Review

Clinical manifestations, imaging and treatment of Sjögren's disease: one year in review 2024

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ABSTRACT

Sjögren's disease is a systemic autoimmune disorder characterised by hyperactivation of B-cells and cytokine production. The condition may evolve from an asymptomatic, indolent course, with glandular involvement, to several extra-glandular systemic manifestations up to lymphoma development. Recent efforts have been undertaken to identify patient phenotypes at the risk of developing specific extra-glandular manifestations in order to improve patient management. A more detailed understanding and characterisation of pathogenetic mechanisms, operating during the course of the disease, may facilitate earlier diagnosis, enable subphenotyping of patients 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 summarise the most recent literature on Sjögren's disease pathogenesis and clinical features focusing in particular on new insights into Sjögren's disease molecular stratification and therapeutic advances in the era of precision medicine.

Introduction

Sjögren's disease (SjD) represents a complex autoimmune disease characterised by a heterogeneous clinical picture and high variability of glandular and extra-glandular manifestations. Recently, research focused on the identification of specific disease clusters by proteomic stratification methods to address the clinical heterogeneity of the disease, and to identify patients at increased risk of lymphoproliferative disorders and specific comorbidities, as cardiovascular risk. Moreover, the expanding knowledge of pathogenetic pathways allowed a deeper identification of the complex mechanisms underlying the risk of lymphoma in these patients. This led to the recent development of several clinical trials addressing specific emerging pathogenetic pathways of the disease. However, 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 to demonstrate clinical efficacy in this heterogeneous disease. Following previous series, in this review we will provide an update of the most recent literature on the disease, focusing in particular on new insights into glandular and extra-glandular manifestations, lymphoproliferation and into recent developments in the diagnostic and prognostic role of innovative imaging techniques. Finally, in the era of precision medicine, we will focus on recent trials on Sjögren's disease therapy trying to analyse potential pitfalls and remaining inquiries which may explain failures of some systemic therapies.

Glandular involvement

SjD is the prototype of autoimmune exocrinopathy resulting in a progressive immune-mediated destruction of the lacrimal and salivary glandular parenchyma that translates into sicca syndrome, the clinical hallmark of disease (1). However, some SjD patients do not present the classic sicca symptoms and/or signs. These subjects may represent a clinically distinct subgroup, as suggested by a recent prospective study on about 500 SjD patients, in which low severity of ocular and oral dryness was associated with a more severe clinical phenotype characterised by greater systemic involvement and less glandular infiltrate (2).

It is known that SjD-associated dry eye disease (DED) has different features

if compared to other forms of DED. Given its significant impact on patient's quality of life (QoL) and the associated risk of severe ocular complications, the availability of tools allowing early identification of these patients represents an unmet need. In the last year, new non-invasive, highly reproducible and cost-effective methods have been proposed for the early diagnosis of SjD-DED and patient stratification. In recent studies, tear film viscosity, reduced corneal epithelium thickness and morphological changes of sub-basal corneal nerve plexus significantly associated with SjD-DED and correlated with other dry eye parameters and with some disease features, as anti-SSA positivity (3-5).

The progressive destruction of glandular parenchyma by immune cell infiltration clinically manifests with xerostomia and progressive glandular hyposecretion, leading to higher risk of dental caries or oral candidiasis. However, despite salivary function progressively worsens in these patients, a recent analysis of 253 consecutive outpatients from the prospective REgistry of Sjögren Syndrome LongiTudinal (RESULT) cohort demonstrated that glandular function, assessed by salivary gland ultrasound (SGUS), sialometry and patient-reported outcome measures (PROMs), did not change significantly up to 5-year follow-up, providing new insights for the clinical management of these patients (6). Moreover, the modest correlation between SGUS and functional and subjective parameters emphasise the importance of a multimodal approach in patient evaluation (6). In this context, analysis of patient serological profile may enhance prognostic stratification. Anti-SSB positivity correlated with a more severe prognosis in terms of salivary function while anti-vimentin antibodies, a protein of the cytoskeleton intermediate filaments, emerged as marker of more severe glandular involvement (7, 8).

Surely, minor SG biopsy (MSGB) plays a central role in the disease diagnostic pathway, particularly in some specific settings, as seronegative patients. However, the focus score (FS) method, despite considered the gold standard for disease diagnosis, does not allow to confirm the diagnosis in the absence of focal lymphocyte aggregates. In this setting, some immune-histochemical markers, as pSTAT1, CD20, CD3 and, to a lesser extent, CD21, allowed to distinguish SjD patients with negative MSGB from non-SjD, also improving the diagnostic performance of MSGB due to the ability to identify germinal centres and patient subgroups with different clinical risk profiles (9-11).

The indication and clinical utility of repeating a second MSGB in patients with suspected or confirmed SjD represent a pending issue. A second MSGB, in case of patient clinical and/or laboratory picture change, may modify the initial diagnosis, identify new overlapping diseases and allow early identification of lymphoproliferative complication (12). Moreover, sequelae of a second MSGB should not be underestimated, considering the reported long-standing or permanent sensory lower lip impairment (13).

The relationship between SjD and periodontal disease represents another important topic, both sharing common pathogenic mechanisms. Indeed, SjD patients display an increased risk of approximately 1.4 times to receive a diagnosis of periodontal disease, as demonstrated in a recent meta-analysis on over 11,000 patients, although the high heterogeneity of included studies deserves caution in data interpretation (14). In this setting, a large Norwegian national population-based study demonstrated that SjD is not significantly associated with a higher risk of developing periodontitis, after adjusting for covariates as age, sex and diabetes mellitus (15). However, the prevention and treatment of periodontal disease is essential in these patients. In this context, a dental implant with overdenture for edentulism treatment may have a positive impact on QoL in SjD (16). Considering the concerns regarding the effectiveness of dental implantology in these patients, these results, although limited by the small sample size, are of clinical relevance as the health of oral cavity and ocular surface influences psychophysical, occupational and social functioning being associated with higher risk of depression or lower QoL (17, 18). In this scenario, reliable and validated PROMs are of utmost importance to understand patient subjective experience and the impact of symptoms on QoL domains. A short version of the PROFAD-SSI (PROFAD-SSI-SF), a questionnaire for the subjective measurement of dryness, pain and fatigue, was recently validated, showing its reliability in the measurement of the subjective burden of the disease and of treatment on patient's QoL (19). Group Concept Mapping (GCM), social media listening (SML) and artificial intelligence (AI)-based linguistic and semantic analysis of social media data have been recently employed as thematic analysis methods to quantify the impact of the disease in the different health-related QoL dimensions and the items identified will be included in future PROMs (20).

Patient sexual dysfunction represents another important aspect of the disease. In the last year, research efforts oriented toward the detection of causative factors, with particular interest in the subjective experience of patients. In a recent SLR and meta-analysis, SjD and systemic sclerosis emerged as the connective tissue disease (CTD) with the greatest prevalence of sexual dysfunction, similar to what observed in malignant gynaecological diseases or endometriosis (21). In addition to disease-related factors, as dyspareunia, constitutional symptoms, treatment adverse events and psychological variables, such as anxiety and depression, emerged as causative factors in SjD-related sexual dysfunction (21). Moreover, psychological factors, emotional feelings, thoughts of inadequacy and guilt or negative behavioural responses of the partner, seem to influence the genesis of this disorder (22). However, the lack of assessment tools and effective therapeutic strategies represent a significant barrier in patient management. In this context, a home-based exercise programme may improve pelvic floor dysfunction and, consequently, global sexual function in SjD patients (23).

Take home messages

- Low severity of dryness may associate with a more severe systemic phenotype and a less glandular infiltrate

(2), while anti-SSB and anti-vimentin positivity correlate with a more severe glandular impairment (7, 8).
- New non-invasive, reproducible and cost-effective methods represent an aid in early diagnosis of SjD-DED (*e.g.* tear film diffusion speed on the cornea; anterior segment optical coherence tomography; *in vivo* confocal microscopy) (3-5).
- MSGB role in SjD prognosis evaluation and differential diagnosis is confirmed (10-11).
- Subjective and objective sicca manifestation deeply impact on physical, psychological and sexual QoL of SjD patients (14-22).

Extra-glandular involvement

The clinical impact of extra-glandular involvement has been recently confirmed in a multicentre retrospective study which demonstrated that high systemic disease activity and cryoglobulinaemia represent the two main factors associated with higher mortality risk in SjD patients (24).

Surely, interstitial lung disease (ILD) represents one of the most frequent and severe extra-glandular involvement, with a pooled prevalence ranging from 17% to 23%, although a recent study highlighted that SjD-ILD may have a more favourable course as compared to other CTD-ILD (25). The features and risk factors for SjD-ILD have been recently evaluated in two meta-analyses and SLR (26, 27). Lymphocytic interstitial pneumonia (LIP) and non-specific interstitial pneumonia (NSIP) emerged as the most frequent patterns, and male sex, advanced age, Raynaud phenomenon and anti-Ro52 positivity were confirmed as independent risk factors for ILD. Beyond individual risk factors, recent literature mainly focused on identifying patient subsets with higher risk of progressive fibrosing phenotype (PF-ILD). Persistent reduction of serum albumin, likely expression of chronic inflammation, fibroblastic activity induced by interleukin (IL)-6 and reduced DLCO, in particular in patients with usual interstitial pneumonia (UIP) pattern, have been identified as independent risk factors for PF-ILD in SjD (28, 29). However, both studies emphasised the absence of baseline radiological, serological and/or laboratory features able to differentiate between progressors and non-progressors, confirming that early diagnosis of ILD remains an unmet need. The modality and age of onset of SjD-ILD also influence the clinical expression and prognosis. Patients with lung involvement at disease diagnosis are characterised by a more rapid ILD progression, severer radiological extension and poorer lung function, representing a subgroup with worse prognosis (30). However, they often display absence of sicca symptoms and lower frequency serological parameters, thus representing a diagnostic challenge (30). Moreover, elderly onset patients (>65 years) have higher incidence of UIP pattern compared to adult-onset patients, higher frequency of small airway obstruction and less severe restrictive deficits, probably expression of a chronic immunological damage leading to fibrosis with lower inflammatory burden (31).

Neurological involvement is the second most frequent extra-glandular complication, characterised by a heterogeneous clinical picture, high morbidity and mortality. Peripheral neuropathy (PN) represents a clinical challenge due to variability of clinical manifestations and lack of specific diagnostic markers. In a recent retrospective study, SjD-PN patients were characterised by older age at disease onset and at diagnosis and lower frequency of rheumatoid factor (RF) and anti-SSA/B positivity (32). Conversely, RF and anti-SSB positivity were found to be independent risk factors for PN in a small retrospective study, supporting the existing literature that links B cell hyperactivity markers with PN development (33). The inconstancy in reported results may be partly due to the retrospective and monocentric nature of the studies, thus limiting generalisability, but also reflects the heterogeneity of SjD-PN, which is not a single entity but rather a group of different clinical and pathophysiological conditions. Recently, some laboratory parameters, widely available in routine clinical practice, emerged as potential biomarkers of SjD-PN, as IgG-anti-α-fodrin or high neutrophil-lymphocyte ratio (NLR) with reduced monocyte-lymphocyte ratio (MLR), likely expression of tissue recruitment with perineural lymphocyte infiltration (34-35).

On the other hand, central nervous system (CNS) involvement is a rare manifestation, characterised by heterogeneous clinical picture and highly variable epidemiological data. In this context, a topic of great interest is the relationship between SjD and CNS autoimmune demyelinating diseases, such as neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS). The main issue arises when the neurological complication precedes sicca syndrome and/or other typical extra-glandular manifestations. This was highlighted in a recent retrospective study, where an initial diagnosis of optic neuritis and transverse myelitis was subsequently interpreted as SjD-related conditions (36). Therefore, in patients with suspected autoimmune disease of the CNS and atypical features, as C3 consumption and anti-SSA positivity, it is essential to consider other conditions. However, occasionally, the two clinical entities may coexist, with a significant impact on patient prognosis. In this context, anti-aquaporin (AQ)4 antibodies, known for their pathogenetic role in NMOSD, may cross-react with AQ-5, highly expressed in SjD exocrine glands, by molecular mimicry mechanisms (37).

In the context of neurological involvement, small fibre neuropathy (SFN) exerts a negative impact on patient's QoL. The increased frequency of SFN in SjD may be expression of an immune-mediated damage, as the reduction of intraepidermal nerve fibre density on skin biopsy is significantly associated with SjD-SFN in comparison to idiopathic forms, providing a rationale for immunosuppressive therapy in the most severe forms of SjD-SFN (38).

The most common form of renal involvement in SjD is renal tubular acidosis (RTA), an underestimated manifestation often antedating disease diagnosis and associated with a slow and progressive decline in renal function leading to chronic kidney disease (CKD). Recently, early onset disease, anti-SSB positivity and articular mani-

festations emerged as independent predictors of SjD-RTA (39, 40).

Finally, SjD is characterised by different haematological manifestations. Among these, immune thrombocytopenia (ITP) represents one of the most frequent, with a prevalence comparable to primary ITP (41). Moreover, SjD patients with low C3 and high IgG levels are characterised by higher probability of therapeutic failure (42).

The clinical picture of SjD is also characterised by chronic constitutional symptoms with multifactorial aetiology, significantly impacting patient health, as fatigue. Depression, in association with insomnia, fibromyalgia and disease activity, emerged as the most frequent independent predictor of fatigue (43). Thus, early diagnosis and treatment of depressive disorders in SjD may have a favourable effect on fatigue and patient QoL. Recently, sarcopenia and pre-sarcopenia emerged as possible biological determinants of fatigue toward a vicious circle in which chronic fatigue translates into lower physical activity with consequent reduced muscular trophism. Interestingly, SjD is associated with a significant higher prevalence of pre-sarcopenia compared to healthy controls and the reduced muscle trophism correlated with anxious-depressive symptoms, suggesting the importance of physical activity and specialised nutritional assessments in these patients (44). The measurement of hand grip strength with digital dynamometer may discriminate between SjD patients with high and low perceived fatigue (45).

Take home messages

- Lung involvement at onset and elderly onset ILD are conditions burdened by worse prognosis (30-31).
- IgG-anti-α-fodrin levels, high neutrophil-lymphocyte ratio (NLR) and the reduced monocyte-lymphocyte ratio (MLR) might be novel predictive factors of SjD peripheral nervous system involvement (34-35).
- Early diagnosis and treatment of depressive disorders in SjD may have a favourable effect on fatigue and patient's QoL, as well as acting through physical activity and specialised nutritional assessment to contrast the establishment of a vicious circle between fatigue and sarcopenia (44).

Comorbidities in Sjögren's disease

Sjögren's disease may be associated with several comorbidities which influence its clinical course, prognosis and therapeutic management. A recent multicentre real-word retrospective study demonstrated that only 14% of deaths were directly related to the disease itself while 60% were caused by cardiovascular disease (CVD) and infections (24). Cardiovascular risk represents still an unmet need in these patients (46). Indeed, large studies demonstrated that SjD is associated with a risk of subclinical atherosclerosis comparable to type 2 diabetes mellitus and with a significant higher risk of incident heart failure in comparison to the general population (47-48). However, data regarding the prevalence and clinical significance of CVD in SjD are still conflicting and mostly derive from small studies with short follow-up. Recent studies have attempted to fill this gap identifying patient subsets with higher CV risk by the development of a nomogram based on ten variables easily assessable in routine clinical practice (49). Moreover, a recent case-control study provided the first evidence that SjD patients are characterised by significant upregulation of serum levels of PCSK9, a regulator of lipid metabolism and marker of CV risk in general population, in comparison to controls (50). However, differently from controls, serum levels of PCSK9 did not correlate with atherosclerosis or CV risk in SjD, suggesting that this molecule may exert different inflammatory effects beyond atherosclerosis in SjD (50). Finally, hyperuricaemia, high ESSDAI score, high focus score, plasma beta2-microglobulin, circulating proinflammatory cytokines, especially IL-6, and anti-SSA/B positivity emerged as factors independently associate with CV risk and endothelial dysfunction (51, 52).

Although the pathogenic mechanisms are only partially understood, an increasing body of literature based on large-scale population-based studies suggests a causal association between SjD and cancer, as head and neck cancer or breast cancer (53-54), with anti-SSA positivity emerging as risk factor (54). However, most of these studies are small sized, retrospective, observational and often monocentric, all factors exposing to high bias risk and strongly influencing the reliability and generalisability of the results. In this context, Mendelian randomisation (MR) may represent a new tool to evaluate the causal relationship between risk factors and outcomes, bypassing the intrinsic limitations of retrospective observational studies. Using MR, Jia *et al*. demonstrated that, apart from the increased risk of lymphoma, SjD has no significant association with cancer and, conversely, appears to be associated with a reduced risk of prostate, breast and endometrial cancer (55-56). Surely, the main limitation of MR studies is that the genomic databases employed for analysis are based mainly on European populations, highly hampering the generalisability of the results considering the role of genetic background and environmental factors in oncogenesis.

Finally, recent studies suggested a possible association between specific comorbidities and some disease features, with possible implications in terms of early diagnosis. A recent multicentre Italian cross-sectional study demonstrated that SjD patients with autoimmune thyroiditis are characterised by a less severe phenotype, higher incidence of fibromyalgia and coeliac disease, lower intake of DMARDs, lower focus score and no increased risk of lymphoproliferative disorder (57).

Autoantibody profiling in SjD

A precise characterisation of SjD patient serological profile may have an important clinical, diagnostic and prognostic implication. Seronegative patients are characterised by older age, shorter disease duration, greater male sex prevalence and increased prevalence of ILD, suggesting a potential more severe prognosis (58). Similarly, anticentromere antibodies (ACA) positivity was associated with advanced age, longer disease duration, more severe sicca syndrome, increased risk of ILD and gastrointestinal involvement and lower prevalence

of RF and anti-SSA/B positivity in a recent retrospective study (59). Recently, research focused on the role and significance of isolated anti-Ro52 positivity which may identify a subset of patients with increased prevalence of cryoglobulinaemia, cutaneous vasculitis and peripheral neuropathy (60).

Finally, phenotypic expression of the disease may be significantly influenced by the age at disease onset and patient gender. Elderly-onset SjD, juvenile and male patients have a distinct clinical presentation, different type of organ involvement and a different prognosis when compared with middle-aged female. Overall, these three subgroups tend to be more aggressive, particularly considering lymphoproliferative complications. Surely, the phenotypic stratification of SjD patients according to age and gender appears pivotal in the era of precision medicine to improve their management and long-term prognosis (61).

Take home messages

- Mendelian randomisation studies on the relationship between SjD and cancer in European populations show no significant association, apart from the known risk of lymphoma (55-56).
- Stratification of SjD patients according to serological profile seems fundamental for clinical management and prognosis, based on the striking different features between subgroups (58-60).

Lymphoproliferative disorders in SjD: an update

Sjögren's disease patients are burdened by a 5-10% lifetime risk of developing lymphoma, which represents the final result of a pathologic interplay between a dysregulated immune system and an active epithelium. Although frequently presenting as an indolent extranodal, marginal type, non-Hodgkin lymphoma (NHL) limited to the salivary glands still represents a major complication. Lymphomagenesis is a multistep, progressive and subtle process; thus, the main research themes in this field focus on its early detection and effective treatment, declined through the stratification of patients and the detection of new biomarkers.

New perspectives on lymphomagenesis and biomarkers

The association between EBV and SjD pathogenesis, with a specific focus on its role in lymphomagenesis, has been recently reviewed. The ability of EBV to interplay with innate immune system and produce B cell activation might explain its causative role in lymphoma development in SjD acting as chronic antigenic stimulator, natural immune response and IFN pathway activator, genetic aberrations (*e.g.* Myc, TNFAIP3) inductor, as well as BAFF and NFkB-dependent B cell receptor (BCR) upregulator (62-63).

The connection between lymphomagenesis and B cell related cytokines, genes and signalling in SjD has always been a topic of extreme interest. As for B cell cytokines, IL-40 expression in SjD and in SjD-associated NHL has been recently evaluated. In particular, IL-40 was found to be upregulated in both SjD salivary gland tissue and peripheral blood, likely due to a concomitant elevation in IL-4 and TGF-β1 expression. In addition to a connection with ESSDAI scores, salivary gland focus score, B-cell IFNγ production and NETosis process, IL-40 was also highly expressed in parotid mucosa-associated lymphoid tissue (MALT) lymphoma associated to SjD, thus representing a possible new target of research (64).

A prospective study on 21 SjD patients with lymphoma *versus* 324 SjD controls without lymphoma applied peripheral whole blood gene expression to investigate the role of B cells genes in SjD-related NHL and demonstrated an overexpression of Bruton's tyrosine kinase (BTK) and proliferation inducing ligand (APRIL) genes before the occurrence of lymphoma in SjD patients with incident lymphoma (65). Moreover, BTK was found to be consistently overexpressed in all subgroups of SjD patients with lymphoma and, at multivariable analysis, the risk of lymphoma was associated with lymphopenia, cryoglobulinaemia, low C4, CD4/CD8 ratio, RF, monoclonal component, ESSDAI ≥5, purpura and parotid swelling (65). Although needing further confirmation, this data brings an interesting novelty, considering both diagnostic and therapeutic implications (*e.g.* role of BTK inhibitors as remibrutinib) (66).

By bulk RNA and single cell analysis, cell signalling steps and players in SjD progression to diffuse large B cell lymphoma (DLBCL) have been also evaluated. BCR signalling was identified as a common enriched signal between DLBCL and SjD peripheral naïve B cells and salivary gland infiltrating cells. Genes associated with this pathway, thus mTOR pathway, as CD79A/B and LAMTOR4, have been highlighted as possible novel biomarkers of SjD progression to lymphoma (67). On this basis, it is worth mention the implication of Akt/mTOR pathway in SjD and associated lymphomagenesis through immunohistochemical detection of the major pathway molecules (Akt and its substrates FoxO1 and PRAS40) in SjD minor salivary glands at different lymphoproliferative stages and in sicca controls (68). Moreover, functional *in vitro* inhibition experiments, through the co-culture of salivary gland epithelial cells and B cells from SjD patients in presence of specific inhibitors, as LY294002, has been proposed (68).

The connection between clonality and lymphoma development in SjD has also been a matter of interest. On a cohort of 207 patients with either suspected SjD or with suspected lymphoma, molecular B cell-expansion was studied on fresh frozen minor salivary glands using standardised multiplex PCR assay combined with heteroduplex analysis by microcapillary electrophoresis. According to the results, B cell clonality in minor salivary glands was detected in 22.8% of SjD patients, significantly more frequent than in controls. B cell monoclonality was associated with known lymphoma predictors, as higher ESSDAI, lymphopenia, hypocomplementaemia, cryoglobulinaemia and RF. Thus, even if no new cases of lymphoma were detected in patients with B cell monoclonality, possibly due to the short follow-up, these results suggest that the evaluation of B cell clonality in minor salivary glands should be considered together with other lymphoma predictive factors, to delineate a subset of patients at higher risk of presenting or developing lym-

phoma (69). In another smaller cohort of 8 SjD patients, extranodal marginal zone lymphoma (eMZL) clonotype was detected both in pre-diagnostic tissue biopsies (from various sites) and in peripheral blood samples taken prior to lymphoma diagnosis; by sequencing of IG heavy chain (IGH) gene repertoire, the dominant clonotype matched the eMZL clonotype of the diagnostic biopsy, consisting in stereotypic IGHV gene combinations (IGHV1-69/IGHJ4 and IGHV4-59/IGHJ5) associated with RF activity (70). Further analysis starting from this data might help to clarify the pathogenetic steps driving to eMZL progression, while helping in SjD patients follow-up and lymphoma early detection (70).

The aforementioned data support the fundamental role of B cell hyperactivation in lymphomagenesis; however, salivary gland epithelium plays an active part in SjD pathogenesis and lymphoproliferative complications as well (71). Thus, an interesting objective of research is represented by the development of cell culture models capable of resembling salivary gland morphology and function, and of allowing the evaluation of their interaction with the immune system counterpart. On this topic, preliminary results were recently presented on the creation of organoids of salivary gland epithelium harvested from 5 SjD patients in different lymphoproliferative stages, MALT lymphoma included, primarily to evaluate the efficacy of new possible epithelial active therapeutic strategies, such the PDE4 inhibitor apremilast (72). This *ex vivo* model successfully mirrored the morpho-functional features of the salivary gland tissue of origin in various histological stages, and further applications are ongoing, both for the creation of complex culture systems of salivary gland epithelium and peripheral blood mononuclear cells, and for drug testing protocols.

Surely, wide research focused on detecting biological markers and *ex vivo* models of lymphomagenesis. However, efforts have been made also in the field of radiomics to identify imaging markers associated to parotid lymphoma development in SjD and to become surrogates of histological evaluation. Previously, sonographic and magnetic resonance imaging (MRI) features of parotid MALT lymphoma were presented (73); moreover, studies on the application of deep learning algorithms to ultrasonographic evaluation and scoring of salivary gland parenchyma in SjD were conducted (74, 75). Recently, a retrospective study conducted on a small cohort of SjD patients evaluated texture analysis (TA) protocols of MRI on parotid glands, depicting high parotid gland parenchymal heterogeneity, quantified by TA features (*e.g.* sum variance), as a characteristic associated to lymphoma development (76). These preliminary results, although needing further examination on wider cohorts, demonstrate a rising interest in the field of radiomics applied to SjD lymphoproliferative complications and should be envisioned together with previously mentioned studies on the role of imaging and artificial intelligence in this disease.

Phenotypic stratification and prompt diagnosis of lymphoproliferative manifestations

Lee *et al*. proposed a 4 stages model (from pre-disease to lymphoma establishment) of SjD evolution, highlighting the complexity of its pathogenesis and the heterogeneity of clinical features (77).

Recently, efforts have been made to stratify SjD phenotypes according to age and gender and different studies are coherent in defining elderly onset SjD, juvenile SjD and male patients as subgroups characterised by high disease severity and elevated risk of developing lymphoproliferative disease (61). On the contrary, a multicentre cross-sectional study conducted on 2546 SS patients from 6 different Italian centres, reported a tendency toward a lower prevalence of lymphoma in the subgroup of SS patients with concomitant autoimmune thyroiditis (57).

Clinical and imaging evaluation plays a key role, since major salivary gland enlargement represents a pivotal risk factor of lymphoma development in SjD. Namely, the results of a multicentre study, conducted on 144 SjD patients with history of lymphoma *versus* 222 SjD controls, highlighted the role of parotid gland swelling as an early predictor of lymphoma. The detection of parotid gland swelling at any time during the disease was significantly linked to NHL lymphoma development, mostly if persistent (2-12 months and >12 months enlargement *vs*. episodic <2 months episodes) (78). Strictly linked to the clinical detection of parotid glandular swelling, is the ultrasound evaluation of major salivary gland. This non-invasive, simple and repeatable imaging technique allows the detection of parenchymal abnormalities and suspicious lesions characteristic of MALT lymphoma, and to safely perform tissue sampling for histological diagnosis, with good accuracy comparable to open surgical approach (79, 80). However, SjD may involve other exocrine glands, mainly lacrimal glands, which can represent another site of lymphoma development. Thus, clinical and ultrasound evaluation of these sites, should always be considered in clinical practice, as well as the application of both conventional and ultra-high frequency ultrasonographic techniques, when feasible (81, 82). Other imaging modalities, as contrast-enhanced MRI and [18F]-fluorodeoxyglucose (FDG)-PET-CT, despite their costs and limited availability, can assist clinicians in objectively detecting and correcting defining the severity lymphoproliferative complications in SjD patients. Recent evidence supports the ability of FDG-PET-CT to detect lymphoma localisation, and to discriminate between patients with and without lymphoma in SjD: lymphoma patients showed higher FDG uptake in the parotid and submandibular glands and more frequently concomitant nodular lung lesions, with threshold SUV values suggestive for salivary gland lymphoma of >3.1 for parotid and >2.9 for submandibular glands. The combination of these features was also discussed (sensitivity of 92% when ≥1/3; specificity 91% when ≥2/3), while the ability of PET/CT to detect systemic manifestations of SjD (*e.g.* nodes, enthesis and lungs) and to direct to the most adequate biopsy location was reported (83).

New perspectives on therapeutic management and outcome

The detection of new therapeutic agents for the management of lymphoproliferative complications is part of the broader effort of designing and conducting clinical trials in SjD. Hopefully, new composite endpoints, as the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) and the candidate Sjögren's Tool for Assessing Response (STAR), will help to better define treatment efficacy also in terms of lymphoproliferative manifestations, as supported by the recent re-evaluation and identification of peripheral and salivary gland biomarkers of response and resistance to B cell depletion from the TRACTISS trial, according to these indexes (84). Moreover, as already mentioned, the search and detection of new lymphomagenesis biomarkers will hopefully conduct to a wider armamentarium of therapeutic strategies, BTK inhibitors. In a phase II randomised double-blind clinical trial, remibrutinib has demonstrated to improve ESSDAI score in SjD patients with moderate to severe disease activity, with favourable safety profile (66). A trend in decreasing serum CXCL13, SSA and SSB auto-antibodies levels, and in downregulating of genes and pathways involved in immunoglobulin production, B cell activation and T cell co-stimulation was reported (66). If a role will be effectively demonstrated for Akt and mTOR pathways in lymphoma development, worthy might be the effort to widen the evaluation on the therapeutic potential of their inhibitors (68). Moreover, B-cell depleting agents and/or BAFF-antagonists are key part of SjD therapeutic research, due to the role of their target in SjD pathogenesis and evolution; on this hand, it will be interesting to analyse the data resulting from the ongoing phase III clinical trial with ianalumab (VAY736; NCT05350072), also in terms of possible applications to lymphoproliferative complications. With this same principle, results on the action of other possible therapeutic strategies, such as CD40L antagonism and TYK2 inhibition (*i.e.* dazodalibep NCT06104124 and deucravacitinib NCT05946941), are awaited. Finally, anti-CD19 CAR-T cell therapy approach to SjD-associated lymphoma is another interesting field as positive results of this strategy on other B cell mediated autoimmune diseases were reported (*e.g.* SLE, anti-synthetase syndrome) (85, 86). Up to date, clinical success was reported in a patient affected by active SjD complicated by DLBCL following anti CD19 CAR-T cell therapy, on both haematological and rheumatological manifestations (87), while phase I studies (NCT05085431 and NCT05859997, NCT06056921) focusing on the safety and efficacy of CD19/BCMA CAR-T cell therapy for SjD are ongoing.

Take home messages

- New biomarkers of lymphomagenesis, with a focus on B cell signalling pathways (*e.g.* BTK, BCR, mTOR/AKT) and related genes and cytokines are extensively studied (64-68).
- The evaluation of B cell clonality in salivary gland tissue and peripheral blood might be of aid in detecting patients at high risk of proliferative disease in early phases (69-70).
- The establishment of functional *ex vivo* models of disease with complex 3D culture systems might shed light on pathogenesis and treatment of SjD and its lymphoproliferative complications (72).
- An early definition of high-risk profiles for lymphoma development is recommended, by combining demographic (*e.g.* gender, age, comorbidities), laboratory markers (*e.g.* cryoglobulinaemia), clinical (*e.g.* parotid swelling, disease activity) and imaging (US, MRI, PET/CT) examination (24, 57, 61, 76, 78-80, 83).
- CAR-T cell therapy might represent a novel approach to SjD and its related lymphoproliferative complications (87); the efficacy of other novel agents should be considered in the future for their action on B cell hyper-activation and tissue microenvironment (anti-BAFF, -BTK, - B/T co-stimulation, -TYK2), and with the aid of new composite endpoints.

New insights in imaging

Imaging is an important tool to objectively evaluate the glands in SjD. In the last year, most studies focused on the diagnostic performance of different imaging techniques in the diagnostic work-up of SjD.

Ultrasound

In line with previous findings, a recent study confirmed that the Outcome Measures in Rheumatology Clinical Trials (OMERACT) scoring system for grey-scale SGUS has good accuracy to predict SjD based on the ACR/EULAR classification criteria (AUC 0.83). SGUS OMERACT score showed moderate to good correlation with salivary flow, and fair to moderate correlation with labial salivary gland biopsy (LSGB) results. The authors also stated that negative SGUS results may help to reduce unnecessary biopsies in anti-SSA-negative patients (88). SGUS showed excellent accuracy (AUC 0.91) to differentiate SjD from its major mimics (*i.e.* sarcoidosis, amyloidosis, HIV infection or chronic HCV infection). Using the Hocevar scoring system (range 0–48), the optimal cut-off value was 15, which showed high sensitivity, specificity, positive and negative predictive values, varying from 85-90%, and a diagnostic odds ratio of 51 (89). As first longitudinal evaluation, SGUS was performed at baseline, 2 and 5 years in 253 patients with SjD from the prospective standard-of-care RESULT cohort. At group level, Hocevar and OMERACT scores did not change up to 5 years of follow-up. At individual patient level, Hocevar scores were stable (within 25% change over time) in 60%, showed an increase in 19% or decrease in 21% of patients at year 5. These findings indicate that a significant change in SGUS scores in clinical trials with well-trained ultrasonographers can be attributed to the effect of treatment (6). Multiple studies investigated the use of ancillary ultrasonographic techniques. Using sound touch elastography (STE) examination, shear wave velocity and Young's modulus showed higher values both in the parotid and submandibular gland in the SjD patients compared to controls. Using ultra-microangiography (UMA) examination, levels of colour pixel percentage (CPP) were significantly elevated in the parotid glands,

but not significantly higher in the submandibular glands of SjD patients compared to controls. The elasticity values of the parotid and submandibular glands and the CPP of parotid glands together showed excellent accuracy (AUC 0.95) to discriminate between SjD and controls. The diagnostic accuracy in detecting salivary gland involvement was significantly better when combining STE and UMA compared to either one used alone. Based on these findings, the combination of STE and UMA may increase the diagnostic performance of ultrasonography in SjD (90).

Two-dimensional shear wave elastography (2D-SWE) of the submandibular and parotid glands showed significantly higher shear wave velocity and elasticity modulus in SjD patients compared to controls. The diagnostic accuracy of SWE was significantly better than greyscale SGUS. The elasticity modulus (kPa) of the parotid gland had the highest diagnostic accuracy (AUC 0.94), with sensitivity of 93% and specificity of 83%. However, SWE parameters showed no correlation with disease characteristics or clinical assessments (91). The mean 2D-SWE value of the lacrimal glands was significantly higher in SjD patients compared to controls and increased parallel with lacrimal parenchymal grade. The diagnostic accuracy to detect lacrimal gland involvement in SjD patients was excellent (AUC 0.90) for 2D-SWE and moderate (AUC 0.77) for US. Lacrimal gland 2D-SWE and US values showed both moderate correlations with objective tests of tear gland function and LSGB (92). Another study also reported that mean 2D-SWE measurements, reflecting loss of elasticity, were remarkably higher in SjD patients compared to healthy controls, both in the lacrimal and parotid glands. 2D-SWE values of the lacrimal glands showed moderate to good correlation with PROMs. A cut-off value of 4.6 kPa in the lacrimal gland elasticity discriminated SjD patients from healthy controls with a sensitivity of 94% and specificity of 87% (93). Based on these studies, the diagnostic performance of 2D-SWE seems promising although experience with this technique is needed.

The potential role of ultrahigh-frequency ultrasound (UHFUS) of the labial glands was explored in 12 paediatric patients with SjD. All patients showed a UHFUS grade of ≥1; 8 patients showed a mild glandular alteration (grade 1), two showed a moderate glandular alteration (grade 2) and two a severe glandular alteration (grade 3). Moderate intraglandular vascularisation was found in 9 patients and three showed mild intraglandular vascularisation. This pilot study indicates that UHFUS is a feasible technique to identify salivary gland alterations in paediatric SjD patients (94). Finally, the value of US to perform a biopsy was investigated based on paired ultrasound-guided core needle (US-guided CN) and incisional biopsies of the parotid gland in 20 patients clinically suspected for SjD. Comparing the results for surface area, presence of focus score, germinal centres and lymphoepithelial lesions showed that US-guided CN is at least equivalent to incisional parotid gland biopsy. When performed by an expert, this minimally invasive technique seems promising for future use in the diagnostic work-up of SjD and also for assessment of repeated biopsies in clinical trials (80).

Magnetic resonance imaging

TA of MRI of the parotid glands was explored as innovative approach in a paediatric SjD cohort of 36 patients and 20 controls, focusing on the relationship between the apparent diffusion coefficient (ADC) and T2-weighted MRI sialography and TA of the parotid glands. Parotid ADC values were significantly lower in the SjD group, particularly in patients with higher disease activity. First-order statistics parameters, characterising basic statistical features of the images, showed moderate correlation with TA from T2-weighted images, indicating potential for assessing parotid gland inflammation (95). The diagnostic performance of MRI and magnetic resonance sialography (MRS) was evaluated in 191 patients clinically suspected for SjD. MRI + MRS showed the highest sensitivity, whereas LSGB showed the highest specificity for diagnosis of SjD. MR grade showed moderate to good correlations with disease duration and PROMs of dry mouth and excellent correlations with salivary flow. MRI grade and MRS grade showed poor concordance (Cohen's kappa 0.25) for diagnosis of SjD, indicating that parotid fat deposition and terminal duct lesions do not occur in parallel. Based on their findings, the authors state that MRS can have diagnostic advantages for patients with early-stage lesions and MRI for late-stage lesions. Adding MRI+MRS to the ACR/EULAR classification criteria improved the sensitivity, whereas the specificity remained the same. Replacing LSGB by MRI+MRS in the ACR/EULAR criteria decreased both sensitivity and specificity (96).

Fluorodeoxyglucose (FDG)-PET/CT

In a recent study exploring the usefulness of [18F]-FDG-PET/CT to detect salivary gland inflammatory conditions, differences in uptake of FDG-PET/CT in salivary glands were compared between two groups of patients with autoimmune diseases, SjD and giant cell arteritis (GCA), and lung cancer patients as non-autoimmune control group. Although SjD patients with presence of glandular swelling showed increased FDG-uptake in the parotid gland, no differences were found in FDG-uptake in the parotid or submandibular gland between the total group of SjD patients and the other two groups. GCA patients showed significantly higher uptake in submandibular glands, both visually and quantitatively, compared to the other two groups. For the tubarial gland, significantly higher SUVmax was found in the SjD group, which indicates that the tubarial gland might play a role in the disease process of SjD (97).

As also discussed in the previous section, [18F]-FDG-PET/CT was found to be useful to discriminate between SjD patients with and without lymphomas. The maximum standardised uptake values (SUVmax) in the parotid and submandibular glands showed good accuracy (resp. AUC 0.83 and 0.79) to predict the presence of lymphoma. When combining visual and quantitative findings (i.e., nodular lung lesions,

parotid SUVmax > 3.1 and submandibular SUVmax > 2.9), sensitivity was high (92%) when at least one of these three features were present, and specificity was high (91%) when at least two features were present. Furthermore, FDG-PET/CT could assist in excluding a SjD-associated lymphoma when none of these three features is present (83).

Take home messages

- SGUS shows accuracy to predict SjD and to discriminate its mimickers, and it may help reducing unnecessary biopsies in seronegative patients (6, 88-89).
- US-guided CN biopsy of the parotid gland is confirmed a promising minimally invasive technique for SjD diagnostic work-up (80).
- The use of ancillary ultrasonographic techniques on major salivary glands, as STE and UMA combination and 2D-SWE, and labial glands UHFUS, may increase the diagnostic performance of US in SjD (90-94).
- MRI TA protocols and MRS of parotid gland seem useful in the evaluation of glandular involvement and impairment, but their role in diagnostic-classification work up in SjD needs further research. (95-96).
- [18F]-FDG-PET/CT is useful to discriminate between SjD patients with or without lymphoma, based on the presence and combinations of specific features (83).
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Update on the treatment of Sjögren's disease

The treatment of SjD remains one of the most difficult riddles to solve in modern rheumatology. Currently, the majority of our treatment armamentarium are limited to topical interventions that provide temporary relief from symptoms, while systemic disease management relies on an organ- and activity-based algorithm using drugs repurposed from other rheumatological conditions with sometimes limited efficacy (98). None of these medications has been shown to significantly deflect the natural course of the disease. As a result, 97% of SjD patients report dissatisfaction with their treatment plans, and half of them express an urgent need for new therapeutic options (99). However, recent advances in understanding the pathophysiological mechanisms underlying the disease have led to the identification of novel treatment targets that are central for SjD specific pathogenesis. In addition, improvements in the design of RCTs - such as the inclusion of patients regardless of disease activity status and the incorporation of more refined outcome measures to assess clinically relevant treatment responses - have provided optimism for future treatment approaches (100).

Targeting B cells

Sjögren's disease is characterised by hypergammaglobulinaemia, elevated levels of kappa and lambda free light chains, lymphadenopathy, presence of ectopic germinal centres in the salivary glands, a broad autoantibody profile and an increased risk of lymphoma, placing B cell hyperactivity at the core of its pathogenesis (101, 102). Consequently, B cell-targeted therapies have shown the highest level of evidence among all biologic treatments for SjD, having been evaluated in large patient cohorts for various clinical indications. Rituximab is currently used in clinical practice for patients with systemic disease, particularly those with manifestations of cryoglobulinaemic vasculitis, pulmonary involvement, or recurrent salivary gland enlargement (98, 103). However, the results of RCTs have yielded controversial outcomes. This inconsistency has been partly attributed to the elevated concentrations of B cell activating factor (BAFF) during B cell repopulation, promoting the survival of autoreactive B cells. As a response, sequential treatment with Rituximab and Belimumab was tested in a phase II trial, demonstrating more prolonged B cell depletion, making the combination a potential option for cases such as refractory cryoglobulinaemic vasculitis. Despite this, clinical responses, as measured by the ESSDAI, did not show improvement compared to monotherapy regimens (104). Ianalumab, a monoclonal antibody targeting the BAFF receptor, is currently under investigation for SjD. BAFF binds with varying affinity to BAFF receptor, but also to the transmembrane activator and CAML interactor (TACI), the B cell maturation antigen (BCMA). A phase IIb trial achieved its primary endpoint, demonstrating a dose-dependent reduction in disease activity, as measured by ESSDAI at week 24, although no significant improvement in patient symptom burden was observed compared to the placebo group (105).

In addition to BAFF, B cell development, differentiation, and survival are also regulated by a proliferation-inducing ligand (APRIL), which is primarily expressed by myeloid cells and acts through several receptors. APRIL binds TACI, BCMA, and heparin sulfate proteoglycans. A recent Phase II randomised, double-blind, placebo-controlled trial evaluated the efficacy and safety of telitacicept, a fusion protein that targets the extracellular BLyS/APRIL-binding domain of the TACI receptor and the Fc fragment of human IgG1, thereby inhibiting partly both BAFF and APRIL (106). This trial included 42 patients, divided into a 1:1:1 ratio (160 mg telitacicept, 240 mg telitacicept, and placebo), resulting in only 14 patients per group. The primary endpoint (change from baseline in the ESSDAI at week 24) was achieved only in the 160 mg telitacicept group, with no dose-dependent response observed. Fatigue, as measured by the Multidimensional Fatigue Inventory (MFI), showed a reduction from baseline in both treatment groups. However, it is important to consider that baseline MFI values were significantly lower in the placebo group (50.7) compared to the treatment groups (58.9 for 160 mg and 59.6 for 240 mg), likely due to the small sample size creating randomisation imbalances. No safety concerns were identified.

Recently, innovative approaches have emerged for targeting B cells still on an observational basis. Daratumumab (anti-CD38), which targets plasmablasts and plasma cells, has been administered to two patients with SjD who had active disease despite prior Rituximab treatment. The first patient presented with autoimmune hyperchylomicronaemia, while the second had cryoglobulinaemia. Both clinical man-

ifestations resolved following treatment with daratumumab for at least 6 months. It is known that daratumumab has the additional benefit of depleting autoantibodies producing cells in the tissue, compared to rituximab (107).

Targeting B cell and T cell co-stimulation

Deregulated interaction between T and B cells plays a central role in the pathogenesis of SjD. Two RCTs evaluating the efficacy of abatacept, a cytotoxic T lymphocyte-associated protein 4 (CTLA-4)–immunoglobulin fusion protein, failed to meet their primary endpoints. However, a recent prospective, open-label observational study involving 68 patients with both SjD and rheumatoid arthritis (RA) demonstrated that abatacept led to a reduction in both the ESSDAI and the ESSPRI from week 12 through week 52. Additionally, a statistically significant improvement was observed in subjective measures of tear production and salivary flow. Nonetheless, these findings should be interpreted with caution due to the study's open-label design, small sample size, lack of a control group, and the confounding factor of concomitant RA.

Except for the CTLA-4 dependent interaction, an additional important pathway involved in T cell-dependent antibody responses, and in B cell differentiation and germinal centre formation, involves CD40–CD40L interactions. Several molecules that block this pathway have been tested in SjD, including iscalimab (anti-CD40) and dazodalibep (108).

Targeting JAK-STAT signalling pathway

Given the crucial role of the JAK-STAT pathway in driving IFN production and other cytokines involved in SjD, its inhibition may offer therapeutic benefits. The promising outcomes of deucravacitinib, an oral selective TYK2 inhibitor, in lupus patients, demonstrating both clinical improvement and a reduction in type I IFN and B cell pathways, have led to an ongoing trial for SjD. Additionally, a multicentre, prospective, open-label, randomised study in China is evaluating the efficacy of baricitinib, a selective JAK1 and JAK2 inhibitor, in combination with hydroxychloroquine (HCQ) versus HCQ alone in patients with active disease (ESSDAI ≥5) (109). In another ongoing study, tofacitinib a selective inhibitor of JAK1 and JAK3 has been selected in the treatment of primary SjD-ILD compared to cyclophosphamide followed by azathioprine. With the potential to suppress IFN signalling and other critical pathways, the effects of JAK-STAT inhibition trials are highly anticipated.

Targeting antigen-presenting cell function

A novel approach for treating autoimmune diseases involves reducing the activation of CD4 T cells. This is achieved through the inhibition of cathepsin S, a serine protease responsible for cleaving the MHC-II-bound invariant chain pro-peptide Lip10, a process necessary for MHC-II-dependent antigenic peptide presentation. In a randomised, double-blind, placebo-controlled phase IIa study, 75 patients with SjD were randomised 1:1 to receive either a cathepsin S inhibitor (RO5459072) or placebo for 12 weeks (110). The primary endpoint, defined as the proportion of patients achieving a ≥3-point reduction in ESSDAI score from baseline, was not met. Additionally, none of the secondary endpoints, including ESSPRI, SF-36 Mental and Physical scores, unstimulated tear production, or mechanically stimulated salivary flow, showed significant improvement. Despite the short study duration, the inhibition of cathepsin S failed to demonstrate efficacy in the treatment of SjD.

Conventional synthetic disease modifying anti-rheumatic drugs

None of the available disease-modifying antirheumatic drugs (DMARDs) are approved for the treatment of SjD by regulatory agencies. Nevertheless, they are recommended by EULAR as corticosteroid-sparing agents, although the absence of head-to-head studies prevents a definitive recommendation of one agent over another (98). A recent report from China indicated that patients treated with HCQ showed notable improvements in ESSPRI scores, serum IgA levels, and Schirmer's test compared to the randomised control (observation) group after 12 months of treatment (111). However, the lack of blinding, the absence of a placebo control, and the small sample size (72 patients) limit the strength of these conclusions. Iguratimod, a DMARD primarily used in China and Japan, likely acts by inhibiting the Akt/mTOR/STAT3 signalling pathway, thereby suppressing T follicular helper cell differentiation. Two large meta-analyses were published last year (112). The first, part of a broader meta-analysis on autoimmune diseases, included 32 RCTs on SjD and demonstrated that iguratimod could reduce ESSPRI and ESSDAI scores while also improving Schirmer test (113). The second meta-analysis focused on the combination of iguratimod and corticosteroids, including 11 studies, and showed that iguratimod improved both ESSPRI and ESSDAI without increasing side effects. However, the lack of studies in diverse geographic populations, short follow-up periods, high bias in data collection, and the overall low quality of the studies included suggest caution when interpreting these results (114).

Topical treatments

Topical treatments have been the mainstay of relief for the cardinal symptoms of dryness in SjD. These include simple lubricating agents such as artificial tears or pharmaceutical eye drops, including cyclosporine and lifitegrast. A recent RCT confirmed the efficacy of 0.05% cyclosporine eye drops in treating dry eye associated with primary SjD. Sixty patients were randomly assigned to three groups (0.05% cyclosporine treatment, artificial tears, or a combination of both) for three months. Results showed that all symptoms (ocular dryness, foreign body sensation, photophobia, and burning), as well as objective measures such as Schirmer's test and ocular staining scores, improved the most with combination therapy. The least favourable outcomes were associated with the use of artificial tears alone (115). In line with these findings, a retrospective study involving 23 patients demonstrated that increasing the cyclosporine dose from 0.05% to 0.1% led to an improvement in

objective dryness measurements when 0.05% cyclosporine proved ineffective. However, this higher dose came at the cost of lower tolerability, with nearly 40% of patients reporting treatment-related adverse events, primarily transient instillation pain (116).

For patients who do not tolerate or respond to cyclosporine, platelet-rich plasma (PRP) and autologous serum (AS) eye drops have been used over the past decade to treat autoimmune-related dry eye. The evidence supporting their efficacy is limited, based on small patient populations with mixed results. In fact, a recent randomised, double-blind study comparing AS and PRP in 38 participants found no significant differences in efficacy or safety after three months of treatment. Given that PRP has a shorter preparation time than AS, it may be a viable and more suitable alternative treatment for dry eye in SjD (117).

Additionally, last year saw the first human trial of lacripep, a synthetic 19-amino acid fragment of lacritin, tested for its safety, tolerability, dosing, and efficacy. Lacritin was discovered by screening natural protein agonists of tear secretion *in vitro* and has been found to be strikingly downregulated in the tears of patients with SjD. This study, conducted across 35 clinical centres in the United States, included three treatment arms (placebo, 22 μM Lacripep, and 44 μM Lacripep, administered three times daily for 28 days, with a 14-day run-in and 14-day washout period). The primary efficacy endpoint (mean change from baseline to day 28 in corneal fluorescein staining total score in the study eye) was not met for either dose of Lacripep. Although this trial is the largest ophthalmic study to date in patients with primary SjD and dry eye, the results diminished initial enthusiasm. Further research is needed to explore lacripep's potential (118).

Non-pharmacological treatment

Given the scarcity of effective treatments for SjD, non-pharmacological interventions focus on symptom management and improving quality of life, particularly addressing dryness and fatigue. Recent development involves the use of non-invasive vagus nerve stimulation (nVNS). Wan-Fai conducted a sham-controlled, randomised trial to assess the effects of nVNS in patients with SjD. Forty participants were randomly assigned to receive either active (n=20) or sham (n=20) nVNS treatments twice daily for 54 days. The results were notable, with significant reductions in PRO-F Physical, PRO-F Mental, and fatigue Visual Analog Scale (VAS) scores at day 56 in the active group. However, it is important to note that a considerable proportion of participants did not complete all the study evaluations (119).

Additionally, a revolutionary study on salivary electrostimulation, called LEONIDAS-1, was conducted last year across two UK centres to assess the feasibility of electrostimulation within the context of a clinical trial. The study included 30 randomised participants (active n=15, sham n=15), with a recruitment rate of 2.73 participants per month. While efficacy outcomes were modest, showing a statistically significant difference only in the xerostomia inventory, the study was not powered for efficacy and lays the groundwork for a future, more robust clinical trials (120).

Take home messages

- The anti-BAFF receptor ianalumab is currently under investigation for SjD in a phase III clinical trial, based on previous positive results on ESSDAI score (106).
- Telitacicept, a fusion protein targeting BLyS/APRIL-binding domain of the TACI receptor and the Fc fragment of human IgG1, was evaluated in a small phase II trial, with positive results, to be correctly interpreted according to trial's construction limitations (107).
- Anti-CD38 daratumumab might be effective in SjD cases refractory to rituximab, possibly due to the additional benefit of locally depleting autoantibodies producing cells (108).
- Targeting B-T cell co-stimulatory pathway seems promising, according to the favourable preliminary results of iscalimab and dazodalibep clinical trials (109).
- The ongoing evaluation of TYK2 inhibitor deucravacitinib will shed more light on the therapeutic action of IFN blockade in SjD.

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