Sjögren syndrome: looking forward to the future

Sara Zandonella Callegher*, Ivan Giovannini*, Sabine Zenz, Valeria Manfrè, Martin H. Stradner, Alojzija Hocevar, Marwin Gutierrez, Luca Quartuccio, Salvatore De Vita and Alen Zabotti

Abstract: Primary Sjögren’s syndrome (pSS) is a heterogeneous disease characterised by a wide spectrum of manifestations that vary according to the different stages of the disease and among different subsets of patients. The aim of this qualitative literature review is to summarise the recent advances that have been reported in pSS, ranging from the early phases to the established disease and its complications. We analysed the diagnostic, prognostic, and management aspects of pSS, with a look into future clinical and research developments. The early phases of pSS, usually antedating diagnosis, allow us to investigate the pathophysiology and risk factors of the overt disease, thus allowing better and timely patient stratification. Salivary gland ultrasound (SGUS) is emerging as a valid complementary, or even alternative, tool for histopathology in the diagnosis of pSS, due to a standardised scoring system with good agreement and performance. Other promising innovations include the application of artificial intelligence to SGUS, ultrasound-guided core needle biopsy, and a wide array of novel diagnostic and prognostic biomarkers. Stratifying pSS patients through the integration of clinical, laboratory, imaging, and histopathological data; differentiating between activity-related and damage-related manifestations; and identifying patients at higher risk of lymphoma development are essential steps for an optimal management and individualised treatment approach. As new treatment options are emerging for both glandular and systemic phases, there is a need for a more reliable treatment response evaluation. pSS is a complex and heterogeneous disease, and many distinct aspects should be considered in the different stages of the disease and subsets of patients. In recent years, efforts have been made to improve our understanding of the disease, and certainly in the coming years, some of these novelties will become part of our routine clinical practice, thus improving the management of pSS patients.

Keywords: activity, biomarkers, damage, histopathology, lymphoma, pathogenesis, preclinical phase, salivary gland, Sjögren’s syndrome, treatment, ultrasonography

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Introduction
Primary Sjögren’s syndrome (pSS) is a connective tissue disease characterised by a wide spectrum of clinical features, extending from exocrine to extra-glandular involvement.1 Over the years, growing efforts have been made to characterise the disease, focusing on its pathogenetic pathways, early diagnosis, biomarkers, imaging tools, and therapeutic strategies.1

The exact pathogenesis of pSS is currently not well understood but appears to be multifactorial.2–4 The pathogenesis is thought to be B-cell-centric, and B-cell activation, immune complex formation, and autoantibodies production are thought to be the key steps.2–4 Nevertheless, T cells (such as Th17 and Th22 cells), follicular dendritic cells, and innate immune system have been proven to participate in the development...
and persistence of inflammation in this systemic disease.5,6 In particular, inflammatory infiltrates in salivary glands (SGs) may form aggregates, organised in ectopic germinal centres (GCs), which might drive chronic stimulation and activation of B cells.7–9

The glandular damage caused by the immune-mediated destruction of exocrine glands, B-cell hyperactivation, and excessive infiltration of inflammatory cells into the gland exposes pSS patients to an increased risk of lymphoproliferative disease,10–12 the highest among various autoimmune diseases.13–15 At present, more studies are needed to address the exact pathogenesis of pSS and pSS-related lymphoproliferative disease. The aims of such studies are to identify the key pathogenetic pathways of the disease, to stratify pSS patients, and to better evaluate the activity-related and damage-related manifestations. Furthermore, the improved definition of biomarkers for lymphoproliferative disease would allow the more precise identification of patients at higher risk of developing lymphoma.

The usefulness of salivary gland ultrasound (SGUS) in patients with pSS was highlighted almost 30 years ago,16,17 and since then, it has proved to be an effective tool in the evaluation of SG structural abnormalities and parenchymal lesions in major SGs.18–20 SGUS is a simple, non-invasive, nonirradiating, and inexpensive technique,21–25 and various studies have reported that its inclusion in pSS classification criteria improves diagnostic accuracy, feasibility, and sensitivity.23,26–28(99,686),(296,774) Keeping the specificity unchanged compared to the American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) criteria.29 Furthermore, ultrasound may guide biopsies for adequate histological sampling in pSS patients with suspected lymphoma, as recently proposed.30–32

The aim of this qualitative literature review is to summarise recently reported advances in pSS, ranging from the early phases to the established disease and to possible lymphoma complications. We analysed the diagnostic, prognostic, and management aspects of pSS, with a look into future clinical and research developments.

Preclinical pSS and early pSS
Preclinical Sjögren syndrome is a phase characterised by laboratory, imaging, histologic abnormalities, and clinical symptoms (e.g. sicca syndrome), although not or not yet fulfilling the pSS classification criteria.

Early Sjögren syndrome can be defined by the fulfilment of the classification criteria31,34 from a short time (i.e. less than 24 months).

Pathophysiology of pSS and new study techniques
Inflammation of the salivary and lacrimal glands (epithelitis) is a hallmark of pSS pathophysiology.35 Lymphocytes infiltrate the perivascular and periductal areas of the glands, where they interact with activated salivary gland epithelial cells (SGECs).35 The majority of lymphocytes involved have been characterised as CD4+ T helper cells and B cells by immunohistochemistry and flow cytometry.30 Individual predefined populations of infiltrating cells have been further studied in more detail.37–39 A comprehensive in-depth analysis of the functional properties and subtypes of all the cells participating in pSS epithelitis has long been hampered by technical restraints.35,40

Two studies took advantage of cytometry by time of flight (CyTOF) to address this issue.40,41 CyTOF is a flow cytometry-based technique that uses antibodies labelled with isotopically pure elements; this approach allows for the analysis of 30 or even more proteins on individual cells. Mingueneau et al.41 analysed mononucleated cells from peripheral blood and SG biopsies of pSS patients. They identified an increase in activated CD4+ and CD8+ T cells, while plasmacytoid dendritic cells were decreased compared with the peripheral blood mononuclear cells (PBMCs) of healthy individuals.41 These results were confirmed by another study comparing the PBMCs of pSS patients with those of patients suffering from systemic sclerosis or systemic lupus erythematosus.40 While CyTOF increases the potential of single-cell analysis in pSS, it is dependent on the availability of antibodies to well-characterised antigens. By contrast, methods analysing the transcriptome allow for an unbiased approach, aiding the generation of new hypotheses. cDNA microarrays have been performed on PBMCs and glandular tissue from pSS to identify the characteristic interferon signature in many patients.42,43 This pattern is most prominent in the subset of cases serologically defined by increased titres of anti-SSA and anti-SSB autoantibodies.42,43
In the near future, the more powerful technique of RNA sequencing (RNA-seq) will replace microarrays. A study analysing SGECs and sorted B cells from pSS SGs underscored the importance of SGECs for B-cell activation and survival. Furthermore, RNA-seq was employed to analyse the PBMCs of the large PRECISESADS cohort, identifying four different clusters of pSS patients that could be used to stratify pSS in the future.

Single-cell RNA-seq (scRNA-seq) combines the power of single-cell analysis with the unbiased approach of RNA-seq. The potential of this novel technique was demonstrated by a first study identifying a previously unrecognised population of peripheral blood cytotoxic CD4+ T cells in pSS patients. Other single-cell sequencing methods will allow analysis of the methylation state (single-cell DNA methylome sequencing) and accessible DNA for transcription factors (single-cell ATAC-seq) of single cells in pSS. Furthermore, tissue-based methods, such as spatial transcriptomics and imaging mass cytometry, will enable us to investigate RNA and protein expression within the SGs in unprecedented resolution. In summary, the rapid development of single-cell and single-omics techniques within the last few years will enable us to unveil a broader picture of pSS pathophysiology.

Risk factors for pSS development

To date, the risk factors for developing pSS have not been well established, primarily because sicca symptoms slowly progress over years and are often initially underestimated by both patients and physicians; therefore, the average diagnostic delay of pSS is 7 years, with most patients already showing SG damage. Furthermore, the current ACR-EULAR classification criteria can be applied if considerable impairment of the glands has occurred, since patients need to suffer from pronounced sicca symptoms to be eligible for the criteria. Thus, no extensive data exist about the early phase of pSS or the risk factors that may lead to it.

Autoantibodies in rheumatic diseases are often detectable years before the first symptoms appear, as also indicated in pSS patients. Theander et al. performed a case–control study analysing pre-disease samples of 117 pSS patients: 81% had anti-SSA or anti-SSB antibodies before manifesting any typical pSS symptoms. In a large-scale research registry for neonatal lupus, asymptomatic mothers with anti-SSA and anti-SSB antibodies of children with neonatal lupus were studied over 10 years, and the probability of an asymptomatic antibody-positive mother developing pSS was 27.9%. Interestingly, mothers with both anti-SSA and anti-SSB antibodies were nearly twice as likely to develop an autoimmune disease, with a higher probability of developing pSS than mothers with anti-SSA antibodies alone. Thus, anti-SSA and anti-SSB antibodies might be a risk factor for the development of pSS.

Furthermore, in an epidemiological study, first-degree relatives of pSS patients had an 11- to 19-fold increased risk of developing pSS, highlighting genetics as a risk factor for the development of pSS.

Established pSS

How will we diagnose pSS in the future?

The diagnosis of pSS is based on a set of clinical, laboratory, imaging, and pathological features, since no single test can alone be diagnostic per se. Minor salivary gland biopsy (MSGB) is considered the gold standard tool and plays a key role in the ACR-EULAR classification criteria for pSS, especially in seronegative patients. MSGB is not devoid of possible adverse events, particularly temporary or permanent paraesthesia (11.7% and 6% of cases, respectively), and lacks of standardisation of surgical procedure and histopathology reporting, although a consensus guidance was
recently published to this end. The strengths of MSGB are its good sensitivity (63.5–93.7%), specificity (61.2–100%) and prognostic value, since it was demonstrated that higher focus score (FS) values are related to a higher risk of more severe extra-glandular manifestations and lymphoma.

The role of SGUS in pSS diagnosis is described below (see section ‘The role of SGUS in pSS diagnosis’). Other promising innovations are ultrasound elastography, the application of artificial intelligence to automatically score SGUS, and the major SG biopsy, which is now reserved for cases of suspected SG lymphoma. Nevertheless, according to Pijpe et al., a surgical major SG biopsy has a diagnostic performance comparable to MSGB in pSS, with 93% sensitivity and 95% specificity, and is repeatable, allowing treatment response evaluation. Ultrasound-guided core needle biopsy (CNB) of major SGs may represent a valid alternative to surgical biopsy (see section ‘Ultrasound-guided core needle biopsy in the diagnosis of pSS-related lymphoma’).

In recent years, efforts have been made to identify diagnostic biomarkers in pSS in tears (i.e. increased tear osmolarity, decreased tear protein MMP-9, LACTO, LIPOC-1) and saliva (i.e. elevated levels of IgA, IgG, lactoferrin, β-2 microglobulin). Further studies are necessary to clarify the clinical utility of these novel biomarkers.

**pSS prognosis and disease activity assessment**

pSS is a chronic, slowly progressing, non-life-threatening disease with a 10-year cumulative survival rate of over 90%. Nevertheless, some patients have a severe disease and may have an increased risk of death, and extra-glandular manifestations are present in 30–50% of patients during the follow-up.

Studies have shown that high baseline systemic activity is associated with a worse prognosis and decreased survival. A recent meta-analysis revealed older age at diagnosis, male gender, extra-glandular and vasculitic involvement, parotid enlargement, low complement levels, and cryoglobulinaemia as factors associated with increased mortality in pSS. Moreover, among autoimmune rheumatic diseases, pSS harbours the highest risk of lymphoma (14-fold higher risk), affecting around 5% of the pSS population.

Several indices have been developed to better evaluate and monitor disease activity. The EULAR Sjögren’s syndrome disease activity index (ESSDAI) is a composite validated and sensitive to change index of systemic disease activity. It encompasses 12 domains (11 organ-specific and 1 biological domains reflecting B-cell activity). For clinical studies, ESSDAI modification was made by removing the biological domain (clinical ESSDAI).

The EULAR Sjögren’s syndrome patient reported index (ESSPRI) is a patient-reported index with the final score representing the mean grade of three subjective components (dryness, musculoskeletal pain, fatigue), each evaluated on a 0–10 scale. As the correlation between ESSPRI and ESSDAI is weak, the indices should be used complementarily.

However, ESSDAI does not completely capture pSS disease activity. It does not reflect activity in glandular limited disease (roughly representing two-thirds of all pSS patients), since glandular inflammation and lymphoproliferation contribute only to a limited extent to the final ESSDAI score, not recognising sufficiently patients at risk of developing lymphoma. Furthermore, pSS patients frequently present with overlapping features of activity and damage, both of which contribute to disease severity.

To overcome this gap, a composite endpoint, Composite of Relevant Endpoints for Sjögren’s Syndrome (CRESS), was developed and validated by the analysis of data from rituximab, tocilizumab, and abatacept trials. CRESS is composed of five complementary items: ClinESSDAI, ESSPRI, lacrimal gland item, SG item, and serological item. Such a composite response measure addressing different aspects of the disease could better appreciate treatment efficacy compared to a single target.

To this end, another composite endpoint was recently developed, the SS Tool for Assessing Response (STAR), elaborated within the multinational NECESSITY Project (https://www.necessity-h2020.eu).

The stratification of pSS patients

pSS is a clinically heterogeneous disease; therefore, stratifying pSS patients is essential to allow better patient management and the proper administration of resources.
The stratification and harmonisation of pSS patients is supported by the HarmonicSS initiative (HarmonicSS.eu; https://cordis.europa.eu), part of the Horizon 2020 project. This initiative aims to collect, evaluate, and harmonise different pSS cohorts based on shared and internationally accepted classification criteria and measures of disease activity and damage, considering health care policy, advanced statistical methods, and advanced informatic technology.

A recent analysis of the international and multicentre registry, the Sjögren Big Data Consortium, which included over 10,000 pSS patients, showed that demographic and geoepidemiological characteristics significantly determine the systemic phenotype of the disease. Male pSS patients have a higher ESSDAI and carry an increased risk of lymphoma. Early-onset pSS (age ≤35 years) is associated with clinical and biological features predictive of severe systemic disease (e.g. SG enlargement, lymphadenopathy, purpura, renal involvement, hypergammaglobulinaemia, hypocomplementemia, presence of autoantibodies) and higher ESSDAI, whereas late-onset pSS (age ≥65 years) is characterised by less frequent autoantibody positivity, lower biological activity, higher prevalence of lung involvement and lower prevalence of arthritis. Considering systemic activity, Black/African American patients exhibit the highest ESSDAI scores, followed by White, Asian and Hispanic pSS patients.

Importantly, the immunoserological profile influences the disease phenotype and represents the traditional basis for stratification of pSS patients. Alternatively, a recent study applied patient-reported symptoms in pSS stratification and conclusively recognised four different disease clusters – low symptom burden, high symptom burden, dryness dominant with fatigue and pain dominant with fatigue – with accompanying distinct serological and molecular markers and responses to immunomodulatory treatment.

SGUS may provide additional help in pSS phenotyping, as normal-appearing SGUS reflects a milder pSS phenotype with preserved salivation, negative lip biopsy and a less pronounced serological profile. Indexes of glandular involvement, such as FS and the presence of GCs, represent other options for pSS stratification, particularly as both seem to be associated with SG enlargement, lymphoma risk, systemic disease and antibody positivity. Molecular markers might, in the future, provide key baseline information for pSS clustering.

Stemming from current knowledge and considering the risk of developing systemic manifestations and poor outcomes, a phenotype-driven prognostic classification of pSS has recently been proposed. The classification distinguishes three pSS subgroups: low-risk pSS patients (with elderly onset, seronegative disease or isolated anti-SSB positivity), intermediate-risk pSS patients (early-onset disease, anti-SSA positivity, Black/African-American ancestry) and high-risk pSS subgroup (males, rheumatoid factor carriers, patients with cryoglobulinaemia and hypocomplementemia, high FS or presence of GCs in SG biopsy).

In summary, pSS is a complex multifaceted disease; nevertheless, through the integration of clinical, molecular, imaging and histopathological data, improved disease stratification is feasible and may be ultimately reflected in the individualised treatment approach.

Long-standing disease
pSS can be considered long-standing when diagnosis and classification criteria fulfilment date several years ago (e.g. at least 10 years).

How to assess damage related to pSS
Damage may occur in early disease, is always present in established disease, but is often heavier in long-standing disease. Overall, the objective glandular hypofunction in pSS could be explained by active inflammation of the gland (infiltration of immune cells), chronic damage (fibrosis and fatty lesions) with loss of functional parenchyma and functional impairment (autonomic dysfunction and receptor-mediated downregulation of saliva).

In chronic inflammatory diseases, such as pSS, the differentiation between active inflammatory lesions (reversible with therapy) and damage-related lesions (not reversible with therapy) is crucial to better stratify patients in terms of specific treatment indications and responses.

Currently, salivary flow rate, SG scintigraphy and, less frequently, sialography are used as diagnostic tools in pSS, since they are included in new and old pSS classification criteria. However, their role in patients’ follow-up is less clear. Salivary flow rate and scintigraphy might have
potential indications for objectively evaluating changes in secretory function in the course of the disease and after treatment, due to their ability to monitor SG functioning over time. However, their use is limited due to reliability issues, invasiveness and radiation exposure.22

Magnetic resonance (MR) could help to identify the changes that occur in major SGs during the different phases of the pSS, differentiating early stages (oedema caused by active inflammation resulting in glandular enlargement) and damage progression (lobular destruction associated with deposition of fibrous tissue and fat, visible as diffuse micro- and macro-cystic changes).22

For the role of SGUS in pSS, see section ‘Focus on salivary gland ultrasound’.

In recent years, two clinical composite indexes for quantifying the amount of damage related to pSS have been proposed: Sjögren’s Syndrome Disease Damage Index (SSDDI)109 and Sjögren’s Syndrome Damage Index (SSDI).110 The SSDDI is composed of a list of 18 irreversible damages affecting 6 organ domains,109 and the SSDI is an unweighted checklist of 27 items divided into 3 lists: ocular, oral and systemic damage.110 Although these two indexes are currently used in clinical practice, they have limitations, such as low external validity and cross-validation, and they may not completely cover the broad spectrum of pSS.111

The role of SGUS in pSS diagnosis

Nowadays, SGUS is gaining a central place in the diagnostic algorithm of suspected pSS,18,120 emerging as a valid complement tool to histopathology and as an alternative tool in cases where biopsy cannot be performed. A recent study reported that adding SGUS as a minor item to ACR/EULAR classification criteria improved sensitivity from 90.2% to 95.6%, with quite similar specificity.27 Furthermore, studies have reported that the combined positivity of SGUS and anti-SSA antibodies provides a high predictive value for the diagnosis of pSS, hypothetically excluding the need for MSGB. MSGB, as well as its diagnostic value, has important prognostic value, since it allows the identification of patients at higher risk of developing severe extra-glandular manifestations and lymphoma.65 By contrast, a negative SGUS with negative anti-SSA antibodies cannot reliably exclude pSS, and in these cases, MSGB is mandatory if pSS is suspected.119,121 The limitations of SGUS are mainly due to reliability issues and the lack of a
To improve the standardisation of the methodology, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) SGUS task force proposed a new four-grade semiquantitative score with good/excellent agreement results (Figure 1).

The role of SGUS in disease activity assessment
The role of SGUS as an instrument to assess pSS activity, follow disease progression or monitor treatment effectiveness has scarcely been investigated.

Cross-sectional studies found an association between SGUS scores and the presence of extra-glandular pSS manifestations, systemic disease activity (evaluated by ESSDAI) and ESSPRI. SGUS could in the future represent a surrogate marker of activity in the ESSDAI glandular domain and a marker of damage progression. Although the issue remains whether relatively robust grey scale scoring systems are sensitive enough to detect morphological changes, recent interventional studies (two rituximab studies and one ianalumab study) reported an improvement of some SG ultrasonographic characteristics, likely related to disease activity.

Recently, the possibility of using Doppler ultrasound to noninvasively assess SG inflammatory activity has been thoroughly investigated. Similar to a well-established evaluation of joint inflammation, the Sjögren ultrasound subgroup of the OMERACT ultrasound working group recently proposed a semiquantitative scoring system to evaluate SG vascularisation in pSS. Although the sensitivity to change of the proposed Doppler scoring system (a change in glandular perfusion secondary to a change in inflammation intensity) still needs to be determined in a longitudinal study, the standardisation of investigation represents the first step towards a better noninvasive evaluation of inflammation in SGs of pSS patients.

In the future, the Doppler scoring system might be combined with the consensual OMERACT grey scale scoring system, leading to a comprehensive global SGUS scoring system and allowing adequate distinction between activity and damage.

The role of SGUS in glandular damage assessment
In pSS patients, SGs show a wide range of abnormalities corresponding to different stages of the

Figure 1. Outcome Measures in Rheumatology Clinical Trials [OMERACT] four-grade semiquantitative scoring system for major salivary gland lesions in primary Sjögren’s syndrome. Ultrasound images of the parotid gland in a four-grade semiquantitative scoring system by OMERACT: (a) grade 0, normal parenchyma; (b) grade 1, minimal change: mild inhomogeneity without anechoic/hypoechoic areas; (c) grade 2, moderate change: moderate inhomogeneity with focal anechoic/hypoechoic areas but surrounded with normal tissue; and (d) grade 3, severe change: diffuse inhomogeneity with anechoic/hypoechoic areas occupying the entire gland surface but surrounded with no normal tissue.
disease, and SGUS allows the detection and characterisation of these variations, including size change, from enlargement to atrophy of the gland (Figure 2), and morphologic alterations with parenchymal heterogeneity due to the presence of hypoechoic lesions described as pseudocystic lesions, hyperechoic bands, fatty deposition and multiple calcifications (Figure 2).120

Pseudocysts in pSS are thought to be early lesions due to parenchymal inflammatory infiltration.134 Subsequently, these pseudocysts may form small punctiform aggregates that are an expression of the anatomical damage to the SGs, and fatty deposition could be present, responsible for the irregularity of the glandular margins.16 In the next stage of the disease, the SG parenchyma appears inhomogeneous due to the presence of hyperechoic bands, an expression of post-inflammatory fibrosis and chronic damage, as their presence is associated with objective SG impairment.19 Eventually, in the late stage, the SGs become atrophic.135

The SGUS scoring systems currently available were created for diagnostic purposes and are mainly focused on the heterogeneity of the SG parenchyma,16,53,122,124,135 thus, to the best of our knowledge, no SGUS scoring system to assess and quantify glandular damage in pSS is currently available.

**Minor salivary gland ultrasound**

To date, most pSS literature has focused on the sonographic assessment of major SGs, leaving the minor SG orphan of evidence.21 Nevertheless, in the histological evaluation of pSS, minor SGs play an important role,34,61 whereas a parotid biopsy is poorly performed in pSS.

The only representative study testing the capability of ultrasound for the diagnosis of pSS assessing labial SGs was performed by Ferro et al.136 Patients with suspected pSS, identified by the presence of sicca syndrome, and healthy controls were included. Inhomogeneity of the labial SGs was the main sonographic change characterising those patients who received a final diagnosis of pSS (42.2%).136 Interestingly, a different sonographic pattern was reported between SSA-positive subjects, both with or without anti-SSB antibodies, and SSA-negative/SSB-negative subjects, the pattern being inhomogeneous in the first group, whereas a normal pattern characterised the group with a negative antibody profile.136 Labial SG inhomogeneity pattern also showed a
significant association with the number of foci and FS of the MSGB ($p < 0.001$). To date, some issues limit the routine use of minor SG ultrasound, for example, the lack of standardised ultrasound definitions for minor SGs, standardised ultrasound technique and technical requirements needed to adequately assess the minor SGs. Due to their anatomical characteristics, minor SG ultrasound would require very high-frequency transducers (the cited work adopted a 70 MHz transducer), which are generally not available in the routine practice of rheumatologists.

**New insights into pSS therapy**

The management of pSS is challenging for clinicians, as the disease expresses a variable clinical profile. In recent years, researchers have focused on modifying disease outcomes, rather than controlling symptoms, to offer innovative and patient-tailored target therapies.

**Topic therapy for sicca symptoms**

As for dry eye and dry mouth management, interest has recently been raised by new topical medications and by new formulations of old drugs (Table 1). The ophthalmic solution Lifitegrast is a lymphocyte function-associated antigen-1 antagonist that prevents T-cell recruitment and activation. The agent AR-15512 [transient receptor potential cation channel subfamily M member 8 (TRPM8) agonist; Aerie Pharmaceuticals, Durham, NC, USA] has been studied for its possible role in restoring tear film volume. NOV03 (100% perfluorohexyloctane, Novaliq, Heidelberg, Germany) acts on Meibomian gland obstruction and lipid layer stabilisation. The topical application of chloroquine (0.03%) for 21 days showed good results on the inflammatory status of the tear film, improving dry eye symptoms, ocular staining and tear film volume. Although topical application of chloroquine showed limited retinal toxicity, further studies are needed to assess its possible side effects. A nanoemulsion solution, Cyporin N (Taejoon Pharm, Seoul, Korea), has been developed to overcome Cyclosporin A poor solubility in tear film.

In the field of nonpharmacological therapies, TrueTear® is an intranasal tear neurostimulator portable device that painlessly stimulates the anterior ethmoid nerve and increases tear production. Thermal pulsation devices such as Lipiflow® can be effective in Meibomian gland

| Table 1. Some innovative and promising therapeutic options for primary Sjögren’s syndrome. |
| Topical drugs for dry eye management | Lifitegrast ophthalmic solution |
| | AR-15512 ophthalmic solution® |
| | NOV03 ophthalmic solution® |
| | Chloroquine 0.03% ophthalmic solution |
| | Cyclosporine A nanoemulsion solution |
| Topical drugs for dry mouth management | Topical liquid pilocarpine |
| Nonpharmacological therapy for dry eye management | Intranasal tear neurostimulator [e.g. TrueTear®] |
| | Thermal pulsation devices [e.g. Lipiflow®] |
| | Intense pulse light |
| | Intraductal Meibomian probing |
| Nonpharmacological therapy for dry mouth management | Neuro-electrostimulation |
| | Sialendoscopy with or without intraductal steroid irrigation |
| Biological drugs | Anti-CD40: CFZ533-Isocalimab [NCT 02291029; NCT03905525] |
| | Anti-BAFF Receptor: VAY736-Ianalumab [NCT 02962895] |
| | Anti-BAFF/anti-CD20: Belimumab/rituximab [NCT02631538] |
| | RNase-Fc fusion protein: RSVL-132 [NCT03247686] |
| | Anti-CD40 Ligand: VIB4920 [NCT04129164] |
| | JAK/STAT inhibitors: Tofacitinib [NCT04496960] |
| | BTK inhibitors: Lou64-Remibrutinib [NCT04035668] |
For dryness and salivary hypofunction management, a small, nonblinded, noncontrolled study reported an improvement of xerostomia with the application of topical liquid pilocarpine, with fewer side effects compared to systemic use. Examples of nonpharmacological methods for dry mouth treatment are the application of neuro-electrostimulation or sialendoscopy with or without intraductal steroid irrigation.

**Systemic therapy**

Several biological drugs targeting B-cell hyperactivity, T-cell co-stimulation and abnormal pro-inflammatory cytokine production have been investigated for autoimmune and lymphoproliferative diseases in clinical trials, most of them failing to achieve primary outcomes, probably due to trial design issues (i.e. patient heterogeneity, strong placebo effect, insensitive outcome measures, efficacy only in a few disease manifestations) (Table 1).

Anti-B-cell therapy, with a drug alone (rituximab or belimumab) or with sequential or combination therapy, may prove effective in some patient’s subsets.

Ianalumab (VAY736), a monoclonal B-cell-depleting antibody that blocks the BAFF receptor, produced a statistically significant amelioration in ESSDAI score when given at high doses (300 mg) and confronted to placebo (NCT02962895). Based on the positive results of the BELISS clinical trial, and the experimental and clinical rationale of the anti-CD20 and anti-BAFF double therapeutic approach, an international clinical trial has evaluated the safety, efficacy and tolerability of belimumab plus rituximab co-administration and monotherapy in active pSS (NCT02631538). The preliminary results support the positive role of the combination therapy in sustainedly improving ESSDAI and stimulated salivary flow over time and in producing B-cell depletion in MSGB.

Recently, promising results have been shown by Iscalimab (CFZ533), a nondepleting anti-CD40 monoclonal antibody, which improved both stimulated and unstimulated salivary flow rates, patient-reported visual analogue scale assessment, disease activity and fatigue index with good safety, together with serum CXCL13 reduction (NCT 02291029). A new clinical trial on multiple doses of CFZ533 in two distinct pSS populations (moderate to severe disease versus low systemic involvement with high symptom burden) is also ongoing (NCT03905525), as well as a study on the efficacy of CD40 ligand antagonist VIB4920 (NCT04129164).

RSLV-132, a fully human RNase-Fc fusion protein, improved severe fatigue in pSS patients, with a reduction of ESSPRI and three other independent patient-reported measures (FACIT-F, ProF, DSST), while increasing the expression of selected interferon-inducible genes.

Other pathways have been evaluated to find new possible therapeutic targets in pSS. Recent clinical trials have focused on kinase pathways, such as the JAK/STAT [e.g. tofacitinib (NCT04496960)] and the BTK pathway [e.g. Lou064-Remibrutinib (NCT04035668)]. Agents directed against specific cytokines, such as IL-7 [e.g. S95011 (NCT04605978)] and IL-23 (e.g. ustekinumab, NCT04093531), have also been tested. Other potential candidates might be Fingolimod, which affects sphingosine pathways, IL-10, IL-27, or the coinhibitory molecule B7-H4. As type I interferon is fundamental in pSS pathogenesis, other rational strategies might range from blocking its receptor (e.g. anti-type I interferon receptor, anifrolumab) to targeting its production (e.g. anti-blood dendritic cell antigen 2, BIIB050). The new-generation microRNA therapeutic approach might also play a future role. Moreover, the interest should be extended to the simultaneous intervention targeting different pathogenetic pathways with biologic and conventional synthetic disease-modifying antirheumatic drugs, as supported by belimumab/rituximab double therapeutic approach and the leflunomide-hydroxychloroquine association. Efforts in this direction might be represented by trials evaluating tibulizumab, a bispecific dual-antagonist antibody that binds BAFF and IL-17 simultaneously (NCT04563195), and the combination of anti-B and T-cell drugs (hydroxychloroquine, lefunomide and mycophenolate mofetil, NCT05113004).
The main purpose of the research on lymphogenesis in pSS in recent years has been to identify epidemiological, clinical, laboratory, histological and imaging features predictive of lymphoproliferative disease (Table 2), aiming to obtain an early diagnosis, better management, and prognosis through a rational stratification of patients.172

Regarding the epidemiological aspect, men have a higher risk of lymphoma and a shorter median time from pSS diagnosis to lymphoma development than women.173,174 A higher prevalence of lymphoma was found in the early (⩽35 years) and late (≥65 years) onset patients.173,174 Younger patients demonstrate a higher frequency of B-cell-associated manifestations, which are known predictive factors of lymphoproliferative disease.10,96 Older patients have an incidence peak of lymphoma within the first 6 years from pSS diagnosis, and in this age group, male gender is the main independent risk factor for lymphoma.10

Several clinical and serological features have been used as lymphoma predictors, as specified in Table 2.172,175–177 Their usefulness has been confirmed through the years, with variable strength of association dependent on study population characteristics and methods of assessment.178–180 The correlation with ESSDAI has also been an object of debate, as the presence of specific clinical and biological manifestations (i.e. persistent major SG enlargement and cryoglobulinaemia) has proven to be useful in identifying pSS patients at a higher risk of lymphoma evolution, rather than the overall disease activity evaluated by ESSDAI.90

Regarding the histopathology of pSS, some conflicting data on the association between GC-like
Some novel biomarkers of pSS-related lymphoproliferation have been studied in recent years (Table 2), but the lack of external validation and prospective evaluation, as well as the intrinsic complexity of lymphoma pathogenesis, still limits their clinical use as single predictive factors.14,179,180,184

The SG ultrasonographic pattern might represent another predictor, due to the proven association with clinical, serological and histological features of lymphoproliferative risk and its ability to define the ESSDAI glandular domain in pSS,21,108,124,126,185 as recently reported by Lorenzon et al.186

Most awaited is the creation of a unique composite predictive model for early patient stratification supported by artificial intelligence, as mirrored by the efforts of the HarmonicSS Project.93

Ultrasound-guided core needle biopsy in the diagnosis of pSS-related lymphoma

Although the suspicion of lymphoma in pSS is mainly clinical, SGUS represents a useful aid in lymphoma diagnosis, as it can detect suspicious patterns of lymphoproliferative disease (e.g. diffuse, large-confluent, hypoechoic areas, and a focal lesion within an altered parenchyma) and guide tissue sampling of the afflicted gland30–32 (Figure 3).

Recent evidence suggests that in pSS patients with major risk factors for B-cell lymphoma,178...
ultrasound-guided CNB can provide adequate sampling for histological examination, immunohistochemical staining and flow cytometry. In the case of a parotid biopsy, ultrasound-guided CNB can be safely performed in the postero-caudal part of the gland, with respect to the facial nerve (Figure 3). In the scenery of a biopsy targeting the submandibular glands, nerve injuries are of no concern.

At present, ultrasound-guided CNB could be a precious procedure for lymphoma diagnosis in pSS patients, not only showing remarkable patient safety and tolerance but also allowing adequate glandular sampling and a definite histological diagnosis. Ultrasound-guided CNB of the major SGs may also be useful in pSS-related lymphoma for prognosis assessment, follow-up and treatment response evaluation. Hopefully, in the future, this procedure might also be used in patients without lymphoma to assess and monitor pSS disease activity and tissue damage.

**Conclusion**

pSS is a heterogeneous disease characterised by a wide spectrum of manifestations that vary according to the different stages of the disease and among different subsets of patients. Knowledge about the disease pathogenesis, as well as a standardised stratification of pSS patients through different biomarkers (tissue, serological, imaging), should be improved. These will help early disease diagnosis, risk assessment of systemic or lymphoproliferative complications, and identification of the degree of activity-related and damage-related manifestations, and will allow a tailored follow-up and treatment strategy (Table 3).

In recent years, many advances have been made in the field of pSS diagnosis and follow-up, such as the development of clinical indices to assess disease activity (ESSDAI, ESSPRI, CRESS), the standardisation of surgical procedures and histopathology reporting of the MSGB, the increased use of major SG biopsy, the new

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**Table 3. Research agenda.**

| Question                                                                 | Answer |
|--------------------------------------------------------------------------|--------|
| Elaborate a deeper knowledge of the pathogenesis of pSS.                 |        |
| Construct a better definition of risk factors for pSS development.       |        |
| Encourage the use of new four-grade semiquantitative score proposed by OMERACT. |        |
| Can the SGUS be added to the pSS classification criteria? Do we need new classification criteria for pSS? |        |
| Can the major salivary gland biopsy be used for the diagnosis of pSS?    |        |
| Which novel biomarkers can be used in clinical practice for pSS diagnosis? |        |
| How can we stratify pSS patients?                                       |        |
| Do we need a new disease activity index? Do we need new damage index?   |        |
| Can the SGUS be useful in patients’ follow-up?                          |        |
| Do different subtypes of pSS patients need to be followed up differently? How should they be followed? |        |
| Encourage the development of new therapies for pSS, both local and systemic. |        |
| Which pSS patients need a systemic treatment?                           |        |
| Construct a better definition of treatment response.                    |        |
| Provide better description of the risk factors of lymphoproliferative disease linked to pSS. |        |
| Can ultrasound-guided CNB be routinely used in pSS management?          |        |
| How could SGUS help in the assessment of salivary gland activity and damage? |        |

CNB, core needle biopsy; OMERACT, Outcome Measures in Rheumatology Clinical Trials; pSS, primary Sjögren’s syndrome; SGUS, salivary gland ultrasound.
OMERACT scoring system for SGUS (Figure 1)\textsuperscript{122,190} and the ongoing studies of new biomarkers.\textsuperscript{73} Hopefully, all these tools will be increasingly used in future routine clinical practice (Table 3).

New treatment options are emerging in pSS, both for glandular symptoms and for systemic manifestation,\textsuperscript{168} due to a deeper understanding of the pathophysiological bases of the disease and increasing ongoing trials, thus making a correct and objective evaluation of the response to treatment even more necessary.

However, pSS patients report an important unmet need for a successful pharmacological and nonpharmacological approach to the three greatest patient-reported disabilities: dryness, fatigue and musculoskeletal pain.\textsuperscript{191} Therefore, further research in these areas is also needed (Table 3).

In conclusion, the findings of past and recent years enable us to gain better insight into pSS. Certainly, in the coming years, some of the current novelities will become part of our routine clinical practice, thus improving the global management of pSS patients.

**Author contribution(s)**

**Sara Zandonella Callegher:** Conceptualisation; Data curation; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.

**Ivan Giovannini:** Conceptualisation; Data curation; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.

**Sabine Zenz:** Conceptualisation; Writing – original draft; Writing – review & editing.

**Valeria Manfrè:** Conceptualisation; Writing – original draft; Writing – review & editing.

**Martin H. Stradner:** Conceptualisation; Writing – original draft; Writing – review & editing.

**Alojzija Hočevar:** Conceptualisation; Writing – original draft; Writing – review & editing.

**Marwin Gutierrez:** Conceptualisation; Writing – original draft; Writing – review & editing.

**Luca Quartuccio:** Methodology; Supervision; Writing – review & editing.

**Salvatore De Vita:** Methodology; Supervision; Writing – review & editing.

**Alen Zabotti:** Conceptualisation; Data curation; Formal analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing.

**ORCID iDs**

Ivan Giovannini \textsuperscript{16} https://orcid.org/0000-0002-1110-2518

Martin H. Stradner \textsuperscript{16} https://orcid.org/0000-0002-7884-6626

Alen Zabotti \textsuperscript{16} https://orcid.org/0000-0002-0573-464X

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