Advances in the diagnosis and treatment of Sjögren disease

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Purpose of review
Sjögren disease (SjD) constitutes a diagnostic and therapeutic challenge due to its clinical heterogeneity and complex pathophysiology. This review synthesizes recent advances in diagnostics, disease stratification, and targeted therapies, highlighting their potential to optimize patient care .

Recent findings
Emerging diagnostic approaches include advanced salivary, lacrimal, and serum biomarkers, refinements of established diagnostic tools, role of specific autoantibodies, and AI-assisted histopathology, improving early detection and risk stratification, particularly for lymphoma-prone phenotypes. Novel immunological insights have enabled phenotype-based classification, guiding the development of targeted therapies against B-cell pathways, cytokines, and co-stimulatory molecules with several agents (e.g., belimumab, ianalumab, telitacicept) showing promise in reducing disease activity scores.

Summary
Recent advances provide a framework for precision medicine in SjD, integrating molecular and imaging biomarkers into patient selection and treatment monitoring. Clinically, this could enable earlier diagnosis, individualized risk assessment, and tailored therapy. Research priorities now include validating diagnostic innovations in diverse populations, elucidating phenotype-specific mechanisms, and conducting adequately powered, biomarker-driven trials to optimize therapeutic efficacy.

Keywords
autoimmunity, biomarkers, precision medicine, Sjögren disease, targeted therapy

INTRODUCTION

Sjogren disease (SjD), as recently renamed to reflect its systemic nature [1▪], is a prevalent autoimmune disease, classically presenting with mucosal dryness, fatigue and joint pain. Other systemic complications, including, among others, synovitis, small airway disease, interstitial lung disease, interstitial nephritis, peripheral neuropathies, cryoglobulinaemic vasculitis or lymphoma can also occur [2]. A female-to-male ratio of 14 : 1 is observed independent of geographical location, while higher disease activity scores and extraglandular involvement were identified in men at diagnosis. Mortality varies depending on the extent of systemic involvement, with cutaneous vasculitis, interstitial lung disease, and lymphoma showing poorer results. The still widely used term, primary Sjogren's syndrome (pSS), refers to Sjogren's syndrome which is not associated with other connective tissue diseases (CTDs) [3].

Regarding disease monitoring, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) scoring systems are widely used to assess systemic disease activity and patient-reported symptoms, respectively. However, the newer Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) and candidate Sjögren's Tool for Assessing Response (STAR) are suggested as providing more holistic endpoints [4].

This review outlines current advances in diagnosing and managing the disease, covering clinical evaluation, laboratory testing, imaging, and histopathology,

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KEY POINTS

- Advances in salivary, lacrimal, and serum biomarkers, alongside artificial intelligence assisted histopathology, are enhancing early detection and risk stratification, particularly for lymphoma-prone phenotypes
- Targeted therapies show promise in reducing systemic disease activity, though large trials have yet to confirm consistent clinical benefit
- Most agents act on B-cell pathways, cytokines, or co-stimulatory molecules, but only a few have shown durable improvements in patient-reported outcomes
- Future work should validate diagnostic tools across diverse populations, clarify phenotype-specific mechanisms, and design biomarker-driven, adequately powered clinical trials to optimize therapeutic efficacy

and discussing treatments for glandular and extra-glandular manifestations targeting underlying disease mechanisms.

DIAGNOSTIC APPROACH

History and clinical examination

History-taking should be comprehensive, aiming to assess the extent of symptoms, evaluate disease burden, consider key differential diagnoses, and detect emerging complications. After documenting ocular and oral dryness (sicca symptoms) and systemic manifestations, clinicians should actively exclude alternative diagnoses such as Hashimoto's thyroiditis, sarcoidosis, amyloidosis, hepatitis C virus and HIV infection, IgG4-related disease, as well as head and neck radiation treatment. A thorough medication history including antidepressants, diuretics, checkpoint inhibitors [5,6▪], and combined oral contraceptive pill (COCP), among others, should be obtained [7]. Features associated with lymphoma development such as salivary gland enlargement or purpura should also be inquired [5]. Lastly, the psychological status of patients should be assessed. Apart from psychological stress being a known trigger for the onset of SjD [5], it has been recently demonstrated that patients with SjD had an elevated hazard ratio for attempted suicide after adjusting for demographics and coexisting conditions [8].

Exocrine gland assessment

Regarding assessment of objective ocular and oral dryness, Schirmer's test, determination of ocular surface scores (OSS) and unstimulated whole salivary flow (UWSF) are performed [5]. A recent study suggests that reducing the UWSF test time from 10 to 5 min does not compromise diagnostic accuracy, while recommending stimulated WSF testing in patients with 10-min UWSF rates of 0.1–0.2 ml/min [9]. Of note, a positive Schirmer's test has been shown to be a stronger predictor of a biopsy scoring more than 2 according to Chisholm and Mason, compared to ANA and anti-Ro/SSA positivity [10]. In-vivo confocal microscopy of the eye has demonstrated that specific changes in the corneal nerve, tear film, and at cellular level are significantly more indicative of SjD than of non-SjD conditions [11].

Laboratory investigations

Baseline laboratory investigations in patients suspected of having SjD should include full blood count, liver, kidney, and thyroid function tests, protein electrophoresis, antinuclear antibodies (ANA), anti-Ro/SS-A and anti-La/SS-B, rheumatoid factor, complement and vitamin D levels [5,6▪]. A chest X-ray should also be performed to exclude sarcoidosis. Notably, rheumatoid factor positivity, low complement levels, and monoclonal gammopathy have consistently been associated with an increased risk of lymphoma in Sjögren's disease [5]. Although all rheumatoid factor isotypes (IgA, IgG, and IgM) predict a more severe disease course, specifically IgA rheumatoid factor, was shown to act as an early potential poor prognostic factor for patients with SjD [12]. Additionally, the IgM- rheumatoid factor and IgA-RF profiles of patients with SjD-RA overlap closely with those of RA patients, while differing markedly from those of patients with SjD alone [13]. Other autoantibodies including anti-mitochondrial, anticitrullinated anti 21-hydroxylase and anticalponin-3 antibodies have been detected in sera of SjD patients [5]. Moreover, recent data highlight the rare occurrence as well as the lack of diagnostic and prognostic value of anti-La/SSB in isolation, observed over a period of 7 years [14].

Systemic sclerosis specific autoantibodies are frequently detected in patients with sicca symptoms and, at high titers, have been independently associated with minor salivary gland biopsy (MSGB) positivity [15]. In a recent report, anticentromere autoantibody positivity was linked to a distinct clinical phenotype characterized by greater systemic involvement, lower prevalence of anti-Ro/SSA, anti-La/SSB, and rheumatoid factor, and higher salivary gland ultrasound scores, particularly reflecting fibrotic changes and sialadenitis [16].

Biomarkers in tears, saliva, and serum

Technological advances have allowed the identification of innovative salivary, lacrimal and serological

biomarkers, revolutionizing the early diagnosis of SjD, offering a noninvasive potential alternative to traditional methods.

Recent studies have identified several promising noninvasive biomarkers for SjD. Tear lactoferrin levels, measured via photo-detection devices, were found to be significantly lower in SjD patients compared to controls [17]. Raman hyperspectroscopy, based on inelastic light scattering, combined with machine learning, has effectively distinguished SjD patients from healthy individuals and radiation-induced xerostomia patients by analyzing saliva's biochemical composition [18]. Additionally, a novel model incorporating salivary biomarkers – complement factor B (CFB), clusterin (CLU), calreticulin (CALR), neutrophil elastase – and serum autoantibodies offers a promising approach to differentiate primary SjD from non-SjD cases [19]. Altered mitochondrial RNA expression in saliva and plasma also discriminates SjD patients from healthy controls, with salivary expression correlating positively with disease activity [20].

Several novel autoantibodies, including IgG against CCL4, M5, TMPO, and OAS3, are more prevalent in SjD, with some (e.g., anti-TONSL, anti-IL6) linked to pulmonary involvement. Diagnostic models using these markers achieved up to 46% sensitivity and 95% specificity, effectively distinguishing SjD, particularly anti-Ro/SSA negative individuals-from controls [21]. Similarly, autoantibodies against D-aminoacyl-tRNA deacylase (DTD2) and retroelement silencing factor-1 peptides were shown to be associated with anti-SSA negative status as well as focus score (FS) positivity [22]. Moreover, elevated growth differentiation factor 15 (GDF15), a cytokine of the transforming growth factor-β (TGF-β) superfamily [23], and fibrinogen-like protein-1 (FGL-1), a hepatocyte-derived protein induced during acute inflammation that promotes T cell activation, show promise in improving disease discrimination [24▪▪].

In another study of 395 SjD patients three distinct phenotypes were identified via cluster analysis: B cell active with low symptoms (BALS), high systemic activity (HSA), and low systemic activity with high symptoms (LSAHS) [25▪▪]. The BALS and HSA clusters exhibited higher levels of CXCL13, IL-7, and TNF-RII compared to LSAHS, with a pronounced interferon (IFN) signature most prevalent in BALS. Although all lymphomas within the BALS group occurred in patients with a high IFN signature, this association was not statistically significant; notably, no lymphomas were observed in the LSAHS cluster [26]. Further, deep flow cytometry immunophenotyping of B and T cell compartments identified CD11c+ FcRL5+ tissue-like memory B cells and IFNγ+ TNFα+ conventional T cells as significantly associated with non-Hodgkin lymphoma in these patients [27].

Additionally, liquid chromatography-tandem mass spectrometry identified IFNγ-inducible biomarkers – kynurenines and neopterin – correlated with increased SjD risk, disease activity, glandular dysfunction, autoantibody presence, and immunological and inflammatory markers [28].

Imaging and histopathology

A recent systematic review showed that major salivary gland ultrasonography (SGUS) offers diagnostic accuracy comparable to MSGB for primary SjD, though MSGB remains more sensitive and specific [29]. Higher SGUS grades correlate with increased disease activity and greater prevalence of lymphoma-related risk factors and extraglandular manifestations [30]. However, the OMERACT ultrasound scoring system has yet to fully replace MSGB due to limited agreement [31].

While MSGB is not mandatory for diagnosing SjD, it offers important prognostic information for lymphoma development and systemic involvement. Biopsy is particularly indicated when SGUS is negative and anti-Ro/SSA antibodies are absent. Conversely, in anti-Ro/SSA seropositive patients, SGUS strongly correlates with biopsy findings [32]. An optimal sample size of five minor salivary glands (or four if large) has been proposed for accurate focus score evaluation [33]. Furthermore, assessing additional histopathological features beyond focus score – such as prelymphoepithelial and lymphoepithelial lesions, plasma cell shift, and germinal centers – significantly enhances diagnostic specificity [34]. Fiorentini *et al*. [35] highlighted differences between seropositive and seronegative patients: seropositive biopsies showed more intense periacinous and periductal lymphocytic infiltration with CD3+ and CD138+ cells, whereas seronegative biopsies exhibited milder infiltration with CD20+ and CD68+ cells, but greater fibrosis and fat replacement. Lymphocytic infiltration severity, fibrosis, and fat replacement increased with age, with fibrosis tending to be periglandular in younger patients [35].

Recent advances demonstrate the revolutionary role of artificial intelligence in SjD diagnostics. Artificial intelligence applied to labial gland biopsy whole-slide images has enabled identification of patients at high risk for extraglandular organ involvement [36]. Additionally, an artificial intelligence model accurately classified minor salivary gland biopsies by focus score ($\geq$1 vs. $<$1), achieving 87% sensitivity, 84% specificity, and 85.2% accuracy, effectively reducing underreporting and inter-observer variability [37].

A recent study found lacrimal gland ultrasound (LGUS) to have a sensitivity of 61.5% and specificity of 87.5% for SjD diagnosis, with positive and negative predictive values of 80.0 and 73.3%, outperforming major salivary gland ultrasound [38]. LGUS showed no significant association with Schirmer's test positivity but was strongly associated with anti-Ro/SSA [odds ratio (OR) 17.4] and anti-SSB antibodies (OR 23.0) [38].

Ultrasound elastography of the salivary glands has also emerged as a promising noninvasive diagnostic tool, with pooled sensitivity and specificity of 80% and 87%, respectively [39]. Specifically, lacrimal shear wave elastography demonstrated even higher accuracy, with 88% sensitivity and 94% specificity [40]. Additionally, FDG-PET/CT plays an important role in excluding pSS-associated lymphomas in patients without PET abnormalities, potentially reducing invasive biopsies, while also detecting systemic involvement and guiding biopsy site selection [41].

ADVANCES IN THERAPY

Since the development of biologic therapies, considerable advances have been made in the treatment of systemic autoimmune diseases. However, SjD management remains a challenging task, with numerous clinical trials on novel therapeutic agents, failing to demonstrate clinical benefits. As a result, therapeutic strategies primarily focus on symptomatic relief, with only limited progress recorded in systemic treatments. This is attributed to various factors, including the syndrome's uniquely complex pathogenic mechanisms, as well as its multiple phenotypes [42]. On this note, a study aimed at elucidating the underlying mechanisms of anti-TNF lack of efficacy in SjD patients revealed increased plasma levels of interferon-alpha (IFN-α) and B-cell activating factor (BAFF) in patients receiving etanercept, a recombinant TNF inhibitor [43]. Crucially, both IFN-α and BAFF are essential factors in SjD etiopathogenesis, hence it is

Table 1. Recommendation per disease manifestation

Disease manifestation	2020 EULAR recommendations	2024 BSR guidelines
Oral dryness	Mild: non–pharmacological (acidic lozenges, sugar–free gum) Moderate: secretagogues (pilocarpine, cevimeline); choleretic (anetholtrithione); mucolytic (bromhexine, N–acetylcysteine), electrostimulation Severe: saliva substitutes	Saliva substitutes for symptom relief Dental care – Oral hygiene Consider pilocarpine if systemic dryness
Ocular dryness	Artificial tears/gels Short-term topical NSAIDs or glucocorticoids Topical cyclosporine Serum eye drops Rescue treatment: plugs/oral secretagogues	Lifestyle measures Lubricating eye drops Serum eye drops Eyelid compresses Topical cyclosporin Consider pilocarpine if systemic dryness Short-term treatment with antibiotics in cases of meibomian gland dysfunction or blepharitis Punctal occlusion for selected cases
Pain and fatigue	Analgesics/pain-modifiers Hydroxychloroquine Glucocorticoids at minimal effective doses	Prioritize exercise for fatigue Hydroxychloroquine is first–line for musculoskeletal pain Escalate via methotrexate, sulfasalazine, leflunomide, azathioprine, low–dose steroids
Systemic/ extraglandular disease	Treat per ESSDAI severity First line: Symptomatic treatment, topical or low-dose systemic steroids Second line: conventional DMARDs Rescue: High dose steroids, cyclophosphamide, rituximab depending on the manifestation Specific considerations: plasma exchange and rituximab in cryoglobulinemic vasculitis, intravenous immunoglobulin in certain types of neuropathy and immune cytopenias, granulocyte colony-stimulating growth factor in severe neutropenia, eculizumab in neuromyelitis optica spectrum disorder, inhaled treatments for bronchial involvement, belimumab in refractory glandular enlargement, abatacept as rescue therapy for arthritis	Matches EULAR approach Systematic use of glucocorticoids, conventional DMARDs (methotrexate, azathioprine, mycophenolate) rituximab for severe organ involvement Concider colchicine for vasculitis, panniculitis, and pericarditis

hypothesized that their overexpression could justify anti-TNF agent treatment failure in SjD.

Current therapeutic decisions for SjD are largely based on clinical expertise and supporting data from various studies, as no evidence-driven guidelines have yet been established [44]. This is exemplified by rituximab, for which the literature provides only limited evidence for systemic treatment. However, specific disease manifestations show improvement following rituximab infusion, making it frequently used in refractory or life-threatening cases.

The 2020 EULAR and the 2024 British Society for Rheumatology Recommendations are among the most recent standardized SjD clinical instructions [6▪,45] (Table 1). Since then, emerging agents have enhanced the SjD treatment armamentarium with promising results.

Since SjD pathogenesis is remarkably complex, multiple molecular targets have been identified (Fig. 1). The implicated mechanisms include, among others, suppressing B-cell survival, proliferation and differentiation by attacking pertinent cytokines such as BAFF and APRIL, as well as their receptors, hindering B and T-cell interaction by inhibiting co-stimulatory molecules (CD40 and CD40 ligand, CD80/86), blocking intracellular signal transduction (JAK/STAT and BTK pathways), and reducing circulating pathogenic autoantibodies by preventing their recycling via FcRn. Combining anti-CD20 and anti-BAFF agents results in amplified B-cell depletion, probably due to the capacity of the former to induce B-cell depletion and of the latter to maintain it [6▪]. Several treatments failed to prove efficacy, while for others clinical testing was interrupted due to safety issues [46,47]. Some targeted therapies, however, demonstrated effectiveness in reducing systemic disease activity to preliminary study findings. Among these belimumab (BAFF inhibitor), ianalumab (BAFF receptor inhibitor), iscalimab (CD40 blocker), dazodalibep (CD40-ligand blocker), remibrutinib (BTK inhibitor), telitacicept (BAFF and APRIL blocker), and nipocalimab (FcRn blocker) reached the primary endpoints, yet larger, confirmatory trials are needed for drug efficacy validation [48–54]. Regarding the study outcomes, belimumab alone achieved a statistically significant reduction in the ESSDAI and ESSPRI scores from baseline at week 52 in the placebo-controlled BELISS study [48]. In addition, in

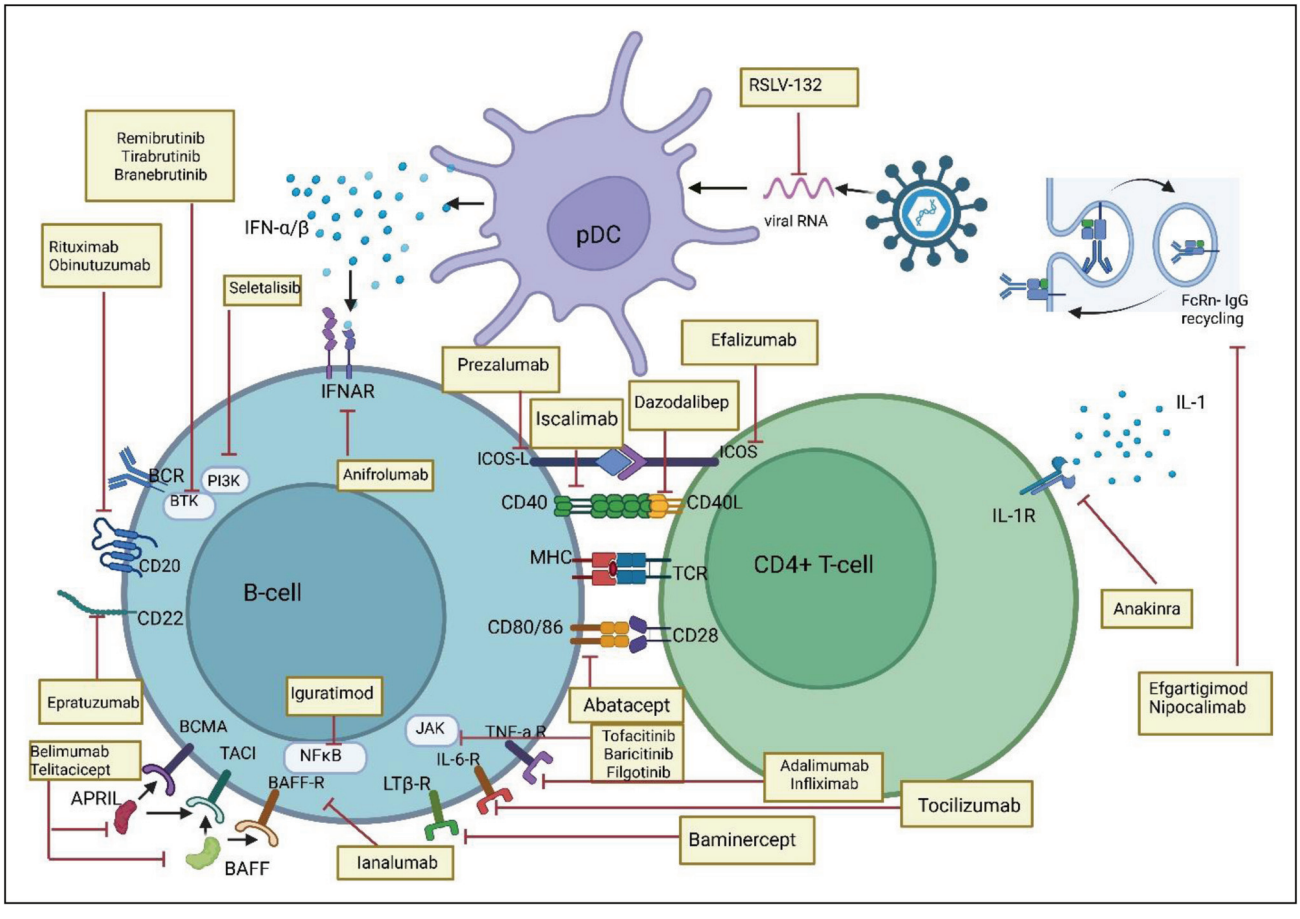

FIGURE 1. Current and prospective therapeutic targets [24▪▪]. Created in https://BioRender.com.

another randomized trial, sequential belimumab and rituximab administration resulted in great B-cell depletion in minor salivary glands and peripheral blood compared to placebo [55]. Ianalumab also achieved a significant dose-related reduction in ESSDAI over a 24-week period, likely due to its dual action of inhibiting B-cell maturation and inducing B-cell depletion [49]. Telitacicept was shown to be effective in reducing both ESSDAI and ESSPRI scores over a 24-week period, in a dose-dependent manner [52]. A randomized trial evaluating the efficacy of dazodalibep demonstrated a significant reduction in ESSDAI at week 24, in patients with moderate-to-severe disease activity, while a significant reduction in ESSPRI was observed in patients with a high symptom burden but limited organ involvement [54]. Intravenous but not subcutaneous administration of iscalimab also succeeded in significantly reducing the ESSDAI compared to placebo after 12 weeks [50]. Nipocalimab achieved the primary endpoint of the DAHLIAS study, which was a significant reduction in the clinically-assessed ESSDAI score at week 24, along with a notable decrease in circulating antibodies, a finding consistent with its mechanism of action [53]. Among BTK inhibitors, remibrutinib is the only one to show statistically significant results, demonstrating a reduction in ESSDAI but not in ESSPRI at week 24 [51]. Lastly, RSLV-132, which acts against viral RNA, that is a key activator of the innate immune response, and epratuzumab, which targets CD22, a B-cell marker, both demonstrated significant improvements in fatigue assessment scores [56,57].

CONCLUSION

Both the diagnostic assessment and therapeutic approach of SjD persist as a challenge. Current diagnostic strategies have improved the rigorous evaluation of SjD, minimizing the need for invasive procedures and aiding in the detection of high-risk disease subtypes. Regarding therapy, despite the emergence of targeted treatments, SjD management has not changed significantly recently, as only a few studies have demonstrated clinical improvement. Nonetheless, late insights into the disease's underlying pathophysiology have facilitated the development and selection of appropriate agents, not only providing symptom relief but also attenuating systemic disease activity.

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Conflicts of interest

There are no conflicts of interest.

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