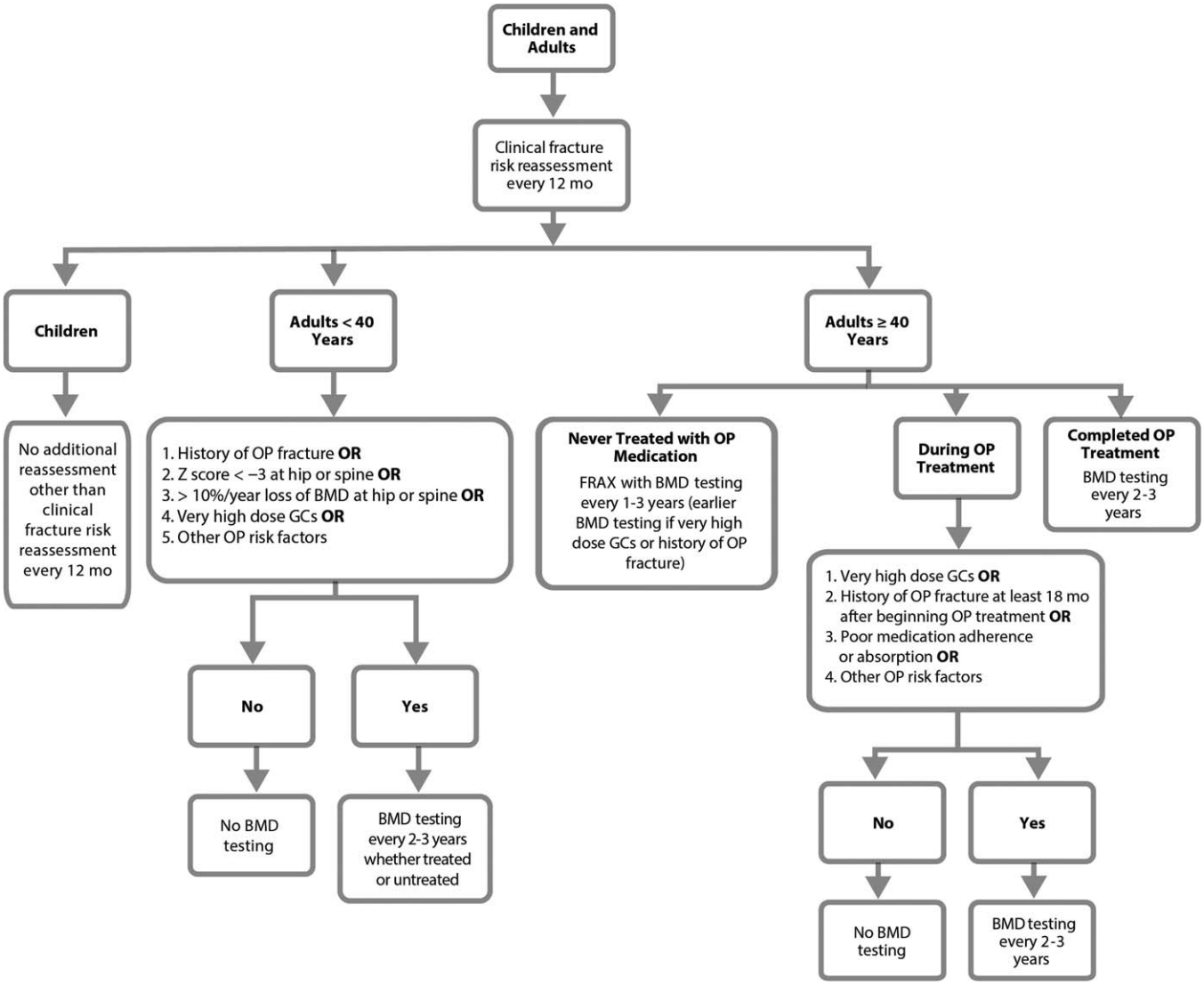

Figure 2. Reassessment of fracture risk. A clinical fracture risk reassessment includes obtaining a history with the details of glucocorticoid (GC) use (dose, duration, pattern of use), an evaluation for falls, fractures, frailty, and other osteoporosis (OP) risk factors (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at ≥3 units/day] or smoking) and other clinical comorbidities, and a physical examination including measurement of weight and height (without shoes), testing of muscle strength, and assessment for other clinical findings of undiagnosed fracture (i.e., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis) as appropriate given the patient's age. Very high-dose GC treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. Reliability of FRAX (https://www.shef.ac.uk/FRAX/tool.jsp) after OP treatment is debated, but FRAX calculation can be repeated in adults age ≥40 years who have not received treatment. It is recognized that in some cases, bone mineral density (BMD) testing may not be available.

weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, smoking, alcohol use at ≥3 units/day).

Reassessment of fracture risk. In all adults and children who continue GC treatment, a *clinical fracture risk reassessment should be performed every 12 months* (Figure 2).

Adults ≥40 years of age. For adults ≥40 years of age who continue GC treatment and are *not treated with an OP medication beyond calcium and vitamin D,* reassessment with FRAX, with BMD testing if available,

Table 2. Recommendations for initial treatment for prevention of GIOP in adults (women not of child-bearing potential and men) beginning long-term GC treatment*

All adults taking prednisone at a dose of ≥2.5 mg/day for ≥3 months

Optimize calcium intake (800–1,000 mg/day) **and vitamin D intake** (600–800 IU/day) **and lifestyle modifications** (balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) **over no treatment or over any of these treatments alone.**

Conditional recommendation because of indirect evidence on the impact of lifestyle modifications on fracture risk, low-quality evidence on the impact of calcium and vitamin D on fractures in GC users, and indirect evidence on the benefit of calcium and vitamin D on fracture risk in the general OP population

Adults age ≥40 years at low risk of fracture

Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, denosumab, or raloxifene.

Conditional recommendation for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments in this low-risk group, costs, and potential harms

Strong recommendation for calcium and vitamin D over IV bisphosphonates and raloxifene because of low-quality evidence on additional antifracture benefit in this low-risk group and their potential harms

Adults age ≥40 years at moderate risk of major fracture

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- IV bisphosphonates
  - Higher risk profile for IV infusion over oral bisphosphonate therapy
- Teriparatide
  - Cost and burden of therapy with daily injections
- Denosumab
  - Lack of safety data in people treated with immunosuppressive agents
- Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate)
  - Lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality)

Conditional recommendations because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with moderate fracture risk

Adults age ≥40 years at high risk of fracture

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- IV bisphosphonates
  - Higher risk profile for IV infusion over oral bisphosphonate therapy
- Teriparatide
  - Cost and burden of therapy with daily injections
- Denosumab
  - Lack of safety data in people treated with immunosuppressive agents
- Raloxifene (for postmenopausal women in whom none of the medications listed above is appropriate)
  - Lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality)

Strong recommendation for oral bisphosphonates over calcium and vitamin D alone because of the strength of the indirect evidence of antifracture efficacy and low harms

All other recommendations **conditional** because of indirect and low-quality evidence comparing benefits and harms of alternative treatments in people with high fracture risk

Adults age <40 years at low risk of fracture

Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, or denosumab.

Conditional recommendation for calcium and vitamin D over oral bisphosphonates, teriparatide, and denosumab because of low-quality evidence on additional antifracture benefit of the alternative treatments, costs, and potential harms

Strong recommendation for calcium and vitamin D over IV bisphosphonates because of low-quality evidence for additional antifracture benefit in this low-risk group and potential harms

Table 2. *(Cont'd)*

Adults age <40 years at moderate-to-high risk of fracture
Treat with an oral bisphosphonate over calcium and vitamin D alone.
Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.
Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. Other therapies if oral bisphosphonates are not appropriate, in order of preference: IV bisphosphonates Higher risk profile for IV infusion over oral bisphosphonate therapy Teriparatide Cost and burden of therapy with daily injections Denosumab Lack of safety data in people treated with immunosuppressive agents
Conditional recommendations because of low- to very low-quality evidence on absolute fracture risk and indirect and low-quality evidence comparing relative harms and benefits of alternative treatments in this age group

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

should be completed every 1–3 years. This reassessment should be performed earlier within this 1–3-year time range for adults age ≥40 years who are receiving very high doses of GCs (initial prednisone dose ≥30 mg/day, cumulative dose >5 gm in the previous year) or those with a history of OP fracture(s). Later or less frequent testing within this range can be done for adults age ≥40 years who are taking lower doses of GCs with no other OP risk factors.

For adults ≥40 years old who continue GC treatment and are *currently treated with an OP medication in addition to calcium and vitamin D*, BMD testing should be completed every 2–3 years during treatment in high-risk patients such as those receiving very high-dose GCs (initial prednisone dose ≥30 mg/day, cumulative dose >5 gm in the previous year), a history of OP fracture occurring after ≥18 months of treatment with antifracture medication (other than calcium and vitamin D), risks for poor medication adherence or absorption, or other significant OP risk factors.

For adults ≥40 years old who *received an OP treatment in the past but are no longer being treated with an OP medication other than calcium and vitamin D,* BMD testing should be done every 2–3 years. Within this range, reassessment should be conducted earlier in patients receiving higher doses of GCs and those with a history of fracture or low BMD, and later in those receiving lower doses of GCs, with higher BMD and no other OP risk factors.

Adults <40 years of age. For all adults <40 years of age who continue GC treatment and are *at moderate-to-high fracture risk* (history of previous fracture, BMD Z score <−3, received very high-dose prednisone [≥30 mg/day and cumulative dose >5 gm] in the previous year, risks for poor medication adherence or absorption, or multiple OP risk factors), BMD testing should be done every 2–3 years.

Recommendations for treatment

The Voting Panel's rationale and strength of recommendations for treatment are detailed in Table 2.

Calcium and vitamin D intake and lifestyle modifications. Optimizing calcium intake (1,000–1,200 mg/day) and vitamin D intake (600–800 IU/day; serum level ≥20 ng/ml) (37) as well as lifestyle modifications (a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day) are conditionally recommended for all patients receiving GC treatment.

Initial pharmacologic treatment. *Adults ≥40 years of age.* Women ≥40 years of age and not of childbearing potential and men ≥40 years of age (Figure 3) who are at moderate-to-high risk of fracture should be treated with an oral bisphosphonate (strong recommendation for those at high risk; conditional recommendation for those at moderate risk). For patients in whom oral bisphosphonates are not appropriate (for example, due to comorbidities, patient preference, or concerns about adherence with an oral medication regimen), IV bisphosphonates should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If bisphosphonate treatment is not appropriate, teriparatide should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If neither oral nor IV bisphosphonates nor teriparatide treatment is appropriate, denosumab should be used rather than the patient receiving no additional treatment beyond calcium and

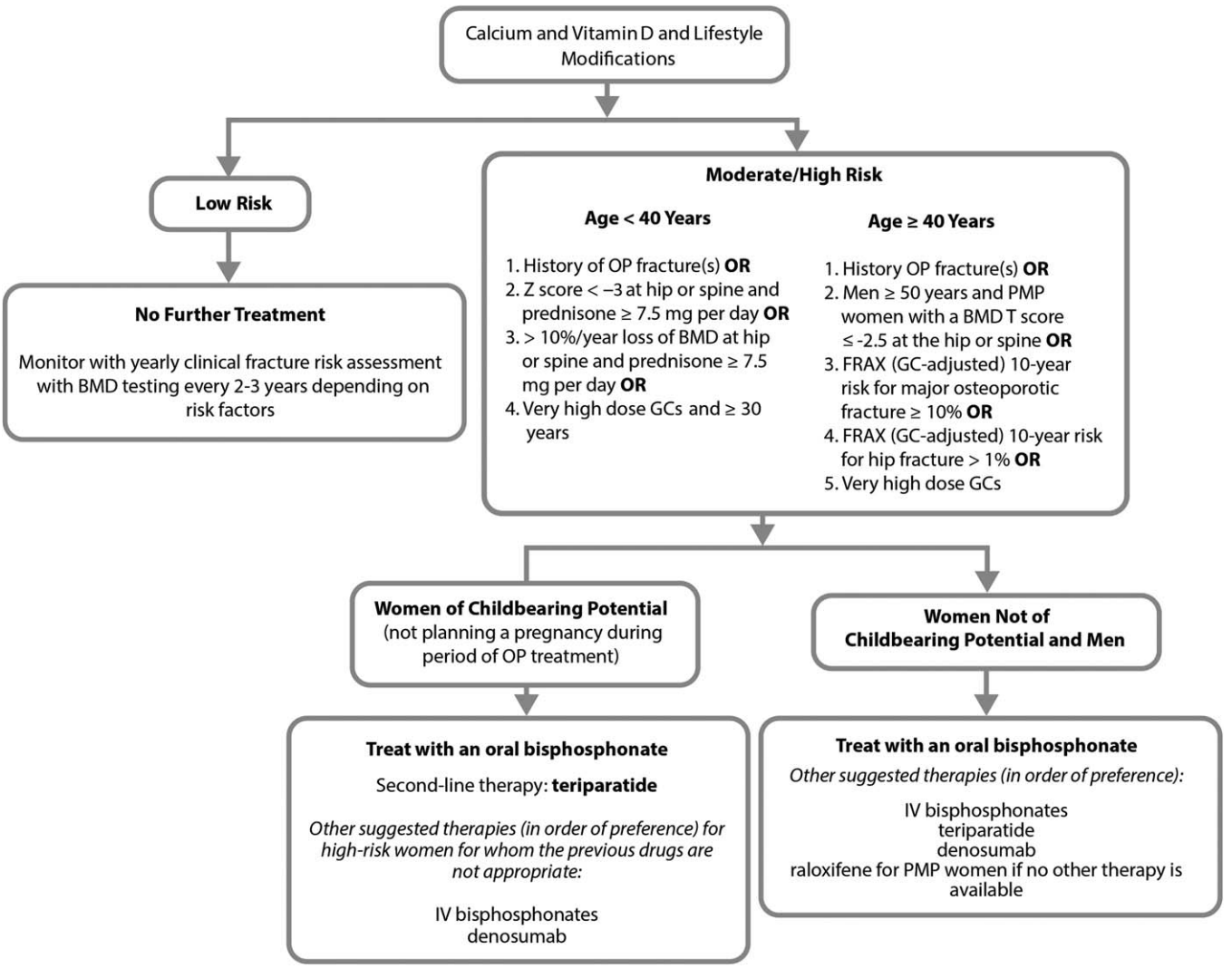

Figure 3. Initial pharmacologic treatment for adults. Recommended doses of calcium and vitamin D are 1,000–1,200 mg/day and 600–800 IU/day (serum level ≥20 ng/ml), respectively. Lifestyle modifications include a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing and resistance training exercise, and limiting alcohol intake to 1–2 alcoholic beverages/day. Very high-dose glucocorticoid (GC) treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. The risk of major osteoporotic (OP) fracture calculated with the FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp) should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is >7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%). It is recognized that in some cases, bone mineral density (BMD) testing may not be available. PMP = postmenopausal; IV = intravenous.

vitamin D. For postmenopausal women in whom none of these medications is appropriate, raloxifene should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. The order of the preferred treatments was determined based on a comparison of efficacy (fracture reduction), toxicity, and cost. These are conditional recommendations.

Adults <40 years of age. For adults <40 years of age (women not of childbearing potential and men) (Figure 3) with a history of OP fracture, or those continuing GC treatment (≥6 months at a dose of ≥7.5 mg/day) who have either a hip or spine BMD Z score <−3 or bone loss of ≥10%/year at the hip or spine as assessed by dual x-ray absorptiometry (DXA), an oral bisphosphonate should

Table 3. Recommendations for initial treatment for prevention of GIOP in special populations of patients beginning long-term GC treatment*

Women of childbearing potential at moderate-to-high risk of fracture (Table 1) who do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active

Treat with an oral bisphosphonate over calcium and vitamin D alone, teriparatide, IV bisphosphonates, or denosumab.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications.
Other therapies if oral bisphosphonates are not appropriate, in order of preference:
- Teriparatide
  - Safety, cost, and burden of therapy with daily injections

Consider the following therapies only for **high-risk** patients because of lack of safety data on use of these agents during pregnancy:
- IV bisphosphonates
  - Potential fetal risks of IV infusion during pregnancy
- Denosumab
  - Potential fetal risks during pregnancy

Conditional recommendations because of indirect and very low-quality evidence on benefits and harms of these treatments to the fetus during pregnancy

Adults age ≥30 years receiving very high-dose GCs (initial dose of prednisone ≥30 mg/day and cumulative dose >5 gm in 1 year)

Treat with an oral bisphosphonate over calcium and vitamin D alone.

Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab.

Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of additional antifracture benefits from other OP medications.

If bisphosphonate treatment is not appropriate, alternative treatments are listed by age (≥40 years and <40 years) in Table 2.

Conditional recommendations because of low-quality evidence on absolute fracture risk and harms in this population

Adults with organ transplant, glomerular filtration rate ≥30 ml/minute, and no evidence of metabolic bone disease who continue treatment with GCs

Treat according to the age-related guidelines for adults without transplants (Table 2), with these additional recommendations:

An evaluation by an expert in metabolic bone disease is recommended for all patients with a renal transplant.

Recommendation against treatment with denosumab due to lack of adequate safety data on infections in adults treated with multiple immunosuppressive agents.

Conditional recommendations because of low-quality evidence on antifracture efficacy in transplant recipients and on relative benefits and harms of the alternative treatments in this population

Children ages 4–17 years treated with GCs for ≥3 months

Optimize calcium intake (1,000 mg/day) and vitamin D intake (600 IU/day) and lifestyle modifications over not optimizing calcium and vitamin D intake and lifestyle modifications.

Conditional recommendation because of lack of antifracture efficacy of calcium and vitamin D in children but limited harms

Children ages 4–17 years with an osteoporotic fracture who are continuing treatment with GCs at a dose of ≥0.1 mg/kg/day for ≥3 months

Treat with an oral bisphosphonate (IV bisphosphonate if oral treatment contraindicated) plus calcium and vitamin D over treatment with calcium and vitamin D alone.

Conditional recommendation because of very low-quality antifracture data in children but moderate-quality evidence of low harms of oral bisphosphonates in children and less potential harm of oral over IV bisphosphonates

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If treatment with an oral bisphosphonate is not appropriate, the same alternative medications listed for adults ≥40 years of age are recommended with the exception of raloxifene, which is not used in men and premenopausal women. These are conditional recommendations.

Special populations. For women who meet criteria for *moderate-to-high risk of fracture* (Table 1) and are of *childbearing potential* (Table 3 and Figure 3), *but do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active,* an oral bisphosphonate should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. If oral bisphosphonate treatment is not appropriate, teriparatide should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. Because of the lack of safety data and the potential fetal harm associated with denosumab in animal studies and with high-dose IV bisphosphonates (38–53), these therapies should be used only in women who are at high risk of fracture in whom treatment with an oral bisphosphonate and teriparatide is not appropriate. Denosumab or IV bisphosphonate treatment should be initiated only after a discussion with the patient about the very low quality of evidence about fetal harms in the event of an unplanned pregnancy. These are conditional recommendations.

There is a lack of data on the safety of currently available OP treatments during pregnancy. Therefore, these guidelines do not include recommendations about OP prevention or treatment, other than calcium and vitamin D intake and lifestyle modification, in women who are pregnant.

For *adults ≥30 years of age who are receiving very high-dose GC treatment* (initial prednisone dose of ≥30 mg/day [or equivalent GC exposure] and a cumulative annual dose of >5 gm) (Table 3), oral bisphosphonate treatment should be initiated. If treatment with an oral bisphosphonate is not appropriate, the age-related recommendations for second-line therapy (Table 2) should be followed (with adjustments for women of childbearing potential as outlined in these guidelines). These are conditional recommendations.

For adults *who have received an organ transplant and who are continuing treatment with GCs* (Table 3),

Table 4. Recommendations for follow-up treatment for prevention of GIOP*

Adults age ≥40 years continuing GC treatment who have had a fracture that occurred after ≥18 months of treatment with an oral bisphosphonate or who have had a significant loss of bone mineral density (≥10%/year)
Treat with another class of OP medication (teriparatide or denosumab; or, consider IV bisphosphonate if treatment failure is judged to be due to poor absorption or poor medication adherence) with calcium and vitamin D over calcium and vitamin D alone or over calcium and vitamin D and continued oral bisphosphonate.
Conditional recommendation because of very low-quality evidence comparing benefits and harms of the compared treatment options in this clinical situation
Adults age ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture
Continue active treatment (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate [if concern with regard to adherence or absorption] or switch to an OP treatment in another class) over calcium and vitamin D alone.
Conditional recommendation because of very low-quality data on benefits and harms in GC-treated patients, but moderate-quality data in the general OP literature on benefits and harms of continuing treatment with oral bisphosphonates past 5 years for people at high risk of fracture
Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at low risk of fracture
Discontinue the OP medication but continue calcium and vitamin D over continuing the OP medication.
Conditional recommendation made by expert consensus; evidence informing it too indirect for the population and very low-quality
Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at moderate-to-high risk of fracture
Complete the treatment with the OP medication over discontinuing the OP medication.
Strong recommendation for high-risk patients based on expert consensus that patients who are at high risk should continue an OP treatment in addition to calcium and vitamin D
Conditional recommendation for moderate-risk patients because of lower fracture risk compared to potential harms

* GIOP = glucocorticoid (GC)–induced osteoporosis; IV = intravenous.

the age-related treatment recommendations outlined in these guidelines for men and women who do not have transplants should be followed if the glomerular filtration rate is ≥30 ml/minute and there is no evidence of metabolic bone disease. An evaluation by an expert in metabolic bone disease is recommended before initiating pharmacologic treatment in adults with a renal transplant (54). The Panel made a recommendation against the use of denosumab because of lack of safety data in this population of patients who are treated with multiple immunosuppressive agents. These are conditional recommendations.

For *GC-treated children 4–17 years of age,* a calcium intake of 1,000 mg/day and vitamin D intake of 600 IU/day is recommended. For children who have had an OP fracture who continue GC treatment at a dose of ≥0.1 mg/kg/day for ≥3 months, treatment with an oral bisphosphonate (or an IV bisphosphonate if oral treatment is not appropriate) is recommended (Table 3). These are conditional recommendations.

Follow-up treatment recommendations. *Initial treatment failure.* For adults ≥40 years of age who are continuing GC treatment who have had a fracture that occurred ≥18 months after beginning treatment with an oral bisphosphonate or had a significant decline in BMD (≥10%/year) after 1 year of treatment (Table 4), treatment with another class of OP medication (teriparatide, denosumab) or an IV bisphosphonate (if treatment failure is judged to be due to poor absorption or poor medication adherence) is recommended rather than the patient receiving no additional treatment beyond calcium and vitamin D alone or continuing oral bisphosphonate treatment. These are conditional recommendations.

Treatment if moderate-to-high fracture risk persists after bisphosphonate therapy. For adults ≥40 years of age who have completed 5 years of oral bisphosphonate treatment (Table 4) who are continuing GC treatment and are assessed to be at moderate-to-high risk of fracture (Table 1), continuation of active OP treatment (in addition to calcium and vitamin D) is recommended rather than the patient receiving no additional treatment beyond calcium and vitamin D. Suggested treatment options include continuing the oral bisphosphonate for 7–10 years, switching to an IV bisphosphonate if absorption or adherence is a problem, or treatment with another class of OP medication (teriparatide or denosumab), depending on the response to the initial bisphosphonate treatment (change in BMD, new fractures) and with consideration of rare risks, including jaw necrosis and atypical femur fractures, which might increase with the duration of antiresorptive therapy. These are conditional recommendations.

Treatment if GCs are discontinued. For adults ≥40 years of age who are treated with OP medication in addition to calcium and vitamin D and are discontinuing GC treatment (Table 4), discontinuation of the OP medication is recommended if fracture risk at the time of GC discontinuation is assessed to be low. Otherwise, the OP treatment course should be completed or continued until the fracture risk is assessed to be low. Continuation of OP treatment in the setting of high risk is a strong recommendation. The others are conditional recommendations.

Application of these treatment recommendations. These recommendations are made for average or typical GC-treated patients. They may not be applicable to GC-treated patients with multiple risk factors or feasible for patients with financial or social barriers to testing and treatment.

DISCUSSION

This report presents the updated ACR recommendations for the prevention and treatment of osteoporosis and fractures in patients receiving glucocorticoid treatment. The goal is to optimize identification of patients at risk of GC-induced fractures so that they can be appropriately treated while limiting the risk and the burden of testing and treatment. The guiding principle for these guidelines was to use outcome measures that are clinically relevant to patients and providers, so in decision-making, data about absolute fracture risk reduction were given priority over BMD changes. The recommendations on the order of first-line treatments were based on the Voting Panel's assessment of antifracture efficacy, potential harms, and costs. Thus, oral bisphosphonates were recommended as the preferred first-line therapy in most clinical situations given their antifracture benefit, safety, and low cost, unless there are contraindications, intolerance, or concerns about patient adherence to treatment.

Robust methodology was used in the literature search. The Voting Panel had a broad representation of clinicians, both primary care providers and subspecialists, with experience in bone health and in prescribing GC medications. In addition, these guidelines include recommendations for the assessment and reassessment of fracture risk and antifracture therapy during GC treatment and for special populations, such as children, people with organ transplants, people receiving very high doses of GCs, and women of childbearing potential.

There are limitations to these recommendations. First, many important clinical situations could not be addressed given the limited scope of this guideline

project. Recommendations addressing initial assessment and reassessment of fracture risk were made as good practice recommendations (36) because, although the Panel believes that the benefits of proceeding according to the guidance far outweigh the undesirable consequences, the supporting evidence is indirect or not available, and the Panel did not formally gather, summarize, or assess the relevant evidence.

We adopted generally accepted thresholds to define high, medium, and low levels of absolute risk of incident fracture (i.e., <10%, 10–19%, and ≥20% 10-year risk of major osteoporotic fracture). These cut points were used to stratify PICO questions and weigh potential benefits versus harms in those different clinical situations. However, the application of these recommendations to a clinical setting requires that the physician assign the individual patient into a risk stratum. For adults age ≥40 years, this can be accomplished using fracture risk calculators that take the GC dose into account, such as the FRAX tool. However, FRAX has important limitations. First, the fracture risk generated when GC use is included as a risk factor estimates the risk that would be associated with moderate-dose prednisone (2.5–7.5 mg/day). To accurately estimate the risk associated with doses of >7.5 mg/day, the clinician must multiply the risk of major osteoporotic fracture and the risk of hip fracture generated with the FRAX by 1.15 and by 1.2, respectively. This adjustment may not adequately estimate the risk associated with very high-dose GC use. FRAX uses hip BMD to calculate fracture risk, but GC use has a greater impact on spine BMD. For GC-treated patients with discordant spine and hip BMD (with lower spine BMD), the Fracture Risk Calculator, which includes spine BMD in absolute fracture risk estimation, is available (https://riskcalculator.fore.org). Finally, there is debate about the validity of FRAX fracture risk estimates after pharmacologic treatment for OP, which should be considered in the reassessment of fracture risk in treated patients.

The available evidence about fracture risk and risk reduction was particularly limited with regard to treatment recommendations in adults <40 years of age and children, and there are no tools available to estimate absolute fracture risk in these age groups. Younger people are often treated with higher doses of GCs, but they have higher bone mass and greater potential for recovery of bone mass when the GC treatment is discontinued. To try to better categorize fracture risk in adults <40 years of age, the Panel considered several risk factors as indicators of moderate-to-high fracture risk—including history of previous fragility fracture, significant decrease in BMD, or low BMD Z score with continued use of prednisone (limiting the recovery of bone mass) at a dose of ≥7.5 mg/day for at least 6 months—in patients <40 years old, as well as in patients ≥30 years old treated with very high doses of GCs (initial prednisone dose ≥30 mg/day with a cumulative dose of >5 gm) (15,18,21–25). The lack of data on long-term outcomes with OP treatment in this age group may lead to under- or overtreatment, but the possible benefits to long-term bone health and the relatively low risks associated with the recommended OP treatments led to the recommendation of treatment with an oral bisphosphonate in addition to calcium and vitamin D. There is a need for more research about absolute risk of fracture in this age group during and after GC use and into later adult life.

Fracture data are very limited in GIOP-specific clinical trials and population studies. Lacking these data, the relative fracture reduction associated with OP medications was extrapolated from the risk reduction ascertained in clinical trials of many different treatments for OP in general. While this step introduced indirectness into the quality of evidence for many PICO questions, it is reassuring that where parallel data from GIOP and non-GIOP trials exist, the derived relative risks for treatment effects from the same intervention are often similar, indicating that the assumption of generalizability may be reasonable (Supplementary Appendix 3 [Summary of Findings Tables 1.4a/b/c, 1.9a/b/c], available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40137/abstract). Imprecision in the estimate of benefits of treatment is increased by these extrapolations. Future clinical trials in GC-treated patients should include fracture as a primary outcome measure.

The Panel faced low-quality evidence regarding the magnitude of benefit GC-treated patients would require as a tradeoff for assuming the burden and risks of treatment for lowering fracture risk, particularly given the uncertainties associated with estimates of benefit. Awareness of the need to attain "minimally disruptive medicine" (55) has increased in recent years, and many of the candidate patients already bear the burden of multiple medications. This burden may influence their willingness to tolerate yet additional treatment. The Panel's assessment was that patients would be willing to take calcium and vitamin D with only a very small absolute risk reduction, that all or virtually all would be willing to take bisphosphonates to achieve a 5-year absolute reduction in vertebral fracture risk of 5%, and that most would choose to take oral bisphosphonates if the fracture reduction were between ≥3% and <5%. Patients who value these small absolute reductions less

highly than the Panel estimated may decide against recommended treatment after discussion of risks and benefits with their providers.

There are concerns about the potential harms of calcium and vitamin D supplementation with regard to cardiovascular risks (56,57). Optimizing calcium intake, however, may be even more important in GC-treated patients because of the increase in urinary calcium excretion during GC use. For this reason, the guidelines suggest optimizing dietary intake of calcium. More research about the benefits and harms of supplemental calcium and vitamin D in GC-treated patients is needed.

Because of these limitations, most of the recommendations in this guideline are conditional or good clinical practice recommendations. Further studies are needed to examine differences in fracture risk in people with different OP risk factors (age, race, and sex), the role of spine imaging using vertebral fracture assessment with DXA or radiography in assessing fracture risk in GC users, the risk of OP medications to the fetus in women of childbearing potential, and the impact of OP treatment versus no treatment on adult bone health and fracture risk in GC-treated children.

GIOP is not a problem that is unique to rheumatology; GCs are widely prescribed by primary care providers and subspecialists. The Panel's judgments regarding patients' values and preferences were informed by input from the primary care physicians, non-rheumatology specialists, and the patient who served on the Panel. This patient highlighted the significant challenges that patients and clinicians confront when making decisions about optimizing bone health during GC treatment of chronic inflammatory conditions.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Buckley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Fardet L, Petersen I, Nazareth I. Monitoring of patients on long-term glucocorticoid therapy: a population-based cohort study. Medicine (Baltimore) 2015;94:e647.
2. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96:115–23.
3. Lane NE, Lukert B. The science and therapy of glucocorticoid-induced bone loss. Endocrinol Metab Clin North Am 1998;27:465–83.
4. Curtis J, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006;55:420–6.
5. Angeli A, Guglielmi G, Dovio A, Capelli G, de Feo D, Giannini S, et al. High prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: a cross-sectional outpatient study. Bone 2006;39:253–9.
6. Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis: a randomized, controlled study. Ann Intern Med 1993;119:963–8.
7. Hansen KE, Kleker B, Safdar N, Bartels CM. A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children. Semin Arthritis Rheum 2014;44:47–54.
8. Van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. J Bone Miner Res 2003;18:913–8.
9. Rodd C, Lang B, Ramsay T, Alos N, Huber AM, Cabral DA, et al. Incident vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: a national observational study. Arthritis Care Res (Hoboken) 2012;64:122–31.
10. LeBlanc CM, Ma J, Taljaard M, Roth J, Scuccimarri R, Miettunen P, et al. Incident vertebral fractures and risk factors in the first three years following glucocorticoid initiation among pediatric patients with rheumatic disorders. J Bone Miner Res 2015;30:1667–75.
11. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.
12. Hall GM, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum 1993;36:1510–6.
13. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 2011;22:809–16.

14. Ettinger B. A personal perspective on fracture risk assessment tools. Menopause 2008;15:1023–6.
15. Van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. QJM 2005;98: 191–8.
16. De Vries F, Bracke M, Leufkens HG, Lammers JW, Cooper C, van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis Rheum 2007:56:208–14.
17. Bultink IE, Lems WF, Kostense PJ, Dijkmans BA, Voskuyl AE. Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. Arthritis Rheum 2005;52:2044–50.
18. Sugiyama T, Suzuki S, Yoshida T, Suyama K, Tanaka T, Sueishi M, et al. Incidence of symptomatic vertebral fractures in women of childbearing age newly treated with high-dose glucocorticoid. Gend Med 2010;7:218–29.
19. Almehed K, Hetenyi S, Ohlsson C, Carlsten H, Forsblad-d'Elia H. Prevalence and risk factors of vertebral compression fractures in female SLE patients. Arthritis Res Ther 2010;12:R153.
20. Li EK, Tam LS, Griffith JF, Zhu TY, Li TK, Li M, et al. High prevalence of asymptomatic vertebral fractures in Chinese women with systemic lupus erythematosus. J Rheumatol 2009; 36:1646–52.
21. Borba VZ, Matos PG, da Silva Viana PR, Fernandes A, Sato EI, Lazaretti-Castro M. High prevalence of vertebral deformity in premenopausal systemic lupus erythematosus patients. Lupus 2005;14:529–33.
22. Sugiyama T, Tatsuno I, Suzuki S, Yoshida T, Tanaka T, Sueishi M, et al. Incidence of symptomatic vertebral fracture with high-dose glucocorticoid treatment in the Chiba-Shimoshizu Rheumatic Cohort between 1986 and 2006. Endocr J 2009;56:591–9.
23. Tatsuno I, Sugiyama T, Suzuki S, Yoshida T, Tanaka T, Sueishi M, et al. Age dependence of early symptomatic vertebral fracture with high-dose glucocorticoid treatment for collagen vascular diseases. J Clin Endocrinol Metab 2009;94:1671–7.
24. Sugiyama T, Suzuki S, Yoshida T, Mayama T, Hashimoto N, Suyama K, et al. Age, initial dose and dose increase are independent risk factors for symptomatic vertebral fractures in glucocorticoid-treated male patients. Intern Med 2011;50: 817–24.
25. Kumagai S, Kawano S, Atsumi T, Inokuma S, Okada Y, Kanai Y, et al. Vertebral fracture and bone mineral density in women receiving high dose glucocorticoids for treatment of autoimmune diseases. J Rheumatol 2005;32:863–9.
26. Solomon DH, Katz JN, Jacobs JP, La Tourette AM, Coblyn J. Management of glucocorticoid-induced osteoporosis in patients with rheumatoid arthritis: rates and predictors of care in an academic rheumatology practice. Arthritis Rheum 2002;46:3136–42.
27. Feldstein AC, Elmer PJ, Nichols GA, Herson M. Practice patterns in patients at risk for glucocorticoid-induced osteoporosis. Osteoporos Int 2005;16:2168–74.
28. American College of Rheumatology Task Force on Osteoporosis Guidelines. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 1996; 39:1791–801.
29. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. Arthritis Rheum 2001;44:1496–503.
30. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum 2010;62:1515–26.
31. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
32. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719–25.
33. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–35.
34. GRADEpro web site. URL: https://gradepro.org/.
35. EVISTA (raloxifene hydrochloride) tablet for oral use initial US approval: 1997 prescribing information. Indianapolis (IN): Eli Lilly and Company; 2007. URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022042lbl.pdf.
36. Guyatt GH, Schünemann HJ, Djulbegovic B, Akl EA. Guideline panels should not GRADE good practice statements. J Clin Epidemiol 2015;68:597–600.
37. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8.
38. Bussiere JL, Pyrah I, Boyce R, Branstetter D, Loomis M, Andrews-Cleavenger D. Reproductive toxicity of denosumab in cynomolgus monkeys. Reprod Toxicol 2013;42:27–40.
39. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology 1999;60:68–73.
40. Ornoy A, Wajnberg R, Diav-Citrin O. The outcome of pregnancy following pre-pregnancy or early pregnancy alendronate treatment. Reprod Toxicol 2006;22:578–9.
41. Illidge TM, Hussey M, Godden CW. Malignant hypercalcaemia in pregnancy and antenatal administration of intravenous pamidronate. Clin Oncol (R Coll Radiol) 1996;8:257–8.
42. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, et al. Pregnancy outcome following in utero exposure to bisphosphonates. Bone 2009;44:428–30.
43. Green SB, Pappas AL. Effects of maternal bisphosphonate use on fetal and neonatal outcomes. Am J Health Syst Pharm 2014; 71:2029–36.
44. Stathopoulos IP, Liakou CG, Katsalira A, Trovas G, Lyritis GG, Papaioannou NA, et al. The use of bisphosphonates in women prior to or during pregnancy and lactation. Hormones (Athens) 2011;10:280–91.
45. McNicholl DM, Heaney LG. The safety of bisphosphonate use in pre-menopausal women on corticosteroids. Curr Drug Saf 2010;5:182–7.
46. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.
47. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can 2008;30:1146–8.
48. Okazaki A, Matsuzawa T, Takeda M, York RG, Barrow PC, King VC, et al. Intravenous reproductive and developmental toxicity studies of cimadronate (YM175), a novel bisphosphonate, in rats and rabbits. J Toxicol Sci 1995;20 Suppl 1:1–13.
49. Graepel P, Bentley P, Fritz H, Miyamoto M, Slater SR. Reproduction toxicity studies with pamidronate. Arzneimittelforschung 1992;42:654–67.
50. Sakiyama Y, Tada I, Yamamoto H, Nakanishi T, Yasuda Y, Soeda Y, et al. The effect of ethane-1-hydroxy-1,1-diphosphonate (EHDP) on fetal mice during pregnancy: with emphasis on implantation and fetal weight. J Osaka Dent Univ 1986;19:87–90.
51. Ibrahim A, Scher N, Williams G, Sridhara R, Li N, Chen G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res 2003;9:2394–9.
52. Boyce RW, Varela A, Chouinard L, Bussiere JL, Chellman GJ, Ominsky MS, et al. Infant cynomolgus monkeys exposed to denosumab in utero exhibit an osteoclast-poor osteopetrotic-like

skeletal phenotype at birth and in the early postnatal period. Bone 2014;64:314–25.
53. Minsker DH, Manson JM, Peter CP. Effects of the bisphosphonate, alendronate, on parturition in the rat. Toxicol Appl Pharmacol 1993;121:217–23.
54. Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney Int Suppl 2009;76 Suppl 113:S1–130.
55. May C, Montori VM, Mair FS. We need minimally disruptive medicine. BMJ 2009;11;339:b2803.
56. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
57. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007;115:827–8.

PANLAR Consensus Recommendations for the Management in Osteoarthritis of Hand, Hip, and Knee

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Objective: The objective of this consensus is to update the recommendations for the treatment of hand, hip, and knee osteoarthritis (OA) by agreeing on key propositions relating to the management of hand, hip, and knee OA, by identifying and critically appraising research evidence for the effectiveness of the treatments and by generating recommendations based on a combination of the available evidence and expert opinion of 18 countries of America.

Methods: Recommendations were developed by a group of 48 specialists of rheumatologists, members of other medical disciplines (orthopedics and physiatrists), and three patients, one for each location of OA. A systematic review of existing articles, meta-analyses, and guidelines for the management of hand, hip, and knee OA published between 2008 and January 2014 was undertaken. The scores for Level of Evidence and Grade of Recommendation were proposed and fully consented within the committee based on The American Heart Association Evidence-Based Scoring System. The level of agreement was established through a variation of Delphi technique.

Results: Both "strong" and "conditional" recommendations are given for management of hand, hip, and knee OA and nonpharmacological, pharmacological, and surgical modalities of treatment are presented according to the different levels of agreement.

Conclusions: These recommendations are based on the consensus of clinical experts from a wide range of disciplines taking available evidence into account while balancing the benefits and risks of nonpharmacological, pharmacological, and surgical treatment modalities, and incorporating their preferences and values. Different backgrounds in terms of patient education or drug availability in different countries were not evaluated but will be important.

Key Words: osteoarthritis of the hand, hip, and knee, consensus recommendations

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Osteoarthritis (OA) is the most common type of rheumatic disease; it is one of the main reasons for presentation to a rheumatologist. As the second most common cause of work disability after cardiovascular disease, OA incurs direct and indirect costs that have a major impact on the world economy and health systems.[1,2]

The reported prevalence of OA ranges from 0.5 to 40% of the general population. The wide variation is attributed to the variability of the clinical features of the disease and the different criteria used for diagnosis.[1,2] Multiple patient factors are associated with an increased risk of OA, with age being the most important, followed by gender, body mass index, and microtraumas.[3–6] This consensus derives from a previous study of Demographic and Clinical Characteristics of 3040 Patients by the PANLAR OA study group, reporting significant differences in handling these patients and the need for reaching an agreement in the management of OA in Latin America, taking into account the conditions of this region.[7]

As there is a lack of standardized criteria for the treatment of OA, the objective of this committee of experts was to obtain agreement on OA treatment and to provide recommendations for the three most common joints affected by OA: the hand, hip, and knee.

METHODS

Literature Research

A group specialized in literature research performed a review of the literature available from 2008 to 2014 in MEDLINE, PubMed (National Center for Biotechnology Information, Bethesda, MD, USA), Cochrane Library (John Wiley & Sons, Inc., NJ, USA), and Embase (Elsevier, Madrid, Spain). The level of evidence and strength of recommendation were evaluated as shown in Table 1, which were proposed and fully consented within the committee based on The American Heart Association Evidence-Based Scoring System.[8]

A total of 896 articles were selected for analysis. The articles were classified according to the model proposed by the Center for Evidence-Based Medicine at Oxford, UK or the Jadad scale.[9] Using these criteria, 108 articles were selected, and individual responses to questions developed through the analysis of the evidence available in the literature were given by the committee of experts.

Participants

Forty-eight experts in the field of OA (rheumatologists, orthopedic surgeons, and physical medicine specialties and OA patients and a general coordinator) representing 18 Latin American countries agreed to take part in this study.

Experts' Consensus

Two sessions were conducted with the aim of reaching agreement on the final recommendations for OA in all three joints. Each participant was asked to contribute independently with questions related to key clinical aspects in the management of hand, hip, and knee OA. The consensus was reached by using a variation of the Delphi technique. The experts answered questionnaires in three rounds. After each round, a facilitator provided an anonymous summary of the experts' forecasts from the previous round and the reasons they provided for their judgments. The experts revised their earlier answers in light of the replies of other members of their panel.

Upon completion of the expert opinions, the document was edited by the Editorial Committee with the final texts approved by members of the working groups.

Recommendations for Hand OA

The recommendations for the management of hand OA are summarized in Table 2 together with the level of evidence supporting them. The treatment propositions are categorized into nonpharmacological, pharmacological, and surgical treatment modalities.

The treatment of hand OA should be individualized according to the type of OA (nodal or erosive), its location and severity, the presence of inflammation, the pain level, the level of disability and reduction in quality of life, the comorbidities and concomitant medication, and the needs and expectations of patients.[10–15]

Nonpharmacological Treatment Modalities

Education with regard to joint protection should be provided (how to avoid adverse mechanical factors) together with an exercise regimen that includes muscle strengthening and range-of-motion exercises (IC).[14–17] Furthermore, the combination of an orthosis (splint) with an exercise regimen to improve pain and functionality in the short and long term and an exercise regimen has been shown to decrease pain and increase the range of motion and strength in hand OA.[10,14,16–27]

Pharmacological Treatment Modalities

Pharmacological modalities of treatment include the use of topical NSAIDs, acetaminophen/paracetamol, and oral NSAIDs. Topical NSAIDs are indicated as being effective and safe for mild to moderate pain, and they are also indicated in elderly patients

TABLE 1. Level of Evidence

Level	Meaning
A	Information from various randomized clinical trials or meta-analyses.
B	Information from a randomized clinical trial or nonrandomized studies.
C	Experts' consensus, case studies, or care standards.
Strength of Recommendation	
Level	**Meaning**
I	There is evidence and/or general agreement that a procedure or treatment is beneficial, useful, or effective.
II	Conflicting evidence and/or differing opinions about the efficacy of a procedure or treatment.
IIa	Evidence and/or agreement favor usefulness or efficacy.
IIb	Usefulness or efficacy is not established by evidence or opinion.
III	Conditions for which there is evidence, general agreement, or both that the procedure treatment is not useful/effective and in some cases may be harmful.

TABLE 2. Recommendations and Level of Evidence Relating to Hand OA

Proposition	Level of Evidence
Nonpharmacological treatment modalities	
1. Education with regard to joint protection together with an exercise regimen including muscle strengthening and range of motion exercises.[14–17]	(IC)
2. The combination of an orthosis (splint) with an exercise regimen to improve pain and functionality in the short and long term.[7,14,16–26]	(IIaB)
Pharmacological treatment modalities	
3. Topical NSAIDs are indicated as being effective and safe for mild to moderate pain in patients with few affected joints and in elderly patients with mild to moderate persistent pain.[13,30–34]	(IA)
4. Acetaminophen/paracetamol (up to 3 g/day) is the preferred oral analgesic for the long-term treatment particularly in elderly patients because of its relative safety in comparison with NSAIDs.[31,32]	(IB)
5. Oral NSAIDs are recommended at the lowest effective dose and for the shortest time possible if patients present inadequate response to acetaminophen/paracetamol.[13,31,35–37,42] The high risk associated with gastrointestinal and cardiovascular events should be considered.	(IA)
6. The use of chondroitin sulfate for pain relief and function is recommended as it has a good safety profile.[38–40]	(IA)
7. Glucosamine and chondroitin sulfate are supported in the treatment of hand and knee OA.[39]	(IB)
8. Steroids or intra-articular hyaluronic acid may be considered for use in the treatment of OA of the symptomatic TMC joint.[28,29,41,43–46]	(IIaB)
9. Intramuscular steroid is not recommended for patients with symptomatic hand OA.[47,48]	(IIIC)
10. The use of diacerein is not recommended as its effectiveness and the risk/benefits profile has not been established.	(IIIC)
11. Adalimumab or infliximab are not recommended in patients with secondary or erosive hand.[29,50,51,53]	(IIIB)
12. Bisphosphonates (clodronate) is not recommended.[54,118–120]	(IIIB)
13. Hydroxychloroquine is not recommended for the symptomatic treatment of erosive hand OA.[52]	(IIIC)
Surgical treatment modalities	
14. Trapeziectomia, arthroplasty with ligament reconstruction and tendon interposition, or arthrodesis may be considered for severe OA of the base of the first finger (rhizarthrosis) if severe pain and/or disability and after conservative treatment have failed.[53–60]	(IIbB)
15. Ligament reconstruction is recommended for stage I. Hemitrapeziectomy, TM joint arthrodesis, implant, or arthroplasty is recommended for stages II and III. Complete removal of the trapezium with or without ligament reconstruction is recommended for stage IV.[59,60,62]	(IIbB)

with mild to moderate persistent pain. For long-term treatment of hand OA, acetaminophen/paracetamol is the preferred oral analgesic. Other treatments in hand OA include the use of chondroitin sulfate for pain relief and function and the use of glucosamine and chondroitin sulfate. Furthermore, the use of steroids or intra-articular hyaluronic acid may be considered for use in the treatment of OA of the symptomatic TMC joint.[28,29,41]

Surgical Treatment Modalities

Surgery (trapeziectomia, arthroplasty with ligament reconstruction and tendon interposition, or arthrodesis) may be considered for severe OA of the base of the first finger (rhizarthrosis) in patients who have severe pain and/or disability and after conservative treatment has failed (IIbB).[53–60] Proper use of arthroplasty or arthrodesis for the affected joints requires careful consideration of the needs of the patient with regard to the affected fingers.[55–60]

Recommendations for Hip OA

The recommendations for the management of hip OA are summarized in Table 3 together with the level of evidence supporting them. The treatment propositions are categorized into nonpharmacological, pharmacological, and surgical treatment modalities.

Nonpharmacological Treatment Modalities

Early rehabilitation is indicated to maintain mobility and prevent impairment of the extension and abduction function of the hip. Patients with hip OA should receive information and education regarding the therapeutic objectives and the importance of changes in lifestyle, which include an exercise regimen, weight reduction, the use of walking aids (walking stick and crutches) and shoe adjustments, and other measures to prevent the progression of joint damage.[62–64]

Available treatment options for pain relief in patients with hip OA include thermotherapy and transcutaneous electrical nerve stimulation (TENS).

Pharmacological Treatment Modalities

The use of acetaminophen/paracetamol is recommended for use in hip OA owing to its safety profile.[65] NSAIDs may be indicated at higher than usual doses to treat more severe pain.[61,66,67] The use of hyaluronic acid in the treatment of hip OA may be beneficial and, thus, could help to reduce NSAID use.[70] In patients who suffer painful relapses and who do not respond to analgesics and NSAIDs, intra-articular corticosteroid injection (ultrasound-guided) may be beneficial to provide fast pain relief (IIaB).[69,70]

Surgical Treatment Modalities

The recommendations for the surgical treatment of hip OA are based on the available literature from the last 2 years.

Total hip arthroplasty is a surgical modality that is undergoing continuous development. It is indicated in patients who have OA accompanied by pain and difficulty walking and whose quality of life is impaired as it improves not only these factors but also patient survival.[73,76] A variety of models and metal implants are available, and different approaches can be chosen such as the use of a cemented, uncemented, or hybrid prosthesis. The available evidence shows that cemented prostheses are as effective as

TABLE 3. Recommendations and Level of Evidence Relating to Hip OA

Proposition	Level of Evidence
Nonpharmacological treatment modalities	
1. Information and education regarding the therapeutic objectives and the importance of changes in lifestyle, which include an exercise regimen, weight reduction, use of walking aids (walking stick and crutches) and shoe adjustments and other measures to prevent the progression of joint damage.[62]	(IB)
2. Strengthening the extensors and abductors improves functionality and can be used to prepare the patient before a hip implant.[61,62,64]	(IB)
3. The use of orthoses is recommended to prevent the progression of degenerative changes and improve hip function.[61,62,64]	(IIbB)
4. Thermotherapy can be performed to relieve pain.[61,62,64]	(IB)
5. Transcutaneous electrical nerve stimulation (TENS) should also be used for pain relief and to reduce stiffness.[62]	(IIbB)
6. Aerobic exercise performed on a regular basis and muscle stretching and strengthening and joint mobility exercises are recommended.[62]	(IB)
7. The use of a walking stick in the contralateral hand is also recommended. The handle should be at the level of the greater trochanter of the femur.[62]	(IIbB)
8. A neuromuscular bandage may be beneficial as it aids analgesia, stimulates circulation, and reduces pressure. Consequently, the patient's posture is improved.[61]	(IIaB)
Pharmacological treatment modalities	
9. The use of acetaminophen/paracetamol is recommended in mild to moderate pain, owing to its safety profile.[63]	(IB)
10. NSAIDs (ibuprofen, naproxen, diclofenac, meloxicam) or selective COX-2 inhibitors (celecoxib, etoricoxib) may be indicated higher than usual doses in more severe pain.[61,66,67]	(IB)
11. Naproxen could be used in patients with cardiovascular risk. It should be administered in conjunction with a proton-pump inhibitor owing to the high gastrointestinal risk.[66]	(IA)
12. Weak opioids such as tramadol may be beneficial if there is no response to NSAIDs or COX-2 inhibitors, no toleration, or are contraindicated.[61]	(IIbB)
13. The use of hyaluronic acid may be beneficial and, thus, could help to reduce the NSAID use.[68]	(IIbB)
14. Intra-articular corticosteroid injection (ultrasound-guided) may be beneficial to provide fast pain relief in patients who suffer painful relapses and who do not respond to analgesics and NSAIDs.[69,70]	(IIaB)
15. Avocado and soybean unsaponifiable may play a useful role, and recent studies have provided the evidence that they may slow the progression of OA.[71]	(IIA)
16. The use of diacerein has reported a high rate of adverse effects, such as diarrhea and risk of liver damage.[49,70,72]	(IIIB)
Surgical treatment modalities	
17. Total hip arthroplasty is indicated when OA is accompanied by pain and walking difficulty and when the quality of life is impaired. It improves not only these factors but also patient survival.[74,75] A variety of models and metal implants are available and different approaches can be chosen such as the use of a cemented, uncemented, or hybrid prosthesis.[77,78]	(IA)

uncemented, especially in the stem (femoral component), whereas uncemented prostheses are more effective for the cup (acetabular component).

Recommendations for Knee OA

The recommendations for the management of knee OA are summarized in Table 4 together with the level of evidence supporting them. The treatment propositions are categorized into nonpharmacological, pharmacological, and surgical treatment modalities.

Nonpharmacological Treatment Modalities

Information and education regarding treatment goals and the importance of lifestyle changes to reduce the degenerative damage of the knee joint should be provided to the patient. Use of support devices such as insoles and knee braces may help to reduce pain and stiffness.[61,80,81]

Pharmacological Treatment Modalities

A wide range of pharmacological treatment modalities is available for patients with knee OA, including acetaminophen/paracetamol, oral and topical NSAIDs, and tramadol. Furthermore, oral administration of hyaluronic acid may have a beneficial therapeutic effect in patients with symptomatic knee OA and may possibly have an even greater effect in relatively young patients.[82] Treatment with chondroitin sulfate, which has a high safety profile, has been shown to have a beneficial effect on symptoms in patients with knee OA. In addition, it has been proven that this effect persists for 3 months after stopping the treatment (carryover effect). Recent studies have provided evidence that chondroitin sulfate use may delay OA progression.[39,83–86] Moreover, the combined use of glucosamine and chondroitin sulfate is indicated in patients with knee OA and moderate to severe pain.[98–100] Many other pharmacological treatment modalities are described in Table 4 (available only online only at…).

Surgical Treatment Modalities

Total knee arthroplasty may be indicated in the treatment of knee OA owing to its outstanding effect on pain and stiffness and the improvement obtained in physical activity 6 months after intervention.[129,130] In patients with a partial rupture of the meniscus, a partial meniscectomy performed arthroscopically may be beneficial, followed by a physical therapy program.[131,132]

DISCUSSION

From the results of a recently published study[7] of the PANLAR OA group, we found it important to have a consensus

TABLE 4. Recommendations and Level of Evidence Relating to Knee OA

Proposition	Level of Evidence
Nonpharmacological treatment modalities	
1. Information and education regarding treatment goals and the importance of lifestyle changes to reduce the degenerative damage of the knee joint should be provided.[61,79]	(IA)
2. Hydrotherapy in a therapeutic tank may be indicated in mild knee pain without swelling or stiffness; it is especially beneficial for elderly patients.[68] A program of exercises for flexibility, mobilization, and stretching can be included.[79]	(IIaA)
3. Mechanotherapy, including flexibility programs and mobilization and stretching exercises, can reduce pain and improve the range of motion of the knee.[79]	(IIbA)
4. Thermotherapy (heat and cold) may help to improve the symptoms of knee OA.[79]	(IIaA)
5. The use heat to reduce pain and stiffness before performing flexion exercises in moderate and persistent pain is recommended.[81]	(IB)
6. A program of flexibility, stretching, and strengthening exercises for symptomatic knee OA is recommended as this reduces pain during walking and climbing stairs and improves the strength of the quadriceps femoris.[83]	(IA)
7. A daily walk is recommended as this improves muscle strength, aerobic capacity, and endurance; facilitates a good night's sleep; and reduces knee pain.[81]	(IA)
8. Aerobic exercise can be implemented gradually and progressively according to each patient's level of fitness at a frequency of three or more times per week, with a minimum duration of 20 to 30 minutes per session.[81]	(IA)
9. Exercises for concentric contraction of the flexor and extensor muscles of the knee are indicated as these have been shown to reduce pain both at rest and during activity.[82]	(IA)
10. Support devices may be useful for reducing pain and stiffness and improving the functionality of the knee.[79] Insoles and knee braces have been shown to decrease valgus or varus and knee pain.	(IIaA)
11. The use of bandage tape may help to reduce pain in patients with joint instability knee OA.[81]	(IIaB)
12. The use of assistive devices such as a walking stick, walker, or crutches is suggested as a preventive measure. A walking stick must be used in the contralateral hand and the height must be adjusted to the level of the greater trochanter, with the elbow bent at an angle of 25 to 30 degrees.[79]	(IIaB)
Pharmacological treatment modalities	
13. Acetaminophen/paracetamol is recommended at a dose of up to 3 g/day for the treatment of mild pain resulting from knee OA. Moderate gastrolesive effects may occur and patients should be monitored for possible hepatic complications.[63,88]	(IB)
14. NSAIDs such as diclofenac, ibuprofen, and naproxen, and selective NSAIDs including celecoxib and etoricoxib are indicated in moderate pain.[89,90] In all cases, gastric protection, such as a proton-pump inhibitor, is required[91] and naproxen is recommended in patients with cardiovascular risk.[92]	(IA)
15. Topical NSAIDs may be indicated in patients with gastrointestinal risk, even though the analgesic response decreases after 1 year of use.[93–95]	(IA)
16. The use of tramadol in the case of severe pain in its various administration forms is recommended.[115]	(IA)
17. Capsaicin gel was shown to be an effective treatment for knee OA accompanied by mild to moderate pain.[96]	(IIB)
18. Intra-articular corticosteroid injection (ultrasound-guided) may be beneficial to provide fast pain relief.[69,70]	(IIaB)
19. Chondroitin sulfate has shown to have a beneficial effect on symptoms in patients with knee OA and a high safety profile. It has been proven that its effect persists for 3 months after stopping the treatment (carryover effect). Recent studies have provided evidence that chondroitin sulfate use may delay OA progression.[39,83–87]	(IA)
20. The combined use of glucosamine and chondroitin sulfate is indicated in patients with knee OA and moderate to severe pain.[97–100]	(IA)
21. Glucosamine may be beneficial for pain relief and for improving joint function in patients.[103,121]	(IA)
22. Avocado soybean unsaponifiable may help to slow the progression of joint damage associated with knee OA.[71,101]	(IIbA)
23. The administration of intra-articular steroids may be reasonable for knee OA accompanied by inflammation.[102]	(IIbB)
24. Intra-articular injection of hyaluronic acid of different molecular weights has proven to be beneficial in the treatment of knee OA.[103,104]	(IIaB)
25. Oral administration of hyaluronic acid may have a beneficial therapeutic effect in patients with symptomatic knee OA and may possibly have an even greater effect in relatively young patients.[82]	(IIbC)
26. The use of strontium ranelate may be beneficial for the treatment of knee pain.[105–107]	(IIbB)
27. Duloxetine may be helpful for knee OA accompanied by chronic pain.[108,109]	(IIbC)
28. The administration of low-dose oral steroids for a maximum of 12 weeks could be considered in patients older than 65 years.[110]	(IIbC)
29. Intra-articular injection of platelet-rich plasma may help to relieve pain associated with knee OA[111–117]; however, our recommendation is to conduct better quality studies.	(IIbC)
30. The use of a supplement containing omega-3 and omega-6 fatty acids, zinc and vitamin E could be considered to reduce pain and stiffness and improve joint function, and also to reduce the intake of NSAIDs/analgesics.[122–126]	(IIbB)

Continued next page

TABLE 4. *(Continued)*

Proposition	Level of Evidence
31. Intra-articular injection of mesenchymal stem cells derived from the infrapatellar fat pad may be effective at reducing pain and improving knee function.[128]	(IIIC)
Surgical treatment modalities	
32. There is no benefit associated with the use of arthroscopy in the treatment of knee OA, even in the presence of a partial meniscal tear.[133]	(IIIA)
33. In patients with a partial rupture of the meniscus, a partial meniscectomy performed arthroscopically may be beneficial, followed by a physical therapy program.[131,132]	(IIaB)
34. Total knee arthroplasty may be indicated owing to its outstanding effect on pain and stiffness and the improvement obtained in physical activity 6 months after intervention.[127–129,134,135] Proper preoperative planning is essential so that deformities (varus or valgus) and long-term instabilities may be corrected.	(IIaB)

on the treatment of hand, hip, and knee OA that could fit the needs of patients and specialists in America because of the significant differences in handling these patients. Moreover, the need to ensure proper care with the least economic impact, in a region in which many countries have large gaps in financial resources, and there is an important clinical diversity and various educational and cultural levels, suggests specific adaptation to regional characteristics. These recommendations for the management of patients with hand, hip, and knee OA are based on the best available evidence of benefit, safety, and tolerability of nonpharmacologic and pharmacologic and surgical treatment modalities and the consensus judgment of clinical experts from a wide range of disciplines balancing the benefits and harms of these treatments and incorporating their preferences and values.

Differences With Regard to ACR, OARSI, and EULAR

Although there are other consensus and guidelines[13,61,62,79] on the treatment of OA in the mentioned locations, this consensus focused on updating the information of the available modalities with the participation of the OA specialist and patients of 18 countries of America.

CONCLUSIONS

These recommendations are based on the consensus opinions of clinical experts from a wide range of disciplines taking available evidence into account while balancing the benefits and risks of nonpharmacological, pharmacological, and surgical treatment modalities, and incorporating their preferences and values. It is hoped that these recommendations will be utilized by healthcare providers involved in the management of patients with hand, hip, and knee OA.

The pharmacological management of OA has traditionally been centered on analgesics and NSAIDs; however, increasing toxicity warnings have been issued recently for paracetamol, traditional NSAIDs, and COX-2 inhibitors, making OA chronic treatment even more challenging. The value and therapeutic efficacy of these agents are unquestionable, but there is growing awareness that they should be used for short time periods and for specific flares of the disease. The use of safer alternatives suitable for long-term administration, such as chondroitin and glucosamine, is advisable and presents growing evidence of efficacy and safety, making them a suitable alternative for long-term control of the disease. On the other hand, the use of nonpharmacological treatments should also be taken into account due to the improvements that these may produce to the quality of life of the patient. Latin America is formed by different countries with background not similar to the European or North American countries in terms of patient education or drug availability. How conditions in different regions of Latin America will need consideration.

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REFERENCES

1. Pereira D, Peleteiro B, Araújo J, et al. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthritis Cartilage*. 2011;19:1270–1285.
2. Grotle M, Hagen KB, Natvig B, et al. Prevalence and burden of osteoarthritis: results from a population survey in Norway. *J Rheumatol*. 2008;35:677–684.
3. Forestier R, Francon A, Briole V, et al. Prevalence of generalized osteoarthritis in a population with knee osteoarthritis. *Joint Bone Spine*. 2011;78:275–278.
4. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2010;18:24–33.
5. Martin KR, Kuh D, Harris TB, et al. Body mass index, occupational activity, and leisure-time physical activity: an exploration of risk factors and modifiers for knee osteoarthritis in the 1946 British birth cohort. *BMC Musculoskelet Disord*. 2013;14:219.
6. Grotle M, Hagen KB, Natvig B, et al. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet Disord*. 2008;9:132.
7. Reginato AM, Riera H, Vera M, et al. Osteoarthritis in Latin America: study of demographic and clinical characteristics in 3040 patients. *J Clin Rheumatol*. 2015;21:391–397.
8. Silber S. A new and rapid scoring system to assess the scientific evidence from clinical trials. *J Interv Cardiol*. 2006;19:485–92.
9. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12. doi:10.1016/0197-2456(95)00134-4. PMID 8721797.
10. Moe RH, Kjeken I, Uhlig T, et al. There is inadequate evidence to determine the effectiveness of nonpharmacological and nonsurgical interventions for hand osteoarthritis: an overview of high-quality systematic reviews. *Phys Ther*. 2009;89:1363–1370.
11. Hagen KB, Smedslund G, Moe RH, et al. The evidence for non-pharmacological therapy of hand and hip OA. *Nat Rev Rheumatol*. 2009;5:517–519.

12. Mahendira D, Towheed TE. Systematic review of non-surgical therapies for osteoarthritis of the hand: an update. *Osteoarthritis Cartilage*. 2009;17:1263–1268.
13. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64:465–474.
14. Beasley J. Osteoarthritis and rheumatoid arthritis: conservative therapeutic management. *J Hand Ther*. 2012;25:163–171; quiz 172.
15. Wenham CY, Conaghan PG. Optimizing pain control in osteoarthritis. *Practitioner*. 2010;254:23–6, 2–3.
16. Valdes K, Marik T. A systematic review of conservative interventions for osteoarthritis of the hand. *J Hand Ther*. 2010;23:334–50; quiz 351.
17. Rannou F, Poiraudeau S. Non-pharmacological approaches for the treatment of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2010;24:93–106.
18. Kjeken I, Smedslund G, Moe RH, et al. Systematic review of design and effects of splints and exercise programs in hand osteoarthritis. *Arthritis Care Res (Hoboken)*. 2011;63:834–848.
19. Ye L, Kalichman L, Spittle A, et al. Effects of rehabilitative interventions on pain, function and physical impairments in people with hand osteoarthritis: a systematic review. *Arthritis Res Ther*. 2011;13:R28.
20. Kjeken I. Occupational therapy-based and evidence-supported recommendations for assessment and exercises in hand osteoarthritis. *Scand J Occup Ther*. 2011;18:265–281.
21. Myrer JW, Johnson AW, Mitchell UH, et al. Topical analgesic added to paraffin enhances paraffin bath treatment of individuals with hand osteoarthritis. *Disabil Rehabil*. 2011;33:467–474.
22. Gomes Carreira AC, Jones A, Natour J. Assessment of the effectiveness of a functional splint for osteoarthritis of the trapeziometacarpal joint on the dominant hand: a randomized controlled study. *J Rehabil Med*. 2010;42:469–474.
23. Ikeda M, Ishii T, Kobayashi Y, et al. Custom-made splint treatment for osteoarthritis of the distal interphalangeal joints. *J Hand Surg Am*. 2010; 35:589–593.
24. Rannou F, Dimet J, Boutron I, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. *Ann Intern Med*. 2009;150:661–669.
25. Boustedt C, Nordenskiöld U, Lundgren Nilsson A. Effects of a hand-joint protection programme with an addition of splinting and exercise: one year follow-up. *Clin Rheumatol*. 2009;28:793–799.
26. Rogers MW, Wilder FV. Exercise and hand osteoarthritis symptomatology: a controlled crossover trial. *J Hand Ther*. 2009;22: 10–17; discussion 19–20; quiz 18.
27. Espinosa MA, C. Cajigas JC, Esquivel JA. Reunión multidisciplinaria de expertos en diagnóstico y tratamiento de pacientes con osteoartritis. Actualización basada en evidencias. *Med Int Mex*. 2013;29:67–92.
28. Swindells MG, Logan AJ, Armstrong DJ, et al. The benefit of radiologically-guided steroid injections for trapeziometacarpal osteoarthritis. *Ann R Coll Surg Engl*. 2010;92:680–684.
29. Fioravanti A, Fabbroni M, Cerase A, et al. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. *Rheumatol Int*. 2009;29:961–965.
30. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2012:CD007400.
31. Marks JL, van der Heijde DM, Colebatch AN, et al. Pain pharmacotherapy in patients with inflammatory arthritis and concurrent cardiovascular or renal disease: a Cochrane systematic review. *J Rheumatol Suppl*. 2012;90:81–84.
32. Stukstette M, Hoogeboom T, de Ruiter R, et al. A multidisciplinary and multidimensional intervention for patients with hand osteoarthritis. *Clin Rehabil*. 2012;26:99–110.
33. Altman RD. New guidelines for topical NSAIDs in the osteoarthritis treatment paradigm. *Curr Med Res Opin*. 2010;26:2871–2876.
34. Barthel HR, Axford-Gatley RA. Topical nonsteroidal anti-inflammatory drugs for osteoarthritis. *Postgrad Med*. 2010;122:98–106.
35. Altman RD. Pharmacological therapies for osteoarthritis of the hand: a review of the evidence. *Drugs Aging*. 2010;27:729–745.
36. Altman RD. Early management of osteoarthritis. *Am J Manag Care*. 2010; (16 Suppl Management):S41–S47.
37. Spies-Dorgelo MN, van der Windt DA, Prins AP, et al. Diagnosis and management of patients with hand and wrist problems in general practice. *Eur J Gen Pract*. 2009;15:84–94.
38. Gabay C, Medinger-Sadowski C, Gascon D, et al. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. *Arthritis Rheum*. 2011;63:3383–3391.
39. Monfort J, Martel-Pelletier J, Pelletier JP. Chondroitin sulphate for symptomatic osteoarthritis: critical appraisal of meta-analyses. *Curr Med Res Opin*. 2008;24:1303–1308.
40. Moran SL, Duymaz A, Karabekmez FE. The efficacy of hyaluronic acid in the treatment of osteoarthritis of the trapeziometacarpal joint. *J Hand Surg Am*. 2009;34:942–944.
41. Shin EK, Osterman AL. Treatment of thumb metacarpophalangeal and interphalangeal joint arthritis. *Hand Clin*. 2008;24:239–250.
42. Smith AS, Dore CJ, Dennis L, et al. A randomised controlled trial of subcutaneous sodium salicylate therapy for osteoarthritis of the thumb. *Postgrad Med J*. 2010;86:341–345.
43. Mandl LA, Hotchkiss RN, Adler RS, et al. Injectable hyaluronan for the treatment of carpometacarpal osteoarthritis: open label pilot trial. *Curr Med Res Opin*. 2009;25:2103–2108.
44. Salini V, De Amicis D, Abate M, et al. Ultrasound-guided hyaluronic acid injection in carpometacarpal osteoarthritis: short-term results. *Int J Immunopathol Pharmacol*. 2009;22:455–460.
45. Bahadir C, Onal B, Dayan VY, et al. Comparison of therapeutic effects of sodium hyaluronate and corticosteroid injections on trapeziometacarpal joint osteoarthritis. *Clin Rheumatol*. 2009;28:529–533.
46. Ingegnoli F, Soldi A, Meroni PL. Power Doppler sonography and clinical monitoring for hyaluronic acid treatment of rhizarthrosis: a pilot study. *J Hand Microsurg*. 2011;3:51–54.
47. Keen HI, Wakefield RJ, Hensor EM, et al. Response of symptoms and synovitis to intra-muscular methylprednisolone in osteoarthritis of the hand: an ultrasonographic study. *Rheumatology (Oxford)*. 2010;49: 1093–1100.
48. Maarse W, Watts AC, Bain GI. Medium-term outcome following intra-articular corticosteroid injection in first CMC joint arthritis using fluoroscopy. *Hand Surg*. 2009;14:99–104.
49. Bartels EM, Bliddal H, Schøndorff PK, et al. Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage*. 2010;18: 289–296.
50. Güler-Yüksel M, Allaart CF, Watt I, et al. Treatment with TNF-alpha inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. *Osteoarthritis Cartilage*. 2010;18: 1256–1262.
51. Chevalier X, Eymard F, Richette P. Biologic agents in osteoarthritis: hopes and disappointments. *Nat Rev Rheumatol*. 2013;9:400–410.
52. Saviola G, Abdi-Ali L, Campostrini L, et al. Clodronate and hydroxychloroquine in erosive osteoarthritis: a 24-month open randomized pilot study. *Mod Rheumatol*. 2012;22:256–263.
53. Kozlow JH, Chung KC. Current concepts in the surgical management of rheumatoid and osteoarthritic hands and wrists. *Hand Clin*. 2011;27:31–41.

54. Diao E, Rosenwasser MP, Glickel SZ, et al. Arthritis of the thumb basal joint: old and new treatments for a common condition. *Instr Course Lect*. 2009;58:551–559.
55. Wajon A, Carr E, Edmunds I, et al. Surgery for thumb (trapeziometacarpal joint) osteoarthritis. *Cochrane Database Syst Rev*. 2009:CD004631.
56. Pritchett JW, Habryl LS. A promising thumb basal joint hemiarthroplasty for treatment of trapeziometacarpal osteoarthritis. *Clin Orthop Relat Res*. 2012;470:2756–2763.
57. Pardini AG Jr, Freitas AD, Chaves AB, et al. Comparative study between trapezium resection and tendon interposition with and without ligamentplasty in the management of carpometacarpal arthrosis of the thumb. *J Hand Microsurg*. 2009;1:7–11.
58. Kapoutsis DV, Dardas A, Day CS. Carpometacarpal and scaphotrapeziotrapezoid arthritis: arthroscopy, arthroplasty, and arthrodesis. *J Hand Surg Am*. 2011;36:354–366.
59. Abzug JM, Osterman AL. Arthroscopic hemiresection for stage II–III trapeziometacarpal osteoarthritis. *Hand Clin*. 2011;27:347–354.
60. Forthman CL. Management of advanced trapeziometacarpal arthrosis. *J Hand Surg Am*. 2009;34:331–334.
61. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72:1125–1135.
62. Hawkeswood JR. Evidence-based guidelines for the nonpharmacological treatment of osteoarthritis of the hip and knee. *BCMJ*. 2010;52:399–403.
63. Verkleij SP, Luijsterburg PA, Bohnen AM, et al. NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. *Osteoarthritis Cartilage*. 2011;19:921–929.
64. Beswick AD, Wylde V, Gooberman-Hill R, et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open*. 2012;2:e000435.
65. Ethgen O, Bruyere O, Richy F, et al. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *J Bone Joint Surg Am*. 2004; 86-A:963–974.
66. Burmester G, Lanas A, Biasucci L, et al. The appropriate use of non-steroidal anti-inflammatory drugs in rheumatic disease: opinions of a multidisciplinary European expert panel. *Ann Rheum Dis*. 2011;70: 818–822.
67. Lanas A, Garcia-Tell G, Armada B, et al. Prescription patterns and appropriateness of NSAID therapy according to gastrointestinal risk and cardiovascular history in patients with diagnoses of osteoarthritis. *BMC Med*. 2011;9:38.
68. Abdulla A, Adams N, Bone M, et al. Guidance on the management of pain in older people. *Age Ageing*. 2013;42(Suppl 1):i1–57.
69. Lambert RG, Hutchings EJ, Grace MG, et al. Steroid injection for osteoarthritis of the hip: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2007;56:2278–2287.
70. Micu MC, Bogdan GD, Fodor D. Steroid injection for hip osteoarthritis: efficacy under ultrasound guidance. *Rheumatology (Oxford)*. 2010;49: 1490–1494.
71. Christensen R, Bartels EM, Astrup A, et al. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage*. 2008;16:399–408.
72. Hand L, PRAC Recommends Suspending Drugs With Diacerein [Medscape Web site]. Available at: http://www.medscape.com/viewarticle/814067. Accessed July 15, 2015.
73. Lynch TS, Terry MA, Bedi A, et al. Hip arthroscopic surgery: patient evaluation, current indications, and outcomes. *Am J Sports Med*. 2013;41: 1174–1189.
74. Dieppe P, Judge A, Williams S, et al. Variations in the pre-operative status of patients coming to primary hip replacement for osteoarthritis in European orthopaedic centres. *BMC Musculoskelet Disord*. 2009;10:19.
75. Shan L, Shan B, Graham D, et al. Total hip replacement: a systematic review and meta-analysis on mid-term quality of life. *Osteoarthritis Cartilage*. 2014;22:389–406.
76. McHugh GA, Campbell M, Luker KA. Predictors of outcomes of recovery following total hip replacement surgery: a prospective study. *Bone Joint Res*. 2013;2:248–254.
77. Somayaji R, Barnabe C, Martin L. Risk factors for infection following total joint arthroplasty in rheumatoid arthritis. *Open Rheumatol J*. 2013;7: 119–124.
78. Hailer NP, Garellick G, Kärrholm J. Uncemented and cemented primary total hip arthroplasty in the Swedish Hip Arthroplasty Register. *Acta Orthop*. 2010;81:34–41.
79. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22:363–388.
80. Fary RE, Carroll GJ, Briffa TG, et al. The effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee: results of a double-blind, randomized, placebo-controlled, repeated-measures trial. *Arthritis Rheum*. 2011;63:1333–1342.
81. Brosseau L, Wells GA, Kenny GP, et al. The implementation of a community-based aerobic walking program for mild to moderate knee osteoarthritis (OA): a knowledge translation (KT) randomized controlled trial (RCT): Part I: The Uptake of the Ottawa Panel clinical practice guidelines (CPGs). *BMC Public Health*. 2012;12:871.
82. Tashiro T, Seino S, Sato T, et al. Oral administration of polymer hyaluronic acid alleviates symptoms of knee osteoarthritis: a double-blind, placebo-controlled study over a 12-month period. *ScientificWorldJournal*. 2012;2012:167928.
83. Wildi LM, Raynauld JP, Martel-Pelletier J, et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann Rheum Dis*. 2011;70:982–989.
84. Möller I, Pérez M, Monfort J, et al. Effectiveness of chondroitin sulphate in patients with concomitant knee osteoarthritis and psoriasis: a randomized, double-blind, placebo-controlled study. *Osteoarthritis Cartilage*. 2010;18(Suppl 1):S32–S40.
85. Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate. *Curr Med Res Opin*. 2008;24:3029–3035.
86. Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2009;60: 524–533.
87. Zegels B, Crozes P, Uebelhart D, et al. Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. *Osteoarthritis Cartilage*. 2013;21:22–27.
88. Schnitzer TJ, Tesser JR, Cooper KM, et al. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. *Osteoarthritis Cartilage*. 2009;17:1–7.
89. Moore RA, Moore OA, Derry S, et al. Responder analysis for pain relief and numbers needed to treat in a meta-analysis of etoricoxib osteoarthritis trials: bridging a gap between clinical trials and clinical practice. *Ann Rheum Dis*. 2010;69:374–379.
90. Hmamouchi I, Allali F, Tahiri L, et al. Clinically important improvement in the WOMAC and predictor factors for response to

non-specific non-steroidal anti-inflammatory drugs in osteoarthritic patients: a prospective study. *BMC Res Notes*. 2012;5:58.

91. Chan FK, Abraham NS, Scheiman JM, et al. Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. *Am J Gastroenterol*. 2008;103:2908–2918.
92. Schjerning Olsen AM, Fosbol EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation*. 2011;123:2226–2235.
93. Underwood M, Ashby D, Cross P, et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. *BMJ*. 2008;336:138–142.
94. Doi T, Akai M, Fujino K, et al. Effect of nonsteroidal anti-inflammatory drug plasters for knee osteoarthritis in Japanese: a randomized controlled trial. *Mod Rheumatol*. 2010;20:24–33.
95. Simon LS, Grierson LM, Naseer Z, et al. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain*. 2009;143:238–245.
96. Kosuwon W, Sirichatiwapee W, Wisanuyotin T, et al. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. *J Med Assoc Thai*. 2010;93:1188–1195.
97. Lee YH, Woo JH, Choi SJ, et al. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. *Rheumatol Int*. 2010;30:357–363.
98. Fransen M, Agaliotis M, Nairn L, et al. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis*. 2015;74:851–858.
99. Sawitzke AD, Shi H, Finco MF, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Ann Rheum Dis*. 2010;69:1459–1464.
100. Martel-Pelletier J, Roubille C, Abram F, et al. First-line analysis of the effects of treatment on progression of structural changes in knee osteoarthritis over 24 months: data from the osteoarthritis initiative progression cohort. *Ann Rheum Dis*. 2015;74:547–556.
101. Maheu E, Cadet C, Marty M, et al. Randomised, controlled trial of avocado-soybean unsaponifiable (Piascledine) effect on structure modification in hip osteoarthritis: the ERADIAS study. *Ann Rheum Dis*. 2014;73:376–384.
102. Hirsch G, Kitas G, Klocke R. Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief—a systematic review. *Semin Arthritis Rheum*. 2013;42:451–473.
103. Miller LE, Block JE. US-approved intra-articular hyaluronic acid injections are safe and effective in patients with knee osteoarthritis: systematic review and meta-analysis of randomized, saline-controlled trials. *Clin Med Insights Arthritis Musculoskelet Disord*. 2013;6:57–63.
104. Shen X, Gatti R. The safety and efficacy of intra-articular dual molecular weighted hyaluronic acid in the treatment of knee osteoarthritis: the I.d.e.h.a. Study. *Orthop Rev (Pavia)*. 2013;5:e33.
105. Reginster JY, Badurski J, Bellamy N, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. *Ann Rheum Dis*. 2013; 72:179–186.
106. Lafeber FP, van Laar JM. Strontium ranelate: ready for clinical use as disease-modifying osteoarthritis drug? *Ann Rheum Dis*. 2013;72: 157–161.
107. Jones B. Osteoarthritis: evaluating strontium ranelate treatment for knee OA. *Nat Rev Rheumatol*. 2012;8:693.
108. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain*. 2009;146: 253–260.
109. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. *Age Ageing*. 2012;41:646–652.
110. Abou-Raya A, Abou-Raya S, Khadrawi T, et al. Effect of low-dose oral prednisolone on symptoms and systemic inflammation in older adults with moderate to severe knee osteoarthritis: a randomized placebo-controlled trial. *J Rheumatol*. 2014;41:53–59.
111. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord*. 2012;13:229.
112. Sanchez M, Anitua E, Azofra J, et al. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. *Clin Exp Rheumatol*. 2008;26:910–913.
113. Sampson S, Reed M, Silvers H, et al. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *Am J Phys Med Rehabil*. 2010;89:961–969.
114. Wang-Saegusa A, Cugat R, Ares O, et al. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. *Arch Orthop Trauma Surg*. 2011;131:311–317.
115. Napolitano M, Matera S, Bossio M, et al. Autologous platelet gel for tissue regeneration in degenerative disorders of the knee. *Blood Transfus*. 2012;10:72–77.
116. Spakova T, Rosocha J, Lacko M, et al. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil*. 2012;91:411–417.
117. Dold AP, Zywiel MG, Taylor DW, et al. Platelet-rich plasma in the management of articular cartilage pathology: a systematic review. *Clin J Sport Med*. 2014;24:31–43.
118. Davis AJ, Smith TO, Hing CB, et al. Are bisphosphonates effective in the treatment of osteoarthritis pain? A meta-analysis and systematic review. *PLoS One*. 2013;8:e72714.
119. Garnero P, Aronstein WS, Cohen SB, et al. Relationships between biochemical markers of bone and cartilage degradation with radiological progression in patients with knee osteoarthritis receiving risedronate: the Knee Osteoarthritis Structural Arthritis randomized clinical trial. *Osteoarthritis Cartilage*. 2008;16:660–666.
120. Iwamoto J, Takeda T, Sato Y, et al. Effects of risedronate on osteoarthritis of the knee. *Yonsei Med J*. 2010;51:164–170.
121. Arti HR, Azemi ME. Comparing the effect of glucosamine and glucosamine with alendronate in symptomatic relieve of degenerative knee joint disease: a double-blind randomized clinical trial study. *Jundishapur J Nat Pharm Prod*. 2012;7:87–92.
122. Laslett LL, Dore DA, Quinn SJ, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. *Ann Rheum Dis*. 2012;71:1322–1328.
123. Bhattacharya I, Saxena R, Gupta V. Efficacy of vitamin E in knee osteoarthritis management of North Indian geriatric population. *Ther Adv Musculoskelet Dis*. 2012;4:11–19.
124. Jacquet A, Girodet PO, Pariente A, et al. Phytalgic, a food supplement, vs placebo in patients with osteoarthritis of the knee or hip: a randomised double-blind placebo-controlled clinical trial. *Arthritis Res Ther*. 2009; 11:R192.
125. Cao Y, Jones G, Cicuttini F, et al. Vitamin D supplementation in the management of knee osteoarthritis: study protocol for a randomized controlled trial. *Trials*. 2012;13:131.

126. Peregoy J, Wilder FV. The effects of vitamin C supplementation on incident and progressive knee osteoarthritis: a longitudinal study. *Public Health Nutr*. 2011;14:709–715.

127. Wenham CY, Grainger AJ, Hensor EM, et al. Methotrexate for pain relief in knee osteoarthritis: an open-label study. *Rheumatology (Oxford)*. 2013;52:888–892.

128. Koh YG, Jo SB, Kwon OR, et al. Mesenchymal stem cell injections improve symptoms of knee osteoarthritis. *Arthroscopy*. 2013;29: 748–755.

129. Sloan FA, George LK, Hu L. Longer term effects of total knee arthroplasty from a national longitudinal study. *J Aging Health*. 2013; 25:982–997.

130. Bhatia D, Bejarano T, Novo M. Current interventions in the management of knee osteoarthritis. *J Pharm Bioallied Sci*. 2013;5:30–38.

131. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *N Engl J Med*. 2013;369:2515–2224.

132. de Groot IB, Bussmann HJ, Stam HJ, et al. Small increase of actual physical activity 6 months after total hip or knee arthroplasty. *Clin Orthop Relat Res*. 2008;466:2201–2208.

133. Shin CS, Lee JH. Arthroscopic treatment for osteoarthritic knee. *Knee Surg Relat Res*. 2012;24:187–192.

134. Luque R, Rizo B, Urda A, et al. Predictive factors for failure after total knee replacement revision. *Int Orthop*. 2014;38: 429–435.

135. Legout L, Senneville E. Periprosthetic joint infections: clinical and bench research. *ScientificWorldJournal*. 2013;2013:549091.

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

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ABSTRACT

Recent insights in rheumatoid arthritis (RA) necessitated updating the European League Against Rheumatism (EULAR) RA management recommendations. A large international Task Force based decisions on evidence from 3 systematic literature reviews, developing 4 overarching principles and 12 recommendations (vs 3 and 14, respectively, in 2013). The recommendations address conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) (methotrexate (MTX), leflunomide, sulfasalazine); glucocorticoids (GC); biological (b) DMARDs (tumour necrosis factor (TNF)-inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), abatacept, rituximab, tocilizumab, clazakizumab, sarilumab and sirukumab and biosimilar (bs) DMARDs) and targeted synthetic (ts) DMARDs (Janus kinase (Jak) inhibitors tofacitinib, baricitinib). Monotherapy, combination therapy, treatment strategies (treat-to-target) and the targets of sustained clinical remission (as defined by the American College of Rheumatology-(ACR)-EULAR Boolean or index criteria) or low disease activity are discussed. Cost aspects were taken into consideration. As first strategy, the Task Force recommends MTX (rapid escalation to 25 mg/week) plus short-term GC, aiming at >50% improvement within 3 and target attainment within 6 months. If this fails stratification is recommended. Without unfavourable prognostic markers, switching to—or adding—another csDMARDs (plus short-term GC) is suggested. In the presence of unfavourable prognostic markers (autoantibodies, high disease activity, early erosions, failure of 2 csDMARDs), any bDMARD (current practice) or Jak-inhibitor should be added to the csDMARD. If this fails, any other bDMARD or tsDMARD is recommended. If a patient is in sustained remission, bDMARDs can be tapered. For each recommendation, levels of evidence and Task Force agreement are provided, both mostly very high. These recommendations intend informing rheumatologists, patients, national rheumatology societies, hospital officials, social security agencies and regulators about EULAR's most recent consensus on the management of RA, aimed at attaining best outcomes with current therapies.

The management of rheumatoid arthritis (RA) has changed dramatically over the past 30 years. Few therapeutic agents existed then, which were either minimally or not efficacious, because of toxicity and the fact that optimal dosing and onset of action had not yet been elucidated for some agents.[1–4] Available therapies were started late rather than early in the course of the disease.[5 6] Early arthritis clinics were emerging,[7–9] and their successes fuelled reappraisal of the classification criteria then available that focused primarily on long-standing disease.[10] A therapeutic target had not yet been defined, because relief of symptoms appeared to be the most important goal and the concept of aiming at disease states like remission or low disease activity was at best aspirational.[11]

To date, we have available numerous efficacious agents. Among the conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs),[12] we adopted methotrexate (MTX), on its optimal use, as the anchor drug[4]; in addition, a number of biological (b) DMARDs have been approved, more recently followed (in many countries) by approval of the first targeted synthetic (ts) DMARD, with more in development.[13] Today, new classification criteria for RA promote the study of patients earlier in their disease course than before[14] and recommendations have been developed to treat patients with RA via strategic algorithms targeting an optimal outcome, irrespective of the types of available therapies.[15–17]

A limited number of measures to assess response in clinical trials and follow disease activity in

clinical practice are widely used[18–21] and the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have jointly developed new definitions for remission which provide an optimal clinical outcome and can be achieved in a significant proportion of patients in trials and practice.[22] Attaining remission according to these criteria, index-based or Boolean, will prevent joint destruction or at least progression of joint damage irrespective of residual subclinical changes,[23 24] optimise physical function, improve quality of life and work capacity[25 26] and reduce comorbidity risks.[27 28]

With this recent evolution of evidence supporting stringent disease control to improve outcomes, interest in purely symptomatic drugs has significantly decreased today and disease modification has become the pivotal attribute of all modern drugs and treatment strategies. Nevertheless, symptomatic agents as well as physical measures, psychological support and surgery may and do have a place in the overall management of RA. However, disease modification is the mainstay of RA treatment and constitutes an amalgam of characteristics: relief of signs and symptoms; normalisation—or at least important improvement—of impairment in physical function, quality of life and social and work capacity; and—as the foremost distinguishing characteristic of DMARDs compared with symptomatic agents—inhibition of structural damage to cartilage and bone. Therefore, showing inhibition of damage progression by radiography is still a pivotal outcome for the classification of a drug as a DMARD, since radiographs can depict bony and cartilage damage and have proven sensitivity to change even over short-term intervals and at very low levels of overall progression in a population.[29 30] Rapid attainment of the targeted end point is now critical, and to achieve the treatment goal of remission or at least low disease activity within the time frame of 6 months, at least 50% clinical improvement within 3 months is desirable.[31]

With rising standards of care and outcomes, RA management has become increasingly complex over the last decade. Despite the availability of many efficacious agents, treatment strategies that have been developed, and outcomes assessments that allow effective follow-up, the high costs of novel therapies have limited the widespread use of these therapeutic options, creating a significant extent of inequity. Therefore, management recommendations on the approach to treating patients with RA have become increasingly useful in providing physicians, patients, payers, regulators and other healthcare suppliers with evidence-based guidance supported by the views of experts involved in many of these novel developments. Indeed, EULAR has recently updated the standardised operating procedures on the development of recommendations, which include cost aspects in addition to accounting for the assessment of evidence and expert opinion.[32]

EULAR developed a first set of recommendations for the management of RA with DMARDs in 2010 and updated them in 2013. They were originally based on the evidence provided by five (2010) and three (2013)[33–35] systematic literature reviews (SLRs). The EULAR recommendations have been widely used. They have been referred to by national rheumatology societies and regional leagues to inform the development of their own recommendations (such as Canadian, French, German, Mexican, Asia Pacific League of Associations for Rheumatology (APLAR), Pan American League of Associations for Rheumatology (PANLAR)), as well as by regulatory authorities.[36–42]

Consistent with our approach to providing recommendations based on the latest evidence, we have continued to evaluate the literature on clinical trials of new agents, new information on established drugs, new strategic studies, new perceptions on outcomes assessments and new insights related to the research agenda[16] over the last 3 years. An abundance of new information motivated us to now further update the EULAR recommendations for the management of RA with DMARDs.

METHODS

After approval by the EULAR Executive Committee, the Convenor (JSS) and methodologist (RL) invited a Steering Committee and a Task Force to work on this update of the EULAR recommendations for the management of RA. The 2010 recommendations and their 2013 update adhered to the original EULAR standardised operating procedures for the development of recommendations[43]; the 2016 update followed the recently amended version of these standards,[32] which also suggest adherence to the Appraisal of Guidelines for Research & Evaluation (AGREE) recommendations in its updated version (AGREE II).[44]

Steering Committee

The Steering Committee included seven rheumatologists, one patient representative and three fellows. This group initially developed the research questions for the three SLRs. These SLRs focused on (i) efficacy of synthetic (s) DMARDs (as monotherapy or combination therapy, including both csDMARDs and ts DMARDs) and glucocorticoids (GC); (ii) efficacy of bDMARDs (as monotherapy or combined with csDMARDs) and (iii) safety aspects of sDMARDs and biological (b) DMARDs. To this end, the original SLRs obtained in 2013[33–35] served as a starting point and an update on the literature published between 2013 and 2016 was performed. New information on treatment strategies was also evaluated in the present SLRs. Formal economic analyses were not performed, but cost aspects were considered throughout the process in line with the current state of the art of developing recommendations,[45 46] EULAR's own previous SLR on cost aspects in the context of DMARD therapy[47] and the advent of biosimilars.[48] The three rheumatology fellows (KC, JN, SR) performed the SLRs (and checked each other's work) exploiting existing publication databases on randomised controlled trials for efficacy and registry data for safety, and also evaluating recent EULAR and ACR congress abstracts. Summary-of-findings (SoF) tables were generated and levels of evidence (LoE) were determined using the standards of the Oxford Centre for Evidence-Based Medicine.[49] The three SLRs informing the Task Force and a detailed description of their methods are published separately.[50–52]

The SoFs of the SLRs were presented to the Steering Committee that formulated a proposal for an update of the recommendations based on this information. The SLR data and the proposals of the Steering Committee were subsequently presented to the whole Task Force for further discussions and ultimately development of the updated recommendations.

Task Force

The Task Force consisted of 50 individuals, including the Steering Committee members. Among the Task Force members were three patients, two health professionals and two delegates of the EULAR young rheumatologists' network Emerging Eular NETwork (EMEUNET). The rheumatologists were all experienced in the treatment of RA and most had frequently participated in clinical trials; moreover, several of them had experience in patient registries of their countries or in various aspects of outcomes research. The patients and health professionals all had experience in consensus finding activities, as well as most of the rheumatologists. Since we also wished the Task Force's work to be informed by rheumatologists from other

regions of the world, aside from a broad representation from 14 European countries, 2 colleagues from Asia, 1 from Australia, 2 from Latin America and 2 from North America were invited to participate. Several of them had actively participated in developing documents of their regional leagues and/or national societies. All Task Force members declared their potential conflicts of interest before the start of the process.

The Task Force agreed on a few principal considerations upfront. First, all recommendations needed to be discussed in the context of new evidence; where no new evidence was available, the former evidence base was followed. Second, any of the previous recommendations (4 overarching principles and 14 recommendations) could be maintained as they had been presented in the 2013 version, amended, shifted in sequence or deleted. Third, drugs that were not (yet) approved in Europe but used elsewhere in the world, or drugs that had not yet undergone regulatory assessment but for which evidence from clinical trials was available, could be considered in recommendations to allow for some anticipation of a potential uptake in clinical practice, with all respective caveats. Finally, there was agreement that all recommendations of 2013, which were either further supported by new evidence or lacked novel information, should be incorporated as previously worded, unless certain components were now considered inappropriate.

After the presentation of the SLR results and the Steering Committee's proposals for the amendment of the recommendations, the Task Force was split into four breakout groups. One group reviewed bDMARDs, the second group csDMARDs, the third tsDMARDs and the fourth GC; all groups proposed draft language for respective recommendations to the whole Task Force. Safety aspects were addressed in each of these breakout groups.

Consensus finding

Representatives of each breakout group reported the results of the respective deliberations and presented proposals for the wording of individual recommendations to the whole Task Force. Thereafter, the voting process took place.

For an overarching principle or recommendation to be accepted for the final document without further change, a majority of 75% of the votes was required in the first ballot. If this result was not achieved, the respective text was amended and subjected to a second ballot, for which a 67% majority was required. If this ballot was not successful, further textual changes were proposed until a ≥50% majority was attained. The recommendations are presented as finally voted on. The results of the respective last ballot are presented as percentage of voting members. Notes captured the contents of the discussions and the reasoning behind each decision to be presented in the comments accompanying the individual items. For various reasons, not every Task Force member was present in the room throughout the whole meeting and, therefore, there were slight variations in the numbers of votes. However, at every point in time >90% of the members participated in the ballots.

After the face-to-face meeting, the recommendations, as agreed by the Task Force, were subjected to an anonymous vote (by email) on the levels of agreement (LoA). Each recommendation received an adjudication on a scale of 0–10, 0 meaning no agreement whatsoever and 10 absolute agreement. During this process, several weeks after the meeting, one individual withdrew from the Task Force, because the inclusion of csDMARD combination therapy in the recommendations had not found a majority during the preceding voting process. This colleague had been present and voted throughout the face-to-face meeting and the respective votes regarding all recommendations are accounted for accordingly, but ultimately the person declined authorship and no vote was cast on the LoA.

The draft of the manuscript was sent to all Task Force members for their comments. After incorporation of these comments, it was submitted to the EULAR Executive Committee for review and approval; at this time, it was again sent to the Task Force members. Final remarks were obtained from members of the Task Force and the Executive Committee and addressed in the manuscript, which was then submitted with approval by the EULAR Executive Committee.

RESULTS

General aspects

As before, the 2016 update of the EULAR RA management recommendations reflects the balance of clinical, functional and structural efficacy, safety, costs and patients' perceptions as perceived by the Task Force. Aspect of drug toxicity were considered in the overall wording of the recommendations, but data are presented only in the Safety SLR[50] because it is assumed that prescribers are aware of the safety information provided in the manufacturers' package inserts of the various agents. Also, EULAR has developed a series of documents dealing with safety aspects of RA drugs,[53–58] and various other publications have addressed these aspects.[59–62] In particular, as also suggested by the safety SLR,[50] the major risk of bDMARDs (and also tsDMARDs) is related to infections, and recommendations for vaccination[56] as well as a score allowing to calculate the risk of infection in patients exposed to bDMARDs have been recently developed.[63 64] For all medications discussed in this paper, the summary of product characteristics document provides valuable information on risks, side effects and need for monitoring. The recommendations given here should in no way be construed so as to detract from that information. In any case, when toxicity constitutes a major issue, a specific warning is provided within the respective recommendation or the accompanying comments. Of note, the three SLRs as well as the text accompanying each item should be regarded as part and parcel of the recommendation. The individual bullet points represent abbreviated conclusions from the discussions and, as such, do not capture all aspects related to a particular theme; rather, such aspects are elucidated in more detail in the respective explanatory part of the Results section.

When classifying DMARDs, the Task Force adhered to the previously used nomenclature[12 16] as shown in table 1. Table 1 also provides a glossary for terms employed in the recommendations. The Task Force did not distinguish between early and established RA regarding the recommendation of the types of drugs, but rather discerned phases of the treatment process by differentiating between patients who are naïve to any DMARD therapy, patients who had an insufficient response (IR) to initial course(s) of csDMARDs and those who had an IR to bDMARDs. There is currently no evidence for differential responses solely based on disease duration, when leaving differences in baseline damage due to delayed treatment initiation aside. Indeed, trials on MTX-naïve patients with RA used different disease durations for inclusion, which ranged from a few months to several years, without appreciable differences in outcomes on indirect comparison.[65–68] However, the Task Force distinguished between early and established RA in terms of the targeted outcome (see recommendation 2). The Task Force also took prognostic factors (table 1) into account, which have similar predictive power irrespective of disease duration.[69] Of note, recommendations for the management of early arthritis, including undifferentiated arthritis, have been recently

Table 1 Glossary and definitions

Term	Definition	
Poor prognostic factors	▶ Moderate (after csDMARD therapy) to high disease activity according to composite measures[71] ▶ High acute phase reactant levels[72 73] ▶ High swollen joint counts[72–74] ▶ Presence of RF and/or ACPA, especially at high levels[72 75] ▶ Combinations of the above[69 76] ▶ Presence of early erosions[72] ▶ Failure of two or more csDMARDs[77]	
Low-dose glucocorticoid	▶ ≤7.5 mg/day (prednisone equivalent)[57 78]	
Meanings of treatment reduction		
Tapering	▶ Usually reduction of drug dose or increase of application interval ('spacing') ▶ May include discontinuation (tapering to 0), but then only after slow reduction	
Cessation, discontinuation	Stopping of a particular drug	
Disease activity states		
Remission	ACR-EULAR Boolean or index-based remission definition[22]	
Low disease activity	Low disease activity state according to any of the validated composite disease activity measures that include joint counts[79–81]	
Moderate, high disease activity	Respective disease activity state according to any of the validated composite disease activity measures that include joint counts[79–81]	
DMARD nomenclature[12]		
Synthetic DMARDs	▶ Conventional synthetic DMARDs (csDMARDs)	For example, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
	▶ Targeted synthetic DMARDs (tsDMARDs)	For example, tofacitinib, baricitinib
Biological DMARDs	▶ Biological originator DMARDs (boDMARDs)	
	▶ Biosimilar DMARDs (bsDMARDs)	

ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; RF, rheumatoid factor.

updated.[70] The present recommendations address the management of patients with RA from the time of its diagnosis and not pre-RA or undifferentiated arthritis.

Overarching principles

As in previous versions, the Task Force endorsed the presentation of general principles for the treatment of patients with RA as overarching (table 2). Their nature is so generic that there was no requirement to base them on specific searches or LoE, but at the same time the group believed it is crucial to communicate them as a foundation on which the actual recommendations were based. However, while all three former overarching principles were maintained as formulated in 2010, the Task Force added a fourth one as overarching principle B.

A. *Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist*. This principle remained unchanged both in its textual details and in its place as item A, a prominent position within the recommendations. Shared decision-making between patient and rheumatologist involves all aspects of the disease: information on the disease and its risks, the modalities of disease assessment, decisions on the therapeutic target and the potential means to reach the target, the development of a management plan and discussions on the benefits and risks of individual therapies. These aspects have also been detailed in recommendations on standards of care.[82] Naturally, 'best care' refers to the recommendations presented here and inherently 'shared decision' relates to all individual recommendations. To this end also quality indicators have been developed more recently.[83]

B. *Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues*. This is a new principle. It derives from previous recommendation 14, the last item of the 2013 version, which was deemed by the current Task Force to represent such a central and self-evident rule to any therapeutic approach that it should constitute an overarching principle rather than a recommendation. Indeed, in line with these considerations, the level of evidence of this recommendation had been rather low in 2013. Withdrawing this item from the recommendations elicited some discussions. Especially the patients brought forward that ending the list of recommendations with an item on patient-related factors would convey prominence to patient preferences and patient aspects in the management of RA. However, the reasoning that this item would even benefit more from being a general principle than a recommendation, which was unlikely to ever be studied in all its subtleties, prevailed to an extent that principle B was unanimously accepted (table 2).

C. *Rheumatologists are the specialists who should primarily care for patients with RA*. Originally presented as item B, the wording of this principle was not changed. Of interest, in 2010 this was even presented as overarching principle A. However, over the last years, it was recognised that shared decision-making and considerations of patient factors should receive the most prominent recognition. Whether positioned as A, B or C, this item addresses the importance of specialty care for a complex disease like RA. There is compelling evidence that being cared for by a rheumatologist is advantageous for the patients in terms of early initiation of therapy, prevention of damage and reduction in surgical procedures.[84–88] Moreover, rheumatologists have the most profound experience regarding the use of csDMARDs and bDMARDs. This includes the adverse event profiles of these drugs, as well as awareness of and experience with comorbidities in RA. Therefore, rheumatologists

Table 2 The 2016 EULAR updated recommendations

	Overarching principles
A	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues
C	Rheumatologists are the specialists who should primarily care for patients with RA
D	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist
	Recommendations
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
4.	MTX should be part of the first treatment strategy
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered
8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD*[1,2] or a tsDMARD*[3] should be considered; current practice would be to start a bDMARD[§]
9.	bDMARDs*[1,2] and tsDMARDs[#3] should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs
10.	If a bDMARD* or tsDMARD[§] has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD
12.	If a patient is in persistent remission, tapering the csDMARD could be considered

The symbols (*, §, #) indicate different levels of evidence which are correspondingly provided together with voting results and levels of agreement in table 3.
[1]TNF-inhibitors: adalimumab, certolizumab pegol, etanercept, golimumb, infliximab boDMARDs or the respective EMA-approved/FDA-approved biosimilars.
[2]Abatacept, rituximab (as first bDMARD under special circumstances—see text), or tocilizumab or respective EMA-approved/FDA-approved biosimilars, as well as other IL-6 pathway inhibitors, sarilumab and/or sirukumab, once approved.
[3]Jak-inhibitors (where approved).
boDMARDs, biological originator DMARDs; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; Jak, Janus kinase; MTX, methotrexate; RA, rheumatoid arthritis; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs.

can provide the 'best care' in accordance with item A, in the sense of a holistic approach. The reasoning behind the term 'primarily' has been discussed amply in previous versions of the recommendations and relates to considerations of multidisciplinary care, including specialty nurses, and to the fact that in certain areas of the world rheumatology training is not sufficiently provided and other experts may have experience in the management of RA. Moreover, some comorbidities, such as chronic hepatitis or interstitial lung disease, may require consultation of, and treatment by, other specialists.

Table 3 Evidence levels, voting results and agreement

	LoE	SoR	Final vote (%)	Level of agreement (0–10)
A	n.a.	n.a.	100	9.9
B	n.a.	n.a.	100	9.9
C	n.a.	n.a.	100	9.8
D	n.a.	n.a.	98	9.7
1.	1a	A	96	9.9
2.	1a	A	91	9.6
3.	2b		100	9.5
4.	1a	A	71	9.8
5.	1a	A	85	9.0
6.	1a	A	98	8.7
7.	5	D	94	8.5
8.	*1b §5	*A §D	96	9.0
9.	*1a #1b	*A #A	96	9.2
10.	*1a §5	A* §D	71	9.1
11.	2b	B	86	9.0
12.	4	C	86	8.5

The symbols (*, §, #) relate to the corresponding symbols in the recommendations (table 2), showing the respective LoE.
LoE, levels of evidence; n.a., not available; SoR, strength of recommendation.

D. *RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist*. Again, this principle is worded exactly as last time, except that it was item C, but also last.[16] It is meant to remind all stakeholders that effective RA therapy—in spite of its direct costs—will reduce the economic burden on the individual patients, their families and society, which includes direct medical costs and indirect costs such as work disability and premature retirement. In this context, it must be borne in mind that direct medical costs accrue beyond those attributed to directly treating the overt manifestations of RA and include costs ensuing from comorbidities related to the inflammatory process. This point, however, is also meant to echo that cost-effective treatment approaches must be preferred as long as safety and outcomes are similar compared with more costly ones and in line with the therapeutic paradigms.[46] In some countries, the high cost of treatment is an important factor limiting the availability of modern therapies (inequity), and this factor has to be considered when choosing a treatment strategy.[89] In this respect, the advent of biosimilars provides potential for reduction of pressure on healthcare budgets.[48] At this point, it also must be considered that many patients still do not attain the therapeutic targets, despite all of our modern therapies and therapeutic strategies. Furthermore, any of the bDMARDs, if applied after at least one csDMARD and a bDMARD has failed, leads to only about 10% good treatment responses in terms of ACR70 rates.[90] These aspects impose the need to continue the search for new therapies or strategies.

Recommendations

General aspects

The Task Force's deliberative process resulted in 12 recommendations. The reduction by two recommendations compared with the past EULAR document may be somewhat surprising given

the allegedly increasing intricacy of therapeutic modalities and strategies. However, the content of recommendation 14 was shifted into the overarching principles as discussed above. Moreover, item 11 of the 2013 version, which addressed the use of tofacitinib, was deleted as a separate item, because Janus kinase (Jak) inhibitors as tsDMARDs have now entered into and expanded other recommendations; this will be discussed in more detail in the context of items 8, 9 and 10. Also former recommendation 6, which addressed the use of csDMARD combinations, was deleted by the Task Force; combination therapy with csDMARDs and the reasons to remove it from its previous prominence within the list of recommendations and the algorithm will be addressed in the discussion on recommendations 4 and 5. While three of the 2013 recommendations were deleted via either complete omission or incorporation into other items, former recommendation 8 which addressed the absence or presence of prognostic risk factors was split into new recommendations 7 and 8; a detailed rationale for this decision is discussed below.

The 12 recommendations form a logical sequence. They start with the need to initiate effective therapy immediately after diagnosis and the requirement to set a treatment target and to assess the disease on the way towards that target, employing a treat-to-target strategy. Such strategy has been strongly embedded into the recommendations since their first version in 2010. With these prerequisites in mind, different drugs or combinations of agents are recommended in the course of the therapeutic procedures, with suggested sequential increments, taking prognostic factors and all approved agents into account. They also mention some agents of potential future interest, even though not yet approved by international regulatory authorities. Thus, the recommendations also include a prospective view on drugs that have undergone phase III trials and were available for evidence assessment; obviously their actual prescription will depend on the regulatory approval status in individual countries. The set of recommendations concludes with suggestions towards reduction of therapy and even withdrawal of some drugs when the desired target has been attained and is sustained.

Individual recommendations

1. *Therapy with DMARDs should be started as soon as the diagnosis of RA is made*. This recommendation remained unchanged compared with 2013 and is one of the mainstays of any treatment approach to RA. It implies (i) the necessity to establish a diagnosis as early as possible, as has been reflected also in the 2010 ACR-EULAR classification criteria[14 91 92] and (ii) the advantage of early initiation of DMARD treatment ('as soon as possible'), which enables prevention of damage in a large proportion of patients.[87 93–95] Because of the generic nature of this bullet point, the Task Force did not specify the type of DMARD here. Indeed, all DMARDs enable a better long-term outcome on early, compared with delayed institution, and the sequence of the types of DMARD therapies is addressed in subsequent recommendations. The Task Force did not deal with pre-RA or undifferentiated arthritis and thus assumed that a diagnosis of RA had already been made. However, it should be borne in mind that any chronic arthritis, even if undifferentiated, requires appropriate treatment, including consideration of DMARD therapy, because it usually does not subside spontaneously,[96 97] and an update of the recommendations for management of early arthritis has just been presented by EULAR.[70] With a LoA of 9.9, this recommendation achieved the highest agreement of all items (table 2). LoE 1a; LoA 9.9.

2. *Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient*. This recommendation addresses two treatment targets: remission, especially in DMARD-naïve patients, and low disease activity, primarily in patients who failed previous therapies. Since clinical remission or low disease activity are mentioned as the sole therapeutic targets, any higher disease activity state has to be regarded as inadequate disease control, thus mandating a therapeutic change, obviously unless patient factors preclude this.[15] Communication with the patient to clarify and agree on the treatment goal and the means to attain this goal is of utmost importance. It allows alignment of the patient's and provider's considerations and aims and enhances adherence. In 2010, the notion 'as soon as possible' was also part of this item[98] and in the current discussion it was specifically decided to mention that the treatment target should be rapidly attained rather than aiming to achieve it in a more distant future. Indeed, there is sufficient evidence that most patients who do not attain significant improvement within 3 months, or do not achieve the treatment target within 6 months, will not reach the desired state subsequently[31 99–101]; exceptions pertain to those patients whose disease activity has been reduced to a level close to the treatment target.

Regarding remission, EULAR and ACR have agreed on Boolean and index-based definitions, the latter based on the Simplified or Clinical Disease Activity Index (SDAI, CDAI).[22] Both correlate highly with the absence of subclinical synovitis by MRI and sonography[102 103] and absence of progression of joint damage.[23] They can even be reliably used when drugs that interfere directly with the acute phase response are employed.[104–107] Moreover, recent strategic clinical trials that compared targeting sonographic remission with targeting clinical remission or low disease activity resulted in the conclusions that aiming at imaging remission had no advantages over the clinical target, but had economic disadvantages.[108 109] Low disease activity also needs to be properly defined and measured. Measures that highly weigh C reactive protein or erythrocyte sedimentation rate (eg, the disease activity score (DAS)28) may not convey sufficiently reliable results when used with agents that interfere with the acute phase response, such as anticytokine agents (especially interleukin (IL)-6 inhibitors) or Jak-inhibitors.[104 107 110]

It is important that the target-state should be sustained. The term 'sustained' is still not defined precisely, and different studies have used different definitions, but some voices in the Task Force suggested at least 6 months as a minimal time frame. This requires follow-up and a strategy to adapt therapy intensity upward or downward, aspects that are dealt with in subsequent recommendations. However, treatment intensification must take patient factors into consideration, especially risks and comorbidities (overarching principle B). LoE 1a; LoA 9.6.

3. *Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted*. This recommendation on treat-to-target is unchanged in position and formulation from the 2013 version. The frequencies of follow-up examinations should be adjusted in accordance with the level of disease activity, namely more frequently, such as monthly, when patients have high disease activity, and less frequently, such as every 6–12 months when the treatment target has been attained and sustained. EULAR generally recommends the use of a composite measure of disease activity that includes joint counts and the ACR-EULAR definitions for remission.[22 111] Improvement by

3 months refers to the fact that if a minimal change is not achieved, there is only a low likelihood of reaching the treatment target. Thus, a change to a better disease activity state should be seen at 3 months or a relative improvement, pertaining to at least 50% improvement in activity by a composite score, at that point in time, in order to have a considerable chance of reaching the target.[31 100 112 113] Of note, adjustment of therapy includes the optimisation of MTX (or other csDMARD) dose or route of administration,[4] or intra-articular injections of GC in the presence of one or few residual active joints, and refers to a change of drugs only if these measures have not been successful or are not appropriate. Furthermore, in an individual patient the treatment target may not have been fully achieved yet at 6 months. But if disease activity is close to the target, one may think about continuing the effective therapy for a few more weeks to make a final judgement, especially since a considerable proportion of patients may attain the target at a slightly later time point than at 6 months.[114 115] Consequently, the change in disease activity from baseline, and its slope should be considered when making treatment decisions. LoE 2b; LoA 9.5.

4. *MTX should be part of the first treatment strategy.* Compared with 2013, when this item read 'MTX should be part of the first treatment strategy in patients with active RA', the recommendation was slightly shortened. The Task Force felt that pointing to active disease was not necessary, since the EULAR recommendations primarily address patients with active disease. Based on its efficacy, safety (especially in the presence of folic acid), the possibility to individualise dose and method of administration as well as relatively low costs, MTX continues to be the anchor ('first') drug for patients with RA both as monotherapy as well as in combination with other drugs ('treatment strategy'; see below). Moreover, MTX appears to reduce comorbidities and mortality in RA.[116 117] In clinical trials of bDMARDs in early arthritis patients, MTX monotherapy has been associated with 25% ACR70 response rates (which brings patients into the range of low disease activity) within 6 months, even though it had not been combined with de novo GC in these trials.[90] MTX should be rapidly escalated, usually to 25–30 mg/week, orally or subcutaneously administered, with folic acid supplementation,[4] and the maximal MTX dose, if tolerated, should be sustained for about 8–12 weeks to judge the MTX treatment response. Indeed, when MTX is rapidly escalated to 25 mg/week, the response rate may even be higher (~40% low disease activity).[118] Of course, contraindications and the potential of early toxicity have to be taken into account; this is addressed in item 5. The doses mentioned here do not pertain to Asian patients. In China, it is not recommended to exceed 20 mg/week[115] and in Japan the maximum recommended dose for MTX is 16 mg/week.[119]

Of note, at this point in time the Task Force decided to delete previous recommendation 6 ('in DMARD-naïve patients, irrespective of the addition of GC, csDMARD monotherapy or combination therapy of csDMARDs should be used'). The inclusion or exclusion of combinations of csDMARDs within the bullet points elicited long debates within the respective breakout group and the whole Task Force (and the withdrawal of one Task Force member).

The first ballot of the Task Force involved a choice of the following two wordings: (a) 'MTX should be part of the first treatment strategy' and (b) 'in DMARD-naïve patients, irrespective of the addition of GC, csDMARD monotherapy or combination therapy of csDMARDs should be used' (identical with the respective 2013 recommendation), with 23 votes favouring (a), 22 votes favouring (b) and one abstention. Therefore, further discussions took place. Advocates in favour of including combination therapy referred to publications suggesting its superior efficacy compared with csDMARD monotherapy and similar efficacy compared with biological agents[120–124]; moreover, in some countries, csDMARD combination therapy is recommended by the national societies as preferred initial therapy.

Other Task Force members pointed to trials that did not show a real benefit of combination therapy (especially when csDMARD monotherapy was combined with GC in the comparator arms)[125–127]; differences in GC cointervention between combination and monotherapy arms in previous trials[128]; issues concerning the design of some investigator initiated trials suggesting superiority of csDMARD combinations[129]; the significantly higher rate of profound responses on combination with bDMARDs compared with the combination with csDMARD therapy after IR to MTX[123] and the higher level of toxicity of csDMARD combinations versus monotherapy.[126 130]

It was also argued that a higher prevalence of adverse events when using combination therapy, even though often mild, may preclude escalation of therapy and result in not reaching a full dose of some of the drugs. Also, the SLR on csDMARDs did not show evidence for superiority of csDMARD combinations compared with csDMARD monotherapy.[52] Moreover, the ACR Committee on the 2015 update of the ACR management guideline, in contrast to previous versions,[131] did not longer recommend csDMARD combination as initial therapy, but prioritised MTX monotherapy.[17] In line, the updated EULAR recommendations for the management of early arthritis do not advocate the use of csDMARD combination therapy.[70] It was also pointed out that choice (a) included the term 'treatment strategy' and thus comprised the option to use csDMARD combinations. These discussions resulted in a new ballot between two versions for recommendation 4: (a) 'MTX should be part of the first treatment strategy' (as above) and (b) 'MTX should be the first csDMARD, either as monotherapy or in combination with other csDMARDs'. In this second ballot a 71% majority voted for version (a). Thus, csDMARD combination therapy is no longer presented explicitly as initial treatment suggestion within the abbreviated list of recommendations. However, it should be mentioned that the simple fact that csDMARD combination therapy is not included in the bullet point anymore does not preclude using it. This is obviously at the discretion of the physician and the patient in light of all pros and cons that had been discussed ('shared decision').

This recommendation ultimately attained a very high LoA (9.8). The Task Force was well aware that in some countries, such as in the UK or Canada, rheumatologists are required to use at least two csDMARDs before the application of bDMARDs is approved by the payers and that combinations of two or three csDMARDs are accepted in lieu of two csDMARD courses. However, for the reasons just mentioned, the Task Force was not in favour of the practice to define an IR to a combination of csDMARDs as a failure of two or more csDMARDs (when in reality it constitutes only one therapeutic strategy) nor to preclude the approval of bDMARD use when a first csDMARD has failed and the patient has bad prognostic markers (see below item 8 and table 1). LoE 1a; LoA 9.8.

5. *In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.* The contents of this recommendation were maintained; however, compared with the previous version of item 5, the wording 'in cases of MTX contraindications' was slightly amended, because it is patients

who have contraindications, rather than 'cases'. The Task Force reiterated the relative safety of MTX and it was also discussed that the frequent fears of patients after reading the package insert should be addressed by providing appropriate information (overarching principle A). Nevertheless, there are occasional contraindications (eg, kidney or liver disease) or intolerances. Under these circumstances, leflunomide (dosed at 20 mg/day without loading dose)[132] or sulfasalazine (escalated to 3 g/day) are regarded the best alternatives. Older trials have suggested similar efficacy for both these drugs compared with MTX, although MTX was used at much lower doses than recommended today.[133 134] However, no new trials have been performed to disprove the previous conclusions. Among all the above agents, only sulfasalazine has an acceptable safety profile during pregnancy.[135] In some countries, parenteral gold is still used and, while clinical efficacy is undisputed, there are controversies regarding its safety[136 137]; in other countries, gold salts are not available any more. In contrast, the use of antimalarials, such as hydroxychloroquine and chloroquine, is still substantial, especially in combination therapy[122] or as monotherapy in patients with very mild disease,[138] particularly in China. Interestingly, antimalarials may have significant positive effects on lipid and glucose metabolism[139] and may reduce cardiovascular risk in RA.[140] However, joint damage is not retarded to a similar extent as with other csDMARDs.[141] This recommendation also uses the term 'treatment strategy' implying, as with MTX, that leflunomide and sulfasalazine can be used as monotherapy or in combination with other csDMARDs or biological agents.[142–145] Indeed, step-up combination therapy is frequently employed, even though comparing step-up combination with switching of csDMARD did not reveal significant differences in outcomes.[146] LoE 1a; LoA 9.0.

6. *Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible*. The added efficacy of GC when combined with csDMARDs is well established. Indeed, hitherto all trials comparing GC plus csDMARD with bDMARDs plus csDMARD revealed similar efficacy.[146 147] In 2013, GC were dealt with in recommendation 7, but the wording was different: 'low-dose GC should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible'. The current wording constitutes a compromise attempting to accommodate most of the concerns and suggestions raised during the Task Force's debate.

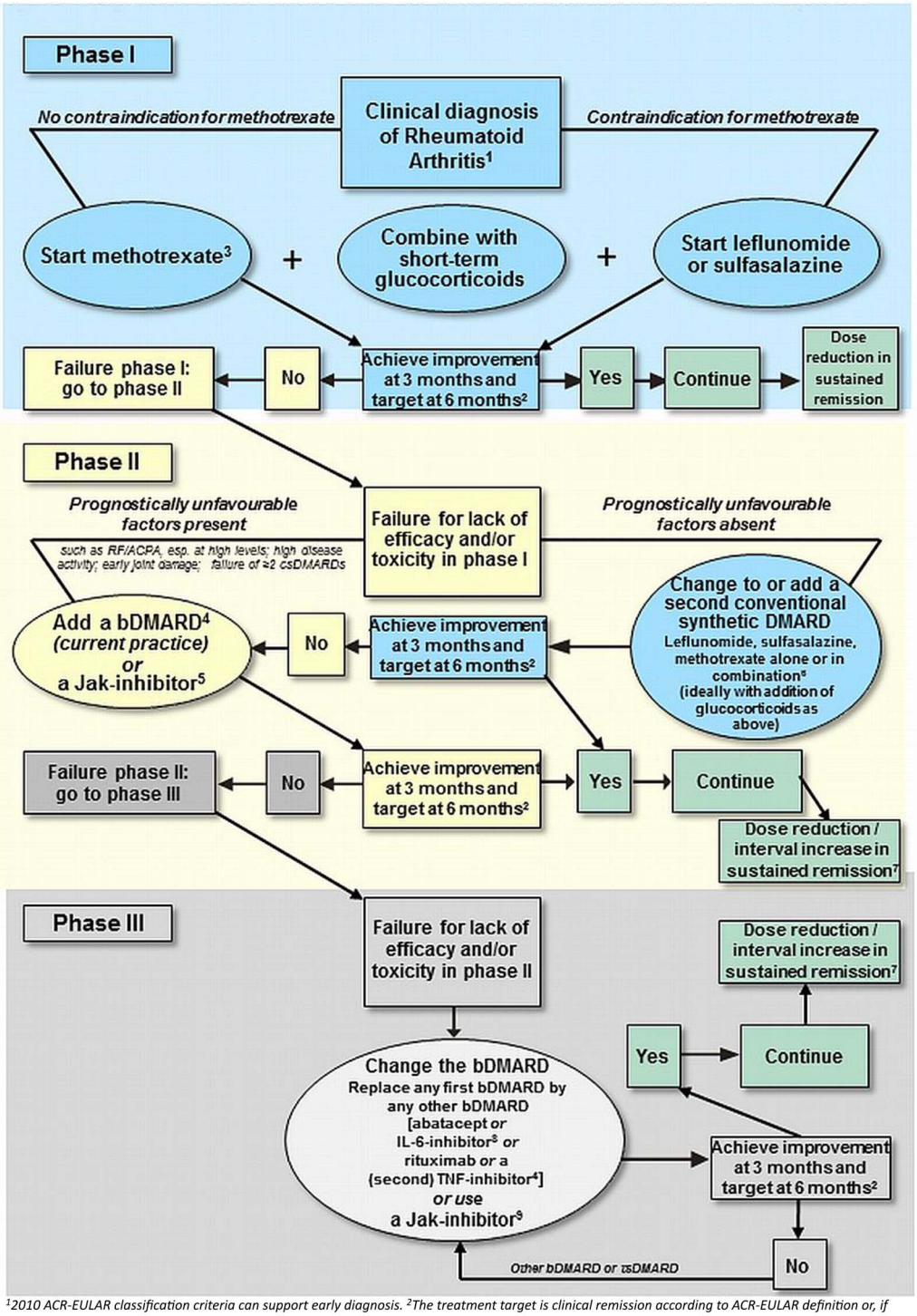
The term 'low-dose' was critically discussed. While all members of the Task Force agreed that high doses of GC should not be used for prolonged periods, it also became clear that the label 'low-dose' (which means a daily dose of 7.5 mg or less prednisone per day),[78 148] while preferred by some Task Force members, does not capture several current ways of GC application. Indeed, recent clinical trials have revealed the efficacy of short-term GC, but at doses >7.5 mg/day, namely orally at 30 mg starting dose,[126] as a single intramuscular injection of 120 mg methylprednisolone[125] or as a single 250 mg intravenous pulse therapy of methylprednisolone.[147] Therefore, the term 'low-dose' was deleted and replaced by 'short-term', leaving the choice about 'dose regimens and routes of administration' (another new piece of wording in this item) to the individual rheumatologist and patient. Indeed, it was argued that a single intramuscular or intravenous application entails a much lower cumulative dose than a few weeks of oral low-dose therapy, but this view was not shared by all Task Force members.

Yet another change involved the replacement of the phrase 'part of the initial treatment strategy' by 'when initiating or changing csDMARDs'. This change clarifies the intention of the Task Force, in that GC should be considered with all csDMARD starts, either as part of a first csDMARD therapy at the time of diagnosis or subsequently if an initial strategy has failed. Finally, the fact that csDMARDs are mentioned specifically implies that GC are typically not needed as a bridging therapy when bDMARDs or tsDMARDs are used, as these usually have a rapid onset of action and the infection risks may be potentiated.[149 150] Thus, it is important to reiterate that the Task Force recommends using GC in combination with csDMARDs primarily as bridging therapy until the csDMARD reaches its maximum effect, and this should be done using one of the dosing and tapering approaches mentioned above, for which respective evidence exists. To reflect the position of the Task Force, the algorithm depicted in figure 1 was modified to show a '+' for the use of GC in the new version rather than a '±' as previously.

By stating '…tapered as rapidly as clinically feasible', the Task Force underlines that GC should be gradually reduced and ultimately stopped, usually within 3 months from treatment start and only exceptionally by 6 months. Long-term use of GC, especially at doses above 5 mg/day, should be avoided because of the many potential risks presented in the SLR.[50 52 57] While some of these risk associations may be due to confounding by indication in patients with high disease activity,[151] the evidence for increased overall and cardiovascular mortality at a dose above a threshold of 7.5 mg/day or a cumulative dose of 40 g is considerable.[152] Of note, applying GC as a sole therapeutic change in patients with IR to csDMARD therapy does not convey good efficacy and is associated with significant adverse events.[153] Moreover, if GC cannot be withdrawn within the time frame mentioned above, the DMARD therapy may have to be considered a failure. Finally, intra-articular GC application may have to be considered in certain instances, such as a residually inflamed or a reactivated joint.

Some Task Force members advocated the chronic use of GC as a possibility for some patients; however, this proposal was not endorsed by the majority. While the bullet point on GC was, as in previous years, most heavily debated, the final wording received a 98% majority vote. However, the LoA was much lower (8.7), in line with previous versions of the recommendations. This relatively low LoA is presumably due to the fact that many Task Force members felt that this point was too liberal and the use of GC should be more restricted, while others were of the opinion that it was too restrictive. LoE 1a; LoA 8.7.

7. *If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered*. This sentence constitutes the first part of previous recommendation 8. It is essentially worded in an identical way, except that the last portion, 'change to another csDMARD strategy should be considered', was reworded as 'other csDMARDs should be considered', in light of the fact that combination with GC has now been recommended clearly also for this step of the treatment algorithm (item 6) and combinations of csDMARDs are not specifically recommended as initial treatment strategy anymore. The poor prognostic factors are presented in table 1. The Task Force also discussed that early intolerance for a csDMARD should not be considered as a treatment failure, which would imply moving immediately to the next phase of the algorithm, but rather require reinstitution of another first csDMARD (replacement). LoE 5; LoA 8.5.



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

Figure 1 Algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on rheumatoid arthritis (RA) management. ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; bDMARD, biological DMARD; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; MTX, methotrexate; RF, rheumatoid factor; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs.

8. *If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD* or a tsDMARD* should be considered; current practice would be to start a bDMARD*[§]. The separation of the second part of previous recommendation 8 ('when poor prognostic factors are present, addition of a bDMARD should be considered') and the new item 7 reflect the Task Force's desire to give stratification by prognostic factors more prominence. The bDMARDs currently available include a series of tumour necrosis factor (TNF)-inhibitors (adalimumab, certolizumab, etanercept, golimumab and infliximab); abatacept (a costimulation inhibitor); tocilizumab (an IL-6 receptor blocker, but in the future also possibly another IL-6 receptor inhibitor, sarilumab and IL-6 inhibitors, such as clazakizumab or sirukumab); rituximab (an anti-B-cell agent); both as biological originator (bo) DMARDs and as European Medicines Agency (EMA)-approved or Food and Drug Administration (FDA)-approved biosimilar (bs) DMARDs.

This recommendation was also expanded to include tsDMARDs, namely the Jak-inhibitor tofacitinib and further Jak-inhibitors, such as baricitinib. In the 2013 update, tsDMARDs (then recommendation 11) were recommended for use after a bDMARD had failed. Since then, more data on tofacitinib, especially regarding long-term safety aspects, and new data for baricitinib have been published. The data suggest that baricitinib may be more efficacious than a TNF-inhibitor.[154] Currently, the term tsDMARDs refers only to Jak inhibition. Tofacitinib is approved in many countries, such as in the USA, Latin America and Asia as well as some European countries, but at the time of developing the present recommendations still not in the European Union; baricitinib had completed phase III trials and was under regulatory review at that time and filgotinib and other Jak-inhibitors are undergoing evaluation in clinical trials (in the meantime baricitinib has been approved in the EU). However, similar to the 2010 recommendations, in which TNF-inhibitors had been given a slight preference over other biologics due to availability of long-term registry data for the former but not the latter, preference is given here to bDMARDs over Jak-inhibitors for the same reason. This notion on current practice is an expert opinion and not based on solid evidence. This bullet point still received a very high vote at the meeting and a high LoA.

The recommendation to use these agents in patients who have bad prognostic factors (rather than those who have not) is also not based on solid evidence in the literature. However, in most trials of bDMARDs and tsDMARDs, the existing inclusion criteria, such as high disease activity, presence of autoantibodies and pre-existing joint damage, assured that patients with bad prognostic factors were included. Nevertheless, formal trials comparing the use of any of these agents in patients with and without bad prognostic markers do not exist. On the other hand, several post hoc analyses revealed the value of using TNF-inhibitors in patients with bad prognostic markers (table 1) relative to those without.[69 76]

The footnote to bDMARDs mentions that all approved bDMARDs may be used without hierarchical positioning, and that EMA-approved or FDA-approved bsDMARDs have similar efficacy and safety as the respective boDMARDs, and should be preferred if they are indeed appreciably cheaper than originator or other bDMARDs or tsDMARDs. Since the 2013 update, several bsDMARDs targeting TNF have been approved in Europe and some in the USA.[155–157] Among the bDMARDs, there is no difference in outcomes, irrespective of their target. This conclusion rests on head-to-head trials, meta-analyses, the results of the SLRs[50–52 158] and indirect comparison (the latter being less reliable and therefore least informative).[13 159 160] Of note, the SLR also included available data from clinical trials of sarilumab, a human anti-IL-6 receptor antibody, and sirukumab, a human anti-IL-6 antibody, both of which are not approved at the present time; based on the SLR, the Task Force regarded these two antibodies and tocilizumab as having overall similar efficacy and safety.[51]

While rituximab is approved for use after TNF-inhibitors have failed, there is ample evidence for its efficacy in bDMARD-naïve patients and early RA.[60 159] It is, therefore, frequently used after IR to csDMARDs, especially when there are specific contraindications to other biological agents, such as past lymphoma or demyelinating disorders, given its efficacy in these diseases.[161 162]

The separation of points 7 and 8 was also based on the reason that the previous bullet point comprised two recommendations and that separating them would give the stratification by prognostic factors better visibility. The poor prognostic factors are presented in table 1 and now also include failure of two csDMARDs; if patients have insufficient efficacy to two csDMARD courses, a further csDMARD may have only little additional impact.[77 127]

The Task Force also discussed whether the use of a bDMARD as first-line therapy should be reconsidered, as had been the case in the original 2010 recommendations. Such use has been tested in a large number of randomised trials and has consistently been found to be statistically superior to MTX monotherapy. Importantly, however, none of the respective phase III trials used a combination with de novo GC in the MTX monotherapy arm and the few investigator-initiated studies that compared first-line bDMARDs plus MTX with GC plus MTX (or with a combination of csDMARDs) did not show a clear clinical or structural advantage of early bDMARD therapy.[127 147] Also, embedded within responders to initial treatment with bDMARDs+MTX are 20%–25% good responders to MTX alone, leading to overtreatment of these patients.[13] Finally, it was shown that patients who had an IR to MTX but then rapidly received bDMARD responded to a similar extent as those who had started with the bDMARD plus MTX.[68] Thus, this proposal for the early use of bDMARDs did not find a majority vote.

Nevertheless, it is still conceivable that an induction regimen followed by the subsequent cessation of the bDMARD and continuation of the csDMARD may become a valuable option in the future; there is some support in the literature for such an approach.[68 163–166] However, this would need further confirmation by additional trials before it could be put into place, especially also because the number of initial responders in whom tapering could be considered does not comprise a majority of the patients. The recommendation, as worded above, received 94% of the Task Force members' votes. LoE *1b, [§]5; LoA 9.0.

9. *bDMARDs* and tsDMARDs[#] should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs*. This recommendation replaces former no. 9 ('in patients responding insufficiently to MTX and/or other csDMARD strategies, with or without GC, bDMARDs (TNF-inhibitors, abatacept or tocilizumab, and, under certain circumstances, rituximab) should be commenced with MTX'). While the individual bDMARDs and tsDMARDs have been already discussed above, item 9 now refers to the fact that all bDMARDs have superior efficacy when combined with MTX than as monotherapy. Compared with the 2013 update, more evidence has now accrued in favour of combination, even for tocilizumab.[167–169] Also for baricitinib, combination therapy conveys better structural, although not clinical or functional

efficacy than monotherapy.[170] However, regarding signs and symptoms, physical function and joint damage, there are indications for a somewhat better efficacy of tocilizumab monotherapy, and more strongly so for Jak-inhibitors compared with MTX.[170–172] Monotherapy of the other biological agents has not been found clinically superior to MTX monotherapy.[66 67 173] MTX can be used at 7.5–10 mg to provide added efficacy to TNF-inhibitors[174 175] and intolerance at these low doses leading to discontinuation is very rare. Moreover, biologics can also be effectively combined with other csDMARDs.[142 144]

Another aspect, namely the occurrence of antidrug antibodies (immunogenicity), was discussed, especially regarding secondary non-response. In this context, the lack of knowledge about the role of non-adherence and non-persistence was also addressed. The Task Force then discussed routine testing of antidrug antibodies and drug levels and felt that there was little place for these in clinical practice, since a good clinical response would not lead to cessation of therapy even in the presence of antidrug antibodies, or low drug levels, and vice versa. Of note, the use of MTX at the doses mentioned above reduces the incidence of antidrug antibodies.[174 175]

For all these reasons the Task Force felt strongly (96% majority) that bDMARDs (and tsDMARDs) should primarily be added to, that is, combined with csDMARDs, such as MTX or leflunomide, leaving the option of monotherapy, with a preference for certain drugs, as an exception in case of intolerance or contraindication to all csDMARDs. LoE *1a, #1b; LOA 9.2.

10. *If a bDMARD* or tsDMARD§ has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action*. A similar recommendation was presented in 2013: 'If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or a biological agent with another mode of action'. Indeed, in a trial published after the elaboration of these recommendations, even primary non-responders to a TNF-inhibitor were shown to have some response to another anti-TNF, making it difficult to draw different conclusions for subsequent therapy for primary compared with secondary failures to TNF-blockers.[176] The addition in the first part ('or tsDMARD') was partly needed because tsDMARDs (Jak inhibition) are now included in the earlier recommendations 8 and 9; 'first' was deleted, because the Task Force did not decide to distinguish between failure of one or more bDMARDs. However, it must be noted that it is currently neither known if a Jak-inhibitor is effective once another one has failed nor established that a second IL-6 receptor inhibitor or inhibitors of the IL-6 ligand are effective if tocilizumab has failed—this is still part of the research agenda. We also lack studies exploring if TNF-inhibitors are efficacious and safe after bDMARDs with other modes of action have failed, and also studies investigating switching between these other modes of action. A few members raised the question if the use of csDMARDs should also be considered when bDMARDs had failed, but this suggestion did not find a majority.

The Task Force was also clear about its recommendations that any bDMARD, including another TNF-inhibitor, could be used if a TNF-inhibitor has previously failed. Thus, drugs with the same or with another mode of action are recommended in this situation. This was based on the data of clinical trials including meta-analyses[158] and on the fact that in contrast to registry data, which may be affected by a variety of confounders, several new prospective studies suggest that there is no difference between these two approaches.[177 178] If a second TNF-inhibitor fails, patients should receive an agent with another mode of action. However, it is self-evident (and supported by the vast majority of the Task Force members) that a bsDMARD of any of the reference boDMARDs should not be used if the respective boDMARD (or another bsDMARD of the same molecule) has failed to induce sufficient efficacy or vice versa. LoE *1a, §5; LoA 9.2.

11. *If a patient is in persistent remission after having tapered GC, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD*. This item remained unchanged compared with the 2013 publication. No new data have been published that contest this conclusion. Tapering here means reduction of dose or extension of interval between applications ('spacing'). It does not necessarily imply discontinuation of a bDMARD, which may lead to a recurrence of disease in a majority of patients.[179 180] However, even if treatment is stopped and patients flare, the majority of them (>80%) will recover their previous good outcome on reinstitution of therapy (but some do not),[180 181] and patients should be informed accordingly. There exist certain predictors in whom tapering will be likely successful and these relate primarily to early RA, depth of improvement and duration of remission[182]; prospective trials taking these aspects into consideration are needed in the future. This item also indirectly bolsters recommendation 9 on combination therapy of bDMARDs with MTX or another csDMARD, since it implies that bDMARDs should primarily, if not only, be tapered and possibly discontinued when combined with a csDMARD, while tapering and stopping of bDMARD monotherapy was not yet sufficiently studied. LoE 2b; LoA 9.0.

12. *If a patient is in persistent remission, tapering the csDMARD could be considered*. The 2013 version of the respective point 13 reads: 'In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician'. This item elicited significant discussions, since it would mean leaving patients with RA either without any or with a low dose of a csDMARD. But in general, no new evidence for or against this view has been found over the last years. In the discussion, controversies emerged. It was mentioned that here tapering means primarily reducing the dose and that discontinuing csDMARDs may be possible only in exceptional cases. Many rheumatologists on the Task Force panel expressed a view stating that csDMARDs should never be stopped. Consequently, this item received the lowest LoA (8.5) of all, although still quite high on the scale of 0–10. Of note, the portion worded 'as a shared decision between patient and physician' was now deleted. It was felt by the Task Force that mentioning the shared decision for this item among all 12 would imply that the other recommendations may not need to involve the patient, or single out this specific recommendation in comparison with all other ones and thus offset overarching principle A. Obviously, the removal of this phrase does not mean that shared decision making with the patients is not important, on the contrary: in line with principle A it is of utmost importance for this and for all other recommendations. LoE 4; LoA 8.5.

The updated recommendations are depicted in an abbreviated way in figure 1. Part and parcel of this figure are the respective footnotes as well as the full text as presented here.

DISCUSSION

The 2016 update of the EULAR RA management recommendations was developed by 50 experts, including patients,

rheumatologists and other healthcare professionals. This was the largest Task Force ever convened for the development of EULAR recommendations, both with respect to the overall number of members and the number of European countries involved, and it is also the first EULAR Task Force with a broad international representation, since rheumatologists from several other continents participated in this activity. This allowed us to also include some views from Asia, and Latin America and North America in the development of the recommendations, an input desired given the information provided in the recent publications of the updated ACR and the APLAR recommendations.[17 39]

The 2016 update presents the hitherto 'leanest' EULAR recommendations for RA management. While in 2010 the document comprised 3 overarching principles and 15 recommendations and in 2013 it contained 3 overarching principles and 14 recommendations, the 2016 update arrived with 4 principles and 12 recommendations. Despite this reduction, in light of a continuously increasing spectrum of therapeutic options and new information on existing agents and therapeutic strategies, this update covers more treatment aspects and is built on a better evidence base than ever before. This is due to the availability of at least partial answers to several of the research questions posed in 2013, such as items 4, 6, 9 and 21,[16] and of many new data on established and novel drugs as well as therapeutic strategies.

The Task Force adhered to several principles established in the course of the development of the 2013 update and even in 2010. For example, aside from evidence on efficacy and safety, economic aspects were generally considered in line with respective general specifications.[45 46] Also, agents that have not yet been approved by regulatory authorities but for which data from phase III trials were available, were considered with the caveat that their use would be only possible on such approval. This pertains to bsDMARDs, for which the Task Force relies on the stringency of the regulatory processes of EMA and FDA, for new IL-6 inhibitors and for Jak-inhibitors, the first of which was only licensed in some parts of the world at the time of developing these recommendations, with increasing availability of data on others. However, in the meantime baricitinib has been approved in the European Union. Finally, the Task Force reiterated its previous conclusions on the importance of stratification according to risk factors of adverse RA outcome,[69 76] once an initial therapy has failed.

The individual recommendations are not numbered by importance, but rather by a logical sequence: what is the treatment target and how should the patient be followed? What is the most prudent treatment approach once the diagnosis has been made? How can therapeutic success be maximised? Which therapies should follow a first treatment failure (phase I) and under which circumstances? Which agent or type of drug should be preferred in the course of the development of the treatment strategies?

Consequently, the first three items, which were either left fully unchanged or were only minimally changed, deal with the time point of starting effective therapy (as soon as the diagnosis is made and thus without any loss of time); with the definition of the treatment target (sustained remission or low disease activity); and with monitoring and the need to reach a significant improvement of disease activity within 3 months and attainment of the targeted state within 6 months. The preferred instruments to be used when following patients have been defined in previous EULAR activities[22 111] and comprise composite measures that include joint counts, such as the CDAI, DAS28 and SDAI as well as the ACR/EULAR remission definitions. Of note, instruments weighing acute phase reactants highly may exaggerate response, especially with IL-6 or Jak-inhibitors.

The treatment target (stringent remission or low disease activity) continues to be clinically defined, since focusing at ultrasonographic remission has not shown better outcomes compared with targeting clinical low disease activity or stringent remission, but rather induced overtreatment and thus inefficient use of healthcare resources.[108 109] Moreover, no strategy trial is available comparing the use of the serologic multibiomarker disease activity (MBDA) test with targeting remission using clinical disease activity assessment by a clinical composite measure (with which MBDA correlates anyway); of note, the MBDA test has been reported to improve to a larger extent on using a bDMARD that directly targets a cytokine compared with one that targets T-cell costimulation, despite similar clinical, functional and radiographic outcomes.[183] Moreover, it must be assumed that such test would falsely indicate high disease activity when an infection occurs. For all these reasons, the Task Force recommends to follow patients in clinical practice using a composite measure which comprises joint counts and may include an acute phase reactant. This clinical assessment is pertinent for every therapeutic phase (figure 1).

Subsequent recommendations, however, have undergone some significant changes compared with the 2013 update. While MTX (or in the presence of intolerance another csDMARD) continues to be considered the pivotal drug once the RA diagnosis has been made (item 4), it is recommended more strongly than before to escalate MTX to a dose of 25–30 mg weekly (with folate supplementation), given further recent insights on the high response rate with such strategy.[4 118] Moreover, the combination of csDMARDs, as monotherapy, with GC is more strongly suggested than before in light of increasing evidence that this combination is not surpassed by csDMARD combinations, even if they are applied with GC, or bDMARDs plus MTX in terms of efficacy and safety.[126 147] In the treatment algorithm (figure 1, phase I), this is reflected by the respective change from '±' to '+' for the addition of GC to csDMARDs. The term 'low-dose' GC has now been replaced by 'short-term' GC, given that various modes of application at different doses have shown to be efficacious. Moreover, the most important factors to reduce the risk of adverse event, such as cardiovascular events, infections, diabetes or hypertension,[151 152 184] was deemed to be rapid tapering to discontinuation and a low cumulative dose of GC. This is, indeed, the case with these alternative GC treatment modalities.

In contrast to the 2013 update, csDMARD combination therapy, with or without GC, is no longer an explicit part of the recommendations. This conclusion was based on the accruing evidence that this csDMARD combination therapy may not be superior to MTX monotherapy plus GC, but may be associated with an increase in adverse events.[126 130] A recent indirect-comparison meta-analysis has suggested a superiority of csDMARD combination versus MTX monotherapy.[185] This study was at odds with a previous direct-comparison meta-analysis[35 186] and with our own SLRs,[35 52 133] and indirect comparisons should also be considered with reservation since their rigour and value is insufficiently understood to date. Interestingly, using a somewhat different approach and based on an independent SLR, the ACR guideline has arrived at a similar conclusion as presented here and recommends MTX monotherapy as the first DMARD in early or established RA.[17] However, the use of csDMARD combination therapy is not precluded by the new recommendations, rather it is at the discretion of the

rheumatologist to apply it in the context of the recommendation on the use of MTX as a (first) treatment 'strategy'.

Once phase I has failed to reach the treatment target, either in the presence of bad prognostic markers or in the absence of bad prognostic markers after a second csDMARD strategy has failed, the Task Force recommends to add any bDMARD or, less preferably, a tsDMARD. If phase II as depicted in the algorithm fails to arrive at the treatment target, another bDMARD or a tsDMARD should be used. The Task Force reiterated its position that if a TNF-inhibitor fails, another TNF-inhibitor—but not a biosimilar of the same molecule!—can be as effective as changing the mode of action. Vice versa, an effective biological agent should not be switched to another bDMARD for non-medical reasons. However, important data are missing for some of the drugs; for example, clinical trials did not address the efficacy of a TNF-inhibitor after bDMARDs with other modes of action or a Jak-inhibitor has failed. Similar questions arise for the other agents and also for the use of IL-6R or IL-6 inhibitors, such as sarilumab or sirukumab, after tocilizumab has failed (box 1).

Early bDMARD treatment, including an induction regimen with subsequent withdrawal of bDMARDs as supported by some strategy trials, was discussed but did not find a majority among the Task Force members. This decision was based on the lack of evidence for superiority of such therapy compared with the use of MTX plus GC. Moreover, when placed in the context of a treat-to-target strategy, the initial use of csDMARDs yields equal results in the long-term. Finally, the cost-effectiveness of first-line bDMARD therapy, especially in light of the reasons just mentioned, is very poor.

The 2016 update of the EULAR recommendations is based on the most recent evidence in the area of RA management and on discussions by a large and broadly international Task Force. The recommendations synthesise the current thinking on approaching RA treatment in a set of overarching principles and recommendations. These have been informed by SLRs on the efficacy and safety of the drugs. The Task Force is convinced that adhering to these recommendations, including shared decision making, defining the treatment target, assessing disease activity regularly with appropriate instruments and applying the sequence of drugs as proposed and in a treat-to-target strategy, will maximise the overall outcome in a vast majority of patients with RA. Still, a considerable proportion of patients will not reach the target despite all efforts, and for these patients new drugs will be needed. Also, new information from research activities on treatment strategies, predictive markers and other aspects will become available in the near future and will likely necessitate yet another update of the recommendations in about 3 years; maybe we will then have new data on the research agenda, including precision medicine approaches in RA which allow predicting who will best respond to which drug at which stage of the disease. Until then we hope that the 2016 update will be broadly applied in clinical practice and/or serve as a template for national societies to develop local recommendations.

Box 1 Research agenda

1. How does MTX monotherapy in combination with glucocorticoids compare with monotherapies of sulfasalazine or leflunomide in combination with glucocorticoids, at the doses of csDMARDs as used today?
2. In what proportion of patients is an induction therapy with a bDMARD+MTX with subsequent cessation of the bDMARD effective in inducing sustained remission?
3. Is the application of a TNF-inhibitor after abatacept, tocilizumab, rituximab or a Jak-inhibitor has failed, safe and efficacious?
4. How safe and efficacious are abatacept, tocilizumab and rituximab after any of the other non-TNF-inhibitor-bDMARDs or a tsDMARD has failed?
5. How safe and efficacious is the use of an IL-6 pathway inhibitor if another IL-6 pathway inhibitor/a Jak-inhibitor has failed?
6. How safe and efficacious is the use of a Jak-inhibitor after another IL-6 pathway inhibitor/another Jak-inhibitor has failed?
7. Is the risk stratification as recommended by EULAR after failure of MTX improving outcome in those with risk factors and not harming those without bad prognostic markers? Do patients who lack bad prognostic factors benefit as much from a switch or addition of a csDMARD as from the addition of a bDMARD?
8. Can we find predictors of differential response to the different bDMARDs and tsDMARDs?
9. When starting a DMARD, how can we best predict who will attain the treatment target (remission or low disease activity) and who not?
10. Can we predict who will maintain remission after withdrawal of a bDMARD?
11. Will we be able to develop precision (personalised, stratified) medicine approaches in RA?
12. Is tapering of bDMARD monotherapy, where potentially indicated, comparable with bDMARD tapering in the presence of csDMARDs?
13. Will RCTs on tapering of bDMARDs following the deducted predictors for successful withdrawal of bDMARDs show success?
14. How good is patient adherence to a bDMARD or tsDMARD and can non-adherence explain secondary loss of efficacy?
15. Is measurement of serum drug or antidrug antibody levels useful in clinical practice?
16. Which biomarkers will help to find better predictors of bad outcome or response and which have failed in the numerous clinical trials that evaluated gene-expression and other biomarkers?
17. What is the effect of csDMARD, tsDMARD and bDMARD therapies on cardiovascular outcomes and to which extent is a potential effect dependent on a clinical response?

Is the use of telemedicine or e-medicine approaches as effective as direct contact in the clinic for treat-to-target strategies? bDMARDs, biological DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; Jak, Janus kinase; MTX, methotrexate; RA, rheumatoid arthritis; RCT, randomised controlled trial; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic DMARDs.

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Correction notice This article has been corrected since it published Online First. At the time of the online publication, baricitinib had received marketing authorisation in the EU; tofacitnib had already received a positive opinion but not yet marketing authorisation in the EU. This has now been obtained between online and print publication.

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REFERENCES

1 Wilske KR, Healey LA. Challenging the therapeutic pyramid: a new look at treatment strategies for rheumatoid arthritis. *J Rheumatol* 1990;17(Suppl 25):4–7.
2 McCarty DJ. Suppress rheumatoid inflammation early and leave the pyramid to the Egyptians. *J Rheumatol* 1990;17:1117–8.
3 Weinblatt ME. Efficacy of methotrexate in rheumatoid arthritis. *Br J Rheumatol* 1995;34(Suppl 2):43–8.
4 Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis* 2009;68:1094–9.
5 Schumacher HR Jr, ed. *Primer on the rheumatic diseases*. 10th edn. Atlanta, GA: Arthritis Foundation, 1993.
6 van der Heide A, Jacobs JW, Bijlsma JW, *et al*. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. *Ann Intern Med* 1996;124:699–707.
7 Huizinga WJ, Machold KP, Breedveld FC, *et al*. Criteria for early rheumatoid arthritis: from Bayes' law revisited to new thoughts on pathogenesis. *Arthritis Rheum* 2002;46:1155–9.
8 van der Horst-Bruinsma IE, Speyer I, Visser H, *et al*. Diagnosis and course of early-onset arthritis: results of a special early arthritis clinic compared to routine patient care. *Br J Rheumatol* 1998;37:1084–8.
9 Emery P, Gough A. Why early arthritis clinics? *Br J Rheumatol* 1991;30:241–2.
10 Aletaha D, Breedveld FC, Smolen JS. The need for new classification criteria for rheumatoid arthritis. *Arthritis Rheum* 2005;52:3333–6.
11 Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? *Ann Rheum Dis* 1995;54:944–7.
12 Smolen JS, van der Heijde D, Machold KP, *et al*. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2014;73:3–5.
13 Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;388:2023–38.
14 Aletaha D, Neogi T, Silman AJ, III, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
15 Smolen JS, Breedveld FC, Burmester GR, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
16 Smolen JS, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
17 Singh JA, Saag KG, Bridges SL Jr, *et al*. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2016;68:1–25.
18 van der Heijde DMFM, van 't Hof M, van Riel PL, *et al*. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* 1993;20:579–81.
19 Prevoo MLL, van't Hof MA, Kuper HH, *et al*. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.

20 Smolen JS, Breedveld FC, Schiff MH, *et al*. A Simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)* 2003;42:244–57.
21 Aletaha D, Nell VPK, Stamm T, *et al*. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res* 2005;7:R796–806.
22 Felson DT, Smolen JS, Wells G, *et al*. American college of rheumatology/European league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.
23 Kavanaugh A, Fleischmann RM, Emery P, *et al*. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64–71.
24 van der Heijde D. Remission by imaging in rheumatoid arthritis: should this be the ultimate goal? *Ann Rheum Dis* 2012;71(Suppl 2):i89–92.
25 Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. *Arthritis Res Ther* 2014;16:R56.
26 Linde L, Sørensen J, Østergaard M, *et al*. Does clinical remission lead to normalization of EQ-5D in patients with rheumatoid arthritis and is selection of remission criteria important? *J Rheumatol* 2010;37:285–90.
27 Provan SA, Semb AG, Hisdal J, *et al*. Remission is the goal for cardiovascular risk management in patients with rheumatoid arthritis: a cross-sectional comparative study. *Ann Rheum Dis* 2011;70:812–7.
28 Thiele K, Huscher D, Bischoff S, *et al*. Performance of the 2011 ACR/EULAR preliminary remission criteria compared with DAS28 remission in unselected patients with rheumatoid arthritis. *Ann Rheum Dis* 2013;72:1194–9.
29 Bruynesteyn K, Landewé R, van der Linden S, *et al*. Radiography as primary outcome in rheumatoid arthritis: acceptable sample sizes for trials with 3 months' follow up. *Ann Rheum Dis* 2004;63:1413–8.
30 Cohen SB, Dore RK, Lane NE, *et al*. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. *Arthritis Rheum* 2008;58:1299–309.
31 Aletaha D, Alasti F, Smolen JS. Optimisation of a treat-to-target approach in rheumatoid arthritis: strategies for the 3-month time point. *Ann Rheum Dis* 2016;75:1479–85.
32 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
33 Ramiro S, Gaujoux-Viala C, Nam JL, *et al*. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:529–35.
34 Nam JL, Ramiro S, Gaujoux-Viala C, *et al*. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:516–28.
35 Gaujoux-Viala C, Nam J, Ramiro S, *et al*. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:510–5.
36 Cardiel MH, Díaz-Borjón A, Vázquez del Mercado EM, *et al*. Update of the Mexican College of Rheumatology guidelines for the pharmacologic treatment of rheumatoid arthritis. *Reumatol Clin* 2014;10:227–40.
37 Wollenhaupt J, Albrecht K, Krüger K, *et al*. The new 2012 German recommendations for treating rheumatoid arthritis: differences compared to the European standpoint. *Z Rheumatol* 2013;72:6–9.
38 Brenol CV, Nava JI, Soriano ER. Proper management of rheumatoid arthritis in Latin America. What the guidelines say? *Clin Rheumatol* 2015;34(Suppl 1):S51–5.
39 Lau CS, Chia F, Harrison A, *et al*. APLAR rheumatoid arthritis treatment recommendations. *Int J Rheum Dis* 2015;18:685–713.
40 European Medicines Agency. Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. 2015. http://www ema europa eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187583 pdf
41 Gaujoux-Viala C, Gossec L, Cantagrel A, *et al*. Recommendations of the French Society for Rheumatology for managing rheumatoid arthritis. *Joint Bone Spine* 2014;81:287–97.
42 Bykerk VP, Schieir O, Akhavan P, *et al*. Emerging issues in pharmacological management of rheumatoid arthritis: results of a national needs assessment survey identifying practice variations for the development of Canadian Rheumatology Association clinical practice recommendations. *J Rheumatol* 2012;39:1555–8.
43 Dougados M, Betteridge N, Burmester GR, *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;63:1172–6.
44 Brouwers MC, Kho ME, Browman GP, *et al*. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839–42.
45 Guyatt GH, Oxman AD, Kunz R, *et al*. Incorporating considerations of resources use into grading recommendations. *BMJ* 2008;336:1170–3.
46 Holloway K, van Dijk L. *The world medicines situation 2011. Rational use of medicines*. WHO/EMP/MIE/2011.2.2. Geneva: World Health Organization, 2011.
47 Schoels M, Wong J, Scott DL, *et al*. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:995–1003.
48 Dörner T, Strand V, Cornes P, *et al*. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75:974–82.
49 OCEBM Levels of Evidence Working Group, Oxford Centre for Evidence-Based Medicine. The Oxford 2011 Levels of Evidence. 2011. http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
50 Ramiro S, *et al*. SLR on safety aspects of DMARDs to inform the EULAR RA management task force. *Ann Rheum Dis* 2016. In press.
51 Nam J, *et al*. SLR on bDMARDs to inform the EULAR RA management task force. *Ann Rheum Dis* 2016. In press.
52 Chatzidionysiou K. SLR on csDMARDs to inform the EULAR RA management task force 2016. *Ann Rheum Dis* 2016. In press.
53 Peters MJ, Symmons DP, McCarey D, *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
54 van der Goes MC, Jacobs JW, Boers M, *et al*. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis* 2010;69:1913–9.
55 Hoes JN, Jacobs JW, Boers M, *et al*. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007;66:1560–7.
56 van Assen S, Agmon-Levin N, Elkayam O, *et al*. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2011;70:414–22.
57 Strehl C, Bijlsma JW, de Wit M, *et al*. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. *Ann Rheum Dis* 2016;75:952–7.
58 Baillet A, Gossec L, Carmona L, *et al*. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis* 2016;75:965–73.
59 Furst DE, Keystone EC, So AK, *et al*. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis* 2013;72(Suppl 2):ii2–34.
60 Buch MH, Smolen JS, Betteridge N, *et al*. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:909–20.
61 Pereira R, Lago P, Faria R, *et al*. Safety of anti-TNF therapies in immune-mediated inflammatory diseases: focus on infections and malignancy. *Drug Dev Res* 2015;76:419–27.
62 Smolen JS, Schoels MM, Nishimoto N, *et al*. Consensus statement on blocking the effects of interleukin-6 and in particular by interleukin-6 receptor inhibition in rheumatoid arthritis and other inflammatory conditions. *Ann Rheum Dis* 2013;72:482–92.
63 Strangfeld A, Eveslage M, Schneider M, *et al*. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? *Ann Rheum Dis* 2011;70:1914–20.
64 Zink A, Manger B, Kaufmann J, *et al*. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014;73:1673–6.
65 St Clair EW, van der Heijde DM, Smolen JS, *et al*. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432–43.
66 Klareskog L, van der Heijde D, de Jager JP, *et al*. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675–81.
67 Breedveld FC, Weisman MH, Kavanaugh AF, *et al*. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.
68 Smolen JS, Emery P, Fleischmann R, *et al*. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet* 2014;383:321–32.
69 Vastesaeger N, Xu S, Aletaha D, *et al*. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. *Rheumatology (Oxford)* 2009;48:1114–21.

70 Combe B, Landewè R, Daien CI, *et al*. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis* 2016; doi: 10.1136/annrheumdis-2016-210602. [Epub ahead of print 15 Dec 2016].
71 Smolen JS, Han C, Van der Heijde DM, *et al*. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor-blockade. *Ann Rheum Dis* 2009;68:823–7.
72 Smolen JS, Van Der Heijde DM, St Clair EW, *et al*. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate without or with concomitant infliximab: results from the ASPIRE trial. *Arthritis Rheum* 2006;54:702–10.
73 van Leeuwen MA, van Rijswijk MH, Sluiter WJ, *et al*. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. *J Rheumatol* 1997;24:20–7.
74 Van der Heijde DM, van Riel PL, van Leeuwen MA, *et al*. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. *Br J Rheumatol* 1992;31:519–25.
75 Scott DL, Symmons DP, Coulton BL, *et al*. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987;1:1108–11.
76 Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, *et al*. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. *Ann Rheum Dis* 2010;69:1333–7.
77 Kiely P, Walsh D, Williams R, *et al*. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity—the early RA network (ERAN). *Rheumatology (Oxford)* 2011;50:926–31.
78 Duru N, van der Goes MC, Jacobs JW, *et al*. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2013;72:1905–13.
79 Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005;23:S93–9.
80 Aletaha D, Ward MM, Machold KP, *et al*. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005;52:2625–36.
81 Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006;32:9–44.
82 Stoffer MA, Smolen JS, Woolf A, *et al*. Development of patient-centred standards of care for rheumatoid arthritis in Europe: the eumusc.net project. *Ann Rheum Dis* 2014;73:902–5.
83 Navarro-Compán V, Smolen JS, Huizinga TW, *et al*. Quality indicators in rheumatoid arthritis: results from the METEOR database. *Rheumatology (Oxford)* 2015;54:1630–9.
84 Widdifield J, Bernatsky S, Paterson JM, *et al*. Quality care in seniors with new-onset rheumatoid arthritis: a Canadian perspective. *Arthritis Care Res (Hoboken)* 2011;63:53–7.
85 Memel DS, Somerset M. General practitioner and specialist care: the perceptions of people with rheumatoid arthritis. *Prim Health Care Res Dev* 2003;4:29–37.
86 Robinson PC, Taylor WJ. Time to treatment in rheumatoid arthritis: factors associated with time to treatment initiation and urgent triage assessment of general practitioner referrals. *J Clin Rheumatol* 2010;16:267–73.
87 Kyburz D, Gabay C, Michel BA, *et al*. The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study. *Rheumatology (Oxford)* 2011;50:1106–10.
88 Feldman DE, Bernatsky S, Houde M, *et al*. Early consultation with a rheumatologist for RA: does it reduce subsequent use of orthopaedic surgery? *Rheumatology (Oxford)* 2013;52:452–9.
89 Nasonov EL, Karateev DE. Does Russia need a treat-to-target initiative? *Rheumatology (Oxford)* 2015;54:381–2.
90 Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol* 2015;11:276–89.
91 Cader MZ, Filer A, Hazlehurst J, *et al*. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: comparison with 1987 ACR criteria in a very early synovitis cohort. *Ann Rheum Dis* 2011;70:949–55.
92 Radner H, Neogi T, Smolen JS, *et al*. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. *Ann Rheum Dis* 2014;73:114–23.
93 van Aken J, Lard LR, le Cessie S, *et al*. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. *Ann Rheum Dis* 2004;63:274–9.
94 Nell VP, Machold KP, Eberl G, *et al*. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2004;43:906–14.
95 Moura CS, Abrahamowicz M, Beauchamp ME, *et al*. Early medication use in new-onset rheumatoid arthritis may delay joint replacement: results of a large population-based study. *Arthritis Res Ther* 2015;17:197.
96 Machold KP, Landewé R, Smolen JS, *et al*. The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. *Ann Rheum Dis* 2010;69:495–502.
97 Verstappen SM, McCoy MJ, Roberts C, *et al*. Beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: results of the STIVEA trial. *Ann Rheum Dis* 2010;69:503–9.
98 Smolen JS, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.
99 Klarenbeek NB, Güler-Yüksel M, van der Kooij SM, *et al*. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann Rheum Dis* 2011;70:1039–46.
100 Aletaha D, Funovits J, Keystone EC, *et al*. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. *Arthritis Rheum* 2007;56:3226–35.
101 Schipper LG, Fransen J, den Broeder AA, *et al*. Time to achieve remission determines time to be in remission. *Arthritis Res Ther* 2010;12:R97.
102 Ranganath VK, Motamedi K, Haavardsholm EA, *et al*. Comprehensive appraisal of magnetic resonance imaging findings in sustained rheumatoid arthritis remission: a substudy. *Arthritis Care Res (Hoboken)* 2015;67:929–39.
103 Sakellariou G, Scirè CA, Verstappen SM, *et al*. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. *Ann Rheum Dis* 2013;72:245–9.
104 Genovese MC, Kremer J, Zamani O, *et al*. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016;374:1243–52.
105 Gabay C, Emery P, van Vollenhoven R, *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013;381:1541–50.
106 Smolen JS, Aletaha D. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. *Arthritis Rheum* 2011;63:43–52.
107 Fleischmann R, van der Heijde D, Koenig AS, *et al*. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? *Ann Rheum Dis* 2015;74:1132–7.
108 Dale J, Stirling A, Zhang R, *et al*. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. *Ann Rheum Dis* 2016;75:1043–50.
109 Haavardsholm EA, Aga AB, Olsen IC, *et al*. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. *BMJ* 2016;354:i4205.
110 Fleischmann R, Kremer J, Cush J, *et al*. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495–507.
111 Aletaha D, Landewé R, Karonitsch T, *et al*. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Ann Rheum Dis* 2008;67:1360–4.
112 Curtis JR, Luijtens K, Kavanaugh A. Predicting future response to certolizumab pegol in rheumatoid arthritis patients: features at 12 weeks associated with low disease activity at 1 year. *Arthritis Care Res (Hoboken)* 2012;64:658–67.
113 van der Heijde D, Keystone EC, Curtis JR, *et al*. Timing and magnitude of initial change in disease activity score 28 predicts the likelihood of achieving low disease activity at 1 year in rheumatoid arthritis patients treated with certolizumab pegol: a post-hoc analysis of the RAPID 1 trial. *J Rheumatol* 2012;39:1326–33.
114 Smolen JS, Wollenhaupt J, Gomez-Reino JJ, *et al*. Attainment and characteristics of clinical remission according to the new ACR-EULAR criteria in abatacept-treated patients with early rheumatoid arthritis: new analyses from the Abatacept study to Gauge Remission and joint damage progression in methotrexate (MTX)-naive patients with early erosive rheumatoid arthritis (AGREE). *Arthritis Res Ther* 2015;17:157.
115 Li R, Zhao JX, Su Y, *et al*. High remission and low relapse with prolonged intensive DMARD therapy in rheumatoid arthritis (PRINT): a multicenter randomized clinical trial. *Medicine (Baltimore)* 2016;95:e3968.
116 Choi HK, Hernán MA, Seeger JD, *et al*. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173–7.
117 Wasko MC, Dasgupta A, Hubert H, *et al*. Propensity-adjusted association of methotrexate with overall survival in rheumatoid arthritis. *Arthritis Rheum* 2013;65:334–42.
118 Emery P, Bingham CO III, Burmester GR, *et al*. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naive patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study. *Ann Rheum Dis* 2017;76:96–104.
119 Atsumi T, Yamamoto K, Takeuchi T, *et al*. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. *Ann Rheum Dis* 2016;75:75–83.

120 Mottonen T, Hannonen P, Leirisalo-Repo M, *et al*. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999;353:1568–73.
121 O'Dell JR, Haire CE, Erikson N, *et al*. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334:1287–91.
122 Moreland LW, O'Dell JR, Paulus HE, *et al*. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum* 2012;64:2824–35.
123 O'Dell JR, Mikuls TR, Taylor TH, *et al*. Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 2013;369:307–18.
124 van Vollenhoven RF, Geborek P, Forslind K, *et al*. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. *Lancet* 2012;379:1712–20.
125 de Jong PH, Hazes JM, Han HK, *et al*. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann Rheum Dis* 2014;73:1331–9.
126 Verschueren P, De Cock D, Corluy L, *et al*. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. *Ann Rheum Dis* 2015;74:27–34.
127 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, *et al*. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146:406–15.
128 Smolen JS, Aletaha D, Keystone E. Superior efficacy of combination therapy for rheumatoid arthritis. Fact or fiction? *Arthritis Rheum* 2005;52:2975–83.
129 Landewé RB, Smolen JS, Weinblatt ME, *et al*. Can we improve the performance and reporting of investigator-initiated clinical trials? Rheumatoid arthritis as an example. *Ann Rheum Dis* 2014;73:1755–60.
130 Verschueren P, De Cock D, Corluy L, *et al*. Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. *Ann Rheum Dis* 2017;76:511–20.
131 Singh JA, Furst DE, Bharat A, *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:625–39.
132 Cutolo M, Bolosiu H, Perdriset G. Efficacy and safety of leflunomide in DMARD-naive patients with early rheumatoid arthritis: comparison of a loading and a fixed-dose regimen. *Rheumatology (Oxford)* 2013;52:1132–40.
133 Gaujoux-Viala C, Smolen JS, Landewé R, *et al*. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1004–9.
134 Emery P, Breedveld FC, Lemmel EM, *et al*. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39:655–65.
135 Götestam Skorpen C, Hoeltzenbein M, Tincani A, *et al*. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75:795–810.
136 Rau R, Herborn G, Menninger H, *et al*. Radiographic outcome after three years of patients with early erosive rheumatoid arthritis treated with intramuscular methotrexate or parenteral gold. Extension of a one-year double-blind study in 174 patients. *Rheumatology (Oxford)* 2002;41:196–204.
137 Lehman AJ, Esdaile JM, Klinkhoff AV, *et al*. A 48-week, randomized, double-blind, double-observer, placebo-controlled multicenter trial of combination methotrexate and intramuscular gold therapy in rheumatoid arthritis: results of the METGO study. *Arthritis Rheum* 2005;52:1360–70.
138 Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol* 2011;23:278–81.
139 Hage MP, Al-Badri MR, Azar ST. A favorable effect of hydroxychloroquine on glucose and lipid metabolism beyond its anti-inflammatory role. *Ther Adv Endocrinol Metab* 2014;5:77–85.
140 Sharma TS, Wasko MC, Tang X, *et al*. Hydroxychloroquine use is associated with decreased incident cardiovascular events in rheumatoid arthritis patients. *J Am Heart Assoc* 2016;5:e002867.
141 Van der Heijde DM, van Riel PL, Nuver-Zwart IH, *et al*. Sulphasalazine versus hydroxychloroquine in rheumatoid arthritis: 3-year follow-up. *Lancet* 1990;335:539.
142 Strangfeld A, Hierse F, Kekow J, *et al*. Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. *Ann Rheum Dis* 2009;68:1856–62.
143 De Stefano R, Frati E, Nargi F, *et al*. Comparison of combination therapies in the treatment of rheumatoid arthritis: leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha. *Clin Rheumatol* 2010;29:517–24.
144 Burmester GR, Mariette X, Montecucco C, *et al*. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. *Ann Rheum Dis* 2007;66:732–9.
145 Genovese MC, McKay JD, Nasonov EL, *et al*. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008;58:2968–80.
146 Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, *et al*. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005;52:3381–90.
147 Nam JL, Villeneuve E, Hensor EM, *et al*. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). *Ann Rheum Dis* 2014;73:75–85.
148 Buttgereit F, da Silva JA, Boers M, *et al*. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002;61:718–22.
149 Listing J, Kekow J, Manger B, *et al*. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. *Ann Rheum Dis* 2015;74:415–21.
150 Lahiri M, Dixon WG. Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2015;29:290–305.
151 van Sijl AM, Boers M, Voskuyl AE, *et al*. Confounding by indication probably distorts the relationship between steroid use and cardiovascular disease in rheumatoid arthritis: results from a prospective cohort study. *PLoS ONE* 2014;9:e87965.
152 del Rincón I, Battafarano DF, Restrepo JF, *et al*. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheumatol* 2014;66:264–72.
153 Choy EH, Kingsley GH, Khoshaba B, *et al*. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. *Ann Rheum Dis* 2005;64:1288–93.
154 Taylor PC, Keystone EC, van der Heijde D, *et al*. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis (RA) and an inadequate response to background methotrexate therapy: results of a phase 3 study [Abstract]. *Arthritis Rheum* 2015;67(Suppl 10):L2.
155 Yoo DH, Prodanovic N, Jaworski J, *et al*. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. *Ann Rheum Dis* 2017;76:355–363.
156 Choe JY, Prodanovic N, Niebrzydowski J, *et al*. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:58–64.
157 Emery P, Vencovsky J, Sylwestrzak A, *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:51–57.
158 Schoels M, Aletaha D, Smolen JS, *et al*. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor α inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis. *Ann Rheum Dis* 2012;71:1303–8.
159 Porter D, van Melckebeke J, Dale J, *et al*. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. *Lancet* 2016;388:239–47.
160 Weinblatt ME, Schiff M, Valente R, *et al*. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum* 2013;65:28–38.
161 Hauser SL, Waubant E, Arnold DL, *et al*. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008;358:676–88.
162 Coleman M, Lammers PE, Ciceri F, *et al*. Role of rituximab and rituximab biosimilars in diffuse large B-cell lymphoma. *Clin Lymphoma Myeloma Leuk* 2016;16:175–81.
163 Emery P, Hammoudeh M, Fitzgerald O, *et al*. Sustained remission with etanercept tapering in early rheumatoid arthritis. *N Engl J Med* 2014;371:1781–92.
164 Detert J, Bastian H, Listing J, *et al*. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week

48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844–50.
165 Bijlsma JW, Welsing PM, Woodworth TG, *et al*. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. *Lancet* 2016;388:343–55.
166 Bejarano V, Conaghan PG, Quinn MA, *et al*. Benefits 8 years after a remission induction regime with an infliximab and methotrexate combination in early rheumatoid arthritis. *Rheumatology (Oxford)* 2010;49:1971–4.
167 Burmester GR, Rigby WF, van Vollenhoven RF, *et al*. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. *Ann Rheum Dis* 2016;75:1081–91.
168 Kaneko Y, Atsumi T, Tanaka Y, *et al*. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). *Ann Rheum Dis* 2016;75:1917–23.
169 Dougados M, Kissel K, Conaghan PG, *et al*. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. *Ann Rheum Dis* 2014;73:803–9.
170 Fleischmann R, Takeuchi T, Schlichting D, *et al*. Baricitinib, methotrexate, or baricitinib plus methotrexate in patients with early rheumatoid arthritis who had received limited or no treatment with disease-modifying anti-rheumatic drugs (DMARDs): phase 3 trial results [abstract]. *Arhritis Rheum* 2015;67(Suppl 10). http://acrabstracts.org/abstract/baricitinib-methotrexate-or-baricitinib-plus-methotrexate-in-patients-with-early-rheumatoid-arthritis-who-had-received-limited-or-no-treatment-with-disease-modifying-anti-rheumatic-drugs-dmards-p/ (accessed 4 Jan 2016).
171 Lee EB, Fleischmann RM, Hall S, *et al*. Radiographic, clinical and functional comparison of tofacitinib monotherapy versus methotrexate in methotrexate-nave patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:S1049.
172 Jones G, Sebba A, Gu J, *et al*. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010;69:88–96.
173 Emery P, Burmester GR, Bykerk VP, *et al*. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann Rheum Dis* 2015;74:19–26.
174 Maini RN, Breedveld FC, Kalden JR, *et al*. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552–63.
175 Burmester GR, Kivitz AJ, Kupper H, *et al*. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. *Ann Rheum Dis* 2015;74:1037–44.
176 Smolen JS, Burmester GR, Combe B, *et al*. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *Lancet* 2016;388:2763–74.
177 Torrente-Segarra V, Acosta Pereira A, Morla R, *et al*. VARIAR study: assessment of short-term efficacy and safety of rituximab compared to an tumor necrosis factor alpha antagonists as second-line drug therapy in patients with rheumatoid arthritis refractory to a first tumor necrosis factor alpha antagonist. *Reumatol Clin* 2016;12:319–322.
178 Manders SH, Kievit W, Adang E, *et al*. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. *Arthritis Res Ther* 2015;17:134.
179 Emery P, Hammoudeh M, Fitzgerald O, *et al*. Assessing maintenance of remission with reduced dose etanercept plus methotrexate, methotrexate alone, or placebo in patients with early rheumatoid arthritis who achieved remission with etanercept and methotrexate: the PRIZE study. *Ann Rheum Dis* 2013;72(Suppl 3):399.
180 Smolen JS, Emery P, Ferraccioli GF, *et al*. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. *Ann Rheum Dis* 2015;74:843–50.
181 Tanaka Y, Hirata S, Saleem B, *et al*. Discontinuation of biologics in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2013;31(Suppl 78):522–7.
182 Schett G, Emery P, Tanaka Y, *et al*. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. *Ann Rheum Dis* 2016;75:1428–37.
183 Fleischmann R, Connolly SE, Maldonado MA, *et al*. Brief report: estimating disease activity using multi-biomarker disease activity scores in rheumatoid arthritis patients treated with abatacept or adalimumab. *Arthritis Rheumatol* 2016;68:2083–9.
184 Dixon WG, Abrahamowicz M, Beauchamp ME, *et al*. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012;71:1128–33.
185 Hazlewood GS, Barnabe C, Tomlinson G, *et al*. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. *BMJ* 2016;353:i1777.
186 Katchamart W, Trudeau J, Phumethum V, *et al*. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev* 2010;(4):CD008495.

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

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NORMAS ARGENTINAS DE NEFROLOGÍA

Normas para el Manejo de Infecciones Urinarias

1ª Sección: **Normas Generales**
Publicación completa en el presente número

2ª Sección: **Normas Aplicadas a los Distintos Síndromes**
Publicación en próximos números

3ª Sección: **Anexos**
Publicación en próximos números

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Normas para el Manejo de las Infecciones Urinarias (UI) 2003

Introducción

Desde su constitución en el año 1984, el Consejo de Infecciones Urinarias (CIU) se fijó como meta remediar el serio problema que origina la ausencia de normatizaciones en infecciones urinarias (IU), lo que provoca severos problemas en la salud pública y muy frecuente iatrogenia.

Es así, como en el año 1985, publica en el "Acta Bioquímica Clínica Latinoamericana" sus primeras recomendaciones, que tomaron difusión latinoamericana.

Luego en el año 1987 edita un libro de bolsillo, de 95 pág. con las principales recomendaciones consensuadas en 19 síndromes de IU.

Posteriormente se actualizan en forma parcial en la "revista de nefrología, diálisis y transplante". Y ha sido tema de debate en distintos congresos, jornadas, cursos y las reuniones anuales del CIU.

El presente trabajo significa una puesta al día de los avances registrados. Se ha dividido el trabajo en dos partes. La primera actualiza las normas generales en el diagnóstico, etiología, fisiopatología, tratamiento y evolución. En la segunda parte, se aplica estas recomendaciones a 26 síndromes de IU.

De un modo especial se señala en el Cap. 10, la importancia de las IU en la salud pública. Se considera a esta afección como la agresión bacteriana más frecuente del humano. Y una de las más descuidadas, con todas las consecuencias individuales y sociales que derivan de esta anarquía en el manejo.

Son responsables de estas Guías, el Comité de redacción integrado por los Dres. Amílcar Challú, Eduardo Castiglioni (nefrólogos) y Alicia Farinati (microbióloga). En la elaboración de los capítulos, han intervenido además los Dres. Alicia Fernández (nefróloga), Pablo Contreras (urólogo), María Pérez y Gutiérrez (nefropediatra), María Eugenia Escobar (ginecóloga) y Silvina de Luca (imagen). Todos ellos integrantes de la mesa directiva del CIU.

Dada la extensión de la obra, su publicación se hará en varias entregas. En la presente edición abarcamos los Capítulos 1 a 10.

Este Comité en nombre del CIU, se considerará muy gratificado si se le hacen

llegar las sugerencias que permitan una mayor utilidad de estas recomendaciones. Las direcciones electrónicas de los autores, se señala al pie.

Por último deseamos destacar que estas guías o normatizaciones, han sido posible por el estímulo y la perseverancia del Presidente de la Sociedad Argentina de Nefrología, Dr. Oscar Ernesto Alvarez. A él nuestro reconocimiento.

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Capítulo 1
Definiciones en Infecciones Urinarias (IU)

Entendemos por IU al conjunto de síndromes provocados por la presencia de gérmenes en el tracto urinario.

Otras definiciones usadas

Algunos autores prefieren hablar de la respuesta inflamatoria del tracto urinario a la colonización de gérmenes.
Sin embargo resulta difícil definir qué se entiende por respuesta inflamatoria. Es bien conocido que no se expresa por manifestaciones clínicas, ya que las IU pueden ser silentes o de baja sintomatología. La inflamación tampoco se refleja en alteraciones sedimentarias, ya que puede existir IU con sedimentos limpios.

Algunas definiciones útiles

Resulta conveniente definir algunos términos que serán usados a lo largo de estas Guías. Otras definiciones se verán al encarar los distintos síndromes

1- Bacteriuria significativa: recuento de colonias igual o superior a 10.5 ufc/ml, en muestra recogida por micción espontánea (chorro medio). Es significativa cualquier número ufc/ml si se recoge por punción vesical o renal.

2- IU de parénquima: cuando la bacteriuria proviene del parénquima renal o de la próstata.

3- IU de vías cuando proviene de vejiga o uretra.

4- Bacteriuria complicada: cuando existe alteración de las vías o factores de riesgo o gérmenes multirresistentes. Por oposición de habla de IU no complicada, cuando la IU acontece en un paciente en buen estado de salud e indemnidad del aparato urinario.

5- Síndrome miccional: polaquiuria, disuria, urgencia tenesmo. Se reemplaza por síndrome de frecuencia/urgencia o disuria/urgencia .

6- IU silente, o bacteriuria encubierta: IU con muy poca sintomatología.

7- Nefropatía por reflujo: se utiliza cuando existen escaras asociadas con reflujo vésico ureteral, acompañadas o no por gérmenes.

8- Piuria: presencia de más de 6 a 8 leucocitos por campo.

9- Síndrome uretral femenino (disuria/ urgencia) con leucocituria y sin gérmenes.

Sinonimia

Existe una variada sinonimia aplicada a las IU, caracterizando los distintos síndromes. Las principales de ellas son: cistitis, IU encubiertas, IU silentes, pielonefritis, nefritis intersticial bacteriana, sépsis urinaria, bacteriurias asintomáticas. Hay términos como pielitis que deben ser descartados. Asimismo no existe una justificación para el llamado síndrome uretral. El término IU crónica, debe ser reemplazado por IU recurrente, con sus variables: recaída, reinfección o persistencia.

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Capítulo 2
Clasificación de las Infecciones Urinarias

Múltiples formas de presentación

Las IU se presentan en múltiples formas clínicas. Estos síndromes son el resultado de la interacción de distintos factores (edad, géneros de evolución, uropatógenos, etc). Señalamos algunos de ellos, agrupados:

1. Según localización: IU altas y bajas.
2. Según edad: IU del lactante, del recién nacido, de la pubertad, de la juventud, de la edad adulta, de la edad avanzada.
3. Según género: del hombre, de la mujer.
4. Según germen: IU por proteus, por pseudomona, por enterococcus, por gérmenes inusuales, por gérmenes multirresistentes.
5. Según actividad sexual: en la mujer en período sexual activo, en la menopausia.
6. Según sitio de adquirida la IU: IU nosocomial, IU ambulatoria, IU residencial.
7. Según evolución: episodio único, recurrente, persistente, recaída.
8. Según alteración del terreno: IU complicada o no, IU de riesgo.
9. Según enfermedades subyacentes: IU en el diabético, en nefropatía clínica, en el litiásico, en el poliquístico, en malformaciones urinarias.
10. Por sus síntomas: sintomáticas, asintomáticas (Bacteriurias asintomáticas BA), IU encubiertas, IU pausintomáticas.

Los síndromes se pueden multiplicar, haciendo jugar todos los factores señalados. Esto complica de alguna manera el manejo del paciente.

Agrupación de los síndromes de IU adoptado por el CIU

El Consejo de Infecciones Urinarias ha adoptado una clasificación que permite englobar este polimorfismo de síndromes. La misma es:

- IU con riesgo potencial para la vida del paciente: Sepsis urinaria, IU alta, prostatitis, IU del embarazo.

- IU con riesgo potencial de falla renal: RVU, malformaciones, binomio litiasis-IU.

- IU benignas, pero con riesgo potencial de recurrencia: IU en la mujer en período sexual activo.

- IU controvertidas: bacteriuria asintomática, IU del geronte, vejiga neurogénica.

Ventajas del agrupamiento propuesto

El agrupamiento propuesto permite manejar al paciente infectado, con una unidad de criterio. Cada uno de estos 4 grupos, presenta características comunes que se reflejan en

- Etiología
- Mecanismo fisiopatológico involucrado
- Presentación clínica
- Metodología diagnóstica
- Prioridades terapéuticas
- Evolución

Esta unidad de criterio se verá reflejada a lo largo de esta publicación.

Otras clasificaciones

Distintos tratadistas han propuesto agrupamientos, tendientes a simplificar el enfoque de las IU. Algunas de estas propuestas son:

- IU de parénquima e IU de vías. Es una clasificación sencilla, práctica y recomendable.

- IU complicada y no complicada. La principal objeción es definir qué se entiende por complicada.

- IU alta e IU baja.

- IU en el paciente obstruido

Cómo caracterizar un paciente con IU

Es altamente recomendable que en presencia de un paciente con IU, se procure individualizarlo, considerando los siguientes factores:

1. Si el paciente es ambulatorio o está internado
2. Género, edad
3. Episodios: Primero. Recurrente (persistencia, recaída, reinfección)
4. Complicada, no complicada, de riesgo
5. Localización alta o baja
6. Mono, polimicrobiana, germen problema
7. Sintomática, asintomática
8. De vías o de parénquima
9. Riesgo de vida, de IR, benignas

Así entonces, un paciente que se presenta a la consulta, en lugar de caracterizarlo simplemente como IU, se individualiza mejor señalando (como ejemplo):

(1) Paciente ambulatoria (2) de 67 a.,femenina (3) con primer episodio de IU (4) presumiblemente no complicada (5) presumiblemente baja, (6) a *E.coli* (7) sintomática (8) de vías (9) benigna

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Capítulo 3

Consideraciones Epidemiológicas en las Infecciones Urinarias

La infección del tracto urinario es un diagnostico común entre los pacientes evaluados en la consulta médica, tanto externa como en internados. De hecho, los autores rotulan a las IU como la 2ª enfermedad bacteriana humana y otros la señalan como la 1ª causa. Las infecciones urinarias afectan a ambos sexos y en cualquier edad. Frecuentemente no es diagnosticada en vida. Tiene un alto nivel de recurrencia y es la segunda causa de ingreso a HDC (causa única o agregada)
Como se verá en el Cap 10, cada año en los Estados Unidos, las IU resultan en más de 7 millones de visitas médicas. Todo ello implica un costo considerable como se analiza en el mismo Cap. La mayoría de esas infecciones ocurren en mujeres jóvenes quienes se presentan con síntomas de cistitis bacteriana aguda no complicadas o pielonefritis, con buena respuesta al tratamiento ATB. Cierta población de pacientes tienen causas predisponentes que complican el tratamiento. Las IU complicadas pueden ocurrir en el hombre, niños, mujeres embarazadas, ancianos o pacientes inmunodeprimidos y en aquellos con enfermedades neurológicas.

Algunos Datos Epidemiológicos

Se sintetizan los datos epidemiológicos, con estas referencias actuales:

- Consultas médicas por IU en USA 8.000.000/año
- IU diagnosticadas en internación 1.500.000/año
- Internados por cuadros agudos IU 125.000/año
- 1% neonatos
- 30% más 60 años
- El 12% de los hombres y el 40% de las mujeres sufren como mínimo 1 episodio de IU durante su vida
- El 5% de la atención primaria corresponde a casos de IU

Referencias: Waren y O´Hanley, 1998

Influencia de la edad y género

Las poblaciones que deberían ser consideradas para realizar estudios epidemiológicos de prevalencia son los neonatos (ambos sexos), los escolares (sexo femenino), las embarazadas y los ancianos.

La prevalencia de las IU es mayor en las mujeres y aumenta con la edad en ambos sexos , siendo las más frecuentes entre los ancianos.

La presencia de bacteriuria es :

- 5% en las mujeres jóvenes y 0.1% en los hombres de mediana edad.
- 20% en las mujeres y 10% en hombres a los 65ª de edad.

Se incrementa la prevalencia en las mujeres > de 70ª al 30% y hasta el 50% en las mayores de 80ª.

La relación de bacteriuria en mujeres respecto a varones es de 3:1 en los ancianos, contrastando con la proporción 20:1 que se observa en la población más joven.

Bacteriuria Asintomática (Am Fam Physician 2001;63:257-68.)

15 a 24 años	Mujer	2.7%
	Hombre	<0.1 %
80 años	Mujer	20 a 50%
	Hombre	6 a 20%

En función de la edad y género, las dos modalidades clínicas más diagnosticadas son en orden decreciente:

Niño:	Pielonefritis aguda Bacteriuria asintomática
Niña:	Bacteriuria asintomática Pielonefritis aguda
Hombre adulto:	Prostatitis Uretritis gonocócica
Mujer gestante:	Pielonefritis aguda Bacteriuria asintomática
Ancianos:	Infección nosocomial IU por obstrucción
Ancianas:	Cistitis recidivantes Pielonefritis crónica

Influencia del nivel socioeconómico

Se han demostrado como causas importantes de predisposición a las infecciones urinarias. La prevalencia de bacteriuria en mujeres embarazadas de bajo nivel económico es > del 7% y en las de medio o elevado 1-2%.

Influencia de patología subyacentes

La presencia de enfermedades / anomalías congénitas o adquiridas del aparato urinario son causas predisponentes de infecciones urinarias, bien por instrumentación o por la alteración de la libre circulación de la orina en los conductos. La frecuencia con que cada una de ellas ejerce la predisposición del enfermo a la infección está relacionada directamente con la capacidad agresora sobre los mecanismos defensivos o funcionales. Así por ejemplo, los cistoceles femeninos elevan la tasa de frecuencia de bacteriuria al 23%, las malformaciones congénitas del aparato urinario al 57%, la hidronefrosis y nefrolitiasis superan el 85% y los sondajes con drenaje a permanencia eleva la incidencia de IU.

Enfermedades comunes en la población geriátrica como diabetes (neuropatía diabética), hipertrofia prostática ,rectoceles, cistoceles , prolapsos uterinos ; como también el uso de medicación con anticolinérgicos cuyos efectos colaterales pueden contribuir a una anormal contracción del músculo detrusor.

En la premenopausia los estrógenos circulantes favorecen la colonización del epitelio vaginal por Lactobacillus que mediante el catabolismo del glucógeno para formar ácido láctico, mantienen un pH ácido vaginal que dificulta la colonización por uropatógenos.

El conocimiento de estos datos epidemiológicos sirve para alertar al médico y prevenirle sobre la búsqueda de una infección urinaria o una bacteriuria en aquellos casos en que la clínica no es demostrativa.

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Capítulo 4
Fisiopatología de las Infecciones Urinarias

Interrelación germen-huésped

Como en toda infección, debemos interpretar las IU como una interacción entre un agente agresivo (los uropatógenos), y un organismo que intenta defenderse. Por un lado, los gérmenes llegan al tracto urinario, colonizan, lesionan la mucosa, invaden y desarrollan mecanismos de supervivencia. Por su parte, el organismo se defiende en forma inespecífica y específica para este tipo especial de agresión.

Las vías de la infección

Los gérmenes patógenos pueden acceder al tracto urinario por 3 vías, la canalicular o ascendente, la vía hematógena y, la vía linfática. La ruta ascendente es la forma principal de acceso. Esto implica que para llegar al tracto urinario debe recorrer un largo camino desde su fuente (intestino) hasta el lugar donde coloniza (vejiga): periné, uretra y luego ascender a pelvis renal e intersticio. En ese largo trayecto puede colonizar distintos sectores.

La virulencia de los gérmenes

Los gérmenes poseen una virulencia propia que les permite superar los distintos obstáculos que le presenta el organismo. Es extraordinaria la capacidad de adaptación a un medio hostil y las nuevas exigencias.

No está adecuadamente aclarado si existen cepas determinadas genéticamente para atacar el tracto urinario o el intestino. Y si genéticamente determinan IU sintomáticas o no o IU alta o baja.

Cómo infectan los uropatógenos

Los gérmenes desarrollan habilidades que le permiten superar las primeras

resistencias que le presenta el organismo, penetrar el uroepitelio y mucosa, invadiendo y diseminándose.
Para cumplir esta finalidad, se adhiere al uroepitelio, se multiplica (acelerada o lentamente según las circunstancias) y se prepara para invadir y diseminarse.

Poseen capacidad para colonizar (adherencia fimbriada o afimbriada), para lesionar (hemolisina, distintos antígenos bacterianos), invadir y sobrevivir (reproducción, nutrientes, osmoprotectores)

Capacidad de colonizar

Es el primer paso de la agresión bacteriana. Los gérmenes que van ascendiendo se adhieren al epitelio urogenital, primero del introito y vagina y luego de las vías urinarias.
La adherencia se efectúa por 2 mecanismos de adherencia: fimbriada o afimbriada (ligandinas). Las fimbrias son estructuras pediculadas, específicas de determinados gérmenes que le permiten fijarse en forma selectiva a receptores específicos.
Estas fimbrias en general se dividen en manosa sensible (MS) y manosa resistente (MR), según que el receptor específico posea D-manosa o no.
Las fimbrias MS se adhieren a receptores de mucina que se hallan en las células superficiales del epitelio transicional. Asimismo se unen a la proteína de Tamm Horsfall. Al descamarse las células se elimina las bacterias adheridas. Se discute cuál es el rol que juegan en las IU. Es posible que contribuyan a la adherencia inmediata y que luego cambie su fimbriación a MR.
Las fimbrias MR se consideran las más virulentas, produciendo tanto IU bajas como altas. Se dividen en K, P, R subtipo S o P. Se adhieren a receptores específicos tipo glicoesfingolípidos (P) o gal-gal (R). Otras fimbrias MR son menos importantes. Las bacterias con estas fimbrias pueden colonizar el intestino grueso, trasformándolo en reservorio de las IU.
Las adhesinas no fimbriadas, ligandina, son distintas para cada germen. Se distribuyen en forma difusa por la superficie de los gérmenes, con un número por consiguiente ilimitado. Intervienen más en la colonización con citotoxicidad lenta, comparado con las adhesinas fimbriadas.

Capacidad de lesionar

Inicialmente las fimbrias lesionan el uroepitelio, al expoliar los nutrientes o blanqueando los receptores comunes de intercambio metabólico. Luego actúan

las hemolisinas como los agentes más importantes de lesión, produciendo microulceraciones. Inician así los episodios agudos de IU. Contribuyen a la lesión con posterioridad los antígenos bacterianos, que se anclan a las células del uroepitelio con receptores CD 14. Son activadores de los macrófagos y del factor citotóxico necrotizante (FCN).

Capacidad de invadir

En el juego de colonización, lesión y variación de la virulencia se produce la invasión a la submucosa vesical o al parénquima renal.

Capacidad de sobrevivir

La adaptación y la sobrevida de los gérmenes a las condiciones hostiles del huésped, constituye un aspecto fascinante de la virulencia de los gérmenes. Pueden permanecer adheridos al uroepitelio por un tiempo muy prolongado, esperando el momento adecuado para invadir, reproduciéndose a un ritmo muy lento, ahorrando energía y nutriéndose del medio. En este estadío, puede observarse selección de población y/ó desarrollo de nuevos genes.

Uno de los aspectos importantes de la nutrición de los gérmenes y que contribuyen con la virulencia en la adquisición de hierro que se hace a base de moléculas de aerobactinas y enteroquinas, denominados sideróforos. El hierro es pobre en los vertebrados, pero rico en la orina.

Además puede nutrirse de otras bacterias y células muertas

Por otro lado se protege de los neutrófilos por la leucocidina. En el parénquima renal, se protege de la osmolaridad, con los propios protectores que fabrica el riñón, para evitar daño en las células tubulares.

Los gérmenes esperan el momento adecuado para invadir. Cuando las condiciones son aptas aumentan su velocidad de reproducción, incrementando el inóculo y superando la fagocitosis. Asimismo puede cambiar su expresión de fimbriación, pasando de afimbriada o MS a MR que es más patógena.

Genera asimismo distintos mecanismos de resistencia a los antimicrobianos.

En un estudio sobre 53 pacientes, se demostró que la virulencia de la Escherichia coli está ligada en un 49 % a la fimbriación MR, También en un 49% a la formación de hemolisinas, en un 47% a presencia de aerobactina y 17% al antígeno K.

Cómo se defiende el organismo

El organismo se defiende del germen, con mecanismos específicos e inespecíficos. La primera y más importante barrera, es la vejiga, donde se concentran el mayor y principal obstáculo a la infección. Si se supera la vejiga, los gérmenes encuentran más facilidad para infectar.

La orina posee una acción bactericida, dependiendo de su osmolaridad, la concentración de hidrogeniones, urea, ácidos orgánicos, zinc y en menor medida de poliaminas hidrofílicas de bajo peso molecular.

Existen elementos químicos como la proteína de Tamm Horsfall, la capa de glucosaminoglicano, la glicoproteína 1 y la IgA secretora.

Pero la acción más importante es la mecánica, el lavado por el chorro urinario.

La antiadherencia

Los elementos señalados más arriba (proteína Tamm Horsfall, la glucosaminoglicano, la glicoproteína y la IgA secretora) entran en competencia con los receptores específicos y atrapan los gérmenes y los eliminan por la descamación. Otras sustancias menos importantes son algunos oligosacáridos de bajo peso molecular. La carga electrostática actúa como mecanismo de antiadherencia.

Esta acción antiadherente se observa en todo el epitelio urogenital.

Mecanismos inmunológicos en las IU

Es incierto el papel que juegan estos mecanismos en las IU. Fundamentalmente el riñón y la próstata poseen capacidad antigénica; la submucosa vesical posee una capacidad menor. Las inmunoglobulinas no se filtran por el glomérulo, se secretan a nivel local.

Los Ac como respuesta a los Ag bacterianos son los Anti lipopolisacáridos (Ag O); anti polisacáridos capsulares (K); anti fimbrias MR y MS (H); anti proteína Tamm Horsfall. Los Ag activan también el complemento.

Se cree que los Ac potenciarían la respuesta inflamatoria y reducirían el daño tisular y la posibilidad de bacteriemia. En alguna forma prevendrían las recurrencias. La inmunización con fimbrias P protege a las ratas.

Pero, en contrapartida, las IU pueden persistir en ausencia de bacterias por el depósito de Ag-Ac en el intersticio. Son hechos clínicos que en las hipogammaglobulinemias no hay mayor incidencia de IU, y que las bacterias persisten aún en presencia de títulos de Ac elevados.

Reacción inflamatoria

Contra lo que se aceptaba, actualmente se admite que la reacción inflamatoria juega un rol importante en las defensas contra los uropatógenos. Es así que los antiinflamatorios obstaculizan la erradicación de la IU.

Con la colonización de gérmenes, se produce una estimulación de citocinas (IL 6 y 8) y a su vez estimulan las células inmunitarias (esta estimulación se observa también con fimbrias aisladas y lipopolisacáridos).

La IL 6 produce fiebre y reactantes de fase aguda (aumento de la eritrosedimentación, leucocitosis, leucocituria, aumento de la PCR, la IgA y los Ac). La IL 8 estimula neutrófilos, activa el complemento y produce Ac.

Los neutrófilos y los linfocitos aparecen más tardíamente; no sólo ejercen su función conocida, sino capturan los gérmenes MS. Se acumulan en la mucosa y se eliminan aumentando la leucocituria. En el intersticio se pueden apreciar acúmulos de macrófagos.

Genética en IU

La densidad, número y tipo de receptores está determinado genéticamente. Los individuos del grupo sanguíneo P, ABO, Rh no secretor sintetizan globósidos gal.-gal., receptores de MR y presentan el riesgo mayor de contraer IU.

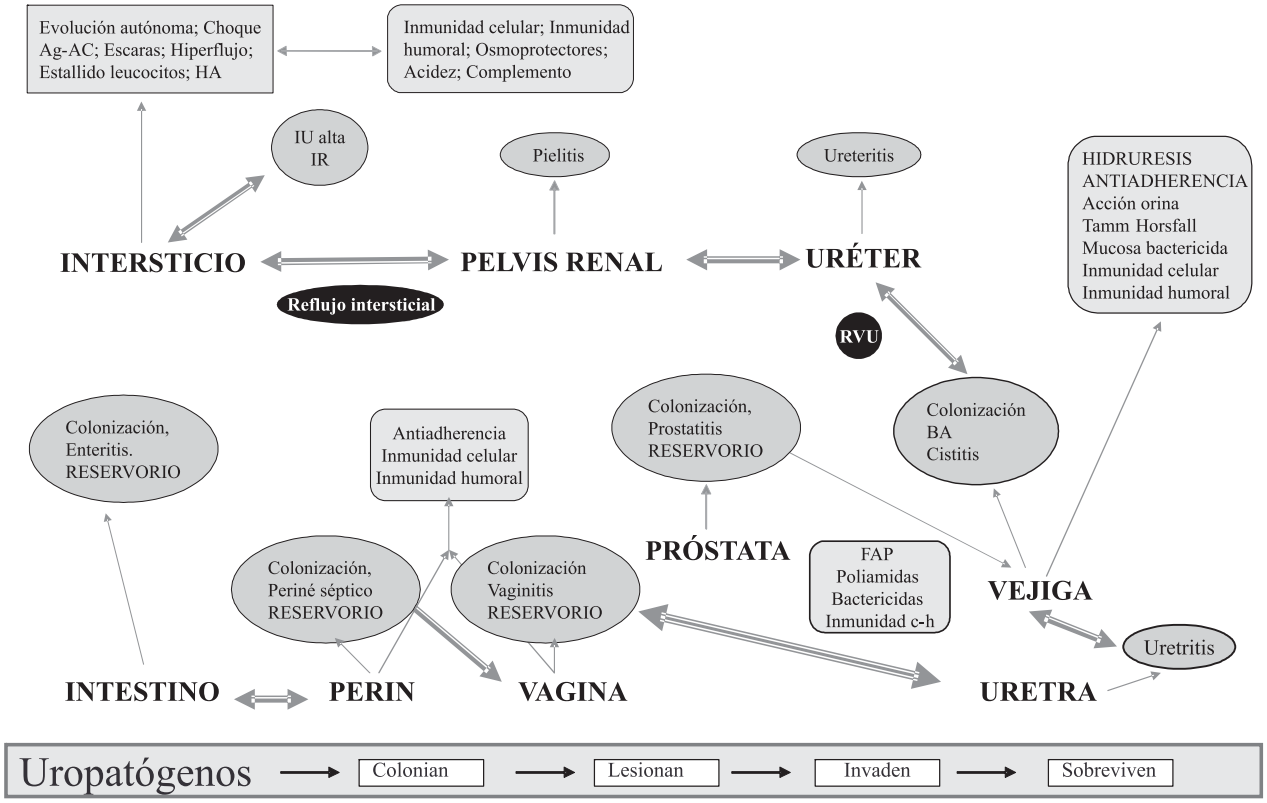
Situaciones especiales

Los mecanismos descriptos corresponden a pacientes no obstruidos. Se entiende fácilmente el ascenso de los gérmenes en los pacientes. En cambio los no complicados, especialmente, los que poseen indemnidad de las vías excretoras, son motivo de estudios constantes. Situaciones especiales como la recurrencia y la evolución a la IRC serán considerados más adelante. Existen elementos que permiten interpretar las IU como enfermedad psicosomática a través de mecanismos psiconeuroinmunológicos.

Secuencia de la infección

Se aprecia en la figura siguiente.

Algorritmo fisiopatológico



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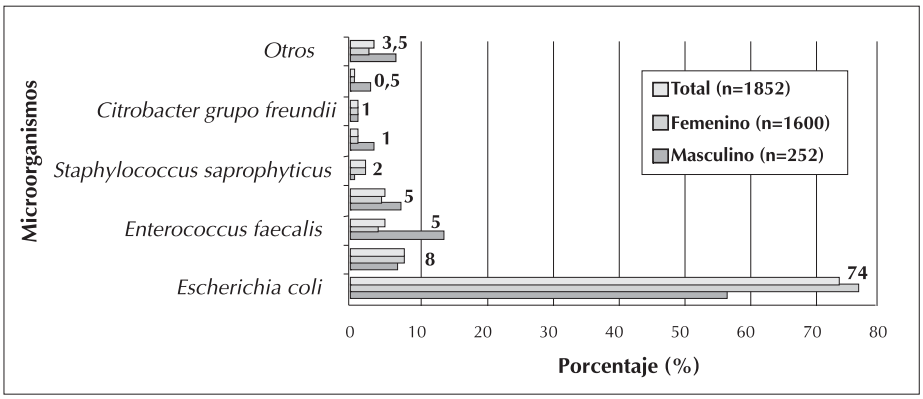
Capítulo 5
Etiología en las Infecciones Urinarias

Al considerar la etiología de las IU, se debe tener presente que las mismas se producen generalmente por vía ascendente . Por lo tanto los microorganismos prevalentes son los que se hallan en el contenido intestinal. A partir de este reservorio, en la mujer pueden colonizar la vagina y zona periuretral. En el hombre, las bacterias pueden colonizar la zona periuretral y ascender por la uretra. (Cap. 4)

Si admitimos que los componentes de la flora intestinal son los agentes etiológicos más importantes, deberíamos encontrar bacterias anaerobios como agentes de IU. Sin embargo no es así, ya que éstos son excepcionales. Por eso, se debe tener en cuenta que existen otros factores que ya fueron mencionados como factores de virulencia (Cap. 4) que le confieren a ciertos microorganismos el carácter de uropatógeno cuando los poseen.

Hay otros microorganismos que pueden aprovechar algunas circunstancias como por ejemplo, *Pseudomonas aeruginosas* y otros bacilos gram negativos no fermentadores asociados con catéter urinario.

A continuación y sólo a título de ejemplo, ponemos una tabla que grafica los agentes etiológicos encontrados en IU ambulatorias



Prevalencia de microorganismos aislados de urocultivo de pacientes adultos ambulantes

Uropatógenos

(E. coli, **otras enterobacterias)**
Otros baacilos gram negativos **(sobre todo en pacientes con IU complicada)**
S. saprophyticus
Enterococcus **spp**

Contaminantes

Difteroides
Staphylococcus ***coagulasa negativos***
Lactobacillus **spp**

Via hematógena

Staphylococcus aureus
Mycobacterium tuberculosis
Staphylococcus **coagulasa negativos**
Levaduras
Leptospira **spp**

Prevalencia de microorganismos aislados de urocultivo de pacientes adultos hospitalizados

En el paciente hospitalizado se suelen encontrar los mismos microorganismos pero aparece una mayor diversidad de bacilos gram negativos (otras enterobacterias y bacilos gramnegativos no fermentadores) y aparece entre los primeros agentes etiológicos *Enterococcus faecalis* , particularmente en el área de los servicios de Urología. La característica común a todos ellos es la multirresistencia pues muchas veces las IU se asocian a pacientes internados durante tiempo prolongado y/o portadores de sonda que favorecen la aparición de la flora hospitalaria o de la institución que, seguramente, se ha sometido a la presión selectiva de los antimicrobianos muchas veces utilizados sin controles adecuados.

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Capítulo 6
Clínica de las Infecciones Urinarias

Las IU presentan una sintomatología dispar. En algunos casos la misma es bien típica e induce de inmediato al diagnóstico. En otras circunstancias, la misma es encubierta requiriendo un buen ejercicio clínico para llegar al diagnóstico. Asimismo las infecciones pueden cursar en forma totalmente asintomática.

Para complicar los cuadros clínicos, los síntomas no son patognomónicos, de modo tal que cuadros que parecen típicos, no corresponden a IU. Por lo mismo es conveniente identificar estas distintas situaciones.

Síntomas típicos de IU

Las formas bajas de IU, presentan el síndrome de urgencia/frecuencia, asociados frecuentemente con estranguria, polaquiuria, disuria.

En cambio las formas altas, presentan lumbalgia, fiebre contractura lumbar frecuente.

En una serie personal sobre 1333 IU ambulatorias, se hallaron los siguientes síntomas.

1309/1333 IU ambulatorias

Lumbalgia	764	58,37
Fiebre	366	27,96
Disuria	932	71,20
Asintom ticas	90	6,88
Lumbalgia + Fiebre	275	21,01
Lumbalgia + Disuria	539	41,18
Disuria + Fiebre	255	19,48

Síntomas extraurinarios

Con relativa frecuencia, en especial en los extremos de la vida, se aprecian síntomas extraurinarios, tales como náuseas o vómitos, astenia, malestar general, disconfort, cuadros confusionales en los ancianos.

Formas oligosintomáticas

Con frecuencia los pacientes refieren síntomas aislados, como incontinencia, fiebre, lumbalgia, etc.

Gran parte de los pacientes con IU recurrentes, identifican nuevos episodios con ciertas características que le hacen sospechar una recurrencia: olor fuerte, olor característico, astenia, cambios de coloración.

Inespecificidad de los síntomas

En la práctica diaria se identifican pacientes con síntomas característicos de IU bajas, y sin embargo los cultivos no desarrollan y su evolución posterior, descarta un proceso infeccioso. Es el caso de mujeres con vaginitis, o de pacientes con trastornos de la motilidad vejiga, prolapsos, etc

También es posible hallar síntomas que sugieren una IU alta, en procesos de columna o cuadros infecciosos no renales. En el Cap. 6 se describen IU asintomáticas.

De estos hallazgos se concluye que hay pacientes infectados en sus vías urinarias, sin síntomas específicos y pacientes con síntomas que sugieren una IU que padecen otra patología.

Los síntomas no indican necesariamente localización de la IU.

Fairley (1971) ya había llamado la atención sobre la correlación entre síntomas sugestivos de IU bajas en pacientes con bacteriuria renal y a su vez, aunque en menor cuantía, síntomas sugerentes de IU alta en presencia de bacteriuria vesical. Estos estudios se refieren a 23 pacientes.

En 1333 pacientes ambulatorios de la serie personal, hallé un 73% de disuria en IU altas y un 51% de lumbalgias en IU bajas.

Los síntomas en 1333 IU ambulatorias
Signos IU alta en 725 IU bajas

Lumbalgia + Disuria + Fiebre	120	16.55
Lumbalgia + Disuria	204	28.14
Lumbalgia + Fiebre	60	8.28
Disuria + Fiebre	37	5.10
Total signos altos	421	58.15
Sólo signos bajos	304	41.99

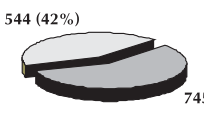
Octubre 2001 *Curso Superior Médico Nefrólogo*

Los síntomas en 1333 IU ambulatorias
Signos IU baja en 531 IU altas

Disuria	388	73.07
Signos altos	143	26.93

Octubre 2001 *Curso Superior Médico Nefrólogo*

Serie de 1333 pacientes ambulatorios *(Challú 1994)*



Estos datos demuestran síntomas bajos en las IU altas, así como síntomas altos en las IU bajas.

Disuria en IU altas: 398/544 (73%)
Lumbalgia en IU Bajas: 383/745 (51%)

Octubre 2001

Estos hallazgos orientan hacia una terapéutica precoz. La presencia de episodios altos en IU demostradamente bajas, implica el ascenso de gérmenes. Una medicación oportuna y precoz, puede limitar la colonización alta de gérmenes, evitando su ascenso.

Correlación de los síntomas y clasificación de las IU.

En el capítulo 2 se ha brindado una clasificación de las IU que resulta útil para la práctica diaria. La sintomatología se ajusta a los síndromes descriptos. Así el grupo de IU con riesgo potencial de vida, o con riesgo para el órgano, presentan síntomas sugestivos de IU alta. Los síndromes benignos, generalmente muestra síntomas sugestivos de IU baja.

Episodios transitorios de IU.

En la polifacética manifestaciones clínicas de la agresión infecciosa del aparato urinario, se constatan episodios transitorios a los cuales, por su misma condición de transitorios, no se le asigna importancia o no son investigados adecuadamente.

Señalamos algunos de estos episodios

Episodios transitorios de IU

- *Variaciones en la expresión de fimbriación*
- *Bacteriurias encubiertas*
- *Bacteriurias intermitentes*
- *Episodios altos en IU bajas*
- *Episodios bajos en IU altas*

Cada una de estas situaciones merece una descripción aparte que exceden los límites de este trabajo. En los Cap. 4 y 25 se hacen referencia a los mismos, como también más arriba en este mismo Capítulo.

Disfunciones urinarias

Se conocen situaciones transitorias o disfunciones, que también suelen pasar inadvertidas en la clínica de las IU. Se dan algunos ejemplos:

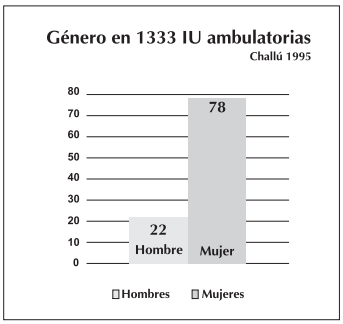
Disfunciones urinarias

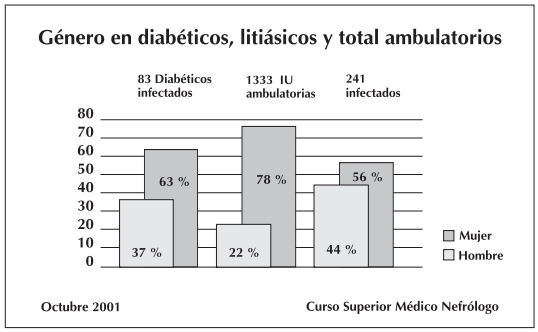
- *El Riñón como efector de conflictos psicológicos*
- *Disfunción transitoria del esfínter urinario*
- *Sindrome uretral irritable*
- *Disfunción urodinámica en la infancia*
- *Reflujo vésico ureteral transitorio*
- *Reflujo intersticial*

Valen los mismos comentarios del apartado anterior. En el Cap. 25 se hace referencia a las IU como forma de somatización. Tanto la disfunción transitoria del esfínter urinario, como la disfunción urodinámica en la infancia y el síndrome uretral irritable, aparecen como formas de los trastornos psicológicos en las vías urinarias. El reflujo vésico ureteral transitorio es un intento de explicar el ascenso de los gérmenes, es un postulado difícil de demostrar, aunque existen elementos que permitirían afirmarlo. El reflujo intersticial acontece en presencia de gérmenes en la pelvis renal y es posible demostrarlo radiológicamente.

Características clínicas por género

1. Adquiere características propias en el hombre y la mujer
2. Los datos epidemiológicos, muestran que en la Argentina según el último censo, la proporción de hombres y mujeres es similar (51% mujer). Sin embargo la prevalencia de IU en la mujer es sensiblemente superior al hombre





Existen diferencias según patología, como se observa en la figura 2.

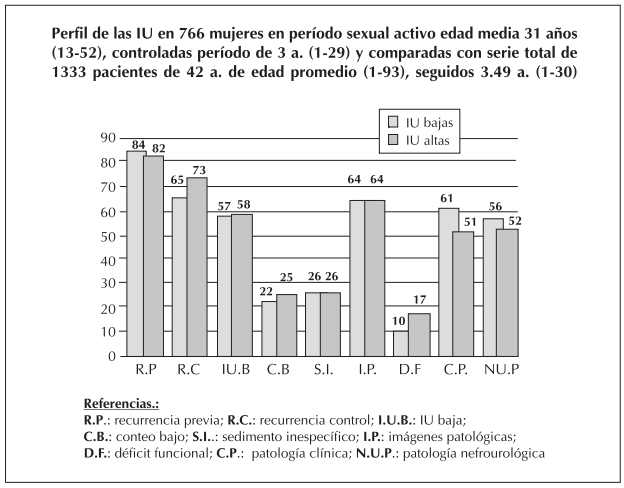
3. **Características en la mujer:**

3.1. En la mujer sus condiciones anatómicas y fisiológicas determinan una mayor frecuencia (Cuadro)

3.2. Los principales situaciones en la mujer está determinada por su actividad sexual:

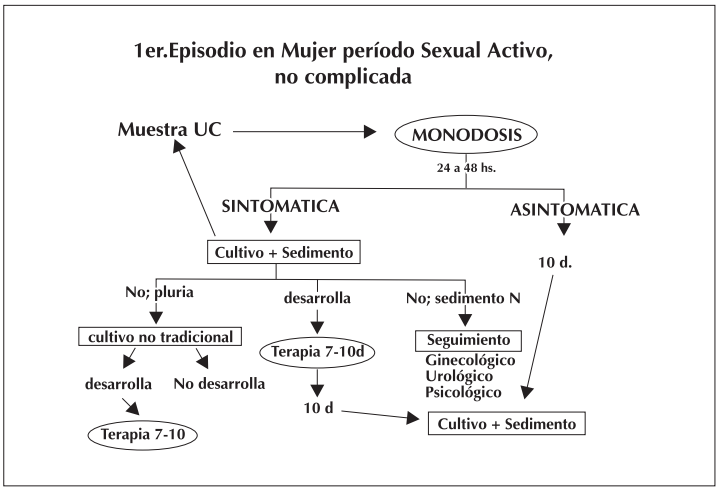
- 3.2.1. Ello incluye la infección post coito (Cap. 26)
- 3.2.2. La disuria es sumamente frecuente y plantea problemas especiales (Cap. 26)
- 3.2.3. El embarazo plantea especiales situaciones que facilitan la IU alta (Cap. 17)
- 3.2.4. En la menopausia, la falta de actividad hormonal determina una mayor propensión a las IU (Cap. 33)
- 3.2.5. EL síndrome uretral femenino bacteriano y no bacteriano es objeto de controversias (Cap. 26)

En la fig. siguiente se señalan las principales características en 766 mujeres en edad reproductiva



Diagnóstico diferencial: como se señala en los Cap. 7-4 y 26, las manifestaciones clínicas de la IU baja pueden observarse en pacientes con procesos no infecciosos (especialmente vaginales).

El manejo de las IU en la mujer, se visualiza en este esquema



4. **Características en el hombre**

a. La próstata actúa como una barrera antibacteriana importante (ver Cap. 4)

b. La principal patología es la prostatitis (Cap. 15 y 29)

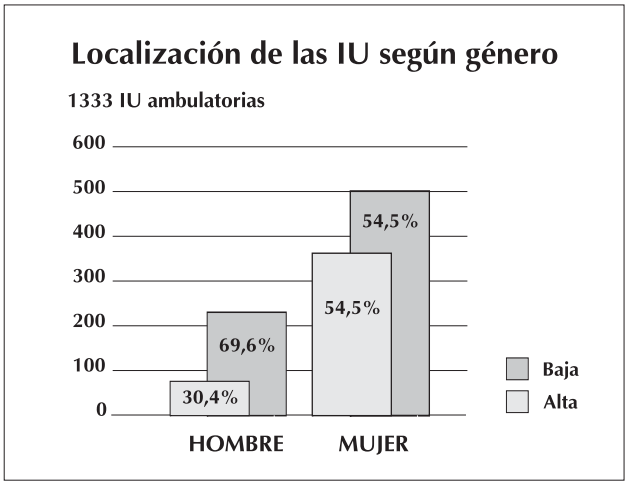
c. La uretritis es frecuente en hombres jóvenes (Cap. 27)

5. En una serie de 1333 pacientes ambulatorios, se han visto estas diferencias por género.

IU alta ambulatoria en el hombre y la mujer (2)
1333 casos

	Masculino	Femenino
Flora policromada	14.7%	11.4%
Sedimento infeccioso	71.2%	75.3%
Función renal alterada	26% ES	14.5%
Patología general	37.4% ES	23.3%
Diabetes	29% ES	18.8%
Alteraciones nefrourológicas	90%	83.1%

Challú . 1994



Características clínicas por edad

Las IU aparecen con mayor frecuencia en los dos extremos de la vida. En pediatría (ver Cap. 31 y 32), en las personas mayores de edad (Cap. 34). Entre estos extremos se plantean problemas generalmente ligados a la actividad sexual (Cap. 25 y 26).

Se considerarán las IU en niños menores de 2 años (Cap. 31) en mayores de 2 años (Cap. 32), en la mujer en edad reproductiva (Cap.25 y 26) y en las personas de edad avanzada (Cap. 34).

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Capítulo 7-0
Metodología Diagnóstica

La finalidad del diagnóstico en IU, consiste en

1- Demostrar la existencia de una IU.

2- Diagnosticar los factores predisponentes que han determinado esa IU.

3-Individualizar al paciente en su situación singular (ver Cap. 2, último apartado)

4- Diagnosticar fracaso de la terapia.

La existencia de una IU

Se demuestra mediante los síntomas y signos clínica (Cap 7-1), el urocultivo (Cap. 7-2 y el Sedimento Urinario (Cap. 7-3).

Los factores predisponentes, en especial obstructivos, mediante las imágenes (Cap. 7-4).

Individualizar al paciente: mediante la sumatoria de todos los elementos diagnósticos, priorizando la clínica.

El fracaso de la terapia: mediante el urocultivo y sedimento intraantibioterapia

Falsos positivos y falsos negativos

El primer concepto que se impone en el diagnóstico IU, es la presencia de falsos positivos y falsos negativos, lo que hace que ningún elemento diagnóstico *per se* es patognomónico de IU.

Tomando como ejemplo los urocultivos. Un urocultivo puede desarrollar y no ser IU (falso positivo), sino el resultado de una contaminación. De la misma manera, un urocultivo puede no desarrollar y el paciente está infectado (bacteriurias intermitentes, focos cerrados, etc).

Siguiendo con el sedimento urinario, puede mostrar leucocituria, proteinuria y no corresponder a una IU (falsos positivos en el lupus y otras neuropatías).

Asimismo una IU puede presentar un sedimento normal, no inflamatorio.Estos

falsos positivos y negativos, se repiten en todos los elementos diagnósticos lo que constituye una causa frecuente de mala praxis.
En especial los síntomas que inducen a sospechar una IU baja (ver Cap. 7-1 y 25) se hallan presentes en numerosas patología extraurinarias, en especial ginecológicas. En consecuencia medicar sin tener todos los elementos diagnósticos evaluados juiciosamente es una causa frecuente de error.
Excepcionalmente una prueba terapéutica puede coadyuvar al diagnóstico (ver en especial Cap. 18)

Síntesis diagnóstica

En la tabla siguiente, se combinan los elementos principales de diagnóstico (clínica, urocultivo y sedimento y excepcionalmente la prueba terapéutica), para presumir o certificar una IU.

Tabla 11
Diagnóstico de IU

Entidad	Clínica	Cultivo	Sedimento	Prueba terapéutica
IU presumida	Positiva	ND	Inespecífico	
IU probable	Positiva	ND	Infeccioso	
IU probable	Negativa	< 10.5 ufcml	Inespecífico	
IU cierta	Positiva	> 10.5 ufcml	Infeccioso	
IU cierta	Positiva	< 10.5 ufcml	Inespecífico	
IU cierta	Negativa	< 10.5 ufcml	Infeccioso	
IU cierta	Positiva	ND	Inespecífico	Positiva

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Capítulo 7-1
Diagnóstico Clínico

El síndrome de infección urinaria se caracteriza por su polimorfismo, lo que condiciona un cuadro clínico no patognomónico y solo la interrelación de los síntomas y signos el laboratorio y el resto de los exámenes complementarios permitirá arribar al diagnóstico.
Los síntomas mas característicos son:

Trastornos Miccionales

Sugieren una infección urinaria baja (cistitis, uretritis, prostatitis) aunque también se observa en un tercio de las infecciones urinarias altas.
Los síntomas característicos son: Polaquiuria, disuria. estranguria "micción en gotas", ardor miccional y tenesmo vesical o rectal,

Algias asociadas a la IU

El dolor lumbar o en flanco a nivel del ángulo costovertebral con puño percusión y palpación dolorosa, característica de infección urinaria alta.
En las prostatitis el dolor se ubica en periné y recto con tacto rectal intensamente doloroso.
En algunas formas de cistitis se constata dolor suprapúblico.

Cuadro Febril

La fiebre más común en infección urinaria alta, prostatitis o infección urinaria complicada obstrucción de vía urinaria, huésped inmunocomprometido, diabetes. Es superior a 38 grados con escalofríos.
En la IU baja es común la febrícula.

Modificación Física de la Orina

En la infección urinaria la orina puede ser turbia, a veces hematúrica y mal oliente, esto último puede sugerir la presencia de determinados microorganismos- olor amoniacal por gérmenes ureolíticos o fétido por coliformes.

Síntomas Atípicos

Con frecuencia las infecciones urinarias son mono u oligosintomáticas, predominando algunos de los síntomas descriptos más arriba.

Existen frecuentemente formas asintomáticas o cuadros donde los síntomas y signos están dados por la patología subyacente. En el embarazo, la hipertensión arterial, las uropatías obstructivas, la diabetes, y pacientes inmunocomprometidos esta situación debe pesquisarse ya que puede desencadenar cuadros sépticos con riesgo para el órgano y para la vida.

Recurrencia

El cuadro clínico puede variar desde un episodio agudo aislado hasta un proceso recurrente. Esta última forma de presentación es mas frecuente en el sexo femenino en dos etapas de la vida: jóvenes con vida sexual activa o mujeres post-menopaúsicas.

Comentario Final

Sólo se puede afirmar que los síntomas y signos descriptos son sugestivos de infección urinaria, el conjunto de métodos complementarios de diagnóstico, donde se destaca el examen bacteriológico, confirmará o desechará tal presunción. No es infrecuente que en pacientes con clínica completa de infección urinaria no pueda establecerse la etiología bacteriana, pese a lo cuál se indican terapéuticas antimicrobianas que resultan ineficaces, costosas y no exentas de riesgo. En otros casos la investigación insuficiente no permite realizar el diagnóstico y el tratamiento adecuado.

Corresponde enfatizar que el correcto diagnóstico clínico, producto de un adecuado conocimiento de la enfermedad, es el eje del diagnóstico de la IU. Ello permitirá descartar los frecuentes falsos positivos y falsos negativos.

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Capítulo 7-2
Metodología del Diagnóstico Microbiológico

Se considerará sucesivamente:
1- Recolección de muestras; 2- Informe del urocultivo; 3- Interpretación del urocultivo. 4- Actitud del microbiólogo ante resultados obtenidos; 5- Actitud del médico ante resultados de laboratorio no concordantes.
Los métodos de tamizaje (catastro) se considerarán en otro capítulo

Recolección de muestras

Se considerará sucesivamente: pacientes sin sonda que controlan o no los esfínteres; pacientes con sonda; punción suprapúbica; pacientes con vejiga neurogénica;

Pacientes sin sonda con micción espontánea que controlan los esfínteres.

Retención: El paciente debe tener como mínimo 3 horas de retención de orina. Puede utilizarse la orina de cualquier momento del día (preferentemente la primera orina). En pacientes con imposibilidad de retención vesical es válida cualquier muestra con la mayor retención posible.

Higiene en la mujer: Antes de recolectar la orina debe efectuar una cuidadosa higiene. Para ello se deben separar los labios vaginales y lavarse prolijamente, usando gasa o algodón y empleando agua y jabón (un jabón nuevo, sin usar). El lavado lo debe hacer desde adelante hacia atrás (nunca al revés). De inmediato debe pasar abundante agua por la zona. Seguidamente debe preparar un tapón vaginal consistente en una torunda de algodón envuelta en gasa que debe introducir profundamente en la vagina para evitar que caiga flujo vaginal en el frasco de orina. La torunda de algodón puede reemplazarse por el clásico tampón. En pacientes premenárquicas, que no usen tampones, se extremarán las medidas de higiene.

Higiene en el hombre: antes de recolectar la orina debe efectuar una cuidadosa higiene. Para ello debe retraerse el prepucio y lavar el glande con agua y jabón (empleando un jabón nuevo). De inmediato debe pasar abundante agua por la zona lavada para eliminar todo resto de jabón.

Obtención de la muestra en la mujer: A continuación de la higiene, separando bien las piernas, debe orinar en el inodoro y hacia la mitad de la micción

interponer el frasco estéril para recolectar orina. Se cierra el frasco.

Obtención de la muestra en el hombre: A continuación de la higiene, manteniendo el prepucio retraído, debe orinar un chorro prolongado de orina en el inodoro y luego hacia el final de la micción seguir recolectando la orina dentro del frasco estéril. Es conveniente recolectar la primera porción de orina (10 mi) en frasco estéril separado para efectuar su cultivo, teniendo en cuenta la patología del varón, que con cierta frecuencia puede presentar únicamente uretritis con sintomatología común a cualquier tipo de infección urinaria. Se cierra el frasco.

Conservación y transporte: una vez recolectada la orina, debe conservarse de inmediato en la heladera entre 4 y 100 C (nunca en el congelador). En esas condiciones puede mantenerse, si es imprescindible, hasta 24 h. Es preferible, sin embargo, que se remita al laboratorio lo antes posible, refrigerada adecuadamente.

Pacientes sin sonda con micción espontánea que no controlan los esfínteres (lactantes)

Retención: para una mejor interpretación de los resultados se debe intentar el control del tiempo aproximado de máxima retención vesical. Es conveniente suministrar líquidos 30 min antes de la recolección.

Higiene en la niña: se separan los labios mayores y se lava de adelante hacia atrás la zona uretro vulvar. Se debe utilizar jabón nuevo y no usar desinfectante. Lavado posterior con agua.

Obtención de la muestra en la niña: mantener las piernas separadas y obtener la muestra al acecho.

Obtención de la muestra en el niño: mantener el prepucio retraído y obtener la muestra al acecho.

La muestra de orina para estudio microbiológico en lactantes **nunca se debe recoger con bolsitas colectoras.** En ambos sexos se recoge sólo la porción final de la micción.

Conservación y trasporte: seguir las instrucciones indicadas más arriba.

Pacientes con sonda vesical

Para la obtención de la muestra es preferible efectuar punción suprapúbica. De no ser posible, se punza la sonda previa desinfección a 10 cm de su inserción en el meato. No se efectúa clampeo de la sonda. La muestra se obtiene con jeringa y aguja estériles. En cuanto a la conservación y trasporte, se siguen las instrucciones indicadas previamente.

Punción vesical suprapúbica (PSP).

Se considerarán sucesivamente: Indicaciones.; Operador.; Técnica en neonatos y lactantes.

Indicaciones

Mandatarias en neonatos.; lactante grave internado; lactante con urocultivos reiteradamente contaminados; investigación de microorganismos que integran la flora normal de la uretra o plantean dudas en la interpretación de los resultados (*Mycoplasma spp.*, anaerobios, *Candida spp* u otros hongos oportunistas, variantes bacterianas, etc.).

Opcionales: Vejiga neurogénica; Paciente dialisado. Pacientes con sonda.

Operador

Debe ser practicada por un médico con experiencia en esta técnica.

Técnica en neonatos y lactantes

Tener presente que en estos estadios de la vida, la vejiga es un órgano abdominal.

Verificar que la vejiga esté llena mediante percusión abdominal hasta encontrar la matidez suprapúbica característica. Si es posible, establecer el ritmo miccional, aunque sea mediante los datos aportados por la madre.

Localizar el sitio de punción en la línea media a 1 cm aproximadamente de la sínfisis pubiana, desinfectar con povidona-iodo y removerlo con alcohol y/o solución fisiológica estéril.

La punción se efectúa con una aguja 40/7 o 50/8 adosada a una jeringa de 10 cm3 estériles. Hay que tener la precaución de que la aguja penetre en forma perpendicular a la piel.

Interpretación del Urocultivo

El estudio microbiológico de orina (urocultivo) debe ser cuali y cuantitativo, es decir se deberá efectuar la tipificación del microorganismo aislado y a la vez el recuento de colonias. Este último procedimiento puede obviarse cuando la muestra fue obtenida por punción suprapúbica.

Para poder interpretar adecuadamente el significado de un urocultivo es necesario que la **muestra venga acompañada de los siguientes datos**: sexo y edad del paciente; patología de base; diagnóstico presuntivo; tiempo de retención; maniobras instrumentales previas (si las hubo); medicación recibida dentro de las 24 h previas al estudio.

Del mismo modo es imprescindible determinar: pH; densidad/osmolaridad; características del sedimento urinario, incluyendo proteinuria.

Recuento de colonias: sobre la base de estos datos, los recuentos de colonias serán cuidadosamente interpretados. La cifra de 105 ufc/ml propuesta por Kass no debe ser un factor limitante, pues existen verdaderas infecciones urinarias con

recuentos de colonias menores y también orinas contaminadas con más de 100.000 ufc/ml de un solo tipo de germen. El recuento de colonias no es comparativo, es decir que no se puede asumir de ninguna manera mejoría de un paciente que en estudios sucesivos presente disminución de la cifra del recuento de colonias, mediando o no tratamiento específico y aislándose el mismo microorganismo. Recordemos que para definir la identidad entre dos aislamientos (es decir la misma cepa) es necesario que se cumplan ciertos requisitos como la identidad del biotipo, antibiotipo y lo que es más preciso, el genotipo.

Resultados falsos positivos

Más de 105 ufc/ml sin infección urinaria, puede acontecer en las siguientes circunstancias: pacientes con uretritis; contaminación vaginal por falta de higiene previa o incorrecta colocación del tapón vaginal o en las niñas con higiene incorrecta o deficiente o con vulvovaginitis; contaminación fecal en lactantes; contaminación del jabón o los desinfectantes usados para efectuar la higiene previa; orinas mal conservadas (sin refrigerar).

Resultados falsos negativos

(menos de 104/ml existiendo infección urinaria), pueden darse en las siguientes circunstancias: Baja densidad (u osmolaridad)-, Tiempo de retención insuficiente; pH inferior a 5,0 o superior a 8,5; Existencia de focos renales que no drenan a los túbulos o bien obstrucciones ureterales completas; Infecciones producidas por bacterias que no desarrollan en los medios habituales utilizados; Presencia de antibióticos, quimioterápicos, restos de desinfectantes u otros fármacos inhibitorios en la orina (vitamina C, ácido acetilsalicílico)

Es particularmente importante agotar los recursos para la identificación precisa pues de esta manera se facilita la interpretación de resultados posteriores (reinfección o persistencia) en caso de infección urinaria recurrente;

Antibiograma: normalmente se emplea el método de difusión con discos,utilizando la técnica de Kirby y Bauer y según patrones de la NCCLS.

Deben expresarse los resultados como sensible, intermedio o resistente, tomando en cuenta los diámetros de los halos de inhibición establecidos por recomendaciones internacionales. Los antibióticos y quimioterápicos deberán informarse exclusivamente por sus nombres científicos y no por sus marcas comerciales. Debe recordarse que la carga de los discos comercializados hasta el momento guarda relación con la concentración sérica y no la urinaria del antibiótico (ver antibióticos e IU).

Actitud del Microbiólogo ante los resultados obtenidos

Se solicitará un nuevo estudio microbiológico, siempre que sea posible., en muestras de orina obtenidas por micción espontánea, cuando se obtenga:

Muestras polimicrobianas; muestras con sedimento infeccioso que no desarrollan; muestras con sedimento normal y recuentos entre 10^4-10^5 ufc/ml en pacientes que no controlan los esfínteres o cuando se sospecha una falla en la obtención o conservación de la muestra; recuperación de microorganismos poco frecuentes en infecciones urinarias; discordancia entre el pH y especie de microorganismos aislados (ej., pH 5.0 y Proteus mirabilis).

Hay situaciones especiales en que la reiteración del cultivo debe efectuarse mediante PSP .

Actitud del Médico ante resultados del laboratorio no concordantes con el cuadro clínico

Ante orinas negativas con síntomas sospechosos de infección urinaria pensar en :

- Bacteriuria intermitente. En este caso solicitar estudio seriado;
- Síndrome uretral femenino. Solicitar estudio de la primera y última porción de la orina;
- Posibilidad de TBC renal. Solicitar estudio adecuado mediante bacterioscopia y cultivo de BAAR en muestras sucesivas de orina;
- Obstrucción completa del árbol urinario. Verificar si existe dicha obstrucción y solicitar estudios periódicos.

Infección Asociada a Catéter Urinario

Sonda < 7 días	Rto. 10^4 ufc/ml (Punción Aspirativa.)	No más de 2 microorg.
Sonda > 7 días	Cualquier recuento (PSP)	
Sonda retirada	Rto. 10^5 ufc/ml (OCM)	No más de 2 microorg.
	Rto. 10^3 ufc/ml Seriado de 2 muetras ó Rta al Tto.	

Se considera IU ante

10^4 ufc/ml en general

10^2 ufc/ml en SDF + piuria o leucocituria

10^3 uf c/ml en pacientes con sonda permanente

Cualquier recuento en las muestras provenientes de PSP.

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Capítulo 7-3
Sedimento Urinario

El sedimento urinario constituye un método seguro y rápido para el diagnóstico de infección urinaria. Aunque se constata la frecuencia de falsos positivos y falsos negativos.

La recolección de una muestra de orina útil significa: a) orina concentrada-salvo insuficiencia renal crónica conocida o sospechada b) micción reciente y c) observación inmediata con luz ordinaria o contraste de fases.

La observación del sedimento puede hacerse en el momento de la consulta no se modifica por el uso de antibióticos y autoriza a iniciar tratamiento mientras se espera el resultado del estudio bacteriológico.

El hallazgo de mas de 5 leucocitos/hematíes en la mujer y 2 leucocitos/hematíes en el hombre por campo microscópico indican una leucocituria o hematuria significativa y es sugerente de infección urinaria pero no específica.

Por el contrario pueden observarse infecciones urinarias sin leucocituria.

La piocituria -leucocitos con modificaciones estructurales de tipo degenerativo- es un hallazgo frecuente. Los piocitos en acúmulos o colgajos son indicio de contaminación vaginal y se evita previo a la recolección (Colocando un tapón vaginal).

Tanto la leucocituria como la piocituria no son específicos de infección urinaria ya que puede encontrarse en enfermedades del intersticio renal no bacteriana y o nefropatía por reflujo. La leucopiocituria con cultivo convencional negativo induce a sospecha de infección por gérmenes no habituales (anaerobios, chlamidias, Bacilo tuberculoso)

Los cilindros leucocitarios son de observación poco frecuente, indican localización alta de la infección. Con el microscopio electrónico de barrido se identifica el cilindro bacteriano de alta especificidad pero baja sensibilidad, ya que no todas las infecciones altas lo presentan.

La hematuria, cuando se observa, por lo general es microscópica y no específica. Las formas macroscópicas se relacionan con cuadros clínicos típicos(cistitis hemorrágica, PN granulomatosa, infección urinaria asociada a litiasis o tumores).La presencia de hematíes dismórficos señala la localización alta de la infección.

La proteinuria en valores no superiores al gramo/24 horas no guarda relación con este proceso y está más vinculada a lesión intersticio-tubular de origen bacteriano o no. EL incremento de la proteinuria puede indicar evolutividad en una IU con compromiso funcional.

En orinas hipotónicas se pueden encontrar células redondas con citoplasma granular cuyas partículas muestran movimiento browiano. Se llaman células centellante y se las vinculó con IU alta. Los falsos positivos y negativos le quita valor a este hallazgo.

La observación con contraste de fases de orina recién emitida no centrifugada "gota fresca" es un método útil para el diagnóstico de bacteriuria, pero debe correlacionarse con el cultivo de orina. Las bacteriurias masivas que a veces impiden ver otros elementos formen, por lo común son contaminantes por error de recolección (flujo vaginal, muestras de pacientes con sonda)

Los cristales de fosfato amónico magnésico que acompañan a las leucopiociturias orientan a la presencia de gérmenes ureolíticos

El examen general de orina, mal llamado orina completa, muestra fallas relacionadas a la inadecuada obtención de la muestra, dilución de la orina, contaminación que sumado al escaso interés del observador hacen que no sea un método confiable para el diagnóstico de I.U.

Los métodos de cuantificación de los elementos formes de la orina (Técnica de Addis o Hamburger) requieren mayor complejidad en la recolección y una cámara cuentaglóbulos, pueden reemplazarse por el sedimento fresco, sin tinción si es observado por personal idóneo o el mismo nefrólogo; la cantidad de los elementos no es fundamental sino la calidad, cuando además se los relaciona con el cuadro clínico.

Recomendación

El estudio del sedimento urinario debe realizarse siempre en procesos agudos y como fase previa a la realización del cultivo. Se acepta que las orinas sin proteinuria, leucopiociturias, microhematuria y gérmenes son muestras sin interés bacteriológico, por lo que puede no solicitarse el cultivo, salvo que una fuerte sospecha clínica incline a favor de una IU con presentación atípica.

Deben exceptuarse orinas obtenidas por punción vesical o renal, o cuando el cuadro clínico y o las condiciones generales del paciente indiquen otra conducta.

El sedimento urinario debe acompañar siempre al urocultivo.

Diagnóstico por el Sedimento Urinario

La cuidadosa observación del sedimento de orina fresca, concentrada y/o centrifugada observada mediante microscopio de contraste de fases o con óptica común y condensador bajo, con un aumento de 400x, constituye un método rápido y seguro para el diagnóstico y control evolutivo de las infecciones urinarias.

El examen cuantitativo del sedimento urinario es posible realizarlo en el momento de la consulta, no se modifica por el uso de antibióticos y permite orientar la terapéutica hasta la llegada de los estudios bacteriológicos.

La leucocituria superior a los 2.000.000 de elementos según técnica de Addis o a 2.000 elementos según técnica de Hamburger, es indicativo de infección urinaria, aunque no específica.

A la inversa es posible observar infecciones urinarias sin leucocituria.

La piocituria (presencia de piocitos o leucocitos agrupados o con sus características estructurales alteradas) es un hallazgo frecuente, pero, al igual que la leucocituria, no específico, pudiendo estar presente en las infecciones urinarias activas, en las infecciones urinarias en vías de curación y en cualquier otra inflamación no bacteriana. La presencia de leucopiocituria con cultivos reiterados negativos en medios convencionales, debe hacer pensar en microorganismos no habituales.

El hallazgo de cilindros leucocitarios, si bien poco frecuente, indica localización renal de la infección. La presencia de otro tipo de cilindros es habitual, aunque carece de valor diagnóstico.

La hematuria generalmente es microscópica y no específica. Sin embargo puede presentarse hematuria maeroscópica, siendo el signo predominante en una forma clínica de la enfermedad. La presencia de hematíes crenados o con otras alteraciones morfológicas, puede ser de ayuda para el diagnóstico de localización, indicando infección alta.

La proteinuria es de poca cuantía y guarda escasa relación con este proceso.

El colorante de Stenheimer-Malbin permite la visualización de grandes células pálidas, de aspecto titilante, que se vinculan con localización renal de la infección. La frecuencia de falsos positivos y falsos negativos le resta valor a este hallazgo y actualmente no se suele utilizar.

El examen general de orina, como ya se ha señalado, no es un método confiable para el diagnóstico de las infecciones urinarias. Las fallas dependen de errores en la recolección de las muestras (última de la noche y primera de la mañana), de dilución de la orina, contaminación al pasar por la zona genital y frecuentemente, inexperiencia o desinterés del observador.

En cambio la observación de la orina recién emitida no centrifugada (gota fresca) es un método particularmente útil para el diagnóstico de bacteriuria significativa. El criterio diagnóstico es la presencia de bacterias. Es un método simple que se correlaciona estrechamente con el cultivo cuantitativo.
De no ser posible cuantificar el sedimento urinario, se puede recurrir a la lectura de elementos por campo, teniendo solamente valor de orientación, a condición que se correlacionen los valores con el volumen de la muestra remitida.

Sedimento

Leucocitos : Puntos de corte
En general > de 5 PMN (400x)

Variación de la sensibilidad y especificidad del sedimento de orina según el sexo y la edad

Parámetro	**Mujeres (n=217)**		**Hombres (n=286)**		**Niños (n=982)**	
	> 45 a.	=< 45 a.	> 45 a.	45 a.	Sed	Rto.cámar
Sensibilidad	81%*	88%*	92%	100%	53%	55%
Especificidad	91%*	96%*	89%	94%	91%	91%
VPP (+)	74%	83%	74%	73%	86%	86%
VPP (-)	94%	97%	97%	100%	66%	69%

p< 0,05, Sed: sedimento entre "porta y cubreobjeto" > 5 leuc/cpo de 400X, Rto. Cámara de Neubauer. Fernández Canigia L., y cols. VIII Cong. Arg. Nefrología, 1992; Bantar C y Lopardo H. Urocultivo, 1997.

Variación de la sensibilidad y especificidad del sedimento de orina según sexo en pacientes Trasplantados

Parámetro	**Mujeres (n=24)**		**Hombres (n=40)**	
	>5 leuc.	> 10 leuc.	>5 leuc.	> 10 leuc.
Sensibilidad	68%	45%	74%	68%
Especificidad	73%*	85%*	83%*	91%*
VPP (+)	38%	42%	37%	50%
VPP (-)	91%*	87%	96%*	95%

p< 0,05, Sedimento entre "porta y cubreobjeto" > 5 leuc/cpo de 400X,. Fernández Canigia L.,y cols. VIII Cong. Arg. Nefrología, 1992.

Criterios de informe de un cultivo de orina monomicrobiano en pacientes adultos.

Recuento de colonias UFC/ml	Criterio de informe según leucocituria en el sedimento	
	> de 5	< de 5
Mujeres		
$> 10^5$	BS	BSp
$10^4 - 10^5$	BS	NM
10^3	BS	NEG
Hombres		
$> 10^5$	BS	BSp
$10^3 - 10^4$	BS	NEG
BS: bacteriuria significativa, BSp: Bacteriuria significativa probable, Bantar C y Lopardo H. Urocultivo, 1997-		

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Capítulo 7-4
Estudio por imágenes

En la segunda parte de este trabajo, al analizar los 26 sindromes de IU, se considerarán los distintos métodos de diagnóstico por imagen. En este apartado se brinda una visión práctica sobre los métodos según frecuencia de utilización, oportunidad de indicación, beneficios, limitaciones, iatrogenia.

Los estudios según frecuencia de utilización

El ideal de los estudios por imagen sería buena relación costo/beneficio, indolora, no invasiva, segura, escasa radiación, capaz de detectar todas las anormalidades, que se pueda repetir sin riesgo para el paciente. Lamentablemente, no se posee un estudio con esas características. Por ello, se dividen los estudios por imagen en tres grupos según su ugtilización.

En el **Gpo. 1**, de los más útiles, se hallan la ultrasonografía, acompañada de una placa simple de árbol urinario. Asimismo en los niños, la cistouretrografía.

Le siguen el urograma excretor y en los niños el centellograma renal **(Gpo. 2).**

Luego con menor frecuencia de utilización, la tomografía computada, la resonancia nuclear magnética, el ecodopler, la arteriografía renal. **(Gpo. 3).**

Gpo.1 La ecografía

Se analiza con más detalle en el diagnóstico urológico. Señalaremos que, acompañada de la placa simple de árbol urinario, constituye el método de rutina en el diagnóstico.

Se destaca la inocuidad del método, su rapidez de realización, la falta de efectos secundarios, la posibilidad de repetición y el costo accesible.

Un resultado espectacular de este método es el diagnóstico prenatal, que permite la rápida corrección de alteraciones de las vías urinarias.

Entre sus limitaciones se debe señalar que el estudio es dependiente del aparato utilizado, surgiendo distintas generaciones con mayor resolución. Pero, por sobre todo, de la formación del médico operador. Se ha sugerido que la ecografía debiera ser manejada por el urólogo o el nefrólogo para una mejor interpretación de los estudios. En su defecto, una interacción con el operador.

Además son frecuentes los falsos positivos (imágenes prestadas). No brinda datos

sobre el reflujo vésico ureteral, la patología ureteral (salvo obstrucción litiásica) y la funcionalidad del riñón, salvo la relación parénquima-sinusal, que orienta a la IRC.

La ecografía es mandataria en las IU del hombre en cualquier momento de su vida, en niños de cualquier género, en la recurrencia y ante la sospecha de un proceso obstructivo.

Se debe solicitar conjuntamente con ecografía vesical y determinación del residuo postmiccional. En el hombre se acompañará del estudio prostático transabdominal.

Gpo.1 Cistouretrografía

Se considera indispensable para el diagnóstico de reflujo vésico ureteral.

Se conocen 4 métodos: miccional, miccional digitalizada, directa por radionúclidos e indirecta por radionúclidos. En los niños se impone ante cualquier alteración revelada por la ecografía o en la recurrencia. En los adultos se ve muy limitada por la manipulación y frecuente iatrogenia.

Gpo.2 Urograma excretor

Hasta la generalización de la ultrasonografía era el método de elección en el estudio morfológico renal, que brinda además datos funcionales. La iatrogenia, reacciones adversas al iodo, el tiempo que demanda el estudio, su costo, el personal necesario, han ido limitando su indicación.

Conserva indicaciones precisas, cuando se trata de dilucidar obstrucciones ureterales, estudiar la indemnidad de la vía excretora, etc.

Gpo.2 Gammagrafía renal

Determinada con el DMSA (ácido dimercaptosuccínico) 99m Tc, es un método de estudio complementario, que tiene vigencia en estudio de las escaras en los niños post IU. Posee una alta especificidad. Las alteraciones post IU alta, ya se detectan en la primera semana, a diferencia de otros métodos que tardan más en demostrar alteraciones.

Gpo.2 Cistografía

Acompaña la cistouretrografía. Puede solicitarse en forma aislada, aunque la necesidad de instrumentar y el personal, limita su indicación.

Gpo.3 Tomografía computada

Un elemento más en el diagnóstico complementario del urograma excretor y que

resulta útil para determinar sitios de obstrucción, dilatación vías, etc.

Gpo.3 Resonancia magnetonuclear
Alternativa a la TC.

Gpo.3 Ecodopler renal
Indicado cuando se desea estudiar la vascularización renal. Es de poca utilidad en IU.

Gpo.3 Arteriografía renal
Brinda imágenes precisas del sistema vascular renal. Posee pocas indicaciones en IU.

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Capítulo 7-5
Diagnóstico de Localización

Importancia del diagnóstico de localización

Poder diferenciar una IU alta de una baja, resulta de singular importancia para evaluar el tipo y duración del tratamiento, los estudios a efectuar, los controles ulteriores y la evolución probable del paciente. Además permite distinguir lo que hemos llamado dinámica de las IU, o sea pacientes con IU alta y que presentan síntomas bajos y la inversa o sea síntomas altos en IU bajas.

Los métodos de diagnóstico propuestos

Se pueden clasificar en métodos directos o indirectos. Los primeros son invasivos, requieren una instrumentación y personal entrenado. Ellos son la punción biopsia renal, el cateterismo uretral (test de Stamey) el lavado vestal (test de Fairley)

Los métodos indirectos en cambio no son invasivos, no originan iatrogenia y no es necesario personal especializado para su realización. Ellos son los anticuerpos circulantes, los anticuerpos ligados, el diagnóstico por imagen, el sedimento urinario, las pruebas funcionales renales, la excreción de enzimas y de un modo especial la valoración clínica del paciente.

Los métodos directos

La punción biopsia renal, aparte de ser un procedimiento agresivo, presenta falsos negativos, ya que la punción puede caer en zona normal. Recordar que la IU alta es una afección focal.

La punción suprapúbica, presenta numerosos errores y no permite determinar localización de la bacteriuria vesical.

La prueba de Stamey, (recolección de muestras por cateterización ureteral), tiene la ventaja que permite diferenciar IU localizada en uno u otro riñón, inclusive en los casos de doble sistema pielocaliceal, en uno u otro sector del riñón. Falsos negativos: bacteriuria intermitente y como falsos positivos infección vesical +RVU. Pero su gran inconveniente es la iatrogenia y que requiere personal especializado.

La prueba de Fairley, (recolección de muestra luego del lavado de la vejiga), es

menos agresivo y además de fácil realización. Pero igualmente requiere instrumentación y puede originar iatrogenia. No resulta útil en la vejiga neurogénica.
Resumiendo, se trata de métodos agresivos, no exentos de riesgo, que requiere personal entrenado y que no es posible generalizarlo en la práctica clínica diaria.

Los métodos indirectos

El más sencillo, probablemente sea la prueba de concentración. La disminución de la osmolaridad es un indicativo de IU alta.
Los métodos enzimáticos incluyen el dosaje de la 5-isoenzima de la láctico dehidrogenasa y la alfa 2-microglobulina. La frecuencia de falsos positivos le quitan valor a estas determinaciones.
El dosaje de anticuerpos antiproteína de Tamm.Horsfall es un método atractivo, pero padece del mismo problema: frecuencia de falsos positivos.
El dosaje de anticuerpos anti bacterianos, resulta de utilidad. Aunque presenta poca especificidad. Inicialmente se indicó valores superiores a 1/80 para IU alta. Actualmente se señala superior a 1/500. Pero presenta numerosos falsos positivos.
Los anticuerpos ligados a bacterias (método de Thomas) aparecen a los 11 días de la infección parenquimatosa y requiere inmunofluorescencia. Se observan con frecuencia falsos negativos.

Interpretando la localización en las recurrencias

Norby propone el siguiente cuadro para interpretar la localización de una IU recurrente:

	Riñón-próstata	Vejiga
Cepa	Igual	Diferente
Recurrencia	< 7 días	> 7 días
Ac circulantes	altos	bajos
Ac revestidos	positivos	negativos

El diagnóstico de localización es clínico

Ninguno de los métodos descriptos por sí mismo hace diagnóstico de localización. La mayoría de ellos no son utilizables en la práctica diaria.
No obstante, ninguno de ellos por sí mismo determina el diagnóstico. Además no son métodos sencillos y que puedan aplicarse en la rutina diaria. La gran morbilidad de las IU obliga a recurrir a métodos sencillos y económicos.
Por lo mismo cobra valor utilizar un criterioso examen clínico, y utilizar todos los elementos posibles para conformar el diagnóstico.

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Capítulo 7-6
Diagnóstico Urológico

Objetivo

En primer lugar, se trata de confirmar presencia de IU y luego, descartar en primera instancia los siguientes factores:

1- obstrucción
2- colecciones
3- litiasis
4- compromiso prostático

La metodología diagnostica de toda IU incluye: 1) confirmar infección urinario (estudios bacteriológicos); 2) evaluar respuesta inflamatoria (sedimento de preferencia cuantitativo); 3) determinar funcionalismo renal (de preferencia clearence de creatinina y prueba de concentración).

El Algoritmo diagnóstico

Se sigue una metodología que comprende:

- Anamnesis detallada.

Hincapié en el hábito miccional previo.

- Examen físico incluyendo tacto rectal. Exámenes Complementarios:

- Exámen de orina completa.

Urocultivo Laboratorio básico
Estudio con imágenes
Flujometría
Urodinamia
Uretrocistoscopía

Los estudios complementarios se van solicitando, a medida que el cuadro clínico lo justifique.

Corresponde investigar un proceso obstructivo orgánico o funcional subyacente en presencia de:

a. IU recurrente, en especial en hombres y niños
b. Cierto tipo de uropatógenos *(Proteus)*

c. Síndrome clínico característico
d. IU en hombres mayores de 50 años de edad
e. Pacientes con problemas neurológicos

Los estudios ecográficos

Se solicita simultáneamente ecografía renal y vésico prostática y medición del residuo post miccional. Este método es considerado por algunos autores como una extensión del examen físico y en manos del urólogo aporta una importante información sobre los siguientes aspectos: Por la sencillez e inocuidad del método se considera de primera elección.

- Renal: interesa determinar: forma, tamaño, posición, relación parénquimo sinusal, la presencia de dilataciones del sistema excretor, la presencia de masas ocupantes y litiasis.

En los casos de obstrucciones del sistema excretor sin causa aparente deberá continuarse con otros estudios (urograma excretor, TAC, etc.)

- Ureteres: solo se observan en casos de dilatación y puede en algunos casos identificarse la causa de la obstrucción.

- Vejiga: el grosor parietal es un dato que se relaciona de manera estrecha con la obstrucción infravesical. Asimismo la ausencia de imágenes endoluminales debe ser corroborada ya que las infecciones a repetición pueden ser el signo de aparición de un tumor vesical.

- Próstata: si bien la ecografía suprapúbica no es un buen método para evaluar la próstata, la misma nos dará una idea aproximada del tamaño y las características prostáticas (por ejemplo un lóbulo medio prominente que habitualmente son altamente obstructivos).

La ecografía transrectal tiene indicaciones muy precisas y en el caso del paciente con ITU solo ayudará a clarificar la sospecha clínica de absceso prostático.

- Residuo post miccional: el residuo post miccional significativo >50 ml es un dato de debe ser tomado en el contexto en el cual fue realizado, ya que habitualmente para realizar una ecografía se sobredistiende la vejiga, la retención urinaria es prolongada y el ambiente en el cual el paciente orina es extraño para éste (habitualmente son lugares muy fríos). Debido a ello el residuo medido por eco, sin conocer las condiciones en que se realizó debe ser corroborado por cateterismo antes de definir una conducta a partir de ello.

Es conveniente que el estudio ecográfico se acompañe de una placa simple de árbol urinario, con eventuales cortes tomográficos.

Otros estudios por imagen

En especial se considera el urograma excretor con las secuencias tradicionales, incluyendo placa en posición de pie y la cistograffa pre y posmiccional. Se efectuarán placas retardadas, de acuerdo con el mejor criterio del radiólogo interviniente. Cistouretrografía pre y posmiccional.

Como alternativos a estos estudios, puede solicitarse:

- Tomograffa axial computada.
- Centellogramo renal con galio.

Flujometría Urodinamia

Se evaluará adecuadamente la necesidad de efectuar estudios urodinámicos y/o endoscópicos.

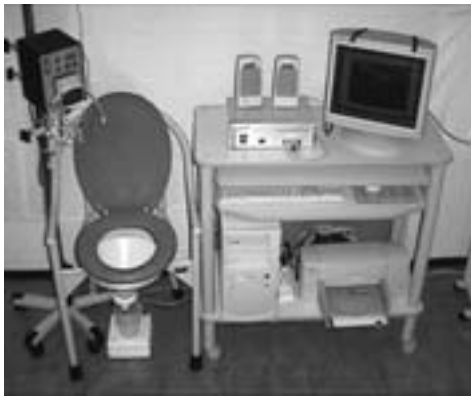
- Flujometría: es un estudio no invasivo, simple y sencillo que nos da una aproximación sobre las características del vaciado de la parte inferior del aparato urinario. Se acepta que flujo > 15 ml/seg., salvo excepciones, se asocian a ausencia de obstrucción infravesical.

En el caso de encontrar una trazado anormal, este estudio no permite conocer la causa del mismo y deberá ser completado con algún estudio urodinámico.

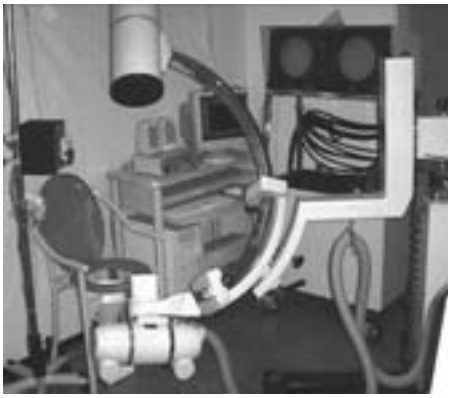
- Urodinamia: dentro de esta denominación se incluyen los siguientes procedimientos :

Cistometría, estudio de flujo - presión, electromiografía perineal y perfil uretral. En aquellos pacientes en quienes de sospecha una alteración del llenado o del vaciado vesical debe realizarse un estudio urodinámico.

En relación a las infecciones urinarias las causas van a relacionarse con el vaciado vesical. Con la urodinamia podemos documentar la presencia de una obstrucción infravesical, hipoactividad del detrusor y trastornos en la sinergia de contracción del detrusor y relajación del tracto de salida. Todas estas causas pueden producir un vaciado anormal que colabore a la producción o reiteración de episodios de ITU.



Equipo de Flujometría



Equipo de Videourodinamia

En casos seleccionados puede requerirse de la ***videourodinamia*** que aporta el dato anatómico al funcional. Es de resaltar que la diabetes o la Enfermedad de Parkinson, que aumentan su incidencia con la edad, pueden provocar algunas de las alteraciones antes citado o provocar trastornos mixtos.

- Uretrocistoscopía: como se citó anteriormente la presencia de un tumor urotelial debe descartarse en pacientes con infecciones a repetición sin causa aparente.

Este estudio nos permite evaluar la uretra, en la cual debemos constatar la ausencia de obstrucciones (por ej. estenosis o hiperplasia prostática) y las características de la mucosa y pared vesical que puede presentar signos de hipertrofia muscular (vejiga de lucha) con celdas columnas y divertículos secundarios a obstrucción infravesical, la implanteción de los meatos ureterales y las características del trígono. Este procedimiento puede además de diagnóstico ser terapéutico ya que algunas de las causas obstructivas citadas puede resolverse por vía endoscópica.

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Capítulo 7-7

Método de Tamizaje ("Screening")

Estos métodos fueron primitivamente desarrollados a los efectos de realizar catastros de infecciones urinarias en grandes núcleos de población.

Permiten la detección de probables infectados en forma rápida y tal vez económica.

Facilitan la pesquisa de infecciones asintomáticas. Los casos detectados como positivos deben ser evaluados por los métodos clásicos empleados en infecciones urinarias, pues los métodos catastrales no sirven a los fines diagnósticos, sino que su única finalidad es poder descartar los pacientes no bacteriúricos.

Se agrupan en:

1. Métodos microscópicos
2. Métodos químicos
3. Métodos de microcultivo

Los métodos microscópicos

Comprenden:

1. Coloración de Gram de la orina directa o centrifugada;
2. Coloración de Gram de la orina directa preinoculada 2 horas a 37 º C.

Limitaciones: requieren microscopio, colorantes, etc. y se obtienen falsos negativos por la dificultad que ofrece a veces la visualización de microorganismos.

Los métodos químicos

Comprenden:

1. Prueba de catalasa;
2. Prueba de reducción de nitratos;
3. Prueba de reducción de trifeniltetrazolio;
4. Prueba de la hipoglucosuria.

En general se basan en la propiedad de ciertas bacterias de producir una reacción bioquímica. Su limitación es importante, puesto que no todas las especies producen estas reacciones y en algunos casos se requieren concentraciones elevadas para que la prueba sea positiva.

Métodos de microcultivos

El método de microcultivo utilizable, es el de los portaobjetos recubiertos de medios de cultivo. Como método de catastro es bueno, puesto que es bajo el número de falsos negativos.

Valor de los métodos de tamizaje (Sadebac 2002)

Microscópicos

- Estudio del sedimento en fresco: leucocitos, cilindros, eritrocitos, cristales, cuerpos ovales, etc.
- Coloración de Gram de la orina sin centrifugar o del sedimento.
- Requerimientos: correcta recolección de la orina, observador experimentado
- Interpretación: con coloraciones
  - En la orina entera (200x): 1 microorganismo en tres campos: positivo
  - (400x) para estudio de cantidad y morfología: S: 99% con $>10^5$ ufc/ml; E: 58%
- Coloración naranja de acridina (fluorocromo)
- Interpretación : similar a cualquier coloración
- Requerimientos: idem más un microscopio de fluorescencia
- Inconvenientes: 45% de falsos positivos

Enzimáticos

Leucocito esterasa (LE): ácido indoxil-carboxílico y una sal de diazonio. En presencia

- de LE, cambio de color
- Indica presencia de leucocitos enteros o lisados
- S: para >de10 PMN/campo de >aumento (HPF) o $>10^5$ UFC/ml es de 75 a 96%; E: 94-98%; VPN: 92%
- Falsos positivos: a. ascórbico, T. vaginalis, albúmina (>300mg/dl), ATB
- Falsos negativos: < 5 a 10 PMN (HPF)

Prueba de los nitritos : las enterobacterias reducen los nitratos a nitritos

- Nitritos + ac. arsanílico compuesto diazotado que reacciona con 1,2,3,4- tetrahidrobenzoquinolin-3-ol rojo
- S: 35-80%; E: 92 a 100%
- Problemas: no detecta Enterococcus spp, Staphylococcus spp, Acinetobacter u otros bacilos gram negativos no fermentadores.
- Interferencias: con urobilinógeno elevado, vit C

Combinación de Leucocito-esterasa (LE) + Nitritos

S: 79 a 93%; E: 82 a 98%

Prueba de catalasa

Si hay >10^5 UFC/ml: S: 93%

Si hay piuria: 10^2 UFC/ml

Problemas: no detecta a los NO productores de catalasa (*Streptococcus* spp, *Enterococcus* spp)

Métodos de filtración

- Sistema colorimétrico-electrostático para bacterias y GB (Filtracheck-UTI)
- Bac-T-Screen y Vitek System: semiautomatizados para bacterias y GB
- S:76 a 97% para >10^5 UFC/ml; VPN 99%

Bioluminiscencia

- UTIScreen: semiautomatizado, sistema luciferin-luciferasa para detectar el ATP liberado de las bacterias viables
- S: 95% si hay >10^5UFC/ml; VPN: 99% con 10^4 UFC/ml, S: 85%
- Problema : falsos negativos con conteos bajos

Otros métodos

Conductancia eléctrica: detecta bacterias por medición de cambios en el flujo de una corriente eléctrica a través del medio.

Electroquímica: detecta incremento de voltaje causado por las bacterias viables.

Cultivos

Portaobjeto con medio que se sumerge en la orina.

Problemas : no distingue colonias diferentes en general (posible contaminación)

Estría de una gota de orina en placa con medio.

Es más adecuado ya que permite varias estrías en una placa y permite distinguir con más precisión diferentes tipos de colonias (contaminación de infección)

Conclusión

- No hay ningún método de tamizaje que tenga el 100% de Sensibilidad y el 100% de Especificidad.
- Es preferible buscar aquellos que tengan alto VPN (valor predictivo negativo).

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Capítulo 8
Terapéutica de las Infecciones Urinarias

Objetivos de la terapia

El tratamiento de las IU busca por un lado eliminar la bacteriuria, prevenir la recurrencia y evitar que la IU progrese y origine daño renal.

El general el primer objetivo se logra en un porcentaje elevado, así como evitar el progreso de infección y consiguiente daño renal; en cambio la recurrencia es difícil de erradicar.

Pasos en la terapia

Se consideran los siguientes pasos:

1. Evaluación clínica del paciente
2. Establecer una correcta relación médico/ paciente
3. Plantear una adecuada estrategia microbiana:
    a. Elección del fármaco
    b. Inicio de la medicación antimicrobiana
    c. Dosis
    d. Duración
4. Estar atento al fracaso de la terapia
5. Corrección de los factores predisponentes, en especial obstructivos.

1- Evaluación del paciente

La terapia debe ser individualizada. Por lo mismo antes de adoptar conductas activas, se procurará:

1- Conocer su estado general, situación metabólica, funcionalismo renal, hábitos higiénicos-dietéticos, conducta miccional, estado de potenciales reservorios (intestino, ginecológico, próstata).

2- Descartar proceso obstructivo de las vías u otros factores condicionantes del huésped.

3- Evaluar posibles alteraciones psicológicas.

4- Ensayar una interpretación fisiopatológica ajustada a la situación especial del paciente.

5- Procurar clasificar al paciente según se ha señalado más arriba.
Este estudio previo puede demandar más o menos tiempo, en función de un criterioso juicio clínico.

2- Establecer una correcta relación médico paciente

La relación entre IU y problemas psicológicos, se establece en dos niveles. Por un lado un conflicto emocional puede expresarse somatizando y condicionando la aparición de procesos de IU. Por otra parte, un episodio de IU, genera alteraciones psicológicas de distinta magnitud. Estar atento a estas fantasías, contener al paciente y tratar de resolver los conflictos emocionales, se impone como paso previo a la terapia.
Por otra parte es aconsejable una actitud equilibrada frente a las recurrencias. No fabricar enfermos, pero tampoco dejar de controlar adecuadamente al paciente, teniendo en cuenta el alto número de enfermos asintomáticos. Conviene explicar al paciente claramente la fisiopatología y la evolución probable de su proceso. Explicar la ruta ascendente de los uropatógenos, sus características especiales, la frecuencia de recurrencia, la evolución, etc.

3- Estrategia antimicrobiana

a) Elección del fármaco:

1- AM recomendados

La industria farmacéutica ofrece un sinnúmero de antimicrobianos, muchos de ellos con indicación útiles en IU. En DPF 2002, vemos la oferta de 419 antibióticos, 39 antimicóticos y 40 quimioterápicos. Esto se presta a confusión, ya que a pesar de la propaganda de la industria no todos actúan en las IU. La selección de un fármaco útil se efectúa utilizando los siguientes parámetros:

Factores que determinan la elección de un antimicrobiano en las IU

- Características farmacodinámicas
    - Actividad antimicrobiana
    - Patrones de resistencia
    - Acción bactericida
    - Modificación ecología intestinal y/o vaginal
- Acción farmacocinética
    - Absorción, distribución, eliminación
    - Valoración frente a constantes del organismo
    - Niveles tisulares y urinarios

- Impacto en el huésped
  - Menor nefrotoxicidad.
  - Menores efectos secundarios
- Factores sociales y económicos
  - Costo
  - Vía administración.

Aplicando estos parámetros, se seleccionan los siguientes antimicrobianos:

Antimicrobiano	Uso	Antimicrobiano	Uso
Acetil cefuroxima	A	Ceftriaxona.	I
Ampicilina (Amoxicilina, Ampicilina + IBL)	A	Gentamicina, (amikacina)	I
Cefalexina (Cefadroxilo)	A	Imipenem+Cilastatin	I
Nitrofuranos	A	Teicoplanina	I
Trimetoprima	A	Vancomicina	I
Ciprofloxacina (norfloxacina; Ofloxacina, Pefloxacina)	A I	Ceftazidima	I Pse
Cefixima	A	Piperacilina (Piperacilina +Tazobactama; Piperacilina +Clavulónico)	I Pse
Aztreonan	I	Cefoperazona (Cefoperazona+SB)	I Pse
Cefepima	I	Clindamicina	CE
Cefotaxima,	I	Macrólidos	CE
Ceftizoxima	I	Nitroimidazólicos	CE

Ref. (a) de uso preferencial en ambulatorios. (i) de uso preferencial en internados (e) casos especiales. (Pse antipseudomónicos)

2- Elección del fármaco según germen

	Coli	Pseudo	Enteroco	Proteus	Staphilo	Klebs.	CE
Acetil cefuroxima	2						
Ampicilina (Amoxicilina, Ampicilina + IBL)	3		2	1		3	
Cefalexina (Cefadroxilo)	2		-				
Nitrofuranos	2		2				
Trimetoprima	3			3			
Ciprofloxacina (norfloxacina; Ofloxacina, Pefloxacina)	1	2		2		1	
Cefixima	1					2	
Aztreonan							
Cefepima						1	
Cefotaxima,	1					1	
Ceftizoxima						1	
Ceftriaxona.						1	
Gentamicina, (amikacina)	1	1		3		2	
Imipenem+Cilastatin		1					
Teicoplanina					2		
Vancomicina			1		1		
Ceftazidima		1					
Piperacilina (Piperacilina +Tazobactama; Piperacilina +Clavulánico)	1	1				3	
Cefoperazona (Cefoperazona+SB)		1					
Clindamicina					3		1
Macrólidos							1
Nitroimidazólicos							1

b- Inicio de la medicación antimicrobiana

Se plantean las siguientes alternativas:

1. Medicación a ciegas
2. Medicación conociendo el germen aislado
3. Medicación conociendo germen y antibiograma

1- Medicación a ciegas

La medicación a ciegas o empírica, tiene indicaciones muy precisas: por la urgencia de la situación clínica o porque existe imposibilidad de efectuar cultivo. Las siguientes son las reglas de la medicación a ciegas:

1. Siempre que sea posible, recoger la muestra del cultivo, antes de iniciar la terapia.
   a. A las 24 hs. ajustar según resultados.
   b. Si la terapia fracasa, ajustar a las 48 hs según antibiograma.

2. Si el paciente se halla internado, utilizar el fármaco aconsejado de acuerdo a las tablas de gérmenes más frecuentes, la situación clínica y el estado general del mismo.
3. En las recurrencias, utilizar el último antimicrobiano que ha sido eficaz. Prevenir contra la automedicación.
4. Los fármacos a usar, se señalan en apartado anterior.

2- Medicación conociendo el uropatógeno recuperado

A las 24 hs de efectuado el cultivo se determina el germen. Ello permite efectuar ajustes en la medicación instaurada en forma empírica

3- Medicación conociendo el uropatógeno y el antibiograma

Es la situación ideal para instaurar la terapéutica correcta. Mandatoria en caso de quimioprofilaxis. Y toda vez que la medicación empírica no mejore los síntomas. A las 48 hs. de sembrado, es posible contar con el antibiograma adecuado. No obstante, no siempre coincide la sensibilidad in vitro con la efectividad in vivo, por lo cual se monitoreará la evolución clínica y la respuesta en el urocultivo.

c) Dosis

Las dosis no difieren de las normalmente indicadas. Se ajustarán por función renal y por edad (ver capítulos respectivos).

d) Duración de la terapia

No existe consenso sobre la duración, de modo que se señalarán las utilizadas por según la experiencia de los autores. Se considerarán: 1- dosis única (mal

llamada monodosis). 2-períodos cortos. 3-convencional. 4- prolongado. 5-quimioprofilaxis.

1- Dosis única

Se indica una única dosis activa del fármaco, en una situación clínica bien definida: en la mujer en período sexual activo ante la sospecha de IU baja no complicada.

Se han ensayado múltiples fármacos, siendo los que más usamos: la ciprofloxacina y las cefalosporinas de segunda generación. Posee ventajas y desventajas, por lo cual no se ha generalizado su uso. Entre las ventajas se señalan: menor toxicidad, poca repercusión sobre la flora fecal y vaginal, menor recurrencia, mejoría de la ecuación costo/benficio, facilidad administración, aceptación por el paciente.. Las desventajas induce a la automedicación y a descuidar la evolución ulterior de la IU baja, minimizando su significado.

2- Período corto

3 días de medicación. Está indicado como alternativa en la IU baja no complicada, en las recurrencias y en la quimioprofilaxis ante la reaparición de la bacteriuria o la sintomatología.

3- Convencional

5 a 7 días de AM. De utilidad en la mayor parte de las IU. Ciertos fármacos, poseen acción residual (ej. ciprofloxacina), lo que prolonga su eficacia.

4- Períodos prolongados

15 a 30 días. Señalados por algunos autores en la IU alta o la IU de riesgo (embarazo, agresión parenquimatosa).

5- Quimioprofilaxis

Se habla de quimioprofilaxis cuando se instala un tratamiento por varios meses, en presencia de recurrencia.

Se efectúa un ciclo corto o convencional a dosis usuales. Esterilizada la orina se utiliza un AM en monodosis, administrado por la noche, luego de la última micción. Ordinariamente se utilizan nitrofuranos, o la asociación TMT con sulfas, aunque se han ensayado todos los AM.

El concepto de quimioprofilaxis, es mantener un nivel en orina de AM, que impida su ascenso por las vías urinarias.

Se realiza control con urocultivo 1 vez al mes. Si el cultivo es positivo se indica un ciclo corto y se vuelve a las monodosis nocturnas.

4- Fracaso de la Terapia

Como mínimo se debe esperar 48 hs, para la remisión de los síntomas. En esa

circunstancia es conveniente efectuar cultivo intraantibioterapia. Y pasar a otro AM a la espera de contar con un nuevo cultivo.
Las causas de fracaso, pueden atribuirse a bajas dosis, que haya una alteración en la biodisponibilidad, que la duración haya sido incorrecta, o a la selección de nuevos gérmenes.

5- Corrección de los factores predisponentes

No hay tratamiento adecuado de las IU, sin la corrección de factores predisponentes. Sólo se enuncian los principales aspectos:

1- Corrección hábitos miccionales. Especialmente los retenedores sociales.
2- Asegurar una correcta hidruresis.
3- Higiene del periné. Proscribir el bidé. Utilizar toallitas higiénicas. Limpieza delante atrás y no la inversa.
4- Eliminar en lo posible, todo factor que implique una obstrucción del flujo urinario.
5- En pacientes no obstructivos, se ha ensayado el jarabe de arándano. No está comercializado, por lo cual es difícil indicar su uso.
6- Acidificar la orina no ha dado resultados objetivables.
7- La posibilidad de modificarla ecología intestinal a través de los prebióticos ofrece una alternativa interesante en la corrección del principal reservorio de las IU.

Enfoque microbiológico en el uso AM

Hoy se considera que las infecciones renales no bacteriémicas pueden ser tratadas por los niveles urinarios de ATB debido al baño de orina que refluye en forma retrógrada hacia la médula renal con alta concentración de ATB (ej. C1G, amox+IBL, nitrofuranos).
Para que un ATB sea útil en infecciones en pacientes normoinmunes, su nivel en el lugar de la infección debe superar 2 a 5 veces la CIM90 de la especie infectante por lo menos durante 40 minutos para especies gram positivas y 60-90 minutos para especies gram negativas. Para cumplir este objetivo, se debe relacionar el nivel urinario con la CIM 90, que es la concentración inhibitoria mínima del antibiograma necesaria para inhibir el 90% de los aislamientos.

ATB	Dosis mg/kg	Nivel serico mg/L	Nivel urinario mg/L	Corte para R mg/l	CIM90 *E.coli*
AMP	30	4	500	>16	>2000
AMX/SUL	25/25	8/5	600/300	>16/8	512/256
CEFALEX	20	6	1200	>16	32
CEFADOX	15	9	1500	>16	32
CEFIXIMA	8	2	75	>2	0.12
CEFTIBUT	9	7	60	>16	0.06
NITROFUR	2	3	170	>64	64
TMS en TMP	3	5	20	>2	128

Ref. R : en mg/l : límite por arriba del cual una bacteria se considera como resistente

Correlación de nivel urinario y CIM 90 para *E.coli*

	Dosis mg/kg	Nivel urinario mg/l	CIM90
AMP	**30**	**500**	**>2000**
AMP+IBL	**25+25**	**600-300**	**512/256**
Cefalexina	**20**	**1200**	**32**
Cefadroxilo	**15**	**1500**	**32**
Cefixima	**8**	**75**	**0.12**
Ceftibuteno	**9**	**60**	**0.06**
Nitrofuranos	**2**	**170**	**64**
TMS	**3/15**	**20/160**	**128/1000**

Los antibiogramas por difusión (discos o tabletas) NO dan información sobre los niveles urinarios, por lo que, en IU bajas las resistencias son clínicamente falsas para algunos ATB (Ax-SB,C1ªG, Nitrof) y pueden ser verdaderas para otros (AMP, TMS)

Los niveles de las cefalosporinas de 1ª generación en orina superan en el 100% de los casos las concentraciones que corresponden a las CIM90 de *E.coli, P.mirabilis y S.saprophyticus* (JM.Casellas,2000)

Antibióticos útiles en IU

Tomando en cuenta los conceptos anteriores, la eliminación renal , en forma activa, la eliminación de la flora periuretral y vaginal, el fácil cumplimiento y el bajo costo la elección de antibióticos, se reduce a:

Vía oral	Vía parenteral
•Aminopenicilinas (1)	•Gentamicina
•Aminopenicilinas +IBL (1)	•Amicacina
•Cefalosporina 1 Generación (1)	•Piperacilina
•Cefalosporina 2 Generación	•Piperacilina+TZB
•Cefalosporina 3 Generación	•Imipenem
•Cotrimoxazol	•Vancomicina
•Nitrofuranos (2)	•Teicoplanina
•Fluorquinolonas (3)	

Observaciones:

1: Mayor resistencia, no eliminan flora periuretral y vaginal, mayor recaída

2: Indicado especialmente en quimioprofilaxis (no selecciona cepas resistentes) y en las cistitis

3: Comparación fluorquinolonas y TMT-SMX: EN IU no complicadas similar acción; en complicadas: fluorquinolonas supera a TMT.

No son útiles

- Cloranfenicol
- Macrólidos (salvo en el caso de gérmenes de desarrollo en medios de cultivo no convencionales)
- En las embarazadas (ver Cap. 17) Fluorquinolonas, TMS y nitrofuranos (último trimestre)

Antibióticos a informar

Para normatizar el ensayo de antibióticos en el antibiograma, se señalan los siguientes:

Enterobacteriácea. Uso ambulatorio

Ampicilina, Cefalotina, AMS / AMC, TMS, Norfloxacino / Ciprofloxacino, Gentamicina, Nitrofurantoina

Si es *Enterococcus* spp
Ampicilina, Ciprofloxacino, Nitrofuranos

Es necesario conocer si es o no resistente a la vancomicina. Si esto ocurriera hay que investigar la sensibilidad a:
Tetraciclina, Mino/doxiciclina, Linezolid, Quinupristina/Dalfopristina, Rifampicina.

Capítulo 9
Evolución

Las IU pueden curar, recidivar, permanecer asintomáticas, evalucionar a la IRC o producir la muerte del paciente.

Es clásico el esquema de Kunin que representa la historia natural de la enfermedad. (Fig. 1)

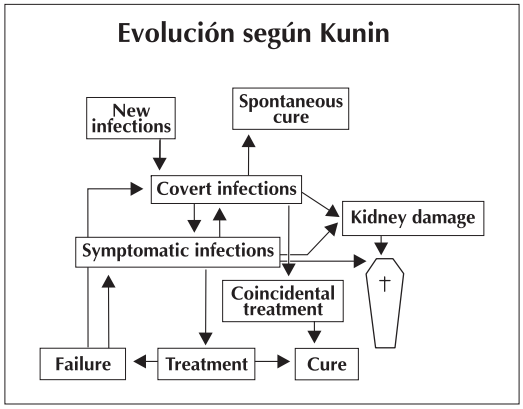


Fig. 9-1

Dinámica de las IU

La anterior figura se completa interpretando mejor la dinámica de las IU. En la figura 9-2 desarrollamos los fenómenos que observamos en nuestra práctica y permite una mejor interpretación de esta afección. Así puede observarse como una IU baja se transforma en Alta, como una bacteriuria asintomático puede colonizar parénquima, etc

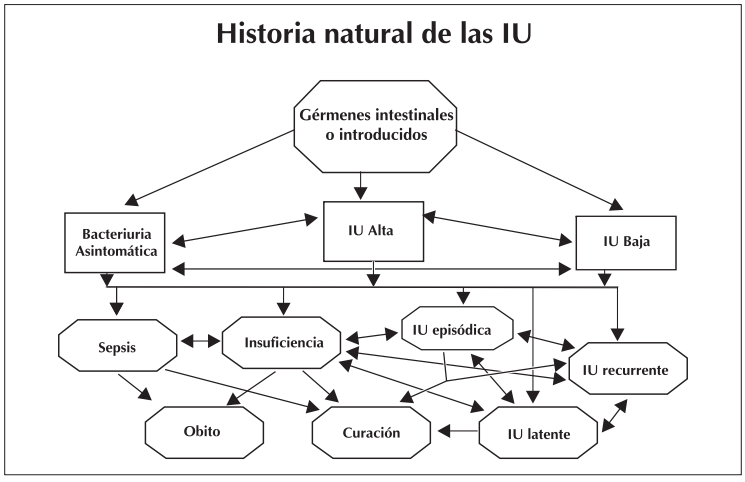


Fig. 9-2

Los episodios altos en IU bajas y viceversa

Tanto las IU altas, como las bajas pueden presentar síntomas que sugieren una localización distinta. Estas situaciones las denominamos episodios altos o bajos (ver Cap. 6).

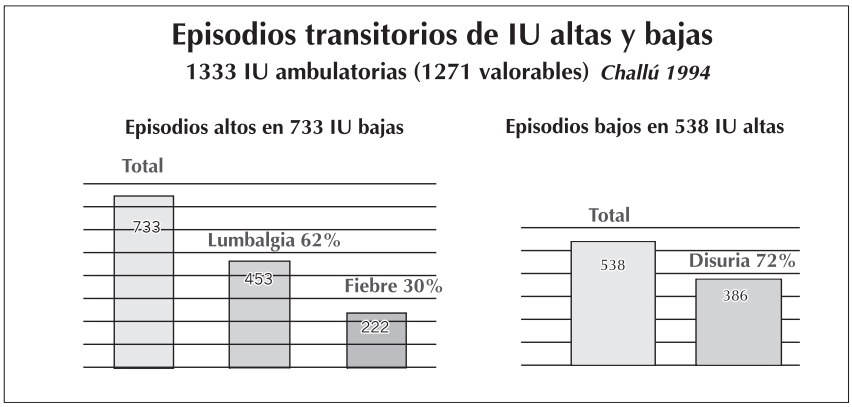


Fig. 9-3

Evolución en los distintos síndromes de IU

La evolución previsible en los grupos de síndromes, es la siguiente:

- Grupo IU con potencial riesgo de vida: Alta mortalidad en las IU hospitalarias. Curación con pocas probabilidades de secuelas
- Grupo IU con potencial riesgo de falla renal: Si no se corrige el terreno, alta posibilidad de evolucionar a la IRC
- Grupo IU benignas. Evolución benigna con altas posibilidades de recurrencia
- Grupo IU no suficientemente aclaradas: Evolución imprevisible

Evolución en pacientes ambulatorios

En una serie de 1333 IU ambulatorias, se documenta la siguiente evolución

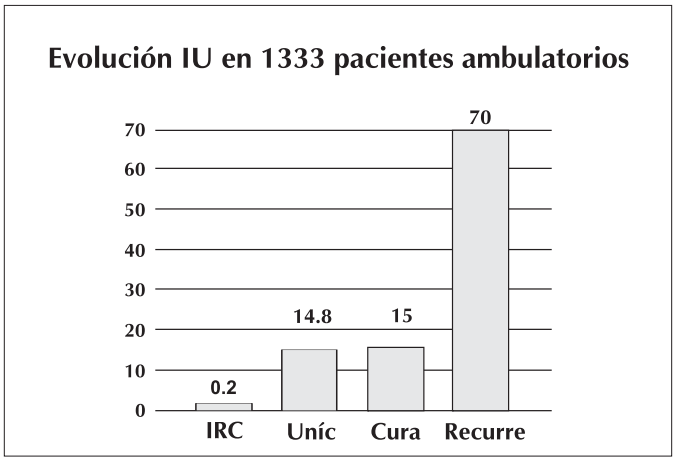


Fig. 9-4

Curación

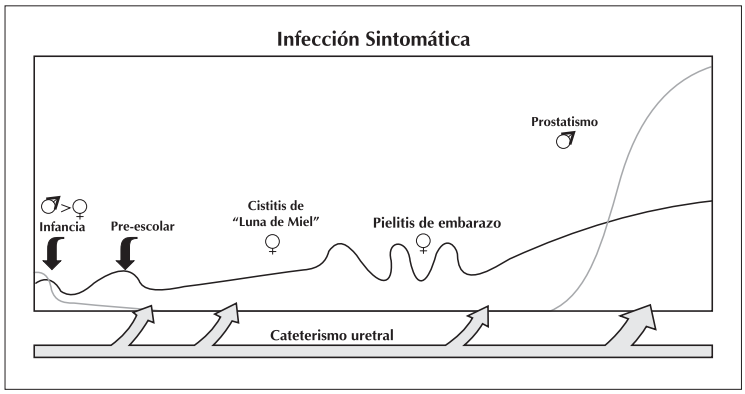


Fig. 9-5

El clásico esquema evolutivo (fig. 9-5) induce a pensar que la IU es una enfermedad continua que comienza en la infancia y se continúa a lo largo del tiempo. En realidad los hechos vienen a señalar que la bacteriuria comprobada, supone procesos nuevos sobre un terreno que admite su colonización. Su comportamiento a recurrencia, que semeja una enfermedad metabólica, está señalando que no se han corregido las condiciones del huésped que permitieron la IU.

La curación definitiva, es posible.

En un número limitado de pacientes puede producirse una autolimitación. En otros pacientes, en los cuales se aprecia una eliminación de la bacteriuria pueden haber recibido antibióticos por otros motivos, lo que provocó la esterilización de la orina.

Cuando se ha conseguido controlar la bacteriuria, es conveniente no hablar de curación del paciente, sino de esterilización de la orina o a lo sumo de curación del presente episodio de IU.

Controles Evolutivos

Dada las características evolutivas que se han señalado, es conveniente aconsejar a los pacientes un control periódico y estar atento a los síntomas o signos de IU típicos o atípicos. Se procurará no exagerar los controles, no sólo por el problema costo/beneficio (Cap. 10) sino para evitar la ansiedad y fantasías del paciente (ver más arriba).

Los controles a efectuar dependerán de cada cuadro clínico, como se verá en el segundo sección.

En términos generales se procede del modo siguiente:

1. Consulta clínica, ante la sospecha de IU o para evaluar resultados estudios.
2. Cultivo + sedimento a)intraantibioterapia, cuando no hay respuesta a las 48 hs de iniciado el tratamiento; b) a los 7 días de suspender la medicación; c) en casos leves a demanda según sus síntomas; en la bacteriuria asintomática, controles anuales.
3. Imágenes: Si demuestra patología se repetirá según criterio clínico. En recurrencia ecografía anual.

Capítulo 10
Costo/Beneficio

Por su alta morbilidad, la recurrencia, la incidencia en la progresión a la IRC, su importancia en el tratamiento sustitutivo de la IRC, el costo del diagnóstico y tratamiento y controles evolutivos, la IU es un problema que preocupa a la Salud Pública. Se han aconsejado medidas tendientes a disminuir los costos, aplicando una ecuación costo/beneficio.

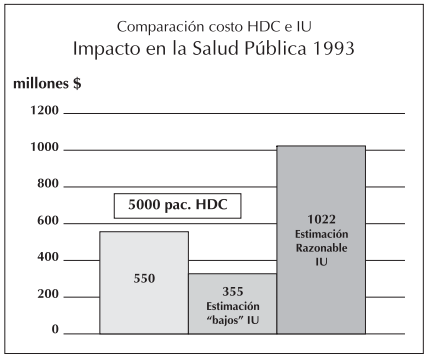
Dificultades para calcular costos

Se consideran costos directos, a saber: consultas, métodos de diagnóstico, medicamentos, internación, complicaciones. A su vez costos indirectos afectado a la infraestructura necesaria empleados, estructura administrativa, seguros, mantenimiento, amortización, alimentación, trasporte, impuestos. Por último los costos sociales que afectan al paciente: salarios perdidos, problemas sociales, calidad vida, etc. son los que lamentablemente muchas veces orientan la terapéutica

Las dificultades para recabar estos datos, hacen que los cálculos sean aproximados.

Una evaluación de costos en Argentina

En el año 1993, efectué una investigación analizando costos de diagnóstico inicial mínimo costo de AM en las formas leves y severas y 2 controles en el año. Analicé todos los casos presumidos de IU, efectuando una estimación de mínima y una estimación razonable. No consideré los costos indirectos. Para evaluar costos, hice la comparación con los costos de 5000 pacientes en diálisis. Estos fueron los resultados:



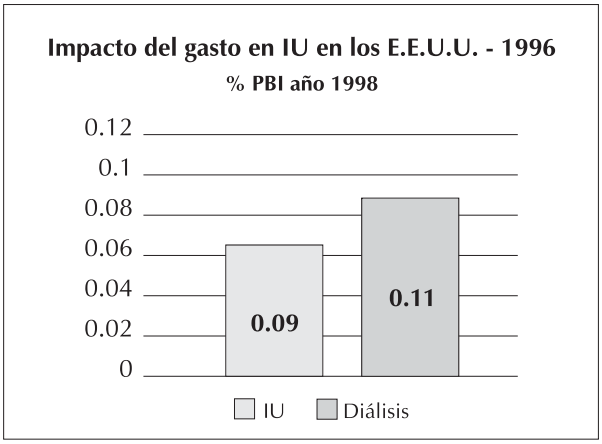
Una evaluación de gastos en USA

Mobley and Warren (1996), estimó los gastos en el tratamiento de las IU en estas cifras, las que he comparado con los datos existentes del gasto en HDC en USA.

Costos de las IU en USA

Consultas médicas por IU	8,000,000/año
IU diagnosticadas en internación	1,500,000/año
Internados por cuadros agudos IU	125,000/año
Costo anual IU estimado	**U$S 8,000,000,000**

"Urinary Tract Infections" Mobley and Warren 1996, ASM Press Washington



Cómo disminuir los gastos

La forma de aminorar los gastos, apuntan por un lado a reducir los gastos del diagnóstico inicial y de los controles; y reducir los costos del tratamiento. Por otra parte, lo que se considera más importante a optimizando el manejo en el diagnóstico, en los controles del seguimiento y en la terapia.

Optimizar los recursos en diagnóstico

Se jerarquizará la actitud del médico tratante, de acuerdo a las siguientes guías: **1**- priorizar el criterio clínico en el diagnóstico. **2**-Procurar interpretar fisiopatológicamente cada caso. **3**- Reconocer las formas atípicas de IU. Tener presente el subregistro de las IU. **4**- Aceptar que el diagnóstico es equívoco, con frecuentes falsos positivos y falsos negativos. **5**- Graduar los estudios según formas clínicas ya señaladas (Cap. 2).

Limitar los estudios iniciales al urocultivo y sedimento, aunque dependerá del cuadro clínico. Si hubiera necesidad de imágenes, se indicará ecografía más Rx simple de árbol urinario.

Hay situaciones que deben ser cuidadosamente evaluadas, en las cuales puede medicarse sin efectuar urocultivo El diagnóstico de localización sigue siendo un ejercicio clínico (Cap. 7-5).

Como ya se ha señalado (Cap. 7-7). El mejor *screening* es la clínica, y los cultivos múltiples.

En cuanto a los controles de seguimiento no se deben multiplicar los controles (Cap. 9) . Poner especial énfasis en no "fabricar" pacientes. Hay que controlar al paciente clínicamente utilizando cuidadosamente todos los criterios , y efectuar eventualmente algún estudio por imágenes

Los dos grandes riesgos en el seguimiento de estos pacientes son: por un lado subestimar la enfermedad y sus consecuencias. Y por oposición, "fabricar pacientes" con controles rigurosos y seguidos.

Se repite el concepto visto en el Cap. 9 : no confundir esterilización de la orina con curación del paciente. Y tener presente siempre la dinámica de las IU (Cap. 9)

Optimizar recursos terapéuticos

Los AM mal indicados, o prolongados innecesariamente, son el factor mayor en el costo de las IU. Por mal uso o prolongando innecesariamente o medicando cuando no es necesario. La mala praxis ha llevado además a un alarmante aumento en la resistencia bacteriana.

Otro error que incide en el costo, es reducir el tratamiento al uso de antimicrobianos, dejando de lado la corrección de los factores que han condicionado la IU.

Los ciclos cortos y la dosis única abaratan costos, sin reducir efectividad. Se ha comprobado que el tratamiento precoz, mejora la evolución de las IU, por lo que se recomienda recurrir a la medicación empírica, siguiendo las recomendaciones brindadas en el Cap 8.

Se debe confeccionar una lista consensuada y actualizada periódicamente de AM útiles.
En casos seleccionados se puede autorizar la automedicación, previendo los riesgos que conlleva esta práctica.

Prevención en IU

Se considera en los siguientes niveles: población sana, población de riesgo, pacientes con patología nefrourológica, en el infectado.

1. En la población sana

1.1. Finalidad: detección precoz, tratamiento precoz, evitar complicaciones; evitar daño renal.

1.2. Metodología: interrogatorio Tiritas reactivas Multicultivos

1.3. Oportunidad de los estudios: En momentos especiales: ingreso a universidades, ingreso a FF.AA., preocupacional. En población cautiva: establecimientos educacionales, en instituciones religiosas, en las FF.AA., establecimientos educacionales.

1.4. Contenido: Reconocer síntomas y acudir precozmente a la consulta Adoptar normas higiénico dietéticas

1.5. El método mas importante, el mas económico y al alcance de todos son las campañas de educación de la comunidad (comunidad general, comunidad médica, comunidad nefrológica).

1.6. En la Unión Europea se implementó un programa de prevención del cáncer ginecológico. El costo de la detección oportuna y el tratamiento temprano de las alteraciones cervicales redujo como mínimo en 50% del requerido para tratar el cáncer invasor. Un programa similar en México, comprobó una reducción mínima del costo en 40%. No existen trabajos que permitan demostrar que el costo de detección de las IU devenga en un menor costo final. Se sugiere su implementación, siguiendo las experiencias señaladas.

2. En la población de riesgo

2.1. Se considera: Embarazadas, Hospitalizados Preoperatorio, Diabéticos, HA

2.2. Metodología Clínica, cultivo + sedimento

3. En patología renal

3.1. especialmente los pacientes con IRC en tratamiento conservador. En el paciente en tratamiento sustitutivo de la función renal (Tx, Diálisis). Mandatorio al ingresar a plan de diálisis crónica o evaluación pretrasplante. En la patología urológica, especial en pacientes obstruidos.

3.2. Metodología: Clínica + Cultivo + sedimento Eventual imagen

Consensuar normatizaciones

Esta ha sido la preocupación inicial del CIU. Y objeto de sucesivas publicaciones. Las guías consensuadas, son el mejor instrumento para optimizar el manejo de las IU y bajar costos.

Esta actitud médica, debe extenderse en planes educativos en todos los niveles, como se ha señalado.

El tratamiento durante el embarazo, la IU en la vejez, la bacteriuria del cateterizado y la bacteriuria asintomática son algunos de los problemas que requieren mayor cuidado y necesidad de recomendaciones.

Todos ellos presuponen un conocimiento de esta afección. Constituye el mejor método de bajar costos. EL mal manejo de las IU incrementa enormemente los costos.

El programa de salud renal adoptado por la SLANH, debe considerar en un lugar destacado la prevención de las IU.

Riesgos al intentar disminuir costos

El riesgo mayor cuando se busca optimizar recursos y reducir costos, es aumentar el mal manejo de las IU. Ya existe un alerta generalizado sobre la mala praxis en todos los niveles asistenciales. Si se prioriza reducir gastos, es probable que aumente la mala praxis y la iatrogenia. Se debe estar prevenido ante esta contingencia.

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Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

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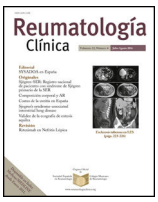

Artículo especial

Recomendaciones de la Sociedad Española de Reumatología sobre el tratamiento y uso de terapias sistémicas biológicas y no biológicas en artritis psoriásica

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RESUMEN

Objetivo: La primera finalidad de este documento de recomendaciones es proporcionar al clínico la mejor evidencia disponible y, en su defecto, la mejor opinión consensuada por los panelistas para un uso racional y fundado de las diversas opciones de tratamiento con fármacos antirreumáticos modificadores de la enfermedad (FAME) sintéticos y biológicos en artropatía psoriásica (APs). El presente documento también incide sobre aspectos importantes en el manejo de la APs, como el diagnóstico precoz, los objetivos terapéuticos, las comorbilidades y la optimización del tratamiento.
Métodos: Las recomendaciones se consensuaron a través de un panel de 8 reumatólogos expertos, previamente seleccionados por la Sociedad Española de Reumatología (SER) mediante una convocatoria abierta. Las fases del trabajo fueron: identificación de las áreas claves para la actualización del consenso anterior, análisis y síntesis de la evidencia científica (sistema modificado de Oxford, CEBM, 2009) y formulación de recomendaciones a partir de esta evidencia y de técnicas de consenso.
Resultados: Se emiten un total de 17 recomendaciones para el tratamiento de los pacientes con APs. Seis de ellas de carácter general, que abarcan desde la transcendencia del diagnóstico y tratamiento precoz hasta la importancia de las comorbilidades. El resto, las 11 específicas, se centran en las indicaciones de los FAME y la terapia biológica en las diferentes formas clínicas de la enfermedad. Así mismo, se abordan las situaciones de fracaso a un primer biológico y se incluyen los algoritmos de tratamientos y una tabla con las diferentes terapias biológicas.
Conclusiones: Se presenta la actualización de las recomendaciones de la SER para el tratamiento de la APs con FAME y terapia biológica.

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Keywords:
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Recommendations
Disease modifying antirheumatic drugs (DMARDs)
Biologic therapy
Spanish Society of Rheumatology

Recommendations of the Spanish Society of Rheumatology on treatment and use of systemic biological and non-biological therapies in psoriatic arthritis

A B S T R A C T

Objective: The main purpose of this recommendation statement is to provide clinicians with the best available evidence and the best opinion agreed upon by the panelists for a rational use of synthetic disease modifying antirheumatic drugs (DMARDs) and biologicals in psoriatic arthritis (PsA) patients. The present document also focuses on important aspects in the management of PsA, such as early diagnosis, therapeutic objectives, comorbidities and optimization of treatment.
Methods: The recommendations were agreed by consensus by a panel of 8 expert rheumatologists, previously selected by the Spanish Society of Rheumatology (SER) through an open call. The phases of the work were: identification of key areas for updating the previous consensus, analysis and synthesis of scientific evidence (modified Oxford system, Centre for Evidence-based Medicine, 2009) and formulation of recommendations based on this evidence and by consensus techniques.
Results: Seventeen recommendations were issued for the treatment of PsA patients. Six of them were of general nature, ranging from the early diagnosis and treatment to the importance of assessing comorbidities. The other 11 were focused on the indications for DMARDs and biological therapy in the distinct clinical forms of the disease. Likewise, the situation of failure of the first biological is addressed and treatment algorithms and a table with the different biological therapies are also included.
Conclusions: We present the update of SER recommendations for the treatment of PsA with DMARDs and biologics.

Introducción

La artritis psoriásica (APs) es una enfermedad heterogénea debido a la diversidad de fenotipos músculo-esqueléticos que presenta (artritis periférica, enfermedad axial, entesitis, dactilitis), así como a las manifestaciones extraarticulares, particularmente piel y uñas, pero también de otros órganos (uveítis, enfermedad intestinal inflamatoria)[1,2]. Aunque la psoriasis cutánea y la APs comparten ciertos procesos fisiopatológicos, como la angiogénesis y el aumento de expresión de citocinas proinflamatorias, presentan diferencias como la desigual eficacia de ciertos fármacos en la piel y la articulación[3,4].

Los fármacos sintéticos modificadores de la enfermedad convencionales (FAME-c) que se utilizan fueron ensayados primero en artritis reumatoide (AR) y, en general, cuentan con una limitada evidencia sobre su eficacia en APs[5,6]. Por otro lado, la incorporación de las terapias biológicas inhibidoras del TNF-alfa (i-TNF) ha supuesto una mejora fundamental en el manejo de esta enfermedad. No obstante, hay un porcentaje considerable de pacientes con APs en los que estas terapias están contraindicadas, pierden su eficacia o desarrollan efectos adversos.

Afortunadamente, la APs ha pasado de ser una enfermedad cuyos tratamientos venían derivados de la AR a ser una enfermedad prioritaria para la investigación y desarrollo de nuevas dianas terapéuticas. Las terapias biológicas dirigidas a modular la vía IL23/IL17 (ustekinumab, secukinumab), así como los fármacos sintéticos modificadores de la enfermedad con una diana específica (FAME-e) (apremilast), son ya una realidad para nuestros pacientes[7]. Aunque todos ellos han demostrado eficacia y seguridad en el tratamiento de la APs, por la ausencia de ensayos clínicos en los que se comparen directamente (estudios «head to head») o de experiencia clínica recogida en registros, no existen claras recomendaciones sobre en qué orden, etapa o dominio de la enfermedad deberían ser administrados los diferentes fármacos disponibles[8].

También resulta muy relevante, en el manejo de la APs, definir bien el objetivo a alcanzar con la terapia, así como utilizar determinadas estrategias de tratamiento (control estricto).

Por todo lo anterior, es preciso establecer unas recomendaciones basadas en la evidencia más reciente y en la opinión de expertos sobre el tratamiento de la APs. Recientemente, EULAR[9] y GRAPPA[10] han revisado sus recomendaciones de 2011 y 2009, respectivamente. Aquí presentamos la actualización de las recomendaciones de la Sociedad Española de Reumatología (SER)[11], que intenta ser un instrumento útil para que los reumatólogos españoles optimicen el manejo terapéutico de la APs. El presente documento no solo recoge los principales aspectos del control y del tratamiento con fármacos biológicos, sino que también incide sobre aspectos importantes en el manejo de la APs, como el diagnóstico precoz, los objetivos terapéuticos, el uso de FAME sintéticos, las comorbilidades y la optimización del tratamiento. No obstante, el foco principal de las recomendaciones se sitúa sobre las estrategias terapéuticas con FAME sintéticos y biológicos. En ningún caso estas recomendaciones pretenden constituirse en un protocolo estricto de manejo y tratamiento de la enfermedad, sino servir de base para incrementar la calidad en la asistencia de los pacientes con APs y ayudar a la toma de decisiones terapéuticas.

Material y métodos

En este proyecto se ha utilizado una síntesis cualitativa de la evidencia científica y técnicas de consenso («juicio razonado» y «Delphi modificado») que recogen el acuerdo de expertos en base a su experiencia clínica y a la evidencia científica.

Fases del proceso

En el desarrollo del documento de Recomendaciones se han seguido una serie de pasos que se describen a continuación:

Creación del grupo de trabajo. La elaboración del documento se inició con la constitución de un panel de expertos elegidos mediante una convocatoria abierta a todos los socios de la SER. La Comisión de Guías de Práctica Clínica (GPC) y Recomendaciones de la SER valoró el currículum vitae de los solicitantes de acuerdo con criterios objetivos de aportación al conocimiento de la APS, principalmente, por la participación en publicaciones en revistas de impacto en los últimos 5 años. El panel de expertos quedó constituido por 8 reumatólogos miembros de la SER. La coordinación de los aspectos clínicos y metodológicos fue realizada por uno de estos

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Tabla 1
Recomendaciones SER sobre el tratamiento y uso de terapias biológicas en la artritis psoriásica. Recomendaciones generales

Recomendaciones generales	GR	GA ≥ 4
Recomendación 1. La artritis psoriásica es una enfermedad musculoesquelética inflamatoria crónica cuyo diagnóstico, tratamiento y control evolutivo debería ser realizado por el reumatólogo	D	100%
Recomendación 2. La artritis psoriásica tiene una presentación clínica muy heterogénea y unas comorbilidades asociadas que, en ocasiones, precisan de un manejo multidisciplinar. El manejo coordinado con el dermatólogo es importante, sobre todo en aquellos pacientes con psoriasis moderada-grave	D	100%
Recomendación 3. El objetivo terapéutico de la artritis psoriásica es controlar la inflamación y preservar la capacidad funcional de los pacientes, alcanzando la remisión clínica o mínima/baja actividad de la enfermedad según los diferentes índices validados	D	100%
Recomendación 4. Establecer un objetivo terapéutico y realizar una monitorización clínica estrecha son cruciales para alcanzar un control óptimo de la actividad clínica y una respuesta terapéutica adecuada. Una vez conseguido el objetivo terapéutico, un seguimiento trimestral parece razonable	D	100%
Recomendación 5. El perfil de riesgo cardiovascular se debe tener en cuenta tanto en la evaluación como en el manejo terapéutico de estos pacientes	D	100%
Recomendación 6. La decisión terapéutica más adecuada dependerá del criterio del especialista y se realizará de forma consensuada con el paciente. Esta decisión se tomará basada principalmente en la evidencia científica y las características del paciente y de su enfermedad	D	100%

GA: grado de acuerdo; GR: grado de recomendación; SER: Sociedad Española de Reumatología.

reumatólogos, como investigador principal (IP), y por una especialista en metodología, técnico de la Unidad de Investigación (UI) de la SER.

Identificación de las áreas claves para la actualización del consenso anterior. Todos los miembros del grupo de trabajo participaron para estructurar el documento y establecer los contenidos y aspectos claves. Se optó por la actualización de las recomendaciones provenientes tanto del Consenso anterior como de la última versión de la ESPOGUIA 2015[12]. Primero se identificaron las preguntas clínicas que podrían tener más impacto en la utilización de terapia biológica en la APs. Después se fijaron aquellos contenidos y resultados que no precisaban responder a la formulación de pregunta de investigación. Se definió también la metodología a seguir en el proceso de elaboración de las recomendaciones.

Búsqueda bibliográfica. Las preguntas clínicas se reformularon en 7 preguntas con formato PICO. Para responder a las preguntas se diseñó una estrategia de búsqueda y se realizó una revisión de la evidencia científica de estudios publicados hasta febrero de 2016. Se utilizaron las bases de datos: PubMed (MEDLINE), EMBASE, y Cochrane Library (Wiley Online). Se completó el proceso con una búsqueda manual de referencias, pósteres y resúmenes de congresos que consideraron de interés los revisores y expertos. Las estrategias de búsquedas bibliográficas, de las 7 revisiones sistemáticas (RS), pueden consultarse en el material suplementario que estará detallado en un anexo metodológico en la página web de la SER.

Análisis y síntesis de la evidencia científica. Varios reumatólogos, del grupo de trabajo de revisores de la evidencia de la SER, se encargaron de revisar sistemáticamente la evidencia científica disponible. Tras la lectura crítica del texto completo de los estudios seleccionados para cada revisión, elaboraron un resumen mediante el uso de un formulario homogeneizado incluyendo tablas y texto para describir la metodología, resultados y calidad de cada estudio. Se detallaron los motivos de exclusión de los artículos no incluidos en la selección. Se evaluó el nivel global de la evidencia científica utilizando la modificación de los niveles de evidencia del Centro Oxford de Medicina basada en la Evidencia (CEBM) (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009).

Formulación de recomendaciones. Finalizada la lectura crítica, el IP y los componentes del grupo de expertos procedieron a la formulación de recomendaciones específicas basadas en la evidencia científica. Esta formulación se ha basado en la «evaluación formal» o «juicio razonado», resumiendo previamente la evidencia para cada una de las preguntas clínicas. Se tuvo en cuenta, también, la calidad, cantidad y consistencia de la evidencia científica, la generalidad de los resultados, su aplicabilidad y su impacto clínico. Para la formulación de las recomendaciones se utilizaron dos rondas de consenso; primero, en una reunión presencial, con el sistema de consenso de «juicio razonado», todos los expertos redactaron y discutieron las recomendaciones y se discutieron en presencia del metodólogo; después, mediante un cuestionario Delphi, se consensuó el grado de acuerdo de los expertos con la redacción de cada una de las recomendaciones usando una escala Likert del 1 al 5 (1: absolutamente en desacuerdo; 2: moderadamente en desacuerdo; 3: ni acuerdo ni desacuerdo; 4: moderadamente de acuerdo; 5: absolutamente de acuerdo). Se definió alto grado de consenso en la redacción cuando el porcentaje de panelistas que otorgaron valores ≥ 4 en la escala de Likert fue superior al 75%. El nivel de evidencia y la graduación de la fuerza de las recomendaciones se establecieron en base al sistema modificado de Oxford 2009.

Exposición pública. El borrador de este documento de Recomendaciones SER fue sometido a un proceso de exposición pública por parte de socios miembros de la SER y de distintos grupos de interés (industria farmacéutica, otras sociedades científicas y asociaciones de pacientes), con objeto de recoger la valoración y su argumentación científica de la metodología y las recomendaciones.

Estructura

El documento recoge todas las recomendaciones formuladas subdivididas en dos apartados: principios generales y recomendaciones específicas. A partir de las recomendaciones se ha elaborado un algoritmo terapéutico que presenta de forma resumida la aproximación al tratamiento tras el diagnóstico de APs.

Resultados

El total de recomendaciones formuladas sobre el tratamiento y uso de terapias biológicas en APs es de 17 (tablas 1 y 2).

Recomendaciones generales

- *Recomendación 1.* La APs es una enfermedad musculoesquelética inflamatoria crónica cuyo diagnóstico, tratamiento y control evolutivo debería ser realizado por el reumatólogo.
- *Recomendación 2.* La APs tiene una presentación clínica muy heterogénea y unas comorbilidades asociadas que, en ocasiones, precisan de un manejo multidisciplinar. El manejo coordinado con el dermatólogo es importante, sobre todo en aquellos pacientes con psoriasis moderada-grave.
- *Recomendación 3.* El objetivo terapéutico de la APs es controlar la inflamación y preservar la capacidad funcional de los

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Tabla 2
Recomendaciones SER sobre el tratamiento y uso de terapias biológicas en la artritis psoriásica. Recomendaciones específicas

Recomendaciones específicas	GR	NE	GA ≥ 4
Recomendación 7. Se recomienda una intervención farmacológica precoz con FAME-c en pacientes con artritis psoriásica, principalmente en aquellos con factores de mal pronóstico basales, con la finalidad de mejorar los signos y los síntomas, la capacidad funcional y la calidad de vida	D	4	100%
Recomendación 8. Se recomiendan los FAME-c (metotrexato, leflunomida, sulfasalazina) como tratamiento de primera línea de la artritis psoriásica periférica activa	C	2b	100%
Recomendación 9. Se recomienda el metotrexato como primera elección, por sus efectos sobre la artritis y la psoriasis	D	4	100%
Recomendación 10. Se recomienda la utilización de apremilast para el tratamiento de artritis periférica, tras fracaso o intolerancia a FAME-c, cuando se considere que es más conveniente que la terapia biológica por el perfil del paciente	C	2b	100%
Recomendación 11. Se recomienda el uso de terapia biológica en pacientes con artritis psoriásica periférica refractarios al menos a un FAME-c	A	1b	100%
Recomendación 12. Se recomienda la utilización de terapia biológica, tanto en monoterapia como en combinación con FAME-c, para todas las manifestaciones periféricas de la artritis psoriásica. La terapia combinada con metotrexato puede aumentar la supervivencia de los fármacos monoclonales i-TNF, sobre todo los quiméricos	C	2b	100%
Recomendación 13. Se recomienda, en pacientes con artritis psoriásica periférica y fallo a un i-TNF, cambiar a otra terapia biológica, ya sea otro i-TNF o un fármaco con otro mecanismo de acción, como i-IL12/23 o i-IL17 o FAME-e (apremilast)	B	1b, 2b	100%
Recomendación 14. Se recomienda, en pacientes con artritis psoriásica y entesitis refractarios a AINE y tratamiento local, el uso de terapia biológica o FAME-e (apremilast)	C	2b	100%
Recomendación 15. Se recomienda, en pacientes con artritis psoriásica y dactilitis refractaria a AINE y tratamiento local con infiltraciones de corticoides, el uso de terapia biológica o FAME-e (apremilast)	C	2b	100%
Recomendación 16. Se recomienda, en pacientes con formas predominantemente axiales de artritis psoriásica refractarias a AINE, el uso de terapia biológica (i-TNF o i-IL17)	D	4	100%
Recomendación 17. No se recomienda el uso de FAME-c en formas axiales de artritis psoriásica	C	2b	100%

AINE: antiinflamatorios no esteroides; FAME: fármacos antirreumáticos modificadores de la enfermedad; FAME-c: FAME sintéticos convencionales; FAME-e: FAME específico; GA: grado de acuerdo; GR: grado de recomendación; i-IL12, i-IL23 o i-IL17: inhibidor de la interleucina 12, 23 o 17; i-TNF: inhibidor del factor de necrosis tumoral; NE: nivel de evidencia; SER: Sociedad Española de Reumatología.

pacientes, alcanzando la remisión clínica o mínima/baja actividad de la enfermedad según los diferentes índices validados.

- *Recomendación 4.* Establecer un objetivo terapéutico y realizar una monitorización clínica estrecha son cruciales para alcanzar un control óptimo de la actividad clínica y una respuesta terapéutica adecuada. Una vez conseguido el objetivo terapéutico, un seguimiento trimestral parece razonable.
- *Recomendación 5.* El perfil de riesgo cardiovascular se debe tener en cuenta tanto en la evaluación como en el manejo terapéutico de estos pacientes.
- *Recomendación 6.* La decisión terapéutica más adecuada dependerá del criterio del especialista y se realizará de forma consensuada con el paciente. Esta decisión se tomará basada principalmente en la evidencia científica y las características del paciente y de su enfermedad.

La APs es una enfermedad con una presentación clínica muy heterogénea que incluye manifestaciones articulares y extraarticulares[1,4]. El médico responsable de su diagnóstico y tratamiento debe ser el reumatólogo, puesto que es el especialista con mayor conocimiento y experiencia en el manejo clínico y terapéutico de esta enfermedad[9,13,14]. Sin embargo, debido a la diversidad de su expresión clínica y a las comorbilidades asociadas, es importante realizar un manejo multidisciplinar del paciente[15–17].

El objetivo clínico al tratar pacientes con APs no está tan bien definido como en la AR[18–22]. Independientemente del índice de actividad que se use para monitorizar la actividad clínica, la prioridad debe ser controlar la inflamación lo antes posible y mejorar la capacidad funcional y calidad de vida de los pacientes con APs[23–25]. La remisión clínica puede ser difícil de alcanzar principalmente en APs de larga evolución[26–28]. En este subgrupo puede ser suficiente obtener mínima/baja actividad de la enfermedad —conseguir 5 de los 7 criterios propuestos, que abarcan desde manifestaciones musculoesqueléticas y cutáneas hasta valoración del propio paciente—[24,29,30]. Aunque no hay consenso sobre la mejor herramienta para monitorizar la actividad clínica, se recomienda el uso de índices validados y cuantificables que tengan en cuenta tanto parámetros de actividad inflamatoria (afectación articular [periférica y/o axial], dactilitis, entesitis y reactantes de fase aguda) como parámetros más subjetivos que repercuten en la función y calidad de vida del paciente (dolor, fatiga, evaluación global del paciente, capacidad funcional y calidad de vida)[22,23,31–34].

Un ensayo clínico reciente ha demostrado mejores desenlaces cuando se realiza una monitorización estrecha (*control estricto*, cada 4 semanas) frente a la práctica clínica habitual (cada 12 semanas)[35]. Aunque, actualmente, no está claro el mejor intervalo de monitorización de los pacientes, parece razonable realizar un control más estrecho (cada 4 semanas) tras el diagnóstico de la enfermedad o siempre que sea necesaria la evaluación de la respuesta a un tratamiento. Una vez alcanzado el objetivo terapéutico, se puede realizar una monitorización trimestral[9,35].

Se dispone, actualmente, de varias guías para el manejo de pacientes con APs que suponen una herramienta crucial para el abordaje terapéutico de estos enfermos[9,36]. En práctica clínica, sin embargo, se recomienda tener en cuenta, a la hora de tomar decisiones terapéuticas, las comorbilidades asociadas a la enfermedad, así como la opinión del paciente, explicando el riesgo/beneficio de cada una de ellas, ya que esto puede favorecer una mayor adherencia y cumplimentación del tratamiento.

El abordaje del riesgo cardiovascular en los pacientes con enfermedades inflamatorias crónicas es importante desde que se conoce la conexión entre la inflamación, la disfunción del endotelio y el incremento de la aterogénesis[37]. Asociado al papel de la inflamación se ha observado, en los pacientes con APs, un aumento de los factores de riesgo cardiovascular (hipertensión, diabetes, dislipidemia, etc.) cuya consecuencia es una mayor prevalencia de eventos cardiovasculares[38]. Otro aspecto significativo en el que tenemos que incidir es la prevención de la obesidad, ya que además de ser un factor de riesgo cardiovascular puede asociarse a una peor respuesta a los tratamientos inmunosupresores y a una mayor dificultad de alcanzar un estado de mínima actividad de la enfermedad[39].

De la revisión sistemática en este campo, se infiere que los datos epidemiológicos son insuficientes para llegar a conclusiones definitivas sobre los efectos de los fármacos biológicos y FAME-c en eventos cardiovasculares en los pacientes con APs. Sin embargo, los i-TNF y metotrexato (MTX), actuando como inhibidores de la inflamación, pueden tener efectos cardioprotectores[40].

Por otra parte, la decisión terapéutica del especialista debe ser lo más costo-eficiente posible con el mayor beneficio clínico para

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el paciente, sin que ello suponga una carga extra para el sistema nacional sanitario.

Recomendaciones específicas

Intervención precoz

- *Recomendación 7.* Se recomienda una intervención farmacológica precoz con FAME-c en pacientes con APs, principalmente en aquellos con factores de mal pronóstico basales, con la finalidad de mejorar los signos y los síntomas, la capacidad funcional y la calidad de vida (NE: 4, GR: D).

Aunque la evidencia científica es escasa y controvertida en este campo, se encontraron 6 estudios que responden de forma indirecta a esta pregunta. Entre los factores que influyen sobre la progresión de la lesión estructural articular destacan la mayor duración de la enfermedad[41,42] y el retraso diagnóstico en pacientes con APs precoz[43].

Diversos estudios han evaluado la capacidad funcional tanto en APs precoz como en APs establecida[35,43,44]. Se ha objetivado que el retraso diagnóstico, el hábito tabáquico, la edad avanzada, el sexo femenino y una historia previa de tratamientos i-TNF se asocian con una peor capacidad funcional[41,43].

En el registro sueco de APs precoz se encontró que una menor duración de los síntomas, un HAQ basal bajo y la enfermedad axial en varones fueron factores predictivos independientes de mínima actividad de la enfermedad[44]. Los autores sugieren que el diagnóstico precoz en pacientes con afectación poliarticular puede ser importante para iniciar tratamiento específico de forma más anticipada[44]. Por tanto, aunque no existen muchos estudios que incidan sobre este tema, podemos considerar como factores de mal pronóstico las formas poliarticulares con reactantes inflamatorios elevados, el retraso diagnóstico y terapéutico, la dactilitis, la presencia de erosiones basales y el hábito tabáquico.

En el estudio TICOPA se demostró que la intervención terapéutica precoz y el seguimiento clínico estrecho (cada 4 semanas) consiguieron mejores respuestas clínicas (medidas por ACR y MDA) que la práctica clínica habitual (cada 12 semanas) en una cohorte de APs precoz, aunque no encontraron diferencias en la progresión radiográfica a las 48 semanas[35], en gran medida por la poca progresión global de ambas cohortes. Por otra parte, un estudio abierto realizado en 35 pacientes con APs observó que un retraso de 3 meses en el inicio del tratamiento con MTX no tenía un impacto clínico relevante[45].

Artritis periférica

Los antiinflamatorios no esteroideos (AINE) y corticoides orales, usados a la dosis mínima necesaria durante el menor tiempo posible, pueden ser útiles como tratamiento sintomático de la APs periférica, sin que esto suponga un retraso en el inicio del tratamiento modificador de la enfermedad en aquellos pacientes en los que esté indicado. El uso de terapia local en forma de infiltraciones de corticoides se recomienda especialmente en el caso de entesitis y dactilitis, y también tiene utilidad en la artritis periférica monooligoarticular. El empleo de la ecografía puede ser de utilidad en la guía de estos procedimientos.

Fármacos antirreumáticos sintéticos modificadores de enfermedad (FAME).

Fármacos antirreumáticos sintéticos modificadores de enfermedad convencionales (FAME-c).

- *Recomendación 8.* Se recomiendan los FAME-c (MTX, leflunomida, sulfasalazina) como tratamiento de primera línea de la APs periférica activa (NE: 2 b, GR: C).
- *Recomendación 9.* Se recomienda el MTX como primera elección, por sus efectos sobre la artritis y la psoriasis (NE: 4, GR: D).

En los pacientes con APs periférica, se recomienda el uso de FAME-c como primera opción terapéutica, entre los cuales el MTX debería ser el de elección, siendo la leflunomida y la sulfasalazina otras opciones válidas. Los ensayos clínicos de MTX, por diferentes circunstancias de carácter metodológico, no han conseguido mostrar datos concluyentes sobre su eficacia en APs[46]. Sin embargo, la amplia experiencia en la práctica clínica habitual y los datos procedentes de estudios observacionales y registros sugieren que MTX es eficaz en APs. Así, en el registro noruego, la supervivencia de MTX a los 2 años fue del 65%[47] y en el estudio TICOPA[35] el 22% de los pacientes con MTX en monoterapia alcanzaron la mínima actividad de la enfermedad. Respecto al papel de los FAME-c en la inhibición del daño estructural, por el momento no hay suficiente evidencia[48], aunque quizás el MTX a dosis altas pueda tener algún efecto[49]. Por todo lo expuesto, se aconseja la utilización de MTX como primera línea terapéutica en base a la amplia experiencia clínica, su eficacia, también, en dominios como la piel[50], su bajo coste y su acceso universal.

Fármacos antirreumáticos sintéticos modificadores de enfermedad con diana específica (FAME-e): apremilast.

- *Recomendación 10.* Se recomienda la utilización de apremilast para el tratamiento de artritis periférica, tras fracaso o intolerancia a FAME-c, cuando se considere que es más conveniente que la terapia biológica por el perfil del paciente (NE: 2 b, GR: C).

Apremilast es una pequeña molécula que inhibe a la fosfodiesterasa 4 (PDE-4). La inhibición de la PDE-4 provoca un aumento de los niveles intracelulares de monofosfato de adenosina cíclico (AMPc) modulando la expresión de citocinas inflamatorias[51]. Los datos de eficacia de apremilast en artritis periférica, en base a resultados de los ensayos clínicos, parecen inferiores a la terapia biológica[52–54]. La ausencia de datos sobre progresión radiográfica, la falta de experiencia en su uso, y de estudios comparativos con FAME-c o biológicos, hace que actualmente haya dudas sobre su lugar en el algoritmo terapéutico de la APs periférica. Por otra parte, su perfil de seguridad es bueno apoyando su utilización en aquellos pacientes en los que, por la presencia de comorbilidades o antecedentes de infecciones severas, no se aconseja el uso de otras opciones terapéuticas[55]. Además, puede favorecer la pérdida de peso (entre 5-10%), aspecto interesante en los pacientes con APs y sobrepeso/obesidad.

Terapias biologicas (i-TNF, anti-IL12/23, anti-IL17).

- *Recomendación 11.* Se recomienda el uso de terapia biológica en pacientes con APs periférica refractarios al menos a un FAME-c (NE: 1 b, GR: A).

En aquellos pacientes con APs periférica en los que los FAME hayan sido ineficaces, o hayan tenido que retirarse por intolerancia, estaría indicado el uso de la terapia biológica. En relación con los agentes i-TNF, diferentes ensayos clínicos han demostrado que son eficaces en todos los dominios de la APs. Se ha evidenciado, también, que poseen un efecto significativo sobre la inhibición del daño estructural[48,56–58]. Disponemos, además, de 2 nuevos agentes con mecanismo de acción diferente, el ustekinumab (i-IL12/23)[59–61] y secukinumab (i-IL17)[62,63], los cuales han demostrado, recientemente, ser eficaces en controlar las manifestaciones de la APs y en la inhibición del daño radiográfico, por lo que son opciones igualmente válidas para los pacientes con APs y respuesta inadecuada a FAME, especialmente en aquellos casos con afectación cutánea grave.

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A pesar de la ausencia de ensayos clínicos que comparen de manera directa la eficacia de las diversas moléculas disponibles, no parece que las diferencias entre ellas sean significativas. Todas son una buena opción de tratamiento en el caso de fracaso a FAME sintético. Sin embargo, basándonos en los años de experiencia en la práctica clínica y la que reflejan los distintos registros internacionales, el panel de expertos sugiere como primera opción los inhibidores de TNF, siendo los demás fármacos opciones igualmente válidas por lo que en último caso debe ser el criterio médico el que prevalezca.

En la tabla 3 se representan las terapias biológicas con indicación actual para el tratamiento de la APs en nuestro país.

- *Recomendación 12.* Se recomienda la utilización de terapia biológica, tanto en monoterapia como en combinación con FAME-c, para todas las manifestaciones periféricas de la APs. La terapia combinada con MTX puede aumentar la supervivencia de los fármacos monoclonales i-TNF, sobre todo los quiméricos (NE: 2 b, GR: C).

Así como en la AR se ha demostrado la utilidad de la terapia biológica en combinación con FAME y la SER recomienda específicamente su uso[64], en APs hay más controversia. No existen comparaciones directas de eficacia y seguridad entre el tratamiento combinado de MTX y terapia biológica frente al tratamiento con terapia biológica en monoterapia en APs. Los datos procedentes de los ensayos clínicos no objetivan diferencias significativas en cuanto a desenlaces de eficacia (respuestas ACR) o de seguridad entre los pacientes en tratamiento combinado y pacientes con tratamiento biológico en monoterapia[55,57,63–76].

Por lo tanto, no se pueden extraer conclusiones válidas de eficacia ni de seguridad para cada fármaco biológico combinado con MTX comparado con terapia biológica en monoterapia. En general, la combinación con MTX no mostró una mejoría clínica significativa[65]. Sin embargo, la terapia combinada con MTX en algunos registros aporta mayor supervivencia del fármaco, especialmente en anticuerpos monoclonales, sobre todo con infliximab, por lo que se podría considerar su uso en esta circunstancia[77–80].

- *Recomendación 13.* Se recomienda, en pacientes con APs periférica y fallo a un i-TNF, cambiar a otra terapia biológica, ya sea otro i-TNF o un fármaco con otro mecanismo de acción, como i-IL12/23 o i-IL17 o FAME-e (apremilast) (NE: 1 b, 2 b; GR: B).

Los datos procedentes de los ensayos clínicos indican que la respuesta a un segundo agente i-TNF es buena, aunque inferior en general a la que se obtiene en pacientes no expuestos previamente a estos fármacos. Los registros muestran una ligera reducción de la supervivencia del segundo biológico en comparación con el primero, y claramente peor en el caso del tercero.

No existen estudios que comparen la utilidad de usar un segundo i-TNF frente a un cambio de diana terapéutica (IL12/23 o IL17), por lo que en la actualidad ambas opciones terapéuticas son igualmente válidas. Tanto en los estudios de ustekinumab como en los de secukinumab, al igual que ocurre con los fármacos i-TNF, se demuestra que la respuesta a dichos fármacos en los pacientes que no han sido expuestos previamente a biológicos es superior si se compara con la que se obtiene en los pacientes que ya han fallado a un i-TNF, por lo que la eficacia esperada siempre será mejor cuanto antes utilicemos el fármaco biológico, independientemente de cuál sea este[63,81–90]. Apremilast también demostró mayores respuestas ACR20 en pacientes que no habían sido expuestos previamente a terapia biológica[53].

La figura 1 representa un algoritmo para el manejo de la artritis periférica.

Entesitis

- *Recomendación 14.* Se recomienda, en pacientes con APs y entesitis refractarios a AINE y tratamiento local, el uso de terapia biológica o FAME-e (apremilast) (NE: 2 b, GR: C).

En aquellas formas de APs con afectación predominantemente entesítica se recomienda el uso en primer lugar de AINE, fisioterapia e infiltraciones locales perientésicas con corticoides, pese a que hasta la fecha no hay estudios aleatorizados y controlados con placebo que avalen su eficacia. No existe evidencia que apoye el uso de FAME-c en entesitis. No obstante, en los pacientes con APs y entesitis se podría valorar el uso de FAME-c siempre que haya artritis periférica asociada. Si a pesar del tratamiento anterior no se consigue una buena respuesta, el uso de terapia biológica o apremilast sería la opción correcta[91]. Los fármacos i-TNF[92] y posteriormente ustekinumab[59,60], secukinumab[63,82] y apremilast[54] han demostrado eficacia en el tratamiento de las entesitis, sin que existan datos que objetiven superioridad clara de un fármaco respecto al resto. Por este motivo, todos ellos serían una buena opción de tratamiento en caso de refractariedad a AINE y/o tratamientos locales. Sin embargo, basándonos en los años de experiencia en la práctica clínica y la que reflejan los distintos registros internacionales, el panel de expertos sugiere como primera opción los i-TNF, siendo los demás fármacos opciones igualmente válidas por lo que en último caso debe ser el criterio médico el que prevalezca.

La figura 2 representa un algoritmo para el manejo de la entesitis.

Dactilitis

- *Recomendación 15.* Se recomienda, en pacientes con APs y dactilitis refractaria a AINE y tratamiento local con infiltraciones de corticoides, el uso de terapia biológica o FAME-e (apremilast) (NE: 2 b, GR: C).

En aquellas formas de APs con presencia de dactilitis se recomienda el uso, en primer lugar, de AINE e infiltraciones locales con corticoides, aunque por el momento no disponemos de estudios aleatorizados y controlados con placebo que avalen su eficacia. En los pacientes con APs y dactilitis se podría valorar el uso de FAME-c siempre que haya artritis periférica asociada. Los FAME-c tienen un tamaño de efecto en general pequeño en dactilitis puras[92]. Los fármacos i-TNF[92], ustekinumab[59,60], secukinumab[63,82] y apremilast[54] tienen datos favorables en dactilitis, sin evidenciar superioridad ninguna de unas moléculas frente a las otras. Estos fármacos son una opción terapéutica en aquellos pacientes en los que las medidas locales hayan fracasado. Sin embargo, basándonos en los años de experiencia en la práctica clínica y la que reflejan los distintos registros internacionales, el panel de expertos sugiere como primera opción los i-TNF, siendo los demás fármacos opciones igualmente válidas por lo que en último caso debe ser el criterio médico el que prevalezca.

La figura 3 representa un algoritmo para el manejo de la dactilitis.

Afectación axial

- *Recomendación 16.* Se recomienda, en pacientes con formas predominantemente axiales de APs refractarias a AINE, el uso de terapia biológica (i-TNF o i-IL17) (NE: 4, GR: D).
- *Recomendación 17.* No se recomienda el uso de FAME-c en formas axiales de APs (NE: 2 b, GR: C).

A falta de estudios específicos en APs con predominio de afectación axial, se siguen las recomendaciones generales para espondiloartritis axial (EspA axial), que incluyen, además del

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Tabla 3
Terapias biológicas disponibles para el tratamiento de la artritis psoriásica, según ficha técnica

Terapia biológica	Principio activo	Posología y administración	Indicaciones	Contraindicaciones	Eventos adversos[a]
i-TNF alfa	Adalimumab	-Dosis: 40 mg -Vía: subcutánea -Frecuencia: cada 2 semanas	Artritis psoriásica activa y progresiva en adultos cuando la respuesta a la terapia previa con FAME haya sido insuficiente	-Hipersensibilidad al principio activo o excipientes -TBC activa, infecciones graves como sepsis e infecciones oportunistas -IC moderada a grave (NYHA clases III/IV)	-Muy frecuentes: reacción en el lugar de inyección (dolor, enrojecimiento) -Frecuentes: cefalea, infección respiratoria, urinaria, herpes, diarrea -Poco frecuentes: LES, TBC, arritmia, sepsis, citopenia -Raros: ICC, esclerosis múltiple, linfoma, tumor sólido maligno
	Certolizumab	-Dosis: 200 mg o 400 mg -Vía: subcutánea -Frecuencia: inicial (400 mg en las semanas 0, 2 y 4), mantenimiento (200 mg cada 2 semanas o 400 mg cada 4 semanas)	Artritis psoriásica activa en adultos, cuando la respuesta previa al tratamiento con FAME haya sido inadecuada	-Hipersensibilidad al principio activo o excipientes -TBC activa, infecciones graves como sepsis e infecciones oportunistas -IC moderada a grave (NYHA clases III/IV)	-Muy frecuentes: ninguno -Frecuentes: infecciones bacterianas y víricas, leucopenias, cefalea, HTA, náuseas -Poco frecuentes: sepsis, TBC, infecciones fúngicas, neoplasias del sistema linfático, tumores sólidos, cánceres de piel no melanoma -Raros: pancitopenia, esplenomegalia, melanoma, pericarditis, EPI, neumonitis
	Etanercept	-Dosis: 25 o 50 mg -Vía: subcutánea -Frecuencia: 25 mg 2 veces por semana (intervalo de 72-96 h); 50 mg una vez a la semana	Artritis psoriásica activa y progresiva en adultos cuando la respuesta a una terapia previa con FAME ha sido inadecuada	-Hipersensibilidad al principio activo o excipientes -Sepsis o riesgo de sepsis -Infecciones activas (incluyendo crónicas o localizadas)	-Muy frecuentes: reacción en el lugar de inyección, infección respiratoria, urinaria, cutánea -Frecuentes: alergia, autoanticuerpos -Poco frecuentes: infecciones graves, trombocitopenia, psoriasis -Raros: pancitopenia, TBC, LES
	Golimumab	-Dosis: 50 mg -Dosis: 100 mg en pacientes con artritis psoriásica, con un peso corporal de más de 100 kg y que no alcancen una respuesta clínica adecuada después de 3 o 4 dosis, se puede considerar el aumentar la dosis de golimumab a 100 mg administrados una vez al mes -Vía: subcutánea -Frecuencia: 1 vez al mes, el mismo día de cada mes	Solo, o en combinación con MTX, está indicado en el tratamiento de la artritis psoriásica activa y progresiva en adultos, cuando la respuesta al tratamiento previo con FAME no ha sido adecuada	-Hipersensibilidad al principio activo o excipientes -TBC activa, infecciones graves como sepsis o infecciones oportunistas -IC moderada o grave (NYHA clases III/IV)	-Muy frecuentes: infección tracto respiratorio superior -Frecuentes: celulitis, herpes, bronquitis, sinusitis, HTA, infecciones fúngicas superficiales, anemia, anticuerpos, reacción alérgica, depresión, insomnio, cefalea -Poco frecuentes: TBC, ICC, sepsis, neoplasias, ↑ glucosa, lípidos, trombosis, arritmia, trastornos oculares -Raros: reactivación hepatitis B, linfoma, pancitopenia

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Tabla 3
(*continuación*)

Terapia biológica	Principio activo	Posología y administración	Indicaciones	Contraindicaciones	Eventos adversos[a]
	Infliximab	-Dosis (según peso corporal): 5 mg/kg -Vía: perfusión i.v. durante 2 h -Frecuencia: tras primera dosis, otras a las 2 y 6 semanas. Después, 1 cada 6-8 semanas	Artritis psoriásica activa y progresiva en pacientes adultos cuando la respuesta a la terapia previa con FAME no ha sido adecuada Deberá administrarse en combinación con MTX, o usarse en monoterapia si hay contraindicación o intolerancia al mismo	-Hipersensibilidad al principio activo, excipientes u otras proteínas murinas	-Muy frecuentes: reacción infusional
				-TBC activa, infecciones graves como septicemia, abscesos e infecciones oportunistas	-Frecuentes: cefalea, infección respiratoria, herpes, diarrea
				-IC moderada a grave (NYHA clases III/IV)	-Poco frecuentes: LES, TBC, sepsis, citopenia -Raros: ICC, esclerosis múltiple, linfoma
i-IL17A	Secukinumab	-Dosis: 150 mg -Dosis refractaria a terapia biológica previa: 300 mg -Vía: subcutánea -Frecuencia: inicio en la semana 0, 1, 2 y 3. Luego, mensualmente de mantenimiento, comenzando en la semana 4	Artritis psoriásica activa en pacientes adultos que han mostrado una respuesta inadecuada a tratamientos previos con fármacos FAME	-Hipersensibilidad grave al principio activo, o a algunos de sus excipientes	-Muy frecuentes: infecciones de vías respiratorias altas
				-Infecciones activas clínicamente relevantes (p. ej., TBC activa)	-Frecuentes: herpes oral, rinorrea, diarrea
					-Poco frecuentes: urticaria, conjuntivitis, neutropenia, candidiasis oral, pie de atleta, otitis externa -Raros: reacciones anafilácticas
i-IL12/23	Ustekinumab	-Dosis inicial de 45 mg administra da por vía subcutánea, seguida de otra dosis de 45 mg 4 semanas después y posteriormente cada 12 semanas -Como alternativa se puede utilizar una dosis de 90 mg en los pacientes con un peso superior a 100 kg	Artritis psoriásica activa en pacientes adultos cuando la respuesta a tratamientos previos no biológicos con FAME ha sido inadecuada	-Hipersensibilidad al principio activo o a alguno de los excipientes	-Muy frecuentes: nasofaringitis y cefalea
				-Infecciones activas clínicamente importantes (p. ej., TBC activa)	-Frecuentes: mialgias, dolor de espalda, cansancio, diarrea, mareos
					-Poco frecuente: infecciones víricas vías respiratorias, infección micótica, depresión, psoriasis pustular, reacciones lugar infección -Raros: reacciones anafilácticas

Los datos de la presente tabla están obtenidos de la ficha técnica de la Agencia Española del Medicamento y Productos Sanitarios (AEMPS).
EPI: enfermedad pulmonar intersticial; FAME: fármacos modificadores de la enfermedad; HTA: hipertensión arterial; IC: insuficiencia cardíaca; ICC: insuficiencia cardíaca congestiva; i.v.: intravenoso; LES: lupus eritematoso sistémico; MTX: metotrexato; NYHA: New York Heart Association; TBC: tuberculosis; TNF: factor de necrosis tumoral.
[a] Eventos adversos: muy frecuentes (al menos 1 de cada 10 pacientes); frecuentes (al menos 1 de cada 100 pacientes); poco frecuentes (al menos 1 de cada 1.000 y menos de 1 de cada 100); raros (al menos 1 de cada 10.000 y menos de 1 de cada 1.000 pacientes).

ejercicio físico, el uso de al menos 2 AINE a dosis máximas durante un periodo de 4 semanas cada uno[93]. En aquellos pacientes en los que estas medidas sean ineficaces se puede iniciar terapia biológica. El uso de FAME-c no está justificado, por falta de evidencia sobre su eficacia a nivel axial. No existe, por el momento, evidencia científica suficiente para indicar el uso de apremilast en pacientes con EspA axial. Un estudio piloto en fase II doble ciego, controlado con placebo y realizado en un solo centro, valoró la eficacia de apremilast 30 mg frente a placebo durante 12 semanas, en 36 pacientes con espondilitis anquilosante activa[94]. Aunque existían diferencias a favor de los pacientes tratados con apremilast, estas no alcanzaron significación estadística, incluido el cambio en BASDAI a la semana 12 que fue el objetivo principal del estudio.

A falta de estudios comparativos, el primer agente biológico debería ser, atendiendo a la práctica clínica habitual, un i-TNF. No obstante, los datos recientemente publicados de secukinumab en

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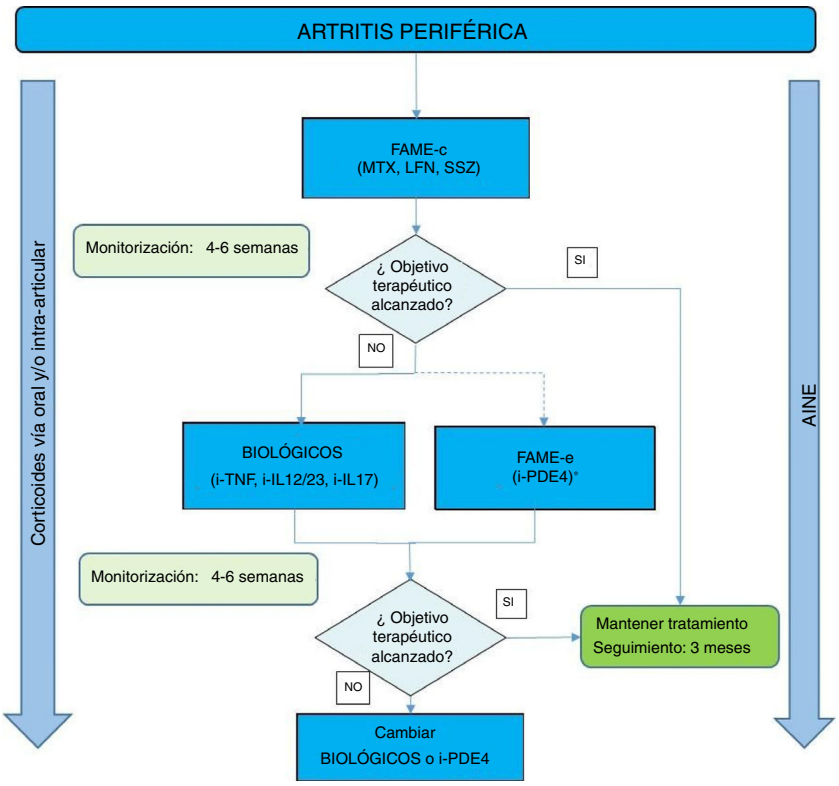

Figura 1. Algoritmo de tratamiento de la artritis periférica.
FAME: fármacos antirreumáticos modificadores de la enfermedad; FAME-c: FAME convencionales; FAME-e: FAME específicos; i-TNF: inhibidor del factor de necrosis tumoral; i-IL12, i-IL23 o i-IL17: inhibidor de la interleucina 12, 23 o 17; i-PDE4: inhibidor de la fosfodiesterasa 4. LFN: leflunomida; MTX: metotrexato; SSZ: sulfasalazina.

espondilitis anquilosante son igualmente óptimos[95], aunque en la actualidad no existe indicación de este fármaco en la forma no radiográfica.

Una reciente publicación de ustekinumab[96] de un análisis post-hoc de sus 2 ensayos clínicos en APs demostró, en el subgrupo de pacientes con espondilitis psoriásica, una mejoría significativa de los índices BASDAI y ASDAS-PCR a la semana 24.

En referencia al efecto de las terapias biológicas sobre el daño estructural en APs axial, por el momento no disponemos de ensayos que demuestren efecto significativo, aunque hay datos a favor de un posible efecto enlentecedor de la progresión radiográfica espinal asociado a la terapia biológica en EspA axial[97,98].

La figura 4 representa un algoritmo para el manejo de la enfermedad axial.

Discusión

Este nuevo documento de Recomendaciones de la SER pretende servir de guía en el tratamiento con FAME sintéticos y terapia biológica para los profesionales que atienden a pacientes con APs. Estas recomendaciones, basadas en la mejor evidencia científica disponible y en la experiencia clínica de expertos en APs, toman como base las recomendaciones provenientes tanto del Consenso anterior como de la última versión de la ESPOGUIA 2015[12].

La APs representa una de las artritis crónicas más heterogéneas desde el punto de vista clínico, lo cual supone que las distintas aproximaciones terapéuticas y las diferentes modalidades de evaluación de resultados en esta entidad son un reto actual para cualquier clínico que diagnostique y trate a esta población[8]. A pesar de que en los últimos años se han ido incorporando nuevos fármacos con mecanismos de acción distintos, y se han testado diferentes modalidades de tratamiento (estrategias T2T), el manejo global de los pacientes con APs sigue siendo un reto. Por tanto, la primera finalidad de este documento de recomendaciones es proporcionar al clínico la mejor evidencia disponible (y, en su defecto, la mejor opinión consensuada por los panelistas) para un uso racional y fundado de las diversas opciones de tratamiento con FAME sintéticos y biológicos en APs.

Se han mantenido aquellas aportaciones valiosas del documento previo de consenso en APs, por tanto, lo dicho en aquel documento sobre los FAME-c se mantienen en el presente[11]. A diferencia del anterior documento de consenso para el uso de biológicos en APs, en el presente documento se proporcionan una serie de principios jerárquicos de manejo de la enfermedad, se revisa la mejor evidencia sobre las nuevas moléculas surgidas y aprobadas desde el anterior consenso, y se aporta un algoritmo de manejo de la APs. Con todo ello, el grupo de expertos espera que el manejo de la APs en nuestro país se guíe por la mejor evidencia, reduciendo a un mínimo la variabilidad propia del manejo de cualquier proceso médico complejo como lo es la APs.

Recientemente se han publicado las recomendaciones EULAR y GRAPPA para el manejo de la APs[9,10]. Nuestro documento, si bien puede solapar algunos aspectos contenidos en dichas recomendaciones, se ha adaptado al máximo a la realidad asistencial de los pacientes con APs en España, aspecto que puede resultar clave para la generalización de las recomendaciones contenidas en el mismo.

A diferencia de las recomendaciones de GRAPPA que tocan aspectos relativos a la afectación cutáneo-ungueal de la enfermedad psoriásica, nuestro documento no aborda estos aspectos, pues estimamos que ambos procesos en su manejo corresponden al dermatólogo, y la Academia Española de Dermatología y Venereología (AEDV) publica con regularidad documentos consenso parecidos al nuestro, pero obviamente centrados en el manejo de estos 2 dominios[99].

En los últimos años se han ido incorporando al arsenal terapéutico de la APs terapias novedosas por su mecanismo de acción. Este

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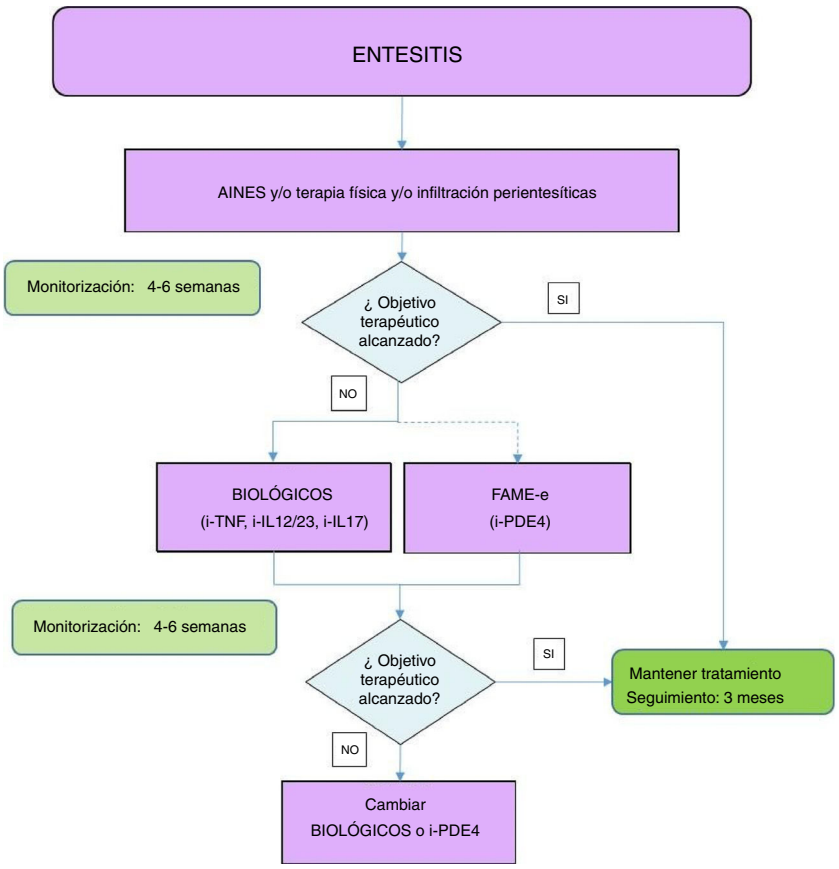

Figura 2. Algoritmo de tratamiento de la entesitis.
AINE: antiinflamatorios no esteroides; FAME: fármacos antirreumáticos modificadores de la enfermedad; FAME-e: FAME específicos; i-TNF: inhibidor del factor de necrosis tumoral; i-IL12, i-IL23 o i-IL17: inhibidor de la interleucina 12, 23 o 17; i-PDE4: inhibidor de la fosfodiesterasa 4.

documento ha incorporado estas nuevas evidencias, sobre todo en lo referente a la inhibición de la ruta IL12/23 e IL17 (ustekinumab y secukinumab, respectivamente). A este respecto se ha decidido situar a los i-TNF, i-IL12/23 e i-IL17 al mismo nivel, aspecto que se plasma también en el algoritmo terapéutico. Este hecho se basa en que, a pesar de la ausencia de ensayos clínicos que comparen de manera directa la eficacia de las diversas moléculas disponibles, no parece que las diferencias entre ellas sean significativas. En el apartado de nuevos fármacos también hemos incorporado un nuevo FAME con diana específica, el inhibidor de PDE-4 (apremilast). Solo la experiencia clínica despejará las dudas que existen sobre su lugar en el algoritmo terapéutico de la APs[7]. Las recomendaciones referentes a estos nuevos fármacos para la APs se basan en la mejor evidencia disponible, pero deben ser valoradas desde la cautela que impone el que son fármacos de reciente incorporación. Por tanto, los aspectos de efectividad y seguridad a medio-largo plazo son aún desconocidos desde una perspectiva «real world evidence» (RWE) o de práctica cotidiana.

La APs y la psoriasis son entidades con un numeroso grupo de comorbilidades asociadas, lo que ha llevado a algunos expertos a proponer el concepto de enfermedad psoriásica para capturar mejor ese carácter sistémico de ambas entidades[100]. Dentro de esas comorbilidades, quizá la más relevante sea la de índole cardiovascular. Es por ello que en este documento se han incorporado recomendaciones concretas al respecto, si bien reconociendo que este dominio de la enfermedad está en plena evolución y las posibles bondades de los FAME sintéticos y biológicos sobre la reducción del riesgo cardiovascular necesitan ser sustentadas con más evidencias.

Uno de los aspectos más presentes en la literatura reciente es el de optimización de las terapias biológicas. En el presente documento no se hace una recomendación concreta al respecto ya que no existen datos publicados que sean consistentes, pero sí se recoge la necesidad de evaluar de modo individualizado este tipo de estrategia. La optimización de las terapias biológicas se ha incorporado a la rutina de manejo de estos pacientes en nuestro país, existiendo razones de seguridad, efectividad, costes y equidad asistencial para apoyar este tipo de aproximación. Recientemente, la SER y la Sociedad Española de Farmacia Hospitalaria han publicado un documento de posicionamiento para la optimización de la terapia biológica en distintas enfermedades reumatológicas, incluyendo la APs[101]. Con todo, este aspecto va dirigido principalmente a los i-TNF, pues dada la muy reciente incorporación de otros biológicos no i-TNF, no es posible hacer una extrapolación sobre optimización a estos nuevos agentes.

En el momento actual solo se ha publicado un ensayo sobre aproximación T2T en APs (estudio TICOPA) que parece indicar que esta modalidad de manejo puede conseguir mejores resultados en los desenlaces cutáneos y articulares en comparación con un manejo estándar, si bien a costa de más eventos adversos[35]. Creemos que aún se precisa de más información sobre este tipo de abordaje de la enfermedad antes de realizar una recomendación positiva al respecto. Por otra parte, aunque la evidencia para una intervención precoz con FAME en APs no se apoya en evidencias muy sólidas, resulta obvio que un diagnóstico temprano de la enfermedad, un reconocimiento de los factores de pronóstico adverso o de mala evolución, y la consiguiente instauración de intervenciones farmacológicas precoces, deben sentar las bases de un mejor manejo de la

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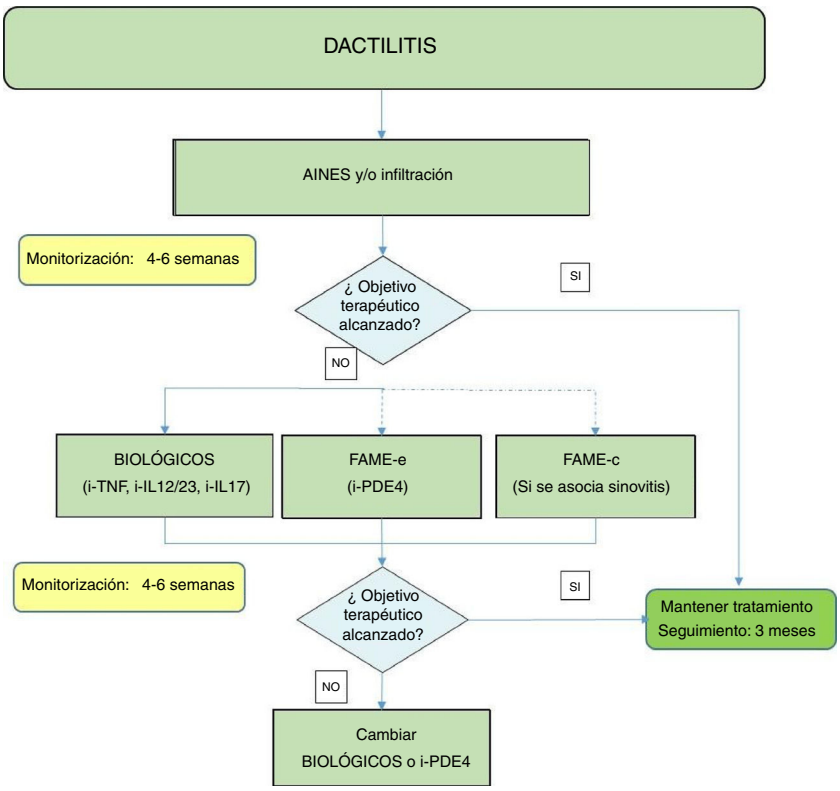

Figura 3. Algoritmo de tratamiento de la dactilitis.
AINE: antiinflamatorios no esteroides; FAME: fármacos antirreumáticos modificadores de la enfermedad; FAME-c: FAME convencionales; FAME-e: FAME específicos; i-TNF: inhibidor del factor de necrosis tumoral; i-IL12, i-IL23 o i-IL17: inhibidor de la interleucina 12, 23 o 17; i- PDE4: inhibidor de la fosfodiesterasa 4.

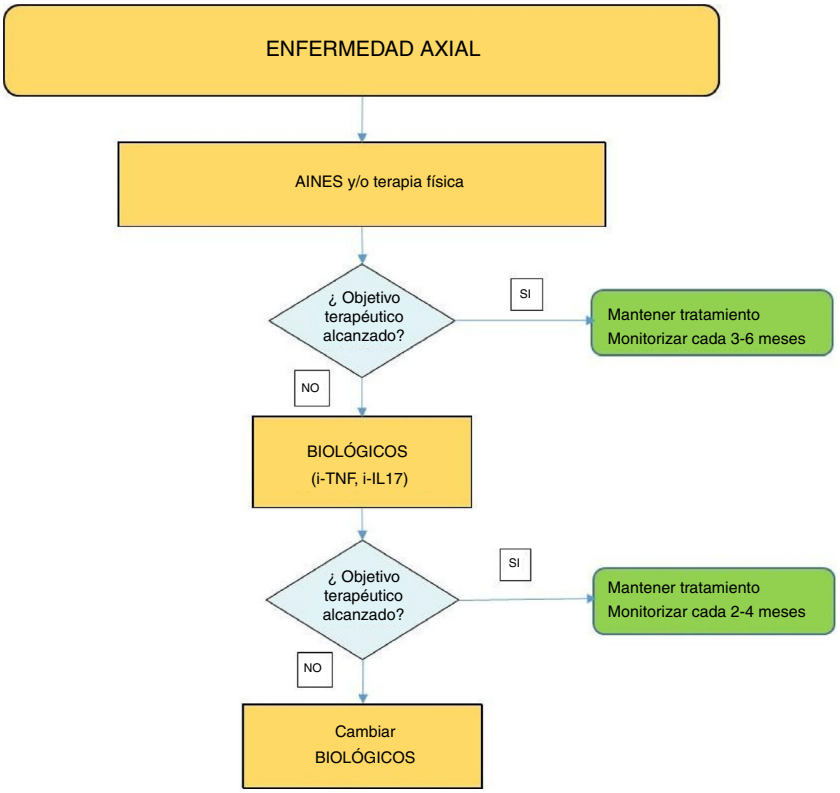

Figura 4. Algoritmo de tratamiento de la enfermedad axial.
AINE: antiinflamatorios no esteroides; i-TNF: inhibidor del factor de necrosis tumoral; i-IL17: inhibidora de la interleucina 17.

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enfermedad en todos sus dominios, y, por ende, una mejora general en la evolución de la APs[102].

Tampoco estas recomendaciones señalan nada con respecto al uso de biosimilares en APs. Un biosimilar es un fármaco biológico que contiene una versión de la sustancia activa de un producto biológico original ya autorizado (fármaco de referencia). En relación con su producto original, un biosimilar debe demostrar una alta similitud en cuanto a calidad, actividad biológica, seguridad y eficacia, aspectos que deben ser contrastados por medio de los correspondientes ensayos clínicos aleatorizados. Actualmente, el uso seguro de estos productos en nuestro país está garantizado gracias al marco regulatorio establecido en términos de calidad, criterios preclínicos y clínicos por autoridades reguladoras como la EMA. La intercambiabilidad y sustitución terapéutica de estos medicamentos no debería hacerse de forma automática y bajo criterios puramente económicos, pues el beneficio del paciente debe primar siempre en nuestras decisiones. Por tanto, el panel de expertos de estas recomendaciones está en la línea con lo ya expresado por la SER en su documento de posicionamiento al respecto[103].

En resumen, este nuevo documento de recomendaciones reúne la mejor evidencia disponible, incorporando aquella referida a nuevas moléculas y nuevos enfoques de tratamiento en APs, junto con la visión de reumatólogos expertos en esta enfermedad. La esencia de este manuscrito ha sido recoger todos aquellos aspectos que ayuden al clínico a tomar una decisión terapéutica razonada ante un caso de APs. Esto significa que, a la hora de elegir un determinado fármaco, dicha decisión debería incorporar aspectos propios de la enfermedad (fenotipo clínico, severidad, factores de mal pronóstico) junto con otros propios de cada molécula (evidencia, experiencia, eficacia, seguridad, optimización). En algunos casos los costes económicos podrían ser una circunstancia a tener en cuenta, sobre todo cuando no se puedan establecer diferencias en base a una evidencia científica, sin que ello suponga una limitación absoluta del criterio médico, que es la base de la decisión final.

Necesariamente, en un futuro próximo será preciso revisar y actualizar las recomendaciones contenidas en este documento, pues en el horizonte cercano están nuevas moléculas, nuevos modos de tratamiento, y seguramente contaremos con mejores evidencias sobre aspectos que aún la demandan, como el rol terapéutico de los actuales y futuros tratamientos sobre el riesgo cardiovascular, el uso de biosimilares, o la optimización de las actuales y futuras terapias biológicas.

Agenda de investigación

A pesar de que estas recomendaciones deberían resultar útiles para un mejor abordaje de la APs, el panel de expertos reconoce que quedan múltiples aspectos por cubrir en la futura agenda de investigación. Entre otros se pueden mencionar los siguientes:

- Evaluar desde una visión RWE la verdadera efectividad y seguridad de las nuevas moléculas aprobadas para la APs.
- Estudiar si existe un fenotipo particular de la APs en la que quepa el uso inicial de terapia biológica sin necesidad previa de FAME sintéticos.
- Analizar el papel terapéutico de combinación de nuevos FAME sintéticos (apremilast) con la terapia biológica o FAME sintéticos convencionales.
- Valorar biomarcadores farmacogenómicos de respuesta terapéutica.
- Profundizar en los efectos terapéuticos de las actuales y futuras moléculas sobre la reducción del riesgo cardiovascular de esta población.
- Buscar las evidencias que apoyen el uso terapéutico precoz de los FAME actuales y futuros sobre los distintos dominios de la enfermedad psoriásica.
- Estudiar en profundidad el nicho terapéutico que las nuevas moléculas pueden ocupar en los algoritmos de tratamiento de la APs.
- Mejorar las estrategias de optimización de las terapias biológicas en APs.
- Ampliar las evidencias para poder recomendar con solidez las estrategias T2T.
- Analizar el efecto de las terapias biológicas sobre la inhibición progresión radiográfica en las formas APs axial.
- Evaluar el papel de los biosimilares en el manejo de la APs.
- Desarrollar estudios fisiopatológicos en los distintos fenotipos de la enfermedad, para entender qué células y moléculas predominan en cada uno de ellos de forma que mejoremos nuestra estrategia terapéutica.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

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Conflicto de intereses

Chamaida Plasencia Rodríguez ha recibido una beca sin restricciones de Pfizer; honorarios como ponente de Pfizer.

Juan Carlos Torre Alonso ha recibido financiación de MSD, Abbvie, Pfizer, Celgene, Janssen para la asistencia a cursos/congresos; y ha recibido honorarios como ponente y consultoría de MSD, Abbvie, Pfizer, UCB, Celgene y Novartis.

Juan D Cañete Crespillo ha recibido financiación de Novartis, Janssen y Celgene para la asistencia a reuniones, congresos y cursos; honorarios de Abbvie, Janssen y Celgene en concepto de ponencias; y ha recibido financiación de Abbvie, Celgene, Boehringer, Janssen y Novartis en concepto de consultoría para compañías farmacéuticas u otras tecnologías.

Ruben Queiro Silva ha recibido financiación de Abbvie, Celgene, Pfizer, MSD, Janssen y UCB para la asistencia a reuniones, congresos, cursos y en concepto de ponencias; financiación de Janssen y Celgene por participar en una investigación; y ha recibido ayuda económica de Novartis, Abbvie, UCB, Celgene y Pfizer en concepto de consultoría para compañías farmacéuticas u otras tecnologías.

Mireia Moreno Martínez-Losa ha recibido financiación de Abbvie, Pfizer, MSD, Janssen, Celgene, MSD, Roche y UCB para la asistencia a reuniones, congresos, cursos y en concepto de ponencias; y ha recibido ayuda económica de Janssen en concepto de consultoría para compañías farmacéuticas u otras tecnologías.

Raquel Almodóvar González ha recibido financiación de Abbvie, Pfizer, MSD, Roche para la asistencia a reuniones, congresos y cursos; honorarios de Abbvie, Celgene, Novartis, Pfizer, Roche, UCB en concepto de ponencias; y ha recibido financiación de Abbvie, Jansen, MSD, Novartis, Pfizer, Roche para la realización de programas educativos o cursos. Y ha recibido ayuda económica de Abbvie,

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Celgene, Janssen, MSD, Pfizer, UCB en concepto de consultoría para compañías farmacéuticas u otras tecnologías.

Carlos Montilla Morales ha recibido financiación de Abbvie, MSD y Janssen para la asistencia a reuniones, congresos, cursos y en concepto de ponencias. Ha recibido ayuda económica de Janssen en concepto de consultoría.

Julio Ramírez García ha recibido financiación de MSD, Abbvie, Pfizer, Bristol, UCB, Novartis, Janssen, Celgene y Roche en concepto de ponencias científicas y para la asistencia a reuniones, congresos y cursos de formación.

Petra Díaz del Campo Fontecha ha declarado su ausencia de conflicto de intereses.

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Bibliografía

1. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3:55–78.
2. Siegel EL, Orbai AM, Ritchlin CT. Targeting extra-articular manifestations in PsA: A closer look at enthesitis and dactylitis. Curr Opin Rheumatol. 2015;27:111–7.
3. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61:451–85.
4. FitzGerald O, Haroon M, Giles JT, Winchester R. Concepts of pathogenesis in psoriatic arthritis: Genotype determines clinical phenotype. Arthritis Res Ther. 2015;17:115.
5. Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewe R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis. 2014;73:3–5.
6. Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, FitzGerald O, Winthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: Current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2012;71:319–26.
7. Ramiro S, Smolen JS, Landewé R, van der Heijde D, Dougados M, Emery P, et al. Pharmacological treatment of psoriatic arthritis: A systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2016;75:490–8.
8. Olivieri I, d'Angelo S. Psoriatic arthritis in 2015: Advancement continues in imaging, tight control and new drugs. Nat Rev Rheumatol. 2016;12:76–8.
9. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016;75:499–510.
10. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol. 2016;68:1060–71.
11. Fernández-Sueiro JL, Juanola Roura X, Cañete JD, Torre-Alonso JC, García de Vicuña R, Queiro R, et al. Documento SER de consenso sobre el uso de terapias biológicas en la artritis psoriásica. Reumatol Clin. 2011;7:179–88.
12. Sociedad Española de Reumatología. Grupo de trabajo ESPOGUIA. Guía de práctica clínica para el tratamiento de la espondiloartritis axial y la artritis psoriásica. [monografía en Internet]. Madrid: Sociedad Española de Reumatología; 2015.
13. D'Angelo S, Palazzi C, Gilio M, Leccese P, Padula A, Olivieri I. Improvements in diagnostic tools for early detection of psoriatic arthritis. Expert Rev Clin Immunol. 2016;12:1209–15.
14. Durham LE, Taams LS, Kirkham BW. Psoriatic arthritis. Br J Hosp Med (Lond). 2016;77:C102–8.
15. Queiro R, Coto P, Rodríguez J, Notario J, Navio Marco T, de la Cueva P, et al. Multidisciplinary care models for patients with psoriatic arthritis. Reumatol Clin. 2017;13:85–90.
16. Torre Alonso JC, Carmona L, Moreno M, Galíndez E, Babío J, Zarco P, et al. Identification and management of comorbidity in psoriatic arthritis: Evidence- and expert-based recommendations from a multidisciplinary panel from Spain. Rheumatol Int. 2017;37:1239–48, http://dx.doi.org/10.1007/s00296-017-3702-9.
17. Di Minno MN, Peluso R, Iervolino S, Lupoli R, Russolillo A, Scarpa R, et al. Obesity and the prediction of minimal disease activity: A prospective study in psoriatic arthritis. Arthritis Care Res (Hoboken). 2013;65:141–7.
18. Leeb BF, Andel I, Sautner J, Fassl C, Nothnagl T, Rintelen B. The Disease Activity Score in 28 joints in rheumatoid arthritis and psoriatic arthritis patients. Arthritis Rheum. 2007;57:256–60.
19. Mumtaz A, Gallagher P, Kirby B, Waxman R, Coates LC, Veale JD, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis. 2011;70:272–7.
20. Schoels M, Aletaha D, Funovits J, Kavanaugh A, Baker D, Smolen JS. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010;69:1441–7.
21. Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis. 2013;72:986–91.
22. Salaffi F, Ciapetti A, Carotti M, Gasparini S, Gutierrez M. Disease activity in psoriatic arthritis: Comparison of the discriminative capacity and construct validity of six composite indices in a real world. Biomed Res Int. 2014;2014:5281052014.
23. Gladman DD, Landewe R, McHugh NJ, Fitzgerald O, Thaci D, Coates L, et al. Composite measures in psoriatic arthritis: GRAPPA 2008. J Rheumatol. 2010;37:453–61.
24. Helliwell PS, FitzGerald O, Fransen J. Composite disease activity and responder indices for psoriatic arthritis: A report from the GRAPPA 2013 meeting on development of cutoffs for both disease activity states and response. J Rheumatol. 2014;41:1212–7.
25. Armstrong AW, Gelfand JM, Garg A. Outcomes research in psoriasis and psoriatic arthritis using large databases and research networks: A report from the GRAPPA 2013 Annual Meeting. J Rheumatol. 2014;41:1233–6.
26. Van den Bosch F, Kavanaugh A, Kron M, Kupper H, Mease PJ. Clinical remission in patients with active psoriatic arthritis treated with adalimumab and correlations in joint and skin manifestations. J Rheumatol. 2015;42:952–9.
27. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Criteria, frequency, and duration of clinical remission in psoriatic arthritis patients with peripheral involvement requiring second-line drugs. J Rheumatol Suppl. 2009;83:78–80.
28. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology (Oxford). 2008;47:872–6.
29. Coates LC, Cook R, Lee KA, Chandran V, Gladman DD. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. Arthritis Care Res (Hoboken). 2010;62:970–6.
30. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: A proposed objective target for treatment. Ann Rheum Dis. 2010;69:48–53.
31. Tillett W, Eder L, Goel N, de Wit M, Gladman DD, FitzGerald O, et al. Enhanced patient involvement and the need to revise the core set — Report from the Psoriatic Arthritis Working Group at OMERACT 2014. J Rheumatol. 2015;42:2198–203.
32. Machado PM, Raychaudhuri SP. Disease activity measurements and monitoring in psoriatic arthritis and axial spondyloarthritis. Best Pract Res Clin Rheumatol. 2014;28:711–28.
33. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: Assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum. 2008;59:686–91.
34. Nell-Duxneuner VP, Stamm TA, Machold KP, Pflugbeil S, Aletaha D, Smolen JS. Evaluation of the appropriateness of composite disease activity measures for assessment of psoriatic arthritis. Ann Rheum Dis. 2010;69:546–9.
35. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): A UK multicentre, open-label, randomised controlled trial. Lancet. 2015;386(10012):2489–98.
36. Coates LC, Ritchlin CT, Kavanaugh AF. GRAPPA treatment recommendations: An update from the GRAPPA 2013 Annual Meeting. J Rheumatol. 2014;41:1237–9.
37. Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis Rheum. 2007;57:1074–80.
38. Jamnitski A, Symmons D, Peters MJ, Sattar N, McInnes I, Nurmohamed MT. Cardiovascular comorbidities in patients with psoriatic arthritis: A systematic review. Ann Rheum Dis. 2013;72:211–6.
39. Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis. 2015;74:813–7.
40. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in

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rheumatoid arthritis, psoriasis and psoriatic arthritis: A systematic review and meta-analysis. Ann Rheum Dis. 2015;74:480–9.
41. Tillett W, Jadon D, Shaddick G, Cavill C, Korendowych E, de Vries CS, et al. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. Ann Rheum Dis. 2013;72:1358–61.
42. Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? Ann Rheum Dis. 2011;70:2152–4.
43. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2015;74:1045–50.
44. Theander E, Husmark T, Alenius GM, Larsson PT, Teleman A, Geijer M, et al. Early psoriatic arthritis: Short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis. 2014;73:407–13.
45. Scarpa R, Peluso R, Atteno M, Manguso F, Spano A, Iervolino S, et al. The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: Results of a pilot randomised 6-month trial with methotrexate. Clin Rheumatol. 2008;27:823–6.
46. Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatology (Oxford). 2012;51:1368–77.
47. Lie E, van der Heijde D, Uhlig T, Heiberg MS, Koldingsnes W, Rodevand E, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2010;69:671–6.
48. Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis. 2014;73:414–9.
49. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: Results from a longitudinal observational cohort. J Rheumatol. 2008;35:469–71.
50. Schmitt J, Rosumeck S, Thomaschewski G, Sporbeck B, Haufe E, Nast A. Efficacy and safety of systemic treatments for moderate-to-severe psoriasis: Meta-analysis of randomized controlled trials. Br J Dermatol. 2014;170:274–303.
51. Schett G, Sloan VS, Stevens RM, Schafer P. Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases. Ther Adv Musculoskelet Dis. 2010;2:271–8.
52. Schett G, Wollenhaupt J, Papp K, Joos R, Rodrigues JF, Vessey AR, et al. Oral apremilast in the treatment of active psoriatic arthritis: Results of a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2012;64:3156–67.
53. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73:1020–6.
54. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. J Rheumatol. 2015;42:479–88.
55. Crowley J, Thaci D, Joly P, Peris K, Papp KA, Goncalves J, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). J Am Acad Dermatol. 2017;77:310–7.
56. Kavanaugh A, McInnes IB, Mease P, Krueger GG, Gladman D, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: Results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). Ann Rheum Dis. 2014;73:1689–94.
57. Mease P, Maldonado M, Wollenhaupt J, Deodhar A, Gladman D, Stach C, et al. Effect of certolizumab pegol over 48 weeks on signs and symptoms in patients with psoriatic arthritis with and without prior tumor necrosis factor inhibitor exposure. Rheumatology (Oxford). 2014;53 Suppl. 1:i137–8.
58. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. J Rheumatol. 2006;33:712–21.
59. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382:780–9.
60. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990–9.
61. Kavanaugh A, Ritchlin C, Rahman P, Puig L, Gottlieb AB, Li S, et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: Results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. Ann Rheum Dis. 2014;73:1000–6.
62. Van der Heijde D, Landewe RB, Mease PJ, McInnes IB, Conaghan PG, Pricop L, et al. Brief Report: Secukinumab provides significant and sustained inhibition of joint structural damage in a phase III study of active psoriatic arthritis. Arthritis Rheumatol. 2016;68:1914–21.
63. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386:1137–46.
64. Sanmartí R, García-Rodríguez S, Álvaro-Gracía JM, Andreu JL, Balsa A, Cáliz R, et al. 2014 update of the Consensus Statement of the Spanish Society of Rheumatology on the use of biological therapies in rheumatoid arthritis. Reumatol Clin. 2015;11:279–94.
65. Behrens F, Canete JD, Olivieri I, van Kuijk AW, McHugh N, Combe B. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: A systematic review of the literature. Rheumatology (Oxford). 2015;54:915–26.
66. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005;52:3279–89.
67. Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, et al. Adalimumab for long-term treatment of psoriatic arthritis: Forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum. 2007;56:476–88.
68. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: Safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004;50:2264–72.
69. Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. BMJ. 2010;340:c147.
70. Combe B, Behrens F, McHugh N, Brock F, Kerkmann U, Kola B, et al. Comparison of etanercept monotherapy and combination therapy with methotrexate in psoriatic arthritis: Results from 2 clinical trials. J Rheumatol. 2016;43:1063–7.
71. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60:976–86.
72. Kavanaugh A, McInnes IB, Mease PJ, Krueger GG, Gladman DD, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: Results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. Ann Rheum Dis. 2013;72:1777–85.
73. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005;52:1227–36.
74. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: Results of the IMPACT 2 trial. Ann Rheum Dis. 2005;64:1150–7.
75. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: Results from the IMPACT 2 trial. Ann Rheum Dis. 2007;66:498–505.
76. Van der Heijde D, Kavanaugh A, Gladman DD, Antoni C, Krueger GG, Guzzo C, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. Arthritis Rheum. 2007;56:2698–707.
77. Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: Results from a longitudinal, observational, multicenter study. Arthritis Rheum. 2008;59:234–40.
78. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Lexberg AS, Rodevand E, et al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: Results from 440 patients included in the NOR-DMARD study. Ann Rheum Dis. 2014;73:132–7.
79. Glintborg B, Ostergaard M, Dreyer L, Krogh NS, Tarp U, Hansen MS, et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor alpha therapy: Results from the nationwide Danish DANBIO registry. Arthritis Rheum. 2011;63:382–90.
80. Hoa S, Choquette D, Bessette L, Sauvageau D, Haraoui B, Pelletier JP, et al. Comparing adalimumab and etanercept as first line agents in patients with psoriatic arthritis: data from the Rheumadata_ clinical database and registry [abstract]. Arthritis Rheum. 2013;65 Suppl. 10:S145.
81. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73:48–55.
82. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med. 2015;373:1329–39.

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83. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Kalstad S, Rodevand E, et al. Switching between TNF inhibitors in psoriatic arthritis: Data from the NOR-DMARD study. Ann Rheum Dis. 2013;72:1840–4.
84. Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor alpha inhibitor therapy: Results from the Danish Nationwide DANBIO Registry. Arthritis Rheum. 2013;65:1213–23.
85. Kristensen LE, Lie E, Jacobsson LT, Christensen R, Mease PJ, Bliddal H, et al. Effectiveness and feasibility associated with switching to a second or third TNF inhibitor in patients with psoriatic arthritis: A cohort study from Southern Sweden. J Rheumatol. 2016;43:81–7.
86. Soubrier AS, Bele-Philippe P, Cortet B, Ramdane-Sebbane N, Bacle-Boutry MA, Lemeunier L, et al. Treatment response, drug survival and safety of anti-tumour necrosis factor alpha therapy in 193 patients with psoriatic arthritis: a twelve-year «real life» experience. Joint Bone Spine. 2015;82:31–7.
87. Coates LC, Cawkwell LS, Ng NW, Bennett AN, Bryer DJ, Fraser AD, et al. Sustained response to long-term biologics and switching in psoriatic arthritis: Results from real life experience. Ann Rheum Dis. 2008;67:717–9.
88. Ruwaard J, Kneepkens E, Marsman A, Vogelzang E, van der Horst-Bruinsma IE, Rispens T, et al. Efficacy of switching tumor necrosis factor α inhibitor to a second tumor necrosis factor α inhibitor and the influence of drug levels and anti-drug antibodies in patients with ankylosing spondylitis and psoriatic arthritis. Ann Rheum Dis. 2015;74:271.
89. Gladman DD, Sampalis JS, Illouz O, Guerette B. Responses to adalimumab in patients with active psoriatic arthritis who have not adequately responded to prior therapy: Effectiveness and safety results from an open-label study. J Rheumatol. 2010;37:1898–906.
90. Genovese MC, Mease PJ, Greenwald MW, Ritchlin CT, Beaulieu AD, Deodhar A, et al. Efficacy and safety of brodalumab over one year in patients with psoriatic arthritis with and without prior exposure to a biologic. Ann Rheum Dis. 2014;73:1052–3.
91. Orbai AM, Weitz J, Siegel EL, Siebert S, Savage LJ, Aydin SZ, et al. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. J Rheumatol. 2014;41:2290–4.
92. Rose S, Toloza S, Bautista-Molano W, Helliwell PS. Comprehensive treatment of dactylitis in psoriatic arthritis. J Rheumatol. 2014;41:2295–300.
93. Juanola Roura X, Zarco Montejo P, Sanz Sanz J, Muñoz Fernandez S, Mulero Mendoza J, Linares Ferrando LF, et al. [Consensus Statement of the Spanish Society of Rheumatology on the management of biologic therapies in spondyloarthritis except for psoriatic arthritis]. Reumatol Clin. 2011;7:113–23.
94. Pathan E, Abraham S, van Rossen E, Withrington R, Keat A, Charles PJ, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. Ann Rheum Dis. 2013;72:1475–80.
95. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an Interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med. 2015;373:2534–48.
96. Kavanaugh A, Puig L, Gottlieb AB, Ritchlin C, You Y, Li S, et al. Efficacy and safety of ustekinumab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: Post-hoc analyses from two phase III, multicentre, double-blind, placebo-controlled studies (PSUMMIT-1/PSUMMIT-2). Ann Rheum Dis. 2016;75:1984–8.
97. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Continuous long-term i-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. Ann Rheum Dis. 2014;73:710–5.
98. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013;65:2645–54.
99. Daudén E, Puig L, Ferrándiz C, Sánchez-Carazo JL, Hernanz-Hermosa JM. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis: Psoriasis Group of the Spanish Academy of Dermatology and Venereology. J Eur Acad Dermatol Venereol. 2016;30 Suppl. 2:1–18.
100. Husni ME. Comorbidities in psoriatic arthritis. Rheum Dis Clin North Am. 2015;41:677–98.
101. González-Álvaro I, Martínez-Fernández C, Dorantes-Calderón B, García-Vicuña R, Hernández-Cruz B, Herrero-Ambrosio A, et al. Spanish Rheumatology Society and Hospital Pharmacy Society Consensus on recommendations for biologics optimization in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. Rheumatology (Oxford). 2015;54:1200–9.
102. Helliwell P, Coates L, Chandran V, Gladman D, de Wit M, FitzGerald O, et al. Qualifying unmet needs and improving standards of care in psoriatic arthritis. Arthritis Care Res (Hoboken). 2014;66:1759–66.
103. Abad Hernández MÁ, Andreu JL, Caracuel Ruiz MÁ, Belmonte Serrano MÁ, Díaz-González F, Moreno Muelas JV. Position paper from the Spanish Society of Rheumatology on biosimilar drugs. Reumatol Clin. 2015;11:269–78.

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RHEUMATOLOGY

Editorial

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New use for tociluzimab in giant cell arteritis

Will this change the drug treatment algorithm?

GCA a disease that has been difficult to investigate in clinical trials, with only steroids as the main treatment option and non-researched treatments as a secondary option. The disease has a significant morbidity and mortality [1], and this is especially the case with long-term treatmentis with steroids [2]. There are a significant number of patients with relapses, and GCA has traditionally been treated by a variety of practitioners including primary care, ophthalmology, elderly care and rheumatology with different treatment regimes [3]. One of the catastrophic sequelae has been visual loss, which can occur in up to 11% of patients with the disease [4].

Tociluzimab (TCZ), an IL-6 inhibitor, has been advocated as a useful treatment in vasculitis [5] and has been shown to be effective in the induction and maintenance of remission in a small randomized phase II study of GCA [6]. At the American Congress of Rheumatology in Washington DC, November 2016, a study was presented that could alter the way in which the disease is approached in the future [7]: the Phase III GiACTA trial results were announced. This is a trial using TCZ in GCA, and is unique in many ways: it is the biggest GCA study to date; it has a novel approach to treatment; patients and clinicians are blinded to tapering the dose of steroid below 20 mg; each centre needs a clinical and laboratory team; and it is powered in an unusual way.

The study incorporated 251 patients recruited over 22 months from 14 countries and 76 sites randomized to 4 treatment regimes. Patients were randomized to placebo with short steroid taper (26 weeks), placebo with long steroid taper (52 weeks) or TCZ in two doses either weekly or every 2 weeks with a short steroid taper. Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or ESR $\geqslant$30 mm/h attributable to GCA. An increase in the prednisone dose was also required. A single CRP elevation ($\geqslant$1 mg/dl) was not considered a flare unless CRP remained elevated ($\geqslant$1 mg/dl) at the next study visit. Remission was defined as the absence of flare and normalization of the CRP ($<$1 mg/dl). Sustained remission was the absence of a flare following the induction of remission within 12 weeks of baseline and maintained to week 52. The primary end point was sustained remission from weeks 12 to 52 and adherence to the protocol-defined prednisone taper.

The estimated effect size was quite high at 40%. Alpha was set at 0.01 and the primary end point (superiority) tested at 0.005. All of the other end points were tested at 0.01, which is unusual for a superiority trial.

The 251 patients, of whom 132 (52.6%) had relapsing disease, had a mean (S.D.) age 69 (8.2) years. The patients were 75% female and 98.6% Caucasian. The study met its primary end point with 56 of 100 (56%) patients achieving sustained remission in the weekly dose of TCZ and 26/49 (53.1%) in the Q2W dose (n = 49) *vs* 7/50 (14%), with a 6 month steroid taper regimen and 10/49 (17.6%) in the 12 month steroid taper regimen. These were both highly significant with $P < 0.0001$. There was a significant steroid sparing effect and no safety signals. There were good patient-reported outcomes. The trial is due to run into another year as an open label extension.

These data represent a breakthrough in GCA and importantly show that trials in diseases difficult to study are possible. It also demonstrates a wider use of the drug TCZ. However, it raises several questions. Firstly, who would benefit from this drug? It would not be easy to promote its use in all newly diagnosed patients, and therefore markers for severity need to be developed in the newly diagnosed. Patients with disease that will inevitably lead to loss of vision need to be identified. Furthermore the timing of the start of treatment needs to be ascertained.

Secondly, we know that it works in those who have flares, but we do not have a breakdown on whether the effect was equal in those who had flared and those who had primary active disease. Another question in those who are flaring is, when would be the best time to give TCZ? This is not answered by the study but could be addressed by *post hoc* analyses.

Thirdly what is the cost benefit? We are unsure how much cost is saved by reducing the steroid burden and flare and these considerations need to be taken into account.

These questions need to be answered with careful consideration of the cost before these exciting trial findings become applicable to the clinician dealing with GCA on a regular basis. There are also implications for workload if TCZ becomes a drug routinely used in this condition, as a significant proportion of GCA is dealt with in primary care and the need to refer for biologics might swamp already stretched rheumatology services.

However, the trial shows that using IL-6 inhibition might play a bigger role in the rheumatic diseases than was originally thought, with some data indicating its utility in other forms of vasculitis and even in systemic sclerosis [8].

In summary, TCZ has demonstrated an ability to stop flares and achieve remission in GCA and to reduce steroid need. If we manage to establish treatment algorithms,

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our traditional management of GCA might undergo fundamental change.

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References

1 Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003;49:703–8.

2 Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. Arthritis Care Res 2015;67:390–5.

3 Mackie SL, Pease CT. Diagnosis and management of giant cell arteritis and polymyalgia rheumatica: challenges, controversies and practical tips. Postgrad Med J 2013;89:284–92.

4 Chen JJ, Leavitt JA, Fang C *et al*. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. Ophthalmology 2016;123:1999–2003.

5 Salvarani C, Magnani L, Catanoso M *et al*. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. Rheumatology 2012;51:151–6.

6 Villiger PM, Adler S, Kuchen S *et al*. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 2016;387:1921–7.

7 Stone JH, Tuckwell K, Dimonaco S *et al*. Efficacy and safety of tocilizumab in patients with giant cell arteritis: primary and secondary outcomes from a phase 3, randomized, double-blind, placebo-controlled trial [abstract]. Arthritis Rheumatol 2016;68 (Suppl 10):911.

8 Khanna D, Denton C, Spotswood H *et al*. Safety and efficacy of subcutaneous tocilizumab in early systemic sclerosis: results from the open-label period of a phase 2 randomized, controlled trial [abstract]. Arthritis Rheumatol 2016;68 (Suppl 10):969.

Vaccination Recommendations for Adults With Autoimmune Inflammatory Rheumatic Diseases in Latin America

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Background/Objective: Patients with autoimmune inflammatory rheumatic diseases (AIRDs) are at increased risk of contracting severe infections and suffering complications, particularly when they are receiving immunomodulating therapy. Vaccination is an important means to prevent many potential infections and thereby reduce the morbidity and mortality associated with AIRD. The purpose of this consensus document is to provide health care professionals with recommendations for the vaccination of AIRD patients who reside in Latin America. The recommendations were developed by an expert committee from the region based on a review of the literature and their clinical experience.

Methods: The Americas Health Foundation (AHF) used PubMed and EMBASE to identify clinicians and scientists with an academic or hospital affiliation and who had published in the field of adult vaccination and rheumatic diseases since 2010. As a result of this effort, AHF convened an 8-member panel of clinical and scientific experts from Latin America. Both the AHF and panel members conducted a careful literature review to identify relevant publications in the areas of adult vaccination and rheumatology, and the sum of the articles identified was provided to the entire panel. Prior to the conference, panelists were each asked to prepare a written response to a salient issue on the subject, identified by AHF.

Results and Conclusions: During the conference, each response was edited by the entire group, through numerous drafts and rounds of discussion until a complete consensus on vaccination recommendations for adult patients with AIRDs was obtained, including 7 key recommendations.

Key Words: Autoimmune, immunosuppression, recommendations, rheumatic disease, vaccination

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Patients with autoimmune inflammatory rheumatic diseases (AIRDs) are at increased risk of infectious diseases and their complications. Autoimmune inflammatory rheumatic disease comprises more than 2 dozen different diseases (e.g., rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], systemic sclerosis, spondyloarthritis).[1,2] The heightened risk of infections in these patients is due to the nature of the diseases themselves, as well as the various immunomodulatory medications routinely prescribed. Some of the infectious complications, which in some cases even result in mortality, are vaccine-preventable diseases.[3] In patients with AIRD, the risk of acquiring a confirmed infection can be 1.7 times higher than in the general population. Also, the course of infection can be more severe; the risk of an infection requiring hospitalization has been shown to be 1.8 times higher than in healthy persons.[4]

Vaccination is both an individual right and a social responsibility; vaccination, in addition to providing direct personal benefit, is the responsibility of all citizens and their government because primary prevention of disease through vaccination also indirectly protects those who cannot be vaccinated. Vaccination is also one of the most cost-effective and cost-saving tools to reduce the burden of infections in a population. Adult vaccination, in particular, is often indicated for the primary prevention of infectious diseases or as a means to boost immunity when the previous immune response was insufficient. Special at-risk groups, such as patients with AIRD, require more attention.[5]

Thus, a robust and comprehensive adult vaccination program is extremely important. Although many reports have recently appeared[2,6–8] reviewing the safety and efficacy of vaccinations in adult patients with various rheumatic diseases, none have addressed the relatively unique needs and conditions in Latin America (e.g., yellow fever [YF], dengue, Argentine hemorrhagic fever) and specifically in patients with AIRD. One report from the Brazilian Society of Rheumatology recommended a vaccination strategy for patients with RA.[5] Other reports from Colombia addressed vaccination in patients with rheumatic diseases.[9,10] These initiatives are of great value because they stimulate the various rheumatology societies of other Latin American countries to develop the vaccination strategies for patients with rheumatic diseases.

In Latin America, it is difficult to find comprehensive epidemiological data that objectively evaluate the incidence of AIRD in all countries in the region. This uncertainty also extends to the incidence of vaccine-preventable diseases, the extent of which is very unclear.[11] The most frequently associated infectious agents in patients with AIRD, such as influenza virus, *Streptococcus pneumoniae*, and herpes zoster (HZ) virus, have established vaccination schemes. However, once again, information suggests that the vaccination coverage for these infectious diseases in patients with AIRD remains low.

Despite the worldwide shift from acute to chronic diseases that has occurred primarily because of improved sanitation and the advent of vaccination, the Latin American region still suffers

from a large burden of infectious diseases. For example, the dengue virus disease represents one such case. The Word Health Organization recommends that countries consider the introduction of the CYD-TDV vaccine in geographic environments (national or subnational) where epidemiological data indicate a high burden of the disease.[12] It is also worth mentioning other viral infectious diseases of epidemiological importance that are transmitted by mosquitoes (mosquito bites), such as Mayaro fever, chikungunya fever, and Zika fever, for which vaccines have not yet been developed. Another case is malaria disease; despite many decades of intense research and development effort, there is currently no commercially available malaria vaccine for adults.[13,14]

The aim of the present article is to provide health care professionals with a comprehensive and updated set of vaccination recommendations for the region. To achieve this goal, the Americas Health Foundation convened Latin American experts in rheumatic and infectious diseases and immunology to develop consensus recommendations for the vaccination of patients with AIRD. The authors of this report independently developed this consensus document, relying on a comprehensive review of the literature and their personal expertise.

VACCINATION RECOMMENDATIONS

The 2 most important criteria when developing recommendations for vaccination are the safety and efficacy of the vaccine. Safety in AIRD is generally defined as the likelihood of the vaccine triggering either an adverse event or a flare of the autoimmune disease. Efficacy in AIRD is defined as the ability of the vaccine to prevent the disease for which the vaccine is given. For many vaccines, immunogenicity is a surrogate marker for efficacy. However, the timing of vaccination, the immunogenicity given by seroconversion, and the development of blocking antibodies in titers are all factors involved in conferring protection against infection, a result that does not happen in all vaccinated individuals. As a result, rheumatologists should consider the aforementioned variables when making vaccination decisions, as well as the activity or inactivity of the disease, and clinical conditions such as complement deficiency, hyposplenic/asplenic patients, therapy with or without immunosuppressive drugs, and immunosenescence, which is related to the chronicity and activity of the disease, as well with the chronological age of the patient. Following vaccination with some antigens, such as hepatitis B, it can be useful to request antibody titers to verify if protection has developed.[15–17] It is important to note, however, that no serological tests are commercially available to assess immune responses for some vaccines, including for those diphtheria, tetanus, and hepatitis A.

Because published studies regarding vaccine efficacy are often conducted in healthy subjects, few data exist on vaccine efficacy in patients with AIRD. Moreover, there are often no data on some of the diseases encompassed by AIRD. In this report, we extrapolated the data available for various rheumatic diseases to AIRD as a whole, because the diseases that fall under this category have many common features, and patients with AIRD receive many similar therapies.

Vaccines are generally safe for most patients with rheumatic diseases, considering that they neither worsen the activity nor reactivate manifestations of the disease. However, there are some concerns about the safety of live attenuated vaccines when administered in patients on immunosuppressive agents. In this context, the risk of vaccine-induced infection may be enhanced.

There are several kinds of vaccines available, such as inactivated (composed of killed whole viruses or bacteria, fractions of either, or toxoids), live attenuated viruses or bacteria, recombinant (produced by genetic engineering technology), and vaccines developed in cell cultures (made by growing viruses in animal cell cultures). In addition, vaccines can be adjuvanted. An adjuvant is defined as a component that potentiates the immune response to an antigen and modulates it toward a desired immune response.[18]

Inactivated vaccines demonstrate a total lack of infectious potential and thus are safe.[19] Inactivated vaccines are not associated with a greater number of adverse events in AIRD patients or with the worsening of systemic inflammatory activity.[5] Inactivated or recombinant vaccines may have the disadvantage of inducing a less optimal immune response, sometimes requiring the use of adjuvants or transporting proteins (i.e., carriers) or the administration of booster shots.[5,20–22]

Live attenuated vaccines may be contraindicated in AIRD patients receiving immunosuppressive agents.[2,6] Vaccines in this group should preferably be administered before beginning immunosuppressive therapy to ensure that viral replication is over before immunosuppression occurs. When the patient is already receiving immunosuppressive treatment, vaccination should be postponed until therapy has been discontinued for an appropriate period of time (e.g., 1 month after glucocorticoids, 3 months after cytotoxic and human immunoglobulin treatment, 6 months after rituximab [RTX], or a period corresponding to 4 half-lives for other biologic agents).[5] Moreover, if a patient requires more than 1 live attenuated vaccine, to ensure vaccine efficacy, all such vaccines must either be administered at 1 time or be separated from each other by at least 4 weeks. Inactivated vaccines, however, may be administered at any interval independent of the administration of other inactivated or live attenuated vaccines.

In recent years, more data on the safety of live attenuated vaccines in patients with rheumatic diseases have been published, and there is increasing evidence to support vaccination with such vaccines in patients on immunosuppressive therapy. The use of immunosuppressive drugs such as methotrexate (MTX) (at a dose of <0.4 mg/kg per week) and azathioprine (at a dose of <3.0 mg/kg per day), low doses of glucocorticoids (<20 mg/d prednisone or equivalent), or short-term glucocorticoids (<14 days) or local glucocorticoid injections are not considered sufficiently immunosuppressive to question the safety of live attenuated vaccines. However, most of the time, these vaccines may still be contraindicated for patients on higher doses of immunosuppressive therapy.[2]

The first step in improving vaccination status in the individual patient is to assess his/her actual vaccination profile.[23] The vaccination history should be taken at the first visit, to the rheumatology outpatient clinic, and at regular intervals thereafter. At the initial visit, the patient should be reminded of the importance of vaccination, and this should be re-explained at office visits or by a paper reminder. For patients who did not receive the appropriate vaccination schedule for any particular vaccine, vaccination should continue with the missing doses and not restart the schedule. It is always beneficial to administer vaccines as soon as possible after the diagnosis of AIRD and prior to the initiation of immunosuppressive drugs.

What follows are the recommendations for the administration of specific vaccines in adults with AIRD in Latin America. The Table provides a synopsis of the recommendations discussed in the following sections.

Influenza Vaccine

There are several types of influenza vaccines available including inactivated vaccine (trivalent or quadrivalent), live attenuated virus vaccine, recombinant vaccine, and a vaccine developed in cell culture. Latin American countries almost entirely use the inactivated influenza vaccine.

Many published studies have assessed the immunogenicity, efficacy, and safety of nonadjuvanted trivalent inactivated influenza (TIV) vaccine, adjuvanted TIV vaccine, or adjuvanted monovalent vaccine (A/H1N1) in RA patients or in patients with other AIRDs.[24,25] A small number of RA patients who were undergoing treatment with RTX and vaccinated with nonadjuvanted TIV did not achieve sufficient protection to prevent influenza.[26] Another study using nonadjuvanted TIV demonstrated that although the immune response was lower in RA patients treated with RTX, seroprotection was achieved for some influenza antigens.[27] Given that most studies achieved at least a partial response, the administration of nonadjuvanted TIV is not precluded in RA patients undergoing RTX treatment.[27] However, most experts agree that the response to influenza vaccination can be improved if the vaccine is given 4 weeks before, or 6 months after, RTX administration.[24] In studies that assessed the response to influenza vaccine in RA patients, MTX and therapy with tumor necrosis factor (TNF) inhibitors did not affect immunogenicity.[28,29]

Treatment with abatacept in RA patients has been found to significantly reduce the humoral immune response to influenza vaccination.[30] In contrast, a more recent study showed that abatacept-treated RA patients are able to develop an appropriate immune response after seasonal influenza vaccination.[31] Thus, it is unclear whether treatment with abatacept results in a diminished immune response to influenza vaccination.

Patients with RA undergoing treatment with tocilizumab (TCZ), with or without MTX, who were vaccinated against influenza, showed that the vaccine conferred protection and that neither severe adverse effects nor RA flares were observed.[32]

Tofacitinib showed no impairment of seroconversion after influenza vaccine administration in patients with RA, although seroprotection was not achieved in all treated patients.[33,34]

Another study showed that in many AIRDs vaccination with nonadjuvanted influenza H1N1 did not find either moderate or severe adverse effects after vaccination.[35] In order to improve the immunogenicity of influenza vaccines, adjuvanted vaccines have recently been developed. Most of the adjuvants, which are oil-in-water squalene based, helped produce an adequate immune response and had no adverse effect or impact on disease status.[36–38] However, some adjuvants have been implicated in the new syndrome named ASIA (autoimmune/inflammatory syndrome induced by adjuvants), which describes clinical features of 5 immune-mediated conditions.[39,40] In this regard, more studies are needed to evaluate this outcome in patients with AIRD.[41]

The above studies support the annual administration of influenza vaccine for all patients with AIRD. It is not possible to establish before vaccination which patient will respond better to influenza vaccine based on disease status or treatment. No flares of rheumatic disease have been clearly demonstrated after vaccination even with the use of adjuvanted vaccines. Timing of vaccination depends on local epidemiology and national guidelines. The influenza vaccine is considered very safe and has been used worldwide in annual campaigns.[6,27,42] To provide additional protection to AIRD patients against influenza, influenza vaccination of household contacts is recommended.

Pneumococcal Vaccine

Respiratory tract infections are very common among patients with AIRD. *Streptococcus pneumoniae* is responsible for almost half of all cases of community-acquired pneumonia and many other invasive diseases such as meningitis and sepsis. There are 2 vaccines available for the adult population: 13-valent conjugated pneumococcal vaccine (PCV13) and 23-valent polysaccharide pneumococcal vaccine (PPV23). There are several studies that evaluated the response of these vaccines in patients with AIRD undergoing different treatments.

Two studies show that TCZ administered as monotherapy to patients with RA does not impair antibody response after PPV23 vaccination.[22,43] Among patients starting tofacitinib, there is a decreased humoral response after PPV23 administration compared with placebo, particularly among those who also received MTX.[33] In those studies demonstrating a decreased humoral response, however, one should not conclude that the patients were not protected against pneumococcal infection. Regarding long-term protection, data show that antibody levels against PPV23 antigens are preserved for at least 10 years in patients with AIRD (across all ages) who are treated with TNF inhibitors, TCZ, and low-dose prednisone.[44] Another study showed that vaccination with PCV13 in patients receiving etanercept (ETN) for RA is safe and effective.[45]

There are few studies that assess actual protection against disease by vaccination. One such study showed that the first conjugated pneumococcal vaccine, the heptavalent vaccine, achieved favorable results reducing by nearly half the risk of serious pneumococcal infections in vaccinated compared with nonvaccinated AIRD patients.[46] Regardless of the impact of treatment or other factors (such as age) on the response to pneumococcal vaccines in patients with RA or other rheumatic diseases, these vaccines should be administered to all AIRD patients.

Considering that PCV13 showed an improved immune response against serotypes common to both vaccines and that PPV23 covers more pneumococcal serotypes than PCV13, it is recommended to use a sequential vaccination scheme that consists of PCV13 as priming and then PPV23 at least 8 weeks later for all immunocompromised patients, including those with rheumatic diseases.[47] A booster dose of PPV23 5 years after the first dose is also recommended. A third dose is recommended after age 65 years when more than 5 years has elapsed since the last dose. An algorithm for pneumococcal vaccination in AIRD patients is shown in the Figure 1.

With regard to safety, both vaccines PCV13 and PPV23 are well tolerated in patients with AIRD. The adverse events are mild and limited to the vaccine application site.[43] Moreover, data suggest that pneumococcal vaccines do not induce exacerbation of RA.[48]

Herpes Zoster Vaccine

There is an increased risk of the development of HZ in AIRD patients.[49] Risk factors related to HZ infection include age, female sex, and the use of glucocorticoids, biologics, and tofacitinib (which doubled the risk compared with biologics).[50] A live attenuated vaccine is shown to be efficacious for preventing HZ in persons 50 years or older in the general population and even more so for avoiding postherpetic neuralgia.[51,52] There was no association of an increased incidence of HZ within 42 days after vaccination in AIRD patients, thus suggesting the vaccine is safe.[53] In addition, in this study, 2 years after vaccine administration, the incidence of HZ in vaccinated patients was less than that observed in unvaccinated individuals, thus demonstrating that the vaccine is effective. This observation suggests that HZ vaccination is indicated for use in patients with AIRD, subject to an individualized risk-benefit analysis. There is also an adjuvanted nonlive HZ vaccine under development that has demonstrated a 97% efficacy in a 2-dose schedule and that may be a useful tool to immunize immunosuppressed individuals in the future.[54]

The current recommendations for HZ live attenuated vaccine administration in patients with AIRD include those who receive low-dose, short-term, and local glucocorticoids, MTX (<0.4 mg/kg per week), or azathioprine (<3.0 mg/kg per day). In those who receive other immunosuppressive agents, the decision about vaccine

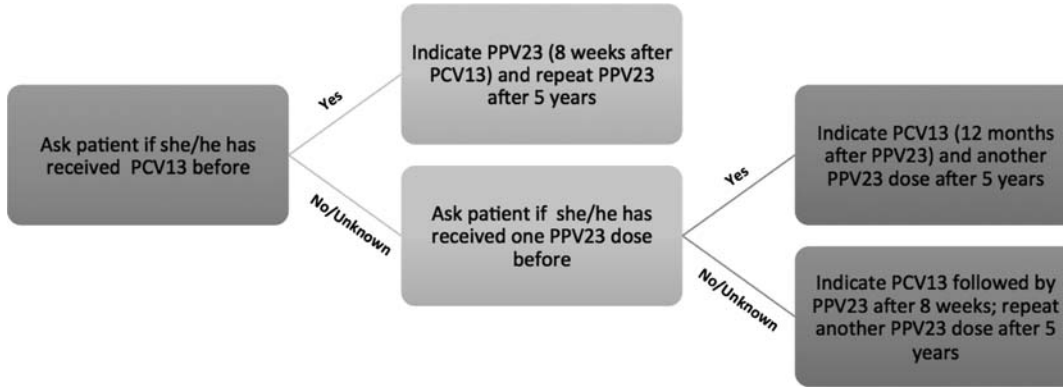

FIGURE 1. Recommended pneumococcal vaccination algorithm for patients with AIRD. Adapted from the Centers for Disease Control and Prevention (CDC).[47]

administration should be made on a case-by-case basis, and vaccination should either be administered at least 2 weeks before immunosuppression begins or be deferred until at least 4 half-lives after therapy discontinuation.[55] The recurrence of HZ infection can also be prevented by the use of the HZ vaccine.[56]

Hepatitis B Vaccine

In most Latin American countries, among adults, hepatitis B vaccination is provided only to those at high risk. The vaccine is developed by recombinant DNA technology and is immunogenic and safe in patients with AIRD. In 1 study, 68% of immunized RA patients developed an adequate immune response, and their treatment with low-dose glucocorticoids, MTX, azathioprine, sulfasalazine, or antimalarial drugs did not affect the antibody response.[57] In addition, in SLE and Behçet disease patients, the vaccine also produced an adequate response regardless of treatment.[58,59]

In all AIRD patients, serologic status for hepatitis B should be assessed prior to treatment initiation with immunosuppressive drugs, particularly in those patients who are going to receive biological agents. Patients with negative serology for hepatitis B should receive a complete hepatitis B vaccination scheme (0, 1, and 6 months). In all AIRD patients, a serological test to assess vaccine response should be performed 1 to 2 months after the third dose; an antibody response of 10 IU/mL is adequate.[60] For those with an inadequate response, it is recommended to repeat the entire vaccination scheme and retest to determine the response.

The hepatitis B vaccine is also considered safe in patients with AIRD. In RA and SLE, for example, vaccination against hepatitis B has been associated with neither a significant deterioration of any clinical measure or laboratory test associated with disease activity nor other important adverse events.[57,58]

Human Papillomavirus Vaccine

Patients with AIRD may be at a higher risk of cervical cancer because of their disease and the immunosuppressive medications they receive.[61,62] The human papillomavirus (HPV) vaccine is an inactivated virus vaccine. Studies on the immunogenicity and safety of the vaccine in patients with AIRD show that it is both safe and effective.[63] There are 2 vaccines available in Latin America. One vaccine is bivalent (HPV2), and the other is quadrivalent (HPV4); both are inactivated, virus-like particles. Both contain the 2 serotypes mostly associated with cervical cancer, 16 and 18, and the HPV4 also contains serotypes 6 and 11, which are associated with the development of genital warts. There is a nonavalent vaccine, soon to be available in Latin America, which includes 5 additional serotypes (31, 33, 45, 52, and 58) that are associated with cervical and other HPV-related cancers.[64] Both of the available vaccines are highly efficacious to prevent anogenital lesions associated with HPV16 and HPV18 in men and women.

With regard to vaccine immunogenicity, in a study of women with inflammatory bowel disease undergoing biologic treatment with TNF inhibitors (infliximab or adalimumab), a high rate of seropositivity was obtained after 3 doses of HPV4 (100% for serotypes 6, 11, and 16 and 96% for serotype 18).[65] There are no data regarding the efficacy of HPV vaccines in RA patients. However, the HPV4 vaccine is well tolerated and reasonably effective in patients with stable SLE and does not induce an increase in disease activity. It is worth mentioning that although there is a 2-dose scheme for women younger than 15 years, in immunocompromised hosts of any age, the 3-dose vaccination schedule is the only one recommended. Based on the burden of illness, the risk of development of malignant HPV-associated disease in AIRD patients, and considering the safety and efficacy of the vaccine in studies of patients with AIRD,[63,65] the HPV vaccine is recommended for young women and men with AIRD.

Hepatitis A Vaccine

Inactivated vaccines, such as hepatitis A virus vaccine, can be safely administered to immunosuppressed patients. This vaccine should be administered to AIRD patients who are seronegative for hepatitis A.[5] Regarding efficacy of hepatitis A virus vaccine in patients with AIRD undergoing treatment with MTX and TNF inhibitors, a 2-dose scheme with a 6-month interval provided 86% protection for RA patients.[20]

Tetanus/Diphtheria and Tetanus/Diphtheria/Pertussis Vaccine

The vaccine is initially given in infancy as part of a basic vaccination schedule and, subsequently, to maintain protection against these diseases. In adults, the tetanus/diphtheria vaccine should be administered in all adults, including AIRD patients, as a booster dose every 10 years. Pertussis is not infrequent in adults, who are the main transmitters of this disease to infants, particularly breastfeeding infants who have a high risk of death from the disease.

The vaccine available to prevent pertussis is a denominated acellular, inactivated vaccine and is only available combined with diphtheria and tetanus (Tdap). As with all other inactivated vaccines, it is safe in AIRD patients.[6] In patients with AIRD receiving RTX in the preceding 6 months, protection against tetanus might be diminished, and immunoglobulin against tetanus should be administered in case of tetanus exposure.[5,66] In some countries of the region, Tdap is recommended for women in every pregnancy in

order to improve protection of the newborn against pertussis and tetanus. We recommend that Tdap be given in each pregnancy after week 20 in all patients with AIRD.

Meningococcal Vaccine

Meningococcal monovalent (serogroup C) and tetravalent (serogroups A, C, W, Y) conjugated vaccines are available. Also, a vaccine against *Neisseria meningitidis* serogroup B developed by reverse vaccinology is available in some countries in Latin America. There are few data published on the efficacy of these vaccines in AIRD patients. One study showed that serogroup C conjugated vaccine does not produce flares of juvenile idiopathic arthritis (JIA) and generates adequate antibody levels, even in patients receiving high doses of immunosuppressive medication.[67] Meningococcal vaccines should be given every 3 to 5 years to AIRD patients who have functional or anatomical asplenia or complement deficiency. The type of vaccine administered depends on the epidemiology of the meningococcal diseases and serogroup distribution in each country.[2]

Yellow Fever Vaccine

Yellow fever is endemic to limited areas within Latin America, primarily in tropical areas, has no effective treatment, and carries a high level of mortality. The national immunization schedules of some Latin American countries include YF vaccination in childhood for residents of endemic areas and recommend administration to travelers in these areas. Also, because of International Health Regulations,[68,69] YF vaccination may be a requirement for travelers from YF endemic countries to other countries free of the diseases, but where the vector is present. In this case, when there is no risk of acquiring the disease, AIRD patients can obtain a waiver for YF vaccination from the health authorities.

The YF vaccine is a live-attenuated vaccine that is highly immunogenic and provides lifelong protection.[70] Although the risk of serious adverse events is rare, reports indicate that YF vaccine can cause 2 clinically relevant syndromes known as YF vaccine–associated neurotropic disease and YF vaccine–associated viscerotropic disease (YEL-AVD).[71] Yellow fever vaccine–associated viscerotropic disease generally occurs 3 to 5 days after vaccination and is characterized by fever, malaise, jaundice, oliguria, cardiovascular instability, and hemorrhage secondary to a platelet disorder.[72] Increased risk of developing YEL-AVD might be associated with autoimmune diseases. Cases of YEL-AVD have been reported in patients with SLE, polymyalgia rheumatica, Crohn disease, ulcerative colitis, and other AIRDs.[5,73]

On the other hand, a Brazilian retrospective study evaluated 70 patients with AIRD who were inadvertently vaccinated against YF. The therapeutic schemes included MTX, glucocorticoids, sulfasalazine, leflunomide, cyclophosphamide, and biological agents. Among these patients, adverse reactions were no more frequent than among immunocompetent individuals.[74] Another Brazilian study included 17 RA patients revaccinated against YF (which is no longer necessary)[75] while receiving infliximab therapy, and there were also no relevant adverse events.[76] Thus, it seems that YF vaccination may be safe, but an individualized assessment of risk-benefit should be conducted.[5]

Varicella Vaccine

History of varicella infection should be verified in persons with AIRD at the time of the disease's diagnosis. Those who have had varicella or were vaccinated against it can be considered immune to the disease. For those who are seronegative for varicella, the vaccine in a 2-dose schedule with an 8-week interval can be administered before the initiation of treatment for AIRD. It is worth remembering that this vaccine, like other live-attenuated vaccines, may be contraindicated to immunosuppressed individuals, especially when the risks of acquiring the disease surpass the potential risks of vaccination.[5]

Measles, Mumps, and Rubella Vaccine

This live attenuated virus vaccine is recommended in most Latin American countries and is generally administered in a 2-dose schedule after the first year of life and during early childhood; it provides protection for life. In adults with AIRD who have not received both doses at the appropriate times, a serological assessment should be performed. If serology is negative for any of the 3 diseases, 2 doses of the measles, mumps, and rubella (MMR) vaccine, separated by at least 4 weeks, should be administered after assessment of the risks and benefits, keeping in mind that it is a live attenuated vaccine.[8] While measles and rubella have been eliminated in Latin America, it is common for mumps outbreaks to appear in adolescents and young adults.

The MMR vaccine has a good safety profile and is well tolerated. The safety of the MMR vaccine was assessed in patients with JIA.[77,78] In a randomized trial, MMR booster vaccination, compared with no booster, did not result in worse JIA disease activity and was immunogenic in children with JIA who had undergone primary immunization.[79] There are no studies on the safety of the MMR vaccine in adults with AIRD.[5]

Dengue Vaccine

Dengue is a viral infection transmitted by the mosquito of the genus *Aedes* that can affect a large proportion of the population that live in Latin America. There are 4 dengue virus serotypes (DEN1, DEN2, DEN3, and DEN4), and the disease is characterized by fever, rash, malaise, myalgia, headache, nausea, and vomiting and can evolve to severe dengue or death in a few cases, particularly in those individuals who have been previously infected. Recently, a recombinant, live attenuated vaccine that contains all of the virus serotypes has become available in some countries of the region and is mainly directed to adolescents and young adults who live in endemic areas. The vaccine is given in a 3-dose schedule (0, 6, and 12 months). The efficacy in adolescents is greater than 60% to prevent disease and is even more efficacious for the prevention of dengue complications.[80] There are no data available regarding efficacy and safety of this vaccine in AIRD, but considering that it is a live-attenuated vaccine, it may be contraindicated in those AIRD patients receiving high-dose immunosuppressive drugs.

Argentine Hemorrhagic Fever Vaccine

Argentine hemorrhagic fever is a viral disease produced by the arenavirus Junin that is transmitted by rodents and is mainly observed in rural areas in the central region of Argentina. The live-attenuated vaccine (Candid 1) has been found to have 95% efficacy and should be given as 1 dose to persons 15 years or older who live or work in an endemic area.[81] No data are available regarding the administration of this vaccine in adults with AIRD. Considering that it is a live-attenuated vaccine, it may be contraindicated in patients receiving high doses of immunosuppressive drugs.

Tuberculosis Vaccine

Tuberculosis is a very prevalent disease among adults in most Latin American countries; however, vaccination is not indicated in adults. Bacillus Calmette-Guérin vaccine, primarily used to prevent severe forms of tuberculosis in newborns, does not protect individuals already infected with *Mycobacterium tuberculosis*, and its administration in adults, which includes adult AIRD patients,

TABLE 1. Immunization Recommendations for Adults With AIRD in Latin America

Vaccines	Dosage	Can Treatment Adversely Impact Vaccination Efficacy?	Can Treatment Adversely Impact Vaccination Safety?	Caveats/Issues
Influenza (I) (inactivated, adjuvanted, and nonadjuvanted)	1 Annual dose	Yes, rituximab and abatacept may diminish	No	Vaccination of household contacts and pregnant women is important.
Pneumococcal vaccines				
13-Valent conjugated (PCV13) (I)	1 Dose	Yes, immunosuppressors may diminish	No	For immunization scheme, see Figure.
23-Valent polysaccharide (PPV23) (I)	2 Doses (5-y interval); additional dose after age 65 y (if last dose was given before age 60 y)			
Herpes zoster (LA)	1 Dose for persons aged >50 y	No	Yes, the assessment of risk-benefit is prudent	Live attenuated vaccines may be indicated in patients receiving low-dose[a] immunosuppressive drugs.
Hepatitis B (I)	3 Doses (0, 1, and 6 mo)	Yes, immunosuppressors may diminish	No	Check serology before and after vaccination.
HPV (I)	3 Doses (0, 1, and 6 mo) for bivalent; 3 doses (0, 2, and 6 mo) for quadrivalent	No	No	Women—no age limit; men—up to age 26 y (may also be beneficial at later ages).
Hepatitis A (I)	2 Doses, minimum interval of 6 mo	Yes, with TNF inhibitors and MTX, but very limited data	No	Vaccines should be given only in patients who are seronegative for hepatitis A.
Tdap or Td (tetanus/diphtheria) (I)	Basic vaccination schedule followed by booster shot with Td every 10 y	Yes, RTX may diminish	No	Vaccinate pregnant women after week 20 with Tdap.
Meningococcal vaccines (I)	Only for patients with functional or anatomical asplenia or complement deficiency: 1 dose every 3–5 y	No data	No	Recommendations vary across countries and year to year, depending on bacterial serogroup.
YF (LA)	1 Dose for those living in endemic areas or traveling to such areas	No (limited data)	Yes (limited data); assess risk-benefit	Live attenuated vaccines may be indicated in patients receiving low-dose[a] immunosuppressive drugs.
Varicella (LA)	2 Doses, 8-wk interval in patients with negative history for varicella zoster infection or vaccination	No data	Yes (limited data); assess risk-benefit	Live attenuated vaccines may be indicated in patients receiving low-dose[a] immunosuppressive drugs.
MMR (LA)	Two doses at least 4 wk apart in those with negative serology for any of the 3 diseases	No data	Yes (limited data); assess risk-benefit	Live attenuated vaccines may be indicated in patients receiving low-dose[a] immunosuppressive drugs. Patients aged >50 y are considered immune.
Dengue (LA)	Doses (0, 6, and 12 mo)	No data	No data; assess risk-benefit	Live attenuated vaccine may be contraindicated in persons receiving high-dose immunosuppressive drugs.

Argentine hemorrhagic fever (LA)	1 Dose given to persons aged ≥15 y	No data	No data; assess risk benefit	Vaccine administration limited to persons residing in endemic areas of Argentina. Live attenuated vaccine may be contraindicated in persons receiving high-dose immunosuppressive drugs.
Tuberculosis (bacillus Calmette-Guérin) (LA)	Not indicated for adults	No data	No data	—

[a]Low dose is defined as glucocorticoids (<20 mg/d prednisone or equivalent), short-term corticosteroids (<14 days), local corticosteroid injections, or MTX (<0.4 mg/kg per week) or azathioprine (<3.0 mg/kg per day) at the doses indicated.
I indicates inactivated; LA, live attenuated.

does not provide protection against disease.[5] Therefore, treatment against latent tuberculosis infection or early detection of the infection in immunosuppressed hosts such as AIRD patients is of the utmost importance. Since the development of TNF inhibitors, some immunosuppressive biologics have been associated with an increased risk of reactivation of latent tuberculosis infection and new cases of TB.[82]

Other Vaccines

There is a group of vaccines that may be considered in special situations and that deserve mention despite not being included in the Table 1.

- Polio
  Bivalent oral polio vaccine. This is a live attenuated vaccine and is contraindicated for AIRD patients and members of their household. Thus, AIRD patients and members of their household should instead receive the inactivated polio vaccine.
  Inactivated polio vaccine. Inactivated polio vaccine is a parenteral vaccine and is indicated for infant household members of patients with AIRD and for patients with AIRD who plan to travel to polio endemic areas.

- Rabies: The rabies vaccine is an inactivated virus vaccine and should be considered in special situations, such as:
  pre-exposure: in case of occupational risk or for travelers who plan to spend long periods in countries or areas where the disease is endemic; and
  postexposure: in case of an accident presenting the potential risk of contracting rabies disease, which is both rare and fatal.

- Typhoid fever
  The inactivated vaccine is recommended (at least 2 weeks before travel) for travelers going to a destination with unfavorable sanitary conditions.

- *Haemophilus influenzae* type B
  The *H. influenzae* type B inactivated vaccine is 1 dose given to AIRD patients who have functional or anatomical asplenia or complement deficiency.

Other Considerations

It is important to note that patients with AIRD who are planning to travel should consult an infectious disease specialist to receive the appropriate vaccination indications, based on the destination and conditions of travel, and at least 6 months prior to departure.

Finally, one especially vulnerable group to consider is pregnant women with AIRD. Both pregnant women and their fetuses are at an increased risk of infectious diseases and their complications. Therefore, it is essential that they receive the influenza vaccine in any trimester of gestation, as well as the Tdap vaccine after the 20th week of pregnancy. Both of these vaccines are inactivated, safe, and effective.

KEY RECOMMENDATIONS

1. Assess vaccination status upon diagnosis of AIRD.
2. Complete vaccination of household contacts is recommended to provide additional protection of immunocompromised persons.
3. Vaccinations should ideally be administered prior to initiating immunosuppressive therapy.

4. For patients who did not receive the appropriate vaccination schedule for any particular vaccine, continue with the missing doses and do not restart the schedule.
5. Vaccination with live attenuated vaccines may be permissible during treatment with immunosuppressive agents after an individualized risk-benefit analysis is performed. Vaccination with inactivated vaccines is safe.
6. Because of safety and efficacy, live attenuated vaccines should ideally be administered at least 2 weeks before immunosuppressive therapy begins or be deferred until at least 2 weeks after discontinuation of synthetic immunosuppressive drugs; 4 weeks after discontinuation of glucocorticoids; 12 weeks after discontinuation of immunoglobulins, cytotoxic drugs, or alkylating agents; and, in the case of biological agents, at least 4 half-lives after discontinuation of therapy.
7. If an AIRD patient requires more than 1 live attenuated vaccine, all such vaccines must either be administered at one time or be separated from each other by at least 4 weeks. Inactivated vaccines may be administered at any interval independent of the administration of other inactivated or live attenuated vaccines.

REFERENCES

1. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum*. 2010;62:75–81.
2. van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2011;70:414–422.
3. Glück T, Kiefmann B, Grohmann M, et al. Immune status and risk for infection in patients receiving chronic immunosuppressive therapy. *J Rheumatol*. 2005;32:1473–1480.
4. Doran MF, Crowson CS, Pond GR, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum*. 2002;46:2287–2293.
5. Brenol CV, da Mota LM, Cruz BA, et al. 2012 Brazilian Society of Rheumatology consensus on vaccination of patients with rheumatoid arthritis. *Rev Bras Reumatol*. 2013;53:4–23.
6. Cordeiro I, Duarte AC, Ferreira JF, et al. Recommendations for vaccination in adult patients with systemic inflammatory rheumatic diseases from the Portuguese Society of Rheumatology. *Acta Reumatol Port*. 2016;41:112–130.
7. Westra J, Rondaan C, van Assen S, et al. Vaccination of patients with autoimmune inflammatory rheumatic diseases. *Nat Rev Rheumatol*. 2015;11:135–145.
8. Morel J, Czitrom SG, Mallick A, et al. Vaccinations in adults with chronic inflammatory joint disease: immunization schedule and recommendations for patients taking synthetic or biological disease-modifying antirheumatic drugs. *Joint Bone Spine*. 2016;83:135–141.
9. Zuccardi PG, Eraso Garnica RM, Ramirez Gomez LA. Immunization of patients with rheumatic diseases [in Spanish]. *Rev Colomb Reumatol*. 2006;13:65–75.
10. Gómez JM, Gómez-Rincón JC, Alí-Munive A, et al. Guías para la inmunización del adolescente y adulto en Colombia. *Doc Actual Infect*. 2016;20:192–210.
11. Glück T, Müller-Ladner U. Vaccination in patients with chronic rheumatic or autoimmune diseases. *Clin Infect Dis*. 2008;46:1459–1465.
12. World Health Organization. Dengue Vaccine: WHO Position Paper—July 2016. Weekly Epidemiological Record, 2016: no. 30, vol. 91: 349–364, Available at: http://www.who.int/wer/2016/wer9130.pdf?ua=1. Accessed July 10, 2017.
13. World Health Organization. Malaria Vaccine Development. May 27, 2016. Available at: http://www.who.int/malaria/areas/vaccine/en/. Accessed June 9, 2017.
14. Torjesen I. Medicines agency rejects a quarter of requests for documents it holds on drugs. *BMJ*. 2012;345:e8684.
15. Wright SA, Taggart AJ. Pneumococcal vaccination for RA patients on TNF-alpha antagonists. *Rheumatology (Oxford)*. 2004;43:523.
16. Hohensinner PJ, Goronzy JJ, Weyand CM. Telomere dysfunction, autoimmunity and aging. *Aging Dis*. 2011;2:524–537.
17. Stratton K, Ford A, Rusch E, et al Committee to Review Adverse Effects of Vaccines; Institute of Medicine. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: National Academies Press (US); 2011.
18. Kallerup RS, Foged C. Classification of vaccines. In: Foged C, Rades T, Perrie Y, et al, eds. *Subunit Vaccine Delivery*. Washington, DC: Springer; 2015:15–29.
19. Bühler S, Eperon G, Ribi C, et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. *Swiss Med Wkly*. 2015;145:w14159.
20. Askling HH, Rombo L, van Vollenhoven R, et al. Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study. *Travel Med Infect Dis*. 2014;12:134–142.
21. Mok CC, Ho LY, Fong LS, et al. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. *Ann Rheum Dis*. 2013;72:659–664.
22. Bingham CO 3rd, Rizzo W, Kivitz A, et al. Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: results of a randomised controlled trial (VISARA). *Ann Rheum Dis*. 2015;74:818–822.
23. Müller-Ladner C, Müller-Ladner U. Vaccination and inflammatory arthritis: overview of current vaccines and recommended uses in rheumatology. *Curr Rheumatol Rep*. 2013;15:330.
24. Perry LM, Winthrop KL, Curtis JR. Vaccinations for rheumatoid arthritis. *Curr Rheumatol Rep*. 2014;16:431.
25. Abu-Shakra M, Press J, Buskila D, et al. Influenza vaccination of patients with systemic lupus erythematosus: safety and immunogenicity issues. *Autoimmun Rev*. 2007;6:543–546.
26. Gelinck LB, Teng YK, Rimmelzwann GF, et al. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. *Ann Rheum Dis*. 2007;66:1402–1403.
27. Oren S, Mandelboim M, Braun-Moscovici Y, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. *Ann Rheum Dis*. 2008;67:937–941.
28. Hua C, Barnetche T, Combe B, et al. Effect of methotrexate, anti–tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2014;66:1016–1026.
29. Kivitz AJ, Schechtman J, Texter M, et al. Vaccine responses in patients with rheumatoid arthritis treated with certolizumab pegol: results from a single-blind randomized phase IV trial. *J Rheumatol*. 2014;41;648–657.
30. Ribeiro AC, Laurindo IM, Guedes LK, et al. Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2013;65:476–480.
31. Alten R, Bingham CO 3rd, Cohen SB, et al. Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. *BMC Musculoskelet Disord*. 2016;17:231.
32. Mori S, Ueki Y, Hirakata N, et al. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2012;71:2006–2010.

33. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:687–695.
34. Tsuru T, Terao K, Murakami M, et al. Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with tocilizumab. *Mod Rheumatol*. 2014;24:511–516.
35. Saad CG, Borba EF, Aikawa NE, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. *Ann Rheum Dis*. 2011;70: 1068–1073.
36. Gabay C, Bel M, Combescure C, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. *Arthritis Rheum*. 2011;63:1486–1496.
37. Elkayam O, Amir S, Mendelson E, et al. Efficacy and safety of vaccination against pandemic 2009 influenza A (H1N1) virus among patients with rheumatic diseases. *Arthritis Care Res (Hoboken)*. 2011;63:1062–1067.
38. Milanetti F, Germano V, Nisini R, et al. Safety and immunogenicity of co-administered MF59-adjuvanted 2009 pandemic and plain 2009–10 seasonal influenza vaccines in rheumatoid arthritis patients on biologicals. *Clin Exp Immunol*. 2014;177:287–294.
39. Pellegrino P, Clementi E, Radice S. On vaccine's adjuvants and autoimmunity: current evidence and future perspectives. *Autoimmun Rev*. 2015;14:880–888.
40. Watad A, Quaresma M, Brown S, et al. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome)—an update. *Lupus*. 2017;26:675–681.
41. Murdaca G, Orsi A, Spanò F, et al. Influenza and pneumococcal vaccinations of patients with systemic lupus erythematosus: current views upon safety and immunogenicity. *Autoimmun Rev*. 2014;13:75–84.
42. Fomin I, Caspi D, Levy V, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. *Ann Rheum Dis*. 2006;65:191–194.
43. Mori S, Ueki Y, Akeda Y, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. *Ann Rheum Dis*. 2013;72:1362–1366.
44. Broyde A, Arad U, Madar-Balakirski N, et al. Long-term efficacy of an antipneumococcal polysaccharide vaccine among patients with autoimmune inflammatory rheumatic diseases. *J Rheumatol*. 2016;43; 267–272.
45. Rákóczi É, Perge B, Végh E, et al. Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept. *Joint Bone Spine*. 2016;83:675–679.
46. Nagel J, Geborek P, Saxne T, et al. The risk of pneumococcal infections after immunization with pneumococcal conjugate vaccine compared to non-vaccinated inflammatory arthritis patients. *Scand J Rheumatol*. 2015; 44:271–279.
47. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
48. Elkayam O, Paran D, Burke M, et al. Pneumococcal vaccination of patients with systemic lupus erythematosus: effects on generation of autoantibodies. *Autoimmunity*. 2005;38:493–496.
49. Marra F, Lo E, Kalashnikov V, et al. Risk of herpes zoster in individuals on biologics, disease-modifying antirheumatic drugs, and/or corticosteroids for autoimmune diseases: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2016;3:ofw205. eCollection 2016.
50. Winthrop KL, Yamanaka H, Valdez H, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2014;66: 2675–2684.
51. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.
52. Schmader KE, Levin MJ, Gnann JW Jr., et al. Efficacy, safety and tolerability of herpes zoster vaccine in persons aged 50–59 years. *Clin Infect Dis*. 2012;54:922–928.
53. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA*. 2012;308:43–49.
54. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372: 2087–2096.
55. Harpaz R, Ortega-Sanchez IR, Seward JF, et al. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1–30.
56. Mills R, Tyring SK, Levin MJ, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. *Vaccine*. 2010;28:4204–4209.
57. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2002;61:623–625.
58. Kuruma KA, Borba EF, Lopes MH, et al. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. *Lupus*. 2007;16:350–354.
59. Erkek E, Ayaslioglu E, Erkek AB, et al. Response to vaccination against hepatitis B in patients with Behcet's disease. *J Gastroenterol Hepatol*. 2005;20:1508–1511.
60. Garrido López BC, Navarro Compain MV, Navarro Sarabia F, et al. Vaccines and chemo-prophylaxis in rheumatoid arthritis: is a vaccine calendar necessary? *Reumatol Clin*. 2011;7:412–416.
61. Zard E, Arnaud L, Mathian A, et al. Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: a meta-analysis of the literature. *Autoimmun Rev*. 2014;13:730–735.
62. Raposo A, Tani C, Costa J, et al. Human papillomavirus infection and cervical lesions in rheumatic diseases: a systematic review. *Acta Reumatol Port*. 2016;41:184–190.
63. Pellegrino P, Radice S, Clementi E. Immunogenicity and safety of the human papillomavirus vaccine in patients with autoimmune diseases: a systematic review. *Vaccine*. 2015;33:3444–3449.
64. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372:711–723.
65. Jacobson DL, Bousvaros A, Ashworth L, et al. Immunogenicity and tolerability to human papillomavirus-like particle vaccine in girls and young women with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013; 19:1441–1449.
66. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2011;70:909–920.
67. Zonneveld-Huijssoon E, Ronaghy A, van Rossum MA, et al. Safety and efficacy of meningococcal C vaccination in juvenile idiopathic arthritis. *Arthritis Rheum*. 2007;56:639–646.
68. World Health Assembly. *International Health Regulations (2005)*. Geneva: World Health Organization; 2006. Available at: http://www.who.int/ihr/publications/9789241580496/en/. Accessed February 21, 2017.
69. World Health Assembly. *Implementation of the International Health Regulations (2005), WHA67.13*. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA67-REC1/A67_2014_REC1-en.pdf. May 24, 2014. Accessed February 21, 2017.
70. Staples JE, Gershman M, Fischer M, et al. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-7):1–27.

71. Thomas RE, Lorenzetti DL, Spragins W, et al. The safety of yellow fever vaccine 17D or 17DD in children, pregnant women, HIV$^+$ individuals, and older persons: systematic review. *Am J Trop Med Hyg*. 2012;86:359–372.

72. Gershman MD, Staples JE, Bentsi-Enchill AD, et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine*. 2012;30: 5038–5058.

73. Seligman SJ. Risk groups for yellow fever vaccine–associated viscerotropic disease (YEL-AVD). *Vaccine*. 2014;32:5769–5775.

74. Mota LM, Oliveira AC, Lima RA, et al. Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases. *Rev Soc Bras Med Trop*. 2009;42:23–27.

75. World Health Organization. Vaccines and vaccination against yellow fever: WHO position paper—June 2013. *Wkly Epidemiol Rec*. 2013;88: 269–283. Available at: http://www.who.int/wer/2013/wer8827.pdf?ua=1. Accessed February 21, 2017.

76. Scheinberg M, Guedes-Barbosa LS, Mangueira C, et al. Yellow fever revaccination during infliximab therapy. *Arthritis Care Res (Hoboken)*. 2010;62:896–898.

77. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. *Ann Rheum Dis*. 2007;66:1384–1387.

78. Borte S, Liebert UG, Borte M, et al. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. *Rheumatology (Oxford)*. 2009;48: 144–148.

79. Heijstek MW, Kamphuis S, Armbrust W, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. *JAMA*. 2013;309: 2449–2456.

80. Hadinegoro SR, Arredondo-García JL, Capeding MR, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *N Engl J Med*. 2015;373:1195–1206.

81. Maiztegui JI, McKee KT Jr, Barrera Oro JG, et al. Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. AHF Study Group. *J Infect Dis*. 1998;177:277–283.

82. Acevedo-Vásquez E, Ponce de León D, Gamboa-Cárdenas R. Latent infection and tuberculosis disease in rheumatoid arthritis patients. *Rheum Dis Clin North Am*. 2009;35:163–181.