

Novel Therapeutic Strategies in Primary Sjögren's Syndrome

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ABSTRACT: Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease mainly affecting exocrine glands. However, a subgroup of patients experience extraglandular manifestations, which worsen disease prognosis. To date, evidence-based guidelines for the management of pSS are lacking, hence the therapeutic approach is mainly based on expert opinions and data from other connective tissue diseases. In recent years, several studies have explored the efficacy and safety of biologic agents in pSS. After the failure of tumor necrosis factor inhibitors, the attention has focused on compounds directly targeting B or T lymphocytes. The aim of this review article is to provide an overview of available data about B and T cell targeting in pSS and of future directions based on ongoing trials.

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- An active serological profile, suggestive of B-cell chronic activation, characterizes a subset of patients at high risk for systemic complications
- Serological markers of disease severity should be considered in the management of pSS
- Patients displaying this clinical and/or immunological higher risk pattern should receive closer follow-up and earlier and more aggressive immunosuppressive treatment

Recent systematic reviews highlighted the lack of evidence-based recommendations for the majority of drugs commonly used in the spectrum of extra-glandular involvement [5-7].

In this context, recent advances in the understanding of pSS pathogenic mechanisms, as well as the introduction of biologic treatments that selectively target cellular and soluble mediators of inflammatory/autoimmune response, led to major changes in the management of pSS. However, the rationale for using immunosuppressive and biologic agents in pSS is mainly based on their efficacy in other autoimmune disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), expert opinion, and uncontrolled studies. Although many different systemic autoimmune diseases may share clinical manifestations, it should be recognized that underlying pathogenic mechanisms may be different. In this setting, the best example is the use of anti-tumor necrosis factor (TNF) agents in pSS. Although TNF, a pro-inflammatory mediator, is highly expressed in pSS salivary glands, anti-TNF agents are not effective in pSS. In previous trials using either the chimeric monoclonal antibody (mAb) infliximab or the soluble receptor etanercept, neither clinical nor histological improvement was observed [7].

A large body of evidence has been pointing to a central role of B cells in the development, maintenance, and progression of the disease, with multiple roles at different points of pSS pathophysiology [12]. B-lymphocyte hyperactivity, minor salivary gland (MSG) infiltration, and development of B-cell follicles containing germinal center (GC)-like structures represent the hallmarks of the disease. Excessive B-cell activation is responsible for a number of extra-glandular manifestations and serological features of pSS, including hypergammaglobulinemia, cryoglobulinemia,

Primarily Sjögren's syndrome (pSS) is a systemic autoimmune disorder characterized by chronic inflammation of exocrine glands leading to tissue damage and progressive secretory impairment that seriously affect the quality of life [1]. In contrast, systemic involvement plays a key role in the disease prognosis. In particular, Ioannidis et al. [2] first proposed a prognostic classification to subdivide pSS patients into two groups according to the presence or absence of risk factors: palpable purpura and low C4 levels. A recent investigation in a large pSS patient population supported the role of low C3/C4, hypergammaglobulinemia, rheumatoid factor (RF), and cryoglobulinemia as markers of disease severity in pSS [3]. In another study [4], the prevalence of the pSS patient subset at higher risk for severe systemic manifestations was about 15%. Furthermore, another Italian multicenter study demonstrated for the first time that, among pSS patients with salivary swelling, only those with low C4, cryoglobulins, anti-La antibodies, and leukopenia presented an increased risk of lymphoma development [4]. These findings suggest three important concepts:

elevated levels of free light chains and β 2-microglobulin, presence of anti-Sjögren's-syndrome-related antigen A (anti-SSA)/Ro and anti-Sjögren's syndrome type B (SSB) /La autoantibodies, RF, hypocomplementemia, hypergammaglobulinemic purpura, arthritis, vasculitis, neuropathy, and glomerulonephritis [8]. Finally, prolonged B-cell survival and aberrant B-cell activity may lead to the development of non-Hodgkin lymphoma (NHL) in 5% of pSS patients [1]. Considering the above-mentioned findings, B-lymphocyte targeting for therapeutic purposes appeared to be an intriguing approach worth investigating.

B-cell depletion therapy with the anti-CD20 mAb rituximab (RTX) in pSS has shown conflicting, but promising, results in clinical trials [9,10]. The heterogeneity of both primary outcomes and selected patients probably accounts for the resulting variability of randomized trials and open-label studies. Moreover, failure to achieve consistent clinical benefits with B-cell depletion therapy in some patients may be due to abnormalities unrelated to B-cell compartment, imbalance in T-cell subsets, and/or depletion of regulatory T cells.

Although the available data does not allow drawing definitive conclusions on the efficacy of RTX, B-cell depletion may be considered a therapeutic option for selected pSS patients. In particular, RTX treatment seems to be effective in glandular swelling in some systemic manifestations and in early and active disease. The debate about the real effectiveness of RTX in pSS underscores the idea that development of sensitive and reproducible outcome measures for pSS is an important unmet need. Moreover, the ideal primary endpoint to assess treatment efficacy in pSS remains unknown. Although the European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity score (ESSDAI) includes different domains related to the large variability of clinical and laboratory aspects of the disease, it does not incorporate assessments of dryness and has not been extensively validated in controlled trials. Moreover, it should be recognized that patients included in clinical trials who display the same score may not present an overlapping clinical and serological picture. Furthermore, visual analogical scale (VAS) improvement derived from expert opinion is based on subjective measures and may contribute to result variability. Finally, the optimal RTX regimen required to reach disease improvement in pSS is still unclear.

B CELL TARGETING: BEYOND RITUXIMAB

Epratuzumab is a monoclonal antibody directed against another B-cell-specific transmembrane protein, CD22, which primarily acts as a negative regulator of the B-cell receptor. Moreover, CD22, acting as a homing receptor, may play a role in the entry of B cells into the target tissues of pSS patients. This humanized anti-CD22 Immunoglobulin G (IgG) seems to modulate B-cell activity rather than induce B-cell depletion in the circulation

[11]. In an open-label study, 16 pSS patients received epratuzumab infusions (360 mg/m²) at 2 week intervals [12]. Fourteen patients received all four infusions without any significant adverse reaction, one received three infusions, one experienced a mild acute reaction to the first infusion and withdrew from the study protocol. Interestingly, human anti-human antibodies were found in three patients, but they were not associated with adverse events. A composite endpoint including Schirmer's test, non-stimulated whole salivary flow, fatigue, erythrocyte sedimentation rate, and IgG level was devised to assess the clinical response, defined as a 20% or greater improvement in at least two parameters. Schirmer's test, non-stimulated whole salivary flow, and VAS fatigue scores were the most commonly improved parameters. A clinical response was noted in 53% of patients at week 6 and in 67% at 32 weeks. Unlike RTX, this anti-B-cell antibody leads only to partial B-cell depletion. Although epratuzumab holds promise for the treatment of pSS, randomized placebo-controlled trials are needed.

Another biologic approach to deplete pathogenic B-lymphocytes may be the targeting of soluble factors involved in their survival, activation, and expansion. Important cytokines involved in B-cell survival and activation of B-cells are B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), both belonging to the TNF family. BAFF, also named

In recent years, biologic agents have shown to be effective and safe in treating primary Sjögren's Syndrome (pSS)

B-lymphocyte stimulator (BlyS), is involved in B-cell survival and humoral immune responses, playing a critical role in B-cell homeostasis. BAFF is produced by multiple cel-

lular types, including epithelial cells and T- and B-lymphocytes. BAFF overexpression prevents the depletion of autoreactive cells in the periphery and therefore, a higher number of autoreactive B-cells undergo maturation. BAFF, but not APRIL, binds to BAFF-R, widely expressed by human peripheral B-cells, except for BM plasma cells [13]. BAFF and APRIL may also activate B-cells by interaction with the receptor TACI (a transmembrane activator and calcium-modulating and cyclophilin ligand interacting protein), predominantly expressed on human CD27+ memory B-cells, activated B-cells and plasma cells.

Elevated levels of BAFF and APRIL have been found in serum, saliva, and salivary glands of patients with pSS [14-16]. In their sera, BAFF levels correlate with gammaglobulin levels, anti-SSA, and/or anti-SSB antibodies. Furthermore, higher BAFF levels are observed in patients with GCs in salivary glands [17,18]. BAFF, however, is a very complex cytokine with multiple forms and variants displaying different effects, making the interpretation of these observations difficult [13]. The pathogenic role of BAFF in pSS-associated lymphoproliferation has been demonstrated in both pre-lymphomatous stage and mucosa associated lymphoid tissue (MALT) lymphomas [19]. Moreover, pSS patients co-affected by severe clinical manifestations associated with B-cell lymphoproliferation have higher

BAFF serum levels than patients without co-morbidities [20]. Finally, B-cell depletion therapy with RTX in pSS patients results in a rise of serum BAFF levels, which decreases when B-cells start to reappear [21]. By contrast, serum APRIL levels are not affected by B-cell depleting therapy. In addition, consistent BAFF-driven B cell activation at baseline both in the peripheral blood and in MSGs has been associated with failure of RTX therapy [22,23].

Considering the aforementioned concerns, BAFF-blocking agents were proposed as potentially effective therapeutic targets in pSS. The Belimumab in Sjögren's syndrome (BELISS) trial is the first open-label phase II study conducted in pSS patients to investigate the efficacy and safety of belimumab, a human monoclonal antibody neutralizing soluble BAFF [24]. The patients received 10 mg/kg belimumab at weeks 0, 2, and 4 and, then every 4 weeks. If response was observed at week 28, or if the clinician and the patient agreed to continue the study in the absence of side effects, treatment was continued until week 52. Although an improvement of objective measures of salivary and lacrimal secretion was not observed, more than half of the patients achieved an improvement in several disease features. Such features included subjective symptoms of dryness, fatigue, and pain as well as objective activity scores and/or in laboratory markers of disease-related immune system dysregulation, namely serum levels of free light chains of immunoglobulin, β 2-microglobulin, monoclonal component, and C4 levels. In addition, the mean ESSDAI and EULAR Sjögren's syndrome patient reported index (ESSPRI) significantly decreased and the safety profile was good. Subsequently, 19 patients terminated the 52 week study, with a response rate of 86.7% [25]. The improvement in ESSDAI and ESSPRI observed at week 28 showed a trend to further improvement at week 52. The decrease in biomarkers of B-cell activation observed at week 28 persisted unchanged until week 52. However, salivary flow, Schirmer's test, and focus score of salivary biopsies did not change. Furthermore, safety of treatment was confirmed. Thirteen patients were followed after the end of the BELISS trial and drug suspension [26]. The ESSDAI score and serum BAFF levels were doubled 12 months after the end of the trial, and RF and IgG levels were significantly increased.

A detailed analysis of B lymphocyte subsets revealed that while at baseline pSS patients displayed higher proportions of circulating B cells, mainly those with a transitional and naïve phenotype, the treatment with belimumab reduced these cell subsets. In particular, no significant difference between treated patients and controls could be longer detected [27].

B-cell targeting is the best characterized approach in primary Sjögren's Syndrome (pSS) but also the targeting of several other pathogenic actors, including T lymphocytes and their products, which holds a therapeutic potential

Based on these results, randomized, double blind, controlled studies for the use of belimumab in larger pSS populations are encouraged.

As mentioned, a number of patients with MALT lymphoma, mainly of the parotid gland, experience a treatment failure when RTX monotherapy is used. Quartuccio et al. [28] addressed this issue and provided evidence for a key role of BAFF. In particular, it appeared that the lack of response to RTX may arise from both tissue and systemic over expression of this B-cell related

cytokine. In fact, despite B cell depletion, the micro-environment able to promote their repopulation remained stable over time. This intriguing evidence may provide the rationale to combine direct B-cell depletion induced

by RTX and indirect B-cell targeting employing anti-BAFF antibodies [29]. In addition, this novel approach may replace chemotherapy in combination with RTX, thereby reducing the burden of adverse events.

T CELL TARGETING

It is now well established that different T-cell subpopulations participate in the development and maintenance of glandular inflammation in pSS. Historically, CD4+T helper type 1 (Th1) cells and their products were thought to be major players in the induction of chronic tissue damage involving exocrine glands. However, the discovery of T helper type 17 (Th17), T follicular (Tfh), Th22, and regulatory T cells (Tregs) cells challenged the long-standing Th1/Th2 paradigm of the immune response [30]. CD4+ T lymphocytes exert their pathogenic effect both directly, via the secretion of soluble inflammatory molecules (including interferon (IFN)- γ , IL-17, and IL-21), and indirectly through the cross talk with B lymphocytes, which eventually leads to autoantibody production. T-cell activation requires the cognate interaction with antigen presenting cells (APCs), mainly dendritic cells (DCs) but also B lymphocytes. The next step, which is mandatory to building both the normal and the abnormal autoimmune response, is the second co-stimulatory signal [31].

One of the main co-stimulatory molecules that delivers this second signal to T cells is the CD28. The CD28 molecule binds to its ligand B7 (CD80 or CD86) on APC and enhances the

Efficacy and safety concerns for biologic therapy in primary Sjögren's Syndrome (pSS) are currently under intense investigation in a number of ongoing clinical trials

T-cell receptor (TCR)-initiated T-cell activation. Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) also binds to B7, but delivers an inhibitory signal to T cells ending their activation. In

pSS, salivary gland epithelial cells express B7 molecules with an increased affinity for CD28 leading to a decreased binding for CTLA4 [32]. On this basis, the CTLA4 fusion molecule abatacept, which is currently licensed for the treatment of RA,

has also been explored for pSS. The first open-label pilot study investigated the effects of abatacept in RA patients with secondary SS [33]. Abatacept induced a slight improvement of eye dryness assessed by the Schirmer's test and to a lesser extent of oral dryness. Moreover, it reduced IgG and RF levels, although a decrease of anti-SSA antibody titer was not observed. In a small open label trial performed in 15 pSS patients, abatacept was able to significantly decrease ESSDAI at 24 weeks; however, RF and IgG decreased and secretory function did not improve [34]. Of interest, Adler et al. [35] reported that abatacept can also interfere with chronic inflammatory sialadenitis as confirmed by a reduction of the number of lymphocytic foci in pSS MSGs. In addition, they also reported that an improvement of secretory function following abatacept treatment could be only detected by correcting for disease duration. In light of these promising results, a large placebo controlled phase III clinical trial evaluating abatacept in patients with pSS is currently ongoing (NCT02067910).

FUTURE PERSPECTIVES

IL-6 is an important mediator of the acute phase response, activating both T and B cells and playing a very important role in the balance among Treg cells, Th17 cells, and Tfh cells [36]. Many cell types can produce this cytokine, although the primary sources of IL-6 are monocytes/macrophages at sites of inflammation. In patients with pSS, however, it has been shown that an alternative source of IL-6 may be activated B cells [37]. IL-6-producing B cells have been observed in labial salivary glands of pSS patients. In addition, serum level of IL-6 are increased, but they drop after B-cell depletion therapy in pSS patients with RTX, but not after placebo treatment [38]. These observations suggest that B cells are an important source for IL-6 in pSS patients. Moreover, increased IL-6 levels have been observed in the serum, saliva, and tears of patients with pSS [39] suggesting that the inhibition of IL-6 may represent an interesting potential therapy in pSS. In this context, a French multi-center randomized placebo-controlled trial of tocilizumab, which is a humanized anti-IL-6 receptor monoclonal antibody, is ongoing (A Randomized, Double-blind, Parallel, Placebo-controlled Trial to Evaluate the Efficacy of Tocilizumab for the Treatment of Primary Sjögren's Syndrome, NCT01782235). This study includes patients with systemic disease activity (ESSDAI ≥ 5). The primary outcome is based on the change in the ESSDAI score (decrease of at least 3 points of the basal ESSDAI).

Several studies over the last decade have suggested that T cells expressing the pro-inflammatory cytokine IL-17. The IL-17 producing T lymphocytes (Th17) are important in the pathogenesis of pSS (reviewed in [40]). Such growing data provide the rationale for targeting IL-17 axis for therapeutic purposes in pSS. Two monoclonal antibodies against IL-17 (the fully human IgG1k secukinumab, and the humanized IgG4

ixekizumab) are being investigated in inflammatory arthritides and a clinical trial evaluating secukinumab in dry eye patients is currently ongoing (trial NCT01250171).

CONCLUSIONS

Over the last decade, a number of biologic agents have shown promising results in pSS treatment. However, additional investigation of pathogenic mechanisms is needed to design more effective and safe compounds to be used in the near future.

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Capsule

A site-specific switch for cancer cells

To metastasize, cancer cells must switch from epithelial (polarized and fixed) into mesenchymal (motile and invasive) phenotypes to disseminate and colonize both primary and metastatic sites. Zhou and colleagues found that the long non-coding RNA H19 acted as a site-specific microRNA sponge to promote an epithelial or mesenchymal switch in tumor cells. In epithelial-like tumor cells in primary and

metastatic sites, H19 sequestered miR-200b/c and ultimately inhibited migration. In mesenchymal-like disseminated cells in circulation, H19 sequestered a different microRNA, Let-7b, and ultimately promoted migration.

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Eitan Israeli

Capsule

Plasmodium leftovers cause bone loss

Malaria patients sometimes develop long-term consequences of infection, such as bone loss and growth retardation. Lee and colleagues found that the *Plasmodium* by-product hemozoin can remain in the bone marrow and cause bone loss. Mice infected with a mutant *Plasmodium* that did not produce hemozoin did not undergo bone loss. Hemozoin-

induced inflammatory responses in osteoclast and osteoblast precursors, resulting in bone resorption. Treating infected animals with alfacalcidol, a vitamin D3 analog, prevented this bone loss.

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