UC Berkeley

UC Berkeley Previously Published Works

Title

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

Permalink

https://escholarship.org/uc/item/8cx2r5z3

Journal

Arthritis Care & Research, 69(4)

ISSN

2151-464X

Authors

Carsons, Steven E

Vivino, Frederick B

Parke, Ann

et al.

Publication Date

2017-04-01

DOI

10.1002/acr.22968

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at https://creativecommons.org/licenses/by/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Arthritis Care & Research
Vol. 69, No. 4, April 2017, pp 517–527
DOI 10.1002/acr.22968
© 2016, American College of Rheumatology

ORIGINAL ARTICLE

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

STEVEN E. CARSONS,[1] FREDERICK B. VIVINO,[2] ANN PARKE,[3] NANCY CARTERON,[4] VIDYA SANKAR,[5] RICHARD BRASINGTON,[6] MICHAEL T. BRENNAN,[7] WILLIAM EHLERS,[8] ROBERT FOX,[9] HAL SCOFIELD,[10] KATHERINE M. HAMMITT,[11] JULIUS BIRNBAUM,[12] STUART KASSAN,[13] AND STEVEN MANDEL[14]

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 posed 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 extraction and drafted guidelines. Quality of evidence and strength of recommendation were rated using the American Society of Clinical Oncology's modification of the Grading of Recommendations Assessment, Development, and Evaluation. Guideline recommendations 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 adoption 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 and 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, including 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 autoimmune rheumatic disorder that affects up to 3.1 million Americans (1). The prevalence doubles when including those with an additional connective tissue disease. The disease is associated with a 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

Supported by the Sjögren's Syndrome Foundation.
[1]Steven E. Carsons, MD: Winthrop-University Hospital Campus, State University of New York, Stony Brook, Mineola; [2]Frederick B. Vivino, MD: University of Pennsylvania, Philadelphia; [3]Ann Parke, MD: University of Connecticut Health Center, Farmington; [4]Nancy Carteron, MD: University of California at San Francisco; [5]Vidya Sankar, DMD: University of Texas San Antonio Dental School, San Antonio; [6]Richard Brasington, MD: Washington University, St. Louis, Missouri; [7]Michael T. Brennan, DDS: Carolinas Medical Center, Charlotte, North Carolina; [8]William Ehlers, MD: University of Connecticut Health Center, Farmington; [9]Robert Fox, MD: Scripps Memorial Hospital Xi-Med, La Jolla, California; [10]Hal Scofield, MD: University of Oklahoma Health Sciences Center, Oklahoma Medical Research Foundation, and Oklahoma City Department of Veterans Affairs Medical Center, Oklahoma City; [11]Katherine M. Hammitt, MA: Sjögren's Syndrome Foundation, Bethesda, Maryland; [12]Julius Birnbaum, MD: Johns Hopkins University, Baltimore, Maryland; [13]Stuart Kassan, MD: University of Colorado, Denver; [14]Steven Mandel, MD: Lenox Hill Hospital, New York, and Hofstra Northwell School of Medicine, Hempstead, New York.

Dr. Carsons has received consulting fees from Biogen Idec, honoraria from NS-LIJ Health Systems, and serves on the

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Significance & Innovations

- First description of US clinical practice guidelines for primary Sjögren's syndrome.
- Includes recommendations for the use of biologic agents, and management of fatigue and inflammatory musculoskeletal pain.

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 and physician requests for guidance.

The primary goal of the SSF initiative was to improve the quality and value of care in Sjögren's 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 clinicians. 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 staffed 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 the 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 second major rheumatic/autoimmune disease (or primary Sjögren's syndrome as it traditionally has been referred to). While guideline recommendations provide a rational approach to various 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 a 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.

advisory board for Nicox (less than $10,000 each). Dr. Vivino has received consulting fees from Biogen Idec, Nicox, Immco Diagnostics, and Takeda (less than $10,000 each). Dr. Parke has received consulting fees from UCB, GSK, and Biogen Laboratories (less than $10,000 each). Dr. Carterton has received consulting fees from Valeant Pharmaceuticals (less than $10,000), owns stock in Genentech/Roche, receives book royalties from Penguin and from Taylor and Francis Group, and is on the board of directors of Healthwell Foundation. Dr. Brasington has received consulting fees from Pfizer (less than $10,000) and has an immediate family member who owns stock in Amgen. Dr. Fox has received consulting fees from UCB, Takeda, and Pfizer (less than $10,000 each), and has received consulting fees from Allergan (more than $10,000). Dr. Scofield has received consulting fees from UCB and honoraria from Eli Lilly (less than $10,000 each).

Address correspondence to Steven E. Carsons, MD, Division of Rheumatology, Allergy and Immunology, Winthrop University Hospital, 120 Mineola Boulevard, Suite 410 Mineola, NY 11501. E-mail: scarsons@winthrop.org.

Submitted for publication December 19, 2015; accepted in revised form June 21, 2016.

MATERIALS AND METHODS

Principles. The SSF CPG committee adopted the principles of the Appraisal of Guidelines for Research and Evaluation, an international appraisal instrument for assessing guidelines quality (10,11). One of the most important and overriding principles during the project was that physician and patient priorities be taken into consideration at the outset of this process. All key stakeholders, including patients, practicing and academic rheumatologists, and the SSF as a patient advocacy organization, were included in the guidelines development initiative. Surveys of patient priorities were conducted during an SSF National Patient Conference and through use of SSF 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 Professor 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 narrowed to 16 topics (see Supplementary Appendix 1A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract) that were ranked by vote of the working group. Significance was rated on a 1–5 Likert scale (where 1 = possibly important 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 the 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

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

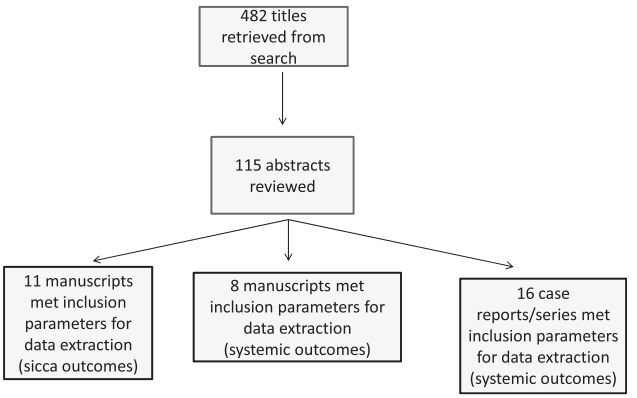

Figure 1. Quorum diagram for biologic topic review group.

management strategies for fatigue? Each topic question was assigned to a topic review group (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 rheumatologists. 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 using MEDLINE/PubMed and the Cochrane database to search for peer-reviewed articles published in English between January 1, 1988 and April 13, 2015. Literature search results for each topic are summarized by the quorum diagrams (Figures 1–3). Individual search strategies, inclusion 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 non-Hodgkin's lymphoma, but intervention studies must have been primarily designed to measure outcomes related to primary Sjögren's syndrome. Acceptable end point measures were decided a priori by TRG consensus and were used to build worksheets for data extraction. Studies reviewed included meta-analyses, systematic reviews, and randomized controlled 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 2. Quorum diagram for fatigue topic review group.

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 to 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 evidence (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 quality rating among the outcomes critical for comparison between interventions. In the absence of any data, the quality of evidence was rated as very low, as were all recommendations based on 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 scale and terms used for strength of recommendation can be found in Supplementary Appendix 1D (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract).

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

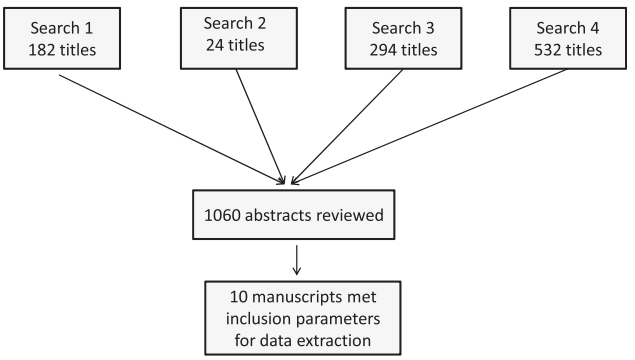

Figure 3. Quorum diagram for inflammatory musculoskeletal pain topic review group.

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1. Recommendations from the biologic topic review group

Recommendation	Strength
1. Tumor necrosis factor (TNF) inhibitors*	
TNF inhibitors should not be used to treat sicca symptoms in patients with primary Sjögren's syndrome	Strong
100% agreement in round 1	
2. Tumor necrosis factor inhibitor cautions†	
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:	Strong
Lymphoma and other malignancies‡	
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	Weak
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	Weak
87.1% agreement in round 3	
5. Rituximab for systemic symptoms§	
Rituximab may be considered as a therapeutic option for adults with primary Sjögren's syndrome and any or all of the following systemic manifestations:	Moderate
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¶	
Patients and health care providers should be aware that, although uncommon, significant harms may be associated with the use of rituximab and should exercise caution and observe for the following when using rituximab in Sjögren's syndrome patients:	Strong
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	

* 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 therapy is indicated for the treatment of inflammatory arthritis.
† Patients and physicians should refer to the Food and Drug Administration (FDA) label for additional information.
‡ 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.
§ 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.
¶ Patients and physicians should refer to the FDA label for additional information.

(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 each included study. The data extraction table for quality in Supplementary Appendix 1C and the guideline protocol worksheet template in Supplementary Appendix 1B display the 11 parameters used to assess evidence quality, including an overall quality rating for each study (available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22968/abstract). A draft of

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

each guideline recommendation and strength of 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 to 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 CEP 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 achieve 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 interest was identified if any participant had any relationship with an affected company, regardless of 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 project. 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 drafted.

For more detailed information on the Sjögren's syndrome CPG development process, including 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).

Tumor necrosis factor (TNF) inhibitors. TNF inhibitors should not be used to treat sicca symptoms in patients with primary Sjögren's syndrome. This recommendation is based on a small controlled trial (14) and a multicenter RCT (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 monitor for toxicities listed in Table 1. Despite theoretical concerns regarding lymphoma in Sjögren's syndrome, there is no evidence that the subset of RA patients with Sjögren's syndrome who have been treated with anti-TNF agents have an increased incidence of lymphoma. Therefore, 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 the treatment of inflammatory arthritis.

Table 2. Recommendations from the fatigue topic review group

Recommendation	Strength
1. Exercise	
Education about self-care measures should include advice about exercise to reduce fatigue in Sjögren's syndrome	Strong
100% agreement in round 1	
2. Dehydroepiandrosterone (DHEA)	
DHEA is not recommended for treatment of fatigue in Sjögren's syndrome	Strong
90.2% agreement in round 1	
3. Hydroxychloroquine	
Hydroxychloroquine may be considered in selected situations to treat fatigue in Sjögren's syndrome	Weak
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	Strong
97.4% agreement in round 1	

Rituximab. Rituximab may be considered as a therapeutic option for keratoconjunctivitis sicca in patients 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 for 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, have 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 based 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 without cryoglobulinemia, severe parotid swelling, inflammatory arthritis, pulmonary disease, and peripheral neuropathy, especially mononeuritis multiplex. This recommendation is based on a nonrandomized comparator trial (18) and case reports and series, which reported on end-organ outcomes for a total of 175 patients as well as registry studies (19,20). The recommendation is 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

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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

Recommendation	Strength
1. Hydroxychloroquine (HCQ)	
A first line of treatment for inflammatory musculoskeletal pain in primary Sjögren's syndrome should be HCQ	Moderate
94.4% agreement in round 1	
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	Moderate
91.6% agreement in round 1	
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	Moderate
88.9% agreement in round 1	
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	Strong
97.2% agreement in round 1	
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.	Moderate
91.4% agreement in round 1	
5. Leflunomide*	
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	Weak
80% agreement round 1	
6. Sulfasalazine*	
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	Weak
83.3% agreement round 1	
7. Azathioprine*	
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	Weak
86.1% agreement in round 1	
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	Moderate
91.7% agreement in round 1	
9. Cyclosporine†	
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	Weak
78.4% agreement in round 1	

* 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.
† 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.

the moderate strength of recommendation was based on expert opinion, with CEP agreement reaching 97% 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. *Self-care measures.* Education about self-care measures should include advice about exercise to reduce fatigue in Sjögren's syndrome (Table 2). These measures have been demonstrated to reduce fatigue in RA (21), systemic lupus erythematosus (SLE) (22–24), and multiple sclerosis (25), as well as in 1 small RCT in Sjögren's syndrome (26).

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 an elevated erythrocyte sedimentation rate (ESR) or other extraglandular manifestations (e.g., arthralgias, rash, and lymphadenopathy). A subsequent RCT failed to verify this initial observation but was of relatively short duration (28). Nonetheless, comments from the CEP from rounds 1 and 2 demonstrated strong support for maintaining an option for use of HCQ for fatigue. A change of recommendation from the former statement: "HCQ should not be used for fatigue" to the current

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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, the CEP members cited clinical experience with HCQ and a favorable safety profile in this setting 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 patients 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 (14,15). 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 pain. 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 (28) 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 (27,35,37), and the favorable safety profile of HCQ compared to other DMARDs. If HCQ is not effective 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 and was based on extrapolation from long-term experience in RA and SLE as well as 2 studies in 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.

If either HCQ or methotrexate alone is not effective in the treatment of inflammatory MSK pain 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 Sjögren's syndrome, short-term (1 month or less) corticosteroids of ≤15 mg/day may be considered (97% agreement). Long-term (more than 1 month) ≥15 mg/day corticosteroids may be useful in the management of inflammatory MSK pain in primary Sjögren's syndrome, but efforts should be made to find a steroid-sparing agent as soon as possible. If HCQ and/or methotrexate or short-term (≤1 month) corticosteroids are not effective in the treatment of inflammatory MSK pain in primary Sjögren's syndrome, leflunomide may be considered. If HCQ and/or methotrexate, corticosteroids, or leflunomide are not effective in the treatment of 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 be 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 better choice than leflunomide or sulfasalazine for the treatment of all extraglandular manifestations, including inflammatory MSK pain. If none of the above agents are effective in the treatment of inflammatory MSK pain in primary Sjögren's syndrome, cyclosporine may be considered.

DISCUSSION

Among all chronic autoimmune rheumatic disorders, Sjögren's syndrome remains one of the 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 illness. 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 selection 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 for Sjögren's syndrome over time, a relative paucity of large randomized clinical trials, changing outcome measures, and the large number of null trials. We therefore decided a priori that to 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 cases to achieve a meaningful response. The heterogeneity of the disease group also makes it difficult 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 problem also inherently limit the power of the study. Until recently, none of the composite outcome measures in use except for the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (41) and EULAR Sjögren's Syndrome Patient Reported 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 biomarkers will help to resolve these issues.

For the majority of patients with Sjögren's syndrome, the burdens of cost and potential side effects of biologic therapy, at the present time, still outweigh the potential

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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 extraglandular manifestations and sicca signs and symptoms (17). The guidelines recommend this treatment approach for Sjögren's syndrome patients with internal organ or systemic involvement, but only for those individuals who have already failed DMARDS and/or corticosteroids due to lack 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 and 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 similar 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 careful 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, and 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, oral 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 sicca 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 is not currently known. In addition, the CEP emphasized that the proposed guideline recommendations do not preclude the use of TNF alpha inhibitors in Sjögren's syndrome patients with overlapping features of RA or in situations where TNF inhibition is otherwise indicated for the treatment of another inflammatory illness.

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 numerous, 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 disease groups.

Among pharmacologic therapies, HCQ remains the most widely prescribed treatment in the US 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-controlled 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 alternate outcome measures are needed before concluding that use of HCQ should be precluded in this 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 for agents deemed to have similar efficacy and safety profiles were grouped together to allow the 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 to support the use of DMARDs for this indication and therefore labeled the quality of evidence 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 modified Delphi consensus process. In certain instances, however, the strength of a recommendation 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 syndrome, clinicians may choose other DMARDS in certain situations or in more severe cases where the 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-responsive MSK pain and persistent symptoms who require another DMARD for steroid-sparing effect, and patients with objective evidence of synovitis.

In summary, Sjögren's syndrome remains a highly prevalent, chronic autoimmune rheumatic disease with many unmet clinical needs. CPGs were developed for the oral (40), ocular (39), and rheumatologic/systemic manifestations of Sjögren's syndrome to inform clinicians' management of patients in the US population. In addition, this process has defined the need for future study in many areas (see future directions for research in Supplementary Appendix 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 or treatment-responsive patients for participation in clinical trials. Guidelines will be revised as new studies are published.

ACKNOWLEDGMENTS

The SSF recognizes the guidance provided by the ACR, especially ACR Senior Director of Quality, Amy Miller, and ACR Quality of Care members Drs. Liana Fraenkel, Kenneth Saag,

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

and Ted Mikuls. The SSF also thanks the over 100 volunteers who have participated to date, including guideline methodologists, rheumatologists, nurses, other professional specialists who were included as needed, and Sjögren's syndrome patients and the university librarians experienced in literature searches for guidelines who contributed to this initiative. The authors thank Dr. Barbara Segal for her contributions to the fatigue topic review group. We also thank Patricia Hurley, MSc, as our methodology consultant, and Dr. Holger Schünemann for his expert advice regarding GRADE methodology. The authors acknowledge the invaluable contributions of Dr. Elaine Alexander (deceased). We thank Ms. Debra Famigletti for assistance in preparation of the manuscript.

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 submitted for publication. Dr. Carsons 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.

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

Analysis and interpretation of data. Carsons, Vivino, Parke, Carteron, Sankar, Brasington, Brennan, Ehlers, Fox, Scofield, Hammitt.

REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al, for the National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part I. Arthritis Rheum 2008;58:15–25.
2. Strömbeck B, Ekdahl C, Manthorpe R, Wikström I, Jacobsson L. Health-related quality of life in primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. Scand J Rheumatol 2000;29:20–8.
3. Valtýsdóttir ST, Gudbjörnsson B, Lindqvist U, Hällgren R, Hetta J. Anxiety and depression in patients with primary Sjögren's syndrome. J Rheumatol 2000;27:165–9.
4. Segal B, Bowman SJ, Fox PC, Vivino FB, Murukutla N, Brodscholl J, et al. Primary Sjögren's syndrome: health experiences and predictors of health quality among patients in the United States. Health Qual Life Outcomes 2009;7:46.
5. Bowman SJ, St Pierre Y, Sutcliffe N, Isenberg DA, Goldblatt F, Price E, et al. Estimating indirect costs in primary Sjögren's syndrome. J Rheumatol 2010;37:1010–5.
6. Callaghan R, Prabu A, Allan RB, Clarke AE, Sutcliffe N, Pierre YS, et al, for the UK Sjögren's Interest Group. Direct healthcare costs and predictors of costs in patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46:105–11.
7. Fox PC, Bowman SJ, Segal B, Vivino FB, Murukutla N, Choueiri K, et al. Oral involvement in primary Sjögren's syndrome. J Am Dent Assoc 2008;139:1592–601.
8. Ekström Smedby K, Vajdic CM, Falster M, Engels EA, Martínez-Maza O, Turner J, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood 2008;111:4029–38.
9. American College of Rheumatology policy and procedure manual for clinical practice guidelines. 2015. URL: http://www.rheumatology.org/portals/0/Files/ACR%20Guideline%20Manual_Appendices_updated%202015.pdf.
10. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003:12:18–23.
11. The AGREE Next Steps Consortium. Appraisal of guidelines for research and evaluation II. May 2009, updated 2013. URL: http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf.
12. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al, for the GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
13. Loblaw DA, Prestrud AA, Somerfield MR, Oliver TK, Brouwers MC, Nam RK, et al. Guidelines, American Society of Clinical Oncology clinical practice guidelines: formal systematic review-based consensus methodology. J Clin Oncol 2012;30:3136–40.
14. Sankar V, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, et al. Etanercept in Sjögren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240–5.
15. Mariette X, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, et al. 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.
16. Faustman DL, Vivino FB, Carsons SE. Treatment of primary Sjögren syndrome with rituximab: comment on Devauchelle et al 2014 [letter]. Ann Intern Med 2014;161:376–7.
17. Meijer JM, Meiners PM, Vissink A, Spijkervet FK, Abdulahad W, Kamminga N, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960–8.
18. Carubbi F, Cipriani P, Marrelli A, Benedetto P, Ruscitti P, Berardicurti O, et al. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multicenter, follow-up study. Arthritis Res Ther 2013;15:R172.
19. Gottenberg JE, Cinquetti G, Larroche C, Combe B, Hachulla E, Meyer O, et al, for the Club Rhumatismes et Inflammations and the French Society of Rheumatology. 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;72:1026–31.
20. Gottenberg JE, Guillevin L, Lambotte O, Combe B, Allanore Y, Cantagrel A, et al, for the Club Rheumatismes et Inflammation. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;64:913–20.
21. Neuberger GB, Press AN, Lindsley HB, Hinton R, Cagle PE, Carlson K, et al. Effects of exercise on fatigue, aerobic fitness, and disease activity measures in persons with rheumatoid arthritis. Res Nurs Health 1997;20:195–204.
22. Tench CM, McCarthy J, McCurdie I, White PD, D'Cruz DP. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. Rheumatology (Oxford) 2003;42:1050–4.
23. Robb-Nicholson LC, Daltroy L, Eaton H, Gall V, Wright E, Hartley LH, et al. Effects of aerobic conditioning in lupus fatigue: a pilot study. Br J Rheumatol 1989;28:500–5.
24. Carvalho MR, Sato EI, Tebexreni AS, Heidecher RT, Schenkman S, Neto TL. Effects of supervised cardiovascular training program on exercise tolerance, aerobic capacity, and quality of life in patients with systemic lupus erythematosus. Arthritis Rheum 2005;53:838–44.
25. Neill J, Belan I, Ried K. Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: a systematic review. J Adv Nurs 2006;56:617–35.
26. Strömbeck BE, Theander E, Jacobsson LT. Effectiveness of exercise on aerobic capacity and fatigue in women with primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46:868–71.
27. Fox RI, Dixon R, Guarrasi V, Krubel S. Treatment of primary Sjögren's syndrome with hydroxychloroquine: a retrospective, open-label study. Lupus 1996;5 Suppl 1:S31–6.

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

28. Gottenberg JE, Ravaud P, Puéchal X, Le Guern V, Sibilia J, Goeb V, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA 2014;312:249–58.
29. Virkki LM, Porola P, Forsblad-d'Elia H, Valtysdottir S, Solovieva SA, Konttinen YT. Dehydroepiandrosterone (DHEA) substitution treatment for severe fatigue in DHEA-deficient patients with primary Sjögren's syndrome. Arthritis Care Res (Hoboken) 2010;62:118–24.
30. Hartkamp A, Geenen R, Godaert GL, Bootsma H, Kruize AA, Bijlsma JW, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjogren syndrome: a randomised controlled trial. Ann Rheum Dis 2008;67:91–7.
31. Norheim KB, Harboe E, Gøransson LG, Omdal R. Interleukin-1 inhibition and fatigue in primary Sjögren's syndrome: a double blind, randomised clinical trial. PLoS One 2012;7:e30123.
32. Meiners PM, Vissink A, Kroese FG, Spijkervet FK, Smitt-Kamminga NS, Abdulahad WH, et al. Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis 2014;73:1393–6.
33. Mariette X, Seror R, Quartuccio L, Baron G, Salvin S, Fabris M, et al. Efficacy and safety of belimumab in primary Sjogren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis 2015;74:526–31.
34. Steinfeld SD, Tant L, Burmester GR, Teoh NK, Wegener WA, Goldenberg DM, et al. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phase I/II study. Arthritis Res Ther 2006;8:R129.
35. Kruize AA, Hené RJ, Kallenberg CG, van Bijsterveld OP, van der Heide A, Kater L, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. Ann Rheum Dis 1993;52:360–4.
36. Fox RI, Chan E, Benton L, Fong S, Friedlaender M, Howell FV. Treatment of primary Sjögren's syndrome with hydroxychloroquine. Am J Med 1988;85:62–7.
37. Fauchais AL, Ouattara B, Gondran G, Lalloué F, Petit D, Ly K, et al. Articular manifestations in primary Sjögren's syndrome: clinical significance and prognosis of 188 patients. Rheumatology (Oxford) 2010;49:1164–72.
38. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjögren's syndrome. Clin Exp Rheumatol 1996;14:555–8.
39. Foulks GN, Forstot SL, Donshik PC, Forstot JZ, Goldstein MH, Lemp MA, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. Ocul Surf 2015;13:118–32.
40. Zero DT, Brennan MT, Daniels TE, Papas A, Stewart C, Pinto A, et al, for the Sjögren's Syndrome Foundation Clinical Practice Guidelines Committee. Clinical practice guidelines for oral management of Sjögren disease: dental caries prevention. J Am Dent Assoc 2016:147:295–305.
41. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al, for the EULAR Sjogren's Task Force. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. Ann Rheum Dis 2010;39:1103–9.
42. Seror R, Ravaud P, Mariette X, Bootsma H, Theander E, Hansen A, et al, for the EULAR Sjogren's Task Force. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. Ann Rheum Dis 2011;70:968–72.
43. Cornec D, Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, et al. Development of the Sjögren's Syndrome Responder Index, a data-driven composite endpoint for assessing treatment efficacy. Rheumatology (Oxford) 2015;54:1699–708.
44. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Puéchal X, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med 2014;160:233–42.
45. Zandbelt MM, de Wilde P, van Damme P, Hoyng CB, van de Putte L, van den Hoogen F. Etanercept in the treatment of patients with primary Sjögren's syndrome: a pilot study. J Rheumatol 2004;31:96–101.
46. Segal B. Fatigue in primary Sjogren's syndrome. In: Ramos-Casals M, editor. Sjogren's syndrome: diagnosis and therapeutics. London: Springer Verlag; 2012. p. 129–43.
47. Khan O, Carsons S. Occurrence of rheumatoid arthritis requiring oral and/or biological disease-modifying antirheumatic drug therapy following a diagnosis of primary Sjögren's syndrome. J Clin Rheumatol 2012;18:356–8.

APPENDIX A: SJÖGREN'S SYNDROME FOUNDATION 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, Nancy Carteron, William Ehlers, Michael T. Brennan; (Biologic Therapy for Systemic Disease) co-chair Nancy Carteron, co-chair Steven E. Carsons; (Fatigue) co-chair R. Hal Scofield, co-chair Robert 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.

Consensus expert panel rheumatology. Senada Arabelovic, DO (Tufts University School of Medicine, Boston, MA), Alan Baer, MD, FACP, FACR (Johns Hopkins University School of Medicine, and Jerome L. Greene Sjögren's Syndrome Center, Baltimore, MD), Herbert S. B. Baraf, MD, FACP, MACR (Arthritis and Rheumatism Associates, Wheaton, MD, and George Washington University School of Medicine, Washington, DC), Neha Bhanusali, MD (University of Central Florida College of Medicine, Orlando), Julius Birnbaum, MD, MHS (Johns Hopkins University School of Medicine, and Jerome L. Greene Sjögren's Syndrome Center, Baltimore, MD), Donald Bloch MD (Massachusetts General Hospital, Boston, MA), Richard Brasington, MD, FACP, FACR (Washington University in St. Louis School of Medicine, St. Louis, MO), Nancy Carteron, MD, FACR (University of California at San Francisco), Harjinder Chowdhary, MD, FACR (New England Rheumatology, Norwich, University of Connecticut School of Medicine, Farmington, and Yale University School of Medicine, New Haven), Andreea Coca, MD, FACR (University of Rochester Medical Center, Rochester, NY), Stamatina Danielides, MD (Virginia Commonwealth University, Richmond), Denise Faustman, MD, PhD (Harvard Medical School, and Massachusetts General Hospital, Charlestown), Theresa Lawrence Ford, MD, FACR (North Georgia Rheumatology Group, Lawrenceville), Joseph Forstot, MD, FACP, FACR (Rheumatology Associates, Boca Raton, FL), Robert Fox, MD, PhD, FACP, FACR (Rheumatology Clinic, La Jolla, CA), Paul Howard, MD, MACP, FACR (Arthritis Health, Scottsdale, AZ), Judith James, MD, FACR (Oklahoma Medical Research Foundation, Oklahoma City), Chadwick R. Johr, MD, FACR (University of Pennsylvania, Philadelphia), Stuart Kassan, MD, FACP, FACR, MACR (Colorado Arthritis Associates, Lakewood, and University of Colorado, Denver), Janet E. Lewis, MD, FACR (University of Virginia, Charlottesville), Arthur Mandelin, MD, PhD, FACR (McGaw Medical Center, and Northwestern University, Chicago, IL), Timothy Niewold, MD, FACR (Mayo Clinic, Rochester, MN), Ghaith Noaiseh, MD, FACR (University of Pittsburgh Medical Center, Pittsburgh, PA), Justin Peng, MD, FACR (Arthritis and Rheumatism Associates, Washington, DC), Ruben Peredo, MD (University of Michigan, Ann Arbor), Stanley Pillemer, MD, MACR (American Biopharma Corporation, Gaithersburg; formerly, NIH Sjögren's Clinic, Bethesda, MD), Astrid Rasmussen, MD, PhD (Oklahoma Medical Research Foundation, Oklahoma City), Westley Reeves, MD, FACR (University of Florida, Gainesville), Guada Respicio Duque, MD, MSs, FACP, FACR (Rheumatology, Arthritis, and Rheumatism Associates, Wheaton, MD), Bruce Rothschild, MD, FACR (Rheumatology Human Motion Institute, Indiana, PA), Nora Sandorfi, MD (Hospital of the University of Pennsylvania, Philadelphia), R. Hal Scofield, MD, FACR (Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, and

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Department of Veterans Affairs Medical Center, Oklahoma City), Daniel Small, MD, FACR (Sjögren's Center of Florida, and Sarasota Arthritis Center, Sarasota), Harry Spiera, MD, MACR (Rheumatology Associates, New York, NY), Robert Spiera, MD, FACP, FACR (Hospital for Special Surgery, New York, NY), E. William St. Clair, MD, FACR (Duke University Medical Center, Durham, NC), Neil Stahl, MD, FACR (Arthritis and Rheumatology Disease Associates, Burke, VA), Katherine Temprano, MD, FACR (Saint Louis University, St. Louis, MO), Thomas Terenzi, MD, FACR (St. Francis Medical Center, Hartford, and University of Connecticut School of Medicine, Farmington), Edward Treadwell, MD, FACR (East Carolina University School of Medicine, Greenville, NC), Daniel Wallace, MD, FACP, FACR (Cedars-Sinai Medical Center, West Hollywood, CA), Jeffrey W. Wilson, MD (Rheumatology of Central Virginia Family Physicians, Lynchburg, VA, and Duke University Medical Center, Durham, NC), Christopher Wise, MD, FACR (Virginia Commonwealth University Medical Center, Richmond), Angus Worthing, MD, FACR (Arthritis and Rheumatism Associates, and Georgetown University Medical Center, Washington, DC), Scott Zashin, MD, FACR (Dallas Rheumatology, Presbyterian Hospitals, and University of Texas Southwestern Medical School, Dallas).

Consensus expert panel oral. Oral members participated in the Biological Therapy-Sicca Symptoms guidelines only, with the exception of Ilias Alevizos. Ilias Alevizos, DMD, MMSc (National Institute of Dental and Craniofacial Research, Sjögren's Clinic, Bethesda, MD), Ibtisam Al-Hashimi, BDS, MS, PhD (TAMU-Baylor College of Dentistry, Dallas, TX), Troy Daniels, DDS, MS (University of California at San Francisco School of Dentistry), Andres Pinto, DMD, MPH (Case Western Reserve University, Cleveland, OH), James Sciubba, DMD, PhD (Greater Baltimore Medical Center, Baltimore, MD), Carol M. Stewart, DDS (University of Florida Health Science Center, Keystone Heights).

Consensus expert panel ocular. Ocular members participated in the Biological Therapy-Sicca Symptoms guidelines only. Esen K. Akpek, MD (Johns Hopkins Wilmer Eye Institute, Baltimore, MD), S. Lance Forstot, MD, FACS (Corneal Consultants of Colorado, Denver), Gary Foulks, MD, FACS (University of Louisville School of Medicine, Louisville, KY), Peter Donshik, MD (Ophthalmology, Bloomfield, and University of Connecticut Health Center, Farmington), Michael Lemp, MD (Georgetown University, and George Washington University, Washington, DC), J. Daniel Nelson, MD (Health Partners Medical Group, St. Paul, and University of Minnesota, Minneapolis), Kelly Nichols, OD, MPH, PhD (University of Alabama at Birmingham).

Consensus expert panel other professional health specialists. Evelyn Bromet, PhD (Sjögren's patient; Stony Brook University, Stony Brook, NY), Fred Friedberg, PhD (Stony Brook University, Stony Brook, NY), Heidi Kukla, RN, BSN, CCRN, CNIII (Elliot Hospital, Manchester, NH), Steven Mandel, MD, PC (neurology Private Practice, New York, NY), Donald Lewis MacKeen, BS Pharm, MS Pharm, PhD (CEO MacKeen Consultants, Venice, FL; formerly Georgetown University Medical School, Washington, DC), Joan Manny, RN (Sjögren's patient; formerly NIH Sjögren's Clinic, Bethesda, MD), Lynn Petruzzi, RN, MSN (Sjögren's patient; formerly West Shore Surgery Center, Mechanicsburg, PA), Sarah Schafer, MD (Sjögren's patient; Public Health and General Preventive Medicine, Oakland, CA), Nancy Schoofs, RN, PhD (Sjögren's patient; Grand Valley State University, Grand Rapids, MI).

21514658, 2017, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/acr.22968 by University Of California, San, Wiley Online Library on [21/03/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License