Is there any prospect of biologic therapies working in Sjogren's Syndrome?

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ABSTRACT

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease characterized by xerostomia and xerophthalmia. In at least one-third of patients, the disease may be complicated by extraglandular involvement, with musculoskeletal, cutaneous, renal, pulmonary, hematologic or neurological manifestations. Due to the lack of evidence-based recommendations, current therapeutic options for the treatment of pSS are mainly empirical, often reflecting their use in other autoimmune diseases. Nevertheless, recent advances in the understanding pathogenic mechanisms have highlighted immunopathological pathways in which pSS encourage the belief that blocking them may be of value in the treatment of the disease.. 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. Better understanding of the pathophysiology in pSS is needed, to optimise develop evidence-based guidelines for the use of biologic therapy in this disease. The aim of this article is to review the use of new biologic therapies in pSS.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic, autoimmune, rheumatic disease (ARD) characterized 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 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. Immunosuppressive drugs are used in patients with severe systemic involvement, with very limited scientific evidence (2). Interestingly, biologic drugs were more frequently prescribed in pSS in overlap with other autoimmune diseases, highlighting the lack of therapies specifically targeted to treat the pSS patient (3).

Following recent advances in our understanding of the pathogenesis of pSS many pathways, are being targeted by biologic therapies.

Guidelines for the treatment of pSS have been recently developed by the Sjogren Syndrome Foundation for the management of sicca and articular manifestations (4).

However, there are no validated guidelines for the management of the other manifestations of the disease.

In this review, we discuss the currently available literature about new potential therapeutic options targeting the main pathways involved in the pathogenesis of the pSS.

B-cell target therapies

B cells play a central role in the development of pSS, through the production of autoantibodies (notably anti-Ro/SSA, anti-La/SSB, rheumatoid factor, cryoglobulins) and through the infiltration of salivary glands and the development of B-cells follicles containing germinal centres, which represent the hallmark of the disease (5–7).

This infiltration of polyclonal B cells is not limited to the salivary glands, but may also involve other mucosa-associated lymphoid tissues and can proliferate evolving into non-Hodgkin's lymphoma. This evidence 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 (8).

Subsequent small studies evaluated the efficacy of rituximab in pSS (table 1). Some authors reported a beneficial effect on the main patient symptoms (fatigue, dryness and pain) and extra-glandular manifestations (9–12). Four randomized controlled trials have now been undertaken.

One trial (13) was performed in United Kingdom (UK) and included only 17 patients. The study failed to reach the primary endpoint, but suggested that, of the patient symptoms, fatigue was the most likely to improve.

A second trial (14) was conducted in the Netherlands and included 30 patients, showing that stimulated and unstimulated salivary flow rate was improved after 2 infusions of rituximab.

The French Tolerance and Efficacy of Rituximab in Sjögren's syndrome (TEAR) study (15) including 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 randomized controlled trial of anti-B-cell therapy conducted in UK, the TRACTISS study (16), 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.

Possible explanations for the discrepancies in these studies include differences in patient characteristics and background medications used. Moreover, the primary endpoints in these trials were very subjective measures, notably the patient-assessed VAS scores. The EULAR SS Patient-Reported Index (ESSPRI) and the EULAR SS Disease Activity Index (ESSDAI) are composite indices to assess objectively symptoms and systemic disease activity, respectively (17,18). 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 erythrocyte sedimentation rate (ESR), showed a ≥30% improvement in at least two of the five outcome measures in comparison to infliximab (19). This study supports the importance of the choice of outcomes to evaluate the efficacy of a treatment.

Recently, Cornec et al. tried to determine whether the severity of salivary-gland involvement, assessed by ultrasonography (SGUS) and histopathology, could influence the response to rituximab (20).

The SGUS grade or histological focus score was significantly higher at inclusion in non-responders in comparison to responder patients, suggesting that these scores may be employed as potential biomarkers to predict response to rituximab in pSS. In a subsequent placebo-controlled trial, sequential parotid gland biopsies were taken at baseline and after 12 weeks of treatment in 20 rituximab-treated and 10 controls (21). They showed that absolute numbers of CD20+ cells/mm^2 of parenchyma of parotid gland tissue are predictive for the responsiveness of patients with pSS to rituximab treatment. Moreover, in the rituximab-treated group, a significant reduction of lymphocytic infiltration, germinal centres and lymphoepithelial lesions in parotid gland parenchyma was observed.

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 stabilizing high resolution computed tomography score (22). For peripheral neurological involvement associated with cryoglobulinemia 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.

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 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 (23). 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 on objective measures such as unstimulated salivary flow and Schirmer's test. These results would suggest a possible drug efficacy, but need to be confirmed in a randomized controlled trial. The same group showed that half of the patients displayed an intense BAFF-driven B-cell activation and did not respond to rituximab (24).

Follow-up data of BELISS study (25) 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 W28 to W52 due to an increase either in the pain VAS or in the fatigue VAS. However, after belimumab discontinuation, the systemic disease activity, assessed by ESSDAI, ignificantly increased at 12 months (26). Similarly, a significant increase of rheumatoid factor was observed, supporting the likely efficacy of belimumab to ameliorate biomarkers of B cell activation in pSS patients.

Interestingly, a double-blind, randomized, 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 (table2).

Epratuzumab is a monoclonal antibody that modulate B-cell activation targeting CD22, a co-receptor of B-cell receptor (BCR). Epratuzumab showed promising results in a small open label study on unstimulated whole salivary flow, fatigue, ESR and IgG (27). A randomized controlled trial is needed to confirm this finding.

Costimulatory molecules

Two open-label studies have explored whether Atacicept (which blocks the link between the antigen presenting cell and the T cell) might be effective in Sjögren's, Abatacept is a fully human soluble fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) linked to the modified Fc portion of human IgG1.

In the first study (28), 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) (29) assessed the efficacy of abatacept in 15 patients with pSS. Disease activity, as assessed by ESSDAI, patient symptoms, as 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 functions remained unchanged.

In the analysis of salivary gland biopsies taken in all 15 patients enrolled in ASAP study (30), the number of germinal centres per mm^2 was reduced 24 weeks after abatacept administration. Moreover, the number of germinal centres per mm^2 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 is an ongoing phase III ASAP trial (table 2) (NCT02067910).. The primary end point of the study is to evaluate efficacy of weekly subcutaneous administration of abatacept on ESSDAI score at 24 weeks

Tumor necrosis factors blockers

TNFα plays a role in the expression of endothelial adhesion molecules and in release of metalloproteinases (31). However, evidence from two randomized controlled trials suggests that TNF inhibitors do not ameliorate sicca symptoms or other manifestations in pSS. In the first study, the Trial of 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 (23). 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 randomized controlled trial including 28 patients with pSS (32). Again, the response, defined as the improvement of VAS for pain, fatigue and dryness compared to placebo, was not reached. However, TNF α inhibitors can be used in SS patients with overlapping features of RA(4).

Interleukin targeted therapy and other promising target

Currently, studies of many other biological molecules able to interfere with different pathways, are in progress (Table 2). Interleukin (IL)-6 has been found at higher levels in serum, tears and saliva of SS patients in comparison to healthy control and correlated directly with disease activity (33–35). Thus, tocilizumab (which

blocks the IL-6 receptor), a recombinant humanised monoclonal antibody, could be interesting in patients with pSS.

The ETAP study, a phase III randomized controlled trial designed to assess efficacy and safety of tocilizumab, is ongoing (NCT01782235).

Blocking of another proinflammatory cytokine, IL-1, has been tested in pSS with anakinra, the recombinant IL-1ra, but again, this treatment was ineffective in patients with pSS (36).

Regarding other potential therapeutic targets, germinal center-like stuctures have been shown to support chronic activation of autoimmune B cells and to predict the development of lymphoma. Baminercept, a fusion protein that includes the lymphotoxin-beta receptor (LTbR), has been shown to be able to prevent the formation of germinal center-like stuctures. However, despite evidence from mechanistic studies, baminercept failed to improve glandular and extraglandular disease significantly in patients with SS in a randomized controlled trial (37). Morever, baminercept therapy was associated with a higher incidence of liver toxicity.

CD T follicular helper cells sustain the persistence of germinal center-like stuctures. ICOS (inducible T-cell costimulator) controls their localization in the B-cell follicle. Clinical application of an anti ICOS ligand in pSS is under investigation (NCT02334306).

It could be speculated that small molecules able to modulate JAK/STAT signals, may be effective in the treatment of pSS.

CONCLUSIONS

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 Sjögren's have failed completely and none has been as compelling as the trials of various biologics [eg anti-TNF α, Rituximab, IL-g blockers] in RA, Ankylosing Spondylitis and even SLE.

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 Sjögren's perhaps even more so. Thus a patients who has had Sjögren's for say 10 years, is likely to have largely fibrosed ie damaged, labial glands and no biologic can ever alter that or improve their function. Thus the dryness of the eyes/mouth in these patients is simply irreversible. Consideration needs to be given to restricting patient

recruitment to those diagnosed within say the previous 5 years or even [as the diagnosis is often delayed in Sjögren's] to those whose symptoms have lasted < 5 years.

In addition to distinguishing Sjögren's patients on the basis of the duration of their symptoms it is important to recognize the diversity of their clinical features (38). For some patients Sjögren's is little more than a 'nuisance' disease 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 Sjögren's. It would seem most important that a careful balance of more and less aggressive disease is achieved in the arms of any Sjögren's clinical trial.

CONCLUSIONS

At present, there is no biologic treatment approved for pSS and most of the 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 Sjögren's are still uncommon and most involve small number of patients. Moreover, the translation of indications (generally from RA) may not produce the desired result in pSS eg 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. The development of the new 2016 ACR/EULAR classification criteria (39) and more careful and appropriate patient selection the recent validation of ESSDAI and ESSPRI as outcome measures could aid the optimization of trial design for future drug developments..

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Table 1. Main clinical studies for rituximab in pSS.

Authors	Year of publication	Study Design	Patient population	Follow up (w)	Regimen	Primary endpoint
Pijpe et al.(8)	2005	Open label Phase II study	15	12	375 mg/m2 at w 0, 1, 2, and 3	VAS score of dryness and pain, salivary flow rate, schirmer test (reached)
Gottenberg et al (9)	2005	analysis of autoimmune and Rituximab registry	78	24	1 g at w 0 and 2	ESSDAI (reached)
Dass et al. (13)	2008	RCT pilot	17	24	1 g at w 0 and 2	Fatigue (reached)
Pijpe et al. (13)	2009	Open label Phase II study	5	12	375 mg/m2 at w 0, 1, 2, and 3	Histologic change on parotid biopsy and salivary flow (reached)
Meijer et al. (14)	2010	RCT	20	48	1 g at w 0, 2	Improvement in the secretion of stimulated whole saliva (reached)
Devauchelle-Pensec et al. (15)	2014	RCT (TEARS trial)	122	24	1 g at w 0 and 2	At least improvement in 2/4 VAS scales on fatigue, global disease, pain, and dryness (failed)
Bowman et al. (16)	2017	RCT (TRACTISS trial)	133	48	1 g at w 0, 2, 24, 26	30% reduction in VAS score of fatigue or oral dryness (failed)

Cornec et al. (19)	2015	Post hoc analysis of RCT (TEARS trial)	122	24	Rituximab 1 g at w 0 and 2 Infliximab 5 mg/kg at w 0, 2, and 6	Improvement of at least 30% in at least 2/5 item from VAS fatigue, oral dryness, ocular dryness, unstimulated whole saliva and ESR(reached for Rituximab, failed for Infliximab)

RCT: randomized controlled trial; ESR: erythrocyte sedimentation rate; W: week; VAS: visual analogic scale; ESSDAI: EULAR Sjogren Syndrome Disease Activity Index

Table 2. Ongoing trials in primary Sjögren syndrome on clinicaltrials.gov

Trial identifier	Name	Target	sponsor	Study design	Primary outcome	Secondary outcome
NCT02631538	Belimumab and rituximab	BAFF and CD20	GlaxoSmithKline	Phase 2 RCT	safety	ESSDAI- stimalated salivary flow Bcell quantification in salivary gland biopsy
NCT02291029	CFZ 533	CD40	Novartis	Phase 2 RCT	ESSDAI change w12	ESSPRI patGDA, phyGDA SF-36 MFI
NCT02334306	AMG 557/MED1587	ICOSL	MedImmune/Amgen	Phase 2 RCT	ESSDAI change d99	laboratory and histologic changes ESSPRI safety
NCT02149420	VAY736	BAFF receptor	Novartis	Phase 2 RCT	ESSDAI change w12	ESSPRI patGDA, phyGDA SF-36 MFI
NCT02610543	UCB5857	PI3K	UCB	Phase 2 RCT	ESSDAI change w12	ESSPRI Change in salivary flow and Schirmer's test
NCT02775916	CDZ173	PI3K	Novartis	Phase 2 RCT	Improvement ESSPRI	ESSDAI patGDA , phyGDA
NCT02067910 ASAPIII	Abatacept	Costimulation of T cells	Groningen University and BMS	Phase 3 RCT	ESSDAI change w24	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
NCT01782235	Tocilizumab	IL-6 receptor	Strasbourg University	Phase 3 RCT	Improvement ESSDAI>3	NA
NCT02701985	RO5459072	Cathepsine S inhibitor	Hoffmann-La Roche	Phase 2 RCT	ESSDAI	ESSPRI SF-36
NCT02464319	hrIL-2	Human recombinant	Peking University People's Hospital	Phase 2	ESSDAI	CD4+ T cells, follicular helper

		IL-2		RCT		T cells, IL-17 producing helper T cells
NCT02614716	LY3090106	NA	Eli Lilly and Company	Phase 1 RCT	safety	Pharmacokinetics

RCT, randomized controlled trial; BAFF, B cell activating factor; ICOSL, inducible T cell co-stimulator ligand; PI3K, phosphoinositide 3-kinase; patGDA, Patient Global assessment; phyGDA, Physician Global assessment; MFI, Multidimensional Fatigue Index; PASS, Patient Acceptable Symptom State; FSFI, Female Sexual Function Index ; WPAI, Work Participation and Activity Impairment questionnaire

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