Cytotoxics or biologicals in the treatment of Sjögren’s syndrome?

Treatment of Sjögren’s syndrome has been largely empiric, aimed mainly at alleviation of sicca complaints. In the absence of solid data, systemic extraglandular features and lymphoma have been variably managed with several immunosuppressive and cytotoxic agents including among others azathioprine, methotrexate and cyclophosphamide. Over the last few years appreciation of the contributory role of B-cells in Sjogren’s syndrome pathogenesis led to anti-CD20 and to a lesser extent anti-CD22 usage with promising results. Biological agents against novel therapeutic targets including B-cell activating factor and costimulatory molecules are currently tested in ongoing trials.

**KEYWORDS:** biologic agents  cytotoxic  immunosuppressive drugs  lymphoproliferation  Sjögren’s syndrome  systemic features  treatment

Clio P Mavragani¹, Michael Voulgarelis² & Haralampos M Moutsopoulos*²

¹Department of Experimental Physiology, School of Medicine, University of Athens, Athens, Greece
²Department of Pathophysiology, School of Medicine, University of Athens, M. Askas 75, 11527 Athens, Greece

*Author for correspondence: Tel.: +30 210 746 2512/3 Fax: +30 210 746 2664

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**Learning objectives**

Upon completion of this activity, participants should be able to:

- Describe empiric treatment of SS aimed mainly at alleviation of sicca complaints
- Describe the role of cytotoxics/immunosuppressives in treating SS and its associated manifestations
- Describe the role of biologics in treating SS and its associated manifestations

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Laurie Barclay, MD, Freelance writer and reviewer, Medscape, LLC.

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Sjögren’s syndrome (SS) is a chronic autoimmune disease characterized by chronic lymphocytic infiltration of salivary and lachrymal glands. SS-related chief complaints – namely oral and ocular dryness – are chronic and often distressing, compromising the quality of life to a major degree. Several systemic features also occur quite commonly involving virtually any organ system including, among others, the joints, skin, lung, liver, kidney and to a lesser extent the nervous system. Of note, a small percentage (approximately 5%) of SS patients sharing several adverse predictors such as purpura, parotid gland enlargement and/or low complement levels are prone to lymphoma development sometime during disease course [1]. For many years, treatment of SS manifestations was mostly empirical, directed mainly to the alleviation of sicca symptoms and represented by eye lubricants, saliva substitutes and stimulators of the compromised glandular secretion. Despite the undisputable autoimmune origin of the syndrome, solid evidence for the systemic use of immunosuppressive/cytotoxic agents is rather scarce with their use mainly implemented in the management of systemic manifestations [2]. Advances in the SS field over recent decades pointed to B-cell activation as a major contributor in disease pathogenesis allowing the designation of targeted therapies against B-cell lineage with promising results [3,4]. In the current perspective, we seek to discuss the appropriate settings of cytotoxic/immunosuppressive or biological agents use, focusing on the treatment of local and systemic SS manifestations.

Immunosuppressives/cytotoxics

With the exception of local cyclosporine, collective evidence has so far failed to demonstrate a significant impact of classical cytotoxics/immunosuppressives in alleviation of SS-related sicca symptoms [5,6]. However, despite the lack of rigorous clinical data, their use could prove valuable in the management of systemic disease manifestations such as joint involvement, parenchymal disease (e.g., interstitial lung disease, autoimmune liver disease) or severe vasculitic and nervous system involvement [2].

- **Antimalariais**
  
  Despite the remarkable decrease of hypergammaglobulinemia and autoantibody levels, earlier studies, failed to support hydroxychloroquine (HCQ) as an effective agent in the management of sicca symptoms [7-9]. Recent data from an open-label study revealed a potential contribution in improvement of subjective symptoms of eye dryness such as gritty and burning sensation. Disease progression has been prevented as evidenced by the worsened objective dryness scores (Shirmer’s test, lissamine green, break-up time) in the placebo group and the significantly reduced tear BAFF levels – a central mediator in disease pathogenesis [10,11] – in the HCQ group [12]. Inhibition of cholinesterase activity, heightened in the salivary glands from primary SS patients [13], has been proposed as a potential mechanism accounting for the improvement of salivary function. Musculoskeletal complaints such as arthralgias, myalgias, fibromyalgia-like features or even an intermitent nonerosive polyarthropathy are responsive to HCQ administration [2,7,8]. Of note, a case of vasculitis has been reported after HCQ cessation indicating a potential immuno-noregulatory function in controlling disease activity [14]. In another retrospective analysis, improvement in objective indices of salivary production has been reported, an effect most pronounced in antifodrlin-positive patients [15].

- **Corticosteroids**
  
  While local symptoms are resistant to steroid administration [16], systemic disease manifestations such as interstitial lung disease, glomerulonephritis, autoimmune liver disease, nervous system involvement and vasculitic
lesions seem to respond at a standard dose of 0.5–1 mg/kg of body weight daily [2,17,18]. Intravenous pulses (1 g methylprednisolone for three consecutive days) might be beneficial in cases of CNS involvement.

**Azathioprine**

In a mouse model, administration of azathioprine led to a reduction of the extent of lymphocytic infiltration in the salivary glands [19]. However, in a 6-month double-blind, placebo-controlled trial of 25 primary SS patients, low-dose azathioprine (1 mg/kg body weight/day) has been proven ineffective, with safety issues being raised, since six out of 25 patients withdrew because of side effects [20]. Despite the lack of controlled data, azathioprine at a dose of 2 mg/kg bodyweight/day seems to be beneficial in the treatment of interstitial lung disease, glomerulonephritis and nervous system involvement [2,18].

**Mycophenolate sodium**

In an open-label 6-month pilot study, mycophenolate sodium (MPS) up to 1440 mg daily has been administered in 11 patients with primary SS with promising results in terms of subjective improvement of ocular dryness and a reduced need for artificial tear administration. Except for two patients with short disease duration, no statistically significant improvement in objective indices of salivary and lachrymal function has been noted. Of interest, a significant reduction in γ globulins and rheumatoid factor (RF) levels as well as an increase in complement levels has been observed. It should be noted that three out of 11 patients experienced side effects (vertigo, gastrointestinal disturbances and pneumonia) and were not included in the final analysis [21].

**Cyclophosphamide**

The alkylating agent cyclophosphamide, is reserved for very serious or life threatening conditions such as glomerulonephritis refractory to prednisolone, systemic necrotizing vasculitis or severe neurological involvement. It is most commonly administered intravenously (0.5–1 g/m² of body surface/month) for a total of 6 months. Potential serious toxic effects, such as bone marrow suppression, infertility and cancer development imply the designation of cyclophosphamide as a last therapeutic resort. Particular attention is required in SS patients prone to monoclonal transformation, since a 100-fold increase in lymphoma development has been previously reported in this population cohort [22,23].

**Methotrexate**

Identification of proinflammatory cytokines in the minor salivary gland tissues from SS patients [24], prompted the use of methotrexate at a dose of 0.2 mg/kg body weight in an open trial at a weekly basis for 1 year. While subjective symptoms of oral and ocular dryness have been improved, lachrymal or salivary flow rates remained unaltered. Of note, parotid gland enlargement, dry cough and purpura rates have been reduced [25]. Nevertheless, methotrexate has a place in the management of primary SS-related polyarthritis [2].

**Cyclosporine**

The beneficial effect of topical use of cyclosporine in lachrymal function in two SS mice models [26] led to two parallel multicenter randomized double-blind studies in which administration of local cyclosporine drops twice daily (0.05 or 0.1%) led to significant improvement in both objective and subjective parameters of ocular dryness [27]. In patients with severe dry eye a more frequent dosing of topical cyclosporine 0.05% than twice daily has been recently suggested, with local burning and irritation being the main side effects in a small percentage of patients [28]. Despite the presence of activated T cells in the minor salivary gland biopsies from SS patients [29], oral administration of cyclosporine at a dose of 5 mg/kg bodyweight/day in a double-blind study has been inefficacious in terms of objective indices of lachrymal and parotid flows. However, improvement of subjective xerostomia and retardation of the evolution of the histopathological SS lesions were noted [30]. In a recent case report the beneficial effects of low-dose cyclosporine (1.5 mg/kg/day) in the management of refractory interstitial cystitis has been demonstrated [31].

**d-penicillamine**

The role of d-penicillamine at a dose of 250 mg/day for the first 3 months, followed by 500 mg/day for the next 3 months in sicca features was investigated in a 6-month prospective open-label study of 19 patients with primary SS [32]. The rate of treatment cessation was high (eight out of 19 participants) mainly due to loss of taste. In the remainder of the participants, a statistically significant increase in basal salivary flow was observed after 3 months with no effect on Schirmer’s test and stimulated parotid salivary flow after 6 months. In isolated cases, a beneficial effect of d-penicillamine in the treatment of chronic sensory ataxic neuropathy has been previously reported [33].
Sulphasalazine
Despite the immunomodulatory effects of sulphasalazine in rheumatoid arthritis, data on sulphasalazine in the management of SS are restricted. In an earlier report Yeoman and Franklin failed to demonstrate a reduction in the score of lymphocytic infiltrations in a mouse model [34].

Mizoribine
Mizoribine (a suppressor of lymphocytic proliferation) at a dose of 50 mg three times a day for 16 weeks has been proved efficacious in the treatment of SS. In the setting of a multicenter open-label study, alleviation of sicca complaints coupled with significant improvement in salivary function has been documented [35,36]. While no serious adverse effects related to the drug have been noted, several side effects such as liver function and peripheral blood abnormalities have been recorded. Patients with moderate lymphocytic infiltration and reduced levels of intralobular fibrosis at the level of salivary gland biopsy are more likely to respond to mizoribine therapy [37].

Biological agents
The recent advances in identification of distinct biological pathways in the understanding of SS pathological lesion opens new avenues in the generation of innovative targeted therapies.

Anti-TNF therapies
In spite of the documented presence of TNF-α in SS minor salivary gland tissues [24], anti-TNF agents – both infliximab and etanercept – failed to demonstrate a meaningful clinical effect in these patients [38–40], with γ globulin levels and serum IgM titers being increased significantly in the infliximab-treated group [38]. Augmentation of the already activated Type I IFN pathway and subsequent BAFF increase in etanercept-treated primary SS patients compared with placebo, might be a plausible explanation for anti-TNF failure in these patients [41].

Anti-B-cell treatment
The increasingly recognized pivotal role of B-cells in the pathogenesis of SS in conjunction with the beneficial role of anti-B-cell therapies in rheumatoid arthritis and lymphoma, a well recognized complication of primary SS, led to clinical trials of targeted therapies directed against cells of B-cell lineage [42,43]. A growing body of evidence suggests rituximab, a monoclonal antibody against the surface B-cell molecule CD20, as a dominant player in the management of SS, while fewer data are available in regard to the role of anti-CD22 and anti-BAFF agents.

Rituximab
The mechanism of rituximab induced B-cell depletion is not fully understood, but is likely to employ antibody-dependent cell-mediated cytotoxicity, complement-mediated lysis, growth inhibition and apoptosis [44]. Initial data assessing the effectiveness of rituximab in alleviation of sicca-related features in primary SS were rather conflicting. However, it has been quickly realized that the major determinant of therapeutic success of rituximab in terms of improvement in subjective and objective salivary measures is mainly related to the presence of residual salivary gland function and disease duration, with patients with earlier disease onset and preserved salivary function being the most likely to respond [45–47]. This concept was convincingly demonstrated in a recent randomized controlled study including 30 primary SS patients with a rate of stimulated whole saliva secretion of ≥0.15 ml/min. In the rituximab group, significant improvements of the stimulated whole saliva flow rate as well as visual analog scale scores for sicca symptoms have been observed compared with placebo. In the same study, no effect in Schirmer test scores and break-up time at weeks 5 and 48, although there was a significant decrease in conjunctival staining scores after two infusions of rituximab [48].

Following some encouraging reports in small case series [46,47], the beneficial effect of rituximab in the treatment of fatigue was demonstrated in two randomized controlled trials (as secondary and primary, and end point, respectively) using rituximab 1 g or placebo at days 0 and 15 with significant improvements in visual analog scale and Multidimensional Fatigue Inventory scores compared with placebo [48,49]; in a recent study improvements in quality of life scores have also been observed [50].

Extraglandular manifestations resulting from immune complex pathology as a result of ongoing B-cell activation, such as cryoglobulinemia, peripheral neuropathy and/or cutaneous vasculitis, have successfully responded to rituximab administration at various therapeutic regimens [51–53]. In the large majority of the studies, RF levels, hypergammaglobulinemia and hypocomplementemia respond effectively to rituximab [51,52,54], while anti-Ro/SSA and anti-La/SSB remain detectable after rituximab therapy since they are mainly produced...
by long-lived plasma cells, in which the CD20 molecule is absent [48,52]. Notably, salivary gland infiltrates including both B- and, to a lesser extent, T-cells have been remarkably reduced, while salivary gland acini have been restored after 12 weeks of rituximab treatment in parotid gland biopsies from primary SS patients who had objective signs of salivary improvement [55]. Taken together, these data highlight the instrumental role of B-cells in orchestrating the SS immunopathological lesion.

B-cell CD20 antigen is present on the surface of RF-positive mature B-cells, which produce monoclonal cryoglobulins with RF activity, accounting for manifestations such as palpable purpura, peripheral neuropathy and low serum C4 levels. Given that the latter features have been previously shown to be associated with lymphoma development in the setting of SS-together with the beneficial role of rituximab in the treatment of aggressive B-cell lymphoma, several case series so far have tested the efficacy of rituximab in the management of SS related lymphoma [23,56]. Patients with localized parotid gland mucosa associated lymphoid tissue (MALT) lymphoma in the absence of of M-protein, cryoglobulins, IgM RF >100 KIU/l and/or severe extraglandular manifestations, seems to require a ‘wait and see’ policy. In contrast, extranodal MALT lymphoma in association with the presence of the above features seem to benefit from rituximab treatment [57]. Furthermore, it has been previously shown that aggressive B-cell non-Hodgkin lymphomas benefit from combination therapy with rituximab and CHOP in regards to improved survival compared with CHOP chemotherapy alone [52,58].

On the other hand, the potential beneficial effects of rituximab treatment prior to lymphoma development in terms of delay or even lymphoma prevention is a challenging issue in patients with known adverse predictors but remains to be tested, since no data are currently available.

**Anti-CD22**

CD22 is a 135-kDa transmembrane sialoglycoprotein of the immunoglobulin superfamily. CD22 is expressed at higher levels in the cellular membrane on mature B-cells, and is absent on differentiated plasma cells. Its dual functional role as a homing receptor for recirculating B-cells as well as a down-modulating coreceptor for B-cell antigen receptor (BCR), implies the potential beneficial effect from its downregulation in the treatment of excessive autoimmune responses. The safety and efficacy of the humanized anti-CD22 monoclonal antibody, namely epratuzumab, has been tested in an open-label, Phase I/II study including 16 primary SS patients with 6 months of follow-up. CD22, found to be overexpressed in B-cells from SS patients, was downregulated by epratuzumab leading to meaningful clinical responses in regard to fatigue, patient and physician global assessments and a composite score including Schirmer-I test, unstimulated whole salivary flow, fatigue, erythrocyte sedimentation rate (ESR) and IgG [59,60].

**Anti-BAFF**

Growing evidence over the last few years has emphasized the contributory role of BAFF (a cytokine belonging to the TNF family) in the pathogenesis of SS through expansion of transitional type 2 (T2) and marginal-zone (MZ)-like B-cells in the salivary glands and promotion of autoantibody production, as evidenced by heightened levels of this cytokine in association with the presence of autoantibodies against Ro/SSA and La/SSB antigens [11,61]. It is noteworthy that BAFF transgenic mice develop a phenotype resembling that of human lupus and as the mice age, lymphocytic infiltrates infiltrate the salivary glands [40]. Selective BAFF inhibition can be achieved either with monoclonal antibody to BAFF (belimumab) or with soluble BAFF receptor (such as briobacept – a fusion protein of IgG–Fc and the extracellular domain of the BAFF receptor). Atacicept – a fusion molecule of IgG–Fc and the extracellular domain of the TACI (the shared receptor for BAFF and a proliferation-inducing ligand) – is a blocker of both BAFF and its homolog a proliferation-inducing ligand [3,62]. Taken together, targeting the BAFF holds significant promise in the treatment of SS, with results from several ongoing trials being awaited.

**Monoclonal antibodies against type I IFN**

Activation of type I IFN pathway in the setting of primary SS has been convincingly demonstrated. Elevated type I IFN plasma levels, increased expression of IFN-inducible genes in peripheral mononuclear cells and labial salivary gland biopsies from primary SS patients indicate this cytokine as a potential orchestrator of the immunological response in primary SS and a novel therapeutic target given that monoclonal antibodies against IFNα are currently tested in clinical trials in systemic lupus erythematosus and dermatomyositis/polymyositis [63]. Surprisingly enough, earlier studies have
demonstrated a beneficial role of IFNα per se in alleviation of sicca symptoms and improvement of salivary gland function [64] possibly through induction of aquaporin-5 expression. Combined results from two Phase III clinical trials have been reported on a total of 497 primary SS patients who received 150 international units of human IFNα or placebo three-times per day for 24 weeks by the oromucosal route. While unstimulated whole saliva flow has been significantly increased in the IFNα group, oral dryness and stimulated whole salivary flow were not significantly improved [65].

Costimulation as a therapeutic target
Since salivary gland epithelial cells in primary SS have been previously suggested as having an antigen-presenting role evidenced by the inappropriately expression of class II and other costimulatory molecules, targeting costimulation seems a logical approach [66]. While early blockade of the ICAM-1/lymphocyte function-associated antigen-1 interaction in an experimental model with a chimeric protein composed by soluble ICAM-1 and the Fc portion of the IgG (soluble ICAM-1/Fc) resulted in reduction of lymphocytic infiltration, intervention at a later disease stage seemed to deteriorate the SS like phenotype, when infiltrates have already formed within the salivary glands. In view of these findings, the authors suggest that caution should be taken targeting the ICAM-1 axis in human SS given that the vast majority of patients are diagnosed when inflammation is already present within the salivary glands [67]. Studies with abatacept, an inhibitor of costimulation already tested in rheumatoid arthritis with successful results, are underway in SS.

Conclusion
In an attempt to address the question of cytotoxics/immunosuppressives or biologicals in the treatment of SS, several issues should be taken into consideration. First, it should be borne in mind that in their large majority, primary SS patients share a benign course manifested mainly with oral and ocular dryness that might require sole application of local measures and the usage of muscarinic agonists (pilocarpine and cevimeline). For these cases, as it has been previously mentioned, systemic cytotoxics/immunosuppressives, in their vast majority, do not seem to offer substantial help. On the other hand, among currently available biological agents, anti-B-cell strategies and particularly rituximab has shown promising results in the alleviation of subjective and objective indices of oral dryness, in the presence of residual salivary gland function, with less pronounced data in regard to improvement of ocular dryness. However, no data to date allow the direct comparison of the effect of muscarinic agonists plus local measures and rituximab, and therefore at this stage, prescribing rituximab as a first line agent for the alleviation of isolated sicca features seems unlikely.

For years management of severe extra-glandular features in the setting of primary SS such as peripheral neuropathy, cutaneous vasculitis or severe glomerulonephritis required the usage of high-dose steroids along with cyclophosphamide followed by azathioprine as maintenance therapy, a regimen associated with substantial toxicity. The implication of ongoing B-cell activation in the pathophysiology of the aforementioned features together with promising results mostly derived by retrospective registry data or as secondary points in the two randomized controlled trials suggests rituximab as a major therapeutic player in this context. However, the impact of rituximab in the prevention or delay of lymphoma development in these patients with indices of intense B-cell activity remains to be determined. In patients with joint involvement, HCQ and methotrexate seem first-line viable options, while in refractory cases administration of rituximab could be considered.

With regard to lymphoma management, combination of cytotoxics with rituximab provide survival benefit in SS-related aggressive B-cell lymphomas and therefore it is highly recommended, while localized parotid gland MALT lymphoma seems to require ‘a wait and see’ policy. Whether extranodal MALT lymphoma might benefit from treatment with rituximab remains to be determined.

Future perspective
Identification of novel pathways in the pathogenesis of SS allowed the introduction of new therapeutic approaches in the treatment of the syndrome, with rituximab being revolutionary in the management of systemic features. However, prior to wide implementation of the new treatments in clinical practice several issues such as the time of re-administration, the long-term safety profile as well the identification of biomarkers of response remain to be addressed. In a recently reported pilot study, differential expression of B cell and IFN pathway signaling molecules seemed to be important prognosticators of

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Future science group
response in SS patients receiving rituximab [68]. The design of large randomized controlled trials with anti-CD20, anti-CD22 and anti-BAFF therapies will delineate their role in clinical practice identifying patient subgroups who are likely to respond. Abatacept, composed of an immunoglobulin fused to the extracellular domain of the inhibitory cytotoxic T-lymphocyte antigen-4, is also a promising new therapeutic option requiring further investigation. Finally, given that activation of type 1 IFN signature has been observed in SS patients, identification of patient subsets who would benefit from such an inhibition reserves to be explored.

Executive summary

**Immunosuppressives/cytotoxics**
- Systemic immunosuppressives/cytotoxics are useful in the management of selected extraglandular features (arthritis, peripheral neuropathy, cutaneous vasculitis).

**Biological agents**
- Anti-TNF agents failed to demonstrate a meaningful clinical effect in the alleviation of Sjögren’s syndrome-related clinical features.
- B-cells seem to be central in Sjögren’s syndrome pathogenesis.
- Anti-B-cell strategies, particularly rituximab, have a prominent effect in the treatment of extraglandular features.
- Combination of rituximab with cytotoxics is recommended in high grade B-cell lymphoma.
- Ongoing trials of anti-B-cell activating factor and anticostimulation therapies are underway.

**References**

Papers of special note have been highlighted as:
- of interest
- of considerable interest

23 Skopoulis FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjogren’s

**First randomized controlled study on infiximab treatment on SS.**


**First randomized controlled study on etanercept treatment on SS.**


**Randomized controlled study on rituximab treatment on SS.**


**Randomized controlled study on rituximab treatment on SS.**


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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

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1. Your patient is a 53-year-old white woman with dryness of the eyes and mouth, diagnosed as Sjogren syndrome (SS). Based on the review by Dr. Mavragani and colleagues, which of the following statements about her condition is most likely correct?

- A. SS is characterized by chronic granulocytic infiltration of salivary and lachrymal glands
- B. Other than eyes and mouth, skin and joints are the only other organ systems involved in SS
- C. Empirical treatment may include eye lubricants, saliva substitutes, and stimulants of glandular secretion
- D. Solid evidence supports excellent efficacy of systemic cytotoxics and immunosuppressives for sicca symptoms

2. On examination, you find that the patient described in question 1 has evidence of arthritis and cutaneous vasculitis. Based on the review by Dr. Mavragani and colleagues, which of the following statements about the use of systemic immunosuppressives/cytotoxics is most likely correct?

- A. Systemic immunosuppressives/cytotoxics may be useful in managing arthritis and cutaneous vasculitis associated with SS
- B. Systemic immunosuppressives/cytotoxics are of no value in managing peripheral neuropathy
- C. Understanding the role of T-cells in SS pathogenesis has led to development of new therapeutic agents
- D. Agents targeting including B-cell activating factor are currently approved for use in SS

3. Based on the review by Dr. Mavragani and colleagues, which of the following statements about the role of biologics in treating SS and its associated manifestations is most likely correct?

- A. Anti-TNF agents are extremely effective in alleviating SS-related clinical features
- B. Rituximab may help relieve oral dryness in patients with residual salivary gland function
- C. Anti-B-cell agents are proven to be superior to muscarinic agonists plus local measures for relieving ocular sicca symptoms
- D. Localized parotid gland MALT lymphoma should be immediately treated with a combination of cytotoxics with rituximab