Review

Present and novel biologic drugs in primary Sjögren’s syndrome

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Received on December 21, 2018; accepted in revised form on March 5, 2019.
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Key words: Sjögren’s syndrome, autoimmunity, biological therapies, treatment, review

ABSTRACT
Primary Sjögren’s syndrome (pSS) is a systemic autoimmune disease characterised by xerostomia and xerophthalmia. In at least one-third of patients, the disease may be complicated by extraglandular involvement. Due to the lack of evidence-based recommendations, current therapeutic options for pSS are mainly empirical, often reflecting their use in other autoimmune diseases. Nevertheless, recent advances in the understanding of pathogenic pathways in pSS encourage the belief that blocking them may be of value in the treatment of the disease. Despite failing to demonstrate efficacy in clinical trials, because of the well-established role of B-lymphocytes in the pathogenesis of pSS, rituximab has been the most frequently used to date, but with much less success than in the treatment of patients with rheumatoid arthritis, vasculitis and lupus. However, in the last few years a number of other biologics have been developed and are under investigation. The aim of this article is to review the use of biologic therapies in pSS.

Introduction
Primary Sjögren’s syndrome (pSS) is a chronic, autoimmune rheumatic disease (ARD) characterised by lymphocytic infiltration of exocrine glands. It is potentially serious, with excess mortality due to severe organ involvement and the development of non-Hodgkin’s B cell lymphoma (1).

pSS remains one of the most difficult ARDs to manage. Pharmacologic treatments have the capacity to ameliorate some of the sicca symptoms, but there is no effective therapy that can alter the progress of the disease. Current therapeutic options for the treatment of pSS are mainly empirical, often first used in the treatment of other autoimmune diseases. Treatment goals remain symptom palliation and prevention of complications. Immunosuppressive drugs are used in patients with severe systemic involvement, on the basis of very limited scientific evidence (2-5). Interestingly, biologic drugs were more frequently prescribed in patients with SS overlapping with other autoimmune diseases, highlighting the lack of therapies specifically targeted to treat the pSS patient (4).

Guidelines for the treatment of pSS have been recently developed by the Sjögren’s Syndrome Foundation for the management of sicca and articular manifestations (5). However, the management of systemic features of the disease may require specific immunomodulatory therapies. Recent advances in the knowledge of the pathogenesis of pSS enhance the belief that several biological pathways may be employed as therapeutic targets.

This has encouraged international efforts to test new-generation biotechnological agents in the setting of pSS with a number of open-label and randomised controlled trials that have produced, in many cases, unsatisfactory results. In 2017, the British Society for Rheumatology provided the first UK comprehensive guidelines on the management of both glandular and systemic manifestations of pSS (6). These include some biologic therapies, such as rituximab, for the treatment of refractory pSS.

In this review, we discuss the currently available data, the utility and potential challenges for the use of new potential agents specifically directed against molecules involved in disease pathogenesis, which may represent a potentially more effective approach in pSS in the future.

B-cell target therapies
The inflammatory lesion of pSS consists of T and B cells with distinct biological significance: lesions with T cell predominance appear around the epi-
thelium of salivary glands and the epidermalia of other organs (liver, kidney, trachea and other mucosa associated lymphoid tissue) producing epithelitis with tissue specific manifestations, while B cells predominate in lesions within the salivary glands and are responsible for the development of B-cells follicles containing germinal centres (which represent the hallmark of the disease) and non-Hodgkin’s lymphoma (7-9). The evident B cell involvement provides a rational for the use of rituximab, a chimeric monoclonal antibody targeting CD20, a protein found on the membrane of most B cells, except for stem cells, pro B-cells and plasma cells. The earliest open-label study, which assessed the safety and the biologic effects of rituximab in 15 patients with active pSS, demonstrated a complete depletion of circulating CD20 cells and improvement of subjective and objective parameters of disease activity, including salivary and lacrimal gland function (10).

Subsequent small studies evaluated the efficacy of rituximab in pSS (Table I). Some authors reported a beneficial effect on the main patient symptoms (fatigue, dryness and pain) and extra-glandular manifestations (11-14). Four randomised controlled trials have now been undertaken.

One trial (15) was performed in United Kingdom (UK) and included only 17 patients. The study failed to reach the primary endpoint, but suggested that fatigue was the most likely of the patient symptoms to improve.

A second trial (16) was conducted in the Netherlands and included 30 patients, showing that the stimulated and unstimulated salivary flow rates were improved after two infusions of rituximab.

The French Tolerance and Efficacy of Rituximab in Sjögren’s Syndrome (TEAR) study (17) included 120 patients with either recent active disease and biological markers of B-cell hyperactivity or systemic involvement. However, the primary endpoint, namely a 30mm decrease in at least 2 of 4 visual analogic scale (VAS) score (dryness, global assessment of disease, fatigue and pain) at week 24, was not met. Nevertheless, several secondary endpoints (salivary flow rate, laboratory response) were significantly improved by rituximab compared with placebo. In the largest randomised controlled trial of anti-B-cell therapy conducted in UK, the TRACTISS study (18), the primary endpoint was to determine if rituximab improves VAS of fatigue and oral dryness at week 48 in 133 patients with pSS. However, no significant improvement was detected, except for the unstimulated salivary flow which remained stable in the rituximab arm, while it got worse in the placebo group. A number of reasons may explain why the efficacy of rituximab varied between these studies.

First, the use of different inclusion criteria, leading to differences in baseline patient characteristics, may cause part of this variation. Differences in disease duration between the study populations may influence the response, as early treatment may prevent irreversible damage to the glands. Heterogeneity of the recruited patients regarding the phenotype and the underlying immunopathologic lesion may also contribute to the discrepancy in reported outcomes. Lendrem et al. have identified four distinct pSS clinical phenotypes (Low Symptom Burden, High Symptom Burden, Dryness Dominant and Low Anxiety and Depression) with associated significant differences in IgG, lymphocytes, erythrocyte sedimentation rate (ESR), ESSDAI score, and unstimulated whole saliva between groups (19).

Finally, the primary endpoints in these trials were very subjective measures, notably the patient-assessed VAS scores. Although subjective symptoms, such as fatigue and sicca symptoms, are important target to improve quality of life, they have diurnal variations and may not be sensitive to change. Moreover, fatigue and pain are not subjective symptoms and may be influenced by non-pSS’s-related factors including co-morbidities. Furthermore, response goals were set quite high (≥30 mm change in 2 of 4 VAS scores in the TEARS trial, 30% change of either oral dryness or fatigue VAS score in the TRACTISS trial). The EULAR SS Patient-Reported In-

dex (ESSPRI) and the EULAR SS Disease Activity Index (ESSDAI) are composite indices to assess objectively symptoms and systemic disease activity, respectively (20, 21). However, neither of these tools was used as the primary endpoint in these trials. A post hoc-analysis of TEAR trial employing a different composite index, the SS Responder Index (SSRI), including scores on fatigue, oral and ocular dryness, unstimulated whole saliva and ESR, showed a ≥30% improvement in at least two of the five outcome measures in comparison to placebo (22). This study supports the importance of the choice of outcomes to evaluate the efficacy of a treatment. Forthcoming trials should use composite endpoints, in addition to subjective symptoms and gland function.

In order to identify a subset of patients more likely to respond to anti-CD20 treatment, Devauchelle-Pensec et al. (23) evaluated gene expression profiles in the salivary glands of patients with pSS before and after rituximab treatment. Gene pathway analysis demonstrated differential expression of genes belonging to the B cell and the interferon (IFN) signalling pathway between responders and non-responders.

Recently, in a substudy of TRACTISS trial (24), significant improvement in the salivary-gland involvement assessed by ultrasonography (SGUS), has been demonstrated after rituximab compared with placebo. In a substudy of the TEAR trial, Cornec et al. showed similar results and tried to determine whether the ultrasound score and histopathology could influence the response to rituximab (25). Both baseline SGUS grade and high numbers of infiltrating B cells were significantly higher in non-responders in comparison to responder patients (26). However, opposite findings, regarding the number of infiltrating number of B cells as biomarkers for rituximab responsiveness patients, have been reported in a subsequent study where sequential parotid gland biopsies were taken at baseline and after 12 weeks of treatment in 20 rituximab-treated and 10 controls (27). They showed that higher levels of B cells within the parenchyma of parotid
Table I. Main clinical studies for rituximab in pSS.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Study Design</th>
<th>Patient population</th>
<th>Follow-up (w)</th>
<th>Regimen</th>
<th>Primary end-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pijpe et al. (10)</td>
<td>2005</td>
<td>Open label Phase II study</td>
<td>15</td>
<td>12</td>
<td>375 mg/m2 at w 0, 1, 2, and 3</td>
<td>ESSDAI (reached)</td>
</tr>
<tr>
<td>Gottenberg et al. (11)</td>
<td>2005</td>
<td>analysis of autoimmune and Rituximab registry</td>
<td>78</td>
<td>24</td>
<td>1 g at w 0 and 2</td>
<td>Fatigue (reached)</td>
</tr>
<tr>
<td>Dass et al. (15)</td>
<td>2008</td>
<td>RCT pilot</td>
<td>17</td>
<td>24</td>
<td>1 g at w 0 and 2</td>
<td>Fatigue (reached)</td>
</tr>
<tr>
<td>Pijpe et al. (14)</td>
<td>2009</td>
<td>Open label Phase II study</td>
<td>5</td>
<td>12</td>
<td>375 mg/m2 at w 0, 1, 2, and 3</td>
<td>Histologic change on parotid biopsy and salivary flow (reached)</td>
</tr>
<tr>
<td>Meijer et al. (16)</td>
<td>2010</td>
<td>RCT</td>
<td>20</td>
<td>48</td>
<td>1 g at w 0, 2</td>
<td>Improvement in the secretion of stimulated whole saliva (reached)</td>
</tr>
<tr>
<td>Devauchelle-Pensec et al. (17)</td>
<td>2014</td>
<td>RCT (TEARS trial)</td>
<td>122</td>
<td>24</td>
<td>1 g at w 0 and 2</td>
<td>At least improvement in 24/24 ESSDAI scores on fatigue, global disease, pain, and dryness (failed)</td>
</tr>
<tr>
<td>Bowman et al. (18)</td>
<td>2017</td>
<td>RCT (TRACTISS trial)</td>
<td>133</td>
<td>48</td>
<td>1 g at w 0, 2, 24, 26</td>
<td>30% reduction in VAS score of fatigue or oral dryness (failed)</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; ESR: erythrocyte sedimentation rate; W: week; V AS: visual analogic scale; ESSDAI: EULAR Sjögren’s Syndrome Disease Activity Index.

gland tissue are predictive for the responsiveness of patients with pSS to rituximab treatment, suggesting that histology may be employed as potential biomarker to predict response to rituximab in pSS. Differences in how B-cells in gland sections were analysed and how the disease activity was measured (ESSDAI vs. SSSRI-30), apparently may contribute to explain the apparent diverse findings. (26, 28)

Another possible interpretation is that for the majority of pSS the histopathologic lesion remain stable over time as a result of an in situ immunologic balance (29). In particular, regulatory B cells (Bregs) are emerging immunoregulatory B-cell subsets which have the ability to inhibit the immune response, play an important role in maintaining the balance and tolerance in immune function (30). Interestingly, the proportion of Bregs is higher in clinically inactive than active pSS patients, suggesting that these cells may induce homeostasis and limit the severity of SS (31). Bregs may be disturbed after B cell depletion therapy, leading to a variable outcome depending on the endotype of the disease for each patient. Moreover, the lack of histology progression over time suggests that gland biopsy may be capable of stratifying patients with pSS into distinct subgroups according to the dominating immune responses. Finally, rituximab may be useful for treating some systemic manifestations of pSS. In a retrospective analysis of 10 patients with pSS and interstitial lung disease, rituximab was effective in improving clinical symptoms and pulmonary function tests, and in stabilising high resolution computed tomography score (32). For peripheral neurological involvement associated with cryoglobulinaemia or vasculitis, the analysis of the French nationwide AutoImmune and Rituximab (AIR) registry reported a beneficial effect of rituximab in 69% of patients. This evidence suggests the need to identify potential biomarkers, i.e. disease activity, systemic involvement or glandular inflammation and to predict the subsets of patients who are the most likely to benefit from B cell-targeting therapy.

North American guidelines (5, 33) recommend rituximab as a therapeutic option in patients with serious organ complications or for sicca manifestations in selected patients who fail more conservative and less costly therapies. In the UK guidelines, rituximab is recommended for significant systemic manifestations refractory to other immunosuppressive agents and those with lymphoma, immune thrombocytopenia, vasculitic neuropathy, or cryoglobulinaemia. Other B-cell targets offer alternative therapeutic strategies. Belimumab is a fully human monoclonal antibody designed to target B cell–activating factor (BAFF) or B-cell lymphocyte stimulator (BLyS).

The use of belimumab was approved by Food and Drug Administration (FDA) for treatment of Systemic Lupus Erythematosus (SLE) in March 2011. The increased expression of BAFF in patients with pSS suggested that belimumab may be a promising opportunity also in pSS.

The BELISS study was a small, open-label, phase II trial to assess belimumab in 30 patients with pSS (34). Patients were included if they were positive for...
anti-Ro/SSA or anti-La/SSB antibodies and had either current systemic complications or persistent salivary gland enlargement or early disease or biomarkers of B-cell activation. The primary endpoint was improvement at week 28 in two of five items: reduction of 30% or more in dryness VAS score, fatigue VAS score, pain VAS score, in systemic activity VAS assessed by the physician, and/or >25% improvement in any B cell activation biomarker values. The primary endpoint was achieved by 18 (60%) patients, even if no effect was detected using objective measures such as unstimulated salivary flow and Schirmer’s test. These results suggest some possible drug efficacy, but need to be confirmed in a randomised controlled trial. Corne et al. showed that half of the patients displayed an intense BAFF-driven B-cell activation and did not respond to rituximab (35).

Follow-up data of BELISS study (36) were obtained in 15 responders at week 28 who completed the 52-week protocol. It showed that 13 (86.7%) also responded at week 52, consistent with a stable response to treatment in the long term. Two patients lost their response from week 28 to week 52 due to an increase either in the pain VAS or in the fatigue VAS. However, after belimumab discontinuation, systemic disease activity, assessed by ESSDAI, significantly increased at 12 months (37). Similarly, a significant increase of rheumatoid factor was observed, supporting the likely efficacy of belimumab in modulation of B cell activation in pSS patients.

There is evidence that B cell activating factor increased after rituximab treatment (38) and this could explain why patients in the TEAR trial responded at 4 months, but flared at 6 months. Interestingly, a double-blind, randomised, placebo-controlled trial (NCT02631538) is ongoing to test the co-administration therapy of belimumab and rituximab in patients with pSS. The primary endpoint is the safety of combination therapy while ESSDAI, stimulated salivary flow, oral dryness and B-cell quantification within salivary gland biopsy are secondary endpoints. In addition, a phase II study (NCT02149420) assessing an anti-BAFF receptor is ongoing (Table II).

Epratuzumab is a monoclonal antibody that modulates B-cell activation targeting CD22, a co-receptor of B-cell receptor (BCR). This agent showed promising results in a small phase I/II open-label study, in which 16 patients were enrolled, reducing peripheral B cell counts and improving unstimulated whole salivary flow, fatigue, ESR and IgG (39). Moreover, in a post hoc analyses of the EMBODY trials (NCT01262365 and NCT01261793), patients with SLE and associated SS treated with epratuzumab showed improvement in disease activity, which was associated with a decrease in B cells count and IgM levels (40). These data suggest that epratuzumab may have clinical benefits, but randomised controlled trials are needed to confirm this finding.

Costimulatory molecules

Two open-label studies have explored whether Abatacept (which blocks the CD28:CD80/CD86 T cell costimulatory pathway) might be effective in pSS. In the first study (41), 11 patients with pSS received 8 infusions of abatacept to evaluate histological and laboratory changes. This treatment was effective in reducing glandular inflammation, as assessed by evaluation of lymphocytic foci and FoxP3 cells in minor salivary gland biopsies, and in increasing B-cells and CD4 T-cells in peripheral blood. A slight increase of saliva production was also observed. The Active Sjögren Abatacept Pilot open label study (ASAP) (42) assessed the efficacy of abatacept in 15 patients with pSS. Disease activity, assessed by ESSDAI, patient symptoms, assessed by ESSPRI, Rheumatoid Factor and IgG levels significantly reduced during the 24 weeks of treatment and increased post-treatment. However, measures of salivary and glandular function remained unchanged.

In the analysis of salivary gland biopsies taken in all 15 patients enrolled in ASAP study (43), the number of germinal centres per mm² was reduced 24 weeks after abatacept administration. Moreover, the number of germinal centres per mm² at baseline was associated with improvement in the ESSDAI glandular domain, but not with other ESSDAI domains. Interestingly, Abatacept treatment did not reduce focus score, lymphoepithelial lesions, area of lymphocytic infiltrate, and numbers of CD3+ T-cells or CD20+ B cells, suggesting that it may reduce germinal centre formation by co-stimulation of activated follicular-helper T-cells and inhibition memory B-cells. Currently, there are two ongoing phase III trials (Table II) evaluating efficacy of weekly subcutaneous administration of abatacept.

CFZ533 is a new monoclonal antibody that selectively inhibits CD40, a costimulatory pathway receptor essential for germinal centre responses implicated in pSS pathogenesis. At the 2017 ACR/ARHP Annual Meeting, data from a recently reported phase II study showed CFZ533 to be safe and effective in patients with pSS (44).

Tumour necrosis factors blockers

TNF-α has numerous pro-inflammatory functions and its expression is increased in SS salivary glands (45). However, evidence from two randomised controlled trials suggests that TNF inhibitors do not ameliorate sicca symptoms or other manifestations in pSS. In the first study, the Trial of Remicade in pSS (TRIPSS), 103 patients were randomly assigned to receive infliximab infusions or placebo at weeks 0, 2, and 6 and were followed up for 22 weeks (46). The endpoint, defined as an improvement between weeks 0 and 10 in the values of 2 of the 3 VAS assessment that evaluated pain, fatigue and dryness, was not achieved. Etanercept was tested in a randomised controlled trial including 28 patients with pSS (47). Again, the response, defined as the improvement of VAS for pain, fatigue and dryness compared to placebo, was not reached. The complete therapeutic failure of TNF inhibitors, although TNF-α is abundant in the pSS histopathologic lesions, can be most likely attributed to immunoregulatory (e.g. germinal center formation) rather than the pro-inflammatory properties of TNFa. However, TNF-α inhibitors can be used in SS patients with overlapping features of RA (5).
Kinase inhibitors

IFN is upregulated in patients with pSS and is considered to play a pathogenic role in the disease. Therefore, it could be speculated that small molecules able to modulate interferon signalling pathway, such as Janus kinase (JAK) inhibitors, may be effective in the treatment of pSS. JAK inhibitors have already demonstrated clinical efficacy in RA. In an animal model, filgotinib, a JAK inhibitor with selectivity for subtype JAK1, has been reported to improve salivary flow rate and reduce lymphocytic infiltration of salivary glands by inhibiting IFN signalling pathway, thus suppressing BAFF and chemokine production of salivary gland epithelial cells (48). GS-9876 is a novel Spleen Tyrosine Kinase (SYK) inhibitor which has shown positive effects when combined with JAK inhibitors (49). Phase II studies with filgotinib, GS-9876 and tirabrutinib, inhibitor of the Bruton tyrosine kinase, are in progress (NCT03100942).

Miscellaneous

Currently, studies of many other biological molecules able to interfere with different pathways are in progress (Table II). Interleukin (IL)-6 has been found at higher levels in serum, tears and saliva of SS patients in comparison to healthy controls and correlated directly with disease activity (47-49). Thus, tocilizumab (which blocks the IL-6 receptor), a recombinant humanised monoclonal antibody, might be effective in patients with pSS. The ETAP study, a phase III randomised controlled trial designed to assess efficacy and safety of tocilizumab, is ongoing (NCT01782235). However, diseases with IFN type I pathway activation such as SLE and pSS are not characterised by increased hepatic production of acute phase reactants as CRP and therefore the efficacy of blockade of IL6 is questionable (53-55). Blocking of another proinflammatory...

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**Table II. Ongoing trials in primary Sjögren’s syndrome on clinicaltrials.gov.**

<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Name</th>
<th>Target</th>
<th>Sponsor</th>
<th>Study design</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02631538</td>
<td>Belimumab and rituximab</td>
<td>BAFF and CD20</td>
<td>GlaxoSmithKline</td>
<td>Phase 2 RCT</td>
<td>Safety</td>
<td>ESSDAI-stimulated salivary flow; Bcell quantification in salivary gland biopsy</td>
</tr>
<tr>
<td>NCT02334306</td>
<td>AMG 557/MED1587</td>
<td>ICOSL</td>
<td>MedImmune/Amgen</td>
<td>Phase 2 RCT</td>
<td>ESSDAI change d99</td>
<td>Laboratory and histologic changes; ESSPRI safety</td>
</tr>
<tr>
<td>NCT02149420</td>
<td>VAY736</td>
<td>BAFF receptor</td>
<td>Novartis</td>
<td>Phase 2 RCT</td>
<td>ESSDAI change w12</td>
<td>ESSPRI patGDA; phyGDA SF-36; MFI</td>
</tr>
<tr>
<td>NCT02610543</td>
<td>UCB8557 (Seletalisib)</td>
<td>PI3K</td>
<td>UCB</td>
<td>Phase 2 RCT</td>
<td>ESSDAI change w12</td>
<td>ESSPRI Change in salivary flow and Schirmer’s test</td>
</tr>
<tr>
<td>NCT02067910</td>
<td>Abatacept</td>
<td>Costimulation of T cells</td>
<td>Groningen University and BMS</td>
<td>Phase 3 RCT</td>
<td>ESSDAI change w24</td>
<td>Safety; ESSPRI; DAS28; patGDA; phyGDA; Corticosteroid dose; Salivary and tear gland function; SF-36; MFI; PASS; FSFI; WPAI; NRS score vaginal dryness; laboratory, ultrasound and histologic changes</td>
</tr>
<tr>
<td>NCT02915159</td>
<td>Abatacept</td>
<td>Costimulation of T cells</td>
<td>BMS</td>
<td>Phase 3 RCT</td>
<td>ESSDAI change w24</td>
<td>Safety; ESSPRI; stimulated whole salivary flow; laboratory changes</td>
</tr>
<tr>
<td>NCT01782235</td>
<td>Tocilizumab</td>
<td>IL-6 receptor</td>
<td>Strasbourg University</td>
<td>Phase 3 RCT</td>
<td>Improvement ESSDAI&gt;3</td>
<td>NA</td>
</tr>
<tr>
<td>NCT02701985</td>
<td>RO5459072</td>
<td>Cathepsine S Inhibitor</td>
<td>Hoffmann-La Roche</td>
<td>Phase 2 RCT</td>
<td>ESSDAI</td>
<td>ESSPRI SF-36</td>
</tr>
<tr>
<td>NCT02464319</td>
<td>hIL-2</td>
<td>Human recombinant IL-2</td>
<td>Peking University People’s Hospital</td>
<td>Phase 2 RCT</td>
<td>ESSDAI</td>
<td>CD4+ T cells, follicular helper T cells, IL-17 producing helper T cells</td>
</tr>
<tr>
<td>NCT02614716</td>
<td>LY3090106 (Tibulizumab)</td>
<td>BAFF IL-17A</td>
<td>Eli Lilly</td>
<td>Phase 1 RCT</td>
<td>Safety</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>NCT03100942</td>
<td>Filgotinib, tirabrutinib (GS-4059)</td>
<td>Janus kinase, Spleen Tyrosine Kinase</td>
<td>Gilead Sciences</td>
<td>Phase 2 RCT</td>
<td>Protocol-Specified Response Criteria at w12</td>
<td>ESSDAI and ESSPRI changes w12-24</td>
</tr>
</tbody>
</table>

cytokine, IL-1, has been tested in pSS with anakinra, the recombinant IL-1ra, but again, this treatment was ineffective in patients with pSS (56). Icatinib, a methanesulfonanilide, showed significant inhibition of immunoglobulin production and suppression of IL-1, IL-6 and TNF and recently clinical improvements in disease activity in pSS were reported (57).

Regarding other potential therapeutic targets, germinal centre-like structures have been shown to support chronic activation of autoimmune B cells and to predict the development of lymphoma. Bambercept, a fusion protein that includes the lymphotoxin-beta receptor (LTβR), has been shown to be able to prevent the formation of germinal centre-like structures. However, despite evidence from mechanistic studies, bambercept failed to improve glandular and extraglandular disease significantly in patients with SS in a randomised controlled trial (58). Moreover, bambercept therapy was associated with a higher incidence of liver toxicity. T follicular helper cells sustain the persistence of germinal centre-like structures. ICOS (inducible T-cell co-stimulator) controls their localisation in the B-cell follicle. Clinical application of an anti-ICOS ligand in pSS is under investigation (NCT02334306).

The intracellular kinase PI3Kδ plays a role in the formulation and maintenance of germinal centres in the inflamed glandular tissues. This kinase is also important in B-cell activation and antigen presentation as well as in the production of autoantibodies, T-cell activation, and toll-like receptor signalling. The role it plays in immune regulation has encouraged the development of inhibitors targeting its kinase activity. Leniolisib (CDZ173) is an oral drug that selectively inhibits PI3Kδ. Leniolisib had an acceptable safety and tolerability profile, but failed to provide a clear efficacy based on ESSPRI and ESSDAI in a small placebo-controlled trial (59). Selectalisib is a small-molecule taken orally with preclinical evidence supporting selective inhibition of PI3Kδ at biochemical levels and in murine models (60), thereby supporting the ration-ale to initiate a clinical development programme in autoimmune diseases. Its tolerability and pharmacokinetic and pharmacodynamics profile have been already tested in healthy volunteers and patients with psoriasis (61). A phase II study is currently ongoing in patients with pSS (NCT02610543).

**Conclusions**

pSS has been considered an orphan disease over the last decades, as there is no specific treatment approved that halts the progression of the disease and most approaches used have been derived from therapies introduced for other autoimmune diseases, such as SLE or RA. Based on an increased understanding of the pathogenesis of pSS, the opportunity to focus on new target treatments appears intriguing. B-cells, GC-like structures and T cell costimulation are the most promising targets. However, clinical trials in patients with pSS are still relatively uncommon and most involve small numbers of patients. Moreover, the translation of indications (generally from RA) may not produce the desired result in pSS e.g. as occurred with the anti-TNFα drugs. Even though many clinical manifestations may be shared among different systemic autoimmune diseases, the underlying pathogenic mechanisms may be subtly different. Therapeutic research in pSS is likely to require a more specific approach, identifying biomarkers that characterise the different subsets of the disease.

**How to increase the chances of trials in patients with Sjögren’s being successful**

As the evidence in this review makes clear, many trials to date in pSS have failed and none has been as compelling as the trials of various biologics [e.g. anti-TNF-α, rituximab, IL-6 blockers] in RA, ankylosing spondylitis and psoriatic arthritis.

Part of the problem is likely to relate to the selection of particular patients to be included in clinical trials. Distinguishing clinical features due to activity rather than damage in SLE can be difficult and in pSS perhaps even more so. Some studies have included only patients with early disease (e.g. <5 years from diagnosis) to ensure participants have sufficient glandular function to detect a treatment effect. However, previous studies have shown that the phenotype (clinical manifestations), immunologic profile and histopathology remain stable for the majority of pSS patients from the time of diagnosis (suggesting established and advanced disease stage at diagnosis) and that patients seek medical help, at least 5 years after the onset of symptoms. Therefore, patients with <5 years of symptoms, could have quite advanced disease. This is a unique and additional difficulty for studying pSS patients and point out the necessity to identify biomarkers for very early SS detection.

In addition to distinguishing pSS patients on the basis of the duration of their symptoms it is important to recognise the diversity of their clinical features (38). For some patients, pSS is not a serious concern with some dryness of the eyes and mouth. For others, involvement of the liver, lungs, kidney and peripheral and even central nervous system represents a much more aggressive form of pSS. It would seem most important that a careful balance of more and less aggressive disease is achieved in the arms of any pSS clinical trial. Success in therapeutic trials will depend on a better understanding of disease phenotypes to drive a more careful and appropriate patient selection. The development of the new 2016 ACR/EULAR classification criteria (62) together with the recent validation of ESSDAI and ESSPRI as outcome measures should aid the optimisation of trial design for future drug developments. Moreover, unrevealed pathogenetic pathways could potentially identify more important key molecules in the future.

**Key points**

- Sjögren’s syndrome is a potentially severe systemic autoimmune disease, with many unmet clinical needs. The discovery of novel biomarkers facilitates the development of biological drugs and allows having a target therapy.
- Among the various biologics studied to date, some evidence exists for the
use of rituximab in selected patients with Sjögren’s syndrome who are resistant to less costly therapies, despite rituximab failed to demonstrate efficacy in randomised controlled studies.

- New pathways are currently under investigation, e.g. specific B-cell targets, costimulation of T cells, germinal centre-like structures and interleukin-6.

References


28. DELLI K, HAACKE EA, KROESE FG et al.: In primary Sjögren’s syndrome high absolute numbers and proportions of B cells in parotid glands predict responsiveness to rituximab as defined by ESSDAI, but not by SSRI. Ann Rheum Dis 2016; 75: e34.


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Clinical and Experimental Rheumatology 2019