Clinical manifestations, imaging and treatment of Sjögren's disease: one year in review 2025

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Received on September 11, 2025; accepted on September 30, 2025.

Clin Exp Rheumatol 2025; 43: 2007-2019.

Key words: Sjögren's disease, extra-glandular, lymphoproliferation, imaging, therapy

Competing interests: none declared.

ABSTRACT

Sjögren's disease represents a complex systemic autoimmune disorder mainly driven by T and B lymphocytic infiltration of exocrine gland, activation of different signalling pathways and systemic cytokine production. These interacting pathogenic mechanisms may differently contribute to characterise highly variable phenotypic expression of the disease, ranging from an asymptomatic, indolent course with only glandular involvement to several extra-glandular systemic manifestations. Moreover, approximately 5–10% of patients develop lymphoproliferative disease, with an overall risk reported to be up to 48 times higher in comparison to healthy population. Due to the substantial clinical heterogeneity of the disease, in recent years, research focused to investigate biomarkers able to identify distinct subtypes of Sjögren's disease, facilitate earlier patient recognition and homogenise patient subgroups in clinical trials aiming to develop tailored therapies. Surely, a more detailed understanding of pathogenetic mechanisms and recognition of different disease phenotypes may facilitate earlier diagnosis, enable recognition of patient clusters and suggest novel therapeutic modalities to address the unmet needs of the disease in the upcoming years. In this review, following the others of this series, we will update the most recent literature on Sjögren's disease focusing in particular on new insights into clinical stratification, imaging techniques and targeted therapeutic advances.

Introduction

The high variability and the different severity of clinical expression among patients with Sjögren's disease (SjD) represent a significant unmet need. To overcome this issue, in recent years, research specifically focused on the investigation and analysis of possible molecular, proteomic, clinical and serologic variables able to identify well distinct and specific disease clusters. In particular, these different stratification approaches aimed to address the clinical heterogeneity of the disease, based on both patient-reported symptoms and clustering according to molecular profiles, and to identify patients at increased risk of lymphoproliferative disorders and specific comorbidities. The expanding research on mechanisms underlying disease pathogenesis and the identification of specific proteomic and molecular pathways through transcriptome profiling represented important steps toward the development of targeted therapies for patient subgroups. This led to the recent development of several clinical trials addressing specific emerging pathways of the disease. Despite many of these trials failed to meet their primary outcomes, which may be in part due to the use of study endpoints focused on one specific aspect of SjD or to the short trial duration, recent therapeutic approaches focusing on B cells, B-T cell interactions and interferon-signalling have shown encouraging outcomes in this highly heterogeneous disease. Following previous series, in this review we will provide an update of the most recent literature on the disease, particularly focusing on new insights into glandular and extra-glandular manifestations, mechanisms underlying the lymphoproliferative risk and into recent developments in the diagnostic and prognostic role of innovative imaging techniques. Finally, in the era of precision medicine, the most recent trials will be critically analysed, trying to highlight potential pitfalls which may explain the failures of some systemic therapies.

Glandular involvement

Sjögren's disease (SjD) is a chronic, systemic autoimmune disorder primarily targeting the exocrine glands, particularly the salivary and lacrimal glands (1). The hallmark glandular involvement leads to xerostomia and keratoconjunctivitis sicca, resulting from lymphocytic infiltration and gradual destruction of glandular tissue. Indeed, oral and ocular dryness are typically considered together as hallmark symptoms of SjD. However, Chatzis *et al*. questioned whether these manifestations might represent distinct clinical phenotypes within the SjD spectrum (2). In a large multicentre study involving 1,765 patients, clinical characteristics of individuals presenting with isolated ocular or oral dryness were investigated. Isolated ocular dryness was associated with a lower risk of lymphoma and less frequent salivary gland enlargement, while isolated oral dryness correlated with older age at diagnosis and fewer joint symptoms (2). These results, in accordance with recent advances in disease phenotyping, suggest the presence of distinct clinical subsets in SjD, potentially reflecting divergent pathogenetic pathways. Surely, prolonged hyposalivation in these patients significantly compromises oral function, manifesting in difficulties with speech, mastication and swallowing and predisposing individuals to increased risk of dental caries, erosion, periodontitis and oral infections, as candidiasis and angular cheilitis. Moreover, as recently confirmed in a systematic review and meta-analysis, the glandular impairment and discomfort in SjD patients, especially reduced salivary flow, is strongly associated with a significant decline in oral health-related quality of life (OHRQoL) in comparison to healthy controls (3).

Dry eye disease (DED) represents another prevalent manifestation in patients with SjD and increasing evidence suggests that pro-inflammatory cytokines in the tear film may play a contributory role in its pathogenesis. These inflammatory mediators appear to be involved in ocular surface alterations observed in both SjD-related DED (SjD-DED) and non-SjD-DED. A recent meta-analysis by Li *et al*. quantitatively compared tear cytokine profiles across patients with SjD-DED, non-SjD-DED and healthy controls. The results demonstrated a distinct cytokine signature in SjD-DED patients, characterised by significantly elevated levels of interleukin (IL)-6, IL-8, IL-17, IL-4, IL-12p70 and tumour necrosis factor (TNF)-α, in contrast to both non-SjD-DED individuals and healthy subjects. These findings underscore a more intense inflammatory milieu in SjD-DED and suggest that tear cytokine profiling may be employed as potential diagnostic or therapeutic biomarker to improve clinical and therapeutic management of these patients (4).

Surely, salivary gland biopsy (SGB), particularly of the minor salivary glands, represents a pivotal diagnostic tool for patients with SjD. Although minor SGB is a minimally invasive surgical procedure that is relatively simple and safe to perform, it can be associated with postoperative complications such as lip paraesthesia, pain, bleeding and local swelling. To overcome this issue, recently Li *et al*. proposed the use of auxiliary devices to enhance procedure security, specifically the implementation of chalazion forceps, in a prospective randomised controlled study. Compared to patients who underwent conventional minor SGB, those in whom chalazion forceps were used experienced smaller incisions, reduced bleeding, shorter operative time, less postoperative pain and improved wound healing at 7 days, with high and comparable diagnostic accuracy between the two techniques (5). Surely, in clinical practice, a major unmet need in the interpretation of SGB biopsy is the risk of calculation errors and inter-observer erroneous evaluation of the focus score (FS), a tool traditionally used for diagnostic purposes often misapplied, especially when other histopathological changes coexist. Moreover, FS is not exclusively found in SjD patients but can also be present in healthy individuals and patients with human immunodeficiency virus infection or various autoimmune diseases. Additionally, some SjD patients may exhibit a FS less than the cut-off of 1, age and seropositivity may influence the lymphoid composition of the lymphocytic foci and a considerably high prevalence of focal lymphocytic sialadenitis may be detected in minor SGs of non-SjD individuals (6, 7). Surely, pathological characterisation of salivary glands provides information that go beyond a mere diagnostic or classification utility, providing insights for a stratification of disease severity and for predicting systemic manifestations, thus suggesting that SGB should be included in routine practice, even when not strictly required for diagnostic purposes (8). For these reasons, recent studies have attempted to improve the diagnostic accuracy of minor SGB. Van Ginkel *et al*. investigated the diagnostic capability of multiple histopathological features in addition to FS, such as pre-lymphoepithelial and lymphoepithelial lesions (pre-LELs and LELs), the relative increase in the number of immunoglobulin G plasma cells (the so-called 'plasma cell shift') and the presence of germinal centres (GCs) in 103 patients with suspected SjD. The combination of at least two of these histological features was found to increase specificity to 100% without significantly reducing sensitivity (from 82% to 79%) (9). Furthermore, incorporating at least two of these features into the ACR/EULAR classification criteria (10), increased specificity to 95% with only a minimal reduction in sensitivity. A recent immunohistochemistry characterisation of GCs (with Bcl-6 for B cells, D2-40 for follicular dendritic cells, CD57 to label follicular helper T lymphocytes and Ki-67 to show cell proliferation) in minor SGB of subjects with sicca syndrome demonstrated that GCs can also be depicted in non-autoimmune conditions, as in cases of chronic inflammation (11). However, in SjD, GCs are larger, more active and display stronger immunological markers. Thus, markers like D2-40 and CD57, alongside Bcl-6 and Ki-67, can help better understand and differentiate SjD from other conditions, improving diagnostic accuracy (11).

All these histopathological changes can be demonstrated in both the minor and major SGs; however, it remains unclear whether these changes occur simultaneously in both gland types. To

discern differences in the histological characteristics between labial and parotid SGBs, Nakshbandi *et al*. concurrently biopsied both glands in patients presenting with ocular and/or oral sicca syndrome (12). Interestingly, both minor glands and the parotid gland exhibited comparable histopathological features concerning FS, GC, LELs and plasma cell isotype, suggesting that both glandular sites can be utilised for SjD diagnosis and classification. Nevertheless, minor SGs frequently display a greater percentage of lymphocytic infiltrates compared to parotid glands, a phenomenon observed both in SjD patients and in non-SjD sicca syndrome subjects (12). Conversely, parotid glands demonstrate enhanced B lymphocyte hyper-reactivity in labial glands (12). Beyond its role in diagnosis, minor SGB can also offer prognostic insights. In this setting, patients with a higher proportion of T lymphocytes within the lymphocytic infiltrates appear to face a two-fold elevated risk of experiencing severe disease flares (6). Conversely, the number of B cells and CD4+ T cells demonstrated a weak, yet positive, correlation with improvements in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) over the follow-up (6).

Take home messages

- Tear cytokine profiling reveals a distinct pro-inflammatory signature in SjD-DED (4).
- The use of chalazion forceps in minor SGB may improve patient outcomes, reducing pain, bleeding and healing time without compromising diagnostic accuracy (5).
- Refinements in salivary gland histopathology, such as incorporating additional features (pre-LELs, LELs, plasma cell shift, germinal centres) and using immunohistochemical markers (*e.g*. Bcl-6, D2-40, CD57, Ki-67), can enhance the diagnostic specificity of minor SGB for SjD (8, 10).
- A higher proportion of T cells in minor SGB infiltrates is associated with increased risk of disease flares, supporting the potential prognostic utility of biopsy-based immune profiling (6).

Extra-glandular involvement

The complex pathogenetic background of the disease may account, at least in part, for the high heterogeneity of SjD extra-glandular manifestations. Among the most commonly affected extra-glandular sites, involvement of pulmonary system represents one of the most frequent systemic manifestations, with interstitial lung disease (ILD) being one of the most severe complications. A recent monocentric study conducted on more than 400 SjD Italian patients confirmed that ILD develops in approximately 9% of SjD patients (13). Moreover, male sex, Raynaud's phenomenon and high disease activity at baseline, particularly in the biological domain, were identified as significant risk factors for ILD development (13). While ILD remains the most extensively explored pulmonary manifestation in SjD, recent data have also shed light on SjD-associated airway disease, which can manifest as bronchiectasis, bronchiolitis or bronchial hyperreactivity. In a study by Leudec *et al*., SjD-associated airway disease was more frequently observed in patients with high disease activity, mainly in the biological domain, and predominantly involving both proximal and distal airways, with progressive extension observed in almost 41% of cases but without evolution to ILD during follow-up (14).

Together with respiratory system, manifestations related to peripheral and/or central nervous system involvement represent a major challenge in these patients, due to the variable and non-specific symptomatic appearance and to the intrinsic diagnostic limits. In this regard, previous case reports and case series empirically described signs and symptoms related to dysfunction of the eighth cranial nerve. To deeper characterise this association, Yang *et al*. used the Taiwan's National Health Insurance Database to explore a retrospective cohort study of 20,266 individuals with SjD and 60,798 matched controls (15). The study confirmed that SjD are characterised by a significant higher prevalence of auditory and vestibular disorders, including hearing loss, tinnitus, vertigo and sudden sensorineural hearing loss, in comparison to controls, suggesting that careful audio-vestibular assessment may be considered in SjD patients (15). Similarly, an area poorly explored and limited to few literature case reports is the possible association between SjD and immune-mediated thrombotic thrombocytopenic purpura (iTTP). To overcome this issue, a recent retrospective cohort study compared 30 iTTP-SjD patients to 65 SjD and 45 idiopathic iTTP patients. In comparison to SjD cohort, iTTP-SjD patients were predominantly female, with younger age at SjD diagnosis and higher prevalence of anti-SSA and xerostomia, with no differences on disease activity (16). However, no significant differences in terms of severity, prognosis or relapse rates between iTTP-SjD and idiopathic iTTP patients (16).

As a disease almost exclusively affecting the female sex, SiD has a non-negligible impact on gynaecological and obstetric health with potential effects on hormonal balance, sexual and reproductive function as well as pregnancy and maternal-foetal well-being. A recent meta-analysis aimed to explore the impact of SjD on both maternal and foetal outcomes during pregnancy demonstrated an increased risk of different adverse maternal outcomes, including pregnancy hypertension, preeclampsia/eclampsia, increased risk of thromboembolic disease and premature rupture of membranes and a higher likelihood of caesarean section (17). Beyond maternal health, a significant higher incidence of premature births, low birth weight infants and overall lower live births were also demonstrated (17). Immunological factors are recognised as crucial contributors to female infertility, a connection that has garnered increasing attention in recent years. Extensive research consistently highlights a strong association between reproductive failures and autoimmune diseases. A recent retrospective study assessed the impact of SjD on oocyte and embryo competence, ovarian reserve, clinical and obstetric outcomes. Researchers recruited 47 SjD patients and 141 controls undergoing *in vitro* fertilisation/intracytoplasmic sperm injection (18). Compared to infertile women without SjD, those with SjD had com-

promised oocyte and embryo viability and a reduced ovarian reserve, resulting in inferior IVF success rates. Additionally, SjD patients demonstrated compromised oocyte and embryo development across key stages including oocyte retrieval, maturation, embryo cleavage and blastocyst formation (18). Similarly, potential shared immunepathogenic mechanisms may underlie the association between endometriosis and different autoimmune diseases. A population-based cohort study investigated the association between endometriosis and SjD, revealing that patients with endometriosis had a significantly increased risk of developing SjD and, conversely, patients with SjD showed a significantly higher risk of developing endometriosis (19). The risk of developing endometriosis in SjD patients was lower in those receiving corticosteroids or oral contraceptives (19).

Comorbidities may significantly impact the disease prognosis and long-term management. In this setting, research evidence confirmed the close association between SjD and coeliac disease, with a pooled prevalence of biopsy-confirmed celiac disease in SjD patients of about 6%, substantially higher than in the general population (~0.7%) and strongest in comparison to other systemic autoimmune disease (20). These findings highlight a possible link between the two diseases, likely driven by shared genetic susceptibility, mucosal immune dysregulation and systemic immune activation. Moreover, the evidence of gut microbiota dysbiosis in SjD, characterised by an increased abundance of pro-inflammatory bacteria (such as Proteobacteria) and a depletion of anti-inflammatory microbes, particularly short-chain fatty acid (SCFA)-producing bacteria such as *Ruminococcaceae, Lachnospiraceae, Faecalibacterium, Butyricicoccus, and Eubacterium hallii*, reinforces the hypothesis that molecular mimicry and antigens produced by the gut microbiota may promote gut microbiota-mediated autoimmune and inflammatory activities and that dysbiosis may play a key role in disease pathogenesis and manifestations (21).

Cardiovascular (CV) comorbidity is now considered an extra-glandular manifestation of the disease and a recent meta-analysis of 19 observational studies comprising 1625 patients confirmed its association with an increased risk of subclinical atherosclerosis in comparison to healthy subjects (22). Interestingly, disease duration and systemic inflammation strongly contribute to this risk (22). At molecular level, a prospective study on 199 SjD patients investigated the potential role of microRNAs (miRNAs) as biomarkers for atherosclerosis in SjD (23). Significantly reduced levels of endothelial-protective miRNAs, specifically miR-126-3p, miR-143-3p, and miR-204-5p, were detected in SjD patients and miR-92a, a miRNA associated with cellular inflammation and atherosclerosis, was found to correlate with increased carotid intima-media thickness (23). However, despite CV disease represents a major contributor to adverse prognosis in these patients, a retrospective observational study using the US Nationwide Inpatient Sample demonstrated that SjD patients hospitalised for acute myocardial infarction exhibited significantly improved in-hospital outcomes compared to matched controls (24), in particular for lower risk of in-hospital mortality, cardiogenic shock and cardiac dysrhythmias. The findings, while counterintuitive, deserve deeper analysis and may reflect closer medical surveillance, better chronic disease management and the potential CV benefit of immunomodulatory therapies used in this population (24). However, despite a global favourable survival rate (98.2% at 5 years, 93.8% at 10 years), with deaths mainly attributed to comorbidities, primarily circulatory disease, malignancy and infections, ILD and pulmonary arterial hypertension represent disease-specific causes of increased mortality which require strict awareness (25, 26). Male sex, glucocorticoid use, high disease activity and organ damage, particularly interstitial fibrosis, emerged as significant predictors of mortality (26).

Surely, the average diagnostic latency of about 6 years and the variable disease clinical expression significantly contribute to the failure of current diagnostic and therapeutic approaches in capturing this complexity (27). In this context, patient stratification may improve disease understanding and guide personalised management. In recent period, the identification of different clusters of the disease, characterised by peculiar and distinct disease activity, autoantibody profiles, organ involvement and blood transcriptomic signatures, allowed to unveil clinical and molecular disparities and distinct pathobiological endotypes (28). These findings, which require further validation through tissue analysis, underscore the importance of precision medicine in improving patient outcomes.

Take home messages

- Male sex, Raynaud's phenomenon and high disease activity at baseline, particularly in the biological domain, are risk factors for ILD development in SjD (13).
- Auditory and vestibular disorders are significantly more prevalent in SjD, highlighting awareness about possible eighth cranial nerve involvement in these patients (15).
- SjD significantly impacts female reproductive health, being associated with adverse pregnancy outcomes, increased risk of infertility due to impaired oocyte and embryo viability, and a bidirectional link with endometriosis (17-19).
- Despite an increased cardiovascular risk, partly driven by pro-atherogenic microRNAs, patients with SjD hospitalised for AMI demonstrate favourable in-hospital outcomes, probably reflecting closer problem awareness (24).
- While long-term survival in primary SjD remains high, all-cause mortality is increased, primarily driven by comorbid conditions and severe organ involvement, with specific clinical and serologic predictors identifying high-risk patients (26).

New insights in lymphoproliferative risk

Lymphoma is a major complication and a leading cause of mortality in SjD (29). Over the past year, most literature focused on the use of patient clustering approaches to identify biomarkers predictive of lymphoproliferative compli-

cations and to facilitate their early detection. Additional insights have addressed the ongoing challenges in lymphoma diagnosis and the therapeutic management of SjD-associated lymphomas.

Epidemiology and patient clusterisation

The association between SjD and the risk of non-Hodgkin's lymphoma (NHL) was confirmed in a systematic review and meta-analysis of 15 studies, encompassing a total of 50,308 subjects over a time span from 1997 to 2023. By combining risk measures and assessing heterogeneity, the Authors confirm a statistically significant relationship between SjD and NHL [8.78 (95% CI 5.51, 13.99)], further detailed using SIR [10.50 (95% CI 7, 15.75)], HR [2.82 (95% CI 1.28, 6.18)], and OR [10.50 (95% CI 3.04, 36.28)]. NHL risk decreased with age progression (30).

Building on the well-established link between SjD and lymphomagenesis, the development of an effective patient stratification strategy to enhance diagnosis, guide management, and enable disease-modifying interventions remains one of the most pressing unmet needs in the field. In the last year, researchers have focused on the identification of distinct subgroups of SjD patients, applying cluster analysis based on subjective symptoms, clinical and biological manifestations, and comparing the prognoses across these subgroups. In this setting, a recent hierarchical cluster analysis applied to 534 patients form the Paris-Saclay cohort and to 395 patients from the ASSESS cohort revealed 3 distinct clusters of patients: those with B-cell active disease and low symptom burden (BALS); those with high systemic disease activity (HSA); those low systemic disease activity and high symptom burden (LSAHS) (31). Notably, incident lymphomas occurred exclusively in the BALS (3% of patients, diagnosed a median of 70 months after inclusion) and the HSA clusters (4% of patients, diagnosed a median of 23 months after inclusion), over a 15 year follow up. The later occurrence of lymphoma in BALS cluster than in the HAS cluster, together with the delayed onset of systemic symptoms, supports the interpretation of the BALS cluster as an earlier stage of the disease, potentially progressing towards a more systemic phenotype (HAS) (31).

Novel and traditional predictive biomarkers of lymphomagenesis

These differences in symptom evolution and in lymphoproliferative risk suggest underlying heterogeneous pathophysiologic mechanisms, including biomarkers predictors of lymphoma risk. In the ASSESS cohort, all lymphoma in the BALS cluster occurred in the presence of high INF signature, supporting its role as novel predictive biomarker (32). In a recent analysis of a harmonised dataset of SjD patients, rheumatoid factor (RF) was the earliest and most persistent independent predictor of MALT lymphoma (33). Moreover, a high level of disease activity, primarily driven by B cell related manifestations such as cryoglobulinaemia and glandular, cutaneous and haematological involvement, was observed earlier after SjD diagnosis, stimulating the clinicians to carefully consider these parameters during patients follow up (33).

To investigate other novel potential predictors of lymphoma, the expression of miR-155, BAFF-R, and IL-6R was assessed in baseline labial salivary gland biopsies from 24 SjD patients (5 of whom developed NHL during follow-up) and 20 sicca controls. miR-155 was upregulated in SjD patients, particularly in cases of NHL development. Notably, IL-6R and BAFF-R levels positively correlated with miR-155 expression, supporting a potential role of this axis in B-cell activation and lymphoproliferative evolution in SjD (34). Finally, IgG Fc Glycosylation has emerged as another possible predictor of disease activity and lymphoproliferative risk in SjD. In the Belgian BeSSTT cohort, lower serum IgG Fc sialyation and galactosylation levels were inversely associated with markers of B cell hyperactivation (*e.g.* RF, IgG, IgA, β2-microglobulin, and hypergammaglobulinaemia). Reduced glycosylation was also linked to more severe autoantibody profiles, particularly in triple-positive anti-Ro52/Ro60/SSB+ patients, and to more severe salivary gland involvement (higher Hocevar ultrasonography scores, FS≥1, increased CD20/CD3 ratios, presence of follicular dendritic cells) (35).

Challenges in lymphoma diagnosis

Although the previous findings are promising and may enhance our ability to predict lymphoproliferative complications in SjD, other Authors generally caution that the retrospective design of the studies, and lack of uniform diagnostic criteria of lymphoma may constrain the ability to draw definitive or broadly applicable conclusions on this matter (36).

In fact, lymphoproliferation in SjD represents an intrinsic, continuous, and progressive process, making the diagnosis of lymphoma particularly challenging. In this context, there is growing interest in identifying laboratory and histological features that may enhance diagnostic accuracy. In this last year, reports mainly supported the value of FCRL4 B cells and clonal IGH, IGK and IGL gene rearrangement detection as possible diagnostic positive markers for MALT lymphoma, useful to differentiate between other lymphoproliferative stages (36, 37).

While the repetitive screening ultrasounds (US) of major SGs and neck in asymptomatic patients has a limited role in detecting lymphoproliferative lesions by imaging nor specific SGUS features (*e.g.* SGUS scores, elementary lesions) may be detected during the imaging evaluation (38), a cross-sectional study of 57 SjD patients undergoing parotid biopsy for clinical indication evaluated the utility of SGUS (specifically Hoçevar and OMERACT) as adjunctive tools for lymphoma detection (39). While none of both scores effectively identified established lymphoma, regression analysis revealed significant associations between higher SGUS scores and histopathological markers of lymphoproliferative risk (*e.g.* lymphoepithelial lesions, elevated focus scores) in patients without lymphoma. These findings support the prognostic rather than diagnostic value of SGUS in SjD and highlight the need for prospective validation (39).

Evidence on the therapeutic management of lymphoma in SjD

Evidence-based reports focused on management of SjD associated lymphoma or at higher lymphoproliferative risks, offering interesting insights on the importance of choosing the appropriate therapeutic approach. A multicentre, retrospective observational study involving 106 SjD patients with lymphoma assessed treatment outcomes in terms of progression-free survival, new systemic disease activity and overall survival (40). In the marginal zone lymphoma subtype, first line systemic treatment was the most common choice over localised treatment and 'watch and wait' approach (61% *vs*. 13% *vs*. 23%). Of note, patients with systemic treatment at lymphoma diagnosis had a reduced risk of new SjD activity. In a 7-year follow up, lymphoma-progression-free survival was improved in patients treated with combination therapy (chemotherapy plus anti CD20 *vs*. monotherapy), while no differences in new SjD systemic activity or overall survival according to combination therapy or monotherapy were reported (40). Of note, the efficacy of obinutuzumab in 13 SjD patients immunised against rituximab (RTX) was recently reported. In the patient of the cohort complicated by MALT lymphoma obinutuzumab in association with bendamustin allowed complete haematological, rheumatological and radiological response at 6 months (41). However, prolonged maintenance with anti-CD20 RTX resulted more effective in comparison to other immunosuppressive therapy, delayed and/or on demand RTX treatment.in cutaneous, peripheral nervous system and articular manifestation in a monocentric cohort of SjD patients with cryoglobulinaemic vasculitis (42). Nonetheless, lymphoproliferative-related ESSDAI domains showed more limited improvement, and no difference in NHL occurrence was noted in a 10-year follow up (42).

To date, no clinical trial has specifically targeted SjD patients with established lymphoma. Nonetheless, promising evidence has emerged from a recent phase 2 trials of novel biological agents, which, beyond meeting their primary endpoints, have demonstrated favourable effects on B cell-related immunological activity, a key driver of lymphoproliferation in SjD. Dazodalibep, an anti-CD40L agent, significantly reduced levels of CXCL13 and RF (43). Iscalimab, an anti-CD40 monoclonal antibody, significantly reduced CXCL13 and serum free light chains (44). Telitacicept, a recombinant fusion protein targeting BLyS and APRIL, decreased immunoglobulin levels while increasing serum C4 (45). Remibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, consistently lowered CXCL13 and disease-related autoantibody titres and favourably modulated IgG and IgM levels. Additionally, transcriptomic and proteomic analyses revealed that remibrutinib downregulated genes involved in immunoglobulin production and B cell activation (*e.g*. FCLR5, SOX5, SYNPO, TNFRSF17), as well as proteins implicated in B cell activation, T cell co-stimulation, and inflammatory responses (*e.g*. FCLR4, FCER2) (46).

These findings underscore the need to improve the management of lymphoma in SjD, beginning with the standardisation of clinical activity and relapse assessment specific to SjD-associated lymphomas. Equally important is the selection of the most appropriate therapeutic regimen, tailored to the patient's biological and clinical profile. In parallel, ongoing research should focus on strategies to delay or prevent lymphoproliferative evolution, a key feature of the disease. Long-term follow-up and further studies are essential to clarify the efficacy of emerging therapeutic agents in modulating lymphoproliferation in SjD.

Take home messages

- Recent clustering approaches (*e.g*. BALS and HSA clusters) identify patient subgroups with distinct immunological profiles and lymphoma risk (31).
- Biomarkers such as RF, miR-155, CXCL13, and Fc glycosylation profiles provide early predictive signals of lymphoproliferative evolution (34, 35).
- SGUS, especially Hocevar and OMERACT scores, shows limited specificity for lymphoma diagnosis. However, they may reflect histological changes in patients at high risk, supporting its prognostic utility in longitudinal monitoring (39).
- Systemic therapy at diagnosis and combination regimens (anti-CD20+ chemotherapy) improve progression-free survival (40).
- Early rituximab induction and maintenance in cryoglobulinaemic vasculitis-SjD is more effective than delayed regimens in lowering systemic activity, but not in preventing lymphoma development (42).
- Novel biologics, such as dazodalibep, iscalimab, telitacicept, and remibrutinib, modulate key lymphoma-related pathways (*e.g*. CXCL13, IgG/IgM, BAFF/APRIL, IFN signature) and represent promising tools for future prevention and intervention strategies (43-46).

The role of imaging in SjD: an update

Salivary gland ultrasonography: the cornerstone of SjD imaging

The most substantial body of evidence concerns SGUS, which has been established as a central tool in the diagnosis of SjD. Multiple studies have confirmed the high diagnostic accuracy of grayscale SGUS (47, 48). A recent meta-analysis reported a sensitivity of 0.86 (95%CI: 0.74–0.92) and specificity of 0.87 (95% CI: 0.81–0.92) for the predictive value of SGUS compared with labial SGB as the reference standard (49). Construct validity of the OMERACT semi-quantitative scoring system was further evaluated by comparing SGUS with magnetic resonance imaging (MRI) and unstimulated whole salivary flow rates (U-WSFRs) in 11 patients with SjD. Agreement between OMERACT SGUS (applied by 9 sonographers) and MRI scores (evaluated by 2 radiologist) ranged from 73-91% (median 82%) in the right parotid gland (PG) and 73-91% (median 91%) in the left PG, while lower agreement was noted in the submandibular glands (SMG). Examination of hyposalivation in relation to SGUS scores ≥2 showed agreement rates of 91–100% (median 83%) for PGs and 55–91% (me-

dian 67%) for SMGs. This moderate to strong agreement of OMERACT SGUS with MRI findings and the presence of hyposalivation supported its construct validity (50).

Incorporating SGUS into the 2016 ACR/EULAR classification criteria extends the diagnostic options in patients suspected with SjD. In a large retrospective cohort of 419 patients from the diagnostic trajectory, ROC analysis of the highest SGUS OMERACT score per patient (range 0–3) demonstrated good accuracy (AUC 0.85) to predict clinical diagnosis of SjD, comparable to the total OMERACT (range 0–12; AUC 0.87) and Hocevar scores (range 0–48; AUC 0.8). When incorporating the highest SGUS OMERACT score (cut-off ≥2) as additional item in the ACR/EULAR criteria, the accuracy remained excellent (AUC 0.97), with sensitivity of 96.4% and specificity of 86.5% (51).

Moreover, SGUS can differentiate SjD from other causes of sicca symptoms. SGUS findings between 34 patients with SjD and 34 patients with diabetes mellitus with sicca were compared in a total of 272 glands. SjD patients had significantly higher SGUS scores than diabetes mellitus patients using both the Hocevar (20.93±9.65 *vs*. 3.82±3.71; $p<0.05$) and OMERACT scoring systems (5.96±2.30 *vs*. 2.07±1.65; $p<0.05$). In SjD patients, bilateral submandibular glands were significantly more commonly involved than the ipsilateral parotid glands. Contrarily, in diabetic patients with sicca, the parotid glands were significantly affected more than the submandibular glands (52).

Similarly, a nomogram based on SGUS demonstrated favourable predictive performance in differentiating immunoglobulin G4-related sialadenitis (IgG4-RS) from SjD. The LASSO regression algorithm was applied to identify the most relevant clinical features and SGUS parameters. The final model incorporated clinical variables (sex, xerostomia and salivary gland enlargement) together with SGUS scoring parameters (parotid and submandibular gland US scores). This nomogram achieved excellent discriminatory ability, with AUCs of 0.95 in the training cohort and 0.96 in the validation cohort. Decision curve analysis further confirmed its clinical utility (53).

Reliability exercises have also demonstrated the reproducibility of SGUS. With standardised training, including web-based modules, 14 sonographers achieved good inter- and intra-observer agreement for SGUS using greyscale imaging (B-mode). Among less experienced sonographers, reliability was moderate to almost perfect for homogeneity, fair to moderate for OMERACT scoring, and fair to almost perfect for binary OMERACT scoring. Inter-reader reliability between highly experienced ultrasonographers was almost perfect for homogeneity, substantial for diagnosis, moderate for OMERACT scoring, and substantial for binary OMERACT (54).

Another study analysed the intra-observer and inter-observer reliability of colour Doppler (CD) SGUS performed by two experienced observers, one lesser experienced resident and one inexperienced trainee in 100 patients clinically suspected for SjD. The study showed that intra-observer weighted Cohen's kappa's of individual glands ranged from 0.23 (inexperienced observer) to 0.81 (experienced observer). Intraclass correlation coefficients (ICCs) for intra-observer reliability of the total CD score ranged from 0.53 (inexperienced observer) to 0.90 (experienced observer). The ICC for intra-observer reliability of live scoring compared to static images was 0.72. ICCs for inter-observer reliability of the total CD score were 0.81 for session 1 and 0.71 for session 2. The authors concluded that CD SGUS is a reliable imaging technique to visualise intraparenchymal vasculature in patients suspected of SjD, being a potential asset in daily clinical practice but requiring experience and prior training (55).

Beyond diagnosis, SGUS showed relevant associations with clinical and biological markers in 112 patients with SjD. Hocevar score correlated inversely with unstimulated whole salivary flow and positively with inflammatory biomarkers, including IL-6 and β2-microglobulin. SGUS findings also correlated strongly with ESSDAI and focus scores (56).

A stratification model for staging salivary gland hypofunction using SGUS was proposed by Huang *et al*. (57). Low total OMERACT scores (<5) indicated early-stage dysfunction, while high scores (>9) suggested end-stage disease. Intermediate scores (5-9) required further stratification with total gland scores. Patients with early-stage disease demonstrated significantly lower rates of lacrimal gland involvement and hypergammaglobulinaemia compared with more advanced stages.

In the context of lymphoma detection, the current SGUS scores were not able to identify lymphoma in 57 SjD patients with high clinical suspicion. However, regression analyses in high-risk patients without lymphoma diagnosis revealed significant associations between SGUS scores and advanced histopathological features, including lymphoepithelial lesions and focus scores, suggesting potential prognostic applications for SGUS beyond diagnosis (39).

Ultrasound elastography: quantifying tissue stiffness

Ultrasound elastography (USE) has emerged as a valuable complement to B-mode SGUS, as it enables quantitative assessment of tissue stiffness. In a recent meta-analysis, USE demonstrated a pooled sensitivity of 0.80 (95% CI: 0.71–0.87) and specificity of 0.87 (95% CI: 0.78–0.92) for the diagnosis of SjD. Meta-regression and subgroup analyses identified shear wave elastography technique, measurement site and patient age as significant contributors to study heterogeneity, with diagnostic performance being notably higher in patients aged ≤51 years compared to patients aged >51 years (58). Consistently, a systematic review confirmed the high diagnostic accuracy of USE when comparing patients with SjD to healthy controls (59).

Of note, the utility of USE in distinguishing patients with SjD from healthy individuals was confirmed in a recent study while no statistically significant difference was observed between isolated SjD and associated SjD groups (60). In this study the diagnostic performance of SGUS alone yielded an AUC of 0.82 (95% CI: 0.73–0.89). When

SGUS scores were combined with USE values, diagnostic accuracy was slightly enhanced (AUC: 0.88, 95% CI: 0.80–0.94).

Lastly, USE has been investigated as a potential tool for stratifying SjD patients. In one study, 134 patients were evaluated and classified into four groups based on anti-centromere antibody (ACA) and anti-SSA antibody (SSA) status: ACA^+/SSA^+, ACA^+/SSA^-, ACA^-/SSA^+, and seronegative. In the double-positive group (ACA^+/SSA^+), USE demonstrated fewer minor salivary glands, along with significantly higher mean (Emean) and maximum (Emax) values of Young's modulus compared to ACA-negative groups. Clinically, ACA-positive patients exhibited increased frequencies of Raynaud's phenomenon, hepatic involvement and a higher incidence of malignancy. These findings suggest that ACA-positive patients display greater salivary gland stiffness on USE, reflecting more extensive glandular fibrosis and involvement (61).

Advanced and cross-sectional imaging: MRI and scintigraphy

Several additional imaging modalities provide detailed morphological and functional insights into salivary gland involvement in SjD. A nomogram incorporating SGUS, MRI and MR sialography (MRS) was developed to guide decisions regarding labial SGB in 181 suspected SjD subjects. In the training cohort, SGUS, MRI, and MRS scores were significantly higher in LSGB-positive than LSGB-negative patients (all $p<0.001$). The positive predictive value was 91% for an SGUS score of 3 and 82% for MRI and MRS scores ≥2. The nomogram demonstrated excellent discrimination (C-index =0.94) and good calibration (Hosmer-Lemeshow $\chi^2=3.17$, $p=0.92$) for the prediction of LSGB results (62).

In a recent study, the diagnostic utility of machine learning models based on MRI radiomics for detecting early parotid gland injury was evaluated in 164 SjD patients and 82 healthy controls. Radiomics is the extraction and analysis of quantitative, high-dimensional data from medical images (like CT, MRI, and PET) to uncover patterns not visible to the naked eye. This data, in the form of radiomic features describing shape, texture and intensity, is used with artificial intelligence to improve disease diagnosis, predict treatment response and guide personalised therapy. A radiomics score (Radscore) was developed demonstrating significant differences between SjD patients and healthy controls. Compared to Radscore alone, the inclusion of machine learning models significantly improved the diagnostic performance for early pSS parotid gland damage (63).

Finally, the diagnostic value of scintigraphy was evaluated in a retrospective study of 142 sicca syndrome patients. Significant correlations of scintigraphy were found with USFR and lymphocytic infiltration on labial SGB. Incorporation of scintigraphy parameters into the 2016 ACR-EULAR classification criteria improved the diagnostic performance to distinguish SjD from non-SjD sicca, increasing the AUC from 0.93 to 0.95 (64).

Lacrimal gland ultrasound

The role of lacrimal gland imaging in SjD has received increasing attention, although its clinical utility remains uncertain. A recent systematic review and meta-analysis highlighted insufficient and heterogeneous evidence regarding the predictive value of radiological techniques for lacrimal gland involvement. Across 6 lacrimal gland ultrasonography (LGUS) and 3 lacrimal gland MRI (LGMRI) studies, affected glands consistently exhibited structural heterogeneity (65). On LGUS, glandular heterogeneity was associated with a markedly increased likelihood of involvement (OR:6.18; 95% CI: 3.31–11.55), whereas glandular hyper-echogenicity was not discriminatory. Data were insufficient to evaluate gland size, hypoechoic areas, fibrous bands or vascular parameters. LGMRI studies reported reduced apparent diffusion coefficients and heterogeneity as characteristic findings, though correlations with clinical features such as dry eye and Schirmer test values were inconsistent (65). In contrast, a separate systematic review and meta-analysis examining USE of lacrimal glands demonstrated superior diagnostic performance in diagnosing SjD (66). USE achieved a pooled sensitivity of 0.88 (95% CI: 0.77–0.94), specificity of 0.94 (95% CI: 0.88–0.98), and an AUC of 0.97 (95% CI: 0.95–0.98) (66).

Take home message

- SGUS has high diagnostic accuracy for SjD in daily clinical practice (47, 48).
- With standardised training and experience, grey-scale and CD SGUS show good inter- and intra-observer reliability, supporting its use as a reliable imaging tool in routine clinical practice (55).
- SGUS correlates with salivary flow, inflammatory biomarkers, systemic disease activity, and histopathology, offering clinically relevant insights and staging potential (56).
- USE enhances SGUS by quantifying gland stiffness with high diagnostic accuracy, particularly in younger patients, and demonstrates that ACA-positive patients exhibit greater fibrosis and glandular involvement (59-61).
- MRI radiomics and scintigraphy, enhanced by machine learning, can provide additional structural and functional information and improve diagnostic accuracy (63, 64).
- While LGUS and LGMRI primarily provide structural insights, USE may deliver superior diagnostic accuracy for detecting lacrimal gland involvement in SjD (66).

Update on the treatment of Sjögren's disease

Immunosuppressants

Despite a plethora of advancements in the treatment of many autoimmune diseases, SjD remains obstinately immune to any disease modifying therapies, leaving patients feeling helpless, healthcare providers challenged, and the healthcare system burdened economically. This resistance stems, in part from: i) the complex and only partially understood pathogenesis, which complicates drug development targets, ii) the wide heterogeneity in clinical phenotypes posing challenges in identify-

ing appropriate patient subgroups and selecting optimal clinical trial designs and outcome measures iii) the difficulty in interpreting treatment efficacy using standardised indices. Nonetheless, in recent years, significant progress has been made in addressing each of these challenges, bringing us closer to cutting through this long-standing Gordian knot. Positive results in ongoing phase III clinical studies will most probably signal the official authorisation of the first approved therapy for SjD in the near future. In this exciting new era, emerging therapies primarily, targeting B cells and their interactions with T cells, hold particular promise and warrant close monitoring (67).

Targeting B cells

B cell hyperactivity and dysregulation are hallmark features of SjD, as evidenced by an enriched autoantibody profile, likely driven locally, at sites of tissue damage through the formation of ectopic germinal centres. Consequently, B cell targeting therapies have been at the forefront of our treatment plans. B cells can be targeted through three primary mechanisms: (i) the selective elimination of specific B cell subsets; (ii) the functional inactivation of B cells; and (iii) the inhibition of cytokines critical for B cell activation, function, survival, and proliferation. Among the available therapies, the most extensive clinical experience has been gained with RTX (67). Although rituximab failed to meet its primary endpoints in the two largest randomised controlled trials (RCTs), the TEARS and TRACTISS trials, which administered one and two cycles of rituximab, respectively, it remains the cornerstone of treatment for patients with severe extra-glandular manifestations and systemic disease, as endorsed by current clinical guidelines (68). However, reanalysis of these trials using newer outcome measures, specifically, the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) and the Sjögren Tool for Assessing Response (STAR), revealed significantly higher response rates among RTX-treated patients compared placebo and patients classified as responders by STAR exhibited significantly higher baseline levels CXCXL13, IL-22, IL-17A, IL-17F, and TNF-α while CRESS response was more strongly associated with biomarkers reflective of salivary gland immunopathology (69). One of the main reasons for the loss of efficacy with RTX is the development of anti-drug antibodies. In cases of anti-RTX immunisation, obinutuzumab, a glycoengineered humanised anti-CD20 monoclonal antibody with enhanced antibody-dependent cellular cytotoxicity (ADCC), can be included in the therapeutic armamentarium for SjD, as recently demonstrated in 13 SjD patients with systemic complications (41). In the treatment of refractory autoimmune diseases, an increasingly promising approach is the broader and deeper depletion using CD19 CAR T-cell therapies (70). However, their application in SjD has so far been limited, likely due to concerns about potential severe adverse effects and the observation that SS-A/Ro antibody levels often remain stable even after CD19-targeted CAR T-cell therapy (71). To date, CD19 CAR T-cell therapy for SjD has only been explored in a case of disease-associated aggressive lymphoma, where encouraging outcomes have also coincided with improvement in underlying disease activity (72). A similar therapeutic benefit was observed in a case report involving a patient with AQP4-IgG-seropositive refractory neuromyelitis optica spectrum disorder, coexisting SjD, and immune pancytopenia by treatment with a novel humanised monoclonal antibody targeting CD19 (73). Of particular promise for SjD are bispecific T-cell engagers targeting BCMA, which may offer a safer and more effective alternative by circumventing some of the challenges mentioned previously. Notably, in the past year, teclistamab, a bispecific antibody targeting both BCMA and CD3, was administered to a patient with severe, treatment-refractory SjD. This resulted in a substantial clinical response, with ESSDAI score improving from 34 to 15 (74). However, as these findings are currently limited to single case reports, substantial and rigorous clinical research is required before any of these therapies can be considered suitable treatment options for the disease.

The second strategy for addressing B cell hyperactivity is through functional impairment. This approach underpinned the rationale for evaluating remibrutinib, a BTK inhibitor, in a randomised, double-blind, placebo-controlled phase 2 trial for SjD (46). BTK plays a pivotal role in B cell receptor signalling and the activation of Fc receptors for IgG and IgE. Its inhibition also exerts modulatory effects on macrophages and mast cells, thereby not only inactivating B cells but also altering the inflammatory microenvironment in a way that may be therapeutically beneficial. In this relatively small trial (approximately 25 patients per arm), the primary endpoint of change in the ESSDAI from baseline to week 24 was met (the same was observed using the STAR composite index). However, no significant changes were detected in the ESSPRI nor was there an increase in salivary flow. In addition, a dose-dependent analysis was not performed, leaving it unclear whether the observed benefits were driven by the high-dose or low-dose remibrutinib group. Safety wise remibrutinib was well tolerated and not associated with significant concerns, including liver enzyme elevations, which have been observed with other BKTis.

The third strategy for targeting B cells involves the inhibition of soluble trophic factors essential for B cell survival. In this context, a phase II randomised, double-blind, placebo-controlled trial evaluated the efficacy and safety of telitacicept a fusion protein that binds to the extracellular BLyS/APRIL-binding domain of the TACI receptor. By doing so, telitacicept simultaneously inhibits both BAFF and APRIL, two key survival factors for B cells. The study was limited in size, with only 14 patients enrolled per arm. Interestingly, clinical benefit was observed only in the low-dose telitacicept group, while the high-dose group did not demonstrate significant improvement compared to placebo (45).

Disrupting B and T-cell collaboration

Even though the backbone of most therapeutic strategies tested for SjD have focused solely on B targeting, in-

creasing attention has been directed in recent years toward the critical interplay between B and T cells, a process that, in SjD, appears to occur locally at the site of the aberrant autoimmune response, within the salivary glands (75). This bidirectional interaction extends beyond humoral immunity to cellular pathways, as evidenced by the role of CD40-expressing antigen-presenting cells in promoting T cell activation. Disrupting this pathogenic dialogue by targeting the CD40/CD40L signalling pathway emerged as a major focus of clinical research in SjD over the past year.

Two large and successful phase II studies targeting the CD40-CD40L axis from opposite ends were published in 2024, marking a paradigm shift in the clinical research landscape of SjD (43, 44). Dazodalibep, a non-antibody fusion protein that functions as a CD40L antagonist, and iscalimab, an Fc-silenced, fully human anti-CD40 monoclonal antibody, both demonstrated promising efficacy. Both trials were large, enrolling approximately 200 patients in the dazodalibep study and nearly 300 in the iscalimab trial. Additionally, a new study design was implemented allowing the inclusion of patients with high systemic disease activity and also those with low activity but a high symptom burden. This so-called 'umbrella study' design is particularly well-suited to heterogeneous conditions like SjD, designed to assess the efficacy of a treatment across multiple, mutually exclusive subgroups within a single disease. However, it is important to note that patients with low symptom burden and low disease activity were not included in these trials. Therefore, the findings cannot be generalised to this subgroup. In the high disease activity cohort (ESSDAI ≥5), both the iscalimab and dazodalibep trials demonstrated significant improvements in systemic disease activity. In the iscalimab trial, statistically and clinically meaningful reductions in ESSDAI scores were observed at doses of 150 mg and 600 mg ($p<0.005$) compared to placebo, while the 300 mg group showed a non-significant trend toward improvement (44). Similarly, in the dazodalibep trial, the mean change in ESSDAI from baseline in DAZ-treated participants was -6.3 ± 0.6, compared with -4.1 ± 0.6 in the placebo group, resulting in a least-squares (LS) mean difference of -2.2 ± 0.9 ($p=0.0167$) (43). Notably, in the second cohort, comprising patients with low systemic activity (ESSDAI <5) but high symptom burden (ESSPRI ≥5), dazodalibep also yielded clinically significant benefits. The change from baseline in the ESSPRI total score was -1.8 ± 0.2 in the treatment group compared with -0.5 ± 0.2 in the placebo group, corresponding to an LS mean difference of -1.3 ± 0.3 ($p=0.0002$). All domains of the ESSPRI (dryness, fatigue and pain) showed a similar decrease.

Focusing on T cells

Efforts to disrupt T cell activation in SjD have been explored through various approaches (76), with the most comprehensive and systematic attempts centred around abatacept. However, despite its mechanistic rationale, abatacept failed to demonstrate clinical efficacy in previous large randomised controlled trials. Moreover, it did not show any improvement at the histological level, only affecting the numbers of IgA plasma cells in the salivary gland tissue (77). An alternative strategy involves harnessing the regulatory properties of T cells. In this context, Lorenzon *et al*. conducted an open-label, phase 2a basket trial involving patients with 13 different autoimmune diseases, including SjD, to assess the effects of low-dose IL-2, a cytokine known to promote the expansion and activation of regulatory T cells (Tregs). In the 10 patients with SjD, IL-2 therapy led to a measurable increase in Treg numbers and activation status, accompanied by a trend toward improvement in both ESSDAI and ESSPRI scores (78).

Management of glandular dryness

Until any of the promising treatments currently under investigation proves its efficacy and effectiveness in SjD, the cornerstone of management remains the alleviation of dryness symptoms through systemic or topical therapies. Two muscarinic receptor agonists, pilocarpine and cevimeline, are licensed for the treatment of oral dryness, although only pilocarpine has global regulatory approval. A recent meta-analysis including 383 patients from eight randomised controlled trials evaluating pilocarpine confirmed significant improvement in oral mucosal dryness (79). However, ocular outcomes were mixed: while improvements were observed in the Bijsterveld's score and fluorescein 1% staining, no statistically significant benefits were seen in Schirmer's test or tear film breakup time (79). Similarly, another meta-analysis evaluating the efficacy of cevimeline, which included 302 patients from three RCTs, demonstrated benefits for oral dryness, however outcomes for ocular parameters were not reported (80).

Another agent with antioxidant, anti-inflammatory, and mucolytic properties, N-acetylcysteine, used anecdotally for the treatment of dryness symptoms in SjD, was evaluated in a double-blind, placebo-controlled trial involving 60 patients, but failed to show any benefit in either objective or subjective measures (81). Additionally, when it comes to topical treatments for ocular dryness, both autologous serum and platelet-rich plasma proved to be equally effective in patients with severe dry eye and persistent epithelial defects (82). In the same domain, a prospective, randomised trial involving 60 SjD patients with dry eye compared the use of intense pulsed light (IPL) therapy combined with 0.05% cyclosporine eye drops to treatment with 0.1% sodium hyaluronate eye drops (83). The combination therapy was associated with greater improvements in the Ocular Surface Disease Index, non-invasive tear breakup time, and Schirmer test among other scores. No safety concerns were reported. However, the study's conclusions are limited by the small sample size and the lack of a comparator group receiving CsA monotherapy, which prevents assessment of the additive effect of IPL therapy (83).

Traditional Chinese medicine

Given the limited treatment options currently available for SjD, a variety of alternative and traditional remedies, particularly in countries such as China, have been explored for their anti-inflammatory properties, effects on neu-

ral regulation and potential to alleviate disease symptoms. In recent years, several of these therapies have undergone more systematic evaluation, with varying results. However, the methodological quality of many of these studies remains suboptimal, limiting their reliability. Nevertheless, when used adjunctively with conventional treatments, some of these interventions may offer additional symptom relief (84). A recent propensity score matched study reported that total glucosides of paeony improved dryness symptoms and arthralgia in patients with SjD (85). In another uncontrolled study, a medicinal tea bag formulation (TBDESJS) was associated with enhanced tear production, reduced ocular dryness, and better sleep quality (86). In contrast, a more rigorously designed randomised controlled trial from Korea investigating Korean Red Ginseng found no significant improvement in fatigue levels (87).

Take home messages

- Two landmark phase II trials targeting the CD40–CD40L pathway, dazodalibep and iscalimab, have demonstrated significant efficacy in patients with SjD, particularly those with high systemic disease activity (43, 44).
- Dazodalibep reduced systemic activity and significantly improved patient-reported symptoms in those with low disease activity but high symptom burden, a population often overlooked in past trials (43).
- Remibrutinib, a BTK inhibitor, showed promising efficacy in reducing systemic disease activity in SjD by functionally impairing B cells and modulating the inflammatory environment, without the safety concerns seen with other BTK inhibitors (46).
- Obinutuzumab may offer an effective alternative for SjD patients who develop anti-drug antibodies to RTX, showing promise in treating systemic complications where RTX has failed due to immunogenicity (41).
- Combining intense pulsed light (IPL) therapy with cyclosporine A eye drops improved multiple dry eye parameters in SjD, though the specific contribution of IPL remains unclear and requires further exploration (81).

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