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Sjögren's Syndrome

Treatment Guidelines for Rheumatologic Manifestations of Sjögren's Syndrom Use of Biologic Agents, Management of Fatigue, and Inflammatory Musculoskeletal Pain

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Abstract

Objective

The Sjögren's Syndrome Foundation clinical practice guidelines (CPGs) are designed to improve quality and consistency of care in Sjögren's syndrome by offering recommendations for management.

Methods

Management questions for the systemic manifestations of Sjögren's syndrome were po by the CPG committee with input from patients and rheumatologists. Clinical questions were assigned to a topic review group that performed systematic reviews and data

were reviewed by a consensus expert panel (CEP) composed of 30–40 clinicians from academia and community practices, as well as registered nurses and patients, using a modified Delphi process. A CEP agreement level of 75% was set as a minimum for adop of a guideline recommendation.

Results

Consensus was achieved for 19 recommendations; for 11 additional modules, available data were insufficient to allow a recommendation to be formulated. Of the 19 recommendations, 15 required 1 Delphi round, 2 required 2 rounds, and 2 required 3 rounds.

Conclusion

Key recommendations include a decision tree for the use of oral disease-modifying antirheumatic drugs for inflammatory musculoskeletal pain, use of self-care measures a advice regarding exercise to reduce fatigue, and the use of rituximab in selected clinical settings for oral and ocular dryness and for certain extraglandular manifestations, inclu vasculitis, severe parotid swelling, inflammatory arthritis, pulmonary disease, and mononeuritis multiplex. The CPG committee strongly discouraged the use of tumor necrosis factor inhibitors for sicca symptoms and for the majority of clinical contexts in primary Sjögren's syndrome.

INTRODUCTION

Sjögren's syndrome remains underrecognized despite being a highly prevalent autoimmur rheumatic disorder that affects up to 3.1 million Americans 1. The prevalence doubles whe including those with an additional connective tissue disease. The disease is associated with high burden of illness, diminished quality of life 2-4, and increased health care costs 5-7. Sjögren's syndrome is also associated with an increased relative risk of developing non-Hodgkin's B cell lymphoma 8. Clinical practice guidelines (CPGs) were developed by the Sjögren's Syndrome Foundation (SSF) in response to patient requests for improved care an physician requests for guidance.

Box 1. Significance & Innovations

> First description of US clinical practice guidelines for primary Sjögren's syndrome.

The primary goal of the SSF initiative was to improve the quality and value of care in Sjögre syndrome by developing CPGs for the assessment and management of systemic manifestations, dry eyes, and dry mouth, and to create a guidance document for US clinicia The secondary goal was to obtain broad awareness of these guidelines by key stakeholders including key professional and government organizations, as well as health care insurance entities. The SSF determined key guiding principles at the start of the process, including participation of key stakeholders, transparency, and consistency. The SSF funded and staff conferences for the CPG initiative and copartnered with the American College of Rheumatology (ACR) Quality of Care Committee and staff, which provided guidance throughout this process. The Foundation appointed a chair who then, in conjunction with t SSF, appointed 6 co-chairs for 3 working groups to cover rheumatology/systemic disease, ocular, and oral manifestations (see Appendix A for clinical practice guidelines committee members and working groups). The current article addresses the rheumatologic topics. All working groups followed common processes and a specific order of tasks to reduce bias as much as possible. For the purpose of these CPGs, the chairs and working group members addressed treatment questions among those Sjögren's syndrome patients without a secon major rheumatic/autoimmune disease (or primary Sjögren's syndrome as it traditionally ha been referred to). While guideline recommendations provide a rational approach to variou management issues, clinicians will ultimately use their best clinical judgment in practice. A degree of inherent bias is unavoidable but reduced as much as possible through the use of rigorous and transparent process, the low percentage of potential conflicts of interest by participants as guided by ACR policies 9, and the use of an external consensus panel that voted and commented on the recommendations as they were finalized.

The guidelines provide evidence-based recommendations whenever possible and expert opinion when insufficient evidence exists. These first-ever standard-of-care guidelines for systemic Sjögren's syndrome in the US will improve consistency in practice patterns, inform coverage and reimbursement policies, lead to the design and implementation of needed educational programs, highlight areas for future research, and, most importantly, fill a significant clinical void.

MATERIALS AND METHODS

Principles

The SSF CPG committee adopted the principles of the Appraisal of Guidelines for Research

including patients, practicing and academic rheumatologists, and the SSF as a patient advo organization, were included in the guidelines development initiative. Surveys of patient priorities were conducted during an SSF National Patient Conference and through use of S media (e-mail, website, and Facebook). In addition, patients were appointed to the CPG committee and served on the consensus expert panels (CEPs). Opinions of practicing rheumatologists were obtained during exit surveys at Sjögren's syndrome Meet the Profes sessions held during an ACR annual scientific meeting.

Work process

Initially, 97 potential topics for guideline development were identified by a review of stakeholder surveys. After further face-to-face and e-mail discussions, the list was narrowe 16 topics (see Supplementary Appendix 1A, available on the *Arthritis Care & Research* web si at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract) that were ranked by vote the working group. Significance was rated on a 1–5 Likert scale (where 1 = possibly importa to some and 5 = crucial to all stakeholders). A score of ≥4.0 was established as a cutoff for guideline development. Topics were expressed as clinical questions. This article reports on following 3 questions: Are nonbiologic disease-modifying antirheumatic drugs (DMARDs) useful for the treatment of inflammatory musculoskeletal (MSK) pain? Are biologic agents effective and safe in management of sicca and systemic manifestations? Are there effective management strategies for fatigue? Each topic question was assigned to a topic review gro (TRG) composed of members from specialties relevant to that topic question. The MSK TRG included 3 rheumatologists, the biologic agents TRG included 2 rheumatologists, 2 oral medicine specialists, and an ophthalmologist, and the fatigue TRG included 3 rheumatolog An expert methodologist was recruited to guide the entire process.

Search strategy

The systematic review of the literature was conducted with the assistance of a librarian usi MEDLINE/PubMed and the Cochrane database to search for peer-reviewed articles publish in English between January 1, 1988 and April 13, 2015. Literature search results for each to are summarized by the quorum diagrams (Figures 1-3). Individual search strategies, inclusi parameters, and search terms are provided in Supplementary Appendices 2A–F, 3A–E, and 4A–E (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com /doi/10.1002/acr.22968/abstract). Subjects of included articles were allowed to meet any published Sjögren's syndrome classification criteria. Subjects may have had concurrent no Hodgkin's lymphoma, but intervention studies must have been primarily designed to meas

trials (RCTs), as well as prospective case studies and series where outcomes for treatment were prospectively defined. The minimum treatment followup interval was defined as 12 weeks. Systematic reviews were used to ensure capture of references and to provide a contextual overview for the TRG.

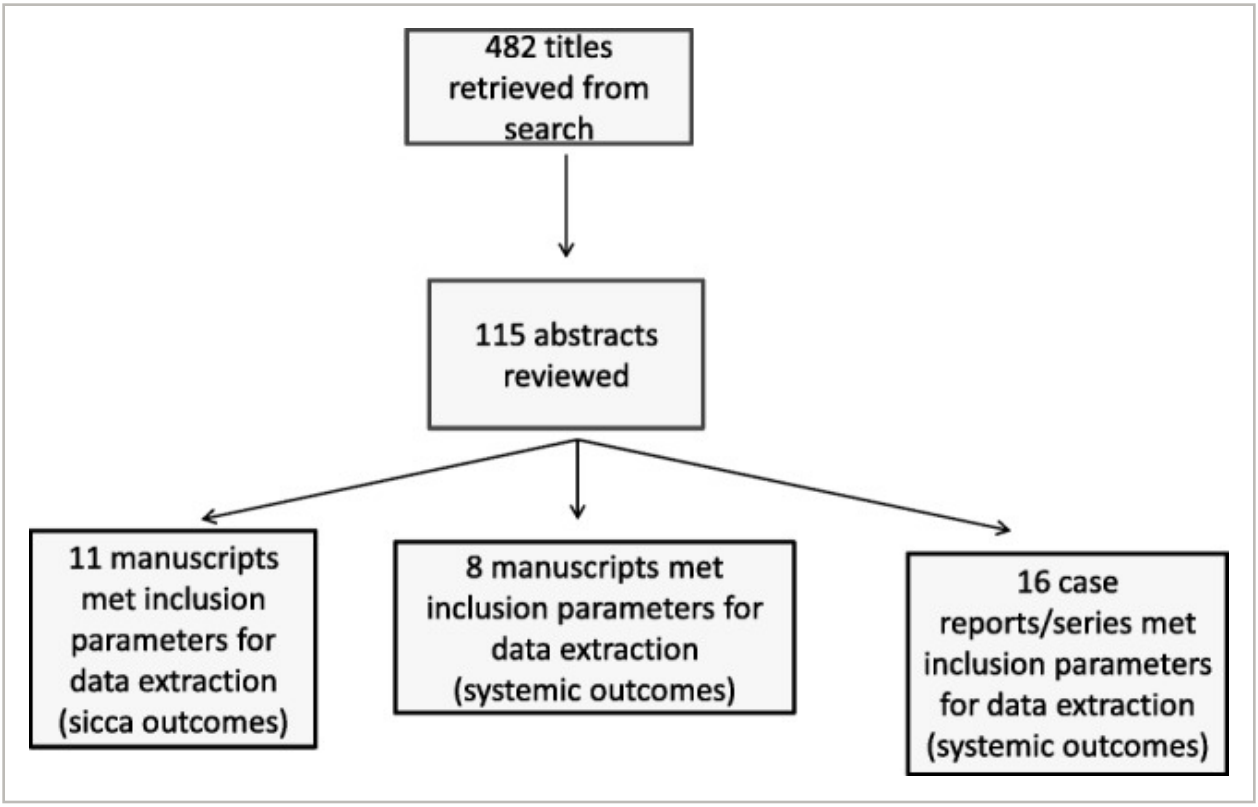

Figure 1

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Quorum diagram for biologic topic review group.

Caption

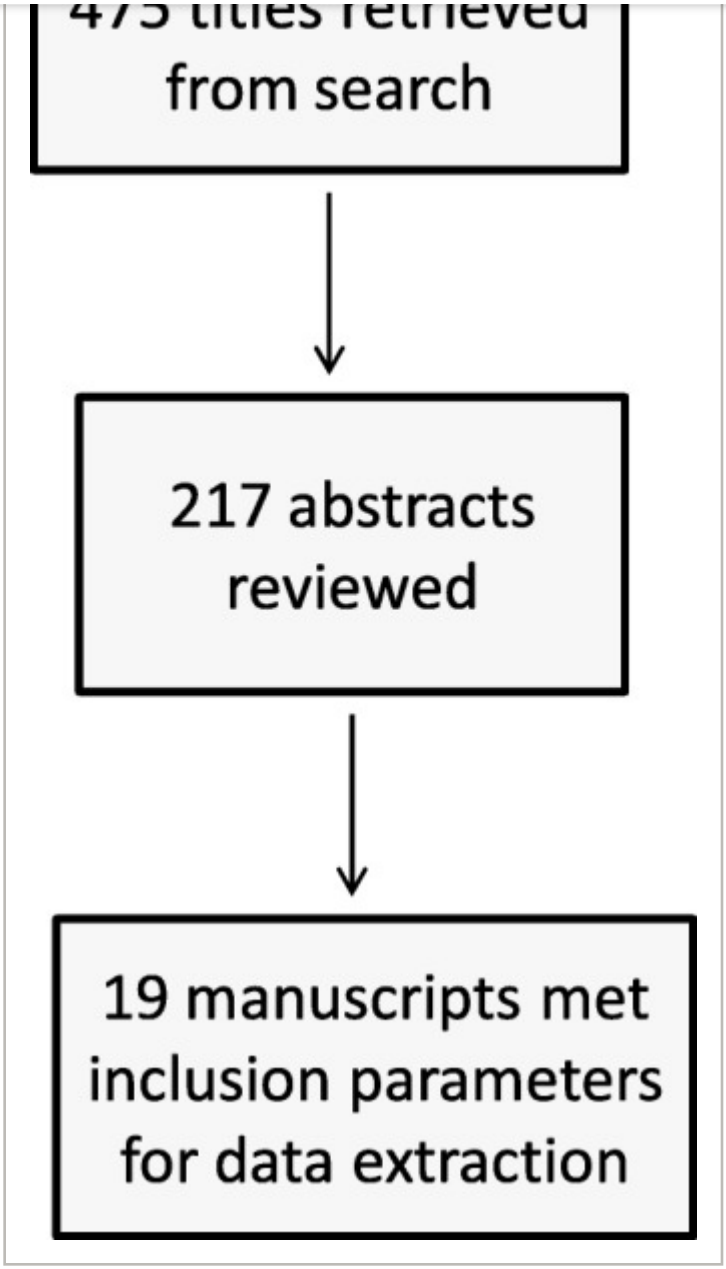

Figure 2

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Quorum diagram for fatigue topic review group.

Caption

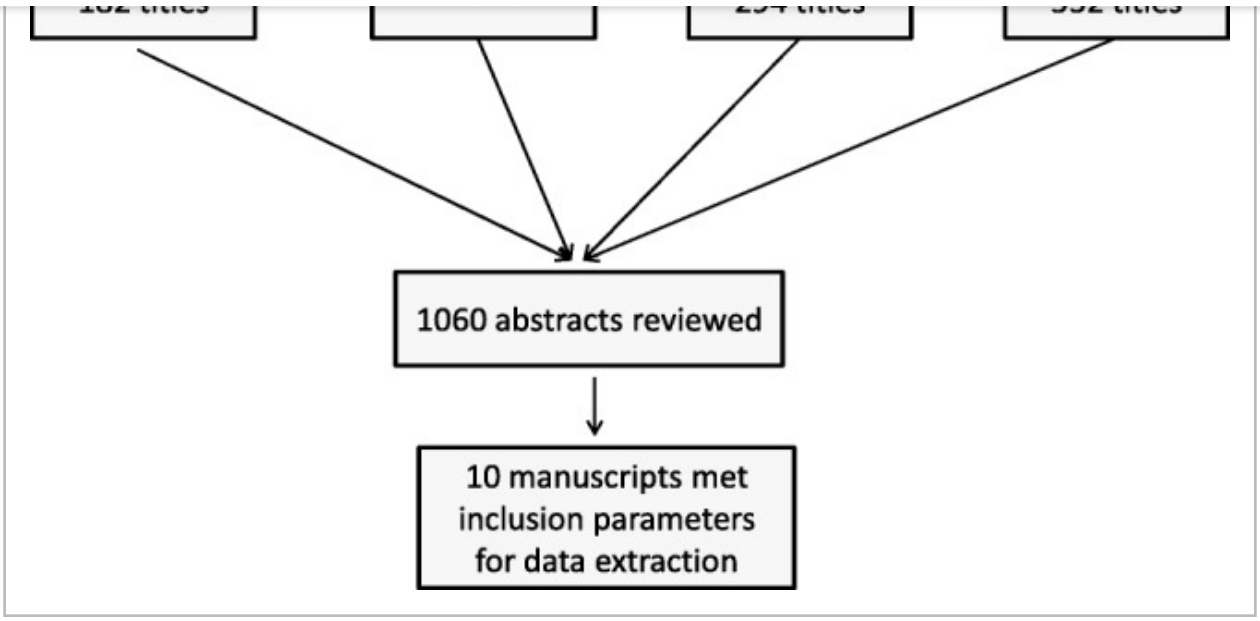

Figure 3

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Quorum diagram for inflammatory musculoskeletal pain topic review group.

Caption

Quality of evidence and strength of recommendation

As presented in the data extraction tables and templates 1 and 2 (see Supplementary Appendix 1B and C available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract), 11 parameters were used t assess evidence quality. These resulted in an overall quality rating for each study. Standardized rating scales according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology were used to assess quality of evidenc (rated as high, moderate, low, or very low) for individual studies and the overall body of evidence for each topic 12. The rating for the overall quality of evidence was the lowest qua rating among the outcomes critical for comparison between interventions. In the absence any data, the quality of evidence was rated as very low, as were all recommendations base case reports, case series, and expert opinion.

The strength of recommendation was rated as strong, moderate, or weak according to the American Society of Clinical Oncology (ASCO) modification of GRADE 13. The ASCO rating s

Guidelines development

Two members of each TRG independently extracted data from selected manuscripts. The guideline protocol worksheet and data extraction tables are available in Supplementary Appendix 1B and C (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract). Studies meeting inclusion/exclusion criteria as developed by each TRG were extracted to record study characteristics, study population, and evidence, and to assess the quality of evidence for ea included study. The data extraction table for quality in Supplementary Appendix 1C and th guideline protocol worksheet template in Supplementary Appendix 1B display the 11 parameters used to assess evidence quality, including an overall quality rating for each stu (available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com /doi/10.1002/acr.22968/abstract). A draft of each guideline recommendation and strength recommendation, accompanied by a clinical rationale, literature review outline, evidence tables, and evidence summary, was then sent electronically to the CEP for voting. Each CEP was composed of 33–41 members, with expertise aligned to the particular guideline topic. Each CEP included practitioners and patients. Achievement of 75% agreement was required approve a guideline recommendation. All CEP comments and agreement percentages were reviewed by the TRG, and draft guidelines were revised as necessary and sent back to the C for revoting (see Supplementary Appendix 1E, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract) until the minimum percent agreement was reached. The maximum number of voting rounds required to achi consensus was 3. If consensus was not achieved after 3 rounds, no recommendation was issued.

Disclosures and management of conflicts of interest

All participants signed ACR conflict of interest forms, and disclosures and/or conflicts of interest were managed in accordance with ACR policy. Conflict of interest statements were revised and reviewed for each working group member on a periodic basis. A conflict of inte was identified if any participant had any relationship with an affected company, regardless the relationship type. No conflicts were identified in the majority (>51%) of all guideline development team members for the duration of the project. The overall CPG chair (project principal investigator) and TRG leaders had no relevant conflicts of interest during the proj The CPG chair was not permitted to vote on any recommendation. Additionally, the TRG leaders were not permitted to vote as members of the CEP on any recommendations they

priority topics, clinical questions, literature reviews, clinical rationales, evidence tables, evidence summaries, additional references, and suggestions for future studies, see Supplementary Appendices 2A–F, 3A–E, and 4A–E (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract).

RESULTS

Biologic therapy for sicca and systemic manifestations of Sjögren's syndrome

After consideration of each literature review, clinical rationale, evidence summary, and recommendation, the clinical practice guidelines consensus panels completed a modified Delphi exercise and reached agreement (e.g., >75% consensus) on the recommendations shown below (Table 1).

Table 1. Recommendations from the biologic topic review group

Recommendation	Stren
1. Tumor necrosis factor (TNF) inhibitors[a]	
TNF inhibitors should not be used to treat sicca symptoms in patients with primary Sjögren's syndrome	Stror
100% agreement in round 1	
2. Tumor necrosis factor inhibitor cautions[b]	
If TNF inhibition therapy is used for rheumatoid arthritis or other related overlap conditions in Sjögren's syndrome patients, health care providers should consider and monitor the following:	Stror
Lymphoma and other malignancies[c]	
Serious infections, including tuberculosis	
Invasive fungal infections	
Hepatitis B reactivation	
Hepatoxicity	
Heart failure	
Cytopenias	

Hypersensitivity, serious infusion reactions

Demyelinating disease

100% agreement in round 1

3. Rituximab for keratoconjunctivitis sicca (KCS)

Rituximab may be considered as a therapeutic option for KCS in patients with primary Sjögren's syndrome and for whom conventional therapies, including topical moisturizers, secretagogues, antiinflammatories, immunomodulators, and punctual occlusion, have proven insufficient — Wea

75% agreement in round 2

4. Rituximab for xerostomia

Rituximab may be considered as a therapeutic option for xerostomia in patients with primary Sjögren's syndrome with some evidence of residual salivary production, significant evidence of oral damage as determined by the clinician, and for whom conventional therapies, including topical moisturizers and secretagogues, have proven insufficient — Wea

87.1% agreement in round 3

5. Rituximab for systemic symptoms[d]

Rituximab may be considered as a therapeutic option for adults with primary Sjögren's syndrome and any or all of the following systemic manifestations: — Moder

Cryoglobulinemia associated with vasculitis

Vasculitis

Severe parotid swelling

Inflammatory arthritis

Pulmonary disease

Peripheral neuropathy, especially mononeuritis

96.9% agreement in round 2

6. Rituximab cautions[e]

Patients and health care providers should be aware that, although uncommon, significant harms may be — Stror

associated with the use of rituximab and should exercise caution and observe for the following when using rituximab in Sjögren's syndrome patients:

- Infusion reactions
- Tumor lysis syndrome in those with non-Hodgkin's lymphoma
- Progressive multifocal leukoencephalopathy
- Hepatitis B reactivation with possible fulminant hepatitis
- Severe mucocutaneous reactions
- Infections
- Bowel obstruction and perforation
- Cardiac arrhythmias and angina
- Cytopenias
- Serious bacterial, viral, or fungal infections
- In pregnancy and nursing, the risk vs. benefit must be carefully considered
- Health care providers should avoid giving live vaccines when patients are taking rituximab

100% agreement in round 1

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a This recommendation should not be interpreted to discourage use of TNF inhibitors in situations where there is overlap of Sjögren's syndrome with RA or other conditions where TNF inhibition therap is indicated for the treatment of inflammatory arthritis.

b Patients and physicians should refer to the Food and Drug Administration (FDA) label for additiona information.

c Health care providers should be cognizant that patients with primary Sjögren's syndrome have an increased risk of non-Hodgkin's lymphoma as compared to the general population.

d These patients should have had a suboptimal response to standard oral disease-modifying antirheumatic drug agents and/or have experienced unacceptable toxicity from these agents or corticosteroids or are incapable of tapering and discontinuing corticosteroids.

e Patients and physicians should refer to the FDA label for additional information.

syndrome. This recommendation is based on a small controlled trial 14 and a multicenter r 15. If TNF inhibition therapy is used for rheumatoid arthritis (RA) or other related overlap conditions in Sjögren's syndrome patients, health care providers should consider and mon for toxicities listed in Table 1. Despite theoretical concerns regarding lymphoma in Sjögren syndrome, there is no evidence that the subset of RA patients with Sjögren's syndrome wh have been treated with anti-TNF agents have an increased incidence of lymphoma. Therefc this recommendation should not be interpreted to discourage use of TNF inhibitors in situations where there is overlap with RA or where TNF inhibition therapy is indicated for th treatment of inflammatory arthritis.

Rituximab

Rituximab may be considered as a therapeutic option for keratoconjunctivitis sicca in patie with primary Sjögren's syndrome and for whom conventional therapies, including topical moisturizers, secretagogues, antiinflammatory agents, immunomodulators, and punctual occlusion, have proven insufficient. Rituximab may be considered as a therapeutic option f xerostomia in patients with primary Sjögren's syndrome with some evidence of residual salivary production and significant evidence of oral damage, as determined by the clinician and for whom conventional therapies, including topical moisturizers and secretagogues, ha proven insufficient. Although a recent RCT did not meet a composite of primary end points (pain, fatigue, sicca symptoms, and global improvement), these recommendations are base on data from analysis of secondary outcome measures 16 and a smaller RCT 17.

Rituximab may be considered as a therapeutic option for adults with primary Sjögren's syndrome and any or all of the following systemic manifestations: vasculitis, with or withou cryoglobulinemia, severe parotid swelling, inflammatory arthritis, pulmonary disease, and peripheral neuropathy, especially mononeuritis multiplex. This recommendation is based o nonrandomized comparator trial 18 and case reports and series, which reported on end-or outcomes for a total of 175 patients as well as registry studies 19, 20. The recommendation also based on extrapolation of the use of rituximab in other rheumatologic conditions, including RA and vasculitis. Overall, the quality of evidence was low, and the moderate strength of recommendation was based on expert opinion, with CEP agreement reaching 9 for this recommendation. Significant risks may be associated with the use of rituximab, and clinicians should exercise caution and monitor Sjögren's syndrome patients closely for the toxicities listed in Table 1.

Guideline recommendations for the management of fatigue in Sjögren's syndrome

Sjögren's syndrome (Table 2). These measures have been demonstrated to reduce fatigue RA 21, systemic lupus erythematosus (SLE) 22-24, and multiple sclerosis 25, as well as in 1 small RCT in Sjögren's syndrome 26.

Table 2. Recommendations from the fatigue topic review group

Recommendation	Stren
1. Exercise	
Education about self-care measures should include advice about exercise to reduce fatigue in Sjögren's syndrome	Stro
100% agreement in round 1	
2. Dehydroepiandrosterone (DHEA)	
DHEA is not recommended for treatment of fatigue in Sjögren's syndrome	Stro
90.2% agreement in round 1	
3. Hydroxychloroquine	
Hydroxychloroquine may be considered in selected situations to treat fatigue in Sjögren's syndrome	Wea
94.4% agreement in round 2	
4. Tumor necrosis factor inhibitors	
Neither etanercept nor infliximab is recommended for treatment of fatigue in Sjögren's syndrome	Stro
97.4% agreement in round 1	

Hydroxychloroquine (HCQ)

HCQ may be considered in selected situations to treat fatigue in Sjögren's syndrome. This approach is largely based on experience in patients with systemic lupus and a 1996 uncontrolled, retrospective study 27 that reported improvement of fatigue in roughly one-third of Sjögren's syndrome patients treated with HCQ. This study evaluated patients with a elevated erythrocyte sedimentation rate (ESR) or other extraglandular manifestations (e.g., arthralgias, rash, and lymphadenopathy). A subsequent RCT failed to verify this initial

used for fatigue" to the current recommendation that "HCQ may be considered in selected situations to treat fatigue" resulted in a nearly 30% increase in agreement in the Delphi consensus process. Although quality of the overall body of evidence was rated as very low, CEP members cited clinical experience with HCQ and a favorable safety profile in this settir as reasons for considering HCQ in Sjögren's syndrome patients with fatigue.

Other treatments

Dehydroepiandrosterone (DHEA) is not recommended for treatment of fatigue in Sjögren's syndrome. This conclusion is based on 2 well-designed RCTs in Sjögren's syndrome patient showing no difference between DHEA and placebo 29, 30. Neither of the TNF inhibitors etanercept or infliximab is recommended for treatment of fatigue in Sjögren's syndrome 1 15. Newer biologic agents, in the opinion of the TRG, have insufficient data and/or clinical experience to make a recommendation regarding the use of anakinra 31, abatacept 32, belimumab 33, and epratuzumab 34 for fatigue in Sjögren's syndrome.

Guideline recommendations for the use of DMARDS for inflammatory MSK pa

The recommendation for the use of DMARDs for inflammatory MSK pain is presented as a decision tree (Table 3). Inflammatory MSK pain largely comprises symptoms related to nonerosive synovitis, polyarthritis, and inflammatory myositis. The first-line treatment for inflammatory MSK pain in primary Sjögren's syndrome should be HCQ. While a recent RCT did not meet the end point for pain, the moderate strength of recommendation and 95% agreement of the CEP is based on the significant reported improvement in inflammatory markers following use of HCQ 27, 28, 35, 36, improvement of MSK pain in other studies 27, 37, and the favorable safety profile of HCQ compared to other DMARDs. If HCQ is not effec in the treatment of inflammatory MSK pain in primary Sjögren's syndrome, methotrexate alone may be considered. This recommendation received 92% agreement from the CEP an was based on extrapolation from long-term experience in RA and SLE as well as 2 studies i Sjögren's syndrome 37, 38. Quality rating for the overall body of evidence for recommendations 1 and 2 was low, and was very low for the remaining recommendations.

Table 3. Recommendations from the inflammatory musculoskeletal pain topic review grou

Recommendation	Stren
1. Hydroxychloroquine (HCQ)	

A first line of treatment for inflammatory musculoskeletal pain in primary Sjögren's syndrome should be HCQ 94.4% agreement in round 1	Moder
2. Methotrexate (MTX) OR recommendation 3 below	
If HCQ is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's syndrome, MTX alone may be considered 91.6% agreement in round 1	Moder
3. HCQ plus MTX	
If either HCQ or MTX alone is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's syndrome, HCQ plus MTX may be considered 88.9% agreement in round 1	Moder
4a. Short-term corticosteroids	
If HCQ plus MTX is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's syndrome, short-term (≤1 month) corticosteroids of ≤15 mg/day may be considered 97.2% agreement in round 1	Stror
4b. Long-term corticosteroids	
Long-term (>1 month) ≥15 mg/day corticosteroids may be useful in the management of inflammatory musculoskeletal pain in primary Sjögren's syndrome, but efforts should be made to find a steroid-sparing agent as soon as possible. 91.4% agreement in round 1	Moder
5. Leflunomide[a]	
If HCQ and/or MTX or short-term (≤1 month) corticosteroids are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's syndrome, leflunomide may be considered 80% agreement round 1	Wea
6. Sulfasalazine[a]	
If HCQ and/or MTX, corticosteroids, or leflunomide (Arava) are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's syndrome, sulfasalazine may be considered	Wea

85.3% agreement round 1

7. Azathioprine[a]		
If HCQ and/or MTX, corticosteroids, leflunomide, or sulfasalazine are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's syndrome, azathioprine may be considered 86.1% agreement in round 1		Wea
8. Azathioprine		
If major organ involvement occurs in the primary Sjögren's syndrome patient, azathioprine may be a better choice than leflunomide or sulfasalazine for the treatment of all extra glandular manifestations, including inflammatory musculoskeletal pain 91.7% agreement in round 1		Moder
9. Cyclosporine[b]		
If HCQ and/or MTX, corticosteroids, leflunomide, azathioprine, or sulfasalazine are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's syndrome, cyclosporine may be considered 78.4% agreement in round 1		Wea

a These 3 recommendations are numbered in order of the preference and experience of the topic review group (TRG). However, the TRG is grouping these together to allow the physician to choose any of the following and in any order based on that physician's experience and the individual patient.

b Few physicians have noted experience with cyclosporine in Sjögren's, and many have stated a greater level of experience with and a preference for using a biologic agent in place of cyclosporine.

If either HCQ or methotrexate alone is not effective in the treatment of inflammatory MSK in primary Sjögren's syndrome, HCQ plus methotrexate may be considered. If HCQ plus methotrexate is not effective in the treatment of inflammatory MSK pain in primary Sjögrer syndrome, short-term (1 month or less) corticosteroids of ≤15 mg/day may be considered (agreement). Long-term (more than 1 month) ≥15 mg/day corticosteroids may be useful in t management of inflammatory MSK pain in primary Sjögren's syndrome, but efforts should made to find a steroid-sparing agent as soon as possible. If HCQ and/or methotrexate or

inflammatory MSK pain in primary Sjögren's syndrome, sulfasalazine may be considered. If HCQ and/or methotrexate, corticosteroids, leflunomide, or sulfasalazine are not effective in the treatment of inflammatory MSK pain in primary Sjögren's syndrome, azathioprine may considered. There was strong agreement (92%) among the CEP that if major organ involvement occurs in the primary Sjögren's syndrome patient, azathioprine would be a be choice than leflunomide or sulfasalazine for the treatment of all extraglandular manifestations, including inflammatory MSK pain. If none of the above agents are effective the treatment of inflammatory MSK pain in primary Sjögren's syndrome, cyclosporine may considered.

DISCUSSION

Among all chronic autoimmune rheumatic disorders, Sjögren's syndrome remains one of t most difficult to manage. Development of CPGs for the ocular 39, oral 40, and systemic/rheumatologic manifestations should substantially improve the quality and consistency of care, guide reimbursement policies, and decrease the overall burden of illne At the present time, no curative or remittive agent exists. Thus, therapeutic goals remain symptom palliation, improved quality of life, prevention of damage, and appropriate select of patients for immunosuppressive therapy.

Several obstacles made the assessment of studies and the overall guidelines development process challenging, including the changing disease definitions and/or classification criteria Sjögren's syndrome over time, a relative paucity of large randomized clinical trials, changin outcome measures, and the large number of null trials. We therefore decided a priori that be included for data extraction, a study was required to meet any published Sjögren's syndrome classification criteria set. A list of acceptable outcome measures for each organ system was defined by the relevant TRG prior to data abstraction. Even with the above measures instituted, a lack of consistent high-quality evidence in the medical literature necessitated use of a modified Delphi process.

The analysis of Sjögren's syndrome trial data revealed many important observations. First, there is no standard for clinically meaningful improvement. It is also difficult to distinguish between disease activity and damage, and therefore it is challenging to identify active case achieve a meaningful response. The heterogeneity of the disease group also makes it diffic to recruit patient populations to study single primary end points. Therefore, the composite indices or multiple parameters that are usually studied simultaneously to circumvent this

Index 42 have been validated. Future use of these, as well as others in development (e.g., Sjögren's Syndrome Responder Index [SSRI]) 43, coupled with discovery of novel biomarker will help to resolve these issues.

For the majority of patients with Sjögren's syndrome, the burdens of cost and potential sid effects of biologic therapy, at the present time, still outweigh the potential benefits, as demonstrated by the evidence. Among the available biologic agents studied in Sjögren's syndrome to date, some evidence exists that rituximab has benefits for certain extraglandu manifestations and sicca signs and symptoms 17. The guidelines recommend this treatmer approach for Sjögren's syndrome patients with internal organ or systemic involvement, bu only for those individuals who have already failed DMARDS and/or corticosteroids due to la of efficacy or unacceptable toxicity. Similarly, the decision to use a biologic agent such as rituximab to treat dry eyes and/or dry mouth would only be appropriate in severe cases an with the necessary input from the patient's ocular and/or oral medicine specialist. The recommendation for possible use of rituximab for keratoconjunctivitis sicca parallels a sim recommendation made independently by the SSF ophthalmology CPG 39. Yet since the full degree of therapeutic benefit remains unclear, this option is only recommended after care consideration of the risk/benefit ratio. Therefore the strength of this recommendation was rated as weak.

Recently, the largest controlled trial of rituximab to date (TEARS trial) failed to meet a composite of primary end points at 6 months 44. However, a statistically significant benefit versus placebo was noted for certain individual parameters (e.g., fatigue, sicca symptoms, a global improvement) at the 6-month interval and/or other time points. TEARS highlights the key issues in Sjögren's syndrome trial design, patient selection, outcome measures, and biologic treatment regimens noted above. Recently, Cornec et al 43, derived an SSRI using positive end points from TEARS. The SSRI quantitated the proportion of subjects demonstrating ≥30% improvement in 2 of 5 on a visual analog scale for ocular dryness, ora dryness, and fatigue, as well as unstimulated whole salivary flow and ESR. In this post hoc analysis, a statistically significant improvement in the SSRI was observed in the rituximab-treated subjects versus placebo.

Evidence from a limited number of studies suggests that TNF inhibitors do not ameliorate s symptoms or other manifestations in established Sjögren's syndrome 14, 15, 45. However, whether this conclusion would change if clinical trials were conducted in very early disease not currently known. In addition, the CEP emphasized that the proposed guideline

Fatigue remains one of the most difficult management dilemmas in Sjögren's syndrome 46 The CPG committee emphasized that causes of fatigue in Sjögren's syndrome are numerou therefore necessitating a comprehensive diagnostic evaluation. Currently, the only strong therapeutic recommendation for fatigue in Sjögren's syndrome is exercise 26. This recommendation provides the same benefit as seen for patients in other rheumatic diseas groups.

Among pharmacologic therapies, HCQ remains the most widely prescribed treatment in th to manage fatigue in Sjögren's syndrome. This practice is largely based on results of uncontrolled studies and clinical experience, since evidence of benefit in placebo-controlle trials is lacking. Thus, the rating for quality of the overall body of evidence was very low and the strength of the recommendation was weak. Nevertheless, the panel felt that additional studies with different patient selection parameters, longer duration of therapy, and alterna outcome measures are needed before concluding that use of HCQ should be precluded in setting.

The spectrum of inflammatory MSK pain in Sjögren's syndrome patients ranges from mild arthralgias and myalgias to frank synovitis with chronic pain 47. In devising a treatment algorithm for this indication, the TRG adopted a sequential approach. Recommendations fo agents deemed to have similar efficacy and safety profiles were grouped together to allow clinician to choose a particular treatment based on his or her clinical experience and the circumstances of the individual patient. The TRG was unable to find high-quality evidence t support the use of DMARDs for this indication and therefore labeled the quality of evidenc for each DMARD guideline as low or very low, depending on the agent. Thus, recommendations were formulated largely based on expert opinion as guided by a modifie Delphi consensus process. In certain instances, however, the strength of a recommendatio was ultimately rated as moderate or strong because the TRG and CEP both agreed with a moderate to high level of confidence that the guideline recommendation reflected best current practice.

Although HCQ remains the first-line therapy for inflammatory MSK pain in Sjögren's syndrc clinicians may choose other DMARDS in certain situations or in more severe cases where th perceived benefits outweigh the risk of increased toxicity. These clinical scenarios include HCQ-responsive patients who must discontinue this therapy due to toxicity or an adverse effect, patients with an inadequate response to HCQ, patients with severe steroid-responsi MSK pain and persistent symptoms who require another DMARD for steroid-sparing effect

disease with many unmet clinical needs. CPGs were developed for the oral 40, ocular 39, ar rheumatologic/systemic manifestations of Sjögren's syndrome to inform clinicians' management of patients in the US population. In addition, this process has defined the nee for future study in many areas (see future directions for research in Supplementary Appen 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com /doi/10.1002/acr.22968/abstract), including new outcome measures, targeted therapies for disease-specific manifestations, and the development of novel biomarkers to identify early treatment-responsive patients for participation in clinical trials. Guidelines will be revised a new studies are published.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellect content, and all authors approved the final version to be submitted for publication. Dr. Carsons had full access to all of the data in the study and takes responsibility for the integr of the data and the accuracy of the data analysis.

Acquisition of data

Carsons, Vivino, Parke, Carteron, Sankar, Brasington, Brennan, Ehlers, Fox, Schofield, Birnbaum, Kassan, Mandel.

Analysis and interpretation of data

CLINICAL PRACTICE GUIDELINES COMMITTEE AND WORKING GROUPS

In addition to the authors, Elaine Alexander, MD, PhD (deceased), contributed to the Rheumatology and Systemic Disease Working Group. Topic review groups were as follows: (Biologic Therapy for Sicca Symptoms) co-chair Vidya Sankar, co-chair Steven E. Carsons, Na Carteron, William Ehlers, Michael T. Brennan; (Biologic Therapy for Systemic Disease) co-ch Nancy Carteron, co-chair Steven E. Carsons; (Fatigue) co-chair R. Hal Scofield, co-chair Robe Fox; (DMARDs and Inflammatory Musculoskeletal Pain) chair Frederick B. Vivino, Ann Parke Richard Brasington. Members of the consensus expert panels below served on at least one panel for the recommendations in this article, and many served on all of the panels.

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