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Review

New strategies for treating Sjogren's syndrome

Alexander V. Blagov[1*], Vasily V. Kashtalap[2], Ksenia O. Lapshina[3], Amina E. Karimova[3], Alikhan Z. Asoyan[1], Alexander Orekhov[3]

[1] Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, Moscow 125315, Russia
[2] Research Institute for Complex Issues of Cardiovascular Diseases, 6 Barbarash Boulevard, 650002 Kemerovo, Russia
[3] Faculty of Biology and Biotechnology, National Research University Higher School of Economics, 33, Profsoyuznaya Street, Building 4, 117418 Moscow, Russia

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Abstract

Sjögren's syndrome (SS) is a complex autoimmune disorder characterized by dryness, fatigue, and systemic involvement, with current treatments largely limited to symptom management. This review explores promising new therapeutic strategies targeting specific molecular pathways implicated in SS pathogenesis, including the roles of B cells, T cells, dendritic cells, cytokines, and neuroendocrine factors. We examine recent advances in drug development and clinical trials focusing on novel biological agents that modulate these pathways, potentially offering a more targeted and effective approach to SS treatment. Ultimately, this review aims to provide an overview of these emerging therapies and their potential to improve outcomes for patients with SS.

Keywords: Sjögren's syndrome, autoimmune disease, B cells, T cells

1. Introduction

Sjögren's syndrome is a complex chronic autoimmune disease that occurs in both primary and secondary forms. The manifestations of SS can be broadly classified into non-specific, periepithelial (involving both glandular and extraglandular areas), extraepithelial (essentially extraglandular), and lymphoma types. SS is typically characterized by decreased function of the salivary and lacrimal glands, resulting in symptoms such as dry eyes and dry mouth [1]. Despite the pronounced glandular symptoms, SS also includes a wider spectrum of extraglandular features characterized by a variety of symptoms affecting both visceral and non-visceral systems. Visceral manifestations involve the pulmonary, cardiac, renal, gastrointestinal, endocrine, central nervous, and peripheral nervous systems. At the same time, non-visceral manifestations are predominantly present in the musculoskeletal system and skin. A growing body of research shows that when assessed, patients with SS with extraglandular symptoms such as fatigue, depression, and anxiety tend to experience lower quality of life compared to their counterparts. A study of 639 patients with SS found that 49.5% had symptoms of depression and anxiety, significantly higher than the general population prevalence of 15.7% [2].

According to a worldwide epidemiological study based on PubMed and Embase data, the incidence rate of SS is 6.92 per 100,000 person-years, and the prevalence rate is 60.82 cases per 100,000 inhabitants or 1 case per 1644 people. The peak age of patients is 56 years. Over the past 15 years, the disease has affected women more often than men [3]. Patients with SS experience constant and unbearable pain with multiple physical symptoms such as dental caries, vaginal dryness, and arthralgia [4].

Current treatment of Sjögren's syndrome is mainly based on symptomatic interventions (such as tear and saliva substitutes, taste and muscarinic agonists, analgesics and fluoride administration for dental caries prevention), steroids, immunosuppressants and biological therapies when systemic complications are relatively severe [5]. However, the effects are often modest or not yet evident and challenges remain in achieving objective disease relief and subjective improvement in patients' quality of life [6]. In recent decades, with a better understanding of the immunological pathogenesis and genetic signature of the di-

* Corresponding author.
E-mail address: al. blagov2014@gmail.com (A. V. Blagov).
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sease, researchers and clinicians have been able to explore more potent and subtle biological targets with promising results in altering the immune balance. Therefore, this review aimed to highlight potential therapeutic options that may be used in clinical practice in the near future.

2. General pathogenesis of Sjogren's syndrome

Numerous variables, including genetic, environmental, neuroendocrine, and immunological (related to leukocytes and cytokines) factors, are involved in the pathogenesis of sickle cell disease (SS) [7]. There are still issues with the clinical diagnosis of SS and an incomplete understanding of the disease's pathophysiology.

2.1. Infection

An important part of the formation of several autoimmune disorders is infection. One possible potential risk for SS is viral infection [8]. Viral infection can change the physiology of epithelial cells, potentially causing tissue injury, inflammation, and upregulation of type I IFN-induced genes. Numerous viral proteins and the Ro-60 antigen have five to six sequential amino acid residues in common. This sequence similarity may be the cause of autoimmune responses [9]. In individuals with SS, Epstein-Barr virus infection can extend B cells and cause their aberrant induction. T cells, B cells, and bone marrow cells can all get infected with the human T-lymphotropic virus type 1 (HTLV-1), which causes cell activation and proliferation. Research has demonstrated that HTLV-1 patients' salivary glands display inflammation and lymphocyte infiltration, and these individuals may have symptoms similar to SS. Moreover, hepatitis C virus, CMV, and human herpes virus type 8 may all be strongly linked to the onset of SS [10].

2.2. Epithelial cells of the salivary glands

In SS, salivary gland epithelial cells (SGE) are essential for the start and development of the immunological response. The first stage of SS development is thought to be abnormal exocrine gland homeostasis. Inflammation comes before exocrine dysfunction. Upon activation with antigens, SGE produces proinflammatory substances that increase immune cell infiltration and operate as antigen-presenting cells, encouraging T-lymphocyte differentiation [11]. Patients with SS have surface expression of CD80/86 on SGE. When mice with SS are treated with anti-CD86 antibodies, the autoimmune damage to their lacrimal and salivary glands is lessened. This implies that such epithelial cells may present antigens and may also promote T-cell activation and proliferation, which in turn causes damage to the glandular tissue. Research has demonstrated that SGE mediates B-cell stimulation and differentiation in SS patients [12].

2.3. B cells

B cells are crucial to the progression of SS. The development of anti-SSA and anti-SSB autoantibodies, as well as glandular edema, are symptoms of enhanced B cell activation in the exocrine glands of SS patients. Ro60-316-335 peptide-immunized mice spontaneously produce several serum autoantibodies and inflammation of the lacrimal gland. Exocrine gland damage in mice was decreased after therapies with B cell-depleted CD20 monoclonal antibodies relative to controls [13]. Accordingly, CD20 monoclonal antibodies are utilized in clinical practice for the treatment of SS. For instance, the chimeric antibody rituximab, which targets the CD20 antigen, diminishes proinflammatory cytokines released from B cells and depletes B cells themselves. Symptoms of SS are considerably relieved by rituximab treatment. The information presented above demonstrates how crucial B cells are to the pathophysiology of SS [14].

2.4. T cells

Animal models of SS with high levels of T cell invasion and cytokine expression in the exocrine glands suggested that T cells and related cytokines are crucial to the progression of the illness. In a mouse model of SS, elevated expression of CXCR4 and CXC12 was discovered, leading to abnormally high T cell infiltration [15]. Mature hematopoietic cells' T cells express unique nuclear matrix binding domain binding protein 1 (SATB1), and animals with SATB1 gene-specific deletion (SATB1cKO) exhibit spontaneously decreased salivary production. Furthermore, the salivary glands of SATB1cKO mice contain elevated T cell counts together with serum anti-SSA and anti-SSB autoantibodies. Reduced salivary production and damage to salivary acinar cells were observed in mice transplanted with SATB1cKO murine T cells, highlighting the significant role of T cells in the pathophysiology of SS [16].

2.5. Dendritic cells

DCs, or dendritic cells, are crucial for triggering and sustaining immunological responses. The body's most significant antigen-presenting cells are DCs. These cells present antigens to T lymphocytes after phagocytosing them. Research has demonstrated that the migration of DCs from peripheral blood to secretory glands, which results in the maturation of Th1 cells in the salivary glands and the generation of high quantities of IFN-γ, which induces inflammation, is the cause of the decline in DC numbers in the peripheral blood of SS patients. DCs encourage T cell penetration into the salivary glands and the activation of primary T cells, which results in proinflammatory cytokines and sialoadenitis as well as pathogenic alterations in SS [17].

2.6. Cytokines

Many different types of cells create and employ a class of cytokines called interleukins (ILs). Therapy aimed at targeting the IL-1 receptor could only alleviate ocular symptoms since studies on autoimmune regulation-deficient animals have demonstrated that deletion of the IL-1 receptor lowers ocular surface keratosis but not breast lymphocyte infiltration. Another member of the IL-1 family, IL-33 serves as both a cytokine and a nuclear factor. Serum IL-33 levels are markedly raised in SS patients, which stimulates IFN-γ and inflammation. This, in turn, enhances initiation of the IL-33/ST2 pathway, exacerbating the condition [18].

The IL-2 family includes IL-2 and IL-21. According to certain research, low-dose IL-2 therapy reduces SS symptoms, lowers the Th17/Treg ratio, and boosts T regulatory cells (Treg) relative to baseline. These findings imply that immunological modulation, as opposed to immunosuppression, should be prioritized in the therapies for sickle cell disease (SS) since IL-2 stimulates the proliferation of

Treg cells [19]. IL-25, commonly referred to as IL-17E, is a member of the cytokine family IL-17. Th2 cell-mediated immunity is strengthened by IL-25, whereas Th1 and Th17 cell-mediated immunity is suppressed. IL-25 is a dual-purpose immunoregulatory agent. By preventing CD4+ T cells from differentiating into Th17 cells, IL-25 reduces inflammation. Additionally, IL-12 and IL-23 are crucial for the advancement of autoimmune mechanisms [20].

The family of cytokines known as tumor necrosis factor (TNF) induces apoptosis, or the death of cells. TNF-α is secreted by monocytes, epithelial cells, and CD4+ T cells and plays a major role in the pathophysiology of SS. Moreover, in mice without serum autoantibodies, elevated TNF-α expression results in exocrine adenitis symptoms. Therefore, the connection between TNF-α and the emergence of SS is yet unknown. In patients with SS, etanercept, a TNF-α antagonist, did not show any effect in two recent clinical trials. [21].

Many different types of cells produce a protein called interferon (IFN), which has strong immunomodulatory properties. IFN comes in three varieties: I, II, and III. The type I IFNs that have been investigated the most in SS are IFN-α and IFN-β. Increased levels of type I IFN and type I IFN-induced gene expression have been reported in the salivary glands and peripheral blood of SS patients [22]. These findings imply that type I IFN plays a significant role in the pathophysiology of SS.

2.7. Neuroendocrine factor

The fact that women are more likely than males to develop SS suggests that the hypothalamic-pituitary-gonadal axis is a key player in the disease's pathophysiology. Disease development in women usually happens after menopause, most likely as a result of insufficient oestrogen secretion. Sex hormones affect cellular immunological responses and humoral immunity in animal models. Aromatase gene deletion in mice leads to the absence of estrogen. These animals spontaneously develop an SS-like phenotype characterized by B-cell infiltration in the salivary glands, death of acinar cells, and release of different autoantibodies. M1 macrophages in adipose tissue and target organs release proinflammatory cytokines due to aromatase insufficiency, which induces SS-like lesions [23]. These findings imply that a significant part of the pathophysiology of SS is played by estrogen.

3. Potential therapeutic strategies for Sjogren's syndrome

3.1. Approach to targeting B cells

Growing interest in biological therapies is based on the recognition of B cell hyperactivity as a central aspect of SS pathogenesis. SS is characterized by increased B cell activity contributing to autoimmune-mediated glandular damage, with approximately 35–40% of patients exhibiting hypergammaglobulinemia, thereby causing symptoms of xerophthalmia and xerostomia [24]. CD20, expressed on B cell precursors, plays a key role in B cell activation, proliferation, and differentiation, making it a rational target to reverse the B cell dysfunction underlying SS. In this context, rituximab (RTX), a chimeric monoclonal antibody directed against CD20, has emerged as a promising therapeutic option. RTX has emerged as a leader in alleviating symptoms such as fatigue and dry mouth. The use of RTX in SS aims to modulate aberrant B-cell responses. The combination of RTX with bendamustine has been evaluated in MALT lymphoma complicating SS. Several studies have demonstrated its efficacy and safety in low-grade B-cell lymphomas, including mantle cell lymphomas and extragastric MALT lymphomas [25]. These studies have yielded a range of results, with variable improvements observed in measures such as fatigue, salivary flow rate, and joint pain. However, results have not been consistently consistent, and several trials have failed to meet their primary endpoints [26], raising concerns about safety and long-term efficacy. Based on current data, RTX did not demonstrate significant differences compared with placebo in terms of pain, fatigue, and dry mouth. Recent studies show that patients with increased levels of B cell infiltration in the parotid glands tend to have a more favourable response to RTX, suggesting that in the future it may be possible to tailor drugs more precisely to individual patients [27].

B cell activating factor (BAFF) and its proliferation-inducing ligand (APRIL) significantly affect B cell maturation, proliferation, and survival. Numerous studies have consistently highlighted the essential involvement of BAFF in the pathogenesis of SS, emphasizing its critical role [28]. Therapeutic interventions aimed at inhibiting B cell activation through disruption of BAFF have been the subject of extensive research. Notable agents in this context include belimumab, an antibody that targets BAFF, and atacicept or telitacicept, a soluble wild-type Fc extracellular domain fusion protein that potently inhibits BAFF and weakly inhibits APRIL signaling [29]. It is important to note that chronic use of BAFF antagonists effectively reduces disease activity but may not affect certain parameters such as salivary flow rate, Schirmer test, and lesion scores in salivary gland biopsies [30].

The BAFF/APRIL system includes not only these two ligands but also three receptors: the BAFF receptor (BAFF-R), also known as the B-cell stimulator receptor 3 (BR3), the B-cell maturation antigen (BCMA), and the transmembrane activator and cyclophilin ligand interactor (TACI) [31]. Both BAFF and APRIL can interact with BCMA and TACI, while BAFF binds exclusively to BAFF-R. These receptors also play a key role in B-cell survival, maturation, and regulation. Drugs targeting these receptors are currently being studied. Ianalumab, a novel antibody targeting BAFF-R, has shown beneficial therapeutic effects in patients with primary SS by influencing ESSDAI score, gland quality, inflammation, perfusion and stiffness [32].

In the search for diverse therapeutic strategies, new avenues have been explored. Particular attention has been paid to targeting CD22, a protein on the surface of B cells, as exemplified by epratuzumab, a humanized IgG1 antibody against CD22. In contrast to the depletion-based approach of RTX, epratuzumab modulates B cell activity, potentially offering an alternative means to mitigate B cell-mediated autoimmunity. Epratuzumab increased disease activity and accelerated B cell/IgM decline in systemic lupus erythematosus (SLE) patients with SS [33]. However, further studies are needed to establish its efficacy. CD38, a glycoprotein found on plasma cells, acts as an adhesion molecule, ectoenzyme, and receptor for activation or proliferation signals. Anti-CD38 antibodies can directly interact with plasma cells via calcium perturbation and signaling or Fc-dependent immune effector mechanisms

Fig.

(complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis). Daratumumab, a monoclonal antibody targeting CD38 on multiple myeloma cells and immune cells, is being studied for potential use in autoimmune diseases such as SS. Its mechanism of action to modulate the autoimmune response is promising, but rigorous clinical trials are needed to establish its safety and efficacy in these specific conditions [34].

3.2. T cell targeted therapy

Current studies indicate that CD4+ T cells are the major lymphocytes infiltrating the salivary and lacrimal glands in the early stages of SS. Furthermore, elevated levels of T cell-associated cytokines are observed in patients with cutaneous manifestations. These findings support the consideration of T cell-targeted therapies, particularly for patients with dermatologic symptoms. Such therapies, exemplified by abatacept, have gained prominence due to their critical role in the complex pathogenesis of SS. Abatacept, a fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 and the modified Fc portion of human IgG1, is approved for the treatment of rheumatoid arthritis (RA). It interferes with the CD80/86-CD28 costimulatory pathway, thereby inhibiting T cell activation. Studies have shown that abatacept reduces the number of circulating follicular helper T cells (Tfh) and the expression of the T cell surface activation marker ICOS in the peripheral blood of patients with SS. This reduction in activated T cells contributes to the suppression of Tfh-dependent B cell hyperactivity [35]. In addition, human cytotoxic T lymphocyte-associated antigen 4 has been shown to regulate CD4+ T cell proliferation and reduce T cell activation in SS. Abatacept was initially found to reduce inflammation and enhance salivary production in SS, and subsequent ROSE and ROSE II trials confirmed improvement in a variety of outcomes including glandular, extraglandular, and systemic manifestations [36]. However, despite these biological effects on biomarkers and immune cells, a phase III study in active primary SS showed that abatacept did not achieve significant clinical efficacy compared with placebo [37].

3.3. Anti-TNF-α directed therapy

Infliximab, the first anti-TNF therapy investigated in SS, initially demonstrated statistical improvement in clinical and functional parameters in a pilot study. However, subsequent larger studies failed to establish any beneficial effects. Issues such as achieving therapeutic concentrations in the salivary glands and overcoming inflammation-related fibrosis may have contributed to this treatment failure [38].

Clinical trial results partially coincide with findings from animal models. TNF appears to attenuate T cell autoreactivity and inflammation, and its absence results in the accumulation of reactive CD4+ T cells. Emerging data from these models point to a protective role for TNF in SS, as TNF deficiency exacerbates SS-like disease, and TNF deficiency in some models is associated with salivary gland inflammation and altered B cell compartments, which may promote lymphoid tumors resembling MALT lymphomas [39].

Anti-TNF-α therapy in SS faces significant challenges and its efficacy has been questioned based on clinical trials and animal model data. The efficacy of anti-TNF therapy, despite its success in other autoimmune diseases, remains controversial in the context of SS, potentially due to the complex and multifaceted role of TNF in the pathogenesis of the disorder. Exploring the discrepancies between pathological mechanisms and the actual therapeutic efficacy of TNF therapy represents an interesting direction of research [40].

3.4. Therapy with IFN and anti-IFN-targeted drugs

IFN activation signaling pathways in SS have generated interest in the use of IFN-α agonists for therapeutic benefit. Early phase trials suggest potential for improvement in dry mouth symptoms and salivary flow [41]. A phase III clinical trial demonstrated that low doses of oral IFN increased unstimulated saliva production. Oral mucosal administration of IFN-α is thought to enhance salivary secretion by upregulating aquaporin 5 transcription without disrupting the autoimmune process [40]. However, larger double-blind placebo-controlled trials involving significant numbers of patients have failed to establish significant differences in dry mouth or stimulated salivary flow. In particular, unstimulated salivary flow was increased in the treated groups, suggesting potential therapeutic effects. Despite these results, the clinical benefit of IFN-α agonists in patients with SS remains uncertain. Continued research and improved treatments are needed to understand the complex interplay of IFN and its modulation in the context of Sjögren's syndrome [40].

3.5. IL-6 targeted therapy

Elevated IL-6 levels observed in serum, saliva, and tears of patients with SS provide a compelling indicator of the key and integral role of the cytokine in the pathophysiological structure of SS [42]. IL-6 is a key factor in B cell activation and T cell differentiation and is associated with fatigue. Tocilizumab, a monoclonal antibody, effectively inhibits IL-6 signaling by blocking the IL-6 receptor. Although tocilizumab is commonly used to treat rheumatoid arthritis, it is not yet approved for the treatment of SS. However, given its ability to disrupt IL-6-mediated inflammatory processes, it represents a promising avenue for intervention in SS. Despite limited clinical data, one report documented the beneficial effects of tocilizumab in a patient with neuromyelitis optica spectrum disorder complicated by SS [43]. In addition, a phase III randomized controlled trial led by French investigators compared tocilizumab with placebo in patients with SS. However, this study failed to demonstrate the efficacy of tocilizumab in systemic involvement and symptoms compared with placebo. Thus, the role of IL-6 targeting in the treatment of SS remains a topic worthy of further investigation. Moreover, elucidation of the broader implications of IL-6 targeting in SS, including its potential impact on fatigue and autoimmune mechanisms, remains a topic of interest and ongoing research [44].

3.6. JAK/STAT Targeted Therapy

Janus kinase (JAK)-signal transducers and activators of transcription (STAT) pathways play a central role in autoimmunity and systemic inflammation by regulating the production of inflammatory cytokines including IL, TNF, granulocyte-macrophage colony-stimulating factors and IFN-γ [45]. Data on JAK and STAT expression in salivary

glands in SS remain scarce. However, in one recent study, the authors demonstrated robust expression of JAK1 and JAK2 in ductal and acinar cells of minor salivary gland biopsies from SS patients. Increased expression of STAT1 and STAT3 in minor salivary gland biopsies from patients with SS, as well as in their blood samples, correlates with activation induced by a number of immune mediators, including IFN-α, IFN-γ, IL-6, IL-17 and IL-22 [46].

JAK inhibitors, approved for the treatment of immune disorders and under investigation in autoimmune diseases, offer a promising therapeutic approach in rheumatology by competitively binding to ATP and modulating critical molecular and biological processes with potential application in SS. In the context of the complex cytokine landscape that characterizes SS, numerous JAK inhibitors, including baricitinib, filgotinib, tofacitinib, oclacitinib, and upadacitinib, have found application in the treatment of autoimmune diseases [47]. In a recent pilot study of 11 patients with active SS, the JAK1 and JAK2 inhibitor baricitinib showed promising results in reducing immune cell infiltration and improving clinical manifestations, although controlled trials are needed for confirmation [48]. Filgotinib, a JAK1 inhibitor, has shown potential in downregulating IFN-related genes and BAFF in SS. The clinical trial, although not meeting the primary and secondary endpoints, may suggest promising results for filgotinib in biomarker-controlled subgroups of SS patients, stabilizing saliva and tear production and reducing IFN activity. The overall safety and tolerability profile is encouraging, indicating the need for more targeted approaches in SS clinical trials [49]. Data on the described therapeutic developments are summarized in Table 1. The main molecular targets of SS are summarized in Table 2.

4. Discussion

As a systemic autoimmune disease, SS causes multiple organ involvement, especially in the salivary and lacrimal glands, which limits endocrine function. In addition to focal inflammation in the salivary gland, patients with SS typically present with acinar atrophy, duct dilation, and fibrosis. Lymphocytic infiltration around the striated ducts in the salivary glands, or so-called periductal foci, is a critical feature for the diagnosis of SS [50]. In addition, comorbidities such as secondary lung disease, renal injury, and lymphoma further reduce the quality of life of patients. The pathogenesis of SS is characterized by the production of inflammatory cytokines and lymphocyte infiltration. IFN and IL-17/IL-23 play a key role in the formation of

Table 1. Potential therapeutic agents for the treatment of SS.

Drug	Target	Shown effectivity in SS	Phase of Development /Approval Status
Rituximab	CD20	Decreased symptoms of SS (dry mouth, joint pain) but it hasn't achieved primary endpoints.	Approved for other autoimmune conditions; Off-label use in SS
Ianalumab	BAFF	Decreased symptoms of SS. It has achieved EESS DAI check points.	Intital clinical trials in SS
Belimumab		Decreased SS activity. it hasn't achieved primary endpoints.	Approved for SLE (Systemic Lupus Erythematosus); Investigational use in SS
Epratuzumab	CD22	Decreased autoimmune B-cell in SLE patients.	Shown clinical efficacy in SLE, Investigational use in SS
Daratumumab	CD38	Unknown.	Investigational
Abatacept	CD80/86-CD28	Decreased Tfh in SS patients. Decreased inflammation. Decreased symptoms of SS. It hasn't achieved primary endpoints in III phase.	Investigational
Infliximab	TNF-α	Decreased symptoms of SS. It hasn't achieved primary endpoints.	Phase I/II of SS efficacy and safety investigation
IFN-α	IFN-R	Decreased symptoms of SS (dry mouth).	Phase III of SS efficacy investigation
Tocilizumab	IL-6R	Decreased neuromyelitis optica symptoms (complication of SS).	Approved for RA (Rheumatoid Arthritis); Investigational use in SS
Baricitinib	JAK1/2	Decreased leukocyte infiltration. Improved clinical manifestation of SS.	Pilot study of efficacy and safety in SS treatment

Table 2. Molecular Targets in Sjögren's Syndrome and Potential Therapeutic Interventions

Molecular Target	Role in Pathogenesis	Potential Therapeutic Strategy	Examples of Agents Targeting This Pathway
CD20 (on B cells)	B cell activation, proliferation, and differentiation; release of pro-inflammatory cytokines.	B cell depletion or modulation of B cell activity.	Rituximab (chimeric monoclonal antibody targeting CD20)
BAFF (B cell activating factor)	B cell survival, maturation, and proliferation; promotes autoantibody production.	Inhibition of BAFF signaling, blocking its interaction with B cells.	Belimumab (human monoclonal antibody that binds to BAFF), Atacicept/Telitacicept (soluble fusion protein that binds to BAFF and APRIL)
APRIL (A Proliferation-Inducing Ligand)	B cell survival, maturation, and proliferation; promotes autoantibody production (weaker than BAFF).	Inhibition of APRIL signaling, blocking its interaction with B cells.	Atacicept/Telitacicept (soluble fusion protein that binds to BAFF and APRIL)
Cytokines (IL-6, TNF-α, Type I IFNs)	Promote inflammation, immune cell activation, and tissue damage; contribute to systemic manifestations of SS.	Cytokine blockade; inhibition of cytokine signaling pathways.	Etanercept (TNF-α antagonist) did not show effects in clinical trials.
Muscarinic Receptors (M3)	Regulate salivary and lacrimal gland secretion.	Stimulation of muscarinic receptors to increase saliva and tear production.	Pilocarpine, Cevimeline (muscarinic agonists)
Oestrogen	Immune modulation; aromatase insufficiency may cause the release of proinflammatory cytokines.	Oestrogen therapy	Aromatase gene deletion in mice leads to the absence of estrogen

inflammatory lesions, and B cells are crucial for infiltrative injury. Th17, B and dendritic cells play a critical role in the aberrant regulation of the immune system [51].

Research into SS therapy is limited by the lack of systematic clinical trials. Many potential therapeutic targets have been identified in the pathogenesis of SS, and some targeted agents have shown reasonable efficacy in vitro or in vivo experimental settings. Unfortunately, translation of these agents into clinical practice is rare. In addition, it is unclear why immune inhibitors have no pharmacological effect in SS compared to other autoimmune diseases.

A successful trial requires a drug with intrinsic efficacy, an appropriate patient population, observation time, and appropriate efficacy criteria. Drugs lacking intrinsic efficacy are mainly the result of misidentification of nonpathogenic parameters, severe side effects of infection, and unclear immunological mechanisms, especially its unclear role in the pathophysiology of a particular symptom. In addition to the drug's intrinsic inefficacy, some trials with negative results underestimated the true efficacy of the therapy. The main factors include excessive patient heterogeneity, too short duration, and inappropriate endpoints.

5. Conclusion

In conclusion, while current treatments for Sjögren's syndrome primarily address symptom management, the evolving understanding of the disease's molecular pathogenesis has paved the way for promising new therapeutic strategies. Targeting key players such as B cells, cytokines, and neuroendocrine factors with novel biological agents holds the potential to improve patient outcomes and quality of life. Future research should focus on refining these targeted therapies, identifying predictive biomarkers for treatment response, and developing personalized treatment approaches to maximize efficacy and minimize adverse effects in this heterogeneous disease.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal roles in study design, work, statistical analysis and manuscript writing.

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