Sjögren's Foundation Clinical Practice Guidelines

Systemic Manifestations in Sjögren's Patients

The Sjögren's Foundation has developed the first U.S. Rheumatology Clinical Practice Guidelines for Sjögren's to ensure quality and consistency of care for the assessment and management of patients by offering recommendations to clinicians for systemic disease management.

Previously, treatment guidelines for serious organ involvement from Sjögren's were borrowed from those used to treat Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA). Among the recommendations, the guidelines address the treatment of inflammatory, musculoskeletal pain in systemic Sjögren's, use of biologic agents and management of fatigue.

Rheumatology Guidelines Summary and Recommendations

For the development of the Sjögren's Foundation Rheumatology Guidelines, a highly rigorous and transparent process was employed with important guidance from the American College of Rheumatology and the Institute of Medicine. An extensive, systematic literature review by Topic Review Groups (TRG) was followed by data extraction and drafting of recommendations to be considered by separate consensus expert panels (CEP) consisting of academic and community practice clinicians, registered nurses and patients. Using a modified Delphi-type consensus process, the CEP reached consensus on eighteen recommendations with consensus set at a minimum of 75% agreement.

DMARDs for Musculoskeletal Pain

Recommendations regarding the use of disease-modifying anti-rheumatic drugs (DMARDs) to treat musculoskeletal (MSK) pain were presented as a decision tree with use of hydroxychloroquine (HCQ) as the first-line therapeutic approach. Although HCQ treatment failed to reach the primary endpoint for pain in a recent, randomized control trial, other studies have shown that following HCQ treatment, Sjögren's patients demonstrated improvement in inflammatory markers and MSK pain. The favorable safety profile of HCQ contributed to the 92% positive agreement of the Rheumatology Working Group. Thus, the recommendation for the use of HCQ received a moderate strength rating and is considered a best clinical practice first-line therapy.

Biological Medications

Biological therapies such as rituximab will become increasingly important in the management of Sjögren's patients and are best used in Sjögren's patients with serious organ manifestations who fail more conservative treatments. There was strong consensus that TNF-α inhibitors not be used to treat sicca symptoms in patients with Sjögren's. This recommendation was qualified by the consideration that clinicians should not withhold TNF-α inhibitor treatment if a patient also suffers from another condition for which such treatment would be indicated.

Fatigue

Fatigue is most effectively managed with self-care measures and exercise. Exercise provides similar benefit to reduce fatigue in Sjögren's patients as was seen for those with RA, SLE or Multiple Sclerosis.

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Figure 1: Treatment Algorithm Based Upon Severity Level and Response to Therapy

Biological Therapies*

* Three rounds of Consensus Expert Panel (CEP) review and voting took place for the RTX /xerostomia Recommendation, and 2 rounds were held for the remainder. Recommendation #5 on RTX/systemic management was reviewed an additional time by the CEP for both Biological Therapies and Fatigue.

	Strength of Recommendation
Recommendation #1 – TNF-α Inhibitors	
TNF-α inhibitors SHOULD NOT BE USED to treat sicca symptoms in patients with primary Sjögren's.* * Note that this recommendation should not be interpreted to discourage use of TNF-α inhibitors in situations where there is overlap of Sjögren's with rheumatoid arthritis (RA) or other conditions where TNF-α inhibition therapy is indicated for the treatment of inflammatory arthritis.	**STRONG**
Recommendation #2 – TNF-α Inhibitor Cautions	
If TNF-α inhibition therapy is used for RA or other related overlap conditions in Sjögren's patients, health care providers should consider and monitor for the following:* • Lymphoma and other malignancies; health care providers should be cognizant that patients with primary Sjögren's have an increased risk of non-Hodgkin's lymphoma as compared to the general population • Serious infections, including tuberculosis • Invasive fungal infections • Hepatitis B reactivation • Hepatoxicity • Heart failure • Cytopenias • Hypersensitivity; Serious infusion reactions • Demyelinating disease *Patients and physicians should refer to the FDA label for additional information	**STRONG**
Recommendation #3 – Rituximab for KCS	
Rituximab MAY BE CONSIDERED as a therapeutic option for keratoconjunctivitis sicca (KCS) in patients with primary Sjögren's and for whom conventional therapies, including topical moisturizers, secretagogues, anti-inflammatories, immunomodulators and punctual occlusion, have proven insufficient.	**WEAK**
Recommendation #4 – Rituximab for Xerostomia	
Rituximab MAY BE CONSIDERED as a therapeutic option for xerostomia in patients with primary Sjögren's 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**
Recommendation #5 – Rituximab for Systemic Symptoms	
Rituximab MAY BE CONSIDERED as a therapeutic option for adults with primary Sjögren's* and any or all of the following systemic manifestations: • Cryoglobulinemia associated with vasculitis • Vasculitis • Severe parotid swelling • Inflammatory arthritis • Pulmonary disease • Peripheral neuropathy – especially mononeuritis *Note: These patients should have had a suboptimal response to standard oral DMARD agents and/or have experienced unacceptable toxicity from these agents or corticosteroids or are incapable of tapering and discontinuing corticosteroids.	**MODERATE**
Recommendation #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 patients:* • Infusion reactions • Tumor lysis syndrome in those with NHL • Progressive multifocal leukoencephalopathy (PML) • 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 on Rituximab. *Patients and physicians should refer to the FDA label for additional information.	**STRONG**

DMARDs for Inflammatory MSK Pain

Recommendations are provided with the following caveats and then listed in a step-by-step process:

- The physician is advised to consider an individual patient's circumstances when weighing risks and benefits of each therapy.
- Insufficient evidence exists on the effectiveness of DMARDs in the treatment of inflammatory musculoskeletal pain in primary Sjögren's. However, recommendations will be formulated based on expert opinion as guided by the consensus group process.
- The following recommendations are listed in order of the Inflammatory Musculoskeletal Topic Review Group's preference for use in the treatment of inflammatory musculoskeletal pain in primary Sjögren's; if one therapy is insufficient in effectiveness, the physician is advised to try the next recommendation in sequence and so on.

Recommendation	Strength of Recommendation
Recommendation #1– Hydroxychloroquine (HCQ)	
A first line of treatment for inflammatory musculoskeletal pain in primary Sjögren's should be hydroxychloroquine.	**MODERATE**
Recommendation #2 – Methotrexate (MTX)	
If hydroxychloroquine is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's, methotrexate alone may be considered.	**MODERATE**
or	
Recommendation #3 – HCQ plus MTX	
If either hydroxychloroquine or methotrexate alone is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's, hydroxychloroquine plus methotrexate may be considered.	**MODERATE**
Recommendation #4a – ST Corticosteroids	
If hydroxychloroquine plus methotrexate is not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's, short-term (1 month or less) corticosteroids of <=15mg a day may be considered.	**STRONG**
Recommendation #4b – LT Corticosteroids	
Long-term (more than 1 month) ≥15mg a day corticosteroids may be useful in the management of inflammatory musculoskeletal pain in primary Sjögren's, but efforts should be made to find a steroid-sparing agent as soon as possible.	Moderate
The following three recommendations are numbered in order of the Topic Review Group's preference and experience. 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.	
Recommendation #5 – Leflunomide	
If hydroxychloroquine and/or methotrexate or short-term (1 month or less) corticosteroids are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's, leflunomide may be considered.	**WEAK**
Recommendation #6 – Sulfasalazine	
If hydroxychloroquine and/or methotrexate, corticosteroids, or leflunomide (Arava®) are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's, sulfasalazine may be considered	**WEAK**
Recommendation #7a – Azathioprine	
If hydroxychloroquine and/or methotrexate, corticosteroids, leflunomide , or sulfasalazine are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's, azathioprine may be considered.	**WEAK**
Recommendation #7b – Potential Change in Order	
If major organ involvement occurs in the primary Sjögren's patient, azathioprine may be a better choice than leflunomide or sulfasalazine for the treatment of all complications including inflammatory musculoskeletal pain.	**MODERATE**
Recommendation #8 – Cyclosporine	
If hydroxychloroquine and/or methotrexate, corticosteroids, leflunomide, azathioprine, or sulfasalazine are not effective in the treatment of inflammatory musculoskeletal pain in primary Sjögren's, cyclosporine may be considered.*	**WEAK**

* 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 in place of cyclosporine.

Fatigue*

* Two rounds of CEP review and voting took place for all Fatigue Recommendations numbered 4 and higher, and 3 rounds were held for Recommendation #3 on HCQ.

Recommendation	Strength of Recommendation
Recommendation #1– Exercise	
Education about self care measures **SHOULD** include advice about exercise to reduce fatigue in Sjögren's.	**STRONG**
Recommendation #2 - Dehydroepiandrosterone (DHEA)	
DHEA is **NOT RECOMMENDED** for treatment of fatigue in Sjögren's.	**STRONG**
Recommendation #3 – Hydroxychloroquine†	
Hydroxychloroquine **MAY BE CONSIDERED** in selected situations to treat fatigue in Sjögren's.*	**WEAK**
* Note the following caveat: The decision to treat fatigue in Sjögren's with hydroxychloroquine requires comprehensive evaluation of disease activity, sicca manifestations and subjective variables and should be individualized according to the clinical context.	
† This Recommendation went through 3 rounds of the Consensus Expert Panel.	
Recommendation #4 - TNF- α Inhibitors	
Neither Etanercept nor infliximab is recommended for treatment of fatigue in Sjögren's.	**STRONG**

For the following 11 therapeutic questions addressed by the Fatigue TRG, there was insufficient evidence to issue a recommendation:

- IL-1 inhibition (anakinra)
- azathioprine
- mycophenolate
- zidovudine
- doxycycline
- lamivudine
- leflunomide
- abatacept
- belimumab
- epratuzumab

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