Biologic treatments in Sjögren’s syndrome

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Summary

Primary Sjögren’s Syndrome (pSS) is characterized by focal lymphocytic infiltration of exocrine glands associated with severe dryness of eyes and mouth in particular. Systemic features such as disabling fatigue, cutaneous vasculitis, lung, neurological, haematological or other systemic involvement also occur. Conventional immunosuppressive therapies such as corticosteroids or disease-modifying drugs, have been used in some patients with these systemic features with variable benefit. Current therapy for dryness is principally symptomatic although medications to stimulate residual glandular secretion can be helpful for appropriate individuals. As the pathogenesis of the condition becomes better understood, particularly, in recent years, the role of systemic B-cell activation, biologic therapies specifically targeted against molecules involved in disease pathogenesis represent a more targeted approach to therapeutic intervention. The greatest experience in pSS is with rituximab, an anti-CD20 (expressed on a subset of B-cells) monoclonal antibody already in use for the treatment of some B-cell lymphomas and rheumatoid arthritis. Randomised placebo-controlled studies in pSS are currently underway. This review discusses the rationale for using biologic therapies in pSS, the current data on rituximab and the potential use of other biologic therapies in pSS in the future.

Primary Sjögren’s syndrome (pSS) is a systemic immune-mediated condition in which inflammation of exocrine glands typically leads to dry eyes and dry mouth and in some patients to chronic salivary gland swelling [1]. The exocrine glands are infiltrated by focal aggregations of lymphocytes clustered around the salivary ducts and described as ‘focal lymphocytic sialadenitis’ on labial gland biopsy. Dryness of other surfaces such as the skin, vagina, bronchial tubes and gastrointestinal tract is common. Systemic features can also occur including variable, severe, debilitating fatigue, neuropathies, skin rashes (purpura, vasculitis),...
interstitial lung disease, renal tubular acidosis and haematological abnormalities. There is a 44 times increased risk of B-cell lymphoma [2]. Typically these are mucosa-associated lymphoid tissue (MALT) lymphomas and may be localized to the salivary glands but can also occur at other locations or be more widespread. High-grade lymphomas such as diffuse large B-cell (DLBCL) lymphomas are also seen. Predictors of lymphoma include lymphopaenia, hypergamma-globulinaemia, low complement C4 levels, and the presence of paraproteins and/or cryoglobulins as well as clinical indicators such as persistent salivary gland swelling, cutaneous vasculitis and neuropathies [3,4].

PSS is about 15 times commoner in women than men and studies over the past few years using the American-European Consensus Group (AECG) Criteria suggest a prevalence of about 1 in 1000 to 1 in 250 adult women in Europe and North America [5]. Traditional disease-modifying therapies, used in conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), have only had modest effects, if at all, in pSS (see below). Approximately three-quarters of patients have serum autoantibodies – anti-Ro and/or anti-La antibodies, often associated with raised total immunoglobulin levels (hypergamma-globulinaemia). This observation, along with the greater increased risk of B-cell lymphoma in pSS has placed B-cell targeted therapies at centre-stage in the search for novel therapies in this condition. Secondary Sjögren’s syndrome describes the presence of the glandular features of Sjögren’s syndrome in patients with a pre-existing rheumatic disease such as RA, SLE or scleroderma. Secondary SS will not be addressed further in this review.

**Disease impact and the justification for biologic therapy in primary Sjögren’s syndrome**

It is straightforward to justify the use of expensive biologic therapies in pSS patients with severe systemic involvement who fail to respond to conventional immunosuppression, despite the rare but potentially serious side effects of biologic therapy. Similarly, the use of rituximab in treating B-cell lymphoma in pSS is now well established (see below). What is less clearcut is the role for biologic therapies in pSS patients with sicca syndrome and/or fatigue alone. One argument is that the current expense of these therapies does not justify their use at this time in patients who do not have systemic involvement. PSS, however, even without systemic involvement, is not a trivial matter: Severe dry mouth is an unpleasant and disabling condition. Variable, severe, debilitating fatigue is also a common symptom in patients with pSS and is comparable in severity to that seen in patients with RA or SLE and is likely to be a significant contributor to reduced health-related quality of life (HRQoL) in patients with PSS [6]. There is evidence to support the argument that fatigue in pSS may have a biological component [7]. There is also a cost to patients and the health service of PSS. In a study that we performed in the UK, the annual direct healthcare costs of having pSS were approximately £2188 per year per patient compared to £2693 per year per patient for RA [8]. Although this study was performed before the widespread use of biologic therapies in RA it suggests that the costs associated with pSS are 50–80% of those associated with having RA. The results of a subsequent study examining indirect costs were very similar [9] and supports the argument that pSS has a significant health economic impact. If a biologic therapy demonstrates symptomatic improvement in pSS then the data on HRQoL may be sufficient to justify the introduction of such therapies into clinical practice as it has been for RA.

**Current therapies for primary Sjögren’s syndrome**

**Therapies for sicca features**

Patients with mild oral and/or ocular dryness may self-manage their symptoms e.g. with artificial tears such as hyaluronate, sipping water frequently, using oral gels/sprays/lozenges and careful dental hygiene. More severe ocular dryness can be managed through careful eyelid hygiene, more regular use of preservative-free viscous artificial tears and blockage of the tear (run-off) ducts so as to keep tears on the surface of the eyes for longer. In the USA and Japan, cyclosporin eye drops are available for use in Sjögren’s syndrome to reduce ocular dryness.

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**Glossary**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AECG</td>
<td>American-European consensus group</td>
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<tr>
<td>BAF</td>
<td>B-cell activating factor</td>
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<tr>
<td>BlyS</td>
<td>B-lymphocyte stimulator</td>
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<tr>
<td>CHOP</td>
<td>cyclophosphamide, Adriamycin, vincristine and prednisolone</td>
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<tr>
<td>CVP</td>
<td>cyclophosphamide, vincristine and prednisone</td>
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<tr>
<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
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<td>ESSDAI</td>
<td>EULAR Sjögren’s Syndrome Disease Activity Index</td>
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<td>ESSPRI</td>
<td>EULAR Sjögren’s Syndrome Patient Reported Index</td>
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<tr>
<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<td>FDA</td>
<td>Food and Drug Administration (USA)</td>
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<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
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<tr>
<td>IFN</td>
<td>interferon</td>
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<tr>
<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
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<td>NMZL</td>
<td>nodal marginal zone lymphoma</td>
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<tr>
<td>PML</td>
<td>progressive multifocal leukoencephalopathy</td>
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<td>pSS</td>
<td>primary Sjögren’s syndrome</td>
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<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
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<td>TEARS</td>
<td>tolerance and efficacy of Sjögren’s disease</td>
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<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
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surface inflammation [10]. Pilocarpine is a muscarinic agonist that stimulates salivary glands to produce saliva provided that there is some remaining functional gland [11]. Cevimeline is a similar drug available in the USA and Japan [12]. Studies of conventional disease-modifying drugs have not shown any major effect on sicca symptoms, although modest benefits have been reported in some cases (see below).

**Systemic therapies; hydroxychloroquine and low-dose prednisolone**

Hydroxychloroquine has been widely used to treat musculoskeletal symptoms such as fatigue and joint pains in pSS [13,14]. There has not been a large double-blind randomised controlled study to prove its effectiveness on these systemic symptoms, although such a study is now recruiting in France (http://clinicaltrials.gov/ct2/show/NCT00632866). Several small studies have also suggested potential benefit in sicca symptoms and glandular function [15,16] reduction in B-cell activating factor (BAFF) [17] and also an in vitro effect on secretory mechanisms [18]. Low-dose prednisolone is also often used although formal evaluation in a small study again did not demonstrate clear benefit [19].

**Conventional disease-modifying therapies**

Azathioprine [20], methotrexate [21], ciclosporin [22], leflunomide [23] and mycophenolate [24] have all been evaluated in small studies. Although some modest improvements were seen in various parameters, none of these studies demonstrated sufficient benefit to warrant general use. In the case of more significant systemic features such as arthritis, interstitial lung disease, cutaneous features or neuropathies, disease-modifying agents such as these may be helpful in individual cases based on extrapolation from the treatment of patients with other systemic rheumatic disease. The same applies to patients with severe systemic involvement e.g. severe progressive sensorimotor neuropathy who may require intensive immunosuppression with intravenous steroids and cyclophosphamide [25].

**Therapy of B-cell lymphoma in primary Sjögren’s syndrome**

Treatment of B-cell lymphoma in pSS varies from a ‘watch and wait’ approach in indolent, localized, MALT lymphoma, to aggressive chemotherapy combined with rituximab for disseminated and/or high-grade MALT or DLBC lymphoma [26,27]. The most widely used chemotherapy regime is CHOP (Cyclophosphamide, Adriamycin, Vincristine and oral prednisolone), or, variants of this regime such as cyclophosphamide, vincristine, and prednisone (CVP) and for the past 5–10 years standard practice is to combine the chemotherapy with the anti-CD20 monoclonal antibody rituximab (CHOP-R or CVP-R) for therapy of high-grade follicular non-Hodgkins lymphoma (NHL) and for low-grade lymphoma that has relapsed after conventional chemotherapy [28,29]. In the first of the above series of 53 patients with pSS and lymphoma, nine patients with asymptomatic low-grade MALT lymphoma were treated expectantly, eight patients with limited-stage MALT lymphomas and extraglandular manifestations were treated with rituximab, 10 MALT lymphoma patients with disseminated disease received chemotherapy with or without rituximab and patients with DLBC received CHOP-R. The prognosis for the patients with MALT and DLBC lymphomas was good with 97–100% 3-year overall survival but for a minority of patients with nodal marginal zone lymphomas (NMZL) it was more guarded at 80% 3-year overall survival. In the second case series of 35 patients with parotid MALT lymphoma, with a median follow-up of 76 months (range: 16–153 months), treatment consisted of ‘watchful waiting’ in 10 patients, surgery and/or radiotherapy in six, rituximab only in 13, and rituximab combined with chemotherapy in six. Complete response was observed in 14 patients, partial response in one patient, and stable disease in 20 patients. The use of rituximab for the treatment of pSS with lymphoma also enabled physicians to gain initial experience of the effectiveness of rituximab on general features of the disease in patients with pSS, in that as well as suggesting potential benefit for systemic and glandular features of pSS in those lymphoma patients with shorter disease duration, they also included data on some patients with pSS alone [30–32]. Rituximab in cancer therapy is not without its risks, however. It can be associated with infusion-related reactions including severe cytokine release syndrome and hypersensitivity. These usually occur within two hours of the first administration and are characterized by severe breathlessness, fever, chills, rigors, urticaria and angioedema. Care should, therefore, be taken when using rituximab in patients with a high tumour burden or a high number of circulating malignant cells. Rituximab when added to chemotherapy has also been associated with worse neutropenia than when using chemotherapy alone. Since lymphoma can be life-threatening in some patients with pSS, it is likely that most patients will accept these potential risks of rituximab in this context. Cytokine release syndrome is likely to be less of an issue in the context of treating pSS alone.

**Biologic therapies – Terminology**

The term biological therapy is generally used to refer to large synthesized molecules such as monoclonal antibodies that are directed against specific targets (table I). In rheumatic diseases these targets are usually either molecules involved in the immune system such as cytokines, or surface molecules, cluster differentiation (CD) or receptors expressed on cells of the immune system such as B or T-cells. They have been in widespread clinical usage over the past decade. They are generally expensive (annual cost/patient circa 4,000–12,000 euros per
year), although over the next few years, as they start to come off patent, the costs of ‘biosimilars’ coming on to the market may be lower. Biologic therapy to block the action of tumour necrosis factor alpha (TNFα) is used to treat RA, ankylosing spondylitis, Crohn’s disease and psoriatic arthropathy [33]. Other biologics already in routine clinical usage in the treatment of RA include Tocilizumab (anti-IL-6) and Abatacept (a fusion protein of CTLA-4 linked to the Fc portion of IgG1 which is similar to CD28 and interferes with T-cell co-stimulation). Belimumab, an antibody directed against B-cell activating factor (BAFF)/B-lymphocyte stimulator (BlyS) has recently been licensed for use in SLE [34] and we have already discussed the use of rituximab in B-cell lymphoma and RA.

**Challenges in clinical trials of biologics in primary Sjögren’s syndrome**

As we move into the era of biologic therapies for pSS it will be a requirement to conduct randomized double-blind controlled trials to demonstrate the effectiveness of these therapies. This requires consideration of inclusion and exclusion criteria for such trials as well as of outcome measures and endpoints. In terms of inclusion and exclusion criteria, the issues will include the level of systemic involvement required (if any), whether to require the presence of serological features such as anti-Ro/La autoantibodies ± hypergammaglobulinaemia, the level of dryness and general symptoms, the degree of glandular dysfunction and of disease duration and whether salivary gland biopsy is mandatory. Another challenge is to determine what to measure in terms of improvement and outcome assessment. The core disease-related domains are assessment of dryness and other disease-related symptoms, assessment of systemic disease-related features and objective assessment of dryness and other glandular-related features. Dryness, fatigue and pain symptoms can be assessed through visual analogue scales and Likert scales either individually or as part of symptom questionnaires [35-37]. A project sponsored by the European League against Rheumatism (EULAR) is taking place in Europe, North America and elsewhere to validate a short symptom questionnaire; the EULAR Sjögren’s Syndrome Patient Reported Index (ESSPRI) [38,39]. This gives equal weighting to three symptoms: dryness, fatigue and pain. Patient global is often added to make a fourth outcome symptom domain e.g. in the Tolerance and Efficacy of Rituimab in Sjögren’s Disease (TEARS) study the primary outcome is a 30% improvement

<table>
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<tr>
<th>Table 1</th>
<th>Summary of potential monoclonal antibodies for primary Sjögren’s syndrome after [150].</th>
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<tbody>
<tr>
<td><strong>Target</strong></td>
<td><strong>Name</strong></td>
</tr>
<tr>
<td><strong>B-cell markers</strong></td>
<td></td>
</tr>
<tr>
<td>CD20</td>
<td>Rituximab, Ocrelizumab, Aftuzumab, Ibrituzumab, tiuxetan, Ofatumumab, TRU-015, Tositumomab, Veltuzumab</td>
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<tr>
<td>CD19</td>
<td>Taplitumomab paptox</td>
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<tr>
<td>CD22</td>
<td>Epratuzumab, Inotuzumab/ozogamicin</td>
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<tr>
<td>Other B-cell markers</td>
<td>Detumomab, Galiximab</td>
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<tr>
<td><strong>Cytokines</strong></td>
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<tr>
<td>Blmys/BAFF ± April</td>
<td>Belimumum, Atacicept</td>
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<tr>
<td>IL-6</td>
<td>Tocilizumab, Elsilimomab, ALD518 IL-6 and Siltuximab</td>
</tr>
<tr>
<td>IL-12/IL-23</td>
<td>Briakinumab (ABT-874), Ustekinumab (CTNO-1275)</td>
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<tr>
<td>Interferon-alpha</td>
<td>Rontalizumab, Sifalimumab</td>
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<tr>
<td>Interferon-gamma</td>
<td>Fontolizumab</td>
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<tr>
<td><strong>Adhesion molecules</strong></td>
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<tr>
<td>VCAM-1</td>
<td>K-13182</td>
</tr>
<tr>
<td>CD11/CD18</td>
<td>Efalizumab/Raptiva (targeting CD11a), Erlizumab (targeting CD18), Ravelizumab/LeukArrest (CD11/CD18)</td>
</tr>
<tr>
<td><strong>Cell-cell interactions</strong></td>
<td></td>
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<tr>
<td>LFA-3/CD2</td>
<td>Alefacept</td>
</tr>
<tr>
<td>CD80/CD86/CD28/CTLA-4</td>
<td>Abatacept, Tremelimumab, Ipilimumab</td>
</tr>
<tr>
<td>CD40L (CD154)/CD40</td>
<td>Ruplizumab (hu5C8, BG9588, Antova), Toralizumab (IDEC-131/E6040)</td>
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</table>
between Day 1 and Week 24 in the values on 2 of 4 VAS measuring global scores of the disease (activity of the disease including extraglandular manifestations), joint pain, fatigue, and the most disturbing dryness (ClinicalTrials.gov NCT00740948). A parallel project is taking place to validate a systemic disease assessment tool; the EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) [40,41] following on from previous work in Italy [42] and the UK [43,44] to develop disease activity and damage indices. Objective measures of unstimulated and stimulated salivary flow and of tear production using Schirmer’s test strips or more sophisticated ocular assessment using a slit-lamp are typically also used as a further domain alongside symptom measures and systemic disease assessment. The major variant among trials, at this time, is defining the details of the primary outcome measure either as a variation of the above, or a composite measure and this is yet to be finalized although the analysis of the data from the EULAR studies may go some considerable way towards clarifying this.

**Risks of using biologic therapies in primary Sjögren’s syndrome and other conditions**

Biologic therapies are expensive and not without potential risk. Anti-TNF therapy in RA is associated with an increased risk of infection [45], particularly of tuberculosis (TB) [46]. Rituximab in RA has so far not been associated with a major increased infection risk [47], which is encouraging. Serum sickness, which is characterized by fever, rash, and joint pains, can occur in patients who receive chimeric monoclonal antibody therapy and has been reported following rituximab therapy. There is the risk of hypogammaglobulinaemia with repeated courses of Rituximab treatment although whether this translates into a major infection risk is not yet clear [48]. Ocrelizumab is a fully humanized anti-CD-20 monoclonal antibody currently undergoing clinical trials in rheumatoid arthritis although its usage may be limited by an increased risk of infections in Asian patients receiving this therapy [49]. Biologic therapies are also potentially associated with an increased risk of one particularly severe side effect: progressive multifocal leucoencephalopathy (PML). This is a rare, fatal, central nervous system demyelinating disease that results from reactivation of the JC virus, which usually occurs in immunosuppressed hosts [50]. PML has developed in patients with RA or SLE who have not received biologic therapy so it is not simply attributable to the medication but there does appear to be an increased risk associated with the medication [51]. Most of the patients who were on biologic therapies when they developed PML had previously received substantial immunosuppression but this is not always the case. PML is rare, but even so, the risk of developing this complication must be considered in the decision to use biologic therapies in pSS and other conditions [52].

**The use of currently available biologic therapies in primary Sjögren’s syndrome**

**Rituximab in primary Sjögren’s syndrome without lymphoma**

Rituximab is already available and licensed for use in RA and lymphoma. The basic rationale for investigating the use of rituximab in pSS has already been described above and is also reviewed elsewhere [53]. In summary: the presence of hypergammaglobulinaemia, anti-Ro/La antibodies, cryoglobulinaemia, low complement C4 levels and hypergammaglobulinaemic purpura suggest B-cell involvement in the extraglandular features of pSS. The link between many of these features and the development of B-cell lymphoma in pSS also provides a strong rationale for the potential use of B-cell depleting therapy in pSS. In many patients, germinal centers predominantly constituted of naïve (IgD+CD20+) and mature (IgD–CD20+) B-cell form within the salivary glands, which appear to be producing anti-Ro/La autoantibodies (figure 1A) [54]. Other clinical features that appear to be at least partially B-cell driven and respond to rituximab include salivary gland swelling [55] and demyelinating [56] and cryoglobulinaemic neuropathy [57]. What is still under investigation is whether rituximab will improve glandular function and fatigue and whether B-cells play a role in the maintenance of the periductal lymphocytic infiltrates that are the hallmark of pSS [58] and are made up predominantly of CD4+ve T-cells. In studies of B-cell depletion (rituximab) therapy, although a reduction in salivary gland B-cell infiltration is seen [59,60], it is less clear whether there is a consequent reduction in salivary gland T-cell infiltration as well [61]. In a retrospective case review of six patients with pSS treated with 4 × 375 mg/m² rituximab methylprednisolone, there was regression of parotid swelling in five of six patients, improvement in articular involvement, improvement in fatigue in two cases, improvement in subjective dryness in three cases, and improvement in cryoglobulinaemia and related vasculitis in two cases [62]. Rheumatoid factor levels decreased in the three responders, whereas anti-SSA/SSB antibodies remained detectable after rituximab. An open-label study of 16 patients treated with the same regime demonstrated improvement in fatigue, pain, dryness, patient global VAS and SF-36 scores [63]. A similar study of 15 patients also demonstrated an increase in stimulated salivary flow rates [30,31]. In a retrospective study of 11 PSS patients with severe systemic features, improvement was observed in nine [32]. In a study in the USA of 12 pSS patients given rituximab 1 g on two occasions 2 weeks apart, significant improvements were seen at 26 weeks in VAS scores of patient and physician global assessments, fatigue and joint pain but not dryness symptoms or salivary flow rates [64]. A 6-month pilot double-blind randomized controlled trial (RCT) of rituximab 1 g at time 0 and 15 days versus placebo in treating fatigue in...
17 patients with pSS. This study showed a significant improvement in the fatigue visual analogue scale (VAS) between baseline and 6 months in patients who received active therapy [65]. This pilot study was not designed to evaluate salivary symptoms or function. A second double-blind randomised controlled trial of 30 patients has also been published [66]. Twenty patients were treated with rituximab 1 g × 2 and 10 with placebo. The active group showed significant improvement in stimulated salivary flow and oral dryness VAS at 6 months whereas the placebo group did not. Both groups showed improvement in fatigue as measured by the multidimensional fatigue inventory. At the present time, a French phase-II, double-blind, placebo-controlled, randomised clinical trial of rituximab has completed recruitment (http://clinicaltrials.gov/ct2/show/NCT00740948) and a second trial has started in the UK (http://ctrui.leeds.ac.uk/tractiss).

Other anti-B-cell directed therapies
As well as rituximab and ocrelizumab, there are a number of other listed B-cell directed monoclonal antibodies (http://www.who.int/medicines/publications/druginformation/en/) including other anti-CD20 directed agents (e.g. afutuzumab, ibritumomab tiuxetan, ofatumumab, TRU-015, tositumomab, veltuzumab), anti-CD19 (e.g. tafilitumomab paptox), anti-CD22 (e.g. epratuzumab, inotuzumab/ozogamicin) or agents that target other B-cell/lymphoma markers (e.g. detumomab, galiximab). Of these, Epratuzumab has been studied in pSS. In an open-label study of four infusions of epratuzumab 360 mg/m² given once every 4 weeks in 16 patients, there was significant improvement at 6 months in a composite endpoint that included unstimulated salivary flow rate, fatigue, ESR and IgG [67]. In addition, there was improvement in fatigue VAS and physician global assessments.

Anti-BLyS/BAFF and other agents directed at B-cell cytokines
The B-cell related cytokine that is currently felt to be of most interest in pSS is B-cell lymphocyte stimulator (BllyS)/B-cell activating factor (BAFF) [68,69]. Blys was discovered at the same time by two independent research groups. A member of the human TNF family, it induces B-cell proliferation and immunoglobulin secretion and soluble BllyS/BAFF is a potent B-cell growth factor in co-stimulation assays. Administration of soluble recombinant BllyS/BAFF to mice disrupts splenic B and T-cell zones and results in elevated serum immunoglobulin concentrations and mice transgenic for BAFF develop autoantibodies and autoimmune phenotypes [70]. In pSS, there is now extensive data on the potential role of BllyS/BAFF in driving B-cell hyperactivity [71–78]. These studies have shown raised soluble BllyS/BAFF levels in the serum, raised expression of BllyS/BAFF by peripheral blood mononuclear cells, epithelial cells, T-lymphocytes and on B-cells within the salivary glands of patients with pSS (figure 1B). Mice deficient in ACT-1, a down-regulator of BllyS/BAFF develops a sjögren’s-like disease [79]. There is also data that in pSS patients with high pre-rituximab treatment levels of BllyS/BAFF, B-cell recovery occurs sooner following rituximab therapy and also that BllyS/BAFF/levels

![Figure 1](image-url)

**Figure 1**
Photomicrophotograph showing sequential sections of minor salivary gland of SS patient stained with CD20 (pink) and IgD (brown) (A) and BAFF (B) showing large aggregates of both CD20+IgD+ naive-like B-cells and IgD-mature-like B-cells. Sequential section showing local expression of the B-cell survival factor within the B-cell aggregates (original magnification × 20 A and B).
increase following B-cell depletion [80]. Persistently raised BlyS/BAFF levels can also be associated with resistance to rituximab therapy in PSS patients with lymphoma [81]. Therefore, it will be important to measure BlyS/BAFF levels as part of any therapeutic trial of rituximab, both before and after therapy and in relating these levels to clinical disease activity. BlyS/BAFF has membrane-bound and soluble forms. There are three receptors for BAFF: BAFF receptor (BR3) and TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) on B and T-cells and BCMA (B-cell maturation antigen) on B-cells. A further member of this family of molecules is APRIL (a proliferation-inducing ligand). APRIL only binds BCMA and TACI, not BAFF-R. This is a complex system in which homo and heterotrimers of BAFF and APRIL can form [82]. The role of APRIL in autoimmunity is less clear-cut although the serum level of soluble APRIL is also raised in patients with PSS. APRIL expression in the salivary glands of SjS patients has also been observed (Barone F. unpublished and figure 2).

A monoclonal antibody that recognizes soluble BlyS/BAFF, belimumab, has successfully completed clinical trials in SLE [83] and is already in clinical use. Although trials of belimumab in pSS have been registered on www.clinicaltrials.gov (table II), the status of these studies is unknown. Atacicept isconstituent fusion protein designed to block the activity of both BlyS/BAFF and APRIL. An initial study of atacicept with mycophenolate in SLE had to be terminated prematurely due to infection in three out of six patients [84]. One reason why BlyS/BAFF is of particular interest in pSS is that it also links with other components of the immune system that may be relevant to pathogenesis in PSS. For example BlyS/BAFF expression is upregulated by other cytokines such as interferon-alpha and gamma and a potential role for viruses in upregulating BlyS/BAFF expression on salivary gland epithelial cells could be exercised, at least in part, through Toll-like Receptors (TLRs) of the innate immune system [85]. These relationships will be discussed further below.

Anti-TNF agents

Since anti-TNF is effective in RA it could potentially have similar benefits on the glandular lesions in pSS. Mariette et al. studied 103 patients who either received infliximab infusions 5 mg/kg or placebo at weeks 0, 2 and 6 with follow-up at 22 weeks [86]. Infliximab did not lead to greater improvement than placebo in dryness symptoms, fatigue, joint pain, short-form–36 (SF-36) item questionnaire scores, objective dryness measures, salivary gland biopsy or serological markers. 27.8% of infliximab-treated patients and 26.5% of placebo-treated patients showed an improvement (> 30%) in the composite primary endpoint of fatigue, joint pain and dryness visual analogue scales. Two small (28 and 15 patients) studies of etanercept showed similarly negative results [87,88]. One potential explanation for this is that in PSS, suppression of TNFα leads to a compensatory increase in other TNF family cytokines including BlyS/BAFF, thus undermining any benefit from TNFα suppression [89].

Anti-IL-1 (anakinra)

IL-1 is a pro-inflammatory cytokine that is associated with fatigue and pyrexia. A randomized controlled trial of an IL-1 receptor antagonist (anakinra) versus placebo in pSS showed...
that six out of 12 patients receiving anakinra had reduced fatigue at 4 weeks compared to only one out of 13 receiving the placebo (P = 0.03) [90].

**Anti-IL-6 directed therapies**

IL-6 is an important mediator of the acute phase response. Its levels are raised in many autoimmune diseases and it can activate both T and B-cells [91]. A number of studies have identified raised IL-6 levels in the serum and salivary glands of patients with PSS [76,92–101]. Whether there is a direct correlation between serum IL-6 or soluble IL-6 receptor levels and clinical features such as fatigue or health-related quality of life in pSS is a matter of ongoing debate [102–104]. Of interest, hydroxychloroquine, often used empirically in pSS (see above) may suppress serum and salivary IL-6 levels [14]. Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody, now in clinical use in RA [105]. Although there is no clinical trial data in PSS, it is an attractive candidate for use in PSS. Other anti-IL-6 monoclonal antibodies in development include elsitlimomab, ALD518 IL-6 and siltuximab.

**Co-stimulation – Abatacept and related therapies**

Another approach that could be adopted in PSS includes targeting co-stimulatory molecules such as the interaction between CD80 and CD86 on the surface of antigen-presenting cells and CD28 on the surface of T-cells using abatacept. Abatacept is a fusion protein of CTLA-4 linked to the Fc portion of IgG1. CTLA-4 is similar to CD28 and interferes with this interaction thus inhibiting T-cell activation. Abatacept is licensed for the treatment of RA [106]. The rationale of using these drugs resides in their activity as T-cell co-stimulation blockers. Reducing the level of antigen-driven T-cell activation within the glands leads to reduced B-cell activation. In terms of other potential pipeline therapies: belatacept is another CTLA-4 Ig fusion protein that has been licensed for use in treatment of renal transplant rejection. Tremelimumab and ipilimumab are monoclonal antibodies that target CTLA-4. ICOS (inducible costimulator of T-cells) is another co-stimulatory molecule critical in the generation of the germinal center reaction. ICOS is a CD28-like molecule that interacts with B7RP-1. An anti-B7RP-1 antibody ameliorated autoimmunity in two mouse models of autoimmunity [107] therefore setting the scene for considering ICOS.

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**Table II**

Clinical trials of biologic therapy posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

<table>
<thead>
<tr>
<th>Title</th>
<th>Reference</th>
<th>Location</th>
<th>Date</th>
<th>Status</th>
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<tr>
<td>Etanercept Therapy for Sjögren’s Syndrome</td>
<td>NCT00001954</td>
<td>National Institutes of Health Clinical Center (CC), USA</td>
<td>1999</td>
<td>Completed</td>
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<td>A Randomized, Double-blind, Placebo-controlled Phase II Clinical Trial of Baminercept, a Lymphotoxin-beta Receptor Fusion Protein, for the Treatment of Primary Sjögren’s Syndrome (ASJ02)</td>
<td>NCT01552681</td>
<td>National Institute of Allergy and Infectious Diseases (NIAID), USA</td>
<td>2012</td>
<td>Not yet started</td>
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<td>Tolerance and Efficacy of Rituximab in Sjögren’s Disease (TEARS)</td>
<td>NCT00740948</td>
<td>University Hospital, Brest, France</td>
<td>2008</td>
<td>Completed recruitment</td>
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<tr>
<td>Raptiva to Treat Sjögren’s Syndrome</td>
<td>NCT00344448</td>
<td>National Institutes of Health Clinical Center (CC), USA</td>
<td>2006</td>
<td>Completed</td>
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<td>Efficacy and Safety of Belimumab in Subjects With Primary Sjögren’s Syndrome (BELISS)</td>
<td>NCT01160666</td>
<td>Hôpitaux de Paris, France</td>
<td>2010</td>
<td>Unknown</td>
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<td>Efficacy and Safety of Belimumab in Primary Sjögren’s Syndrome</td>
<td>NCT01008982</td>
<td>University of Udine, Italy</td>
<td>2009</td>
<td>Unknown</td>
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<td>Effect of B-cell Depletion in Patients With Primary Sjögren’s Syndrome</td>
<td>NCT00426543</td>
<td>University of Copenhagen, Denmark</td>
<td>2007</td>
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<td>Anti-CD20 Antibody Therapy for Sjögren’s Syndrome</td>
<td>NCT00101829</td>
<td>National Institute of Allergy and Infectious Diseases (NIAID), USA</td>
<td>2005</td>
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<td>Fatigue and Interleukin-1 (IL-1) Blockade in Primary Sjögren’s Syndrome</td>
<td>NCT00683345</td>
<td>Helse Stavanger HF, Norway</td>
<td>2008</td>
<td>Completed</td>
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<td>Rituximab Treatment in Sjögren’s Syndrome</td>
<td>NCT00363350</td>
<td>University Medical Centre Groningen, Netherlands</td>
<td>2006</td>
<td>Completed</td>
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blockade in autoimmune conditions. Another co-stimulatory pathway is the LFA-3/CD2 interaction involved in the activation and proliferation of T-cells. Alefacept targets this interaction. It is a fusion protein with potential benefit in psoriasis and T-cell lymphoma [108,109]. Another cell interaction pathway is that between CD40L (CD154), found on T-cells and CD40 found on antigen-presenting cells and B-cells. This system is upregulated in lupus and in PSS [110,111]. A short course of treatment with ruplizumab (hu5C8, BG9588, Antova) in patients with proliferative lupus nephritis has been shown to reduce anti-dsDNA antibodies, increase C3 concentrations, and decrease hematuria, but the trial was abandoned due to increased thromboembolic risk [112]. Toralizumab (IDEC-131/E6040) another anti-CD40L monoclonal antibody has also been studied in SLE [113].

Other future strategies

Targeting other cytokines
Since Sjögren’s syndrome includes both organ-specific inflammation within the exocrine glands and local and systemic B-cell hyper-reactivity, there is a pathologic basis for evaluating a broad range of possible therapeutic targets. As well as Blys/BAFF, TNF-alpha, IL-1 and IL-6 a number of other conventional cytokines have been shown to be upregulated in the salivary glands in PSS [114–119]. These include IL-2, IL-3, IL-4, IL-10, IL-15, IL-21, IL-22, TNF-R1 and TNFR2, TGF-beta, interferon-alpha and gamma, GM-CSF, epidermal growth factor and cytokines of the TH17 system.

T\(_h\)17 system
T helper 17 cells (T\(_h\)17) are a subset of T helper cells that produce interleukin-17 (IL-17). They are considered to be a distinct group separate from T\(_h\)1 and T\(_h\)2 cells and are thought to play a key role in some immune-mediated diseases. T\(_h\)17-related cytokines (IL-6, IL-12, IL-17, TGF-beta and IL-23) are increased in the serum and salivary glands of patients with PSS [100]. The overexpression of IL-12 in transgenic mice leads to a Sjögren’s-like syndrome [120]. IL-18 levels are also raised and correlate with the degree of lymphocytic infiltration in the salivary glands of PSS. Monoclonal antibodies directed against IL-12 and IL-23 biakinumab (ABT-874) and ustekinumab (CNTO-1275) are being studied in psoriasis, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease. Anti-IL-18 antibodies may be available in the future [121].

Targeting interferons and the innate immune system
Interferons are cytokines typically released in response to viral infection. Two main classes, type I (interferon-alpha and beta) and type II (interferon-gamma), are described. In SLE, many patients have upregulated type I IFN levels as well as upregulated downstream genes regulated by type I interferons; the ‘interferon signature’ [122]. There is also evidence that interferon related genes such as STAT4 and IRF5 are over-expressed in pSS [123,124]. Two monoclonal antibodies directed against IFN-alpha are under investigation for potential benefit in ameliorating SLE (rontalizumab, sigalimumab). There is potential evidence of benefit from this approach [125] and in theory, therefore, this approach might also have benefit in PSS. Fontolizumab, a monoclonal antibody targeting IFN-gamma, is being studied in Crohn’s disease. There are a number of reasons why targeting interferons is of particular interest. The first is that IFN-alpha and IFN-gamma upregulate Blys/BAFF expression as described above. In other words, the interferon type I system could be a key upstream driver of the B-cell activation seen in pSS. The second is that type I interferons link up with a number of other systems that could be related to the pathogenesis of pSS. For example, the innate immune system, in which viruses or microbes are recognized by pattern-recognition molecules such as TLRs, which are involved in the activation of both the innate and adaptive immune systems, can trigger interferon release, brings together, at a single stroke, external triggering agents, the innate immune system, interferon upregulation and B-cell activation and glandular dysfunction [85,126,127]. A number of studies have suggested increased expression of TLRs on salivary epithelial cells in PSS [126,128,129]. Upregulation of TLRs may in turn increase expression of adhesion molecules such as ICAM-1 or cytokines such as type 1 IFN or IL-6 [111,112], IL-17, and IL-23 [130]. In theory, therefore, upregulation of TLRs e.g. by viruses, may trigger glandular inflammation and damage in PSS. Inhibitors of TLRs may be useful therapeutic agents in PSS [131]. The interferon-alpha system, however, is paradoxical in that although PSS is associated with raised levels of IFN-alpha as above, low-dose interferon-alpha lozenges may improve symptoms in PSS [132].

Targeting chemokines
Chemokines (small chemotactic cytokines) such as CXCL13 (B-cell attracting chemokine) and CCL21 (secondary lymphoid chemokine – a T-cell homing chemoattractant) are expressed in the lymphoid aggregates in PSS and may be potential therapeutic targets [133]. Other chemokine receptors of lymphoid cells such as CCL22 (stimulated T-cell chemotactic protein-1/monocyte-derived chemokine) and CCL17 (thymus and activation-regulated chemokine) are expressed in the salivary glands of a majority of patients with PSS [134]. Stromal cell derived factor-1 (SDF-1/CXCL12), a constitutive chemokine involved in leukocyte retention within lymphoid tissue, is expressed by epithelial cells in salivary glands [54,135] and the chemokine receptor for SDF-1, CXCR4, is expressed on T-cells that accumulate in the periductal aggregates in PSS. Other chemokines whose levels may be increased in the serum or salivary glands

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of patients with PSS include EBI1-ligand chemokine (ELC), pulmonary and activation-regulated chemokine (PARC), CCL4 [macrophage inflammatory protein (MIP)-1beta], CCL3 (MIP-1alpha), CCL11 (Eotaxin), CCL2 (monocyte chemoattractant proteins MCP-1), CCL5 (RANTES – regulated upon activation, normal T-cell expressed, and presumably secreted) and CXCL8 (IL-8) [76,98,114]. Agents acting on the chemokine system are likely to be attractive therapeutic targets in a range of conditions although the approach may a mixture of small-molecule drugs as well as monoclonal antibodies [136].

Adhesion molecules

Another theoretical approach is to target the adhesion molecules involved in the homing of inflammatory cells into the salivary glands of patients with PSS. A number of studies have shown upregulation of adhesion molecule expression on endothelial and inflammatory cells in PSS including intercellular adhesion molecule-1 (ICAM-1) (CD54), lymphocyte function-associated antigen-1 (LFA-1), LFA-3 (CD58), vascular cell adhesion molecule-1 (VCAM-1), P-selectin (CD62), CD11, CD18 [137–140]. A low molecular weight compound K-13182, which inhibits VCAM-1 expression inhibited mononuclear cell infiltration into the salivary glands of a NOD mouse model of Sjögren’s syndrome [141]. Anti-adhesion molecule antibodies such as Eflalizumab/Raptiva (targeting CD11a), Erlizumab (targeting CD18) and Rovelizumab/LeukArrest (targeting CD11/ CD18) have been developed although their clinical roles are yet to be established. Eflalizumab has been proposed for the treatment of psoriasis but its marketing is currently suspended in Europe and the USA over reports of progressive multifocal leukoencephalopathy. The results of a small pilot study in PSS [http://clinicaltrials.gov/ct2/show/NCT00344448] are awaited. Monoclonal antibodies directed against alpha4 integrin such as Natalizumab and Vedolizumab have been used in Crohn’s disease although the long-term safety of these agents has yet to be established [142].

Therapies directed at regulating glandular secretion

One difficult conundrum in PSS is the lack of correlation between the immunological features of the condition such as anti-Ro/La antibody status, immunoglobulin levels, or the degree of glandular infiltration by lymphocytes and the degree of functional impairment of the glands. There are a number of potential mechanisms that may contribute to this. Firstly inhibition of neuronal signalling of gland secretion is one possibility and anti-muscarinic M3 receptor antibodies have been proposed as a potential candidate [143]. These antibodies are theorized to interfere with the binding of the neurotransmitter acetylcholine on the M3 receptors. A related mechanism is of enhanced breakdown of acetylcholine by excess cholinesterase in PSS [18]. A third potential mechanism is that local cytokine production by inflammatory infiltrates within the glands inhibits glandular function either through inhibition of neurotransmitter signalling [144] or through a direct effect on acinar cell function [145]. Conversely, cholinergic blockade can induce inflammation in salivary glands that mimics PSS [146]. The intracellular process of saliva secretion is complex. For a review, see [147]. There are multiple calcium-dependent chloride channels, cAMP-activated channels, aquaporin water channels. Regulation of the secretory processes is poorly understood. Neuropeptides such as vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) are likely to be involved. Protein lipases and protein kinases [148,149] are likely to be involved in the transduction pathways. Cytokines could influence these processes but a clear picture has yet to emerge. Potentially, however, if these processes were better understood then biological therapies could be targeted towards these processes.

Conclusion

The increasing number of biologic agents being developed for rheumatic and other inflammatory conditions is opening a new era of therapies directed against specific immune targets relevant to different components of disease pathogenesis in PSS, ranging from the systemic B-cell driven features at one end of the spectrum to the organ-specific ‘T-cell’ driven glandular lesions. Pilot clinical data for anti-B-cell therapy with rituximab is encouraging and suggests potential benefit in treating fatigue, dryness symptoms and systemic features. What is particularly encouraging is the sheer range of different potential agents. Is all that is needed is the engagement of the pharmaceutical industry in tackling this complex disabling condition for which there is a huge unmet need. Rituximab is already in clinical use in patients with pSS and B-cell MALT lymphoma and larger trials are ongoing/planned. Belimumab, which targets the B-cell cytokine BlyS/BAFF is now licensed for use in SLE. The evidence to support a clinical trial in pSS is substantial. Anti-IL-6 agents such as tocilizumab could be effective in tackling fatigue and other features of PSS. In terms of agents for which no or more limited pilot data is available, agents directed against interferons and other cytokines, chemokines, adhesion molecules and other cell-cell interactions and TLRs might all have potential benefit. The challenge now is to find ways of setting up pilot studies to evaluate these therapies in PSS.

Disclosure of interest: Dr Bowman consulted for Merck-Serono, chief investigator of the TRACTISS study of rituximab in Sjögren’s syndrome – drug supplied by Roche Pharmaceuticals without charge.
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