Journal of Autoimmunity xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Sjögren's syndrome: Old and new therapeutic targets

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ARTICLE INFO

Keywords:
Sjögren's syndrome
Treatment
Therapeutic targets
Biologic agents

ABSTRACT

Sjögren's syndrome (SS) is a prototype autoimmune disease characterized by oral and ocular mucosal dryness following chronic inflammation of salivary and lachrymal glands, respectively. Profound B cell hyperactivity along with systemic manifestations including fatigue, musculoskeletal complaints, features related to hepatic, pulmonary, renal and nervous system involvement, as well as lymphoma development can be also present. Despite that activation of both innate and adaptive immune pathways has been long well documented in SS pathogenesis, systemic immunosuppression in SS, in contrast to other autoimmune diseases, has been largely inefficacious. Biological agents previously implemented in successful therapeutic outcomes in rheumatoid arthritis (RA), such as anti-TNF agents, anakinra, tocilizumab and rituximab failed to reach primary outcomes in randomized double-blind controlled trials in the context of SS. Abatacept and belimumab, already licensed for the treatment of RA and lupus respectively, as well combination regimens of both rituximab and belimumab hold some promise in alleviation of SS-specific complaints, but data from large controlled trials are awaited. Recent advances in dissecting the molecular pathways underlying SS pathogenesis led to an expanding number of novel biological compounds directed towards type I interferon system, antigen presentation, costimulatory pathways, B and T cell activation, as well as germinal center formation. While targeting of cathepsin-S (Petesicatib), inducible costimulator of T cells ligand (prezalumab), and lymphotoxin beta receptor (baminercept) failed to fulfil the primary outcome measures, preliminary results from two randomized placebo controlled trials on CD40 blockade (Iscalimab) and B-cell activating factor receptor (Ianalumab) inhibition resulted in significant reduction of SS disease activity, with a favorable so far safety profile. Results from administration of other kinase inhibitors, a transmembrane activator and calcium-modulator and cytophilin ligand interactor TACI fusion protein (RC18), as well as low dose recombinant interleukin-2 to expand T-regulatory cells are currently awaited.

1. Introduction

Sjögren's syndrome (SS) is a classical autoimmune disease, which primarily present with symptoms and signs of exocrine gland (mainly salivary and lachrymal) secretory dysfunction, as a result of local inflammation. Nevertheless, SS is commonly expressed with several systemic manifestations as well, including fatigue, musculoskeletal and cutaneous features, liver, renal and pulmonary involvement and lymphoma [1]. Given that epithelial cells have been shown to display a crucial role in organization of local immune response in targeted tissues through antigen presentation of endogenous or exogenous autoantigens, cytokine and chemokine production promoting B cell activation and recruitment of circulating immune cells [2], the term autoimmune epithelitis was coined almost 25 years ago [3].

Though SS shares several characteristics with other systemic autoimmune disorders such as systemic lupus erythematosus (SLE), in terms of female predilection, activation of both innate and adaptive immune pathways, local inflammatory lesions in target organs and presence of serum autoantibodies against intracellular components, immunosuppressives and available biological agents have proved to be unsuccessful in providing a significant therapeutic effect [4]. During the last decades, clarification of underlying pathogenetic pathways in SS fueled international efforts towards the discovery of novel therapeutic modalities targeting both innate and adaptive immune pathways including proinflammatory mediators, activation of type I interferon (IFN) system, antigen presentation, costimulation pathways, B and T cell activation as well as ectopic germinal center formation [5].

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https://doi.org/10.1016/j.jaut.2019.102364
Received 6 November 2019; Accepted 10 November 2019
0896-8411/

2. Targeting of innate immunity pathways (Table 1, Fig. 1)

2.1. Proinflammatory cytokines

Given that upregulation of several proinflammatory cytokines have been previously shown to contribute to SS pathogenesis [6–8], selective blockade of these mediators has been a primary goal. In view of the success of tumor necrosis factor α (TNFα) inhibitors in a plethora of chronic inflammatory disorders [9], both infliximab (a monoclonal antibody against TNFα) and etanercept (a soluble TNF receptor) were among the first biologic agents tested in SS patients with disappointing results in terms of subjective and objective sicca features and fatigue [10–12]. Failure to dampen TNFα levels [13], or augmentation of type I interferon (IFN) pathways and B cell activating factor (BAFF) [14] have been viewed as potential mechanisms of anti-TNF inefficacy in SS. In a phase I, prospective, single-center, open label 12-week study administration of infliximab eye drops is currently tested for the management of SS related corneal melt (ClinicalTrials.gov Identifier: NCT02987686).

A growing body of evidence supports a role of inflammasome and interleukin (IL)-1 related cytokines in SS pathogenesis [15]. The purinergic P2X7 receptor (P2X7R), a calcium permeable cationic channel activated by extracellular ATP, has been shown to mediate assembly of the intracellular sensor Nod-like receptor family protein 3 (NLRP3) inflammasome, ultimately leading to mature IL-1β and IL-18 cytokine production, upon triggering with injurious triggers [16,17]. Intraperitoneal administration of the $P2X_7R$ inhibitor A438079 in an autoimmune exocrinopathy mouse model led to improvement of both salivary gland inflammation and saliva secretion [18]. In an earlier study, administration of the IL-1 receptor (IL-1R) antagonist anakinra for 4 weeks subcutaneously was shown to decrease fatigue levels of SS patients [19], a major burden for SS patients [20]. Moreover, in an experimental animal model with autoimmune-mediated aqueous-deficient ocular dryness, local treatment of anakinra led to repair of the damaged ocular surface, as shown by stabilization of Lissamine green staining [21].

Inhibition of the pleiotropic effects of IL-6 by the recombinant humanized monoclonal antibody against IL-6 receptor (IL-6R) tocilizumab has been previously implemented in the management of several chronic inflammatory states [22–24]. In the setting of SS, isolated case reports revealed a potentially beneficial role of IL-6R blockade [25–27]. According to recently reported preliminary results of an ongoing randomized, double-blind, placebo-controlled, phase III trial (NCT01782235), tocilizumab administration, while failed to demonstrate a significant impact in SS related symptoms, revealed a favorable effect in arthritic complaints [28].

Recently, iguratimod, a novel disease modifying compound with suppressive effects on TNFα, IL-1, IL-6 and B cell function [29], has been shown to be efficacious in both rheumatoid arthritis (RA) [30] and IgG4 related disease [31]. In 25 SS patients receiving iguratimod 50 mg daily for 12 weeks plus conventional treatment, a statistically significant improvement in disease activity indices, as well as inhibition of B cell activating factor receptor (BAFF-R), CD38, and IgD expression on B cells was reported compared to those treated with conventional therapy [32]. Beneficial results in terms of disease activity, hypergammaglobulinaemia and ESR were also recently reported following iguratimod treatment for 12 weeks [33]. However, a case report of potential liver toxicity was reported in a patient with SS following treatment with iguratimod [34].

2.2. IFNs

Activation of IFNs in systemic autoimmune diseases including SS has been first revealed almost 50 years ago [35]. Since then, microarray and gene expression studies confirmed upregulation of type I and II IFN regulated genes in both peripheral blood and affected salivary gland tissues derived from these patients [36–41]. Triggering of plasmacytoid dendritic cells (pDCs) currently considered the chief professional producers of type I IFN [42] by deregulated endogenous nucleic acids, such as Long Interspersed Nuclear Element 1 (LINE-1; L1) genomic repeats, has been viewed as a potential mechanism of type I IFN production in the setting of systemic autoimmunity through activation of Toll-like receptor (TLR) dependent or independent pathways [43]. Of note, pDCs are characterized on their surface by the presence of a leucocyte immunoglobulin-like receptor molecule termed immunoglobulin-like transcript 7 (ILT7)/LILRA4/CD85g [44]. Activation of ILT7 downregulates TLR7/9 mediated IFN production and shifts differentiation of pDCs towards an antigen presenting cell (APC) instead of an IFN producing cell phenotype [45–47]. Alternatively, in view of the significant contribution of the TBK1-TNF receptor associated factor NF-κB activator (TANK) in type I IFN production through IFN Related Factor (IRF)-3 and IRF-7 ligation, TANK inhibition seems a promising therapeutic target. Once is produced, type I IFN binds on the type I IFN receptor and through phosphorylation of Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) results to STAT pathway activation and upregulation of IFN inducible genes [48].

RSLV-132 is an RNase fused to the Fc domain of IgG1 aiming at degrading circulating immunostimulatory RNA in association with immunocomplexes resulting in dampened type I IFN production. It has been already administered in lupus patients with promising effects [49] and is presently evaluated in a phase II, double-blind, placebo-controlled study including 28 SS patients with documented presence of upregulated type I IFN responses and anti-Ro/SSA antibodies (ClinicalTrials.gov Identifier: NCT03247686). In a pilot analysis, beneficial effects on fatigue levels and a good safety profile were demonstrated [50].

Hydroxychloroquine (HCQ), has been previously shown to impair type I IFN production by pDCs derived from lupus patients possibly through interfering with endosomal pH and preventing activation of endosomal TLR-7 and -9 receptors by endogenous nucleic acids [51]. However, and in contrast to an early study in lupus patients [52], administration of HCQ in the setting of a randomized double-blind controlled trial in patients with SS (JOQUER, clinicaltrials.gov Identifier: NCT00632866) failed to improve SS related symptoms [53] despite reducing type I IFN inducible gene expression in treated individuals [54].

As previously described, ligation of the ILT7 receptor on pDCs has the potential of abrogating type I IFN production. In a multicenter, double blind, placebo-controlled, phase I study, an ILT7 receptor antibody (MEDI7734/VIB7734) was administered in 36 patients of type I IFN-mediated autoimmune diseases including SS. While the study was completed, no results are as yet published (ClinicalTrials.gov Identifier: NCT02780674). Additionally, a phase I study evaluating safety and pharmacokinetics of multiple ascending doses of MEDI7734/VIB7734 is currently recruiting new patients (ClinicalTrials.gov Identifier: NCT03817424). Despite encouraging results of monoclonal antibodies against type I IFN receptor in SLE [55] – the prototype type I IFN mediated disease [56]- these agents have not yet been tested in SS.

In a randomized, phase II, double-blind, placebo-controlled study, the efficacy and safety of oral administration of kinase inhibitors including lanraplenib (formerly GS-9876, Tyk2 inhibition) and filgotinib (JAK1 inhibition) was tested in 152 adult subjects with seropositive SS (presence of anti-Ro/SSA or anti-La/SSB) with an EULAR SS disease activity index (ESSDAI) ≥ 5 (ClinicalTrials.gov Identifier: NCT03100942). Finally, while there is no clinical data available yet, administration of BX795 -a TANK inhibitor-led to downregulation of type I IFN inducible genes in SS peripheral blood mononuclear cells [57].

3. Adaptive immunity (Table 2, Fig. 2)

3.1. Antigen presentation

3.1.1. Cathepsin S

Cathepsin S (CatS) is a lysosomal cysteine endopeptidase involved in antigen presentation through degradation of the Major Histocompatibility complex (MHC) class II invariant chain Ii in human and mouse APCs, which is a crucial process for class II–peptide formation [58]. To this end, dampened local inflammatory responses in both lachrymal and salivary glands, as well as abrogated autoantibody production were shown following inhibition of CatS in a murine SS model [59]. CatS activity has been later shown to be highly elevated in both lacrimal glands and tears of the 12-week-old male Non Obese Diabetic (NOD) mice, a model of autoimmune dacryoadenitis [60,61], as well as in tears derived from SS patients [61,62]. Intraperitoneal administration of a peptide based synthetic inhibitor of CatS in a 14–15 week male NOD mice for two weeks, reduced lymphocytic infiltration in lachrymal glands and increased tear production [63], implying a promising therapeutic role for this agent in SS related dry eye disease. In contrast, no beneficial effects in systemic disease activity were demonstrated (ClinicalTrials.gov Identifier: NCT02701985).

3.2. Co-stimulation

Immune responses are profoundly shaped and controlled by co-stimulatory and co-inhibitory receptors and their related ligands. Autoimmune diseases, including SS, have been long characterized by impaired function of either co-stimulation or co-inhibition [64,65]. Administering of an inhibitory signal or blocking a stimulatory pathway modulate an otherwise exaggerated response. The major families of co-stimulatory and co-inhibitory molecules implicated in SS pathogenesis and their related inhibitory targets are displayed in Table 3.

3.2.1. Immunoglobulin (Ig) family

3.2.1.1. CD 80/86 - CD28. The central role of salivary gland epithelial cells in orchestrating local immune responses has been long recognized [3]. These cells have been shown to be equipped with several molecules crucial for the initiation of an immune response towards endogenous or exogenous autoantigens including the co-stimulatory molecules CD80/86 [66], implying an antigen presenting role for these cells. Administration of an anti-CD86 antibody in a murine SS model led to improvement of inflammatory responses in target tissues [67].

T cell activation requires two major signals including that of T cell receptor (TCR) expressed on the surface of T cells with MHC-II on APCs, as well as of CD28 on T cells with CD80/CD86 on APCs. Following T cell activation, upregulation of the inhibitory molecule CTLA on T cells antagonizes CD28, hindering its ligation with CD80/86 on APCs. As a result, T cell responses and subsequent B cell activation become suppressed [68]. On this basis, administration of Abatacept, which is a humanized cytotoxic T-lymphocyte–associated antigen 4 (CTLA4)- IgG1 fusion protein and a successful therapeutic strategy for RA seemed an attractive strategy for SS. Several studies revealed improved disease activity scores [69,70] together with dampened markers of B cell activation [69,71] and B cell signaling [72], as well as reduced lymphocytic infiltrations and increased salivary flow [71], following abatacept administration. Selective attenuation of T follicular cell activity and ensuing B cell hyperactivity has been shown to underlie the beneficial clinical effects [73]. Improvement of salivary secretion, and disease activity scores [70,75] as well as of diffuse weighted magnetic resonance parotid images [74] has been also shown in SS patients in a background of RA. NCT02915159 and NCT02067910 [76] are two phase III randomized, double-blind, placebo-controlled trials exploring the efficacy and safety of subcutaneous abatacept.

In an attempt to selectively block CD28 without affecting CTLA-4 signal, which is essential for proper immunosuppressive T regulatory function [77,78], BMS-931699 (lulizumab pegol) was administered in the context of a phase II clinical trial in 45 SS patients. However, inability to fulfill protocol objectives led to premature termination of the study (ClinicalTrials.gov Identifier: NCT02843659).

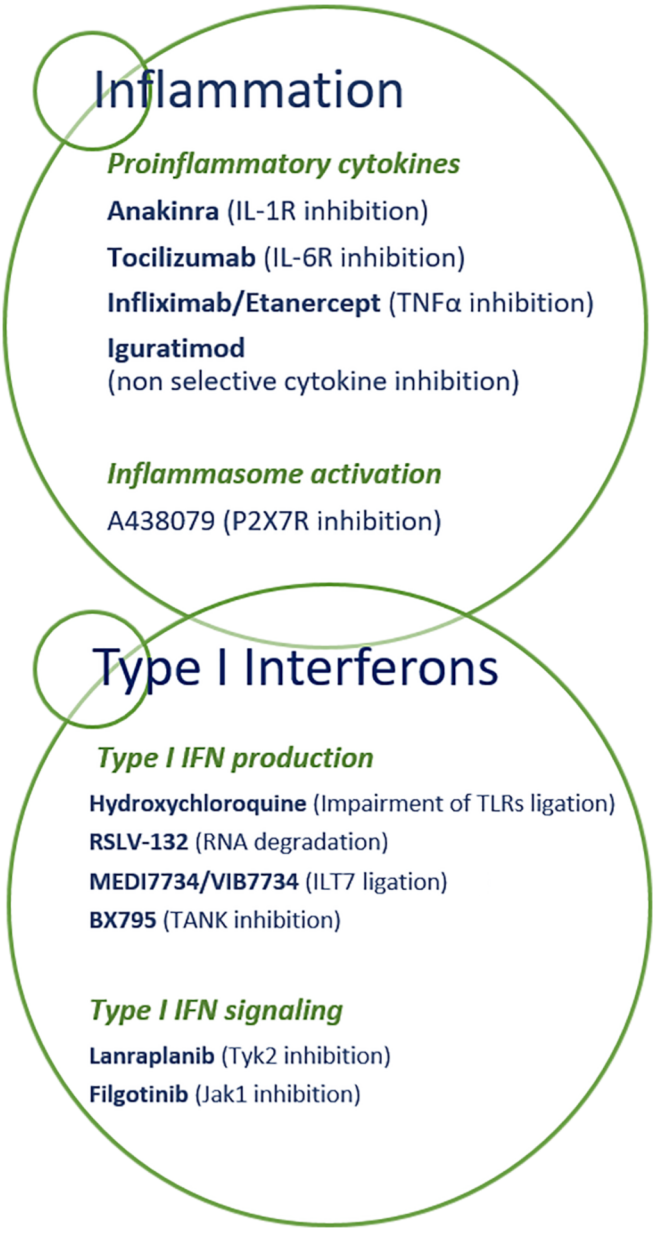

Fig. 1. An overview of biological/chemical agents against innate immunity targets in SS. IL-1R: Interleukin 1 receptor, IL-6R: Interleukin 6 Receptor, TNF: Tumor necrosis factor, P2X7R: purinergic P2X7 receptor, IFN: interferon, ILT7: immunoglobulin-like transcript 7, TANK: TBK1-TNF receptor associated factor NF-κB activator, Tyk2: Tyrosine kinase 2, Jak1: Janus kinase 1.

3.2.1.2. Inducible costimulator of T cells/inducible costimulator of T cells ligand (ICOS/ICOSL). Salivary gland epithelial cells from SS patients were previously shown to express ICOS-L, which along with IL-6 contribute to direct differentiation of naïve $CD4^+$ T cells into the follicular T cell subset. The latter, characterized by Bcl-6, ICOS and C-X-C chemokine receptor (CXCR) type 5 expression, was found to be able to secrete IL-21 promoting B-cell survival [79]. Prezalumab/AMG557/MEDI5872, is a fully human antibody directed against ICOSL, which has been previously shown to have beneficial effects in lupus patients with arthritis [80]. In a recently reported, phase IIa, randomized,

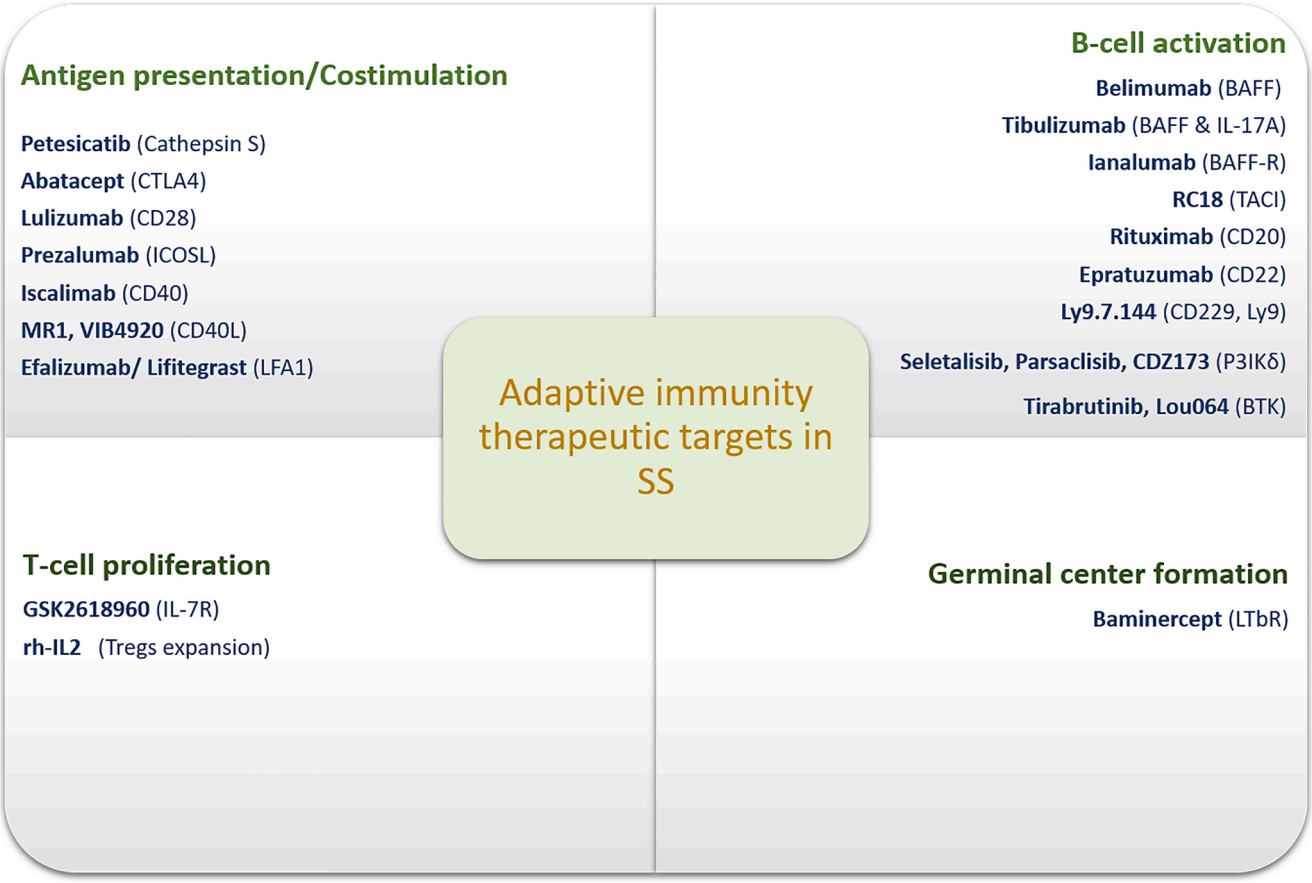

Fig. 2. An overview of biological/chemical compounds against adaptive immunity targets in SS. CTLA4: cytotoxic T-lymphocyte-associated antigen 4, ICOSL: Inducible costimulator of T cells ligand, CD: Cluster of differentiation, CD40L: CD40 ligand, LFA-1: leucocyte function associated antigen-1, IL-7R: Interleukin 7 receptor, rh-IL-2: recombinant interleukin 2, BAFF: B cell activating factor, BAFF-R: BAFF-receptor, TACI: transmembrane activator and calcium-modulator and cytophilin ligand interactor, CD: Cluster of differentiation, PI3Kδ: Phosphatidylinositol 3-kinase delta isoform, BTK: Bruton's tyrosine kinase, LTbR: Lymphotoxin beta receptor.

placebo-controlled study, prezalumab was administered in active primary SS patients (ESSDAI ≥6 and presence of markers of B-cell hyperactivity) once weekly for 3 weeks, then every 2 weeks for 9 weeks. No significant clinical improvement was detected, despite reduction of rheumatoid factor levels [81] (ClinicalTrials gov Identifier: NCT02334306).

3.2.2. Co-stimulatory molecules of the TNF/TNFR family (CD40/CD40L)

Molecules of the TNF/TNFR family have been long considered to display a prominent role in the pathogenesis of chronic autoimmune diseases. Thus, interaction between the transmembrane glycoprotein CD40 on APCs and B cells, as well as in other non-immune cellular populations with its corresponding ligand CD40L on activated CD4 T cells have shown to promote both humoral and cellular immune responses [82]. Given that SS patients have been shown to display heightened serum soluble CD40L and increased CD40L transcripts in the $CD4^+$ T cell compartment [83,84], targeting the CD40/CD40L pathway became a viable option. Subcutaneous or intravenous administration of an inhibitory monoclonal antibody against CD40 (iscalimab/CFZ533) for 12 weeks in the setting of a phase II multi-center, randomized, double-blind, placebo-controlled study led to significant improvement in terms of disease activity and fatigue indices together with reduction of the germinal center related serum C-X-C Motif chemokine ligand 13 (CXCL13). Safety issues have not been emerged so far (ClinicalTrials gov Identifier: NCT02291029) [85]. Administration of iscalimab either subcutaneously (300 mg weekly for 4 weeks) or intravenously (a single dose of 10 mg/kg) followed by 300 mg sc weekly until week 12, revealed similar results [86]. To validate these results, a novel 48-week, 6-arm, randomized, double-blind, placebo-controlled multicenter trial aims to assess the safety and efficacy of multiple CFZ533 doses administered subcutaneously in two distinct SS populations (TWINSS) including moderate-to-severe disease (systemic and symptomatic involvement) and low systemic involvement but high symptom burden (ClinicalTrials.gov Identifier: NCT03905525).

Along the same line, downregulation of genes related to CD40 pathway, reduction in both lymphocytic infiltrations and autoantibody production, as well prevention of ectopic lymphoid structure development following CD40L blockade were observed in a murine SS model. While no data on salivary flow were available, aquaporin 5 expression remained unaffected [87]. A randomized double-blind controlled study exploring the efficacy of the anti-CD40L antagonist VIB4920 in patients with SS has been planned (ClinicalTrials gov Identifier: NCT04129164).

3.2.3. Cell adhesion molecules (leucocyte function associated antigen-1/ intercellular adhesion molecule-1, LFA-1/ICAM-1)

Interactions between LFA-1, a β2 integrin on T cell surface, together with ICAM-1 on several cellular populations including APCs and endothelial cells mediate activation and T cell migration to sites of inflammation [88]. In line with the central role of epithelium in SS pathogenesis [3], upregulation of ICAM-1 at both mRNA and protein level in epithelial cells present in the conjunctival and lacrimal tissues in patients suffering from keratoconjunctivitis sicca [89] or derived from human SS salivary glands [90], imply an antigen presenting function for these cells. Up-regulated expression of ICAM-1 in salivary gland endothelial cells and LFA-1 transcripts in inflammatory lesions were also observed in the MRL/lpr mice, a typical model of autoimmune

Table 1
A summary of randomized double-blind controlled trials targeting innate immune pathways in Sjögren's syndrome.

Clinical Trial Identification number (Acronym)	Compound	Biologic action	Primary Outcome	Primary Outcome fulfilled	Status
Inflammatory pathways					
NCT00683345	**Anakinra**	IL-1R antagonist	Comparison of the fatigue scores at week 4, adjusted for baseline values	No	Completed
	Infliximab	Monoclonal antibody against TNFα	≥30% improvement between weeks 0 and 10 in the values on 2 of the 3 VAS	No	Completed
NCT00001954	**Etanercept**	Soluble TNFα receptor	At least 20% improvement from baseline values for at least 2 of the following 3 domains: subjective or objective measures of dry mouth, subjective or objective measures of dry eyes, and IgG level or erythrocyte sedimentation rate	No	Completed
NCT01782235	**Tocilizumab**	IL-6R antagonist	Improvement in ESSDAI score of ≥ 3 points	No	Completed
Type I IFN pathway					
NCT00632866 (JOQUER)	**Hydroxychloroquine**	Impairment of endosomal pH dampening of type I IFN production	Proportion of patients with an improvement of 30% or more of at least 2 out of the 3 following VAS: 1. the most disabling dryness 2. pain 3. fatigue	No	Completed
NCT03247686	**RSLV-132**	RNAse	Type I IFN inducible gene downregulation	Awaiting results	Complete
NCT02780674	**MEDI7734/VIB7734**	Monoclonal antibody towards IL17	Incidence of treatment-emergent adverse events	Awaiting results	Complete
NCT03817424			Incidence of adverse events	Awaiting results	Currently recruiting
NCT03100942	**Filgotinib**	JAK1 inhibitor	Proportion of participants fulfilling a composite improvement of biologic and patient reported outcomes at week 12, as compared to baseline	Awaiting results	Active but not currently recruiting
	Lanraplenib	TYK2 inhibitor			

IL-1R: Interleukin 1 Receptor, TNF: Tumor necrosis factor, IL-6R: Interleukin 6 Receptor, IFN: interferon, IL17: immunoglobulin-like transcript 7, Jak1: Janus kinase 1, Tyk2: Tyrosine kinase 2, VAS: Visual Analogue Scale, ESSDAI: EULAR Sjogren's syndrome disease activity index.

sialadenitis. Interestingly, blockade of both LFA-1 and ICAM-1 molecules prevented the adoptive transfer of SS in MRL/lpr mice into SCID mice [91]. Recently, a beneficial effect of the LFA-1 inhibitor Lifitegrast in keratoconjuvitis sicca related features was reported in a mouse desiccating stress dry eye model [92]. In the setting of a pilot, proof of concept, randomized, double-blind, placebo-controlled study, administration of efalizumab, a recombinant humanized monoclonal antibody which through binding to human CD11a, the alpha-subunit of LFA-1, hinders the LFA-1/ICAM-1 interaction was given in SS individuals (ClinicalTrials gov Identifier: NCT00344448). However, due to heightened risk of progressive multifocal leukoencephalopathy, the study was prematurely terminated.

3.3. B cell activation

Given that B cell overactivity is a cardinal feature of SS, as evidenced by the presence of profound hypergammaglobulinemia and several autoantibodies [1], direct or indirect targeting of B cells represent a reasonable approach.

3.3.1. BAFF

BAFF is a member of the TNF family with a prominent role in B cell development, survival, and differentiation through interaction with 3 receptors namely BAFF-R, transmembrane activator and calcium-modulator and cytophilin ligand interactor (TACI) as well as B-cell maturation antigen (BCMA) [93]. A compelling body of data strongly support BAFF involvement in SS pathogenesis. Transgenic BAFF mice, as they age they develop autoimmune sialadenitis resembling human SS [94], while SS patients display high serum BAFF levels and/or BAFF/BAFF-R genetic variants in association with autoantibodies, high disease activity and lymphoma development [36,95–98].

In the context of BELISS trial, belimumab, a monoclonal antibody directed against BAFF, was intravenously administered at a dose of 10 mg/kg at weeks 0, 2 and 4 and then every 4 weeks to week 24 in 30 seropositive (presence of anti-Ro/SSA or anti-La/SSB antibodies) SS patients with either early disease (disease duration less than five years), salivary gland enlargement, systemic manifestation or presence of B cell activation markers. At both 28 [99] and 52 weeks [100], a significant improvement in disease activity, fatigue, subjective complaints of mucosal dryness and markers of B cell activation were reported, with no effect on objective measures of oral and ocular dryness (ClinicalTrials.gov Identifier:NCT01160666). Moreover, peripheral transitional and naïve B cells previously found to be increased in untreated SS patients compared to controls returned to normal levels. In contrast, BAFF-R transcripts in B cells shown to be upregulated in SS patients prior to belimumab treatment were restored to normal revels. As a result, a decrease in serum immunoglobulins and autoantibody titers was observed with a rise in C4 complement levels [101]. Following cessation of belimumab treatment, increase in disease activity and markers of B cell activation were observed [102]. Elevated blood and salivary NK cell numbers and high type I IFN activity at baseline have been found to serve as potential biomarkers to belimumab response with the former being associated with worse outcomes [103], while the latter with reduced IgG, IgM and RF serum levels [104].

A tetravalent bispecific antibody targeting both BAFF and IL-17A namely Tibulizumab [105](LY3090106) is currently evaluated regarding safety, tolerability, pharmacokinetics and pharmacodynamics in 32 SS patients (ClinicalTrials.gov Identifier: NCT02614716), with no data available yet.

Recent data derived from a randomized double-blind, placebo-controlled trial revealed a promising role for a single dose of intravenous ianalumab/VAY736, a human IgG1 monoclonal antibody against BAFF-R, which is engineered for direct antibody-mediated B-cell depletion as well. After 24 weeks of treatment, serum BAFF levels and parotid gland stiffness detected by ultrasound were decreased (ClinicalTrials.gov Identifier: NCT02149420) [106]. Though non

Table 2
A summary of randomized double-blind controlled trials targeting adaptive immune pathways in Sjögren's syndrome.

Registration number (Acronym)	Compound	Biologic action	Primary Outcome	Primary Outcome fulfilled	Status
Antigen presentation					
NCT02701985	RO5459072 (Petesicatib)	Cathepsin S inhibitor	Percentage of Participants with decrease in ESSDAI Score ≥ 3 points at 12 weeks	No	Completed
Costimulation					
NCT02915159	Abatacept	CTLA4-IgG1 fusion protein	Change from baseline in ESSDAI at day 169	Awaiting results	Active, not recruiting
NCT02067910 (ASAPIII)			ESSDAI at 24 weeks	Awaiting results	Completed
NCT02843659	BMS-931699 (Lulizumab pegol)	Monoclonal antibody against CD28	Change from baseline in ESSDAI at Week 12	No results available	Terminated
NCT02334306	AMG557/MEDI5872 (Prezalumab)	Monoclonal antibody against ICOSL	Change from baseline in ESSDAI score at day 99	No	Completed
NCT02291029	CFZ533 (Iscalimab)	Monoclonal antibody against CD40	Change in ESSDAI at week 24	Yes	Completed
NCT03905525 (TWINSS)			Change in ESSDAI and ESSPRI at week 24	Awaiting results	Recruiting
NCT04129164	VIB4920	CD40L antagonist	Change from baseline in ESSDAI and ESSPRI at day 169	Awaiting results	Not yet recruiting
NCT00344448	Efalizumab	Anti-LFA-1	Objective ocular and salivary gland measures	No results available	Terminated
B cell survival/signaling					
NCT02614716	LY3090106 (Tibulizumab)	Tetravalent bispecific antibody targeting both BAFF and IL-17A	Drug related adverse events from baseline to day 197	Awaiting results	Completed
NCT02149420	VAY736 (Ianalumab)	BAFF-R blockade	Change in ESSDAI from baseline to week 12, Adverse events	Yes	Completed
NCT02962895			Dose response measured by change in multi-dimensional disease activity as assessed by the physician	Awaiting results	Recruiting
NCT04078386	RC18	Recombinant TACI- antibody fusion protein	Change of ESSDAI score compared to the baseline at week 24	Awaiting results	Recruiting
NCT00740948 (TEARS)	Rituximab	Monoclonal antibody against CD20	30% improvement in the values on 2 of the 4 VAS measuring global scores of the disease (activity, joint pain, fatigue, and dryness) at 24 weeks	No	Completed
NCT00363350			Stimulated whole salivary flow rate at 48 weeks	Yes	Completed
ISRCTN65360827 (TRACTISS)			A 30% reduction at 48 weeks from baseline in either oral dryness or fatigue measured using visual analogue scales	No	Completed
			Change in total ultrasound score at week 48	Yes	Completed
Dass et al, Ann Rheum Dis. 2008			20% improvement in fatigue VAS score at 6 months	No	Completed
NCT02631538	Belimumab & Rituximab	BAFF blockade and B cell depletion	Serious adverse events, adverse events of special interest	Awaiting results	Not recruiting
NCT02610543	UCB/UCB5857 (Seletalisib)	PI3Kδ inhibition	Change in ESSDAI at week 12	No results available	Terminated
NCT03627065	INCB 050465 (Parsaclisib)		% participants with ≥1-point change on salivary gland ultrasonographic score at weeks 4 and 12	Awaiting results	Recruiting
NCT02775916	CDZ173 (Leniolisib)		Safety and tolerability at day 85 Change in ESSPRI and ESSDAI at day 85	Results available	Completed
NCT03100942	Tirabrutinib	BTK inhibition	Proportion of participants fulfilling a composite improvement of biologic and patient reported outcomes at week 12, as compared to baseline.	Awaiting results	Completed
T cell proliferation					
NCT02464319	Low-dose rh-IL-2	Restoration of T-regulatory cells	Change in ESSDAI at 24 weeks	Awaiting results	Completed
NCT03239600	GSK2618960	Monoclonal antibody against IL-7R	Adverse events	No results available	Withdrawn
Germinal Center Formation					
NCT01552681	Baminercept	LTbR antagonist	Change from screening in stimulated whole salivary flow at week 24	No	Terminated

CTLA4: cytotoxic T-lymphocyte-associated antigen 4, CD: Cluster of differentiation, ICOSL: Inducible costimulator of T cells ligand, CD40L: CD40 ligand, LFA-1: leucocyte function associated antigen-1, BAFF: B cell activating factor, IL-17: Interleukin-17, BAFF-R: BAFF-receptor, TACI: transmembrane activator and calcium-modulator and cytophilin ligand interactor, PI3Kδ: Phosphatidylinositol 3-kinase delta isoform, BTK: Bruton's tyrosine kinase, rh-IL-2: recombinant interleukin 2, IL-7R: Interleukin 7 receptor, LTbR: Lymphotoxin beta receptor, ESSDAI: EULAR Sjögren's syndrome Disease Activity Index, ESSPRI: EULAR Sjögren's syndrome patients reported index.

Table 3
Major costimulatory pathways operating in Sjogren's syndrome.

	Antigen presenting cell (Salivary gland epithelial cell)	Activated T-cell	Activated B-cell
Ig family	CD80/86 (B7.1/B7.2)	CD28 CTLA4 or CD152	
	ICOSL (B7h.2)	ICOS	
TNF/TNF-R family	CD40	CD40L	CD40
Cell Adhesion Molecules	ICAM	LFA-1	

Ig: Immunoglobulin, CTLA4: cytotoxic T-lymphocyte-associated antigen 4, ICAM: intercellular adhesion molecule, ICOSL: Inducible costimulator of T cells ligand, CD40L: CD40 ligand, LFA-1: leucocyte function associated antigen-1.

statistically significant, disease activity, fatigue and quality of life indices tended to improve and profound B cell deletion was also achieved [107]. Preliminary results from a randomized parallel assessment study aiming at evaluating efficacy and safety of multiple doses of VAY736 in a large SS cohort with moderate to severe disease activity have been recently released (ClinicalTrials.gov Identifier: NCT02962895). Ianalumab was administered in 190 primary SS patients randomized to receive monthly subcutaneous injections of placebo or one of three VAY736 doses; 5 mg, 50 mg and 300 mg. Anti-Ro/SSA positivity, ESSDAI $\geq$6 and EULAR SS Patient Reported Index (ESSPRI) $\geq$5 were among the eligibility criteria and the dose-response on change of ESSDAI from baseline was set as the primary outcome. Moreover, the proportion of patients with $\geq$3 points improvement on ESSDAI as secondary analysis was calculated. At week 24, a statistically significant change in ESSDAI score was detected only in the group receiving the 300 mg compared to placebo, with responder rates of 42/47 (89.4%) in the 300 mg treatment group vs 30/49 (61.2%) of placebo, implying a promising role for ianalumab in SS. No safety signals emerged in the preliminary analysis [108]. A currently recruiting study also explores the safety and effectivity of RC18, a TACI-antibody fusion protein in primary SS patients (ClinicalTrials.gov Identifier: NCT04078386).

3.3.2. CD20

A recent systematic review explored the efficacy and safety profile of rituximaba, humanized monoclonal chimeric antibody directed towards the B cell molecule CD20 in immune mediated diseases including SS [109]. In a total of 298 included patients derived from four double-blind randomized controlled trials [110,111] (NCT00740948) [112], (NCT00363350) [113], (ISRCTN65360827) and one sub study [114] (65360827), the authors conclude that only two out of five studies achieved their primary endpoint [112,114], which included improvement in stimulated whole saliva flow rate in patients with preserved salivary gland function [112], and a composite ultrasonographic salivary gland score [114], respectively. Fatigue levels assessed by Multidimensional Fatigue Inventory (MFI) scale were shown to significantly improve in SS patients treated with rituximab compared to placebo [112] and a 30-mm decrease in the VAS fatigue score was more common with rituximab than placebo at week 6 and week 16 [111]. However, no statistical significant differences were detected between rituximab and placebo treated SS patients when 20% or 30% improvement in a visual analogue scale of fatigue (VAS-F) were implemented as outcome measures [110,113]. Nevertheless, observational studies, clinical guidelines and expert opinion support a potential role of rituximab for extraglandular manifestations such as purpura, vasculitic neuropathy, cryoglobulinemia and SS related non-Hodgkin's B cell lymphoma [115] [4,116,117].

Following treatment with rituximab, increase in serum BAFF levels (known as BAFFling effect) [118], and the persistence of plasmablasts lacking the CD20 molecule [119], as well the pretreatment overexpression of BAFF in targeted tissues [36,97] have been all postulated as potential mechanisms for rituximab failure in patients with SS [120]. In this context, concomitant anti-BAFF and anti-CD20 in experimental model treatment led to reduction of B cell marginal zone (MZ) compartment [121], implying that BAFF blockade could enable the effectiveness of anti-CD20 treatment in SS patients complicated by MALT lymphoma [122]. A double-blind, randomized, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT02631538) in active (ESSDAI$\geq$5) seropositive (anti-Ro/SSA or anti-La/SSB) SS patients assessing the safety and tolerability profile as well as the effects on disease activity of belimumab/rituximab co-administration in comparison to belimumab monotherapy is currently underway.

3.3.3. CD22

Given that CD22 is a B cell surface protein, involved in B cell receptor (BCR) signaling [123] and survival [124], previous clinical trials have tested the efficacy and safety of epratuzumab in SLE patients [125,126], with only one small open label study performed in SS showing a potential alleviating effect in fatigue and objective measures of oral and ocular dryness [127]. In a recent post hoc analysis including patients with SLE and associated SS, administration of epratuzumab led to improvement in SLE disease activity, reduced B cell numbers and IgM serum levels [128].

3.3.4. Ly9 (CD229)

Ly9 (CD229, SLAMF3), a SLAM family member of cell surface receptors [129] is present on B and T lymphocytes with very high expression levels on NKT cells and MZ B cells [130]. Recently, activation of Ly9 in the NOD.H-2^{h4} murine model displaying features of both glandular and extraglandular inflammation [131] resulted in amelioration of salivary gland inflammation and reduced autoantibody production, implying a potential therapeutic option for human SS as well.

3.3.5. BCR signaling

In view of the significant role of phosphatidylinositol 3-kinase delta isoform (PI3Kδ) in B cell proliferation, migration, and function, this molecule initially attracted particular attention for the treatment of B-cell malignancies [132]. In two murine models of focal sialadenitis reminiscent of human SS, treatment with PI3Kδ inhibitors UCB5857 (Seletalisib) and INCB 050465 (parsaclisib) respectively, led to reduction of lymphocytic infiltrations and autoantibody secretion [133]. In human SS, a phase II, multicenter, double-blind, placebo-controlled, 12-week proof-of-concept study of UCB5857 was prematurely terminated due to enrolment challenges (ClinicalTrials.gov Identifier: NCT02610543). Other PI3Kδ inhibitors including INCB 050465 (ClinicalTrials.gov Identifier: NCT03627065) and CDZ173 (leniolisib) are currently tested (ClinicalTrials.gov Identifier: NCT02775916). Bruton's tyrosine kinase (BTK) inhibitors such as Tirabrutinib implemented in the treatment of B cell malignancies [134] and Lou064 are currently considered in SS patients as well (ClinicalTrials.gov Identifier: NCT03100942 and NCT04035668, respectively).

3.4. T cell proliferation

Given that T cells have been long considered as significant players in salivary gland injury in the setting of SS [135], targeting T cell related cytokines represent a promising therapeutic approach.

3.4.1. IL-7/IL-7R

The IL-7/IL-7R axis, previously shown to fuel autoimmune inflammation through providing T cell survival signals [136] has been shown to be involved in SS pathogenesis as well. Both soluble IL-7R levels in the serum [137] together with heightened IL-7 [138] expression, as well as increased number of IL-7Rα expressing T cells [139] in minor salivary glands were found to be increased in SS patients compared to healthy controls in association with intense inflammation [138,139]. In an SS murine model, IL-7R inhibition improved salivary flows and lymphocytic infiltrations in submandibular glands [140]. Though a humanized monoclonal antibody directed towards IL-7Rα, namely GSK2618960 has been previously planned to get administered in SS patients, the study was withdrawn due to portfolio prioritization (ClinicalTrials.gov Identifier: NCT03239600).

3.4.2. T regulatory cells

An imbalance between Th17 and T regulatory cells has been previously postulated as a significant contributor of the immunopathological lesion in SS patients [141]. Since Treg function is highly dependent on the effects of IL-2 [142], previously shown to be reduced in SS periphery and induce differentiation of Th17 cells [143] administration of small doses of low-dose recombinant IL-2 study in SS patients seemed a rational approach [144]. Though clear effects on disease activity were not demonstrated, reduction of glucocorticoid and hydroxychloroquine use among IL-2 treated patients and normalization of Th17/Treg ratio, mainly through amplification of Treg compartment were reported [144]. Results from a randomized controlled study of subcutaneous administration of IL-2 in 30 SS patients are not yet available (ClinicalTrials.gov Identifier: NCT02464319).

3.5. Ectopic germinal center formation

3.5.1. Lymphotoxin beta receptor (LTbR)

Ectopic lymphoid-like structures in inflamed tissues has been an histopathological hallmark in neoplastic, infectious, chronic inflammatory and autoimmune diseases, including SS. They arise from complex interactions between cellular populations such as IL-17-producing and follicular helper $CD4^+$ T cells, B cells, chemokine signals and proinflammatory mediators, such as IL-7 and lymphotoxin α1β2 (LTα1β2) [145]. The latter signals through LTbR, a member of the tumor necrosis factor receptor superfamily [146]. In an experimental SS murine model with autoimmune inflammation in the lachrymal glands, intraperitoneal injection of an anti-LTbR antibody lessened B cell infiltrations, eliminated high endothelial venules (HEV) and reduced the entry rate of lymphocytes into lacrimal glands improving lachrymal gland secretory function and ocular surface integrity score [147].

In regard to human SS, baminercept, an LTbR fusion protein was administered in 52 patients in a 24 week, randomized, double-blind, placebo-controlled, phase II, clinical trial [148], with disappointing results in terms of salivary gland secretory function and disease activity. Several side effects were reported more often in the study drug subgroup compared to placebo (ClinicalTrials.gov identifier: NCT01552681).

Recently, a potential role of a B cell-derived peptide (PEPITEM), which is involved in T cell trafficking [149] emerged as a potential treatment for SS. After PEPITEM was injected in a murine C57BL/6 SS model, both lymphotoxin beta mRNA transcripts as well as IL-7, lymphoid chemokines (CCL19 and CXCL13) and T-cell chemokine receptor CCR7, all shown to contribute in ectopic germinal center formation in the setting of SS were abated [150].

4. Conclusion

Taken together, with the exception of TNF inhibitors, it seems that biological agents previously proved to be successful in other autoimmune diseases such as rituximab, belimumab and abatacept are promising therapeutic approaches in SS as well. Furthermore, it becomes apparent that following our better understanding of disease pathogenesis emerging novel therapeutic targets hold significant promise for SS management. However, in view of the heterogeneity of SS related clinical phenotypes and the complex underlying molecular pathogenesis, careful selection and characterization of patient subgroups is mandatory to achieve maximum efficacy, while minimize side effects.

The present review was written in tribute to Professor Josef Smolen to honor his contributions as clinical investigator, mentor and medical administrator. Harry Moutsopoulos and Josef Smolen scientific roads were crossed in the early 80's in the 9th floor and the outpatient clinic of the Clinical Center, National Institutes of Health in Bethesda MD, USA. Their common interests and personality compatibility shaped a longstanding friendship and an academic association. Josef Smolen was a smart, well-educated Internist-Rheumatologist eager to dissect the pathogenetic mysteries of systemic autoimmune diseases. Upon his return to Vienna, he developed a renowned center for the study and therapeutic developments for the treatment of systemic autoimmune diseases which became a foster nest for the development of young clinical investigators. Currently, students of Smolen's school direct academic units in Austria and other European countries. Josef, besides his academic talents is a superb administrator. From his early years as a Professor in Europe, his concern and goal was to transform the European League against Rheumatism from a society of physical medicine physicians to a contemporary association of Clinical Investigators. His goal was materialized with the help of Profs R.N.Maini, J.Kalden,L. Van de Putte, F.Breedveld, L.Klareskog, A.Wiik and H.M.Moutsopoulos. The impact of Annals of Rheumatic Diseases is also anticipated to significantly increase under his Editorship.

Declaration of competing interest

Nothing to declare.

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