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# One year in review 2020: comorbidities, diagnosis and treatment of primary Sjögren's syndrome

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## ABSTRACT

Primary Sjögren's syndrome (pSS) is a complex and heterogeneous disorder characterised by a wide spectrum of glandular and extra-glandular features. The discovery of novel biomarkers allowed to characterise the disease not only phenotypically on the basis of clinical presentation, but also on the basis of the endotype. Moreover, a better stratification of patients has important value in the evaluation of mechanisms underlying the risk of lymphoproliferative disorders in these patients. Finally, novel targeted therapies may open new possibilities for the application of personalised medicine in pSS.

## Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease characterised by a wide spectrum of clinical features, extending from exocrine involvement to extra-glandular manifestations. Growing efforts have been made during the last months to deeper characterise the disease, its pathogenetic pathways and ultimate searching for novel biomarkers that may allow an earlier diagnosis and a more precise therapeutic intervention. In this review, following previous others (1-5), we will summarise the most recent literature on SS clinical presentation, diagnosis and treatment. Moreover, interest will be directed to the analysis of recent literature on lymphoproliferative risk and application of salivary gland ultrasonography as diagnostic tool. Finally, we will highlight the state of the art of pSS therapy. In this perspective, we have performed a Medline search of English language articles published in the PubMed database from 1st January 2019 to 31st December 2019.

## Clinical phenotypes and comorbidities

### Glandular manifestations

Involvement of the exocrine glands represents the main feature of pSS. In a recent analysis of a prospective multi-centre Spanish cohort of more than 400 pSS patients, about 94% complained dry eye or dry mouth symptoms at diagnosis and around 30% of patients presented with unilateral or bilateral parotid gland enlargement (6). Moreover, the severity of sicca symptoms may hamper the quality of life. Dry eye in pSS has more severe clinical course and functional damage in comparison to non-SS dry eye. In order to better characterise features of dry eye in pSS, Yoon *et al.* performed a cross-sectional study evaluating 91 pSS diagnosed according to the 2012 American College of Rheumatology (ACR) criteria and 55 non-SS subjects with dry eye (7). Markers of ocular damage, including tear break-up time (BUT), Schirmer test I and corneal/conjunctival staining scores, were significantly worse in pSS patients. Moreover, Authors compared the characteristics of dry eye in pSS patients who did and did not satisfy the 2016 ACR-European League Against Rheumatism (EULAR) classification criteria. Interestingly, there were no significant differences between the two groups in immunologic parameters as well as ocular surface scores while focus score was higher in the group of patients fulfilling the 2016 ACR/EULAR classification criteria (7). These data were further confirmed in a case-control study comparing features and medical and occupational history in patients with pSS, dry eye syndrome and B-cell non-Hodgkin's lymphoma (8). Primary SS patients were characterised by an increased dryness sever-

Competing interests: none declared.

ity in comparison to subjects with dry eye syndrome and healthy controls (8). Interestingly, some novel autoantibodies, including anti-salivary gland protein 1 (SP1), anti-carbonic anhydrase 6 (CA6) and anti-parotid secretory protein (PSP), suggested as useful markers to identify pSS patients at early stage, may be associated with dry eye occurrence in these patients. In particular, anti-CA6 were associated with severe aqueous deficient dry eye (9). However, future longitudinal larger studies are needed to evaluate their specificity in screening dry eye subjects for SS.

Dry mouth represents an adjunctive discomfort in these patients and significantly affects oral health. There are data supporting a link between low salivary flow rates and increased risk for dental caries both in pSS patients and in subjects with other causes of salivary hypofunction. A recent retrospective study compared the risk factors for caries between patients with pSS salivary hypofunction and subjects with non-SS salivary hypofunction (10). The pSS group had a significant higher number of total caries in comparison to other groups. Interestingly, in the pSS group, a focus score greater than 1 was the only factor associated with a greater number of total caries (10). Thus, the increased risk of caries in pSS patients is not sufficiently explained by salivary hyposalivation, and other pSS-related factors should be investigated. In this setting, a recent study explored the association between low salivary flow and altered oral microbial homeostasis in pSS patients, non-SS sicca symptoms and healthy controls (11). The analysis of oral microbiota revealed dysbiosis in the salivary microbiota from pSS and non-SS patients compared to healthy controls. In particular, the salivary microbiome in the pSS group, characterised by lower abundance of *Neisseria* and *Porphyromonas* and a higher abundance of *Veillonella*, differed significantly from non-SS group, thus suggesting that hyposalivation alone is not necessarily the cause of dysbiosis in pSS (11). Finally, xerostomia in pSS patients may be associated with higher risk of periodontal disease (PD), including higher prevalence

of plaque and gingival bleeding. A recent population-based study found that patients with PD have a 50% increased risk of subsequent pSS, thus suggesting that immune-mediated inflammatory mechanisms may contribute to this association (12). However, conclusive evidence regarding increased risk of PD in pSS patients is lacking. A recent meta-analysis and systematic review evaluated PD prevalence in a cohort of 228 pSS patients (13). Outcome measures included plaque index, gingival index, pocket-probing depth, clinical attachment loss, decayed missing filled teeth and decayed missing filling surfaces. No significant increased risk of PD was observed in pSS patients in comparison to controls except for higher susceptibility to caries in the former group.

#### Take home messages

- Dry eye is more severe in patients with SS, compared to subjects with non-SS dry eye (7, 8).
- PSS patients have higher prevalence of dental caries, probably not only due to hyposalivation but also to altered mouth microbiota (10, 11).

#### Extraglandular manifestations

There is growing awareness that extraglandular manifestations represent a clinical challenge in pSS patients due to the heterogeneous clinical presentations. The analysis of a huge international cohort of pSS patients enrolled in the Big Data Sjögren Project Consortium registry showed that more than a quarter of patients may have systemic manifestations not currently included in the EULAR SS Disease Activity Index (ESSDAI), cardiovascular (CV) manifestations being the most frequent (14). Moreover, although many of these manifestations are usually mild and do not affect patient prognosis, some may have a relevant impact on disease outcome and patient quality of life (14). In recent years, considerable effort was directed to the investigation of biomarkers which may identify specific disease phenotypes (15).

Clinical manifestations related to lung involvement in pSS patients are varied and initial symptoms are usually non-

specific. Even though lung involvement may be present in nearly one fifth of patients, it is often under-evaluated despite its important clinical implications. Moreover, patients with pulmonary involvement have a decreased quality of life and an increased mortality as compared to patients without lung disease (15, 16). Respiratory tract involvement in pSS may cause tracheal, bronchiolar, and pulmonary complications including xerotrachea, bronchiolitis and bronchiectasis, pulmonary cysts and bronchus or lung-associated lymphomas (16, 17). Interstitial lung disease (ILD) has been reported in 3-11% of pSS patients and represents a significant cause of morbidity due to its variable course. Non-specific interstitial pneumonitis (NSIP) is the most common subtype, followed by usual interstitial pneumonia (UIP), lymphoid interstitial pneumonia (LIP) and organising pneumonia (OP) (16). Considering that patients with pSS-ILD may have a different prognosis, researchers focused on factors predictive of ILD development at disease diagnosis. Among these, older age, Raynaud's phenomenon and oesophageal involvement have been identified as predictive factors associated with poorer outcome (15). In a retrospective multicentre study including 99 pSS patients with ILD, Kamiya *et al.* demonstrated that elevated serum levels of Krebs von den Lungen-6 (KL-6), a mucin-like glycoprotein expressed on type II alveolar epithelial cells, are associated with higher mortality rate (18). In addition, lower forced vital capacity and older age at diagnosis were significantly associated with worse survival (18). Chest high-resolution computed tomography (CT) patterns may also suggest worse outcome. In a retrospective study, Guisado-Vasco *et al.* evaluated the value of a quantitative CT (QCT) index in identifying the extension of lung disease in pSS patients with ILD (19). There was a statistically significant difference in QCT index distribution between pSS patients with and without ILD. Moreover, higher scores identified patients with more extensive parenchymal involvement (19). Among serologic markers, a retrospec-

tive analysis of the medical records of a wide cohort of Korean pSS patients without features of antineutrophil cytoplasmic antibody (ANCA) vasculitis demonstrated that positivity of ANCA-myeloperoxidase at baseline is predictive of ILD development in pSS (20). Among the wide spectrum of systemic extra-glandular manifestations, renal involvement may significantly influence disease course due to its insidious clinical appearance which may delay the diagnosis. In a recent analysis of 20 pSS patients, tubulointerstitial nephritis (TIN) occurred near or prior to the onset of sicca symptoms manifesting as distal renal tubular acidosis with hypokalaemia (21). On the opposite, glomerular involvement, mainly membranoproliferative glomerulonephritis (GN) with cryoglobulinaemia, manifested years after disease onset with chronic kidney disease, haematuria or nephrotic proteinuria (21). Moreover, TIN was characterised by indolent course not responding to immunosuppressive therapy while GN showed a favourable response to immunosuppressive agents, including rituximab, mycophenolate mofetil and cyclophosphamide (21). Researchers investigated biomarkers useful in identifying renal disease in pSS. In a wide pSS cohort, renal involvement was associated with higher levels of creatinine, cystatin C, and alpha-1-microglobulin ( $\alpha$ 1-MG) (22). Similarly, in a large cross-sectional study of more than four hundred Chinese pSS patients, histological positivity of salivary gland biopsy, reduced C3 levels, hypoalbuminaemia and anaemia were significantly associated with higher risk of renal involvement. Interestingly, xerophthalmia and anti-SSA/Ro52 positivity displayed a negative association (23). This study suggests that pSS patients with renal involvement are characterised by a distinctive clinical profile with higher disease activity, higher prevalence of salivary gland biopsy positivity and elevated inflammation, but a lower prevalence of xerophthalmia. Neurological involvement represents a relevant clinical challenge in these patients due to its heterogeneous presentation, diagnostic complexity and neg-

ative prognostic outcome (24). In fact, these patients usually experience higher level of disease activity and onset or worsening of disease activity in the peripheral nervous system (PNS) domain is significantly associated with higher level of disease activity after long-term follow-up (25). Finally, it exerts a negative impact on patient quality of life due to its disabling symptoms, often requiring immunosuppressive therapies (26). Neurological manifestations account for 10% to 60% of cases, being the PNS involvement the most frequently reported (24). Sensory or pure sensory neuropathies, in particular painful small-fibre neuropathy (SFN) and dorsal root ganglionopathy, have been frequently described as peculiar features (24). These patients are characterised by a distinct clinical and serologic profile as highlighted in a recent cross-sectional study involving pSS patients with biopsy-proven SFN. Patients with SFN were mainly male and had decreased frequency of anti-SSA/Ro 52/60 antibodies and of rheumatoid factor (27). Similarly, in a wide prospective Korean cohort analysis, anti-SSA/Ro-negative patients were characterised by higher prevalence of PNS at ESSDAI domain in comparison to anti-SSA/Ro-positive (28). Besides the glandular disease, joint involvement represents one of the most frequent disease manifestations. It has been reported in 20% up to 60% of pSS patients, and about one third presents synovitis resembling rheumatoid arthritis (RA) (29). In order to characterise the features and the therapeutic outcome of pSS-associated arthritis, Mirouse *et al.* performed a retrospective analysis of a French cohort of 57 pSS patients with at least one episode of clinical and/or echography detected synovitis (30). Patients with synovitis were characterised by higher frequency of parotid gland swelling, lymph node enlargement and a significantly higher ESSDAI score in comparison to patients without synovitis. No difference between groups was detected regarding acute phase reactants, rheumatoid factor positivity or detectable anti-cyclic citrullinated peptide (CCP) antibodies. Of note, no structural erosive progres-

sion was observed during follow-up, including all pSS patients with anti-CCP antibodies, and immunosuppressive agents, including hydroxychloroquine, methotrexate and rituximab, showed a similar good efficacy in reducing pain and joint inflammation (30). A recent systematic review and meta-analysis of ten studies involving 1322 pSS patients demonstrated that anti-CCP antibodies are associated with a significant four-fold higher risk of arthritis in pSS patients and with development of RA (31).

It is well known that pSS is frequently associated with organ-specific autoimmune disorders, in particular with autoimmune thyroid disease. In order to evaluate if autoimmune thyroid disease represents a distinct nosologic condition differing from pSS, Anaya *et al.* performed a retrospective analysis of about 300 pSS patients comparing clinical and serologic features of patients with pSS alone and patients with pSS and Hashimoto's thyroiditis (HT) (32). Primary SS with HT were characterised by higher prevalence of lymphadenopathy and urticaria while anti-Ro/SSA antibodies were more frequent in the pSS group, suggesting that, although SS and autoimmune thyroid disease share common physiopathologic mechanisms as part of the autoimmune background, they should be considered two different entities.

In the recent years, convincing evidence suggested that patients with systemic rheumatic diseases, in particular pSS, may have an increased risk of coeliac disease (CD). A recent multicentre, case-control, Italian study involving more than 1,400 patients with systemic autoimmune diseases, including pSS, systemic lupus erythematosus (SLE) and systemic sclerosis, reinforced this hypothesis (33). Primary SS patients were characterised by significant higher prevalence of CD in comparison to a wide general population (6.78% vs. 0.64%). Moreover, pSS patients with CD were younger at autoimmune disease diagnosis in comparison to non-coeliac group, thus suggesting that screening for CD may be considered in young pSS patients, especially at disease diagnosis.

It is important to consider that concomitant comorbidities, including infection risk, CV disease and non-lymphoma neoplastic diseases (in particular, thyroid gland cancer), may also influence pSS-related morbidity and mortality (34). Indeed, pSS patients are characterised by increased prevalence of subclinical atherosclerosis and higher risk of both cerebrovascular and CV events in comparison to general population (35-37). Multiple interacting mechanisms have been associated to the acceleration of subclinical atherosclerosis and CV damage in these patients. Traditional CV risk factors play a relevant role in the contribution to atherosclerotic damage, as recently highlighted (38). In particular, hypertension emerged as a prominent CV risk factor being more prevalent in these patients and associated with increased risk of overt CV events (39, 40). In a recent study recruiting a cohort of 367 pSS patients, hypertension, older age and extra-glandular involvement were independently correlated with CV events (41). Secondly, inflammatory mediators and disease-related immune markers cooperate with traditional CV risk factors in the pathogenesis of atherosclerotic damage (42). In particular, the highest CV risk appears to be associated with circulating anti-Ro/SSA and La/SSB, as demonstrated in a recent case-control study with a median follow-up of 10 years (43). Finally, adjunctive features, like disease duration, may further increase CV morbidity in pSS (43). In order to evaluate the interplay between disease-specific inflammatory and autoimmune features, and traditional CV risk factors in influencing CV risk, an artificial neural network analysis has been recently applied to a cohort of 408 pSS patients (44). Interestingly, in the entire cohort, hypertension resulted the most prevalent traditional CV risk factor and patients presenting with at least one CV event displayed significant higher prevalence of hypertension (77%) with respect to subjects free from CV comorbidity (35%). This new data mining computational analysis allowed to identify two different patterns of distribution in CV risk factors, pSS-related features and

major CV events. The first was characterised by close interconnection of traditional CV risk factors to each other and to pSS glandular involvement. The second pattern, including ischaemic CV events, was closely associated with extra-glandular disease activity, longer disease duration and some clinical or serological manifestations typical of the autoimmune phenotype, including purpura, leukopenia, low complement and cryoglobulinaemia.

Finally, pSS patients complain a reduced quality of life as result of systemic chronic symptoms, like fatigue, depression and anxiety, which significantly affect health-related quality of life (HRQoL). Indeed, HRQoL reduction in pSS is similar to that reported in other systemic rheumatic disorders, as RA and SLE (45). In pSS patients, impaired HRQoL is associated with fatigue, pain, articular involvement, sicca symptoms, pulmonary manifestations, psychological dysfunction and impaired physical function (45). Patients complain sleep problems, reduced sleep efficiency and daytime hyper-somnolence (46). In addition, mood and several neuropsychological domains such as cognition difficulties with attention, focusing, memory and new learning, are commonly reported problems in pSS (47). In order to better characterise factors contributing to fatigue in these patients, Pertovaara *et al.* have analysed a cohort of 100 pSS patients and depicted that fatigue was associated with disease duration and some inflammatory markers (48). Omdal *et al.* hypothesised that, besides inflammation and cellular stress responses, pain represents another activator of the sickness response, therefore inducing fatigue. In particular, interleukin (IL)-1 $\beta$  signalling in the brain possibly represents a final common pathway for fatigue. Interleukin-1 $\beta$  has also been implicated in depression, thus explaining why fatigue and depression are so tightly associated (49).

#### *Sicca syndrome and immune checkpoint inhibitors*

Rheumatic immune-related adverse events are often reported in patients with cancer receiving therapy with

immune checkpoint inhibitors (ICIs), and sicca syndrome is described as a complication of ICI therapy. Recently, Warner *et al.* evaluated 20 patients who developed sicca syndrome after ICI treatment (50). The median interval between ICI introduction and symptom onset was 70 days. Dry mouth, assessed by reduction of whole unstimulated saliva flow, was reported in all patients. Acute dry eye developed in 6 patients of which 5 had a positive Schirmer test in at least one eye. Only 3 patients had positive test for anti-nuclear antibody (ANA) and 2 for rheumatoid factor and anti-SSA antibodies. Almost all patients underwent labial salivary gland biopsy with demonstration of a mild chronic sialadenitis with focal lymphocytic infiltration in the majority of patients. Interestingly, inflammatory infiltrate was mainly characterised by predominance of CD3+ and CD4+ T cells with paucity of CD20 B cells. In addition to supportive measures and ICI therapy withdrawn, corticosteroids therapy was employed in almost all patients.

Ramos-Casals *et al.*, in the Immuno Cancer International Registry, identified a total of 26 patients who developed sicca syndrome after treatment with ICI (51). These patients were mainly men with a median age at diagnosis of 64 years. Of these, 25 patients developed dry mouth and 17 dry eyes. Minor salivary gland biopsy was performed in 15 patients and depicted mild chronic sialadenitis in 8 subjects and focal lymphocytic sialadenitis in the remaining 7. Immunological markers included positive ANA and anti-Ro/SSA in the majority of cases. In summary, ICIs should be included in the list of drugs causing sicca symptoms but patients developing sicca syndrome after therapy introduction display a specific phenotype different from pSS, mainly characterised by increased prevalence of males, higher age at diagnosis, negative immunologic profile and extra-glandular involvement (51).

#### **Take home messages**

- Over one quarter of patients with pSS display extra-glandular manifestations not included among ESSDAI domains (14).

- Alpha-1-microglobulin ( $\alpha$ 1-MG) may prove a useful biomarker for renal involvement in pSS (21, 22).
- Patients with peripheral nervous system involvement usually display more active systemic disease and lower prevalence of sicca features (24, 28).
- PSS-associated arthritis is usually non-erosive and subjects with positive anti-CCP autoantibodies are at higher risk of developing RA (30, 31).
- Other autoimmune diseases, such as autoimmune thyroiditis and coeliac disease are more prevalent in pSS subjects compared to the general population (32, 33).
- Immune-checkpoint inhibitors can induce sicca syndrome with features of sialadenitis, though clinically, serologically and pathologically distinct from SS (50, 51).

### Lymphoma in pSS: what is new?

#### *Novel biomarkers*

Low miR200b-5p levels in minor salivary glands (MSGs) represent a proposed novel predictor for the development of lymphoma in pSS. Kapsogeorgou *et al.* provided additional data supporting low miR200b-5p as an independent predictor, since the predicting power resulted independent from the degree of MSGs infiltration and focus score (52-54). Another novel biomarker of lymphoproliferation in pSS indicated by Gandolfo *et al.* is thymic stromal lymphopoietin (TSLP). Significantly higher TSLP serum levels were found in pSS patients and, importantly, they increased from fully benign infiltrates to parotid myoepithelial sialadenitis (MESA) and finally to NHL. Of note, TSLP was also studied in pSS pathologic tissues, again stratified from fully benign, MESA and NHL, and in controls. Both RT-PCR immunohistochemistry and immunofluorescence were used. A significant increase in the percentage of TSLP-positive B-cells along with the worsening of B-cell lymphoproliferation was evidenced, maximal in NHL. Furthermore, inducible TSLP (the long isoform of TSLP mRNA) was detected only in higher grades of B-cell lymphoproliferation (MESA and NHL), whereas the short constitutive isoform of TSLP mRNA

was similar in all the pSS biopsies, although significantly higher than in controls. Finally, TSLP expression by salivary epithelium declined along with the progression of B-cell lymphoproliferation, the B-cells themselves increasingly becoming TSLP-positive. A pathogenetic role of TSLP in pSS-associated lymphoproliferation was then supported (55).

The role of TREX1 on the risk of pSS and pSS-related lymphoma was explored by Nezos *et al.* The expression of three single nucleotide polymorphisms of the TREX1 gene (rs11797, rs3135941 and rs3135945) and of IFN-I genes was evaluated in patients with pSS, pSS-associated lymphoma and healthy controls. Patients carrying the rs11797 AA genotype had increased type I IFN-related gene expression in minor salivary glands. Significantly decreased prevalence of the rs11797 A minor allele was detected in pSS patients with non-MALT lymphoma. A genetically related defective type I IFN production could represent a potential mechanism in pSS-related lymphomagenesis (56).

#### *Pathogenetic issues*

Gorodetskiy *et al.* examined the clonal relationship between low- and high-grade NHLs in pSS. Data from 6 pSS patients who had developed MZL and synchronous or metachronous DLBC were analysed, identifying immunoglobulin heavy chain gene rearrangements by means of multiplex PCR and GeneScan fragment analysis. In 5/6 cases, low and high-grade tumour pairs showed identical clonal patterns, despite being located in different sites. Then, the concept that DLBCL frequently results from low-grade lymphoma progression in pSS is supported (57). Xian *et al.* investigated the association between B-cell growth factors and pSS-related autoantibodies in patients with NHL, analysing BAFF, anti-SSA/Ro, IL-14, and tissue specific autoantibodies (TSA) including SP1, CA6 and PSP (58). However, also a high number of pSS-unrelated control NHLs patients were positive for pSS-associated antibodies in this study. Mörth *et al.* detected an increase

in associated autoimmune conditions (17.3%) in patients with DLBCL treated with R-CHOP/CHOP-like regimens, compared to the general population (3-10%) (59). Furthermore, NHL associated with those with autoimmune conditions driven by B-cell responses, mainly women with pSS, SLE and RA, had a worse survival (59).

Paediatric pSS is a relevant subset of pSS. Teshler *et al.* presented two cases of paediatric pSS and reviewed the literature. Importantly, one of the two patients was successfully treated with rituximab and hydroxychloroquine, and did not need chemotherapy. The clinical differential diagnosis between non-malignant parotitis and parotid NHL in pSS was also stressed by the Authors (60).

A useful review by Talotta *et al.* integrates the role of dysbiosis and chronic infections with the epigenetic control of gene expression in pSS patients, and their possible involvement in B-cell lymphomagenesis (61). These factors act by inducing hyperexpression of genes that are mainly involved in the innate and adaptive immune responses and oncogenesis. Major ones are the interferon-I (IFN-I) and IFN-II signature (62) and IFN regulatory factor 5, mediating both viral latency and B-cell transformation (63, 64). Microbial agents may also promote the activation of proinflammatory and survival pathways in the salivary gland epithelium and lymphocytes, through the alteration of the epigenetic background, giving to B and T lymphocytes an activated or transformed phenotype. The role of transposable integrated retroviral elements in B-cell deregulation was also commented (65). The review by Nakamura *et al.* is of value to consider pSS-related lymphomagenesis in the light of marginal zone/MALT lymphomagenesis in general, the Authors focusing on the latter (66).

#### *Lymphoma risk and lymphoma diagnosis*

A novel methodology to develop lymphoma prediction in pSS patients, giving emphasis also on a quality control pipeline for clinical data, was presented by Pezoulas *et al.* (67, 68). Such meth-

odology is represented by a first rule-based, binary supervised learning model. A boosted decision tree model was used to identify prominent features with increased importance for lymphoma development in pSS. The results showed an average accuracy 87.1% with an average area under the curve (AUC) score 88%. This model supported the importance of C4, rheumatoid factor and lymphadenopathy as prominent lymphoma predictors, along with major salivary gland enlargement (67, 68).

Prediction of lymphoma in pSS was reviewed by several Authors. When analysing classic and novel predictive markers of NHL, Kapsogeorgou et al. highlighted the relevance of recent multifactorial predicting models, and of novel analytical approaches in general. These are based on machine learning and on big data analyses, to permit harmonisation of patients and the creation of universal algorithms (69).

Nocturne *et al.* highlighted the need of an international consensus on salivary gland histopathology in pSS and on the immunohistological definition of germinal centres (70). The relevance of histopathology was also stressed by Delli *et al.* (71). The pathogenetic role of CD21 low B cells and SCOLYSS were also reported. SCOLYSS is a recently proposed composite score to predict the risk of lymphoma in pSS, and is currently under investigation. It was reported that seven simple variables, easy to be evaluated will be used: the variables to build SCOLYSS have then been established a priori (70).

Goules *et al.* reviewed the more recently proposed molecular and genetic biomarkers for pSS-associated lymphoma prediction (72), and Retamozo *et al.* emphasised the importance of studying synergistic models of lymphoma risk (73).

Regarding the diagnosis of NHL in pSS, Keraen *et al.* retrospectively examined the usefulness of 18F-FDG-PET-CT. The Authors reported three PET patterns associated with the presence of lymphoma in pSS with moderate to high systemic disease activity. PET-TC was found useful also in guiding the histologic diagnostic procedure and in monitoring response to treatment (74).

### Take home messages

- Thymic stromal lymphopoietin (TSLP) expression in salivary glands correlates with the degree of lymphoproliferation and is highest in non-Hodgkin's lymphoma (55).
- Diffuse large B-cell lymphoma may represent a progression from low-grade B-cell lymphoma (57, 58).
- Dysbiosis and chronic infections may be able to promote B-cell proliferation and transformation by epigenetic modulation of cell survival pathways (61).
- A composite prediction score for lymphoma development is currently under investigation (72, 73).

### Salivary gland ultrasonography (SGUS)-assisted developments: salivary gland biopsy, image segmentation, glandular damage and evaluation of disease activity

*Ultrasound-guided salivary gland biopsy*

Salivary gland ultrasound-guided core needle biopsy (SGUS-guided CNB) is an established, effective and safe procedure currently applied in the diagnosis of salivary gland masses, mainly epithelial tumours. SGUS-guided CNB might have a role also in the management of the frequent pSS patients with salivary gland enlargement, that could underlie an already established lymphoma or be a pre-lymphomatous process. Recently, two pilot studies have highlighted the role of SGUS-guided CNB as a safe and useful technique for evaluation of suspected salivary gland lymphoma in pSS patients. In a retrospective study in patients with suspected parotid lymphoma, Baer *et al.* described that SGUS-guided CNB provided sufficient pathologic material to differentiate a range of salivary gland pathologic findings, from normal salivary gland tissue to a diffuse lymphocytic infiltration, representing either benign lymphoepithelial sialadenitis or MALT lymphoma (75). The accuracy of SGUS-guided CNB for the diagnosis of salivary gland lymphoma has been recently confirmed by Zabotti *et al.* in a prospective cohort of pSS patients with parotid or submandibular gland enlargement (76). Furthermore, differently from the previous study,

SGUS-guided CNB was targeted to the most suspicious sonographic detected glandular area, allowing the sampling of parotid and submandibular glandular tissues with different sonographic patterns. A targeted sonographic approach improves the ability of SGUS-guided CNB for differential diagnosis, and also sarcoidosis and IgG4-related disease were diagnosed. Importantly, the observation of fewer long-term and transient complications in SGUS-guided CNB in comparison to open surgical biopsy, as reported, could have a high impact on the patient's acceptance of the proposed biopsy (76). Last-generation ultra-high-resolution ultrasound (UHFUS) transducers, which can produce frequencies up to 70 MHz and achieve tissue resolution up to 30µm, offer new possibilities to visualise labial salivary glands and to guide diagnostic biopsy procedure. Recently, Baldini *et al.* demonstrated that the mean labial glandular surface area obtained by the high-resolution ultrasound guided procedure was significantly higher than the area obtained by traditional biopsy procedure. This procedure could facilitate the assessment of the focus score (77).

### *The application of image-segmentation and of artificial intelligence to SGUS*

The significant intra- and inter-rater disagreement in SGUS scoring is currently considered as a major obstacle for the acceptance of SGUS as a classification and management tool for pSS. As an alternative to human-dependent assessment of sonographic lesions from SGUS, it is possible to employ computer algorithms for texture analysis and use the extracted features to develop artificial intelligence (AI) algorithms to assist human experts in SGUS scorings (78). Recently, Vukicevic *et al.* in a multi-centre collaboration in the HarmonicSS project, tested various radiomics-based AI algorithms for SGUS scoring in pSS patients, identifying AI algorithms that performed as human experts and could be therefore useful to assist clinicians in SGUS (79). The diagnostic performance of a deep learning system for the detection of pSS by SGUS in 100 patients with a confirmed diagnosis of

pSS according to classification criteria was studied (80). The authors concluded that the deep learning system had a high diagnostic ability for pSS by the use of SGUS images (80). The increase in case collection and sonographic images is needed.

#### *Salivary gland damage*

The role of the SGUS in monitoring the history of pSS in a non-invasive manner, the response to treatment, in predicting the outcomes and in detecting lymphoma, although promising, is still not well delineated (81). The SG abnormalities due to pSS are believed to progress slowly over time, resulting in changes in SGUS findings. Based on the present knowledge, SGUS could help to identify active inflammatory lesions, namely the hypo-anechoic areas, and the damage-related lesions, the hyperechoic bands (82). In a recent study, the hyperechoic bands were identified as the sonographic lesions mainly associated with SG impairment, objectively evaluated by reduced salivary flow rate, in pSS patients with a disease duration  $\geq 5$  years (83).

#### *Evaluation of pSS activity*

It was recently highlighted that the quantification of inflammation and lymphoproliferation within the salivary MALT can be a novel tool to evaluate pSS disease activity (84, 85), also related to the lymphoma risk. Despite being the pathobiologic and phenotypic essence of pSS, glandular inflammation and lymphoproliferation contributes limitedly to ESSDAI. Furthermore, ESSDAI is low in about 30% of pSS who develop NHL and does not appear as a good predictor (86). In a cohort of 30 pSS cases with NHL, persistent SG swelling and cryoglobulinaemia were the major predictors of NHL in pSS. They mirror B-cell clones employing peculiar rheumatoid-factor-related immunoglobulin genes, prone to malignant transformation. A recent subproject within the HarmonicSS project (<https://www.harmonicss.eu>) is the creation of a new composite activity index for pSS, based on histopathology as the golden standard whenever possible, but also with additional “sur-

rogates” of pathologic MALT involvement, clinical (*e.g.* parotid swelling and cryoglobulinaemic vasculitis) and laboratory (*e.g.* low C4, cryoglobulinaemia, rheumatoid factor/idiotypes, free immunoglobulin light chains, serum beta 2 microglobulin). The presence of surrogates was introduced to allow some evaluation also when tissue biopsy is not available or cannot be repeated, for any reason.

#### **Take home messages**

- Salivary gland ultrasound-guided core needle biopsy is a safe and useful technique for evaluation of suspected salivary gland lymphoma in pSS patients (75, 76).
- Application of salivary gland ultrasonography may have importance in the evaluation of disease activity for the future (84, 85).

#### **What is novel in the treatment of pSS**

It is well known that the majority of pSS patients only manifest dry eye and dry mouth-related symptoms, which, however, may have a severe impact on quality of life. Current treatment is based on local tear and saliva substitutes, immunosuppressants and systemic secretagogues, though these strategies are frequently ineffective and scarcely tolerated. For these reasons, a strong scientific effort in this field is directed towards new potential approaches to treat sicca syndrome. Recently, new interesting data have been published from *in vitro*, animal studies, clinical trials and observational studies.

Although there is no strong evidence from clinical trials in support of the effect of conventional disease-modifying antirheumatic drugs (DMARD) on tear and saliva production, nor on the attenuation of sicca symptoms, evidence showing efficacy in animal models is growing. Lee *et al.* demonstrated that NOD mice, a mouse model of diabetes that spontaneously develop sialoadenitis resembling SS, treated with chloroquine in the early stages of the disease are characterised by improvement of tear secretion, corneal damage, lacrimal and salivary gland inflammatory cell infiltration and pro-inflammatory

cytokine secretion via inhibition of autophagy (87).

Local cyclosporin A (CyA) is routinely used to treat xerophthalmia and corneal damage in SS. Despite having demonstrated beneficial effects, its use is limited by the poor tolerability and bioavailability due to the scarce hydrosolubility of the molecule. Scientific efforts are therefore concentrated towards an improvement of the pharmacokinetics properties of topical CyA. A pooled analysis of the results of two phase III randomised clinical trials that tested the effect of a cationic emulsion of CyA on dry eye has been recently performed with involvement of 734 patients of which about 1/3 had SS-related sicca syndrome. The results showed a significant effect on signs and symptoms in the group of pSS patients with severe dry eye, but not in the overall pSS population, with a tolerability profile equivalent to standard CyA formulations (88). Recently, as an emulsion formulation tends to flocculate and sediment over time, a more stable and bioavailable nanoemulsion has been tested in a clinical trial in South Korea with promising results. In fact, it improved both symptoms and signs of dry eye with an equivalent efficacy compared to the approved formulation of CyA. However, the effect of the nanoemulsion was evident at an earlier time-point, presumably due to its higher bioavailability (89).

Other immunosuppressants are undergoing investigation for the local treatment of dry eye in pSS, such as sirolimus, which exerts its activity by inhibiting the signal transduction of interleukin (IL)-2 and, therefore, the activation of B and T cells, essential players in the pathogenesis of the disease. Its potency is higher compared to CyA but similar in terms of water solubility, limiting its capability of penetrating the tear film barrier. Nonetheless, subconjunctival injection of sirolimus following microencapsulation in NOD mice showed a dose-dependent improvement of tear secretion and corneal damage compared to controls, suggesting a potential benefit in pSS patients (90). The mTOR signalling pathway regulated by sirolimus is also inhibited by



metformin, via the activation of AMP-activated protein kinase (AMPK). It is known that the inhibition of mTOR in T cells promotes their preferential differentiation towards a regulatory (Treg) phenotype. Similarly, AMPK activation causes inhibition of signal transducer and activator of transcription (STAT)3 which is involved in the differentiation of Th17 and T follicular helper (Tfh) cells. Based on these data, a study performed on NOD mice treated with metformin showed significant improvement of saliva secretion and a reduction of salivary glands T cell infiltration and pro-inflammatory cytokines levels, along with a promotion of T cell differentiation towards a regulatory (Treg) phenotype (91). A similar effect on Th17, Treg and Breg cells and on pro-inflammatory cytokines in NOD mice salivary glands was observed following the administration of rebamipide, a gastroprotective agent able to enhance prostaglandin synthesis. However, the mechanisms underlying this effect require further research (92).

Some data on approaches other than systemic secretagogues for the treatment of xerostomia have been published and showed an improvement of patient-reported outcomes (PRO) and salivary secretion using salivary stimulants such as malic acid lozenges and citric acid solution, with a stronger effect by the former. Additionally, in a group of patients – 1/3 diagnosed with SS and the other with xerostomia due to other causes – who underwent salivary gland irrigation procedures through the retrograde injection of saline into the four major salivary gland, a significant proportion experienced an increase of unstimulated salivary flow (93). Additionally, two meta-analyses performed on pharmacological treatment of xerostomia in pSS confirmed a positive outcome for interferon- $\alpha$ , cevimeline and pilocarpine (94, 95).

In recent years, potential applications of cell and antigen therapy for the treatment of SS have been extensively investigated and data are progressively accumulating. Human umbilical cord mesenchymal stem cells (hUCMS) are multipotent cells extracted from the Wharton jelly of umbilical cord and

have the great advantage of being accessible and easy to extract. Their ability to modulate the immune response is now well established, however more data are necessary to characterise their behaviour *in vivo*. In a rabbit model of dacryoadenitis, hUCMS were shown to promote macrophage polarisation towards an M2 phenotype, therefore favouring an anti-inflammatory behaviour and ultimately improving damage and function of lacrimal glands (96). One of the limitations of the use of cell therapy is the immunogenicity induced by the injection of allogenic cells into the host. Despite hUCMS should not induce immunogenicity, their survival *in vivo* is relatively short. Multiple methods have been attempted in order to overcome these limitations, including administration of an extract, rather than viable cells, with preliminary data showing equivalent effects (97). An alternative potential method to modulate immune system activity is through therapeutic administration of antigens, resembling a vaccination response. A recent study showed that the administration to a murine model of sialoadenitis of transgenic rice seeds expressing peptide ligands of the M3 muscarinic receptor engineered in order to replace amino acid residues at the sites of interaction with the T cell receptor (TCR), is able to modulate the immune response by increasing salivary flow, reducing glandular inflammation, pro-inflammatory cytokine secretion in the gland and balance between Th17 and Treg cells. These aspects deserve however further investigation (98).

In patients with severe, long-lasting sicca syndrome, complications of the lack of saliva and tears are frequent. One of the most concerning aspects is the increased frequency of caries. One of the objectives of sialogogues prescription, beyond mitigating the symptoms, is the preservation of oral and ocular health. However, unlike the results on animal models and some recommendations, a recent study showed no effect on the rate of caries development in patients treated with pilocarpine compared to controls (99). Similarly, dry eye can sometimes be refractive to all the treatments and may sometimes

complicate with the development of abrasions, ulcerations and occasionally corneal perforations, which require a more aggressive treatment. Shafer *et al.* have attempted the use of cryopreserved amniotic membrane, locally applied on the ocular surface, and showed that after few days the symptoms and ocular surface damage dramatically improved, although the benefit was short-lasting. Being only a case series, it would be interesting to further explore this therapeutic strategy, which may exert its effect acting both as a mechanical barrier and as a modulator of inflammation (100).

As previously mentioned, pSS may be a systemic disease and almost all patients complain of systemic symptoms such as fatigue. Several therapeutic strategies have been attempted in order to improve fatigue, with very scarce outcomes. However, some non-pharmacological strategies may have a potential benefit, such as supervised exercise and non-invasive vagus nerve stimulation, which have been demonstrated to improve fatigue, cardiorespiratory fitness and exercise tolerance. Vagus nerve stimulation was also able to significantly reduce the secretion of pro-inflammatory cytokines by peripheral blood mononuclear cells (PBMC) (101, 102), suggesting a potential wider application of the technique.

In patients with systemic involvement, treatment strategies are mostly based on expert opinion and the use of pharmacological approach is mutated from the evidence in other autoimmune and inflammatory diseases. For this reason, there is great interest in building scientific evidence in support of the use of immunomodulatory and immunosuppressive therapies. Hydroxychloroquine (HCQ), methotrexate (MTX) and leflunomide (LEF) are commonly used in patients with mild systemic disease, especially with articular involvement, but there is very little evidence on their efficacy in SS. Interestingly, there is a rationale supporting the combination of HCQ and LEF. In fact, the pharmacological effect of LEF is mainly directed towards the inhibition of T cell response, while HCQ mainly affects antigen presenta-

tion and B cell response. An additive effect of the two medications has been demonstrated in vitro in terms of pro-inflammatory cytokine secretion, T and B cell proliferation. A clinical trial has also been carried out, though data are not yet available (103). Albeit HCQ is a very well tolerated medication, its widespread use warrants careful attention on the potential adverse events. A recent case-control study suggested a potential association between the use of HCQ in pSS and SLE patients and higher prevalence of non-melanoma skin cancer. However, these data need to be confirmed (104).

Numerous clinical trials have been carried out and others are currently ongoing on the potential effect of target therapy for more severe disease manifestations. Although some molecules, such as rituximab (RTX), are commonly used, little evidence is available and the results from the trials to date are mostly inconclusive (105). Nonetheless, some interesting studies recently explored the effect of the blockade of various pathways. A small open label study has demonstrated a significant reduction of median ESSDAI score, most evident in the articular and glandular domains, following treatment with abatacept (106). Another study demonstrated minimal beneficial effect of ianalumab, a B-cell activating factor (BAFF) receptor blocker, on fatigue and circulating B-cell levels (107). Very interestingly, Combier *et al.* have shown that the development of anti-RTX antibodies in connective tissue diseases is more frequent compared to RA and patients developing infusion reaction due to this phenomenon can be effectively treated with ofatumumab, another CD20 blocker (108).

In addition, some new pathways are attracting interest as potential targets in pSS. In NOD mice, blockade of CD40 ligand was effective in abolishing the formation of germinal centres (GC) in salivary glands. CD40-CD40L pathway, in fact, has a crucial role in the co-stimulation of T and B cells and is strongly involved in isotype switching and GC formation (109). Germinal centres in SS salivary gland also show a markedly increased activity of the  $\delta$  isoform of

phosphatidylinositol 3-kinase (PI3K $\delta$ ) as demonstrated by the increased concentration of downstream peptides in biopsy samples. Thus, Nayar *et al.* have demonstrated that treatment of a murine model of SS with the PI3K $\delta$ -inhibitor eletalasib, actually used for B-cell malignancies, significantly mitigates pro-inflammatory cytokine and chemokine secretion, prevents the formation of GCs and improves salivary function (110).

#### *New advances in the treatment of lymphoma*

Lymphoma development is the main complication decreasing patient survival in pSS. Low grade B-cell NHL of MALT is the largely overrepresented histotype, followed by DLBCL, which may also derive from MALT (15, 111). Treatment decisions for pSS-associated NHL must be case tailored. Treatment of indolent MALT NHL, much more frequent in pSS, may range widely, from a "watch and wait" approach to cytotoxic therapies, low dose radiotherapy or surgical excision. Chemotherapy or chemoimmunotherapy may also be used, with a combination of rituximab with either alkylating agents (cyclophosphamide/chlorambucil), purine analogs (fludarabine, cladribine), or bendamustine. Conversely, the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) is often employed in aggressive NHL (112).

However, the major recent novelties implicate biological agents for the treatment B-cell lymphoproliferative disorders in pSS that do not require aggressive approaches. Although biologics are now being investigated for the treatment of pSS as a whole, their specific role in targeting the pSS subset with heavier B-cell proliferation deserves attention. Biologics might be employed in borderline cases where the diagnosis of a definite B-cell malignancy is difficult, or in prelymphomatous conditions in pSS, mainly cryoglobulinaemic vasculitis with type II mixed cryoglobulinaemia, and persistent parotid swelling with heavy underlying MALT lesions (105, 113-116). Recent studies focused on the fundamental role

of antigen-driven and BAFF-mediated B cell hyperactivation in the evolution of lymphoma in pSS (70, 117, 118). Rituximab monotherapy may be insufficient to deplete the B-cells in the salivary gland tissue, the resistance of B-cells to rituximab being due to the concomitant hyperexpression of BAFF in this microenvironment (119).

Treatment with belimumab, an anti-BAFF monoclonal antibody registered for the treatment of SLE (120), was employed in the BELISS trial in pSS with encouraging clinical results, including pSS with parotid swelling. Novel treatment strategies for pSS-related lymphoproliferation then imply the combination of direct B-cell-depleting and anti-BAFF agents (116).

Very long-term remission of a patient with pSS, parotid NHL of MALT, and cryoglobulinaemic vasculitis was achieved with a sequential treatment with belimumab shortly followed by rituximab, while rituximab alone and belimumab alone, given previously, were both ineffective (113). At present, a double-blind, randomised, placebo-controlled trial (NCT02631538) is testing belimumab/rituximab coadministration (where belimumab is started earlier) in comparison to belimumab monotherapy in pSS.

Another encouraging approach under investigation is the use of ianalumab (VAY736), an anti-BAFF receptor monoclonal antibody (NCT02149420, NCT 02962895), with double anti-BAFF and direct B-cell depleting properties. Ianalumab eliminates BAFF-R-positive mature and immature B cells via antibody-dependent cytotoxicity (ADCC) and induces B-cell apoptosis by blocking BAFF/BAFF-R interaction (107). Epratuzumab, an anti CD22 monoclonal antibody, showed some positive results in an older, small phase I/II open-label study in pSS, and recent post hoc analyses of the EMBODY trials showed improvement in disease activity in patients with SLE and associated SS, with a decrease in B-cells and IgM levels (121).

Other Authors recently focused on T-cell proliferation, T-cell related cytokines and B-cell/T-cell co-stimulation pathways in systemic and local MALT

inflammation, especially in the ectopic germinal centres (122-124). A recent randomised, double-blind, placebo-controlled Phase 3 Study, assessed the efficacy and safety of abatacept, which blocks the CD28:CD80/CD86 T cell co-stimulation in pSS. Although IgG and RF levels decreased, a significant improvement in ESSDAI and salivary or lacrimal gland function was absent (125).

Targeting the CD40/CD40L pathway represents another option under study (109, 126). The safety and efficacy of a monoclonal antibody against CD40 (iscalimab/CFZ533) in pSS patients was assessed in a phase II clinical trial (NCT02291029) with encouraging results. Another double-blind, randomised, placebo-controlled trial (NCT03905525) is ongoing. Furthermore, a randomised double-blind placebo-controlled study exploring the efficacy and safety of VIB4920 is ongoing in pSS (NCT04129164), VIB4920 being a fusion protein designed to bind to CD40L.

Other investigational approaches to target B-cell proliferation in pSS imply the small molecules inhibitors (e.g. selective Jak1-, Syk-, BTK- and PI3k $\delta$ -inhibitor), anti-IL7 therapy (VIB 7734) (NCT03817424), RLSV-132, the fusion IgG1 protein of a human RNase (NCT03247686) low-dose human recombinant IL-2 therapy (NCT02464319), the anti-BAFF/anti-IL17A (tibalizumab), the cathepsin S inhibitor RO545907 (NCT02701985) the co-stimulation blocker prezalumab (anti-ICOS) (NCT02334306) (105, 122, 123, 127, 128).

Finally, if the involvement on TSLP (55, 105) in pSS-related lymphoproliferation will be confirmed, evaluating tezepelumab, i.e. a monoclonal antibody against TSLP studied in asthma and atopic dermatitis (129), might be useful.

All these data are preliminary and intensive research is mandatory before these molecules can be routinely employed in the clinical practice, though a great amount of new data is expected in the next few years, hopefully leading to breakthroughs in the treatment of pSS (122).

### Take home messages

- New formulations of topical cyclosporine A and sirolimus for dry eye treatment may prove superior in terms of bioavailability and efficacy (88, 89).
- Metformin, interferon- $\alpha$ , cevimeline and pilocarpine may be effective in improving salivary and tear secretion (91, 94, 95).
- Human umbilical cord mesenchymal stem cells extracts are able to modulate the inflammatory response in murine models of SS, without being immunogenic (96, 97).
- Recent reports suggest abatacept, ionalumab and ofatumumab may be effective for the treatment of more severe clinical manifestations (105, 106, 107, 111).
- Treatment of pSS-associated lymphoma needs to be tailored on the individual cases. Multiple clinical trials are currently being carried out testing the efficacy of different agents directed towards B-cells and T-cells (112, 116).
- Biologics might be employed in pre-lymphomatous conditions in pSS (e.g. cryoglobulinaemic vasculitis and persistent parotid swelling with heavy underlying MALT lesions) (122, 128).

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