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EXPERT OPINION

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Pharmacotherapy for managing extraglandular symptoms of primary Sjögren's syndrome

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Introduction: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease, characterized by impaired function of the exocrine glands. Many pSS patients also experience extraglandular symptoms. Effective therapeutic interventions for pSS patients are not yet approved. However, advances in understanding of the disease process have led to the development of promising therapeutic targets.

Areas covered: This review provides an overview of current and presumed future strategies for the treatment of extraglandular symptoms in pSS patients, in relation to pathogenesis of the disease. In addition, future approaches for the evaluation of these symptoms in clinical trials will be discussed.

Expert opinion: Of all clinical trials that have been conducted in pSS, only few evaluated the effect of treatment on extraglandular symptoms. This lack of data can be partially explained by: i) heterogeneity of extraglandular symptoms; ii) inclusion of patients with low systemic disease activity in clinical trials; and iii) the former lack of a validated outcome measure to evaluate the systemic disease activity. These methodological issues should be addressed in future clinical trials. The ultimate goal in the management of pSS is evidence-based and personalized treatment of the broad range of symptoms experienced by patients suffering from this disease, including extraglandular symptoms.

Keywords: biologicals, extraglandular manifestations, primary Sjögren's syndrome, treatment

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1. Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease, characterized by lymphocytic infiltration of the exocrine glands [1]. The prevalence of diagnosed pSS is estimated at 0.05% of the general population [2], but misdiagnosis of patients with pSS is common, because of the large diversity in initial clinical manifestations. The most prominent presenting symptoms of pSS include fatigue, and a sensation of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). Whereas translational and clinical research mainly focus on inflammation and functionality of the salivary and lacrimal glands, pSS is undeniably a systemic disease. This is illustrated by the fact that > 50% of the patients experience extraglandular symptoms, including fatigue, arthralgia and Raynaud's phenomenon [3]. Extraglandular manifestations may also involve the lungs, skin, kidneys and nervous system (Table 1).

In the past years, several treatment approaches for pSS were evaluated, but none of them have been approved yet. Many clinical trials focus on primary endpoints concerning sicca features, whereas less attention is paid to the effect of treatment on extraglandular symptoms. To fill this gap, this review focuses on systemic

Article highlights.

- Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that primarily affects the exocrine glands. Effective therapeutic interventions for pSS are not yet available or approved.
- The type I IFN/BAFF/APRIL axis and the IL-6/IL-21 axis play crucial roles in T-cell dependent B-cell hyperactivity seen in pSS. Both axes are promising targets for treatment.
- Many pSS patients experience a variety of extraglandular symptoms, which are heterogenous in nature.
- Organ-specific extraglandular symptoms are related to periepipithelial infiltrations or immune complex deposition.
- Currently, extraglandular symptoms are managed in daily clinical practice with corticosteroids and other conventional immunomodulatory agents.
- Several methodological issues in clinical studies with pSS patients (e.g., the establishment of consensual international classification criteria) need to be resolved to truly rate the efficacy of different treatment strategies on extraglandular symptoms.

This box summarizes key points contained in the article.

immunomodulatory therapies in pSS and their effects on extraglandular symptoms. Promising treatment approaches that are now under investigation will also be discussed.

2. Pathogenesis of pSS

To date, the immunopathogenic mechanism of pSS has not been fully elucidated. A hallmark of the disease is infiltration of T- and B-cells in exocrine tissues, accompanied by loss of glandular architecture and function [4]. Lymphocytic infiltration is in close association with the ductal epithelium and leads to the formation of characteristic lymphoepithelial lesions, in particular in the parotid gland [5]. These infiltrates can become organized lymphoid tissue with segregated T- and B-cell areas and high endothelial venules. In ~ 25% of the pSS patients, germinal centers (GCs) arise within this tertiary (ectopic) lymphoid tissue [6]. GCs facilitate autoantibody production and the local generation of memory B-cells [7].

The periductal localization of the infiltrate illustrates the importance of the epithelium in the disease process. This epithelium is not only the target of the disease but exerts also important immunological functions including cytokine production and antigen presentation [8]. In addition to periductal infiltration of the target tissue, a shift in the plasma cell compartment is a second histological hallmark of pSS. This shift is mostly in favour of IgG-expressing plasma cells. Increased numbers of salivary gland IgG-producing plasma cells may contribute to the circulating levels of autoantibodies in pSS patients [9].

Increased levels of autoantibodies, together with the presence of cryoglobulins and hyperimmunoglobulinemia, reflect the ongoing T-cell dependent B-cell hyperactivity in pSS

patients. Furthermore, pSS patients have an increased risk for the development of mucosa-associated lymphoid tissue (MALT) lymphoma, a subclass of malignant B-cell lymphoma (reviewed by [10]). Two main cytokine axes appear to be involved in this B-cell hyperactivity, *viz.*, the type I IFN/BAFF/APRIL axis and the IL-6/IL-21 axis. Type I IFN and type I IFN-induced genes and proteins are overexpressed in salivary glands and peripheral blood of pSS patients [11-15]. Among these type I inducible proteins are B-cell activating factor (BAFF; also called B Lymphocyte Stimulator (BLyS)) and a proliferating ligand (APRIL), which play essential roles in B-cell activation, homeostasis and differentiation.

In pSS patients, many pro-inflammatory cytokines, such as IL-6 and TNF- α , are elevated in serum [16]. These cytokines are produced by many different cell types, including B-cells. IL-6 is also overexpressed in saliva, tears and minor salivary glands of pSS patients (reviewed by [10]). One of the many effector functions of IL-6 is direct and/or indirect stimulation of B-cell proliferation and differentiation into plasma cells (reviewed by [17]). Indirect stimulation includes the induction of IL-21 production by Tfh-cells [18]. IL-21 is a potent inducer of plasma cell formation and is involved in GC B-cell selection [19,20]. The IL-6/IL-21 axis is therefore thought to play a pivotal role in B-cell activation in pSS patients. Despite the notion that B-cell hyperactivity is a central event in the disease process, the pathogenic role of B-cells in pSS remains to be controversial. Current evidence indicates that this role goes beyond autoantibody production [21], as antigen presentation and cytokine production by B-cells might be significantly involved in pathogenesis of pSS.

Furthermore, IL-6 may contribute to immunopathology by the induction of Th17-cell differentiation, together with TGF- β [22]. In the last decade there has been a growing interest in the role of Th17-related cytokines in pathogenesis of pSS. Elevated numbers of IL-17-positive cells are present in minor salivary glands of pSS patients [23-25]. IL-17 protein expression progressively increases with higher biopsy focus scores in minor salivary glands of pSS patients [24]. Several pathogenic functions of Th17-cells in chronic inflammation have been described, including augmentation of autoantibody production [26] and induction of ectopic lymphoid tissue by upregulation of CXCL12 [27]. In a mouse model of experimental SS, Th17-cells enhance the Th1-response and drive B-cell activation and maturation [28]. Together these data indicate that Th17-cells, which are dependent on IL-6 for their polarization, may also play an important role in the pathogenesis of pSS (reviewed by [29]).

The aforementioned cytokine axes participate in pro-inflammatory amplification loops, which enhance infiltration of lymphocytes and non-lymphoid mononuclear cells to the target tissues of pSS patients. Together with the autoreactivity and possibly also intrinsic defects of the glandular epithelium the inflammation results in dysfunction of the exocrine glands and other tissues and finally in clinical symptomatology.

Table 1. Classification and treatment strategies for major types of extraglandular manifestations.

Extraglandular manifestations	Anatomic system	Current pharmacotherapy based on expert opinion
<i>Non-specific</i>		
Fatigue	-	
Myalgia	Joints/muscles	NSAIDs
Arthralgia/arthritis	Joints/muscles	NSAIDs Hydroxychloroquine Methotrexate Low-dose prednisone Calcium channel blocker Iloprost
Raynaud's phenomenon	Skin	
<i>Periepithelial</i>		
Interstitial nephritis	Urogenital tract	Bicarbonate and/or potassium completion High-dose prednisone
Obstructive bronchiolitis	Respiratory tract	Macrolides Inhaled corticosteroids Inhaled bronchodilators
Interstitial pneumonitis	Respiratory tract	Watchful waiting High-dose prednisone Cyclophosphamide Rituximab*
<i>Immune-complex mediated</i>		
Cutaneous vasculitis	Skin	<i>Mild:</i> Hydroxychloroquine Low-dose prednisone Topical corticosteroids <i>Severe:</i> High-dose prednisone Cyclophosphamide Rituximab*
Peripheral or central neuropathy	Nervous system	Treatment dependent on subtype of neuropathy [140]
Glomerulonephritis	Urogenital tract	High-dose prednisone Cyclophosphamide Rituximab*
<i>Other</i>		
Lymphadenopathy	Lymphatic system	Watchful waiting
Lymphoproliferative disease	Lymphatic system, epithelial tissue	Treatment dependent on subtype of lymphoma [34,36,37]

*After corticosteroids and cyclophosphamide, rituximab is a feasible therapeutic option in patients with severe and/or refractory systemic disease.

NSAIDs: Non-steroidal anti-inflammatory drugs.

Recognition of the various cell types and mediators involved in immunopathology of pSS has opened new ways for the development of selective treatment modalities in pSS.

3. Extraglandular symptoms of pSS

Next to sicca symptoms, the inflammatory process accompanying pSS may also result in extraglandular disease manifestations. Extraglandular symptoms may already be present at the initial stage of disease. Common extraglandular symptoms in pSS patients are fatigue, arthralgia/arthritis, myalgia and Raynaud's phenomenon [3]. Furthermore, numerous organs can be affected by the disease too, including lungs, skin and kidneys. The origin of extraglandular organ involvement can be either periepithelial lymphocytic infiltration or deposition of immune complexes. Extraglandular symptoms of pSS may therefore be differentiated in periepithelial and immune-complex-mediated manifestations (Table 1). Examples of periepithelial manifestations are interstitial nephritis and

obstructive bronchiolitis. Cutaneous vasculitis, peripheral neuropathy, and glomerulonephritis are examples of immune-complex-mediated manifestations [30,31]. Patients with periepithelial manifestations usually have a more stable disease than patients with immune-complex-mediated manifestations.

In addition, hematologic abnormalities, such as leucopenia (including lymphopenia), anemia and thrombocytopenia, are common in pSS patients [32,33]. Patients with pSS also have a 5- to 16-fold increased risk for the development of malignant B-cell lymphoma (reviewed by [34]). 5 – 10% of the patients eventually develops a lymphoma in the salivary glands, particularly of the MALT-type [35,36]. These lymphomas may well reflect the characteristic B-cell hyperactivity seen in these patients. Treatment modalities of MALT lymphoma have recently been reviewed and will not be discussed in this article [34,36,37].

The systemic activity of pSS is strongly associated with several serologic signs, including low C4 levels, hypergammaglobulinemia, cryoglobulinemia and higher levels of

rheumatoid factor and anti-SS-A/SS-B autoantibodies [33,38]. These serologic signs may therefore predict the evolution of extraglandular symptoms and identify patients in need for systemic treatment.

4. Measurement of extraglandular symptoms

To rate the efficacy of treatment of pSS, it is crucial to have international consensus on classification criteria and measurement of disease activity for pSS. Otherwise, results from translational research and clinical trials will be non-comparable. However, the heterogeneity of clinical manifestations in pSS complicates the design of reliable consensus criteria. The revised American-European Consensus Group criteria are commonly used in clinical practice to define patients with pSS [39]. Recently, new classification criteria have been proposed by Sjögren's International Collaborative Clinical Alliance (SICCA) [40]. A group of international experts is now working on the integration of both sets to create consensual classification criteria to be used in clinical trials. The inclusion of promising new tests in these criteria should also be considered [41].

For the measurement of disease activity an international consensus score to rate systemic disease activity was established under the umbrella of European League against Rheumatism: the EULAR SS disease activity index [42]. Together with the EULAR SS patient-related index (ESSPRI), which measures subjective symptoms of dryness, pain and fatigue, the ESSDAI is a promising tool for the evaluation of new therapeutic interventions. Recently, ESSDAI and ESSPRI were validated as tools to monitor disease activity [43-45].

The EULAR Sjögren's Task Force has recently defined low, moderate and high disease activity levels as ESSDAI < 5, $5 \leq \text{ESSDAI} \leq 13$ and ESSDAI ≥ 14 , respectively. The patient acceptable symptom state was defined as ESSPRI < 5. Furthermore, the EULAR Sjögren's Task Force defined a decrease in ESSDAI score ≥ 3 as minimal clinically important improvement (MCII). For the ESSPRI score, a minimal improvement of 15% or a decrease of ≥ 1 point was defined as MCII. Subsequently, they propose that future clinical trials need to include pSS patients with at least moderate disease activity (ESSDAI score ≥ 5) or unsatisfactory symptom state (ESSPRI ≥ 5) to evaluate the effect of treatment on systemic complications or important patient-reported symptoms, respectively [46]. The development of standardized response criteria may increase the potential of clinical trials to demonstrate a clinically relevant change in disease activity. On the other hand, the application of the proposed inclusion and response criteria may cause problems with the inclusion of sufficient numbers of patients in clinical trials, as the median ESSDAI score in pSS patients reported by two prospective cohort studies is 2 to 3 [47,48]. Of note, median ESSDAI scores in these cohorts were assessed at enrollment and are likely to increase during follow-up.

5. Pharmacotherapy for managing extraglandular symptoms

The current treatment of extraglandular symptoms in pSS is not evidence-based, because of the lack of large randomized controlled trials (RCTs). Most therapeutic strategies are adopted from other (B-cell-mediated) autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), with variable success. As the first systemic disease activity score for pSS became only available in 2010, none of the conducted RCTs assessed systemic disease activity as a primary outcome measure so far. The next paragraph summarizes secondary outcomes from these trials with regard to extraglandular manifestations or systemic disease activity. These data are useful for the identification of future treatment modalities for pSS patients with extraglandular symptoms.

5.1 Conventional synthetic immunomodulatory drugs in pSS

5.1.1 Prednisone

Prednisone is a synthetic corticosteroid with broad immunosuppressive effects. In pSS patients, low-dose prednisone is used for the treatment of arthritis and cutaneous symptoms, based on clinical experience. High-dose prednisone is used to treat severe systemic manifestations of pSS. Evidence on the use of prednisone for the treatment of extraglandular symptoms in pSS is limited as trials were small and specifically designed to assess sicca features. As other immunomodulatory drugs, the use of prednisone in pSS is extrapolated from its effectiveness in other autoimmune diseases. Treatment strategies for glomerulonephritis in pSS are, for example, similar to those for lupus nephritis [49]. Some case reports showed improvement of renal disease, neuropathic symptoms and interstitial lung disease in pSS patients after moderate or high doses of prednisone [50-52]. Prednisone may also improve hypergammaglobulinemia, which is associated with systemic activity, and lymphopenia, which is a common extraglandular manifestation in pSS patients [53]. Notwithstanding the positive results reported in case reports and small studies, it should be mentioned that no study specifically assessed the use of prednisone for treatment of extraglandular symptoms in pSS.

5.1.2 Hydroxychloroquine

Hydroxychloroquine is a disease-modifying antirheumatic drug (DMARD) that antagonizes TLR7 and TLR9 [54]. Inhibition of ligand binding to TLRs impairs innate immune responses, including pro-inflammatory cytokine production. Hydroxychloroquine is used for the treatment of articular and skin involvement in pSS patients, based on the efficacy observed in SLE and RA. However, two placebo-controlled trials did not show a clinical benefit of hydroxychloroquine in pSS patients [55,56]. The suggested application of hydroxychloroquine for treatment of articular involvement in pSS is also not confirmed by these trials. Gottenberg *et al.* included

120 pSS patients, of which 40 had arthralgias and 5 had synovitis. The authors concluded that hydroxychloroquine was not superior to placebo in these patients. Too few patients with skin involvement were included to draw any conclusion concerning this manifestation.

5.1.3 Others

Cyclosporine A (CsA) is an immunosuppressant and a specific inhibitor of T-cell activation. CsA is approved for the prevention of organ rejection, but also for the treatment of RA and psoriasis. The risk of kidney toxicity is a concern when prescribing CsA. An open-label study with low-dose CsA in pSS patients with articular involvement is ongoing (NCT01693393). No clear benefit has been demonstrated of other conventional immunomodulatory drugs that were evaluated in pSS patients (reviewed by [57]). These drugs include azathioprine, methotrexate and mycophenolic acid. Treatment with leflunomide showed only modest clinical efficacy in a Phase II open-label study, but did ameliorate leucocytoclastic vasculitis in three pSS patients [58]. The high rate of adverse events reported for these conventional immunomodulatory drugs raises concerns about whether they should be prescribed off-label in pSS.

5.2 Biologic immunomodulatory agents in pSS

Anti-TNF agents were the first biologic drugs evaluated in pSS patients. Unexpectedly these biologicals did not show efficacy [59,60]. In 2005, rituximab was introduced in pSS for the treatment of pSS patients with MALT lymphoma. Thereafter, several open-label and placebo-controlled trials followed to evaluate the efficacy of rituximab in the treatment of pSS (reviewed by [61,62]). Next to B-cells, additional targets for treatment have emerged as a result of advanced understanding of pSS pathogenesis (Figure 1). Conducted and ongoing clinical trials with biological agents in pSS are listed in (Table 2). None of these biologicals have yet been approved for the treatment of pSS.

5.2.1 Rituximab

As mentioned before, B-cell hyperactivity is a prominent feature of pSS. B-cell depletion therapy with rituximab (a chimeric anti-CD20 monoclonal antibody) has therefore been considered a feasible treatment modality for pSS patients. Three placebo-controlled trials describe a reduction in various disease manifestations in pSS patients treated with rituximab [63-65]. Overall, rituximab-treated patients showed significant improvement in fatigue scores. Meijer *et al.* also found a strong tendency toward a significant decrease in the number of reported symptoms of Raynaud's phenomenon, tendomyalgia and arthralgia from baseline to week 24 [64]. A subsequent analysis showed large differences in responsiveness of ESSDAI between rituximab and placebo groups and hereby confirmed the effectiveness of rituximab on systemic disease activity [44]. In accordance with these results, a large observational study by Gottenberg *et al.* showed good efficacy

and tolerance of rituximab in patients with pSS and systemic involvement [66]. The main extraglandular features that improved in this study after rituximab treatment were involvement of the joints, vasculitis, autoimmune cytopenias, pulmonary and kidney involvement. A prospective follow-up study demonstrated that rituximab was superior to DMARDs for improving the ESSDAI. The authors reported a rapid and consistent score reduction of constitutional, lymphadenopathy, glandular, articular and cutaneous domains of the ESSDAI [67]. In contrast, a large placebo-controlled study conducted by Devauchelle-Pensec *et al.* (TEARS study) found no improvement in systemic manifestations in the rituximab group compared with the placebo group [65]. A possible explanation for the absence of an effect on systemic manifestations in this trial is that patients with severe systemic involvement were not included.

Interestingly, a post-hoc analysis of the TEARS study showed that a combination of subjective and objective outcome measurements (Sjögren's Syndrome Responder Index (SSRI)) was sensitive to show a response-rate difference between rituximab and placebo groups. An SSRI-30 response was defined as $\geq 30\%$ relative improvement in at least two of the following five measures: patient-assessed visual analog scale scores for: i) fatigue; ii) oral dryness; and iii) ocular dryness; iv) unstimulated whole salivary flow; and v) erythrocyte sedimentation rate. Although the TEARS study did not show improvement in ESSDAI scores in the rituximab group compared with the placebo group, extraglandular symptoms improved in SSRI-30 responders [68].

It has been suggested earlier that specifically pSS patients with early, active disease with extraglandular manifestations are likely to benefit from treatment [62]. Taken together, available evidence indicates that rituximab treatment improves extraglandular manifestations in pSS patients. Results from the TRACTISS study (ISRCTN65360827), a large placebo-controlled clinical trial will further evaluate the efficacy of rituximab treatment on clinical outcomes in pSS patients [69].

In the meantime, data on the biological effects of rituximab have become available. It is now known that levels of immunoglobulins are hardly affected by treatment and that antibody-independent B-cell functions may contribute to the beneficial effects of rituximab. For instance, rituximab was able to reduce serum levels of different cytokines, including the pro-inflammatory IL-6 and TNF- α [16]. In contrast, BAFF levels increase significantly after rituximab treatment [14,70]. Unpublished data showed that rituximab also affects the T-cell arm of the adaptive immune system, by reducing numbers of circulating Th17-cells (Verstappen *et al.*, submitted). IL-17-positive cells in minor salivary glands of pSS patients were also decreased after rituximab treatment [23].

There is evidence that rituximab treatment induces down-regulation of NF- κ B activity through the up-regulation of Raf-1 kinase inhibitor protein in salivary gland epithelial cells *in vitro* [71]. A subsequent decrease of inflammatory mediators released by epithelial cells together with a reduction in

Figure 1. Targets for systemic treatment with biologic agents in pSS. Different aspects of the inflammatory response in target tissues of pSS are shown. The pathogenic role of epithelial cells in the disease process is reflected by infiltration of mononuclear cells in epithelial tissues. Furthermore, epithelial cells secrete inflammatory proteins, such as type I IFNs, BAFF, IL-6 and chemokines. There is a subsequent migration of various cell types to the tissue and then all elements to carry out (auto-) immune responses are in place. Targets for treatment and biologic agents that are currently under investigation are illustrated. APRIL: A proliferation-inducing ligand; BAFF: B-cell activating factor; DC: Dendritic cell; LTβR: Lymphotoxin β receptor; PC: Plasma cell; pDC: Plasmacytoid dendritic cell; pSS: Primary Sjogren's syndrome; Th-cell: T-helper cell; TLR: Toll-like receptor.

cytokine producing B-cells may underlie the reduced serum levels of pro-inflammatory cytokines in pSS patients treated with rituximab [61].

5.2.2 Epratuzumab

Another biological agent that targets B-cells is epratuzumab, a humanized anti-CD22 monoclonal antibody. CD22 is a B-cell surface molecule that functions mainly as a regulatory molecule of B-cell antigen receptor (BCR) signaling. Anti-CD22 treatment causes partial B-cell depletion (35 – 40%) [72,73], altered B-cell migration [74] and modulation of B-cell receptor-dependent B-cell activation in an agonistic fashion [75]. By these mechanisms, epratuzumab may potentially reduce B-cell hyperactivity in pSS patients. One open-label study investigated the efficacy of epratuzumab in pSS patients and showed improvement of subjective and objective parameters of disease activity, including fatigue [76]. The efficacy of epratuzumab on other extraglandular manifestations was not

evaluated by this study. Currently, anti-CD22 treatment is investigated in SLE with Phase III trials in progress. These data are awaited and may lead to further evaluation of epratuzumab for the treatment of pSS.

5.2.3 Belimumab

In the light of B-cell hyperactivity, BAFF (BLyS) and APRIL play an important role in the pathogenesis of pSS. Both cytokines may be induced or upregulated by IFN and are involved in survival, activation and differentiation of B-cells. BAFF is particularly important for B-cell longevity and APRIL for survival of plasma cells. Patients with pSS have elevated levels of both BAFF (BLyS) and APRIL in serum and saliva compared to healthy controls (reviewed by [10]). Elevated levels of BAFF may well lead to autoimmunity due to less stringent selection of B-cells, as shown in murine models [77,78]. Furthermore, serum levels of BAFF (BLyS) were found to be associated with ESSDAI score and with

Table 2. Systemic, biological therapies in pSS.

Drug	Target	Clinical trial status	Effects on extraglandular symptoms	Publications
Infliximab	TNF- α	Phase III completed (n = 103)	None	[59]
Etanercept	TNF- α	Phase II completed (n = 22 pSS, 6 sSS)	None	[60]
Anakinra	IL-1	Phase II completed (n = 25)	6 patients on anakinra and 1 patient on placebo reported > 50% reduction in fatigue VAS score from baseline to week 4 (post-hoc)	[141]
Rituximab	B-cells (CD20)	Phase II completed (n = 17, n = 30, n = 41)	Improvement in fatigue scores [63,64,67], improvement in ESSDAI [44,67]	[44,63,64,67]
		Phase III: 1 completed (n = 120), 1 underway	Improvement in fatigue VAS from baseline to week 24	[65] ISRCTN65360827
Epratuzumab	B-cells (CD22)	Phase I/II completed (n = 16)	Improvement in fatigue VAS from baseline to week 32	[76]
Belimumab	BAFF/BLyS	Phase II completed (n = 30)	Improvement in ESSDAI and ESSPRI	[83]
VAY736	BAFF/BLyS receptor	Phase II underway		NCT02149420
Abatacept	CD28-mediated co-stimulation	Phase II completed, phase III underway	Improvement in ESSDAI and ESSPRI [85]	[84,85] NCT02067910
Tocilizumab	IL-6 receptor	Phase II underway		NCT01782235
Baminercept	lymphotoxin β receptor	Phase II underway		NCT01552681
Cyclosporin A	T-cells	Phase II underway		NCT01693393

BAFF: B-cell activating factor; BLyS: B lymphocyte stimulator; ESSDAI: EULAR SS disease activity index; ESSPRI: EULAR SS patient reported index; VAS: Visual analog scale.

pSS-associated lymphoproliferative complications [79]. BAFF is therefore a feasible therapeutic target in pSS.

Belimumab, a human monoclonal anti-BAFF (BLyS) antibody, was recently approved for treatment of SLE based on two placebo-controlled studies that showed improvement in SLE disease activity [80,81]. Improvement occurred primarily in the musculoskeletal and mucocutaneous organ systems of SLE patients, which were also the most commonly affected systems at baseline [82]. In the first open-label study with belimumab in pSS, the primary end-point was achieved in 18 patients (60%). Thirteen patients (43%) showed $\geq 30\%$ decrease in physician visual analogue scale systemic activity score. Systemic activity measured by the ESSDAI was also significantly decreased by treatment and improvement was seen primarily in the glandular, biologic and articular domains. Furthermore, treatment with belimumab appeared to have beneficial effects on B-cell activation biomarkers, such as serum IgG and serum-free light chain levels [83]. Patients with extraglandular symptoms may therefore benefit from treatment with belimumab, although improvement in patient-reported symptoms was quite limited in this study. Placebo-controlled trials are needed to further evaluate the efficacy of belimumab in the treatment of pSS.

5.2.4 Abatacept

Given the recognized role for T-cells in pSS pathogenesis, targeting of these cells is considered as a rational therapeutic

option in pSS. Abatacept is a fully human fusion molecule of IgG-Fc and cytotoxic T-lymphocyte-associated protein 4. Herewith abatacept prevents the co-stimulatory interaction between antigen-presenting cells, including B-cells and T-cells. Selective co-stimulation modulation by abatacept is presumed to inhibit full T-cell activation and T-cell-dependent B-cell activation. Two open-label studies evaluated efficacy and safety of abatacept treatment in pSS patients [84,85]. Adler *et al.* included 11 patients, not suffering from extraglandular disease [84]. Meiners *et al.* included 15 patients with a recent disease onset and active disease. In the latter study treatment with abatacept resulted in improvement of extraglandular manifestations as revealed by decrease in ESSDAI scores [85]. ESSDAI domains that showed most improvement were the articular, biological, glandular and constitutional domain. The results of these studies support the given role for T-cells in pSS pathogenesis. A placebo-controlled study in pSS is now in progress to verify results from the open-label studies (NCT02067910). Furthermore, an open-label study with abatacept for patients with inflammatory arthritis associated with SS (primary and secondary) is ongoing (NCT02027298).

6. Emerging therapeutic targets and future perspectives

As described earlier, several B-cell targeted therapies have been evaluated for the treatment of pSS, of which rituximab is the

most studied agent. The knowledge about pSS pathogenesis is now expanding and next to direct targeting of the B-cell, other strategies have emerged for the treatment of pSS. These strategies include blockade of T-cell co-stimulation and scavenging of T- and B-cell derived cytokines. In addition, targeted synthetic DMARDs that inhibit BCR- or cytokine receptor signaling, such as Bruton's tyrosine kinase (BTK) inhibitors and Janus kinase (JAK) inhibitors, have become available. Although we are not able to address all possible therapeutic targets here, we will summarize the most promising future perspectives.

6.1 Type I IFN/BAFF/APRIL axis

6.1.1 Type I IFN

Overexpression of type I IFNs plays an important role in pathogenesis of both pSS and SLE. IFN induction might be an early event of disease pathogenesis, as a result of activation of pattern recognition receptors, including TLRs. A so-called IFN type I signature is present in half of the patients with pSS and identifies a subgroup of patients with higher clinical disease activity [12]. Two studies have evaluated sifalimumab, an anti-IFN α monoclonal antibody, for the treatment of SLE, which is also characterized by involvement of IFN. The first study was designed to assess the safety profile of sifalimumab and additionally found trends toward improvement in disease activity across several outcome measures [86]. A second study found no statistically significant differences in the clinical activity between sifalimumab- and placebo-treated SLE patients [87]. As other IFNs can also bind to the receptor to which IFN α binds [88], IFN pathway activation may be sustained, despite the IFN α blockade. Analysis of salivary gland tissue of pSS patients also demonstrated heterogeneity in IFN pathway activation, with evidence of both type I and II IFN patterns [89]. Targeting of IFN α alone in pSS seems, therefore, not a rational therapeutic option. Individual quantification of the activity of different IFN-induced pathways in pSS patients and specific inhibition of these pathways may be a more successful treatment strategy.

6.1.2 TACI

TACI is one of the three receptors for BAFF and APRIL. Atacicept is a TACI-Ig recombinant fusion protein that binds and neutralizes BAFF and APRIL. As both cytokines are strongly upregulated in pSS it was suggested that dual blockade of these two cytokines by atacicept may be more potent than inhibiting BAFF alone. Because APRIL is also an important survival factor for long-lived plasma cells [90], atacicept may also target long-lived plasma cells in addition to B-cells [91]. In the treatment of RA, two placebo-controlled trials did, however, not show clinical efficacy of atacicept compared with placebo, although immunoglobulins, mature B-cells, plasma cells and rheumatoid factor were decreased after treatment [92,93]. Despite the disappointing clinical efficacy in RA patients, beneficial results on serological features triggered the use of atacicept in other autoimmune diseases that involve

B-cell hyperactivity, such as SLE and pSS. A placebo-controlled study with atacicept in SLE showed that high-dose treatment (150 mg) was associated with a significantly delayed time to first flare; however, safety concerns resulted in early termination of the high-dose treatment arm. There was no difference between atacicept 75 mg and placebo for the flare rate or time to first flare [94]. The potential of atacicept to show safety and efficacy in pSS remains, therefore, elusive.

6.2 IL-6/IL-21 axis

6.2.1 IL-6/IL-6R

IL-6 is a multifunctional pro-inflammatory cytokine that is also presumed to be important for the differentiation of both B- and T-cells. IL-6 induces the polarization of Tfh-cells and production of IL-21 by these cells, which is indispensable for the generation of plasma cells [95]. Furthermore, IL-6 is involved in the differentiation of pathogenic Th17-cells from naive T-cells [22]. Elevated levels of IL-6 are observed in serum, saliva, tears and salivary glands of pSS patients (reviewed by [10]). Targeting of IL-6 is therefore emerging as a novel therapeutic strategy. IL-6 can be secreted by many cell types, including B-cells. Animal studies showed that ablation of IL-6 production by B-cells ameliorates autoimmune disease in mice with experimental autoimmune encephalomyelitis (EAE) and that IL-6 is associated with a reduced Th17-response [96]. The pathogenic role of IL-6 is further supported by a recent study that showed amelioration of nephritis, lymphocyte abnormalities, and secondary Sjögren's syndrome (sSS) features in IL-6-deficient lupus-prone mice [97]. An open-label study in SLE with tocilizumab, an IL-6 receptor antagonist, showed promising clinical and serological responses [98]. This group also showed that treatment with tocilizumab resulted in a decrease in lymphocyte activation and restoration of B- and T-cell homeostasis [99]. The safety and efficacy of tocilizumab in pSS patients remains to be seen. A French multicenter placebo-controlled trial of tocilizumab (NCT01782235) has started and will include pSS patients with systemic disease activity (ESSDAI ≥ 5).

6.2.2 ICOS-B7RP-1

In addition to IL-6, a co-stimulatory pathway that is critical for Tfh-cell development and maintenance is mediated through inducible T-cell co-stimulator (ICOS) and B7RP-1. Tfh-cells are, in their turn, responsible for B-cell activation and secretion of IL-21 [100]. Increased numbers of Tfh-cells and IL-21 were found in peripheral blood and salivary glands of pSS patients (reviewed by [101]). Patients with extraglandular symptoms had even higher proportions of Tfh-cells in peripheral blood compared with patients without extraglandular manifestations [102]. Furthermore, IL-21 levels in serum were positively associated with systemic disease activity assessed by ESSDAI [103]. Tfh-cells are therefore a potential target for treatment in pSS. Animal studies showed that blockade of the ICOS/B7RP-1 pathway with anti-B7RP-1 inhibited T-cell

activation and reduced the numbers of Tfh-cells as well as GC B-cells [104]. However, a recent study in mice showed that blockade of the ICOS/B7RP-1 pathway may not be therapeutically sufficient, because other drivers of Tfh-cell development (such as antigen-presenting B-cells) can compensate for the absence of ICOS-L signaling [105]. Further studies are needed to investigate similarities in the ICOS/B7RP-1 pathway between mouse and human models and to assess whether the ICOS/B7RP-1 pathway is a possible therapeutic target in pSS. Anti-human-B7RP-1 and anti-human-ICOS monoclonal antibodies are currently in early-stage clinical testing in SLE patients.

Next to targeting of the ICOS/B7RP-1 pathway, the effector cytokine of Tfh-cells, IL-21, may also form a possible therapeutic target in pSS. A Phase I, first-in-human study with ATR-107 a fully human monoclonal anti-IL-21 receptor antibody, in healthy volunteers was recently published [106].

6.2.3 IL-17

Th17-cells and their related cytokines (e.g., IL-17, IL-22, IL-23) are recognized as major players in autoimmunity [107,108]. Secukinumab and ixekizumab, fully human anti-interleukin-17A monoclonal antibodies, and brodalumab, an anti-IL-17RA monoclonal antibody, showed efficacy for the treatment of psoriasis [109-111]. In RA, a placebo-controlled trial with secukinumab did not meet the primary efficacy outcome [112], whereas a placebo-controlled trial with ixekizumab did show improvement in RA symptoms [113].

In pSS patients, increased levels of Th17-related cytokines were found in salivary glands and peripheral blood [25,114]. Rituximab treatment caused a significant decrease in IL-17-positive cells in the minor salivary glands of pSS patients [23]. Unpublished data showed that circulating Th17-cells were also decreased after rituximab treatment and that frequencies of IL-17-producing Th-cells were significantly lower in clinical responders than non-responders to rituximab (Verstappen *et al.*, submitted). IL-17 may therefore be considered a promising therapeutic target in pSS.

6.3 Additional therapeutics targets

6.3.1 Lymphotoxin β receptor

A possible therapeutic strategy in pSS is to inhibit the formation of ectopic lymphoid tissue in exocrine glands of pSS patients. Together with homeostatic chemokines (CXCL12, CXCL13, CCL19 and CCL21), lymphotoxin β (LT β) is essential for lymphoid organogenesis and maintenance of both secondary and tertiary (ectopic) lymphoid tissues (reviewed by [115]). These homeostatic chemokines are strongly upregulated in labial salivary gland tissue of pSS patients (reviewed by [10]). CXCL13 in particular seems to play an important role in pathogenesis of pSS. Levels of CXCL13 were elevated in serum and saliva of pSS patients and an elevated salivary CXCL13 level distinguished SS patients with xerostomia from SS patients without xerostomia [116,117]. Furthermore, an increased expression of

CXCL13 within infiltrating cells was significantly related to a higher degree of lymphoid organization in minor salivary glands of pSS patients [118]. Several studies in murine models suggested that CXCL13 expression is dependent on LT β receptor (LT β R) signaling. In a murine model of SS, LT β R-blockade resulted in ablation of the organized (ectopic) lymphoid tissue in salivary and lacrimal glands and was accompanied by a reduction in homeostatic chemokines, including CXCL13 [116,119]. In a murine model of inducible lymphoid neogenesis in the submandibular glands, CXCL13 expression preceded the formation of ectopic lymphoid structures, along with CCL19 and LT β [120]. Together, these findings suggest that LT β R-blockade, with a subsequent reduction of CXCL13, is a potential treatment option in pSS. Of interest, a reduction of ~ 50% in serum levels of CXCL13 was seen after LT β R-blockade with baminercept in RA patients. A placebo-controlled trial of baminercept in pSS is ongoing (NCT01552681).

6.3.2 Intracellular signaling pathways

Advances in our understanding of intracellular signaling pathways downstream of immunological receptors have led to the development of targeted synthetic therapies, such as Janus kinase (JAK) inhibition. JAK is a family of tyrosine kinases that mediates the signaling of cytokine receptors. Once receptors are activated, JAKs initiate the JAK-STAT signaling pathway [121]. Tofacitinib, a targeted synthetic DMARD, was the first JAK-kinase inhibitor approved for treatment of RA [122]. Evaluation of tofacitinib in pSS is appealing, as it blocks the effect of type I and II IFNs, IL-6, IL-17, IL-22, IL-21 and IL-23, all important in pathogenesis of pSS. The inhibition of other signal transducers, such as BTK, spleen tyrosine kinase (SYK) or MAPK, also showed potential for amelioration of autoimmune disease. BTK and SYK play important roles in BCR signaling and MAPKs mediate functional responses of immune cells to a wide range of stimuli [123]. Currently, Btk inhibition is of particular interest for future treatment of B-cell malignancies, including MALT lymphoma, which is frequently seen in pSS patients [124].

6.3.3 CD40-CD40L

Besides CD28-CD80/86 and ICOS-B7RP-1 mediated co-stimulation, the CD40-CD40L co-stimulatory pathway is also evaluated as therapeutic target for autoimmune diseases. CD40-CD40L co-stimulation mediates activation of both innate and adaptive immune cells. This CD40-CD40L pathway is critical for generation of isotype switched memory B-cells and affinity maturation in GCs. Concerns surrounding the development of potentially catastrophic thromboembolic events after CD40L-targeted therapy discouraged the development of new trials [125]. Anti-CD40L monoclonal antibodies without the risk for thromboembolic events have been developed recently [126].

6.3.4 Autoreactive B-cells

A major disadvantage of all available therapies is that beneficial immune responses are also affected. Specific targeting of autoreactive B-cells is, therefore, an exciting development. An interesting approach in this regard is the construction of liposomes that display both CD22 ligand and antigen. By crosslinking of autoantigen-specific immunoglobulins with the inhibitory B-cell co-receptor CD22, suppression of autoreactive B-cells might be achieved [127]. A remark for the use of this approach in pSS is that the role of autoantibodies in initiation and/or perpetuation of the disease is still elusive.

7. Expert opinion

After a long history of translational and clinical research in pSS, not much is known of the etiopathogenesis of extraglandular symptoms. How the pathogenesis is related to the pathogenic events that take place in the exocrine glands is also not clear. Treatment of extraglandular symptoms is mostly based on evidence from other autoimmune/inflammatory diseases and personal experience of the physician. The ultimate goal in the management of pSS is evidence-based and personalized treatment of the broad range of symptoms experienced by patients suffering from this disease, including extraglandular symptoms. Four main questions that need to be answered in order to achieve this goal are addressed below.

7.1 Extraglandular symptoms: Why and when do they arise?

Fatigue, arthralgia and myalgia are common symptoms that are not specific for pSS, as they are shared with most other autoimmune rheumatic diseases. These symptoms present themselves early in the disease process, often before diagnosis. The etiology of general symptoms is multifactorial, though it is likely that chronic inflammation is the underlying cause. Glandular symptoms are more specific for pSS and are present in 80 – 90% of the patients. More than 50% of the patients also develop extraglandular symptoms. Systemic activity of pSS, as reflected by these symptoms, is associated with a IFN type I signature and several serologic signs of B-cell hyperactivation [12,33,38,48]. In addition, the presence of GCs in salivary glands of pSS patients is associated with more severe disease [6]. Extraglandular involvement may therefore reflect a more active state of the disease. The factors that are decisive for lymphocytic infiltration (periepithelial involvement) or deposition of immune complexes (extraepithelial involvement) in certain organ systems remain elusive.

7.2 How to evaluate extraglandular symptoms?

Past clinical trials in pSS mainly focused on sicca symptoms as the primary outcome measure. Often changes in visual analog scores of several subjective symptoms were used to evaluate treatment efficacy. A variety of secondary outcome measures for the evaluation of extraglandular manifestations has been

applied in clinical trials and probably contributed to the inconsistent results obtained with these trials. The great need for a uniform systemic disease activity measure was met by the introduction of ESSDAI, which is now validated to evaluate systemic involvement. The sensitivity to change of ESSDAI is more accurate than other indices that have been used in clinical trials in pSS [128].

The next challenge is to develop a consensual outcome measure, which is supported by both ACR and EULAR. International experts are currently working on the development of consensus classification criteria. Another challenge is the inclusion of patients with extraglandular symptoms that occur less frequently, such as cutaneous, pulmonary or peripheral nervous system involvement. With regard to the evaluation of treatment efficacy on these symptoms, a meta-analysis or a multicenter, registry-based trial may offer a solution.

7.3 Can we realize tailored treatment of extraglandular symptoms?

As mentioned earlier, the heterogeneity in disease manifestations is a hurdle for demonstrating efficacy of biologic therapies in pSS. There is an unmet need for clinically applicable biomarkers that can predict response to treatment. An algorithm is needed how to treat which pSS patient and hereby biomarkers can play an important role. In RA patients for example, high serum levels of IL-6 were, among others, associated with (non)response to rituximab [129–133]. In pSS, cytokines and chemokines may also be important biomarkers, as they drive the inflammatory process in target organs of the disease.

A nice example of a recently identified biomarker in pSS is myxovirus resistance protein A (MxA) [134]. MxA identifies type I IFN bioactivity in patients with pSS and is potentially valuable to stratify patients according to their disease phenotype [135]. Proteomic approaches may also be useful for the identification of biomarkers, especially in saliva and tear samples [136–138].

7.4 Is it beneficial to combine treatments?

Combining biologicals may be beneficial to hit two targets at the same time or to prolong the effects of treatment. The combination of rituximab and blockade of BAFF may, for instance, enhance the effects of B-cell depletion and delay the re-emergence of clinical symptoms [62]. One case-report described amelioration of disease after sequential belimumab-rituximab treatment in a patient with severe, refractory SS, MALT lymphoma and cryoglobulinaemic vasculitis [139]. This combination therefore deserves further evaluation in pSS patients.

Ultimately, the goal of evidence-based and personalized treatment in patients with pSS can be reached by a collaborative effort in translational research and standardized design and performance of clinical trials.

Declaration of interest

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