

Review

The future of targeted treatment of primary Sjögren's syndrome: a focus on extra-glandular pathology

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Abstract

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease defined as exocrine gland hypofunction resulting in dry eyes and dry mouth. Recent interest in biological therapies for pSS has been garnered, however achieving FDA-approval has been challenging due to the numerous complications in the trials. Current literature lacks insight and a molecular target-based approach to the development of biological therapies. This review focuses on novel research in newly defined drug targets and latest clinical trials for pSS treatment. A literature search was conducted on ClinicalTrials.gov using the search term "Primary Sjögren's syndrome". Articles published between 2000 and 2021 in English language were included. Our findings revealed the potential targets for pSS treatment in clinical trials and the most recent advances in understanding of molecular mechanisms underlying the pathogenesis of pSS. A prominent gap in current trials is overlooking the treatment of extraglandular symptoms such as fatigue, depression and anxiety which pervade most patients with pSS. Based on dryness and these symptom-directed therapies, emerging biological agents targeting inflammatory cytokines, signal pathways and immune reaction have been studied and proved the efficacy and safety. Novel therapies may complement existing non-pharmacological methods of alleviating symptoms of pSS. Better grading systems adding extraglandular symptoms to gauge disease activity and severity should be created. The future of pSS therapies may lie in gene therapy, stem cell and tissue engineering therapy.

Keywords: Primary Sjögren's Syndrome, dryness, fatigue, depression, anxiety, clinical trials

1. Introduction

Sjögren's syndrome is a chronic systemic autoimmune disorder characterized by the destruction and diminished function of exocrine glands, mainly salivary and lacrimal glands, resulting in dry eyes and dry mouth[1]. In primary or secondary form, the disease is characterized by the gradual infiltration of lymphocytic cells and atrophy of glandular and ductal cells.

Primary Sjögren's syndrome (pSS) has become increasingly common with a prevalence of 0.3%~3% among the public. Clinical manifestations of the disease are largely classified into exocrine gland and extraglandular disease features, which may be associated with widespread systemic complications involving the thyroid, lungs, kidneys, liver and nervous system. A wide range of cognitive issues in pSS have also been reported

where persistent fatigue occurs in approximately 70% of pSS patients. The dryness and fatigue symptoms of pSS often impose detrimental effects on quality of life as they suffer from difficulties in eating, sleeping and interacting with others [2].

Consensus about the cytokines and molecular entities involved the initiation and maintenance of chronic immune activation in the disease remains difficult to elucidate [1, 3]. Currently, literature surrounding these therapies remains fragmented and no studies has been done to link the cytokines involved in pSS to the novel biological agents. Recent studies on novel drugs have shown that promising results on the improvement of disease prognosis have been met with unintended effects on the immune system, a variety of complications and rising costs for patients [4]. In addition, ESSDAI (EULAR Sjögren's syndrome disease activity index), which is a primary outcome measure in most trials, does not include certain common symptoms such as vaginal dryness (occurring in up to 64% of female patients) [5, 6], fatigue (70% of patients) [7] and mental effects (over 30% of patients) [8].

Given the prevalence and impact of pSS symptoms on quality of life, it is crucial to holistically assess the efficacy of these novel drugs in pSS treatment. This review discusses the updates of molecular mechanisms underlying the extraglandular pathogenesis and associated potential targets for pSS treatment, with a focus on these outcomes and complications of recent clinical trials. We adopt a two-pronged approach which first explores the therapeutic targets in pSS followed by delving into the treatment of pSS in a symptom-centred manner.

2. Potential T and B cell targets for the development of treatment options for pSS

T and B cells are central to the pathogenesis of pSS. Given that this has already been extensively reviewed in literature [3, 9-11], this section aims to discuss updates on the potential targets and provides a framework to investigate the potential targets for disease-modifying therapy (Figure 1).

2.1. CD4+ T helper cells

CD4+ T helper (Th) cells infiltrate target organs and produce multiple cytokines in the peripheral blood, inducing B cell activation, maturation and production of autoimmune antibodies [9]. Th cell lineages are classically categorized according to their cytokine profile as interferon (IFN)- γ -producing Th1 cells, interleukin-4 (IL-4)-producing Th2 cells, IL-17A (IL-17)-producing Th17 cells [12]. However, given the current understanding, these T cell subsets are also capable of producing various or overlapping cytokines. To understand the potential targets for disease-modifying therapy, this review adopts a recently revised classification system which divides the CD4+ Th cells into three subsets according to helper functions, discusses their roles and therapeutic potential in the SS pathogenesis [13].

2.1.1. Type 1 Th cells

Type 1 Th cells mainly activate and attract mononuclear phagocytes like macrophages, monocytes and dendritic cells (DCs). These cells are primary executors of Type 1 immune responses for cellular immunity. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and IFN- γ are the most canonical type 1 cytokines secreted by Type 1 Th cells [14].

GM-CSF functions serves as a powerful communication conduit between T cells and myeloid cells, promoting the survival of mononuclear phagocytes [14]. A research study using a murine model of dry eye disease (DED) discovered that GM-CSF played a pertinent role in DED pathogenesis, not only limited to SS complication. [10] GM-CSF was found to be upregulated in ocular surface and GM-CSF-producing Th17 cells, a subset crucial for SS development, were found in greater abundance in draining lymph nodes [15, 16]. Although being a non-canonical cytokine in classic Th cell lineages, GM-CSF diminished Th17 cell induction and cause an attenuation of corneal inflammation and a decrease in clinical signs of DED [15].

Despite its pivotal role in DED pathogenesis, therapeutic options targeting GM-CSF have yet to be realised in pSS treatment. Otilimab, a recombinant IgG1 monoclonal antibody against GM-CSF, has been developed for treating rheumatoid arthritis (RA) patients [17] while study in SS patients is not available. Therefore, further investigation into the use of GM-CSF-targeted biologics in pSS should be conducted to consider more potential role in the treatment of DED.

IFN- γ is a canonical cytokine which induces the activation of T and NK cells and possesses dual roles in the immunomodulation [18]. Given the association between IFN- γ levels and lymphocyte infiltration in the exocrine glands, therapies targeted at IFN- γ should be considered [19].

2.1.2. Type 2 Th cells

Type 2 Th cells target B cells and polymorphonuclear granulocytes like basophils, eosinophils and mast cells. They generate a variety of cytokines such as IL-4, IL-21 and IL-25, mainly responsible for Type 2 responses in humoral immunity.

A cross-sectional study examining the labial salivary glands specimens of pSS patients found that IL-4-producing Th cells were almost only detected in specimens with GCs [20]. These cells promote B cell maturation and antibody production in the labial salivary glands, which highlights mechanisms causing xerostomia in pSS [20]. Another laboratory study of mice with absent or disrupted IL-4 genes, henceforth IL-4 knockout (KO) mice, discovered that IL-4 was necessary for disease progression from preclinical stage to clinical xerostomia [21]. Despite scarce data on IL-4, elimination or inhibition of IL-4 may be considered for prevention of severe clinical symptoms and signs in genetically predisposed patients.

While IL-21 has not yet been considered as a target for pSS therapy, its role in germinal center (GC) formation, B cell activation and differentiation to plasma cells in pSS makes it a suitable candidate for research [9, 20, 22]. A study of mice with experimental SS (ESS), patients with pSS and patients with pSS-associated lymphoma revealed the critical role of IL-25 in pSS development [23]. In essence, the IL-25/IL-17RB axis was activated and both Th cells and IL-25 cytokines were detected in salivary epithelium particularly at the sites of chronic inflammation of patients and mice with pSS [23], making targeting IL-25 a promising option in pSS therapy.

2.1.3. Type 3 Th cells

Type 3 Th cells act on non-hematopoietic cells at barrier tissue sites comprising of epithelial cells and stromal cells [22]. They produce cytokines IL-17, IL-22 and IL-23 which exert Type 3 immune responses, mainly in barrier immunity. In vivo, a significant increase in protein and mRNA levels of IL-22, IL-23 and IL-17 were detected in the inflamed salivary glands of pSS patients [24].

IL-17 serves important functions both in infectious and autoimmune diseases [16, 25] and pSS is no exception. In a study by Lin et al., IL-17 KO mice did not express overt clinical pSS symptoms and histopathological features after induction of ESS compared with wild-type mice. Interestingly, after adoptive transfer of Th17 cells, this was restored [26]. This was corroborated by a study by Xiao et al., demonstrating that using bortezomib, a proteasome inhibitor which suppressed the secretion of IL-17, effectively ameliorated disease [27]. In addition, $\gamma\delta$ T cell levels which may be an indicator of IL-17 levels was detected in higher frequency in blood and salivary glands of pSS patients [10, 28]. Evidently, IL-17 is required for the initiation and progression of pSS while inhibition of IL-17 alleviates the disease. However, pSS patients are at a higher predisposition for oral candidiasis and inhibition of IL-17 may increase the risk of fungal infections and other side effects considering the antifungal properties of IL-17 [29].

IL-22 belongs to IL-10 family cytokine and acts by modulating tissue responses during inflammation [30]. In pSS, the effect of IL-22 in modulation of epithelial barrier remains to be elucidated [31]. A previous study demonstrated the role of IL-22 in inducing tertiary lymphoid organ-induced pathology, by promoting chemokines production in the

epithelium, like CXCL12 and CXCL13. Thus, this study provided evidence for using IL-22 blocking agents in B cell-mediated autoimmune diseases, which also supported by a translational program of anti-IL-22 therapy in pSS held in the University of Birmingham [32].

The cytokine IL-23, mainly produced by antigen-presenting cells (APCs), is responsible for initiating the formation of IL-17-expressing Th cells as well as promoting the subsequent survival and effector functions of the Th cells and generating “pathogenic” Th17 cells [33]. Activation of the IL-23/IL-17 axis contribute to many inflammatory diseases such as pSS [34], making IL-23 as a promising therapeutic target for the production of disease-modifying drugs. Monoclonal antibodies against IL-23 in current clinical trials include ustekinumab, briakinumab, tildrakizumab, risankizumab and guselkumab [35].

2.2. CD8+ cytotoxic T cells

CD4+ Th cells were traditionally thought to be the predominant T cell subtype infiltrating the glands of pSS. However, emerging evidence suggests CD8+ cytotoxic T cells may also play a role in pSS pathogenesis whose chemotactic migration to target organs is driven by the activation of chemokine receptors. For instance, CXCR3 is upregulated upon chronic antigen stimulation in pSS [36]. However, considering the vital role of the chemotactic migration of CD8+ T cells in antiviral and anticancer mechanisms, targeting these chemokine receptors may not be appropriate in the treatment of pSS [37]. The essential roles of these cells are underscored by the attenuation of SS in mice with deficiency in CD8 [38]. Intraepithelial localisation of CD8+ tissue-resident memory cells is mediated by interaction between integrin CD103 and E-cadherin in epithelial cells [39]. Thus, CD8+ tissue-resident memory cells are an important mediator in causing tissue damage in pSS and a potential target for therapeutics.

2.3. Other effectors related with T cells

Some cytokines, not exclusively produced by T cells, such as IL-1 β and tumour necrosis factor α (TNF- α), were found increasing in pSS, hinting at their possible involvement in the mechanisms causing pSS [40].

2.3.1. IL-1 β

IL-1 β is closely involved in the pathogenesis of various autoimmune diseases as reviewed by Lopalco et al [41]. Given the proteolytic activity of IL-1 β , recent studies suggest that it may contribute to structural destruction of salivary glands in pSS patients [42].

2.3.2. TNF- α

The cytokine TNF- α is postulated to promote apoptosis of glandular epithelial cells and cause inflammation to salivary glands while anti-TNF- α may protect the acinar structure and glandular function [43, 44]. In salivary gland-specific overexpression of TNF- α in a mouse model, severe inflammation and disruption of integrity of tight junction was observed [44]. Infliximab (anti-TNF- α) has proven to be essential in restoration of proper localization of aquaporin-5, a water channel protein responsible for saliva and tear secretion. Moreover, TNF- α -induced matrix metalloproteinase 9 caused damages on extracellular matrix in exocrine glands, which could be prevented by anti-TNF- α agent [45]. Anti-TNF agents are now used in pSS [46], not receiving positive results in other studies due to diverse effects of TNF- α on immune cell subsets [47].

2.3.3. IL-36 α and $\gamma\delta$ T cells

IL-36 α is a novel member of IL-1 family, deriving from $\alpha\beta$ + CD3+ T cells, CD68+ cells and $\gamma\delta$ T cells where higher expression of IL-36 α and IL-36R were detected in $\gamma\delta$ T cells. IL-36 α may be a driver of the DC maturation and Th1/Th17 responses in CD4+ T cells [48]. In pSS patients, the level of IL-36 α increased in both the serum and salivary glands [49]. Given the role of $\gamma\delta$ T cells in producing both IL-36 and IL-17, it was speculated that IL-17+ IL-36+ $\gamma\delta$ T cells may participate in the pSS pathogenesis [49]. Given the pathogenicity of the effector T cells, a combinational therapy targeting anti-IL-36 together with first-line medication may potentiate therapeutic effects.

2.3.4. Treg cells and IL-2

Other players in the pathogenesis of pSS include Regulatory T (Treg) cells in immune tolerance and IL-2 for growth and survival of Treg cells[50]. Low-dose IL-2 therapy showed promising disease outcomes in both murine and human autoimmunity, which also restored the Treg/Th17 balance in pSS, but no obvious improvement was observed in short-term[51]. Considering the serious side effects caused by high-dose IL-2 treatment[52], long-term therapy using low-dose IL-2 may require additional evaluation in pSS.

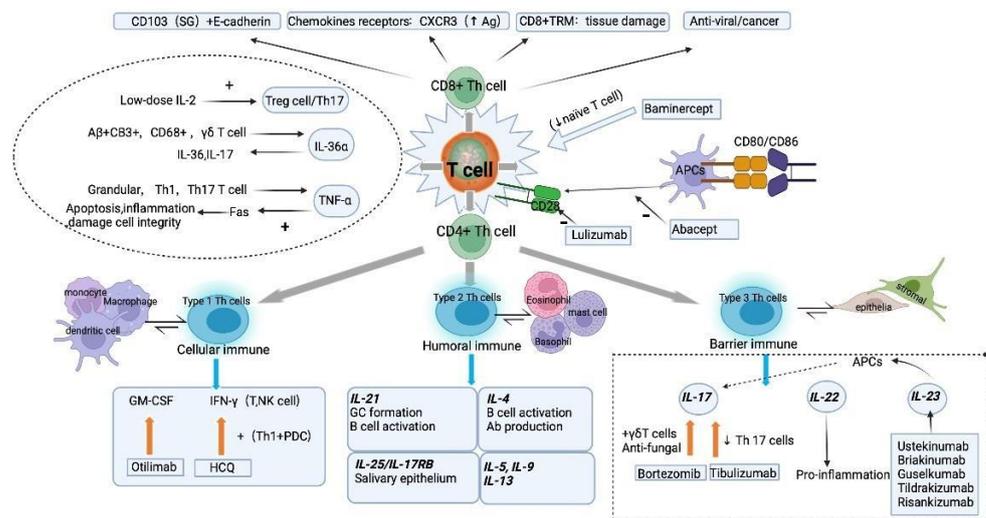


Figure 1. The effect of T cells in the pathologies of pSS.

2.4. B cells

The risk of developing B cell malignancy was highest in patients with pSS compared with other autoimmune diseases. In addition to antigen presentation, autoantibodies and cytokines production, B cells also participate in tissue destruction [3, 11]. Hence, this section aims to focus on the key molecules involved in B cell fate decision and function (Figure 2).

2.4.1. CD40

The CD40 and CD40 ligand (CD40L or CD154) axis are central in T-B interactions in adaptive immunity [53] and targeting CD40 as therapy for pSS has been reviewed [54]. In a SS mouse model, the administration of MR1 (anti-CD154 blocking antibody) treatment suppressed ectopic lymphoid structures and inhibited salivary gland pathology [55]. Single injection of anti-CD40L in young mice prevented the formation of tertiary follicle neogenesis and production of autoantibodies involved in glandular pathology [56]. Similarly, iscalimab, a anti-CD40 monoclonal antibody, showed preliminary efficacy in treating pSS in a phase II clinical trial [57]. Therefore, targeting on CD40 may be a promising and feasible treatment for pSS.

2.4.2. CD20

CD20 is a phosphoprotein consisting of 44 amino acids. CD20 expressed during the transition from pre-B cells to mature B cells and is lost during the development of plasma cells [58]. Rituximab, a monoclonal antibody against CD20, is a widely used in many autoimmune conditions with different effect, making its use in pSS a controversial one. One clinical trial of 133 patients conveyed the statistically significant ($p < 0.05$) finding of improved unstimulated salivary flow rates at week 36 and 48 in the rituximab (anti-CD20) group ($n = 67$) compared with placebo group ($n = 66$) [59]. This was validated by Meijer et al., finding statistically increases in salivary flow rates in the group given rituximab at days 1 and 15 versus the placebo after 48 weeks [60]. However, its safety and long-term efficacy in pSS has yet to be shown, which may be attributed to the persistence of

pathogenic autoantibodies secreted by plasma cells [61]. Anti-CD20 and anti-CatS/MHCII therapies may be viable for options in the treatment of pSS symptoms.

2.4.3. B cell activating factor (BAFF)

BAFF, a member of TNF superfamily proteins, is vital in promoting B cell survival and differentiation. It is found in high levels in serum and target organs of pSS and thus many therapeutic agents against BAFF have been created [62]. Firstly, Ianalumab (VAY736), a BAFF-R inhibitor, induces antibody-dependent cellular cytotoxicity in B cells, which has shown to be useful in improving salivary function in pSS (NCT02149420). Secondly, belimumab is a fully human IgG1 λ recombinant monoclonal antibody directed against BAFF, and in a trial treating pSS with it, observed that 60% of patients reached the primary outcome (improved ESSDAI and ESSPRI), although the dryness symptoms (salivary flow rate and Schirmer test) were not significantly changed [63]. Thirdly, tibulizumab (LY3090106) (NCT04563195), is a bispecific dual-antagonist antibody against BAFF and IL-17, influencing both innate and adaptive immunity [64]. Lastly, iguratimod (IGU) inhibiting nuclear factor-kappa B (NF- κ B) activity inhibited BAFF level in peripheral blood of pSS (NCT04981145, NCT04830644) [65]. Given the efficacies of anti-B cell and anti-BAFF therapies in pSS treatment, synergistic effect of combining the two should be considered and clinical trials of the combination of rituximab with belimumab to treat pSS are on-going [66].

2.4.4. IL-6

IL-6 is a pleiotropic cytokine with pro-inflammatory anti-inflammatory effects [67], whose secretion is critical for B-cell-driven T-cell-mediated autoimmune diseases. A experimental autoimmune encephalomyelitis murine model showed that mice deficient in IL-6 producing B-cells had milder disease than wild-type B-cell mice [68]. However, tocilizumab, a IL-6R inhibitor, did not prove to treat pSS symptoms as compared to a placebo in one clinical trial [69]. Plus with T-B cell interactions in spleen and lymph nodes, it is difficult to evaluate the efficacy of IL-6R inhibition at the immune synapse and impact. Thus, eliminating IL-6-producing B cells and targeting IL-6 might be a new direction in autoimmune diseases but remains challenging.

2.4.5. IL-10

IL-10-producing regulatory B (Breg) cells maintain immune tolerance in inflammatory and autoimmune pathologies. Impairment of Breg cell function with decreased IL-10 production led to increased disease activities of pSS patients and ESS mice [70]. Given diverse phenotype of Breg cells and complexity of transcription factors involved in IL-10 transcription, currently targeting Breg cells in vivo remains an obstacle.

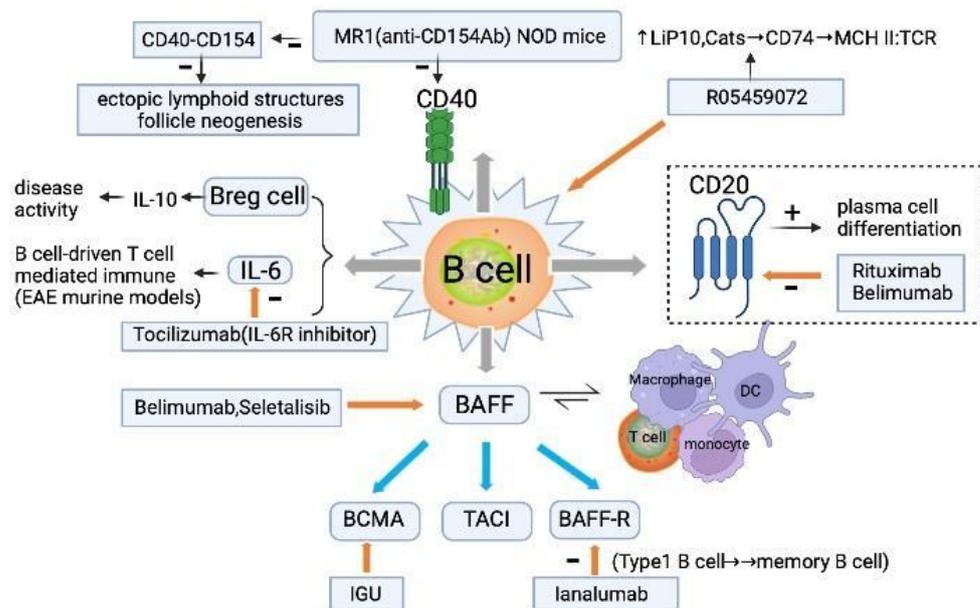


Figure 2. The effect of B cells in the pathologies of pSS.

3. Treatment of exocrine gland disease in pSS

To fill in the lacuna of knowledge regarding the effect of novel therapies on the treatment on certain symptoms in pSS, a symptom-based approach is adopted in Sections 4 to 6.

3.1. Dry mouth (Xerostomia)

Salivary hypofunction leads to xerostomia in pSS patients. Dysphonia, dysphagia, stomatopyrosis (burning mouth), dysgeusia (altered taste), teeth erosion and oral infections are common problems caused by xerostomia [60]. Current treatment include oral swabs, lip moisturizers, topical saliva substitutes, muscarinic agonists, scheduled use of ice water, electrostimulation and acupuncture [71, 72]. Though not life-threatening, dysphagia and awakening from sleep due to oral dryness are debilitating consequences of xerostomia [73] which beg the advancement of drug therapies beyond symptom relief [74]. This section reviews the possible molecular targets that should be investigated.

Although type I IFN is a pro-inflammatory cytokine, low dose IFN α treatment was found to increase aquaporin-5 transcription and protein production in human parotid gland tissue, resulting in enhanced saliva and tear secretion. 150 IU of oral IFN α three times daily demonstrated the greatest potential in improving salivary output in a study [75]. However, multiple adverse effects were discovered including a flu-like syndrome, chest pain and arthropathy, central nervous system depression and myelosuppression [75, 76]. Alternatively, 10-15 mg weekly dose of Methotrexate resulted in increased salivary flow rate [77]. Eculizumab, a humanized mAb binding to complement protein C5, is proved to ameliorate fatigue in myasthenia gravis and may be considered in the alleviation of fatigue in pSS [78].

3.2. Dry eye

Dry eye disease (DED) manifests as itching, grittiness, irritation, foreign body sensation and blurry vision in pSS patients [79]. anti-inflammatory therapies for pSS-DED include DMARDs (Disease-Modifying Anti-Rheumatic Drugs) (Iguratimod and Methotrexate), topical corticosteroids (1% methylprednisolone), antibiotics (Azithromycin, doxycycline and minocycline) and immunosuppressive agents (cyclosporine A and tacrolimus) [80]. The variety of systemic and topical drugs and the intricate titration of doses pose a challenge to developing treatment for DED. Mediators in driving the lacrimal pathology and the latest drugs being trialed for the relief of pSS-DED are discussed.

Varieties of drugs targeting T cells have been considered in DED treatment. Firstly, Abacept (NCT02067910, NCT04186871, NCT02915159) is a selective T cell costimulation inhibitor, may improving tear secretion in pSS by engaging CD28 and suppressing antigen-presenting cells. Secondly, baminercept, a lymphotoxin β receptor IgG fusion protein, inhibits differentiation and proliferation of T cells and decreases CXCL13 levels, which is associated with ectopic lymphocytic structures in the lacrimal and salivary glands of pSS patients [81]. However, the phase II trial failed to significantly improve either glandular or extraglandular pathology in pSS [82]. Thirdly, the combination of lulizumab (an anti-CD28 domain antibody antagonist) and BMS-986142 (a highly selective BTK inhibitor) is being trialed. Lastly, while hydroxychloroquine (HCQ) was recommended by European League Against Rheumatism (EULAR) as an effective suppressor of effector T cells it did not improve tear film break-up time and ocular surface disease index in a recent trial [83]. This was further supported by a meta-analysis, where the efficacy and efficiency of HCQ in relieving the eye dryness was limited [84].

Another candidate for DED treatment is drugs targeting cysteine protease cathepsin S (CatS). CatS may play a crucial role in MHCII processing and T cell stimulation, as it was found to be elevated in the tears of pSS patients. RO5459072, a CatS inhibitor, caused a dose-dependent downregulation of CatS/MHCII-mediated effect and may be a potential target for treatment [85].

There are also emerging biological agents targeting Th1/Th17 cytokines and BAFF pathways. DMARDs such as leflunomide and anti-TNF which ameliorate dryness symptoms in RA patients, may also be considered in pSS patients [86, 87]. Topical use is preferred due to the side effects of these systemic immunosuppressants. 0.005%/0.01% Lacriprep and 0.05% cyclosporine eyedrops have also exhibited promising efficacy in relieving symptoms in pSS [88].

3.3. Vaginal dryness and dyspareunia

Women with pSS may suffer from vulvovaginal dryness, vulvar pruritus and dyspareunia, partially similar to that in postmenopausal women. Histopathological assessment of vaginal mucosa biopsies displayed subepithelial inflammation with lymphocytic infiltrations of CD45+, CD3+ and B cells occurring more frequently in pSS patients. It is postulated to be induced by IFN-mediated, CXCL10 and/or JAK-STAT pathways [6]. The lymphocytic infiltration resulting in decreased transudation of serous fluid into the vaginal vault has been hypothesised. Clinical trials of interest are that of pascalisib and abatacept. The results are highly anticipated with the hope that they may be the future of therapy for vaginal symptoms in pSS.

3.4. Fatigue in pSS

Current trials often neglect the treatment of extraglandular symptoms such as fatigue, depression and anxiety. Approximately 70% of pSS patients claimed persistent fatigue [89, 90]. Evidently, fatigue has significant effects on quality of life, rendering it as one of the key issues in pSS clinical management. Despite being the most common symptom in pSS, the immunology behind fatigue has yet to be established. Currently, factors involved in mechanisms causing fatigue in pSS include IL-1, IL-36 α and humoral autoimmunity.

3.4.1. IL-1

IL-1 is a pro-inflammatory cytokine existing in two biologically active forms: IL-1 α and IL-1 β [91, 92]. Pharmacological experiments have shown that systemic administration of IL-1 β to rats and mice induced a reduction in exercise activity, less food and water intake, social withdrawal, increase in slow wave sleep and cognitive changes in a dose- and time-dependent manner which parallels human fatigue [93]. Studies have found that increased levels of IL-1 receptor antagonist (IL-1Ra) in the cerebrospinal fluid of pSS patients was associated with greater fatigue [94]. This was further supported by a cohort study (n=49) which showed a higher association with serum IL-1 β and hypocretin-1. Of interest, hypocretin-1, the main regulator of sleep and wakefulness, is possibly driven by the IL-6/TNF- α axis, hence may causing fatigue in pSS [95].

Treatment of fatigue in pSS has been challenging, however inspiration may be drawn from a randomized study revealing canakinumab, a human anti-IL-1 β monoclonal antibody, which improved the Short-Form-Vitality-36 score from 12.0 to 48.3 in patients with gout[96]. Thus, targeting IL-1 may be an option for relieving fatigue in pSS.

3.4.2. IL-36 α

As mentioned, IL-36 α plays a role in pSS mechanisms. Interestingly, compared with pSS patients who did not experience fatigue, the expression of IL-36 α was up-regulated in patients with fatigue [97]. Although there was no overt evidence for the function of IL-36 α in causing fatigue in pSS, this possibility should definitely be suspected.

3.4.3. Immunoglobulins

It is speculated that the fatigue in pSS patients may be related to humoral autoimmunity. A study showed that results of the Fatigue scale 14 of a sub-healthy population negatively correlated with their serum immunoglobulin A (IgA) and IgG levels. This was further corroborated by a cross-sectional study which demonstrated a positive correlation between increased IgG levels and risk of pSS-related fatigue[98].

3.4.4. Other mediators

Recent studies found that the intensity of fatigue based on the Profile of Fatigue Questionnaire was negatively correlated with several pro-inflammatory cytokines, including IFN- γ , TNF- α , lymphotoxin α and CXCL10 [99, 100]. Analysis by the logistic regression model revealed that lower levels of IFN- γ and CXCL10 while increased reported pain and depression were the most important predictors of fatigue [99]. This raises an argument against the role of inflammation in the pathogenesis of fatigue in pSS and need greater research given the prevalence and pervasiveness.

3.4.5. Alternative medicine

The future of pSS therapy should consist of a blend of western and alternative medicine, tapping on their synergistic potential while maintaining a balance to minimise the risk of drug-drug interactions. Total glucosides of paeony (TGP), derived from the herb root of the *Paeonia lactiflora* pall, was approved by China Food and Drug Administration to enter the market as a DMARD since 1998. A multi-center study found TGP improved fatigue VAS scores [101]. The mechanisms were based on the balance of Th1/Th2 cytokines and reduction of IFN- γ , IL-4, Fas and FasL expression, revealing on serological assessment [102]. Acupuncture therapy is a well-recognized approach to relieve fatigue in public. A protocol for trial published in 2017 [103], and an ongoing study of acupuncture treatment in pSS may provide such evidence for ameliorating fatigue.

3.4.6. Anti-inflammatory and immunosuppressive treatment for fatigue

The therapies targeting IL-1, IL-36 α and immunoglobulins to pSS-related fatigue is impetus and the current treatment, efficacies and their adverse effects are as follows, mainly including hydroxychloroquine (HCQ), rituximab and TNF- α inhibitors.

A retrospective study of sham-needle-free group in 1996 reported that about one-third of Systemic lupus erythematosus (SLE) patients with SS treated with HCQ had an improvement in fatigue [104]. Based on this, HCQ has been considered into the treatment of fatigue symptoms in pSS. Although a randomized experiment completed in 2012 (NCT00632866) found that HCQ has limited efficacy in improving fatigue [105], the 2016 guidelines continue to support the use of HCQ in selected situations [106].

Rituximab is associated with better Visual Analogue Scale (VAS) scores for fatigue in 17 pSS patients receiving 1,000 mg rituximab for 6 months [107]. A more larger trial (n=120) had similar findings, where VAS scores for fatigue in patients treated with rituximab were also improved [108] due to the elimination of B cell-mediated immune response and immunoglobulin productions.

A pilot study reported fatigue symptoms improved in pSS patients treated with infliximab, inhibitors against TNF- α signaling[109]. A hypothesis from an in vitro study suggested that apart from the blockage of circulating TNF- α molecules, infliximab also

has the added function of inhibiting membrane-bound TNF- α . This may explain why infliximab-mediated interruption has a longer duration of action compared with etanercept, not improving fatigue because the receptor fusion protein detached from membrane-bound TNF- α [110]. Similarly, there lack of evidence on whether the latest biological drugs, such as anakinra (NCT00683345) [111], abatacept (2009-015558-40) [112], belimumab [63] and epalizumab [113] could be applied for treating the fatigue in patients with pSS.

Additionally, dehydroepiandrosterone (DHEA) has been proposed as a treatment for several autoimmune diseases. However, a trial suggested that there were no significant differences in fatigue between pSS patients treated with DHEA or placebo [114]. These findings were supported by another study (NCT00543166), demonstrating DHEA substitution treatment in DHEA-deficient and severely fatigued patients with pSS did not significantly improve fatigue compared to the placebo [115].

3.5. Depression and anxiety in pSS

Psychological complications frequently disturb patients with fatigue and pain [116, 117]. Depression and anxiety occurs in 36.9% and 33.8% of pSS patients in China [118]. In France, anxiety (pSS: 41.5%, non-pSS: 39.5%) and depression (pSS: 28.3%, non-pSS: 26.7%) happen more frequently in pSS patients [119]. A study found that patients who experienced more pain, fatigue, worse oral hygiene and swallowing disorders also had greater anxiety and depression. In female pSS patients, pain ($\beta=0.025$, $P=0.028$) and fatigue levels ($\beta=0.029$, $P=0.004$) were associated with anxiety while pain ($\beta=0.022$, $P=0.047$), fatigue ($\beta=0.033$, $P=0.001$), and xeroderma scores ($\beta=0.030$, $P=0.003$) were strongly associated with depression [117]. Meanwhile, oral health (OR=0.956, $P<0.05$) and swallowing disorders (OR=1.036, $P<0.05$) were significantly associated with anxiety, while fatigue (OR=0.587, $P<0.05$) was positively correlated with depression in pSS [8, 117].

To date, the underlying mechanisms of depression or anxiety in pSS remain unclear, although neurobiological factors are speculated. A recent hypothesis suggests that depression may attributed to neuronal serotonergic and noradrenergic dysfunction, the change of dopamine and brain-derived neurotrophic factor (BDNF) and hyperactivity of hypothalamic pituitary adrenal (HPA) axis in central nervous system. Additionally, gut microbes and amino acids metabolism and autoAbs against neuropeptides were also considered involved in the pathological mechanisms of depression [120]. Dimitrios et al. reported relatively higher serum autoAbs against α -melanocyte-stimulating hormone (MSH) in pSS patients compared with health controls and highly correlated with anxiety states [121], which may result from dysregulation of melanocortin system. A study found an association between humoral autoimmunity and cytokines with depression [122]. While these findings were similar to that in animal models animal models, greater information is needed about anxiety and depression in humans.

Interestingly, BAFF transgenic mice were established to research the mechanism of anxiety, supporting the notion that humoral autoimmunity may partially be responsible for brain inflammation, impaired neurogenesis (stress-related brain responses), and hippocampal plasticity, leading to pSS-related anxiety [123]. Notably, using the same model, further studies suggested that dietary supplementation with n-3 polyunsaturated fatty acids could inhibit hippocampal microglial activation and increase hippocampal progenitor cell proliferation and plasticity [124], thus validating the effect of humoral autoimmunity-mediated neuroinflammation on depression. Given the possible role of BAFF in depression, it is worthwhile to explore BAFF-targeted drugs mentioned above (Table 1).

Except for regular drug options like serotonin selective reuptake inhibitors (SSRIs) [125], compelling evidence suggested that traditional Chinese medicine can relieve anxiety and depression in pSS [126], including the influence of BAFF production and endocrine hormone levels. Additionally, in a randomized-controlled trial (n=45) (NCT02370225),

aerobic exercise greatly improved life quality by relieving fatigue and depression, further supported by studies of supervised walking beneficial for female pSS patients [127]. Additionally, acupuncture (NCT02691377) and dehydroepiandrosterone (NCT00391924) were also shown to have favorable effects on depression and anxiety remaining unclear mechanisms. Thus, a combination of neuroinflammation resolution and aerobic exercise may be considered as alternative approaches for treating pSS patients with depression or anxiety.

4. Discussion

At present, most trials investigating the use of biologics in pSS patients are held in phase II. Using the available tools, ESSDAI and some questionnaire scores, the overview of therapeutic outcomes may be a little confusing due to the subjectivity. Sometimes, the improvement on life quality in patients with pSS are far from satisfactory and the number of approved biologics is relatively small. The challenge lies in developing therapies for a condition with unestablished and complicated mechanisms. Innovative and bolder methods should be explored.

One such method is gene and stem cell treatment. An experiment revealed that the transfer of human aquaporin-1 gene to damaged salivary glands enhanced parotid salivary flow. This safe method in humans is currently an impractical solution to a simple problem and expand the horizons of gene therapy, stem cell and tissue engineering therapy in treatment development in pSS [128]. Success in organoids and rodent models has paved the way in the translation into humans [129]. Research should be expanded in the area of stem cell and tissue engineering therapies which may one day be a cure to pSS. We envision the use of these techniques to replace or treat the glands affected in pSS to halt the infiltration of lymphocytic cells and atrophy of glandular and ductal cells.

Given the overlapping pathogenesis and mechanisms in autoimmune diseases such as RA and SLE, future research should consider therapies used in these conditions which may be translatable to pSS. Currently, there are twenty-two (out of 140) such trials, examples include HCQ, IGU and abatacept which are drugs used in RA that are currently applied to pSS [130].

ESSDAI is a systemic disease activity index that was designed to measure disease activity in patients with pSS. Dry eye symptoms were mostly disregarded in outcome measures in clinical trials of drugs targeting B cells. Despite the debilitating effects on quality of life and sexual ability, vaginal dryness, the most common gynecological involvement, is still often not considered as a primary outcome. A more innovative and creative direction should be taken in pSS treatment research and can involve discussions with neuroscientists and neuropsychiatrists.

5. Methods

Data included in this narrative review were identified in a literature search of the electronic database ClinicalTrials.gov using the search term "Primary Sjögren's syndrome". Only English language articles published between 2000 and 2022 were included. The results were curated by the authors for their relevance in understanding the pathogenesis and treatment options of pSS.

6. Conclusion

In conclusion, this study reviewed the emerging therapies of pSS and analysed them in conjunction with cytokines involved in pSS pathogenesis. Management of pSS should extend beyond symptomatic treatment and consider the mechanisms that underlie pSS to get to the root of the problem. It is critical that pSS treatment should be multipronged, using a combination of non-pharmacological and pharmacological synthetic and biologic therapy to optimize, tapping on the synergistic effects. The therapeutic potential of

DMARDs used in other autoimmune conditions may be considered in pSS treatment in view of the parallels in their pathophysiology. Future research should focus on these pertinent points in their approach to developing therapies that will treat and improve life quality of pSS patients.

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Appendix A

Table 1. Clinical trials in pSS from 2000 to 2022.

NCT Number	Drug	Phase	Target or Route	Duration (years)	N	Primary end point
NCT04093531	Ustekinumab	1	Th-1/IL12 and Th-17/IL23	2 years(January 15, 2020-December 2021)	15	ESSPRI
NCT01601028	Hydroxychloroquine	3	TLR9 and TLR7, IL-6,IL-17,BAFF,etc	2 years (July 2011-August 2013)	39	Serum cytokine level
NCT04546542	Hydroxychloroquine	-	-	3 years(October 1, 2020-December 1, 2023)	75	HCQ blood levels
NCT02067910	Abatacept	3	-	5 years (August 2014-August 2019)	80	ESSDAI
NCT02915159	Abatacept	3	CRP	2-3years (December 6, 2016-July 23, 2019)	250	ESSDAI
NCT04186871	Branebrutinib and abatacept	2		3 years(January 7, 2020-February 10, 2023)	185	SLE: mCLASI activity score response;pSS-ESSDAI;RA : ACR50 response
NCT01693393	Cyclosporin A	2	T cell and cytokines	4 years(March 2010-October 2014)	30	painful and/or swollen joints at end of treatment (EOT)

NCT04916756	Baricitinib	1,2	JAK inhibitors, JAK/STAT	1 year (January 16, 2020-March 25, 2021)	11	ESSDAI
NCT04496960	Tofacitinib	1b-2a	JAK inhibitor,IL-6	3 years(May 18, 2021-February 5, 2024)	30	safety and tolerability of tofacitinib and ESSDAI
NCT02701985	RO5459072	2	Cathepsin S inhibitor, LIP 10,SSA/SSB,TN F- α ,IL-10	1 year(July 5, 2016- July 10, 2017)	75	ESSDAI
NCT03627065	Parsaclisib (INCB050465)	2	PI3K δ inhibitor, B cell, BAFF,dsDNA, SSA, SSB,inhibit AKT phosphorylation	1 year(February 28, 2019-January 2, 2020)	10	Salivary Gland Ultrasound (SGUS) Score for Parotid and Submandibular Glands
NCT02775916	Leniolisib(CDZ173)	2	PI3K δ inhibitor, B cell, Abs	1 year(June 1, 2016-May 17, 2017)	30	AEs, death,ESSPRI,ESSDAI
NCT00101829	Rituximab	1	B cell, anti-CD20	5 years(April 2004-August 2009)	12	Grade 3 or higher AEs
NCT00363350	Rituximab	1,2	B cell, anti-CD20	2 years(August 2006-October 2008)	30	stimulated salivary gland function,Histological/Molecular parameters
NCT00426543	Rituximab (Mabthera)	2	B cell, anti-CD20	3-4 years(January 2007-August 2010)	21	disease symptoms(oral/ocular dryness, myoartralgia and fatigue)
NCT02631538	Rituximab and Belimumab	2	B cell, anti-CD20	3-4 years (February 17, 2016-June 23, 2020)	86	-
NCT00740948	Rituximab	2,3	B cell, anti-CD20	5 years(March 2008-January 2013)	12 2	30% improvement between in the values on 2 of the 4 VAS
NCT04981145	Iguratimod (IGU)	4	BAFF-BCMA/TACI	2 years (July 2021-July 2023)	78	SSRI-30, ESSPRI,Schirmer test, IgG,C3,C4
NCT04830644	Iguratimod (IGU)	2	BAFF-BCMA/TACI	1 year (March 22, 2021-June 2022)	14 4	ESSDAI, ESSPRI
NCT03023592	Iguratimod (IGU)	1,2	BAFF,antibodies	1 year (February 2017-April 2018)	30	ESSDAI, ESSPRI

NCT02962895	Ianalumab (VAY736)	2	-	4 years(June 27, 2017-September 30, 2021)	19 2	multi-dimensional disease activity
NCT02149420	Ianalumab (VAY736)	2	BAFF-R inhibitor, ADCC	4 years(May 23, 2014-February 7, 2018)	27	ESSDAI and AEs
NCT04078386	Telitacicept (RC18)	2	B cell, BLyS/APRIL pathway, CD11c+Age-associated B cells (ABCs)-targeted	2 years(November 21, 2019-June 23, 2021)	42	ESSDAI
NCT01160666	Belimumab	2	BAFF,cytokines	2 years(March 2010-June 2012)	20	dryness ,fatigue ,musculoskeletal pain ,systemic activity VAS and biomarkers
NCT04186871	Branebrutinib (BMS-986195)	2	BTK inhibitor,BCR and FcR	3 years (January 7, 2020-February 10, 2023)	18 5	SLE:mCLASI activity score response; pSS: ESSPRI,ESSDAI,ocular staining, salivary flow and serological marker
NCT02705989	Branebrutinib (BMS-986195)	1	BTK inhibitor,BCR and FcR	1 year(August 18, 2016-August 16, 2017)	43 9	AEs
NCT02843659	BMS-986142 and BMS-931699 (Lulizumab)	2	BTK inhibitor,CD69	1 year(October 18, 2016-July 24, 2017)	45	ESSDAI
NCT02610543	Seletalisib	2	PI3Kδ inhibitor,	2 years (October 2015-December 5, 2017)	27	ESSDAI
NCT04572841	SAR441344	2	T/B cell, anti-CD40L	2 years(November 12, 2020-October 2022)	88	ESSDAI
NCT02291029	Iscalimab (CFZ533)	2	B cell, anti-CD40/CD154, TDARs (T cell-dependent antibody production) and GCs	4 years(October 22, 2014-June 29, 2018)	69	ESSDAI
NCT02334306	AMG 557	2a	anti-BAFF and ICOSL	3 years(June 8, 2015-August 13, 2018)	32	Baseline and Day 99

NCT01552681	Baminercept	2	B cell, LT β R-Ig	3 years(July 2012-June 2015)	52	Stimulated Whole Salivary Flow
NCT01782235	Tocilizumab	2.3	anti-IL 6	5 years(July 24, 2013-July 16, 2018)	110	ESSDAI
NCT04968912	Nipocalimab (M281)	2	anti-FcRn,Ig	2 years(September 21, 2021-December 1, 2023)	150	ESSDAI
NCT00683345	Anakinra	2	anti-IL 1	2 years(January 2008-April 2010)	28	Fatigue Severity Scale

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