Review

Sjögren's syndrome: one year in review 2023

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Received on November 10, 2023; accepted on December 5, 2023.

Clin Exp Rheumatol 2023; 41: 2343-2356.

Key words: Sjögren's syndrome, pathogenesis, B cells, T cells, epigenetics, lymphoma, therapy

Competing interests: C. Baldini is the principal investigator in RCT for GSK, Sanofi, Horizon, Novartis, has received consultancy fees from Horizon and Aurinia, and educational contributions from Sanofi and GSK. The other authors have declared no competing interests.

ABSTRACT

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disorder characterised by the T-cell-mediated hyperactivation of B-cells and cytokine production. The condition may evolve from an asymptomatic, indolent course, with glandular involvement, to extra-glandular systemic manifestations up to lymphoma development. On tissue level, the typical feature is the lymphocytic infiltration of the salivary gland by B-, T- and antigen presenting cells, as mirrored by the diagnostic cornerstone role of minor salivary gland (MSG) biopsy.

Recently, increasing research focused on the investigation of mechanisms underlying the complex pathogenesis of the disease and highlighted the multifactorial nature of SS consisting of concomitant involvement of environmental, genetic, neuroendocrine and immune factors. In particular, many aspects have been investigated regarding genetic and epigenetics, the role of specific B- and T-cell phenotypes and the investigation of disease-specific biomarkers as predictors of disease development, activity, and lymphomagenesis. Surely, a deeper understanding of these multiple mechanisms may facilitate earlier diagnosis, enable subphenotyping of patients and open novel therapeutic possibilities 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 pSS pathogenesis and clinical features focusing in particular on new insights into pSS molecular stratification and therapeutic advances in the era of precision medicine.

Introduction

Primary Sjögren's syndrome (SS) still represents a complex autoimmune disease with multiple concomitant genetic, epigenetic, environmental, inflammatory and immune factors contributing to its pathogenesis. This great heterogeneity in disease pathobiology surely reflects in the high variability of clinical manifestations and disease-specific phenotypes, thus representing a significant barrier to identify reliable biomarkers able to stratify patients according to different prognosis and to develop targeted therapies. Recently, proteomic stratification methods are increasingly applied to address the extreme pathophysiological and clinical heterogeneity of SS with interesting and promising results. Moreover, the expanding knowledge of disease pathogenetic mechanisms and the recent identification of specific and well distinct disease clusters led to the development of several clinical trials addressing specific pathogenetic pathways of the disease, with conflicting results.

Following previous series, in this review we will provide un update of the most recent literature on SS pathogenesis and clinical features, focusing in particular on new insights into SS genetics and epigenetic, innate and adaptive immune system abnormalities, as well as disease-related glandular and extra-glandular manifestations. Finally, in the era of precision medicine, we will focus on recent development and published trials on SS therapy trying to analyse potential pitfalls and remaining inquiries which may explain failures of some systemic therapies.

New insights into pathogenesis

Genetics and epigenetics

The identification and definition of genetic risk of SS represents an essential tool to characterise molecular mechanisms underlying disease pathogenesis and to promote the development of new therapeutic approaches to improve early diagnosis and treatment. In the last year, a relevant contribution to SS ge-

netic come from the study of Khatri et al., who performed the largest genome-wide association study (GWAS) of SS patients of European ancestry, consisting of 3,232 cases and 17,481 controls. Through their investigation, they pinpointed 10 previously unknown genetic risk loci, effectively increasing the total number from 12 to 22 and elucidating a substantial portion of disease heritability. Fine-mapping and deep bio-informatic analyses revealed novel functional implications, collectively impacting the expression of more than 40 additional genes, which are instrumental in the pathogenesis of the disease (1). Moving to epigenetic, a previously uncharacterised long non-coding RNA (lncRNA) called LINC01871 has been demonstrated to be overexpressed in SS patients, regulated by both IFNγ and calcineurin/NFAT signalling pathways, and acted as a key regulator of T cell-driven pathogenesis (2). An important piece of the striking female predominance puzzle in SS was set by Shaw *et al*., who profiled minor salivary gland (SG)-derived mesenchymal stromal cells (MSCs) from female SS patients and controls. The authors demonstrated an X-linked gene skewing towards one of the two X-chromosomes and a deregulation of the HLA-expressed microRNA miR6891-5p. This miRNA induced histone modifications and allelic skewing, providing valuable insights into the mechanisms underlying the gender disparity in SS (3).

Innate and adaptive immunity

Together with genetic and epigenetic mechanisms, dysregulation of innate and adaptive immunity contributes in disease pathogenesis. The transcriptomic, phenotypic and functional profile of type 2 conventional dendritic cells was investigated for the first time in SS patients. Significant alterations in gene signature, antigen presentation (including self-antigens) and CD4+ T cell migratory landscape were found and validated, unravelling their crucial role, and potentially serving as a novel therapeutic target (4). Similarly, plasmacytoid dendritic cells (pDCs) and monocytes from SS patients were also observed to exhibit a hyperresponsiveness to STING DNA-sensing pathway stimulation, irrespective of interferon (IFN)-I activation (5). In a recent interesting study by the Necessity consortium, transcriptomic, proteomic, cellular and genetic data were integrated with clinical phenotypes of 351 SS patients in order to characterise the molecular and clinical variabilities of the disease. Transcriptomic analysis and ultrasensitive digital single molecular arrays of the prospective cohort demonstrated a strong IFN transcriptomic signature, mainly driven by circulating IFNα and not by IFNγ protein levels (6). Interestingly, IFNα protein levels, detectable in 75% of patients, were significantly associated with clinical and immunologic features of disease activity at enrolment and with increased frequency of systemic complications over the 5-year follow-up. Genetic analysis revealed a significant association between IFNα protein levels, a major histocompatibility class II haplotype and anti-SSA antibody, thus suggesting that IFNα more than IFNγ may act as the primary driver of SS pathogenesis (6).

Moreover, in the previous year, the autoreactive B cell repertoire underwent deeper investigation (7, 8). Utilising an integrative multiomic approach in assessment of circulating and tissue resident B cells of SS patients, Broeren et al. demonstrated the presence of a tissue restricted clonal expansion of rheumatoid factor (RF) and anti-nuclear antibody (ANA) clones residing amidst a background of polyclonal repertoire (7). Rheumatoid factor clones displayed an affinity maturation directed towards IgM and depended more on B cell receptor (BCR) integrity, in comparison to ANA repertoires, typified by an immunoglobulin (Ig) G1-directed affinity maturation. Somatic hypermutation and high intra-clonal diversification progressed only in RF clones in patients with associated lymphoma and only after immune repopulation following rituximab, implying their central pathogenetic role. B cell receptor signalling was recently shown to be additionally regulated by the global glycosylation profile of B cells, with SS patients exhibiting hypo sialylation, even though Neys *et al*. did not observe an increased BCR signalling in SS patients compared to sicca controls and healthy subjects (9). However, the authors demonstrated a significant down-regulation of BAFF-receptor expression in SS patients in comparison to non-SS sicca subjects, suggesting that reduced BAFF-receptor expression is a possible sign of early B cell involvement in SS (9, 10).

Regarding the role of T cells in the immunopathogenesis of the disease, several studies warrant attention. A quantitative analysis of labial SG gland tissues of untreated SS patients revealed that the predominant type of resident T cells is represented by activated CD8+ cytotoxic T cells (CD8+ CTLs). Spatial analysis showed an accumulation of FasL expressing CD8+ CTLs around apoptotic Fas-expressing epithelial cells, exposing their potential damaging effect on neighborhood cells (11). Furthermore, an abundance of T follicular helper cells (Tfh) was found to infiltrate the affected tissues. The well-known role of Tfh cells in SS involves T cell-dependent B-cell responses and germinal centre formation, and their correlation with disease activity is well-established. Intriguingly, Liu *et al*. showed that thymocyte selection-associated high mobility group box protein (TOX) promotes Tfh differentiation in SS. Simultaneously, He *et al*. implicated the epigenetic regulator EZH2, operating through STAT3 phosphorylation in CD4+ T cells, as an alternative contributing factor (12, 13).

The role of epithelium

SS is recognised as an autoimmune epithelitis, reflecting the cardinal role of the epithelium as an orchestrator of the autoimmune response. This scientific model was further recently explored with the identification of the LAMP3/HSP70/BMP6 axis, establishing a crucial link between SS gland dysfunction and inflammation. In particular, Mo *et al*. showed that lysosome-associated membrane protein 3 (LAMP3) is markedly overexpressed in epithelial cells causing the release of HSP70 through a caspase-dependent lysosomal exocytosis process. The released HSP70 acts as an endogenous natural Toll-like re-

ceptor (TLR)-4 ligand in mononuclear cells, thereby triggering their activation and subsequent release of BMP6. Notably, BMP6 is a protein associated with secretory hypofunction, thus setting in motion a vicious cycle between the epithelium and the infiltrating inflammatory cells (14). Moreover, Colafrancesco *et al*. demonstrated that SG epithelial cells from SS patients escape cellular turnover exhibiting increased autophagy, increased expression of antiapoptotic molecules and reduced apoptosis compared to patients with non-SS sicca syndrome, suggesting that autophagy may strongly contribute to the pathogenesis of the disease and may be considered a potential new therapeutic target (15).

The role of gut microbiota

Worthy of note is the work conducted by Wang *et al*. focusing around the role of the human microbiome in the etiopathogenesis of the disease, thus contributing to the growing body of literature that highlights a potential link between an imbalance in the gut microbiota and the faecal metabolome and the pathogenesis of SS (16, 17). The authors depicted an oral and, to a lesser extent, gut and vaginal dysbiosis after examining samples of 133 SS patients by 16S ribosomal RNA gene sequencing. Interestingly, these microbial alterations were found to precede the development of the disease (18).

Take home messages

- The largest genome-wide association study of European SS patients' ancestry identified 10 previously unknown genetic risk loci which may be associated to higher risk of disease susceptibility (1).
- A novel long non-coding RNA (lncRNA), called LINC01871, has been demonstrated to be overexpressed in SS patients and to act as a key regulator of T cell-driven pathogenesis (2).
- Transcriptomic analysis of a prospective SS cohort enrolled in the Necessity consortium demonstrated that IFNα may be the main driver of disease and associated with disease activity and increased frequency of systemic complications at follow-up (6).
- Multiomic approaches and quantitative analysis of salivary gland tissues allowed a deeper characterisation of B and T cell phenotypes in the pathogenesis of the disease (7-13).
- The LAMP3/HSP70/BMP6 axis and autophagy have been identified as a novel mechanism exerting a role in SS glandular epithelial cells apoptosis, dysfunction and inflammation (14, 15).

Glandular involvement

Glandular involvement represents a hallmark of SS with dry mouth and dry eyes being the leading symptoms. Besides labial, major salivary and lachrymal glands, recently it has been hypothesised that also SGs located between the throat and the nasal cavity (*i.e*. tubarial glands) might be compromised leading to dry rhinopharynx (19). At present, minor SG biopsy (MSGB) still plays a key role in the diagnostic work-up of suspected SS allowing to detect and quantify the severity of the inflammatory infiltrate within the glands. Recently, major SGB has been proposed as a valuable alternative for both SS diagnosis and prognosis stratification. The combined prevalence of postoperative complications after major and MSGB has been recently evaluated in a systematic review and meta-analysis that included 3208 patients. The authors reported that, although prevalence of post-surgical complications (11%) and of neurological complications (3%) were higher than previously reported, permanent complaints were uncommon (20).

Indeed, the clinical diagnostic utility of repeated MSGB in patients with suspicion of SS has been questioned. Recent literature showed that since a second MSGB changed the initial diagnosis in only a minority of patients, it should be considered only when clinical manifestations deeply change in the course of the disease. Specifically, according to Parreau *et al*., the biopsy should be repeated during follow-up when non-Hodgkin B-cell lymphoma (NHL) is suspected (21). Indeed, in this study, MSGB enabled NHL diagnosis in half of patients with suspected lymphoma.

Salivary gland histopathology is also crucial in the phenotypic and prognostic stratification of the disease. The association between histopathology and biological abnormalities in SS has been widely underlined. In this setting, scleroderma-specific autoantibodies can be frequently detected in patients with sicca complaints and at high titers were independently associated with MSGB positivity (22). Moreover, important contributions have been published on B cell recirculation among ectopic germinal cell structures in the glands and on migration of B cells into the epithelium leading to lymphoepithelial lesions (LEL) formation. These studies allowed to shed new lights on attenuation of the severity of the glandular infiltrate as an important treatment goal to prevent glandular damage and B cell lymphoproliferative complications in SS (23, 24). In particular, lineage tree analysis revealed significant clonal expansion within the MSG with the identification of shared dominant B cell clones suggestive of extensive recirculation across different SGs. Interestingly, several shared clonotypes with high proliferating capacity displayed IgH-VH gene usage common in autoreactive B cells, including VH1-69, which is typical of RF+ B cells representing potential lymphoma precursors (23).

In terms of phenotypic stratification, risk for damage accrual and prognosis, another important contribution in SS has been provided by patients reported outcome (PROM)s collection and symptom-based cluster analysis, an innovative approach that has recently been proposed to provide a better subclassification of patients. McCoy *et al*., by analysis of the Sjögren's International Collaborative Clinical Alliance (SICCA) Registry and the Sjögren's Foundation survey, performed a hierarchical clustering of symptoms by levels of dryness, fatigue and pain. The authors identified four clusters among 1.454 SICCA registrants and 2.920 Sjögren's Foundation survey participants: 1) low symptom burden in all categories (LSB); 2) dry with low pain and low fatigue (DLP); 3) dry with high pain and low to moderate fatigue (DHP); and 4) high symptom burden in

all categories (HSB). A disagreement between objective measures and treatments was demonstrated and patients in the HSB, despite a limited systemic activity, received immunomodulatory treatment most frequently (25). In conclusion, glandular involvement in SS represents a key aspect of the disease and new insights into its characterisation may provide a significant improvement in patient phenotyping and targeted therapy.

Take home message

- Lineage tree analysis revealed several shared B cell clonotypes with high proliferating capacity and displaying IgH-VH gene within salivary gland tissue suggestive of extensive recirculation of B cell clones (22).
- A hierarchical clustering of symptoms by levels of dryness, fatigue and pain of a wide cohort of SS patients allowed the identification of four distinct clusters which may be employed in better patient phenotyping and in target treatment choice (24).

Imaging

Traditionally, the workup of SS has been based on the major SG ultrasonography (SGUS), mainly using B-mode. Recently, a growing interest has arisen in imaging, leading to the US assessment of other exocrine glands, including lacrimal (LGUS) and labial SGs (LSGUS), and in employing different US techniques, as colour-Doppler (CD) and shear wave elastography (SWE). The widespread use of US made it necessary to develop scoring systems that could be appropriate to each contest and reproducible in research and clinical settings.

As regard greyscale, MSG heterogeneity has been assessed by Outcome Measures in Rheumatology (OMERACT) in a semiquantitative scoring system (range 0–3). SGUS OMERACT score proved to be a specific diagnostic tool (90% CI 0.744, 0.965) with good reproducibility (κ=0.73 CI 0.64, 0.81) (26). Moreover, the OMERACT score has also been tested in LSGs showing good inter-observer reliability (ICC values > 0.9 for scores 0 and 1, ICCs of 0.873 for score 2, and 0.785 for score 3) (27). Recently, a study focusing on US characteristic of LGs in SS demonstrated that a semiquantitative score was useful in distinguishing SS patients from those with idiopathic sicca syndrome. The combination of intraglandular branch of lacrimal artery and inhomogeneity on both sides was most suitable for classifying SS (area under curve = 0.724, CI 0.620–0.828) (28). In this setting, LGUS may be considered a feasible, easy to perform, low cost, non-invasive and with a good inter and intra-rater reliability technique to be employed in SS patients, although significant challenges still limit its application (29).

Colour-Doppler may identify abnormal neo angiogenesis and OMERACT semi-quantitative scoring system revealed excellent intra- reader reliability (0.90 CI 0.87–0.93) and good inter-reader reliability (0.80 0.74–0.84), suggesting future employment due to the reproducibility. On the other hand, SWE is a poorly explored, non-invasive technique that quantifies the stiffness of tissues. Major SG SWE displayed a moderate inter-reliability (ICC=0.64), a moderate to good intra-rater reliability (ICC=0.73–0.83) and from good to excellent diagnostic performance (AUC=0.80–0.937) (30). Moreover, LSG SWE has been demonstrated to associate with disease activity, assessed by ESSDAI, IgG levels and hypocomplementaemia (31).

The grey scale SGs method has been also analysed, in particular its associations with histological features, serological characteristics and endotypes. Both in parotid and in LSGs, the inhomogeneity correlated with the focus score of the respective gland. Interestingly, comparable values were found in the different glands, respectively r=0.574 and r=0.532 (32). Importantly, US features suspicious for lymphoproliferation were typified in major and LSG, the most important being very hypoechoic areas and high-intensity Doppler (33). The relationship between US and autoantibodies was deeply explored using the different serological positivity: single Ro-60/SSA, single Ro-52/SSA, Ro-52/SSA Ro60/SSA double reactivity and Ro-52/SSA, Ro-60/SSA and La-SSB triple reactivity. Indeed, SGUS showed increasing values in the different serological groups (34). Furthermore, a higher SGUS was associated with a specific phenotype characterised by dryness dominant with fatigue (34).

Finally, US has proved as useful technique in SG biopsies. In MSGs, US-guided core needle biopsy is safe and non-inferior to incisional biopsy whereas in LSGs can provide samples with a larger area (35, 36).

Take home messages

- The Outcome Measures in Rheumatology (OMERACT) semiquantitative scoring system was demonstrated to be a specific diagnostic tool, with good reproducibility and good inter-observer reliability also in the evaluation of SS labial and lacrimal salivary glands (26-28).
- Major salivary gland shear wave elastography may be considered a novel tool in the evaluation of glandular tissue in SS patients (30, 31).
- Ultrasonography-guided core needle biopsy of major salivary gland has been confirmed as safe and non-inferior to incisional biopsy whereas in labial salivary glands can provide larger samples (35, 36).

Extra-glandular involvement

Extra-glandular involvement has been reported in about one-third of SS patients. Since patients can experience a diverse array of clinical manifestations, extra-glandular involvement surely represents a clinical challenge in SS patients.

One of the most common extra-glandular manifestations is lung involvement, with interstitial lung disease (ILD) being the most frequent, generally associated with poorer prognosis and thus requiring its identification at an early stage (37). Therefore, in 2022, a major effort has been made to try to identify a patient phenotype more likely to develop lung involvement. In this setting, a recent study including around 200 newly diagnosed SS patients demonstrated that, in comparison to sicca-onset patients, SS-ILD ones presented an older age at diagnosis, less pronounced

sialadenitis structural changes and with sicca symptoms probably overshadowed by the respiratory disease (38). Non-sicca onset, older age, longer disease duration and other features, like Raynaud's phenomenon, lymphopenia, low baseline forced vital capacity (FVC) and dry cough seem to predict ILD development (39-41). Moreover, some serum biomarkers, such as eotaxin, TGF-α, NFα and KL6, may be associated with higher risk of ILD, especially highlighting a promising role of KL6 in predicting SS-ILD prognosis (42). Moreover, decreased circulating Th2 cells and an elevated Th1/Th2 ratio have been identified as immunological mechanism underlying the development of ILD in SS in a recent retrospective study (43).

Neurological complications of SS are reported in about 15% of patients and are characterised by a wide spectrum of clinical manifestations, as recently reviewed (44). Moreover, neurological involvement may significantly influence patient prognosis. In this setting, a recent retrospective nationwide study using the French Health insurance database and involving more than 25.000 SS patients, incidence of hospitalisation for dementia, multiple sclerosis, encephalitis and peripheral neuropathy was significantly higher in SS patients as compared to general controls (45). In order to better characterise pathogenic mechanisms potentially involved in neurological involvement, in the last year, some studies focused on corneal nerve fibre analysis by corneal confocal microscopy as potential non-invasive tool to characterise SS patients with neurological involvement. A small cohort of SS patients with neurological involvement were characterised by significantly reduced corneal nerve fibre density and corneal nerve fibre main branch density in comparison to healthy subjects, although no significant difference was detected in comparison to patients with chronic inflammatory demyelinating polyneuropathy (46). Moreover, SS patients with small fibre neuropathy (SFN) display a different corneal nerve plexus density and morphology, mainly characterised by an increased number of nerve plexus neuromas, in comparison to SS patients without SFN, thus suggesting potential different patterns which may specifically characterise SS patients with SFN (47).

Moreover, recent studies focused attention on different features of nervous system involvement in SS, as hearing loss, a condition frequently observed in patients with systemic autoimmune diseases, as well as smell and taste functional impairment (48). In particular, a subclinical vestibular involvement has been demonstrated by vestibular-evoked myogenic potentials and video head impulse tests suggesting that SS patients should be evaluated more carefully to early detect audio-vestibular involvement (49).

Evidence for central nervous system involvement in SS is quite limited. Moreover, significant concerns arise from its diagnostic complexity. In this setting, a recent review highlighted magnetic resonance imaging (MRI) lesions in SS patients, involving the conventional examination, volumetric and morphometric studies, diffusion tensor imaging (DTI) and resting-state fMRI (50). The most common radiological lesions were white matter hyperintensities, scattered alterations hyperlucent on T2 and FLAIR sequences, typically located in periventricular and subcortical areas. To note, DTI and resting-state fMRI examinations showed convincing correlations with cognitive impairment (50), a manifestation often associated with depression and anxiety in SS patients. In this setting, a recent study aimed to characterise patterns of neurocognitive profile in SS patients with cognitive complaints (51). Cognitive complaints were supported by measurable pathological cognitive profiles, as hippocampal profile, besides associated psychiatric disorders (51). Indeed, SS patients with cognitive impairment display diffuse decreased structural connectivity changes mainly in the fronto-parietal network by diffusion tensor imaging (52).

Concomitant comorbidities, including infection risk, cardiovascular (CV) disease and solid neoplastic diseases, may also influence SS-related morbidity and mortality. A large French retrospective study demonstrated that SS patients are characterised by a higher risk of hospitalisation for community infections, especially of bronchopulmonary and intestinal tract, in comparison to matched controls (53). Moreover, a recent meta-analysis confirmed that SS is significantly associated with increased risks of haematological malignancy besides NHL and solid cancer (54). However, the high heterogeneity of studies included, the different design of the studies and the lack of adjustment for potential confounders, as smoking habit, deserve extreme caution in data interpretation. For example, the risk of breast cancer in SS showed a clear geographical distribution, being lower in European countries and higher in Asian countries and Argentina, thus suggesting environmental and local factors contributing to the risk of breast cancer in these patients (55). Finally, in the recent year, studies confirmed the importance of CV comorbidity in SS (56). In particular, the pivotal role of traditional CV risk factors in contributing to CV morbidity was confirmed. In this setting, SS patients are characterised by a significant increased prevalence of hypertension in comparison to the general population and, intriguingly, risk of hypertension was associated with higher disease duration and positive anti-SSA antibody, thus confirming the contribution of disease-specific features in CV disease in these patients (57). Studies also investigated CV risk among diabetic SS patients (58). Interestingly, beside hypertension, hyperlipidaemia and diabetes mellitus itself, SS emerged as independent risk factor for CV risk, suggesting that SS patients with concomitant diabetes mellitus should be monitored more closely to detect CV complications.

Finally, systemic chronic symptoms like fatigue, pain, depression, and sleep disorders are major clinical manifestations of SS, significantly impairing patient quality of life. According to recent findings, fatigue has the largest impact on daily activity and affect performance (59). In this setting, performance, assessed during a sustained maximal voluntary contraction of a hand muscle, is limited by a reduced

capacity of the CNS to sustain output to the muscle (59). Furthermore, a relationship between self-reported fatigue and objective decline in performance has been demonstrated (60). Pain and sleep disorders are also common findings in patients with SS. Different types of pain can be observed in these patients, either simultaneously or at different time points. In particular, a cross-sectional study demonstrated higher frequency and severity of central sensitisation, a pain processing disorder resulting from the persistent activation of spinal and supraspinal neurons, in SS patients as compared to healthy controls, significantly associated with sleep quality disorders (61).

Take home messages

- Some serum biomarkers, such as eotaxin, TGF-α, NFα and KL6, as well as decreased circulating Th2 cells and elevated Th1/Th2 ratio have been identified as potential factors contributing to interstitial lung disease development in SS (42, 43).
- Analysis of corneal nerve fibre pattern and corneal nerve plexus density by corneal confocal microscopy has investigated as potential non-invasive tool to characterise SS patients with peripheral nervous system involvement, including patients with small fibre neuropathy (SFN) display a different (46, 47).
- Early subclinical vestibular involvement has been demonstrated by vestibular-evoked myogenic potentials and video head impulse tests in SS patients (49).
- Infection risk, cardiovascular disease and higher risk of haematologic neoplasia, in particular lymphoma, have been confirmed as the most frequent comorbidities in SS (53, 54, 56).

Novel insights into SS-related lymphoma

Lymphoproliferation and lymphoma development are two major well-described complications in SS, in particular NHLs and extra-nodal marginal zone lymphoma of MSGs (*i.e.* salivary MALT lymphoma). This is explained by the pivotal role of dysregulated hyperactive B-cells in SS pathogenesis and their intricate interactions with other immune system actors and SG epithelium. Many efforts have been made in recent years to shed light on epidemiology and pathogenetic mechanisms of SS-related lymphoma, as well as accurately phenotyping SS-subjects at high lymphoproliferation risk toward a better management of this complication. Hereby, we report the most recent evidences concerning these fields.

Epidemiology: new perspectives

The reported mean prevalence of lymphoma in SS is about 5% with an overall risk ranging from 10.5 to 48-fold higher than healthy population. Despite these data, our view is still limited as most of the previous studies were often small, with a high population heterogeneity and a relatively low number of lymphomas included. To overcome these limitations, two studies, one from Sjögren Big Data Consortium (62) and the other from the Greek group (63), were conducted. In the first, a multicentre analysis was carried out including almost 12.000 SS patients among which 414 affected by a concomitant haematological malignancy, while, in the other study, a harmonised dataset of 878 SS patients recorded from 1981 to 2021 was analysed. In both studies, mature B-cell lymphoma was the most represented with a prevalence in SS cohorts ranging from 3% to 16.7% (62, 63). The main histotypes reported were MALT lymphoma (50% in Big Data and 76% in Greek cohort, respectively), diffuse large B-cell lymphoma (DLBCL) (16% *vs*. 9%) and NMZL (7% *vs*. 6.6%).

Alongside these data, other studies in the last year investigated the prevalence of lymphoma in SS using administrative databases. Saleh *et al*. depicted a prevalence of NHL in Florida of 2.6% in SS patients with a 7.4-fold increased risk in comparison with general population; surprisingly, the most common NHL was DLBCL followed by NMZL, while no MALT lymphoma was reported, probably due to its classification under the term 'other NHL' (64). Treppo *et al*., in a study performed to evaluate cancer risk among individuals with connective tissue disease in Northeastern Italy, confirmed the higher risk of NHL in SS patients (3.84-fold higher than healthy population) (65). This was also confirmed in a large systematic review which demonstrated a significant 13.7-fold higher risk of NHL in SS in comparison to general population, also highlighting the association with other haematological or solid malignancies such as Hodgkin lymphoma, multiple myeloma, leukaemia and thyroid, kidney, liver, prostate and lung cancers (66).

Lymphomagenesis: new perspectives

Pathogenesis of lymphoma in SS is a complex and not yet fully understood phenomenon. According to the most accepted model, lymphomagenesis in SS is a multistep process in which chronic inflammatory antigenic stimulation leads to B-cell hyperactivation. Following the intervention of several predisposing cytokines and the onset of oncogenic events, a benign lymphoproliferation, histologically expressed by lymphoepithelial lesions (LELs), may derail to MALT lymphoma or, in a minority, to DLBCL (67).

According to this model, SG microenvironment is crucial in SS-related lymphomagenesis. In this context, LELs, which are present in about 50% of SS SGs, play a pivotal role, not only as passive expression of lymphoproliferation but also as major actors. This is particularly true considering the recent finding of GPR34 gene mutation in SG MALT lymphomas. GPR34 is a G-protein coupled receptor which, through the binding with its ligand LysoPS, whose main source are LELs, regulates the activation of several pathways involved in apoptosis and cell cycle. The mutation of this gene, together with a paracrine stimulation caused by LELs, leads to a persistent and dysfunctional activation of GPR34 conferring an apoptotic resistance and a high malignant transformation potential to SGs B-cells who display this mutation (68). Moreover, LELs are also a potent source of TLR ligands such as RNA-RNP particles which, in turn, bind soluble IgM-Rheumatoid Factor (RF) promoting the formation of immune-complexes (ICs). ICs represent a strong stimulus for RF-

expressing B-cell clonal expansion induced by the production of BAFF and type I IFN cytokines by the same LELs (69). In association with LELs, also B-cells are critical in SS lymphomagenesis. This has been particularly investigated by Broeren *et al*. (70) and Carlotti *et al*. (71) by the analysis of B-cell repertoire analysis in SG tissues of SS patients. Interestingly, SS MALT lymphoma contained primarily monoclonal RF expansions in SG, compared to SS tissue without lymphoma in which the repertoire was polyclonal (70). Moreover, B-cell clonotypes are characterised by an extensive recirculation among minor SGs of SS patients without and showed high proliferating capacity displayed by IgH-VH gene usage, including VH1-69, which is typical of RF B-cells. Analysis of B-cell clones in affected tissue of SS patients, although highly expensive, may be very promising in order to assist in SS lymphoproliferative risk stratification (71).

In addition to the role of LELs and B-cells, another peculiarity of MALT lymphomas in SS is represented by its mutational profile. According to Bult et al. (72), SS MALT lymphoma shows a relative genomic stability. By whole exome sequencing and FISH in specimens of 17 SS-related parotid MALT lymphomas, the authors demonstrated that, among the main genes involved in classical MALT lymphomagenesis (TBL1XR1, CCR6, TNFAIP3, NOTCH2, PAX5 and APC), in 14/17 patients the mutational burden was low, whereas in the remaining 3 the high mutational burden was associated with severe SS activity, systemic lymphoma relapses and advanced clinical stage; notably, no MALT1 translocations were found. A potential explanation of this discrepancy between SS MALT lymphoma and non-SS MALT lymphoma was that they may share a common ancestor but follow different evolutionary tracks in which, in the case of SS MALT lymphoma, the autoimmune salivary microenvironment is crucial.

In conclusion, the strong interconnection between inflammatory SG microenvironment, B-cell hyperactivation and peculiar oncogenic events that occurs in SS-related lymphomagenesis, which are rarely shared by other lymphomas, may suggest the idea that SS cannot only be considered as a simple autoimmune disease with lymphoproliferative complications but a lymphoproliferative disease itself. Surely, further research is strongly needed to deeply detect the pathogenesis of lymphoproliferation in SS.

New advances in SS-related lymphoma diagnosis: towards a better stratification

In view of the high heterogeneity of SS, many efforts have been made in recent years to ensure a correct stratification of lymphoproliferative risk through a careful patient evaluation of clinical, serological, imaging and histopathological features (73).

Salivary gland enlargement (SGE) is the first and most relevant predictor of NHL in SS. The Greek cohort confirmed this evidence with SGE occurring in 66% of SS patients before lymphoma diagnosis, mainly persistent (77.5%) and involving the parotid gland (92%) (63). Focusing on the relationship between NHL type and clinical presentation, SGE clearly identified SS with MALT lymphoma while lymphadenopathy was more common in NMZL and DLBCL while bone marrow, lungs and digestive tract are rarely involved. Constitutional symptoms were more frequent in DLBCL (62). Moreover, MALT lymphoma occurred mainly in young patients with a relatively short disease duration and characterised by a stage I or II at diagnosis, while DLBCL and NMZL were more frequent in older patients with a longer disease duration and characterised by a more advanced stage at diagnosis (III or IV) (62, 63).

In the context of MALT lymphoma, the importance of accurate parotid swelling (PSW) recording was recently highlighted by a multicentre study by De Vita *et al*. which included 144 SS patients who developed NHL during follow-up compared to 222 SS controls (74). They found that the event 'PSW' recorded at any time during SS course was significantly associated with future NHL development. In particular, the duration of PSW (2-12 months) and the persistence (>12 months) characterised more patients with future NHL development than controls while episodic PSW (<2 months) was similar in both groups (74). Therefore, PSW is an early and potent predictor of lymphoma in SS and its careful monitoring is crucial during the whole course of the disease for a correct lymphoproliferative risk stratification.

Another clinical phenotype to consider in SS patients is lymphadenopathy. Stergiou *et al*. enrolled 1234 SS patients of which 165 (13%) with persistent and stable lymphadenopathy. Although direct evaluation of lymphoma occurrence in this subgroup was not performed, they found a significant association with B-cell hyperactivity features, including SGE, cryoglobulinaemia, higher focus score (FS) and autoantibodies production (75). Moreover, B-cell hyperactivation and PSW are included in ESSDAI biological and glandular domains; despite total ESSDAI may not accurately reflect lymphoproliferative risk in SS, biological and glandular domains showed a statistically significant increase from SS diagnosis to lymphoma diagnosis (63), suggesting the importance of monitoring these domains as possible predictors of lymphoma.

Recently, thanks to a cloud-computing infrastructure and artificial intelligence models developed by HarmonicSS, four biomarkers have been identified as more predictive of NHL development in SS: SGE, cryoglobulinaemia, presence of RF and low C4 (76). Surely, the development of further AI models may aid in the profiling of SS-related lymphoproliferative risk. Importantly, clinicians should be aware that even if MALT lymphoma and DLBCL share many risk factors in SS, some biomarkers of lymphoma development (*i.e*. anti-SSA/Ro, anti-SSB/La, RF, low C4) are more specific for MALT lymphoma than for DLBCL (77).

In the last years, the application of imaging techniques to identify suspicious lesions in SS is increasingly growing. Ultrasonography, thanks to its wide availability, is nowadays the main tool to investigate SGs in patients with PSW or at high lymphoproliferative risk. Its

usefulness is mainly linked to the characterisation of focal lesions that may arise in SS SGs and in their differentiation from other SG mass-forming diseases, such as IgG4-related disease, amyloidosis, ANCA vasculitis, lithiasis as well as adenomas and carcinomas. In SS setting, an OMERACT 3 inhomogeneity combined with very hypoecoic oval, homogeneous, well-shaped lesion with posterior enhancement, hyperechoic septa and hypervascularisation is strongly suggestive for salivary MALT lymphoma and requires further investigations (78). Contrast-enhanced MRI and FDG-PET-CT are two other techniques that could effectively distinguish benign lymphoproliferation from MALT lymphoma and contextually overcome the operator-dependency of US, although more expensive and less available (79). In particular, in FDG-PET-CT scans, a parotid SUV>3.1 and a submandibular SUV>2.9 identify glandular MALT lymphoma with high sensitivity and specificity. Moreover, FDG-PET-CT may also identify other lymphoma localisations, such as regional lymph nodes or lung nodules (79).

Nevertheless, major SG biopsy is essential for the definite SS lymphoma diagnosis and recently US has been employed as a precious support in this procedure. Safety, patient acceptance and diagnostic accuracy of US-guided core needle (US-CNB) biopsy has been demonstrated in 30 SS patients undergoing major SG biopsy for suspected lymphoma in which the US-CNB, performed in the parotid 'safety area' where facial nerve deepen into the gland, was only associated with transient swelling, minimal haematoma, transient paraesthesia or facial palsy, all with spontaneous resolution in few days (80). Moreover, procedure diagnostic yield was optimal, with very few patients (2/30) without adequate samples, and allowed MALT lymphoma diagnosis or its exclusion in almost all patients (80). On the other hands, a recent study by Parreau *et al*. involving 24 SS patients with established NHL demonstrated 50% of probability to diagnose lymphoma by minor SG biopsy (81). This low sensitivity supports the evidence that, although minor SG biopsy remains a valuable tool in SS diagnosis, it is insufficient for the diagnosis of an associated lymphoma.

In the future, an improvement of the diagnostic tools already available (*i.e*. US) and the development of new AI SS models will allow to achieve a better SS-related lymphoproliferative risk stratification with a positive impact both on patient management and on healthcare system, thus avoiding unnecessary procedures and eventually overdiagnosis.

Outcome and management of SS-related lymphoma: what have we learned?

Although most SS-related lymphomas are MALT lymphomas confined to the SGs with a generally favourable prognosis, the rarer but more severe DLBCLs and NMZLs as well as MALT lymphomas with high systemic burden must be considered as their significant impact on life expectancy of SS patients. Analysis of the Big Data Consortium and the Greek cohorts showed a mean overall survival of 87% at 8 years and 78% at 10 years in SS patients with NHL, respectively (62, 63). The main causes of death were neoplastic progression (51%) and infections (31%) (62). In particular, in the Big Data Consortium, MALT lymphoma overall survival at 1, 2 and 5 years was 93%, 90% and 86.5%, respectively (62) while, in the Greek cohort, MALT lymphoma overall survival was 91% at 5 years and 79% at 10 years (63). On the other hand, DLBCL and NMZL overall survival was 54% and 62.5% at 5-years and 41% and 46% at 10-years, respectively, confirming their higher prognostic aggressiveness. Interestingly, while DLBCL and NMZL were characterised by a short-time negative prognosis, MALT lymphoma showed an indolent course in the short term but an overall survival reduction in the long term, highlighting the need of a prolonged and close observation of SS patients with MALT lymphoma due to its late negative evolution risk.

As far as SS-related lymphoma management is concerned, many therapeutic strategies have been undertaken in order to manage B-cell lymphoproliferation, mainly based on B-cell depleting agents (Rituximab) or BAFF-antagonists (Belimumab) (82, 83). This approach is essential in DLBCL treatment but not always necessary in MALT lymphoma, given its non-complete response to Rituximab. Indeed, as recently demonstrated, B-cells are able to recirculation and independently proliferate in SGs and the BAFF-rich prostimulatory salivary microenvironment secondary to an indiscriminate B-cell depletion may lead to an incomplete elimination of the neoplastic clone or to selection of other clones (70, 71).

Management of SS lymphoma still represents an unmet need. New biomarkers, a better stratification and the development of new therapies able to target B cells and the salivary microenvironment (hypothetically, rituximab/belimumab combination, ianalumab or GPR34 inhibitors) may offer a new approach towards personalised treatment of SS patients (68, 84, 85).

Take home messages

- Prevalence of different lymphoma isotypes has been deeply characterised in two wide multicentre SS cohorts (62, 63).
- Lymphoepithelial lesions, peculiar oncogenic events and B cell hyperactivation have been demonstrated to exert a central role in lymphoma pathogenesis (68-72).
- Parotid salivary swelling has been identified as early predictor of lymphoma in SS (74).
- Ultrasonography OMERACT score, contrast-enhanced MRI and FDG-PET-CT are pivotal techniques that may be employed to distinguish benign lymphoproliferation from MALT lymphoma in SS (78, 79).
- Therapeutic strategies based on B-cell depleting agents (Rituximab) or BAFF-antagonists (Belimumab) have been undertaken in order to manage B-cell lymphoproliferation (82, 83).

What is novel in SS treatment

Nowadays, despite the growing knowledge about SS pathophysiology, treatment of SS remains mainly empirical

and symptom-targeted, ranging from saliva and tear substitutes to analgesics and glucocorticoid (GC)s for the management of pain and fatigue. Strong evidence regarding the use of immunosuppressive drugs is still lacking and these drugs are mainly employed as GC-sparing agents (86). The early experience in SS therapeutic trials in repurposing therapies used in other autoimmune rheumatic diseases has often failed to demonstrate efficacy and, for this reason, treatment of SS remains challenging in clinical practice.

Systemic therapy

Recommendations suggest that the use of systemic immunosuppressive therapies, including GCs, should be considered only in patients with active systemic disease, after a careful evaluation of systemic disease activity and organ damage (86).

- B cell target therapy

The use of B cell target therapy has been proposed since the evidence that B cell dysfunction is at the basis of the pathogenetic mechanism of SS. To date, both Belimumab (anti-BlyS) and Rituximab (anti-CD20) have been studied for the management of SS but with heterogeneous results (87).

It has been postulated that the maximal benefit of Rituximab may be achieved in early, active disease, especially in patients with some extra-glandular manifestations, including peripheral nervous system involvement with vasculitis or cryoglobulinaemia, lymphoma and refractory pulmonary involvement (87). The limited efficacy of Rituximab has been associated, at least in part, to an increase of Blys during the repopulation of B cells, leading to high probability of disease relapse. To overcome this issue, a recent randomised double-blinded clinical trial evaluated the safety and efficacy of sequential Belimumab and one cycle of Rituximab administration, compared with Belimumab alone, Rituximab alone and placebo (84). Patients with moderate-to-severe disease activity measured by ESSDAI were evaluated for 68 weeks. All three groups experienced a significant reduction of ESSDAI in comparison to placebo, with the Belimumab-Rituximab group showing the greater score reduction. Side effects were similar among all groups of patients. The different mechanisms of action of the two drugs support the rational of the trial. In particular, Belimumab leads to early decrease of naïve and activated B cells, whereas peripheral memory B cells increase. On the other side, Rituximab leads to depletion in peripheral memory B cells. In this setting, considering the importance of BlyS-mediated signals for B cells maturation and survival, new biological agents interfering with this pathway are under examination. Ianalumab is a human monoclonal antibody able to deplete B cells via two mechanisms of action. From one side, it is able to induce a direct lysis of B cells and, on the other hand, blocks BAFF-receptor, thus interrupting the signalling pathway. A recent double-blind, randomised, dose-finding trial assessed efficacy and safety of different subcutaneous doses of Ianalumab (5 mg, 50 mg, 300 mg every 4 weeks) in 190 SS patients with moderate-to-severe activity (85). The ESSDAI score decreased from baseline in all Ianalumab groups, with the maximal score change in the ianalumab 300 mg group. Of note, an increase of stimulated salivary flow from baseline to week 24 was observed in association with a reduction of RF and immunoglobulin G levels. This result was expected and consistent with previous findings because receptor blockade leads to higher BAFF levels without any biological activity.

- Co-stimulation blockade

At the moment, clinical trials evaluating the effects of sequential Abatacept infusions for 24 weeks have shown disappointing results. Conversely, administration of abatacept for 24 months was associated with an improvement in SG function in a small SS cohort, suggesting that a longer treatment period may be required to exert positive effects. Following this concept, De Wolff *et al*. recently analysed the effect of 48-week abatacept therapy as open-label extension of the ASAP-III trail in 40 SS patients with moderate to high disease activity at baseline (88). Low disease activity (ESSDAI < 5) was observed at week 48 in 50% of patient. Moreover, both Abatacept treated patients than patients shifted from placebo to abatacept in the open-label phase showed significant improvement of ESSPRI scores, especially in the pain and fatigue domains (88). On the other hand, no significant improvement was observed in salivary flow rates and in SGUS scores, suggesting that besides a potential stabilisation of salivary flow rates, Abatacept does not seem to cause major improvements in SG inflammation or morphology.

- Jak-inhibitors

Studies investigating the effect of Janus Kinase (JAK) inhibitors in SS are quite recent and developed since the awareness that JAK-STAT pathway could play a role in the signalling of Type I and Type II IFNs, which levels have been demonstrated to be increased in peripheral blood and in glandular tissue of SS patients. A recent multicentre, double-blind study, randomised a large cohort of active primary or associated SS patients (ESSDAI ≥ 5) to receive three different JAK inhibitors, filgotinib, a JAK-1 inhibitor, lanraplenib, a spleen tyrosine kinase inhibitor, and tirabrutinib, a Bruton's tyrosine kinase inhibitor (89). However, despite the biological rationale of the study, both the primary composite efficacy end point (week-12 proportion of patients fulfilling improvement of C-reactive protein and SS-related symptoms) and the secondary outcome (change from baseline in ESSDAI and ESSPRI) were not met (89). In this setting, some peculiar characteristics of the study, as inclusion of SS patients with associated systemic autoimmune diseases and the composite primary end point, which included also patient-reported symptoms, may have hampered the results. However, consistent with the expected drug mechanisms of action, reductions in immunoglobulin levels were observed in patients who received filgotinib or tirabrutinib, despite an absence of clinical response. Moreover, filgotinib-treated patients demonstrated a reduction in Type I IFN signature

activity and a significant decrease in circulating regulatory B and precursor plasma cells was observed in patients who received tirabrutinib (89). Surely, further studies are needed to explore the effect of JAK inhibitors in SS.

- Low-dose interleukin 2

Interleukin 2 (IL-2) is a cytokine involved in the homeostasis of T cells acting in a dose-depended mechanism. High IL-2 is able to enhance the activity of CD4 T cells, whereas low dose of IL-2 has been proved to increase T regulatory cells (Treg), suppress T follicular helper and T-helper 17 and indirectly regulate the proliferation and maturation of B cells, thus suggesting that low dose of IL-2 might regulate B cell proliferation and induce clinical response in SS.

Low-dose IL-2 (1 million IU subcutaneously every other day for two weeks followed by a 2-week break) were compared to placebo in a double-blind trial which included 60 SS patients with active disease (90). Significant reduction of disease activity by ESSDAI and greater improvement in dryness, pain and fatigue was observed in low-dose IL-2 group. Interestingly, immunological analysis revealed that LD-IL-2 induced an expansion of Treg cells and regulatory $CD24^{high}CD27+$ B cells. No significant increase of infection risk was observed in treated patients suggesting a plausible role of low-dose IL-2 in patients with absolute contraindication to immunosuppressive therapies. However, the very low number of patients included and the lack of subsequent phase III trials suggest extreme caution in the interpretation of the results.

- Conventional synthetic disease-modifying anti-rheumatic drugs

The use of conventional synthetic (cs) immunosuppressant agents is still scarce and the absence of clinical trials comparing the different cs-disease-modifying anti-rheumatic drugs (DMARDs) does not provide specific indications in the employment of these drugs in SS patients. In the last year, no study related to csDMARD therapy in SS has been published, except for a meta-analysis of 19 clinical trials on Iguratimod, an anti-rheumatic drug approved in Japan and China for the treatment of rheumatoid arthritis (91). The meta-analysis, including 1512 Chinese SS patients, demonstrated that Iguratimod may improve ESSDAI and ESSPRI score, increase Schirmer's test score and salivary flow rate. However, the lack of studies in different geographical populations, the short follow-up, the high rate of bias in data collection and low quality of studies included deserve caution in data interpretation.

Topic therapy

Current treatments for dry eye include artificial tears and prescription of eye drops, such as cyclosporine and lifitegrast, a lymphocyte function-associated antigen 1 antagonist approved by the FDA for the treatment of dry eye disease, to reduce ocular surface inflammation. However, their usefulness for the relief of signs and symptoms in patients with dry eyes remains uncertain.

Among the anti-inflammatory topical therapy, cyclosporine was approved by the FDA for the treatment of moderate-to-severe dry eye disease based on an improvement in tear production. Recently, a placebo-controlled, randomised clinical trial was performed in 60 SS patients in order to compare the effect of topical application of tacrolimus 0.03% eye drops *versus* cyclosporine 0.05% eye drops. The study demonstrated that both immunomodulatory eye drops have a comparable effect in improving patient symptoms and ocular surface staining scores including OSDI, frequency of use of artificial tear substitutes, TBUT, van Bijsterveldt score and Schirmer I at the end of 6 months (92). However, no effect was demonstrated in patients with concomitant meibomian gland dysfunction.

In severe cases of dry eye disease, an encouraging alternative is the use of blood-derived sera, such as autologous serum, which provides hydration, nutrition and growth factors that promote cellular trophism within the epithelium, thus improving regeneration. Moreover, autologous serum has an indirect anti-inflammatory effect by neutralisation of inflammatory cytokines and holds bactericide components, such as lysozyme, lactoferrin and immunoglobulins, thus reducing the risk of contamination and infection.

Recently, a randomised, double-blind clinical trial compared the effect of three types of sera, autologous serum, allogeneic serum and umbilical cord serum, for the treatment of severe dry eye syndrome with symptoms lasting for more than 3 months not improving con conventional treatment. A total of 125 eyes of 63 patients were included, of which 23 patients had SS (93). There was a significant main effect of time on visual acuities, Schirmer and BUT tests, fluorescein and lissamine green staining measurements and questionnaire scores reported for the three treatments. However, considering the very low number of SS patients included in the study, further studies are needed to explore the potential role of autologous serum and other blood-derived sera in the treatment of refractory severe dry eye syndrome in patients with SS.

Non-pharmacological treatment

Given the complexity of the disease and the disappointing results of the pharmacological treatment, the non-pharmacological approach may take place especially for the management of fatigue, one of the most challenging hallmarks of the disease. Up to date, none of the drugs tested in different clinical trials showed a significant improvement of fatigue. In this framework, a recent study by Dardin *et al*. explored the effectiveness of resistance exercise training on fatigue in patients with SS (94). In this single-blind randomised trial, the authors compared the effect of 16-week resistance exercise programme with respect to no physical activity in 59 SS patients. A significant improvement in fatigue domain assessed by ESSPRI score and by the short-form Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PROFAD-SSI) was demonstrated in the resistance exercise programme in comparison to control group, while no significant difference was detected between the two groups when fatigue was assessed with the Functional As-

sessment of Chronic Illness Therapy (FACIT)-Fatigue (96). The resistance training programme was well tolerated and patients showed good compliance the exercise programme.

Future perspectives

Current evidence for the efficacy of targeted therapies in SS is still inconclusive as many trials failed to meet their primary outcomes. Nevertheless, recent trials targeting B-cells, B-T cell co-stimulation and IFN signalling have shown promising results. Surely, the complex pathogenetic mechanisms of the disease, which target different pathways in the same patient, the extreme heterogeneity of disease phenotypes with potentially different responses to immunomodulatory therapies, the strict inclusion criteria in clinical trials, the high placebo response rate and the outcomes measures employed may partly explain trail failures. The development of composite endpoints, which include patient reported outcomes and objective disease measures, may surely provide a more holistic approach to disease assessment. The impact of these new tools on therapeutic development that may benefit SS patients remains to be fully evaluated. Indeed, a therapeutic approach focusing only in improving systemic disease activity has the main limit to not consider the drug effect on patient symptoms, thus neglecting a large proportion of SS patients with high symptom burden but low levels of systemic disease activity. Surely, composite endpoints incorporating patient reported outcomes with objective disease measures may provide a more patient-focused approach, but its impact remains to be fully assessed in future clinical trials.

Take home messages

- Among systemic therapy, B cells target therapy could be useful in SS patients; sequential belimumab and rituximab showed a greater reduction of disease activity and equal side effect compared with the single therapy group (89).
- Recent promising targets in the treatment of SS include B cells, co-stimulatory molecules (*i.e.* CD40/CD40L) and signalling cytokine pathways (BlyS/BAFF) (90).
- Longer administration of Abatacept may be beneficial in reducing disease activity in SS patients (91).
- Besides artificial tears, current topic treatment for dry eyes includes anti-inflammatory therapy such as cyclosporine to reduce ocular surface inflammation. The use of blood-derived sera could be considered in some well selected, severe case of dry eye disease (95).
- A non-pharmacological approach may have a place especially for the management of fatigue and muscle symptoms (96).

References

1. KHATRI B, TESSNEER KL, RASMUSSEN A *et al.*: Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells. *Nat Commun* 2022; 13(1): 4287. https://doi.org/10.1038/s41467-023-36369-4
2. JOACHIMS ML, KHATRI B, LI C *et al.*: Dysregulated long non-coding RNA in Sjögren's disease impacts both interferon and adaptive immune responses. *RMD Open* 2022; 8(2): e002672. https://doi.org/10.1136/rmdopen-2022-002672
3. SHAW TM, ZHANG W, MCCOY SS *et al.*: X-linked genes exhibit miR6891-5p-regulated skewing in Sjögren's syndrome. *J Mol Med* 2022; 100(9): 1253-65. https://doi.org/10.1007/s00109-022-02205-3
4. LOPES AP, HILLEN MR, HINRICHS AC *et al.*: Deciphering the role of cDC2s in Sjögren's syndrome: transcriptomic profile links altered antigen processes with IFN signature and autoimmunity. *Ann Rheum Dis* 2023; 82(3): 374-83. https://doi.org/10.1136/ard-2022-222728
5. HUIJSER E, BODEWES ILA, LOURENS MS *et al.*: Hyperresponsive cytosolic DNA-sensing pathway in monocytes from primary Sjögren's syndrome. *Rheumatology* (Oxford) 2022; 61(8): 3491-6. https://doi.org/10.1093/rheumatology/keac016
6. TRUTSCHEL D, BOST P, MARIETTE X *et al.*: Variability of primary Sjögren's syndrome is driven by interferon-α and interferon-α blood levels are associated with the class II HLA-DQ locus. *Arthritis Rheumatol* (Hoboken) 2022; 74(12): 1991-2002. https://doi.org/10.1002/art.42265
7. BROEREN MGA, WANG JJ, BALZARETTI G *et al.*: Proteogenomic analysis of the autoreactive B cell repertoire in blood and tissues of patients with Sjögren's syndrome. *Ann Rheum Dis* 2022; 81(5): 644-52. https://doi.org/10.1136/annrheumdis-2021-221604
8. HOU X, HONG X, OU M *et al.*: Analysis of gene expression and TCR/B cell receptor profiling of immune cells in primary Sjögren's syndrome by single-cell sequencing. *J Immunol* 2022; 209(2): 238-49. https://doi.org/10.4049/jimmunol.2100803
9. NEYS SFH, VERSTAPPEN GM, BOOTSMA H, KROESE FGM, HENDRIKS RW, CORNETH OBJ: Decreased BAFF receptor expression and unnaltered B cell receptor signaling in circulating B cells from primary Sjögren's syndrome patients at diagnosis. *Int J Mol Sci* 2022; 23(9): 5101. https://doi.org/10.3390/ijms23095101
10. MOREL M, POCHARD P, ECHCHIH W *et al.*: Abnormal B cell glycosylation in autoimmunity: A new potential treatment strategy. *Front Immunol* 2022; 13: 975963. https://doi.org/10.3389/fimmu.2022.975963
11. KANEKO N, CHEN H, PERUGINO CA *et al.*: Cytotoxic CD8(+) T cells may be drivers of tissue destruction in Sjögren's syndrome. *Sci Rep* 2022; 12(1): 15427. https://doi.org/10.1038/s41598-022-19397-w
12. PHILLIPS R: T cell differentiation in Sjögren syndrome is regulated by TOX. *Nat Rev Rheumatol* 2022; 18(8): 432. https://doi.org/10.1038/s41584-022-00813-4
13. HE C, YANG Y, CHEN Z *et al.*: EZH2 promotes T follicular helper cell differentiation through enhancing STAT3 phosphorylation in patients with primary Sjögren's syndrome. *Front Immunol* 2022; 13: 922871. https://doi.org/10.3389/fimmu.2022.922871
14. MO YQ, NAKAMURA H, TANAKA T *et al.*: Lysosomal exocytosis of HSP70 stimulates monocytic BMP6 expression in Sjögren's syndrome. *J Clin Invest* 2022; 132(6): e152780. https://doi.org/10.1172/JCI152780
15. COLAFRANCESCO S, BARBATI C, PRIORI R *et al.*: Maladaptive Autophagy in the Pathogenesis of Autoimmune Epithelitis in Sjögren's Syndrome. *Arthritis Rheumatol* (Hoboken) 2022; 74(4): 654-664. https://doi.org/10.1002/art.42018
16. WANG X, PANG K, WANG J *et al.*: Microbiota dysbiosis in primary Sjögren's syndrome and the ameliorative effect of hydroxychloroquine. *Cell Rep* 2022; 40(11): 111352. https://doi.org/10.1016/j.celrep.2022.111352
17. VAN DER MEULEN TA, VISSINK A, BOOTSMA H, SPIJKERVET FKL, KROESE FGM: Microbiome in Sjögren's syndrome: here we are. *Ann Rheum Dis* 2022; 81(7): e114. https://doi.org/10.1136/annrheumdis-2020-218213
18. YANG L, XIANG Z, ZOU J, ZHANG Y, NI Y, YANG J: Comprehensive analysis of the relationships between the gut microbiota and fecal metabolome in individuals with primary Sjogren's syndrome by 16S rRNA sequencing and LC-MS-based metabolomics. *Front Immunol* 2022; 13: 874021. https://doi.org/10.3389/fimmu.2022.874021
19. MENTIS AA, CHROUSOS GP: Tubarial salivary glands in Sjögren's syndrome: are they just a potential missing link with no broader implications? *Front Immunol* 2021; 12: 684490. https://doi.org/10.3389/fimmu.2021.684490
20. VALDEZ RMA, MELO TS, SANTOS-SILVA AR, DUARTE A, GUEIROS LA: Adverse postoperative events of salivary gland biopsies: a systematic review and meta-analysis. *J Oral Pathol Med* 2022; 51(2): 152-9. https://doi.org/10.1111/jop.13229
21. PARREAU S, NOCTURNE G, MARIETTE X *et al.*: Features of non-Hodgkin's lymphoma

diagnosed in minor salivary gland biopsies from primary Sjögren's syndrome patients. *Rheumatology* (Oxford) 2022; 61(9): 3818-23. https://doi.org/10.1093/rheumatology/keab949
22. MARKETOS N, KOULOURI V, PIPERI EP, GEORGAKI ME, NIKITAKIS NG, MAVRAGANI CP: Scleroderma-specific autoantibodies: Should they be included in the diagnostic work-up for Sjögren's syndrome? *Semin Arthritis Rheum* 2022; 55: 152026. https://doi.org/10.1016/j.semarthrit.2022.152026
23. CARLOTTI E, MURRAY-BROWN W, BLIGHE K *et al*.: High-throughput sequencing of IgH gene in minor salivary glands from Sjögren's syndrome patients reveals dynamic B cell recirculation between ectopic lymphoid structures. *Clin Exp Rheumatol* 2022; 40(12): 2363-72. https://doi.org/10.55563/clinexprheumatol/82u3cs
24. PRINGLE S, VERSTAPPEN GM, VAN GINKEL MS *et al*.: Lymphoepithelial lesions in the salivary glands of primary Sjögren's syndrome patients: the perfect storm? *Clin Exp Rheumatol* 2022; 40(12): 2434-42. https://doi.org/10.55563/clinexprheumatol/06an99
25. MCCOY SS, WOODHAM M, BARTELS CM *et al*.: Symptom-based cluster analysis categorizes Sjögren's disease subtypes: an international cohort study highlighting disease severity and treatment discordance. *Arthritis Rheumatol* 2022; 74(9): 1569-79. https://doi.org/10.1002/art.42238
26. ROBIN F, ALBERT JD, LESCOAT A *et al*.: Diagnostic performances of ultrasound evaluation of major salivary glands according to the 2019 Outcome Measures in Rheumatology Ultrasound Scoring System. *Arthritis Care Res* (Hoboken) 2022; 74(11): 1924-32. https://doi.org/10.1002/acr.24631
27. IZZETTI R, FULVIO G, NISI M, GENNAI S, GRAZIANI F: Reliability of OMERACT scoring system in ultra-high frequency ultrasonography of minor salivary glands: inter-rater agreement study. *J Imaging* 2022; 8(4): 111. https://doi.org/10.3390/jimaging8040111
28. KIM SH, MIN HK, LEE SH, LEE KA, KIM HR: Ultrasonographic evaluation of lacrimal glands in patients with primary Sjögren's syndrome. *Clin Exp Rheumatol* 2022; 40(12): 2283-9. https://doi.org/10.55563/clinexprheumatol/em2xlu
29. YANG T, DELLI K, COUMOU AD *et al*.: The lacrimal gland in Sjögren's syndrome: can we unravel its mystery using ultrasound? *Clin Exp Rheumatol* 2022; 40(12): 2428-33. https://doi.org/10.55563/clinexprheumatol/z1lzb1
30. BARBOSA-COBOS RE, TORRES-GONZÁLEZ R, MEZA-SÁNCHEZ AV *et al*.: A novel technique for the evaluation and interpretation of elastography in salivary gland involvement in primary Sjögren syndrome. *Front Med* 2022; 9: 913589. https://doi.org/10.3389/fmed.2022.913589
31. WANG X, WANG A, ZHAN X, XU L, CHANG X, DONG F: Value of conventional ultrasound and shear wave elastography in assessing disease activity and prognosis in female patients with Sjögren's syndrome. *Clin Exp Rheumatol* 2022; 40(12): 2350-6. https://doi.org/10.55563/clinexprheumatol/20028h
32. MOSSEL E, VAN GINKEL MS, HAACKE EA *et al*.: Histopathology, salivary flow and ultrasonography of the parotid gland: three complementary measurements in primary Sjögren's syndrome. *Rheumatology* (Oxford) 2022; 61(6): 2472-82. https://doi.org/10.1093/rheumatology/keab781
33. LORENZON M, TULIPANO DI FRANCO F *et al*.: Sonographic features of lymphoma of the major salivary glands diagnosed with ultrasound-guided core needle biopsy in Sjögren's syndrome. *Clin Exp Rheumatol* 2021; 39(6): 175-83. https://doi.org10.55563/clinexprheumatol/4c36nr
34. KIM JW, JIN R, HAN JH *et al*.: Correlations between salivary gland scintigraphy and histopathologic data of salivary glands in patients with primary Sjogren's syndrome. *Clin Rheumatol* 2022; 41(10): 3083-93. https://doi.org/10.1007/s10067-022-06269-x
35. GIOVANNINI I, LORENZON M, MANFRÈ V *et al*.: Safety, patient acceptance and diagnostic accuracy of ultrasound core needle biopsy of parotid or submandibular glands in primary Sjögren's syndrome with suspected salivary gland lymphoma. *RMD Open* 2022; 8(1): e001901. https://doi.org/10.1136/rmdopen-2021-001901
36. ZABOTTI A, PEGOLO E, GIOVANNINI I *et al*.: Usefulness of ultrasound guided core needle biopsy of the parotid gland for the diagnosis of primary Sjögren's syndrome. *Clin Exp Rheumatol* 2022; 40(12): 2381-6. https://doi.org/10.55563/clinexprheumatol/5n49yj
37. IŞIK ÖÖ, YAZICI A, ÇEFLE A: The respiratory manifestations in patients with primary Sjögren's syndrome: is interstitial lung disease related to disease activity? *Turk J Med Sci* 2022; 52(5): 1737-1743. https://doi.org/10.55730/1300-0144.5513
38. LA ROCCA G, FERRO F, BULLERI A *et al*.: Glandular involvement in primary Sjögren's syndrome patients with interstitial lung disease-onset and sicca-onset, a single centre cross sectional study. *Clin Exp Rheumatol* 2022; 40(12): 2344-9. https://doi.org/10.55563/clinexprheumatol/7bylp2
39. WENG L, CHEN Y, LIANG T *et al*.: Biomarkers of interstitial lung disease associated with primary Sjögren's syndrome. *Eur J Med Res* 2022; 27(1): 199. https://doi.org/10.1186/s40001-022-00828-3
40. HE SH, HE YJ, GUO KJ, LIANG X, LI SS, LI TF: Risk factors for progression of interstitial lung disease in Sjögren's syndrome: a single-centered, retrospective study. *Clin Rheumatol* 2022; 41(4): 1153-1161. https://doi.org/10.1007/s10067-021-05984-1
41. LIN W, XIN Z, ZHANG J *et al*.: Interstitial lung disease in Primary Sjögren's syndrome. *BMC Pulm Med* 2022; 22(1): 73. https://doi.org/10.1186/s12890-022-01868-5
42. KIM YJ, CHOE J, MOON SJ, SONG JW: Blood KL-6 predicts prognosis in primary Sjögren's syndrome-associated interstitial lung disease. *Sci Rep* 2022; 12(1): 5343. https://doi.org/10.1038/s41598-022-09283-w
43. SHI L, WANG J, GUO HX, HAN XL, TANG YP, LIU GY: Circulating Th2 cell reduction and Th1/Th2 imbalance are correlated with primary Sjogren's syndrome-associated interstitial lung disease. *Arthritis Res Ther* 2022; 24(1): 121. https://doi.org/10.1186/s13075-022-02811-z
44. APPENZELLER S, ANDRADE SO, BOMBINI MF, SEPRESSE SR, REIS F, FRANÇA MC JR: Neuropsychiatric manifestations in primary Sjögren syndrome. *Expert Rev Clin Immunol* 2022; 18(10): 1071-1081. https://doi.org/10.1080/1744666X.2022.2117159
45. GOULABCHAND R, GABELLE A, AYRIGNAC X *et al*.: Hospitalization risks for neurological disorders in primary Sjögren's syndrome patients. *J Clin Med* 2022; 11(7): 1979. https://doi.org/10.3390/jcm11071979
46. SEELIGER T, GEHLHAAR MA, OLUWATOBA-POPOOLA I *et al*.: Trigeminal nerve affection in patients with neuro-Sjögren detected by corneal confocal microscopy. *J Clin Med* 2022; 11(15): 4484. https://doi.org/10.3390/jcm11154484
47. LUZU J, LABBÉ A, RÉAUX-LE GOAZIGO A *et al*.: In vivo confocal microscopic study of corneal innervation in Sjögren's syndrome with or without small fiber neuropathy. *Ocul Surf* 2022; 25: 155-162. https://doi.org/10.1016/j.jtos.2022.07.003
48. BŁOCHOWIAK K: Smell and taste function and their disturbances in Sjögren's syndrome. *Int J Environ Res Public Health* 2022; 19(19): 12472. https://doi.org/10.3390/ijerph191912472.
49. ULUSOY B, LIMON M, YILMAZ S *et al*.: Effects of primary Sjögren's syndrome on hearing and vestibular systems. *J Laryngol Otol* 2022; 136(12): 1254-8. https://doi.org/10.1017/S0022215122000391
50. MÓDIS LV, ARADI Z, HORVÁTH IF *et al*.: Central nervous system involvement in primary Sjögren's syndrome: narrative review of MRI findings. *Diagnostics* 2022; 13(1): 14. https://doi.org/10.3390/diagnostics13010014
51. GOULABCHAND R, CASTILLE E, NAVUCET S *et al*.: The interplay between cognition, depression, anxiety, and sleep in primary Sjögren's syndrome patients. *Sci Rep* 2022; 12(1): 13176. https://doi.org/10.1038/s41598-022-17354-1
52. ZHANG XD, LI JL, ZHOU JM *et al*.: Altered white matter structural connectivity in primary Sjögren's syndrome: a link-based analysis. *Neuroradiology* 2022; 64(10): 2011-19. https://doi.org/10.1007/s00234-022-02970-5
53. GOULABCHAND R, MAKINSON A, MOREL J *et al*.: Hospitalizations for infections in primary Sjögren's syndrome patients: a nationwide incidence study. *Ann Med* 2022; 54(1): 2672-80. https://doi.org/10.1080/07853890.2022.2126517
54. ZHONG H, LIU S, WANG Y *et al*.: Primary Sjögren's syndrome is associated with increased risk of malignancies besides lymphoma: A systematic review and meta-analysis. *Autoimmun Rev* 2022; 21(5): 103084. https://doi.org/10.1016/j.autrev.2022.103084
55. DENG J, LIU M, XIAO R *et al*.: Risk, incidence, and mortality of breast cancer in primary Sjögren's syndrome: a systematic review and meta-analysis. *Front Immunol* 2022; 13: 904682. https://doi.org/10.3389/fimmu.2022.904682
56. ATZENI F, GOZZA F, CAFARO G, PERRICONE C, BARTOLONI E: Cardiovascular involve-

ment in Sjögren's syndrome. *Front Immunol* 2022; 13: 879516. https://doi.org/10.3389/fimmu.2022.879516
57. XU X, SHI Y, YANG X *et al*.: Risk factors for hypertension in primary Sjögren's syndrome patients: a nomogram was constructed. *J Hum Hypertens* 2022; 36(11): 996-1002. https://doi.org/10.1038/s41371-021-00603-7
58. SU YJ, LEONG PY, WANG YH, WEI JC: Sjögren syndrome is a hidden contributor of macrovascular and microvascular complications in patients with type 2 diabetes. *Int J Rheum Dis* 2022; 25(10): 1176-85. https://doi.org/10.1111/1756-185X.14400
59. SCHOON H, SLACK E, PEARCE M, NG WF, HACKETT KL: Activity interference in patients with Sjögren's syndrome: a cross-sectional study of 149 patients in the UK. *Rheumatology* (Oxford) 2022; 61(10): 4065-75. https://doi.org/10.1093/rheumatology/keac053
60. PRAK RF, ARENDS S, VERSTAPPEN GM *et al*.: Fatigue in primary Sjögren's syndrome is associated with an objective decline in physical performance, pain and depression. *Clin Exp Rheumatol* 2022; 40(12): 2318-28. https://doi.org/10.55563/clinexprheumatol/70s6cs
61. METIN ÖKMEN B, AYAR K, ALTAN L, YEŞILÖZ Ö: Central sensitisation in primary Sjögren syndrome and its effect on sleep quality. *Mod Rheumatol* 2022; 32(5): 908-14. https://doi.org/10.1093/mr/roab075
62. HERNÁNDEZ-MOLINA G, KOSTOV B, BRITO-ZERÓN P *et al*.: Characterization and outcomes of 414 patients with primary SS who developed haematological malignancies. *Rheumatology* 2022; 62: 243-255. https://doi.org/10.1093/rheumatology/keac205
63. CHATZIS LG, STERGIOU IE, GOULES AV *et al*.: Clinical picture, outcome and predictive factors of lymphoma in primary Sjögren's syndrome: results from a harmonized dataset (1981-2021). *Rheumatology* (Oxford) 2022; 61: 3576-85. https://doi.org/10.1093/rheumatology/keab939
64. SALEH W, ELASHRY MM, WINN N, MONA M, KATZ J, CHA S: A lower prevalence of malignant lymphoma in Sjögren's syndrome patients: A cross-sectional study. *Oral Dis* 2022 Nov 11. https://doi.org/10.1111/odi.14435
65. TREPPO E, TOFFOLUTTI F, MANFRÈ V *et al*.: Risk of cancer in connective tissue diseases in northeastern Italy over 15 Years. *J Clin Med* 2022; 11(15): 4272. https://doi.org/10.3390/jcm11154272
66. ZHONG H, LIU S, WANG Y *et al*.: Primary Sjögren's syndrome is associated with increased risk of malignancies besides lymphoma: A systematic review and meta-analysis. *Autoimmun Rev* 2022; 21: 103084. https://doi.org/10.1016/j.autrev.2022.103084
67. NOCTURNE G, PONTARINI E, BOMBARDIERI M, MARIETTE X: Lymphomas complicating primary Sjögren's syndrome: from autoimmunity to lymphoma. *Rheumatology* (Oxford) 2021; 60: 3513-3521. https://doi.org/10.1093/rheumatology/kez052
68. KORONA B, KORONA D, ZHAO W, WOTHERSPOON AC, DU MQ: GPR34 activation potentially bridges lymphoepithelial lesions to genesis of salivary gland MALT lymphoma. *Blood* 2022; 139: 2186-97. https://doi.org/10.1182/blood.2020010495
69. PRINGLE S, VERSTAPPEN GM, VAN GINKEL MS *et al*.: Lymphoepithelial lesions in the salivary glands of primary Sjögren's syndrome patients: the perfect storm? *Clin Exp Rheumatol* 2022; 40(12): 2434-42. https://doi.org/10.55563/clinexprheumatol/06an99
70. BROEREN MGA, WANG JJ, BALZARETTI G *et al*.: Proteogenomic analysis of the autoreactive B cell repertoire in blood and tissues of patients with Sjögren's syndrome. *Ann Rheum Dis* 2022; 81: 644-52. https://doi.org/10.1136/annrheumdis-2021-221604
71. CARLOTTI E, MURRAY-BROWN W, BLIGHE K *et al*.: High-throughput sequencing of IgH gene in minor salivary glands from Sjögren's syndrome patients reveals dynamic B cell recirculation between ectopic lymphoid structures. *Clin Exp Rheumatol* 2022; 40(12): 2363-72. https://doi.org/10.55563/clinexprheumatol/82u3cs
72. BULT JAA, PLAÇA JR, HAACKE EA *et al*.: Low mutational burden of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in patients with primary Sjögren's syndrome. *Cancers* (Basel) 2022; 14: 1010. https://doi.org/10.3390/cancers14041010
73. CHATZIS L, VLACHOYIANNOPOULOS PG, TZIOUFAS AG, GOULES AV: New frontiers in precision medicine for Sjogren's syndrome. *Expert Rev Clin Immunol* 2021; 17: 127-41. https://doi.org/10.1080/1744666X.2021.1879641
74. DE VITA S, ISOLA M, BALDINI C *et al*.: Predicting lymphoma in Sjögren's syndrome and the pathogenetic role of parotid microenvironment through precise parotid swelling recording. *Rheumatology* (Oxford) 2023; 62: 1586-93. https://doi.org/10.1093/rheumatology/keac470
75. STERGIOU IE, CHATZIS LG, PEZOULAS VC *et al*.: The clinical phenotype of primary Sjögren's syndrome patients with lymphadenopathy. *Clin Exp Rheumatol* 2022; 40(12): 2357-62. https://doi.org/10.55563/clinexprheumatol/263xbc
76. PEZOULAS VC, GOULES A, KALATZIS F *et al*.: Addressing the clinical unmet needs in primary Sjögren's Syndrome through the sharing, harmonization and federated analysis of 21 European cohorts. *Comput Struct Biotechnol J* 2022; 20: 471-84. https://doi.org/10.1016/j.csbj.2022.01.002
77. BALDINI C, BARTOLONI E, BOMBARDIERI M: Highlights of the 15th International Symposiumon Sjögren's Syndrome. *Clin Exp Rheumatol* 2022; 40(12): 2201-10. https://doi.org/10.55563/clinexprheumatol/yt6g9t
78. LORENZON M, SPINA E, TULIPANO DI FRANCO F *et al*.: Salivary gland ultrasound in primary Sjögren's syndrome: current and future perspectives. *Open Access Rheumatol* 2022; 14: 147-60. https://doi.org/10.2147/OARRR.S284763
79. VAN GINKEL MS, ARENDS S, VAN DER VEGT B *et al*.: FDG-PET/CT discriminates between patients with and without lymphomas in primary Sjögren's syndrome. *Rheumatology* (Oxford) 2023; 62(10): 3323-3331. https://doi.org/10.1093/rheumatology/kead071
80. GIOVANNINI I, LORENZON M, MANFRÈ V *et al*.: Safety, patient acceptance and diagnostic accuracy of ultrasound core needle biopsy of parotid or submandibular glands in primary Sjögren's syndrome with suspected salivary gland lymphoma. *RMD Open* 2022; 8: e001901. https://doi.org/10.1136/rmdopen-2021-001901
81. PARREAU S, NOCTURNE G, MARIETTE X *et al*.: Features of non-Hodgkin's lymphoma diagnosed in minor salivary gland biopsies from primary Sjögren's syndrome patients. *Rheumatology* (Oxford) 2022; 61: 3818-23. https://doi.org/10.1093/rheumatology/keab949
82. DE VITA S, QUARTUCCIO L, SALVIN S *et al*.: Sequential therapy with belimumab followed by rituximab in Sjögren's syndrome associated with B-cell lymphoproliferation and overexpression of BAFF: evidence for long-term efficacy. *Clin Exp Rheumatol* 2014; 32: 490-94.
83. DE VITA S, QUARTUCCIO L, SEROR R *et al*.: Efficacy and safety of belimumab given for 12 months in primary Sjögren's syndrome: the BELISS open-label phase II study. *Rheumatology* (Oxford) 2015; 54: 2249–56. https://doi.org/10.1093/rheumatology/kev257
84. MARIETTE X, BARONE F, BALDINI C *et al*.: A randomized, phase II study of sequential belimumab and rituximab in primary Sjögren's syndrome. *JCI Insight* 2022; 7(23): e163030. https://doi.org/10.1172/jci.insight.163030
85. BOWMAN SJ, FOX R, DÖRNER T *et al*.: Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial. *Lancet* 2022; 399: 161-71. https://doi.org/10.1016/S0140-6736(21)02251-0
86. RAMOS-CASALS M, BRITO-ZERÔN P, BOMBARDIERI S *et al*.: EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann Rheum Dis* 2020; 79(1): 3-18. https://doi.org/10.1136/annrheumdis-2019-216114
87. GRIGORIADOU S, CHOWDHURY F, PONTARINI E, TAPPUNI A, BOWMAN SJ, BOMBARDIERI M: B cell depletion with rituximab in the treatment of primary Sjögren's syndrome: what have we learnt? *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S217-24.
88. DE WOLFF L, VAN NIMWEGEN JF, MOSSEL E *et al*.: Long-term abatacept treatment for 48 weeks in patients with primary Sjögren's syndrome: The open-label extension phase of the ASAP-III trial. *Semin Arthritis Rheum* 2022; 53: 151955. https://doi.org/ 10.1016/j.semarthrit.2022.151955
89. PRICE E, BOMBARDIERI M, KIVITZ A *et al*.: Safety and efficacy of filgotinib, lanraplenib and tirabrutinib in Sjögren's syndrome: a randomized, phase 2, double-blind, placebo-controlled study. *Rheumatology* 2022; 61(12): 4797-808. https://doi.org/ 10.1093/rheumatology/keac167
90. HE J, CHEN J, MIAO M *et al*.: Efficacy and safety of low-dose interleukin 2 for primary Sjögren syndrome: a randomized clinical trial. *JAMA Netw Open* 2022; 5(11): e2241451. https://doi.org/10.1001/jamanetworkopen.2022.41451
91. ZENG L, HE Q, YANG K, HAO W, YU G, CHEN H: A systematic review and meta-analysis of 19 randomized controlled trials of igu-

ratimod combined with other therapies for Sjogren's syndrome. *Front Immunol* 2022; 13: 924730. https://doi.org/10.3389/fimmu.2022.924730

92. MOAWAD P, SHAMMA R, HASSANEIN D, RAGAB G, EL ZAWAHRY O: Evaluation of the effect of topical tacrolimus 0.03% versus cyclosporine 0.05% in the treatment of dry eye secondary to Sjogren syndrome. *Eur J Ophthalmol* 2022; 32(1): 673-79. https://doi.org/10.1177/1120672121992680

93. RODRÍGUEZ CALVO-DE-MORA M, DOMÍNGUEZ-RUIZ C, BARRERO-SOJO F *et al*.: Autologous versus allogeneic versus umbilical cord sera for the treatment of severe dry eye disease: a double-blind randomized clinical trial. *Acta Ophthalmol* 2022; 100(2): e396-408. https://doi.org/10.1111/aos.14953

94. DARDIN LP, GARCIA ABA, MINALI PA, PINTO ACPN, TREVISANI VFM: The effects of resistance training in patients with primary Sjögren's syndrome. *Clin Rheumatol* 2022; 41(4): 1145-52. https://doi.org/10.1007/s10067-021-05977-0