Systemic therapy in Sjögren's syndrome and treatment of extraglandular manifestations

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INTRODUCTION — Sjögren's syndrome (SS) is a multisystem disorder that may present to many different specialists including general internal medicine and its subspecialties (especially rheumatology, chest medicine, neurology, hematology, nephrology, psychiatry), surgery and its subspecialties (especially ophthalmology, otolaryngology), and related specialties such as oral medicine. Although it is important that one physician, usually the rheumatologist, assumes overall responsibility for the care of the patient, SS is a paradigm for a condition requiring a team approach to management. Since patients see multiple specialists, treatments often are not coordinated and the therapy for one manifestation may lead to exacerbation of another aspect.

The role of systemic therapies and treatment of extraglandular manifestations of SS will be reviewed here. Topical therapy of sicca symptoms of SS, the clinical manifestations, approach to diagnosis and classification, and the pathogenesis of SS are presented separately. (See "Topical therapy of dry eyes, dry mouth, and other sicca symptoms in Sjögren's syndrome-I" and see "Clinical manifestations of Sjögren's syndrome: Exocrine gland disease" and see "Clinical manifestations of Sjögren's syndrome: Extraglandular disease and prognosis-I" and see "Classification and diagnosis of Sjögren's syndrome-I" and see "Pathogenesis of Sjögren's syndrome-I").

IMMUNOSUPPRESSIVE THERAPY — In view of the immunologically mediated lacrimal gland destruction that occurs in SS, immunosuppression is a logical approach to treatment. (See "Pathogenesis of Sjögren's syndrome-I"). The treatment of systemic manifestations in SS parallels the treatments used in SLE.

Initial treatment — Initial treatment includes antimalarials (hydroxychloroquine up to 8 mg/kg/day) for arthralgias, lymphadenopathy, and skin manifestations. The next step is usually the use of oral or self-injected methotrexate at weekly intervals.

Refractory keratoconjunctivitis sicca — Systemic immunosuppression has been employed for patients with refractory sicca symptoms, with little substantial benefit.

Cyclosporine — In a study that compared oral cyclosporine (5 mg/kg per day) to placebo in patients with primary SS for up to one year, cyclosporine produced subjective improvement in xerostomia but no objective benefit [1].

Methotrexate — Methotrexate (0.2 mg/kg per week) also appeared to reduce sicca symptoms but not objective parameters in a small open study lasting one year [2].

TNF inhibitors — Initial results of anti-tumor necrosis factor alpha therapy appeared promising, however subsequent results have not supported efficacy of either infliximab or etanercept for SS. As examples, in an uncontrolled study in 16 patients treated with infliximab, sicca symptoms, and both patient and physician global assessments, improved in as little as two weeks [3]. The benefit persisted in 10 patients who continued infliximab for one year [4]. However, a subsequent prospective study that randomly assigned 103 patients to receive infliximab or placebo found no significant differences in the change from baseline in pain, fatigue, or sicca symptoms, nor in objective measures of salivary flow, swollen joints, tender joints, erythrocyte sedimentation rate, or CRP [5].

Etanercept has been evaluated in a small prospective uncontrolled study and one randomized placebo-controlled trial [6,7]; it did not appear to be effective in either study [6,7].

Life-threatening disease — For life-threatening extraglandular manifestations, cyclophosphamide (oral or intravenous), mycophenolate mofetil, and azathioprine are often used. Specific uses of these agents are discussed below. (See "Treatment of extraglandular manifestations" below).

Emerging therapies — Recent studies have focused on treatments directed against B cells. Preliminary results are available for studies of Rituximab (anti-CD20 antibody) and epratuzumab (anti-CD22 antibody).

In the future, inhibitors of B cell activating factor (BAFF) with belimumab, an anti-BAFF antibody, and interference with T cell adhesion or co-stimulation with alefacept or abatacept may be applied to SS.

- T cells — Inhibitors of T cell co-stimulation are also in early phases of clinical trials in SS. The agents under investigation include abatacept and alefacept. Efalizumab has also been studied, but has since been voluntarily withdrawn from the United States market because of a potential risk to patients of developing progressive multifocal leukoencephalopathy [8]. Its use has also being suspended in other countries. (See "Progressive multifocal leukoencephalopathy: Epidemiology, clinical manifestations, and diagnosis").

Rituximab — CD20 is expressed on B cell precursors. Rituximab is a chimeric monoclonal antibody directed against CD20. Rituximab leads to the depletion of peripheral blood B cells for a period of six to 12 months, or longer in some patients.

Several cases series have illustrated the potential of rituximab as a therapeutic agent in SS. The range of findings is illustrated by the following studies:

- A Phase II trial was conducted in eight patients with primary SS of less than four years and seven patients with primary SS and mucosa associated lymphoid tissue (MALT) lymphomas. Rituximab (375 mg/m2) was administered intravenously once weekly for four doses) [9]. Favorable responses were observed in all patients in terms of SS symptoms. Among the seven with MALT lymphomas, three lymphomas entered remission, three remained stable, and one progressed. Hypersensitivity (serum sickness) developed in three of the eight patients without concomitant lymphoma.

- Six patients with primary SS were treated with the same 375 mg/m2 regimen. Four of the patients had SS with systemic features. The other two had keratoconjunctivitis sicca symptoms and associated lymphoma [10]. Significant improvement in the subjective feeling of dryness was reported by three patients, and improvements in laboratory features were noted in two others.

- In the third study [11], a retrospective analysis was performed in 16

patients with primary SS who received rituximab for lymphoma (n = 5) or systemic manifestations (n = 11). In this study, only a minority of patients had improvement in sicca symptoms.

- Sixteen patients with primary SS were treated two times with 375mg/m2 at weeks one and two [12]. The treatments were tolerated well. At week 12 there was a significant improvement in VAS scores for fatigue and dryness, tender point count, and SF36.

- Fifteen patients with primary Sjogren's syndrome were treated two times with 375 mg/m2 on days 1 and 8 [13]. By day 15, all patients had complete depletion of B cells. Fourteen patients maintained marked suppression of B cells from between nine and 40 weeks. Eight patients had significant numbers of B cells in the salivary glands before treatment with rituximab. At four months, rebiopsy showed no B cells; this depletion lasted for an additional eight months in the three patients biopsied a third time. Of interest was the observation that those patients with higher serum levels of BAFF had shorter duration of B cell lymphopenia.

In order to understand fully the potential efficacy of rituximab in SS, randomized, controlled trials with carefully defined patients with the disease will be required.

Epratuzumab (anti-CD22) — CD22 is a transmembrane sialoglycoprotein of the immunoglobulin superfamily. CD22 appears during the late pro-B stage of ontogeny, shifting to the high levels on follicular, mantle and marginal zone B cells. The CD22 molecule may act as a homing receptor for re-circulating B-cells through its affinity for sialic acid-bearing glycans on high endothelial venules [14]. This type of adhesive molecule may play a role in the entry of B cells into lacrimal or salivary gland of SS patients.

Antibodies to CD22 were initially used in non-Hodgkin lymphoma [15,16]. Epratuzumab appears to function by modulation of B cells rather than by depletion of these cells in the circulation [17,18]. Given their differing mechanism of action, combine therapeutic approaches using both anti-CD20 and anti-CD22 antibodies may be feasible [19].

In an open label study of 16 patients with SS, four intravenous infusions of epratuzumab (360 mg/m2) were administered (one infusion every two

weeks). The follow-up period was six months. The following results were observed:

- Fourteen patients received all infusions without significant reactions. One patient received three infusions, and one patient discontinued all infusions following a mild infusion reaction with the first.

- B-cell levels had mean reductions of 54 percent and 39 percent at 6 and 18 weeks, respectively, but T-cell levels, immunoglobulins, and routine safety laboratory tests did not change significantly.

- CD22 overexpression on peripheral B cells was downregulated by epratuzumab for at least 12 weeks after therapy.

- A composite endpoint involving the Schirmer-I test, unstimulated whole salivary flow, fatigue, erythrocyte sedimentation rate, and IgG level was used. At least 20 percent improvement in at least two of the parameters constituted a clinical response. Fifty-three percent of the patients achieved a clinical response at 6 weeks, with 53 percent, 47 percent, and 67 percent responding at 10, 18, and 32 weeks, respectively.

Additional investigations of epratuzumab in SS are ongoing.

Recommendation — Of the immunosuppressive therapies discussed above, topical cyclosporine is approved for ocular dryness. Our opinion is that there is currently insufficient evidence to recommend use of systemic immunosuppression to treat sicca symptoms alone, although such therapy may be necessary for severe extraglandular manifestations, particularly for neurologic disease or vasculitis. (See "Treatment of extraglandular manifestations" below).

TREATMENT OF EXTRAGLANDULAR MANIFESTATIONS — In addition to the sicca symptoms, therapy in SS may also require attention to extraglandular symptoms such as arthralgias, fatigue, and systemic disease.

Cutaneous — A variety of cutaneous manifestations have been reported in SS patients. The lesions can be divided into macular, popular, or vesicular. Further, purpura may be palpable or nonpalpable. The finding of

palpable purpura may indicate leukocytoclastic vasculitis and require therapy similar to that for SLE patients with cutaneous vasculitis. (See "Hypersensitivity vasculitis in adults" section on Treatment).

Nonpalpable purpura, especially of the lower extremities, is common in patients with hyperglobulinemia. The finding of localized vesicular lesions should raise the possibility of herpes zoster. General approaches to macular popular rashes include the use of moisturizers as well as antimalarial agents. Topical steroids are useful in areas other than the face, where topical tacrolimus is preferred to prevent thinning of the skin.

Arthralgia — Arthralgias and myalgias are common in SS even when it is not associated with another connective tissue disease. Simple analgesics are tried first, followed by nonsteroidal antiinflammatory drugs. Hydroxychloroquine is generally well tolerated and mild improvement of painful eyes and mouths, arthralgias, and myalgias were noted with antimalarial drug use in some uncontrolled studies [20,21]. However, one small double-blind, placebo-controlled trial using a crossover design in 19 patients [22] found no clinical benefit of hydroxychloroquine (400 mg daily for one year) in terms of symptoms, tear gland function, or salivary scintigraphy.

Although there has been controversy about the risk of ocular (retinal complications), the previous problems were largely reported when doses as high as 15 mg/kg/day were used [23]. A series of large studies using hydroxychloroquine (up to 8 mg/kg/day) indicate that the risk is extremely low (probably less than 1/10,000) if the dose is maintained in the suggested range (preferably at less than 6.5 mg/kg/day). (See "Antimalarial drugs in the treatment of rheumatic disease", section on Ocular effects).

Patients should notify their ophthalmologists that they are taking an antimalarial drug so that eye examinations can be supplemented with visual field examinations, if indicated.

Cardiopulmonary manifestations — Cardiac manifestations include a spectrum of disorders including pericarditis and pulmonary hypertension. The finding of interstitial changes on chest radiography raises the entire spectrum of infiltrative processes ranging from lymphocytic interstitial pneumonitis to "usual interstitial pneumonitis" (UIP). Further, the sudden

development of, or rapid worsening of dyspnea requires evaluation for pulmonary emboli as SS patients frequently have circulating anti-coagulants [24].

Patients with SS and potentially life-threatening cardiopulmonary manifestations are treated with glucocorticoids with or without other immunosuppressive drugs, including oral azathioprine (up to 2.5 mg/kg/day), oral chlorambucil (4 to 8 mg/day) or monthly intravenous cyclophosphamide (500 to 1000 mg) adjusted to achieve a white blood cell count nadir at 7 to 10 days of about 3000 cells/mm3 [25,26].

The number of cycles of cyclophosphamide is generally limited to 6 in an attempt to limit toxicity related to the use of alkylating agents (including sterility in younger patients) has led to newer protocols.

Renal disease — Renal involvement in SS may take several forms. The most frequent is an interstitial nephritis that produces renal tubular acidosis. Renal disease in SS is often asymptomatic, but subclinical renal disease may be exacerbated by the use of certain medications (including NSAIDs). Renal involvement may present with life-threatening hyperkalemia but usually is reflected by low bicarbonate levels on screening electrolytes. The renal tubular acidosis can be corrected with oral sodium bicarbonate. (See "Treatment of type 1 and type 2 renal tubular acidosis").

Patients with primary SS may also develop glomerulonephritis (GN). However, in SS patients suspected of having GN, amyloidosis and mixed cryoglobulinemia must be considered [27]. Therapeutic interventions generally include the use of glucocorticoids, cyclophosphamide, mycophenolate mofetil, or other immunosuppressives and depend upon the results of the renal biopsy. Treatment of GN in SS is the same as for lupus nephritis. (See "Therapy of diffuse or focal proliferative lupus nephritis-I").

Other renal problems include thrombotic glomerulopathy as in the antiphospholipid syndrome (APS). (See "Antiphospholipid syndrome and the kidney" and see "Treatment of the antiphospholipid syndrome-I", section on Catastrophic APS).

Gastrointestinal disorders — A high frequency of SS patients exhibit

symptoms of gastroesophageal reflux disease (GERD), due to the decreased flow of saliva which would naturally buffer the reflux of acidic gastric contents [28]. Further, the use of NSAIDs and glucocorticoids predispose patients to gastritis and peptic ulcer. As noted earlier some patients with GERD will present with symptoms of laryngotracheal irritation (see "Laryngotracheal reflux" above).

Treatment of these problems with proton pump inhibitors, promotility agents, and dietary modification is similar to therapy for patients with GERD without SS. (See "Medical management of gastroesophageal reflux disease in adults").

The finding of an elevated serum alkaline phosphatase level should suggest co-existent biliary cirrhosis; in which case, use of agents that chelate bile salts (eg, Actigall) may prove helpful [29]. (See "Overview of the treatment of primary biliary cirrhosis").

Elevation of serum aminotransferase enzyme levels usually suggests the presence of hepatitis C viral infection (that can mimic SS and may have a positive ANA, positive RF and mixed cryoglobulinemia) [30,31]. Patients with hepatitis C infection who have positive ANAs and SS-like symptoms with interferon alpha have a higher likelihood of complications including arthralgias and thrombocytopenia [32]. (See "Treatment of chronic hepatitis C virus infection: Recommendations for adults-I" and see "Treatment of essential mixed cryoglobulinemia").

Endocrine disorders — SS patients have a higher frequency of hypothyroidism than the general population, perhaps because both conditions appear linked to HLA-DR 3 in Caucasians [33,34]. Periodic questioning about symptoms of hypothyroidism and annual monitoring of thyroid function with a serum thyroid stimulating hormone (TSH) level is prudent. Hypothyroidism in SS responds to thyroid replacement and is treated in the same manner as idiopathic hypothyroidism. (See "Treatment of hypothyroidism-I").

Use of mineralocorticoid analogues may be needed to treat autonomic neuropathy presenting with orthostatic hypotension (see "Neurologic manifestations" below).

Neurologic manifestations — Neurologic manifestations may be

separated into peripheral neuropathies, autonomic neuropathy, and central nervous system manifestations.

Peripheral neuropathies — If a peripheral neuropathy is asymmetric, then consideration of mononeuritis multiplex is warranted. If mononeuritis multiplex is present, and is a manifestation of systemic vasculitis, then aggressive therapy with glucocorticoids and immunosuppressive agents may be required [35,36]. (See "Diagnosis and treatment of vasculitic neuropathy").

Peripheral neuropathies may be sensory or motor. Symmetric peripheral neuropathies are usually predominantly sensory and frequently occur in the setting of hyperglobulinemic purpura. Treatment is aimed at the underlying condition (including immune and non-immune factors such as elevated lipids, endocrine abnormalities or hypertension).

The use of tricyclic antidepressant agents (such as amitriptyline and nortriptyline) is generally avoided as their anticholinergic side effects may preclude achievement of a therapeutic effect. Thus, symptomatic therapy often begins with gabapentin. (See "Overview of polyneuropathy-I").

Peripheral motor neuropathies are more difficult to manage and attention to peripheral demyelinating disorders (such as chronic inflammatory demyelinating polyneuropathy - CIDP) may lead to therapies including intravenous immunoglobulin (IVIG) and/or immunosuppressive agents.

Use of intravenous gammaglobulin (IVIG) may be beneficial for patients with motor or sensory neuropathy that does not respond to glucocorticoids or other immunosuppressive therapy. The possible value of IVIG has been suggested in several small uncontrolled series. The following are illustrative:

- Five patients with SS and ataxic sensory neuropathy were treated with IVIG; four improved, two whom did so following the first infusion [37].

- Among a group of four patients with vasculitic neuropathy who improved following IVIG treatment, one had SS [38].

The optimal dosage of IVIG is uncertain. Randomized trials are not

available. Doses that have been reported anecdotally to be beneficial range from 1 to 2 g/kg given at biweekly to monthly intervals. A typical course of treatment is 400 mg/kg per day for five days. Each of the five doses is administered by slow intravenous infusion over two to four hours. (See "General principles of the use of intravenous immune globulin").

Autonomic neuropathy — Autonomic neuropathy develops in a subset of SS patients and can be documented by tilt table test [39]. The treatment options include fludrocortisone acetate or midodrine. (See "Treatment of orthostatic and postprandial hypotension-I").

Central nervous system manifestations — Central nervous manifestations certainly occur in SS but there is controversy about their prevalence. They may mimic multiple sclerosis, including transverse myelitis and optic neuritis. The underlying pathology may be vasculitis, thrombosis or demyelination.

Treatment for these life threatening disease manifestations has not been examined in controlled trials. One observational study of 14 patients with myelopathy suggested that intravenous glucocorticoids and cyclophosphamide may be of benefit in some patients [40]. Other immunosuppressive agents may be valuable for maintenance.

- **Vasculitis** — Central nervous system involvement due to vasculitis that is confirmed by biopsy or angiography is treated with glucocorticoids and cyclophosphamide in a similar manner as isolated central nervous system vasculitis. (See "Primary angiitis of the central nervous system-I", section on Treatment).

- **Ischemic stroke** — As discussed earlier, thromboembolic events may be more frequent in patients with SS and may be associated with the presence of antiphospholipid antibodies. The evaluation and treatment of stroke and the antiphospholipid antibody syndrome are presented separately. (See "Overview of the evaluation of stroke-I", see "Clinical manifestations of the antiphospholipid syndrome-I", and see "Treatment of the antiphospholipid syndrome-I").

Since patients with either Alzheimer disease or multiple sclerosis frequently exhibit dryness signs and symptoms (as part of their

autonomic neuropathy and demyelinating process), it is important to make sure that important underlying conditions are not mislabeled SS and therapy of the CNS condition delayed.

In addition to the central vascular thrombotic complications associated with anti-cardiolipin antibodies, it is likely that SS patients share the propensity to accelerated atherosclerosis seen in patients with SLE and RA [41].

Fatigue — Fatigue is common in SS. It may be multifactorial. The fatigue associated with active autoimmune process is usually reflected by elevation of acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein. Also, patients with inflammatory arthralgias and myalgias may have disrupted sleep. In these patients, treatment with anti-inflammatory drugs and anti-malarial drugs may prove helpful.

In other patients, a disrupted sleep pattern due to dryness, polyuria (as a result of fluid consumption during the day) may play a role. Treatment of these individuals emphasizes the use of oral lubricants and artificial salivas and minimizing fluids after dinner (to decrease resulting nocturia) may prove helpful.

Endocrine factors such as hypothyroidism or autonomic neuropathy (where orthostatic drop in blood pressure may mimic "fatigue") should be considered and treated.

However, fatigue in SS is rarely associated with elevations in acute phase reactants and the fatigue does not correlate well with either glandular or extraglandular manifestations [42]. Fatigue is often attributed to fibromyalgia [43] or non-restorative sleep [43,44].

Components of fibromyalgia resemble agitated depression and may respond to agents such as selective serotonin reuptake inhibitors (SSRIs) or other antidepressants that have few or no anticholinergic side effects. (See "Initial treatment of depression in adults-I", section on Initial therapy).

Progressive physical therapy for the associated muscle deconditioning and vitamin supplementation may be helpful as diets in SS patients (who often

have difficulty chewing certain foods) may be relatively deficient.

Inflammatory myopathy (myositis) may require immunosuppressive therapy [45]. (See "Initial treatment of dermatomyositis and polymyositis in adults-I").

General anesthesia — Patients with SS are at increased risk from any surgery requiring general anesthesia. Factors responsible include the use of anticholinergic drugs, which further reduce tear production, and the low humidity environment of the operating theater. The reduction in airway secretions in SS increases the risk of inspissated mucus and postoperative atelectasis, while oral dryness may increase difficulty of taking oral medications. Management may include prophylactic use of ocular lubricants, with humidified oxygen and chest physiotherapy to mobilize secretions.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient information: Sjögren's syndrome"). We encourage you to print or e-mail these topics, or to refer patients to our public web site, www.uptodate.com/patients, which includes these and other topics.

SUMMARY — Treatment of SS is generally symptomatic, with most patients requiring treatment only for dryness. Adequate explanation is essential: many subjects, for example, may not realize that their central heating or air conditioning creates a drying environment or that a windy day is likely to make their eyes dryer. Simple measures such as humidifiers, sips of water, chewing gums, and simple replacement tears will be adequate in the majority of subjects. The rest should be told of the wide range of artificial fluids available and encouraged to try several different formulations.

Treatment of other manifestations of SS has been influenced by our treatment of other connective tissue diseases. The most serious (and fortunately rare) complications such as vasculitis and neurologic disease probably require immunosuppression with drugs such as glucocorticoids and cyclophosphamide, as in systemic lupus erythematosus.

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