Management of Extraglandular Manifestations of Primary Sjögren's Syndrome

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KEYWORDS

• Sjögren's syndrome • Joint pain • NSAIDs • Anti-TNF

KEY POINTS

- Primary Sjögren's syndrome can have multiple extra-glandular manifestations ranging from mild to severe.
- Treatment for extra-glandular manifestations is organ specific and therapies are targeted based on the primary organs involved.
- Preferred treatment options used for extra-glandular manifestations of Sjögren's syndrome are usually extrapolated from the physician's experience in treating similar manifestations in other autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematous.
- The lack of immunomodulating disease modifying drugs in Sjögren's syndrome can be frustrating for patients dealing with extra-glandular manifestations, however recent advances in the field has made the future look promising for new therapeutic options.

Primary Sjögren's syndrome (pSS) is an autoimmune inflammatory disorder mainly affecting the exocrine glands. Like many autoimmune disorders, however, pSS is a systemic disease in which many different organs may be affected (**Table 1** and article by Ienopolli and Carsons elsewhere in this issue). Sometimes, extraglandular manifestations like purpura, polyneuropathy, and arthritis can be presenting signs of the disease.[1] In other cases, extraglandular involvement may not be as evident and present subclinically in pSS. In evaluating patients with pSS, extraglandular manifestations should be questioned and considered.

Given the large spectrum of clinical manifestations of pSS, ranging from a limited involvement of exocrine glands to widespread systemic features, clinicians have now distinguished 2 variants of the syndrome: an exocrine gland-localized disease, and a systemic syndrome.[2] Although symptomatic therapy may be enough for most patients with localized glandular symptoms, the lack of immunomodulating disease-modifying drugs in pSS has an important impact on patients with systemic manifestations and severe organ involvement. During the past few years, promising results have been seen with some of the new biologic therapies and others could be considered hypothetically useful in the future for treating extraglandular manifestations of this disorder.

In this article, the current conservative and medical therapies for the more common extraglandular manifestations seen in pSS are reviewed. In addition to reviewing accepted current therapies in pSS, recent research on treatments that are promising for the future are examined as well.

MUSCULOSKELETAL MANIFESTATIONS

Musculoskeletal manifestations, such as arthralgias, myalgias, and nonerosive polyarthritis

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Table 1
Extraglandular manifestations of Sjögren's syndrome

Organ System	Manifestation
Skin	• Xerostosis • Cutaneous vasculitis • Other skin lesions (erythema nodosum, livedo reticulares, lichen planus, vitiligo)
Joints/muscles	• Arthralgia/arthritis • Myalgia/myopathy
Pulmonary	• Interstitial lung disease • Pulmonary fibrosis • Pulmonary hypertension • Small airway obstruction • Bronchiectasis
Cardiovascular/ circulatory	• Pericarditis • Arrythmia • Raynaud phenomenon
Nervous system	• Peripheral neuropathy • Cranial neuropathy • Central nervous system involvement • Autonomic neuropathy
Gastrointestinal	• Dysphagia • Esophageal dysmotility • Autoimmune hepatitis • Pancreatitis
Urogenital	• Interstitial nephritis with renal tubular acidosis • Interstitial cystitis

Modified from Vissink A, Bootsma H, Spijkervet F, et al. Current and future challenges in primary Sjogren's syndrome. Curr Pharm Biotechnol 2012;13:2026–45.

affecting mainly the small joints, are one of the most common comorbidities in pSS and may be difficult to manage. It is important to determine if the cause of pain is more articular or muscular in nature. If arthralgias or polyarthritis is the dominant manifesting symptom, agents used to treat articular manifestations of other connective tissue disease conditions like rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) should be efficacious. However, fibromyalgia is a common coexisting condition in pSS and treatments effective for fibromyalgia are more appropriate for noninflammatory muscular symptoms in pSS. It is also important to differentiate between tenderness secondary to parotid or other glandular inflammation versus arthritic involvement of the temporomandibular joint in pSS. It may be difficult sometimes to differentiate between parotid and temporomandibular joint involvement, but therapies between glandular inflammation and arthritic conditions can differ greatly, thus further demonstrating the importance of determining cause of pain in pSS.

Initially, nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics are the commonly applied treatment of musculoskeletal symptoms in pSS.[2] There are many NSAIDs from which to choose. Although the efficacy of various NSAIDs is similar, an individual's response to therapy can be highly variable.[3] Acetaminophen may have the best safety profile, but its analgesic effect is mild.

Stronger analgesics like opioid (narcotic) therapy have been used in pSS. Opioid therapy in the treatment of more severe forms of acute pain is well established, but opioid administration in chronic pain remains controversial given their addiction potential. The decision to begin long-term opioid therapy in pSS must be weighed carefully.

If a patient's musculoskeletal complaints are more articular and determined to be inflammatory in cause, preferred therapy is based on experience from similar rheumatologic conditions such as RA and SLE. The efficacy of hydroxychloroquine and methotrexate in RA and SLE subsequently led to these medications being studied in pSS. Primary Sjögren's patients with articular symptoms showed improvement when taking hydroxychloroquine over a 1- to 2-year period compared with baseline.[4–6] However, additional randomized controlled trials must be done with hydroxychloroquine. Methotrexate also fared well for arthritis in 1-year studies compared with baseline.[4,7] Again, none of the studies were controlled studies. Although not primarily given for musculoskeletal symptoms in pSS, a few case reports have shown Rituximab to improve articular symptoms when given to several pSS patients.[8] Low-dose corticosteroids are sometimes used and may be needed to control persistent symptoms in pSS.[2] Anti-tumor necrosis factor (TNF) agents such as etanercept, adalimumab, and infliximab have taken center stage for the treatment of autoimmune-rheumatic diseases in the last decade. However, unlike the success found in modulating RA, they were found to have a lack of efficacy for sicca (dry eyes and dry mouth) symptoms in pSS.[1,9] Although ineffective for sicca, anti-TNF agents could be considered for inflammatory polyarthritis refractory to other agents. On the other hand, questions regarding lymphoma risk in anti-TNF agents temper enthusiasm for these agents in pSS.

Recent interest has emphasized nutrition and inflammatory arthritis. Supplements, particularly omega-3 fatty acids and vitamin D, have been studied in the past decade for SLE, RA, and other connective tissue diseases. Omega-3 fatty acids may have a benefit for sicca symptoms,[10] but no