One year in review 2018: Sjögren’s syndrome

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ABSTRACT

Sjögren’s syndrome is a complex and potentially disabling slow progressive, systemic disorder. During the last twelve months several original and important contributions have been published on the pathogenesis, diagnosis and therapy of the disease. This review, following the others of this series is aimed at summarising some of the most significant studies that have been recently published. Regarding the pathogenesis, we will specifically focus on novel insights on miRNA, gut microbiota, adaptive and innate autoimmunity and animal models. Concerning novelties in pSS diagnosis, we will focus on salivary gland ultrasonography and histology. Finally, we will conclude with an update of the clinical manifestations of the disease and with an overview of the future therapies.

Introduction

Sjögren’s syndrome (SS) is a complex and heterogeneous disease potentially leading to disability and quality of life impairment. A number of important scientific contributions were published in 2017 on SS pathogenesis, clinical presentation and treatment. Following the previously published annual reviews (1-12), we will here provide an overview of the recent literature on the pathogenesis, clinical features and novel treatments of SS. We performed a Medline search of English language articles published in the PubMed database from 1st January 2017 to 31st December 2017. The following key words: Sjögren’s syndrome, pathogenesis, diagnosis, salivary gland ultrasonography, biopsy, clinical manifestations, lymphoma, therapy formed the data sources.

Novel insights into pathogenesis

The role of miRNAs

Primary Sjögren’s syndrome (pSS) is a female dominated autoimmune disease of unknown aetiology characterised by inflammation of salivary and lacrimal glands. Keratoconjunctivitis sicca and xerostomia represent the clinical hallmarks. Systemic manifestations include extra-glandular organ involvement, debilitating fatigue and a 15-fold increased risk of lymphoma, most commonly non-Hodgkin’s lymphomas of the B cell type. DNA methylation, histone modification and non-coding RNAs are important contributing factors in the pathogenesis of pSS (13). Aberrant expression of micro-RNAs (miRNAs) has been linked to essentially all complex autoimmune diseases, including pSS. miRNAs are small, non-coding, single-stranded, 22-base nucleotide sequences, which bind approximately 60% of all genes. The human genome may encode over 2500 miRNAs, which have emerged as one of the key cytoplasmic regulators of gene expression mainly at the post-transcriptional level by targeting the 3’ UTR region of target messenger RNAs (mRNAs) for degradation or translational repression. A single miRNA can have hundreds of target genes, and multiple miRNAs can regulate the same target (14). miRNAs play important roles in immune tolerance and prevention of autoimmunity. Differential miRNA expression patterns have been demonstrated in different autoimmune diseases including pSS, analysing either salivary glands or peripheral blood mononuclear cells (PBMCs) (15-17). miRNA-146a and miR-155 are the most essential regulators in pSS. Studies demonstrate that miR-146a expression is increased in PBMCs of SS patients compared to healthy controls and this overexpression in SS is linked with immune functions such as cellular migration, cytokine production and phagocytosis (17). Validated targets of miR-146a-5p include IRF5, STAT1,
IRAK1 and IRAK2 which have been found associated with genetic variation or DNA methylation changes in pSS, thus serving as a negative feedback for immune activation (18-21). Another study described the deregulation of miR-4524b-3p, miR4524b-5p, miR5571-3p, miR5571-5p, miR5100 and miR-574-3p in patient samples derived from pSS patients. The specificity of miR-203, miR-768-3p and miR-574-3p within the exosomes of parotid saliva samples from patients with pSS holds promise for future investigation (14, 17). The role of miR-183, miR-130a and miR-708 down-regulation remains to be elucidated (17). Wang-Renault et al. performed a large-scale analysis of miRNAs in patients with pSS in sorted blood-derived T and B cells and demonstrated cell-type specific miRNA expression patterns, potentially related to the pathophysiology of the disease (18). In CD4 T lymphocytes, -let-7d-3p, -miR-155-5p, -miR-22-3p, -miR-30c-5p, -miR-146a-5p, -miR-378a-3p and -miR-28-5p were significantly differentially expressed in both the discovery and the replication cohort. In B lymphocytes, -miR-378a-3p, -miR-222-3p, -miR-26a-5p, -miR-30b-5p and -miR-19b-3p were significantly expressed (18). Another interesting finding of this study was the increased expression of B-cell activating factor (BAFF) miRNA after inhibiting -miR-30b-5p. BAFF levels have been found to be increased in the serum and salivary gland B, T and epithelial cells of pSS patients compared with controls and correlate with autoantibody production. Blocking BAFF and C-X-C motif chemokine ligand (CXCL13) improves salivary gland function (18). Further studies are required in order to confirm the specific binding sites of -miR-30b on the BAFF mRNA as well as to determine its relevant importance compared with other miRNAs binding to BAFF. The miR-17-92 cluster promotes the survival of B lymphocytes, at least partly through its ability to regulate PI3K signalling and genes expressed downstream of this pathway (18). In a cohort of 28 pSS patients, Wang et al. demonstrated reduced expression levels of miR-181a and -16 in labial salivary gland tissues of SS patients. Furthermore, these miRNAs were increased in patients with SS who possessed high salivary gland pathological focus scores (SGFF), thus suggesting a potential role in the pathogenesis of SS (22).

Despite limited data, it has been suggested autophagy to have a role in the pathogenesis of SS. Recent data demonstrated that enhanced autophagy and apoptosis are involved in Ro/SSA and La/SSB redistribution in secretory epithelial cells of salivary glands. ATG5 and the LC3B-II/I ratio are used as typical markers of autophagy (23). In a cross-sectional case-control study, Byun et al. demonstrated that autophagy markers in tears and the conjunctival epithelium were upregulated in SS patients with dry eyes (DE). Moreover, ATG5 expression correlated positively with the corneal and conjunctival staining scores in SS DE. Additionally, anti-inflammatory therapy with topical corticosteroids attenuated these increases in autophagy markers, which was accompanied by clinical improvement in SS DE patients (23).

Using CPA and gene expression analysis Shah et al. identified 22 DE genes in salivary gland datasets in SS that have not previously been clearly associated with SS pathogenesis. Among these, higher levels of checkpoint kinase 1 (CHEK1), avian erythroblastosis virus E26 oncogene homolog 1 (ETS1), and lymphoid enhancer binding factor 1 (LEF1) were significantly correlated with higher matrix metalloproteinase 9 (MMP9) levels. Higher MMP9 levels have been implicated in degradation of salivary gland structural integrity, leading to hypo-salivation in patients with SS. Salivary gland mRNA expression of MMP9 and the expression of cytokine CXCL10 were higher in patients with SS. CXCL10 has been shown to increase MMP9 expression, thereby potentially impacting SS pathogenesis (24). Other recent studies suggest that enhanced expression of NLRP3 inflammasome-mediated inflammation in peripheral mononuclear cells (25) and the IL-12/IL-35 balance (26) may represent parts of the pathogenetic cascade in SS. Serum IL-35 levels were also associated with low disease activity, in contrast with serum IL-12p70 levels, which were associated with more active disease. In blood cellular subsets both IL12p35 and EBV-induced gene 3 (EBI3) mRNAs were detected only in B cells, with a trend toward a lower level among patients with pSS (26). Moreover, in attempting to identify molecular switches controlling B cell responses in autoimmune diseases, Levels et al. showed that B cell specific transcriptional coactivator Bob1 mRNA expression was significantly increased in pSS patients compared with controls with sicca syndrome without pSS. Similar to observation in rheumatoid arthritis (RA) synovitis, Bob1 expression was strongly correlated with CD21L expression in parotid salivary glands of pSS patients (27).

**Innate and adaptive immunity**

**Innate immunity**

Although the cause of pSS remains poorly understood, it is characterised by exaggerated innate and adaptive immunity. Interaction between genetic susceptibility and environmental triggers is thought to active innate immune system in the early stages of the disease. Genetic studies over the past years identified more than 15 loci for SS and many of these are shared with other autoimmune diseases, especially SLE. SS patients display increased expression of type I and type II IFN-regulated genes in both salivary tissue and peripheral blood. One of the most definitive genome-wide association studies in pSS patients identified single nucleotide polymorphisms in many IFN-inducible genes that are implicated in innate immunity, specifically HLA-alleles, STAT4, IRF5, IL-12A and TNIP1 (27). It is important to point out that assessment of gene expression and activity carries clinical significance. A study of monocytes from pSS patients demonstrated that the presence of a type I signature was associated with higher disease activity and elevated autoantibody levels (7, 27, 28). While underlying causes of IFN activation remain poorly understood, several studies suggest that a viral trigger such as cytomegalovirus, Epstein-Barr virus...
and C virus may contribute to disease initiation and chronicity. Corroborating work shows that some SS patients display an IFN gene signature (vide supra) and IFNα is secreted by plasmacytoid dendritic cells (pDCs) in response to viral agonists in salivary tissues in SS (27, 28). Recent findings indicate that overexpression of the normally silent endogenous virus-like genomic repeat element LINE-1 (long interspersed nuclear element-1) in salivary gland tissues from SS patients, which results from defective methylation, might induce activation of type I pathways thus causing apoptosis of salivary epithelial cells, exposure of endogenous autoantigens to the immune system, upregulation of BAFF expression, increased B cell survival and differentiation and ultimately autoantibody production and immune complex formation (29).

Toll-like receptors (TLRs) are crucial for innate immune activation in SS. Emerging evidence suggests TLR2 and TLR4 signalling is dysregulated locally and systematically in SS. Peripheral blood mononuclear cells from SS patients stimulated with agonists for TLR2 or TLR4 (peptidoglycan (PGN) or lipopolysaccharide (LPS), respectively) secrete higher levels of IL-17 compared with controls (7, 29). Moreover, both TLR2 and TLR4 transcripts are elevated in salivary tissue derived from SS mouse models and SS patients as compared to controls and stimulation of salivary gland epithelial cells (SGECs) with LPS or PGN causes upregulation of the co-stimulatory markers ICAM-1 and MHC-I (29). In addition, several studies in mice and humans suggest an important role for endosomal TLRS (TLR3, TLR7, TLR9) in SS pathogenesis. Interestingly, a recent study found that when pSS patients were segregated on the basis of type I IFN expression, pDCs and monocytes from the IFN-expressing subset expressed elevated levels of TLR7, whereas IFN negative patients expressed normal levels of TLR7 (29). Of significance to SS pathogenesis, the NLRP3 inflammasome which is a key component of the innate immune system, is activated by concomitant stimulation of TLRs and purinergic P2X4/P2X7 receptors. Inflammasome-related genes are elevated in human SS salivary tissue, including P2X7, NLRP3 and caspase-1 and this expression correlates with focal lymphocytic sialadenitis and the presence of anti-Ro autoantibodies (29). Inflammasome hyperactivity is also indicated by the upregulation of both IL-1 and IL-8 in SS patients. Another cytokine of the IL-1 family shown to be increased in both serum and salivary gland biopsies of SS patients is IL-33, acting synergically with IL-12 and IL-23 for the induction of IFNγ secretion by natural killer (NK) and NKT cells (30). IL-6 levels were also found to be heightened in serum, saliva and tears of pSS patients and SS-derived SGECs have been shown to produce IL-6, through which they can activate T-follicular cells (30).

**Adaptive immunity**

The adaptive immune system is often activated by signals generated by the innate immune response. It consists of B and T cells and has been studied extensively in SS. CD4+ T helper cells play a crucial role in the pathogenesis of SS. A large population of CD4+ T cells and small numbers of B cells, CD8+ T cells, macrophages and dendritic cells infiltrate the target organs, such as salivary and lacrimal glands during the early stages of the disease. Th1 derived responses mediate the pathogenesis of SS. In C57BL/6.NOD-Aec1.Aec2 (B6.NOD-Aec) mouse model, IL7 acting via upregulation of Th1 and IFNγ/CXCR3 accelerated the development of SS. This effect was abrogated on blocking IL7Rα. IFNγ is mainly produced by Th1 cells; IFNγ along with IL-12 causes differentiation of CD4+ T cells into Th1 lymphocytes (31). Th17 cells are also observed in the autoimmune lesions of the salivary gland tissues of SS patients. Because Th17 cells can produce IFNγ, they seem to play a critical role in the γ-mediated pathogenesis of SS. Furthermore, IL-18 and IL-23 produced by SGECs also contribute to the disease. Davies et al. analysed MAPK/ERK and JAK/STAT signalling networks in peripheral blood mononuclear cells from pSS patients upon stimulation with IFN-2βb by flow cytometry. Type I IFN induced gene expression was found to negatively correlate with the IFN-2βb induced phosphorylation of STAT3 S727 in T cells and positively with pSTAT1 Y701 in B cells, thus indicating involvement of these pathways in SS pathogenesis (32). Another study which added insight to the autoimmune process in SS was that by Imegenberg-Kreuz et al. who analysed the transcriptome of CD+19 B cells from pSS patients. Among the top upregulated and validated genes were CX3CR1, encoding the fractalkine receptor involved in regulation of B cell malignancies, CCL5/RANTES and CCR1. Increased expression of several members of the TNF superfamily was also identified; TNFSF4/Ox40L, TNFSF10/TRAIL, TNFSF13B/BAFF, TNFRSF17/BCMA as well as S100A8 and –A9/cal-calcitriol, TLR7, STAT1 and STAT2. Among genes with downregulated expression in pSS B cells were SOCS1 and SOCS3, CD70 and TNFA/P3/A20 (33). This study concluded that B cells from pSS patients with anti-SSA antibody positivity display immune activation with upregulated expression of chemokines, chemokine receptors and a prominent type I and type II I signature. B cell hyperactivity is a hallmark of pSS, which is among others reflected by the elevated risk of developing non-Hodgkin’s lymphoma, mostly mucosa-associated lymphoid tissue (MALT) type preferentially develops in the parotid gland. It remains unclear why MALT lymphomas arise predominantly at this location, since all minor and major salivary glands are affected in pSS. For this reason, Haacke et al. studied whether FcγR4 expressing B cells are present in salivary gland tissue (labial and parotid) of pSS patients and whether parotid gland MALT lymphomas in pSS patients express this receptor. They found that FcγR4+ B cells are present in pSS salivary glands, predominantly the parotid gland, in close association with the ductal epithelium forming lymphoepithelial lesions (LELs). They are highly proliferative, genuine PAX+ B cells and were also present in...
pSS-related MALT lymphomas implying a plausible explanation why they develop in parotid glands rather than labial glands in pSS patients (34). In a recent observational study by Barcelos et al., it was demonstrated that in pSS, the presence of lower memory B cells counts was associated with longer disease duration and a more active disease, which could represent a possible role as prognostic marker (35). Therefore, future studies with a large number of patients are required to clearly prove this hypothesis.

The role of gut microbiota

Previously, it was referred that pSS may result in extra-glandular manifestations (EGM). The gastrointestinal (GI) tract may be involved with oesophageal dysmotility, gastroparesis, atrophic gastritis and pancreatic insufficiency being the most commonly encountered in pSS. Increased levels of fecal calprotectin (F-calprotectin) a valid marker for GI inflammation have been found in a subgroup of pSS patients and were associated with concomitant GI disease. To date, a major effort is being made in deciphering the role of complex microbial communities, especially the oral and gut microbiomes in the pathogenesis of multiple autoimmune diseases including pSS (36, 37). In humans, the adult intestinal microbiota ecosystem consists of approximately 1000 species of bacteria, 5 genera of archaea, 66 genera of fungi and an undefined number of viruses, mostly bacteriophages, which play crucial role in the maintenance and regulation of homeostasis in intestinal microflora. Altered microbial composition of the intestine is commonly referred as dysbiosis (37, 38). Gut microbial exposure leads to a continuous diversification of B cell repertoire and the production of T-dependent and independent antibodies, especially IgA. These combined effects provide an elegant educational process to the adaptive immune network. Reduction of the inflammatory signalling cascade by down regulating the NFκ-β pathway and decreased production of IL-8 as well as stimulation of regulatory T cell subsets (Tregs) serve as potential mechanisms through which gut microbe or infectious agents modulate the immune response (39). Tissue transglutaminase (tTg) is a pleiotropic enzyme expressed ubiquitously and abundantly. Despite this coeliac disease tTg plays a significant role in diseases of an inflammatory and autoimmune nature including pSS and SLE. Similarly, microbial transglutaminases (mTgs) may contribute to the induction, development and perpetuation of the autoimmune process (40). Literature data regarding the role of gut microbiota in pSS are limited. In a cohort of 42 pSS patients it was demonstrated that severe intestinal dysbiosis was a prevalent finding in pSS, affecting 21% of the studied patients. In this study severe intestinal dysbiosis was associated with both clinical and laboratory signs of systemic disease activity as well as with laboratory signs of GI tract involvement, as evaluated by F-calprotectin (41). It has been reported that SS patients have greater abundances of Pseudobutyryrivibrio, Escherichia/Shigella, Blautia and Streptococcus, while reduced abundance of Bacteroides, Parabacteroides, Faecalibacterium and Prevotella compared with healthy controls. Furthermore, the severity of ocular and systemic manifestations was inversely proportional to microbial diversity (38, 42). These findings suggest that dysbiotic intestinal microbiome driven by reduced abundance of commensal bacteria and an increased abundance of potentially pathogenetic genera is a hallmark of SS.

Findings from animal models

Animal models that recapitulate human disease are crucial for the study of SS. While several SS mouse models exist, only few pSS models mimic systemic disease manifestations seen in humans. Similar to pSS patients, NOD.B10-H2b/J (NOD.B10) mice develop exocrine gland disease and anti-nuclear autoimmune antibodies. Kiriopolsky et al. provided a comprehensive analysis of local and systemic disease manifestations in female NOD.B10 mice. Exocrine tissue, lung and kidney were analysed. NOD.B10 mice present with robust lymphocytic infiltration of salivary and lacrimal tissue. In addition, they exhibit significant renal and pulmonary infiltration. The investigators identified numerous autoantibodies, including those directed against salivary proteins and concluded that this model is an excellent tool for clinical translational studies, particularly those designed to evaluate EGM in pSS (43). Kim et al. used ten-week-old NOD.B10-H2b mice in order to investigate the effect of subconjunctival administration of anti-high mobility group box1 (anti-HMGB1) on dry eye. They focused on extracellular HMGB1 because they believed that the chronic epithelial cell damage to the corneal or lacrimal glands may trigger the cycle of inflammation by secreting danger signals, such as HMGB1. It is plausible to assume that extracellular HMGB1 acts as an inflammatory cytokine through TLR9 signalling on B cells in this mouse model of SS. It was proposed that anti-HMGB1 treatment would reduce the effector function of B cells in these mice. However, B cell proliferation and the proportion of plasma cells as well as SSA levels were not changed in the draining lymph nodes (44). Lysophosphatidic acid (LPA), a bioactive lysophospholipid, is involved in the pathogenesis of chronic inflammatory autoimmune disease including SS. It was found that autotaxin, an LPA producing enzyme and LPAR1, LPAR3 mRNA and IL-17 mRNA were highly expressed in the exocrine glands of 20-week-old non-obese diabetic (NOD) mice, which show SS symptoms at this age, as compared with non-symptomatic 8-week-old NOD mice. In an adaptive transfer model using NOD lymphocytes, treatment with Ki16425, an LPAR1/3 antagonist restored tear and saliva secretion and decreased symptoms of SS compared with the vehicle-treated group (45). Xu et al. showed that the expression of leptin and its receptor OB-R in mouse models of SS are elevated both locally and systematically during SS progression. Re-combinant serotype 2 adenov-associated viral (Raav2) vectors expressing either OB-R shRNA or none were injected into 4- or 6-week-old BALB/c NOD/Ltj (NOD) mice and resulted in a modest reduction in glandular inflammation in the SS model, thus Leptin/OB-R signalling may be pathogenetically involved.
in SS and may serve as a new marker and a potential therapeutic target (46). NOD mice have also been used in order to explore the pathogenic role of endogenous TNF-α in the development of SS. It was demonstrated that neutralisation of TNF-α during the stage prior to disease onset impedes the development and onset SS-like salivary gland inflammation and secretory dysfunction in NOD mice, indicating a critical pathogenic of TNF-α in the development and onset of SS (47). Khalafalla et al. demonstrated for the first time in salivary gland epithelial cells that P2X7R activation promotes NLRP3 inflammasome, a mechanism involving transmembrane Na+ and K+ flux, ROS production and HSP90 protein function. Moreover, in vivo results show that administration of the P2X7R antagonist, A438079, in the CD28-/−, IFN-γ-/−, NOD.H-2h4 mouse model of autoimmune exocrinopathy reduced salivary gland lymphocytic infiltrates and enhanced salivary secretion, suggesting antagonism of P2X7R as a promising approach to prevent salivary gland inflammation and associated hyposialorrhea in SS (48). A useful tool for understanding the pathogenesis of SS appears to be the SATB1cKO mice, a novel SS model in which the progression and of the disease resemble those of human SS. These mice, in which the SATB1 gene is specifically deleted from haematopoietic cells develop SS by 4 weeks of age, soon after weaning. Female mice presented an earlier onset of the disease than males, suggesting that female SATB1cKO mice are more susceptible to SS (49). Another study tested the hypothesis that Myd88-mediated signalling is required for local and systemic SS manifestations. To this end, Kiri polsky et al. generated NOD.B10Sn-H2b/J (NOD.B10) mice that are deficient in Myd88 (NOD.B10Myd88−/−). These animals showed reduced exocrine and extra-grandular inflammation. Moreover, they had reduced levels of IgM, IgG and anti-nuclear autoantibodies, thus confirming the initial hypothesis (50). To gain a better understanding of neuronal regulation in the immunopathogenesis of autoimmune exocrinopathy, Chen et al. profiled a mouse model of spontaneous, autoimmune exocrinopathy, the autoimmune regulator-deficient (Aire−/−) mouse model. Aire is a putative transcription factor that regulates self-antigen expression in the thymus and thereby prevents autoimmunity by mediating the deletion of potentially self-reactive thymocytes. The investigators concluded that Aire−/− mice provide an exciting model that faithfully mimics key clinical features of SS-mediated peripheral neuropathy and immunopathology (51). It has been recently shown that M3 muscarinic acetylcholine receptor (M3R)-reactive CD3+ T cells play a pathogenic role in the development of murine autoimmune sialadenitis (MIS), which mimics SS. Tahara et al., using splenocytes from M3R knockout (M3R−/−) mice which were immunised with murine M3R peptide mixture and inoculated into recombination activating gene1 knockout (Rag−/−) mice (M3R−/− Rag−/−) with MIS, showed that RORγt antagonism might be a potentially suitable treatment strategy for SS-like sialadenitis through suppression of IL-17 and INF-γ production by M3R-specific T cells (52). Nowadays, experimental data on the implication of autophagy in animal models of autoimmunity remain limited. Murphy Roths Large (MRL)/lymphoproliferation (Ipr) lupus prone mice is used as a mouse model for lupus and secondary SS in order to analyse different autophagic pathways in different lymphoid organs and tissues (53).

Novel insights into diagnosis

In 2016 the novel EULAR/ACR classification criteria for pSS were published (54). Although these criteria have improved the classification of pSS patients, still they do not represent diagnostic criteria for the disease and may fail in the recognition of the disease especially in its atypical presentation (55). On the other hand, there is a compelling need in the scientific community for an early diagnosis of pSS and a better stratification of different disease subsets. Not surprisingly, therefore, in the last twelve months an increasing number of papers have been published aimed at providing novel insights into pSS diagnostic assessment. Great attention has been paid to the role of the biopsy of the minor and major salivary glands for the diagnosis of the disease (56) and, more specifically, to the prognostic significance of the presence of germinal-centre like (GCs) structures in the glandular tissues (57-59). The presence of GCs in the salivary glands of pSS patients has been generally associated with a more severe clinical disease as reflected by a higher focus score (FS), and increased positivity for anti-SSA/Ro and anti-SSB/La autoantibodies (60). Moreover, GCs have also been proposed as a risk factor for the development of lymphoproliferative complications (NHLs) (61). This year, Haucke et al. (57) explored the predictive role of GCs for parotid gland MALT lymphomas in 11 labial gland biopsies from patients with pSS and NHL. The authors observed GCs in 2/11 (18%) H&E stained sections from diagnostic labial gland. Staining for Bcl6 revealed an extra (small) GC in a biopsy of one additional patient. Thus, in patients with pSS who developed parotid MALT lymphoma, GCs were present in 3/11 (27%) prelymphoma labial gland biopsies. In the patients with pSS that did not develop parotid MALT lymphomas, GCs were detected in 4/22 (18%) diagnostic labial gland biopsies with no significant statistical difference. Similarly, the authors did not find any statistically significant difference in MHLs development comparing patients with a FS ≥3 with those with a FS <3. Indeed, as the authors concluded, to better elucidate the prognostic role of GCs for SS-related lymphoma development, uniform histopathological criteria for the assessment of GCs are eagerly awaited. This could be particularly important since novel drugs may be able to decrease GCs, as observed by the same authors with abatacept treatment (62). The prognostic role of the histology for NHL in pSS can be however enriched by further exploratory parameters; among them specific attention has been paid to the characterisation of the NLRP3 inflammasome axis that seems to identify patients with a more severe disease at a greater risk for lymphomas (63, 64).

In addition to salivary gland histology, a number of papers have supported the
use of salivary gland ultrasonography (US-SG) for the diagnosis of SS. A pivotal contribution has been the definition of the US-SG core items definition and their reliability in a multicentre European study coordinated by Joussé-Joulin et al. (65). This work identified echogenicity and homogeneity as the most reliable US-SG items for SS diagnosis. In a prospective cohort of 290 patients, Le Goff et al. observed that adding US-SG to the ACR/EULAR criteria might further improve their sensitivity (66). From this perspective, Mossel et al. showed that the agreement between US-SG and parotid as well as labial gland biopsies was good but was slightly higher for the former (59, 67). The same group suggested that examination of parotid and submandibular glands on one side was sufficient to predict classification of pSS patients according to the ACR-EULAR criteria. To further increase feasibility of US-SG in outpatient clinics worldwide, the authors concluded that only hypoechogenic areas could be scored (68).

US-SG has also been proposed not only for the diagnosis but also for the follow-up of pSS patients. However, it has to be elucidated whether US-SG abnormalities may change over time. In a cohort of 49 subjects with suspected SS, Gazeau et al. (69) found that none of the US-SG abnormalities assessed using a semi-quantitative score changed significantly during a follow-up of nearly 2 years after an initial evaluation for suspected pSS. By contrast, Fisher et al. (70) in the TRACTISS phase III trial with rituximab in pSS, actually demonstrated minimal but statistically significant improvement in US-SG after rituximab compared with placebo. In this multicentre, multiobserver substudy, the authors enrolled 52 patients (n=26 rituximab and n=26 placebo) from nine centres. All the subjects were scanned at baseline and at weeks 16 and 48. Glandular definition (i.e. gland margin) was the only domain to show statistically significant improvement. No difference between rituximab and placebo was observed in any of the additional exploratory ultrasound parameters collected. Moreover, the authors did not find any correlation between US-SG changes and patient-reported outcomes or salivary flow. If the sensitivity to change of US-SG is still questioned, another point of debate is the possibility of using US-SG to monitor damage accrual over time. Interestingly, Martini et al. (71) found a significant correlation between US-SG abnormalities in submandibular glands and unstimulated salivary flow. The authors also found a good inverse correlation between salivary cystatin S and glandular dysfunction, thus reinforcing the complementarity of conventional and novel proteomic tools in the detection of SS diagnostic biomarkers. From this perspective, considering the longstanding need for non-invasive, more accurate diagnostic tools when evaluating pSS patients, an interesting paper has been published by Aqrwi et al. (72) that analysed tears and stimulated saliva of pSS patients by liquid chromatography-mass spectrometry, also evaluating extracellular vesicles from both fluids. The authors found an increased expression of proteins involved in innate immunity (LCN2), cell signalling (CALM) and wound repair (GRN and CALM5) in pSS saliva. Saliva EVs also displayed biomarkers critical for activation of the innate immune system (SIRPA and LSP1) and adipocyte differentiation (APMAP). Tear analysis indicated over-expression of proteins involved in TNF-α signalling (CPNE1) and B cell survival (PRDX3). Although encouraging, the possibility of translating proteomic findings in clinical practice is still in its infancy and additional studies are required to move from the bench to the bedside (73).

**Novel insights into clinical manifestations and prognosis**

**Sjögren’s syndrome in men and women: is it the same disease?**

It has been widely established that women are more prone to develop autoimmune diseases. pSS represents the autoimmune disease with the highest female bias, ranging from a ratio of 10:20:1 (74) even though there is no clear consensus on whether male sex is associated with a more severe disease. Ramirez et al. investigated the clinical presentation of pSS in women and men at diagnosis through the analysis of two independent cohorts (Swedish and Italian). They identified earlier age at diagnosis, more frequent extraglandular manifestations (higher frequency of pulmonary complications, cutaneous vasculitis and lymphadenopathy), more comonitant extraglandular manifestations and higher anti-Ro52 levels to be more frequent in male patients (75). Interestingly, in the same cohort, about half of the male patients were characterised by more than one extra-glandular manifestation at diagnosis, further supporting that the disease is more severe in male patients. The same group, in a large Scandinavian cohort followed for a mean of 9 years, demonstrated that male patients were characterised by significantly higher frequency of serology positivity for antinuclear antibodies, La/SSB, and Ro/SSA + La/SSB. Moreover, interstitial lung disease, lymphadenopathy and lymphoma were more frequently detected in male patients suggesting major immune system activation in male in comparison to female pSS patients (76). All these observations may hint at divergent pathophysiological mechanisms between women and men with pSS and support the hypothesis that pSS in men represents a more severe form of disease, regardless of the lower risk for men to develop the disease. In a recent study, pSS and systemic lupus erythematosus women were examined for rare X chromosome aneuploidies (77). Very rare X chromosome abnormalities were detected in the two groups of patients, suggesting the location of a gene(s) that mediate an X dose effect as well as critical cell types in which such effect is operative and might explain marked sex bias between 46.XX women and 46.XY men.

**Glandular and extra-glandular manifestations**

The peculiar clinical picture of pSS is dominated by signs and symptoms of mucosal dryness resulting from chronic focal lymphocytic inflammation of the exocrine glands and progressive loss of them secretory function. However, many other organs and systems may be affected during the course of the disease in at least one third of patients, causing
vascular disease is a true challenge. A recent study evaluated the accuracy of lung ultrasound in patients who had no alterations in pulmonary function tests or respiratory symptoms demonstrating high sensitivity, specificity and a very good correlation with high resolution chest tomography (82).

Among other disease-specific systemic manifestations, attention has recently been focused on mucocutaneous lesions. Indeed, mucocutaneous lesions may have a prognostic importance in these patients as certain mucocutaneous findings have been demonstrated to confer an increased risk for the development of life-threatening conditions such as B-cell lymphoma (83). A recent large study evaluated the profile and clinical significance of mucocutaneous lesions in a cohort of Chinese pSS patients (84). The most frequently detected lesions were purpuric eruptions, urticaria, Raynaud’s phenomenon and angular stomatitis. The presence of these lesions in pSS patients may suggest a higher activity of the primary disease as some features, including pulmonary interstitial fibrosis, pulmonary bullae, leukaemia and anaemia, were more frequent in patients with mucocutaneous lesions in comparison to patients without. Moreover, patients with mucocutaneous involvement were characterised by a higher level of IgG, lower level of serum C4 and presented new complications compared to pSS patients without skin involvement after a one-year follow-up.

Finally, a retrospective observational study examined the cumulative incidence of a new EGM or associated autoimmune disease from 1 year after establishing pSS diagnosis (85). After 10 years of follow-up, the cumulative incidence of a new EGM or associated AID was 31%. The most frequent events were polyneuropathy, interstitial lung disease, (poly)arthritis, discoid lupus erythematosus/subacute cutaneous LE and Hashimoto’s disease. Non-Hodgkin’s lymphoma (NHL) was not diagnosed during the follow-up (out of three cases, 1 was diagnosed prior and 2 during the diagnosis). Interestingly, patients with cryoglobulins were characterised by a three-fold higher risk of developing these events. On the contrary, age at diagnosis, gender, the presence of ANA, anti-Ro/SSA, anti-La/SSB, IgM-RF, decreased levels of C3 or C4 or hypergammaglobulinaemia did not show any statistically significant differences.

**Lymphoma**

Haematologic malignancies, namely B-cell lymphomas, are one of the most frequent causes of death in pSS with an eight-fold risk of mortality when compared to the general population. NHL occur in approximately 2.7%-9.8% of pSS patients and recent data reported that NHL risk increases 2.2% per year of age with 4.3-fold increased risk in pSS compared to the general population. With regard to the histotypes, diffuse large B-cell lymphoma, mucosa-associated lymphoid tissue lymphoma (MALT) and nodal marginal zone lymphoma are the most prevalent subtypes. Predictable biomarkers of developing lymphoma in patients with pSS have been widely analysed in the last years. A nationwide population-based cohort study involving Spanish pSS patients demonstrated a 11-fold higher risk of developing haematological cancers and the most frequent type was B-cell lymphoma with MALT lymphomas accounting for 60% of cases. Baseline disease activity in the constitutional, lymphadenopathy, glandular and biological domains was associated with a higher risk of haematological cancer.

Interestingly, the authors demonstrated that the prognostic factors for increased risk of lymphoproliferative disease differed according to the subtype of B-cell lymphoma. In particular, the main prognostic factors included activity in the lymphadenopathy domain at pSS diagnosis for all subtypes of haematological neoplasia, cytopenias for non-MALT B-cell and non-B-cell cancer, low C3 levels for MALT lymphomas and monoclonal gammopathy and low C4 levels for non-MALT lymphomas. On the other hand, activity in the constitutional, pulmonary and haematological domains were associated with higher risk of non-B-cell cancers (86). Moreover, a recent study from the Italian Study Group of SS confirmed the relevance of cryoglobulins as prognos-
tic factors for lymphoproliferation. In particular, pSS cryoglobulin positive patients displayed higher systemic disease activity by applying both ESSDAI and CliniESSDAI scores in comparison to negative patients. Interestingly, the ESSDAI domains significantly linked to cryoglobulinaemia were not only the constitutional, cutaneous and peripheral nervous system, notably related to the clinical appearance of cryoglobulinaemia, but also the glandular domain, thus suggesting a strict relationship between cryoglobulinaemia and risk of MALT lymphoproliferation (87).

Recent studies explored the potential role of genetic and epigenetic mechanisms in the pathogenesis of lymphoproliferation in pSS. Indeed, chromosomal and genetic abnormalities are considered major underlying pathogenic mechanisms for NHL lymphomagenesis and epigenetic mechanisms, involving mainly methylation pathways, have been recently proposed as major contributors for both autoimmune disorders and NHL, in particular non-MALT lymphomas (88). A possible role of polymorphisms of the methylene-tetrahydrofolate reductase (MTHFR) gene in contributing to pSS lymphomagenesis has been recently investigated in a Caucasian cohort of 356 pSS patients, of whom 75 had MALT and 19 non-MALT NHL. Increased frequency of c. 677C>T TT genotype and T allele and reduced prevalence of the c. 1298A>C C allele were observed in the non-MALT group compared to healthy controls and patients without NHL, suggesting that MTHFR variants may be involved in SS non-MALT NHL development, through contribution to defective DNA methylation and genomic instability (89). Moreover, the expression of Fc receptor-like protein (4FcrL4) associated with the ductal epithelium forming lymphoepithelial lesions, particularly in the parotid gland, may have an important role in the pathogenesis of pSS and lymphomagenesis of MALT lymphomas (34).

Other potential biomarkers for MALT-NHL were identified in a prospective single-centre Italian study. In more than one hundred pSS women prospectively followed for a mean of 52 months, the authors demonstrated that gene expression of the axis P2X7R-inflammasome in minor salivary glands biopsies was higher in patients autoantibody-positive and in those developing a MALT-NHL over the follow-up, thus suggesting an explorative role of P2X7R-inflammasome axis as potential pathway involved in SS lymphomagenesis (63). Furthermore, a number of significantly over-expressed proteins were identified in the salivary gland tissues of patients with pSS or pSS/MALT lymphoma, including coflin-1, alpha-elongase and Rho GDP-dissociation inhibitor 2 (90).

A severe clinical picture characterised by extraglandular manifestations as well as NHL has been associated with the severity of the inflammatory infiltrate, as defined by the focus score (FS) and/or by the presence of ectopic lymphoid structures (ELS) (60, 61, 91, 92). However, Haacke et al. recently ruled out an association between ELS and lymphoma evaluating the presence of germinal centres (GCs) in labial gland biopsies through a staining combination of haematoxylin and eosin (H&E) and Bcl-6 (58), although previous studies have demonstrated such association (61, 92, 93). Although the calculation of FS is rather intuitive and reproducible (94), discrepancies arise with regard to the assessment of ELS as recently highlighted by Alunno et al. These studies, indeed, suggest the need for a harmonisation of ELS assessment and for the development of univocal recommendations to be used in clinical practice (95). Finally, although there are still no approved therapeutic interventions for pSS, promising results derive from studies evaluating the efficacy of biological disease-modifying anti-rheumatic drugs. In 15 pSS patients included in the open-label Active Sjögren Abatacept Pilot (ASAP study), Haacke et al. depicted a reduction of GCs in parotid gland tissue at 24 weeks of follow-up after 8 infusion of abatacept, probably due to inhibition of local T-cell dependent B-cell activation (62). Another study demonstrated the selective reduction of percentage and number of circulating follicular helper T cells and Treg-cells, with a concomitant decrease in RF, anti-SSA and CXCL13 serum levels, following treatment with abatacept (96). Interesting and innovative results derived from a recent pilot study aimed to evaluate the effect of belimumab, a BAFF-inhibitor, on IFN-induced peripheral blood gene expression in a small cohort of pSS female patients all positive for RF and anti-SSA/SSB (97). Following belimumab administration, baseline type I IFN significantly correlated with the overall decrease of RF from baseline to week 52 and patients with higher IFN score at baseline showed grater changes at same follow-up of immunoglobulin levels and RF while no significant changes with type II IFN were observed. These preliminary data suggest that type I IFN signature may affect the magnitude of biological effect of belimumab on immunoglobulin production, including RF and that SS patients showing higher IFN signature may be the best target for belimumab.

Health-related quality of life and measures of disability in SS patients

Several factors may contribute to the impairment of health-related quality of life (HRQoL) in pSS and the importance of patient perspective is on the increase, so much so that HRQoL has been included as patient-reported outcome (PRO) measures in several clinical studies. Indeed, it is well known that pSS patients suffer from pain and fatigue mainly related to muscular and articular chronic pain and to a secondary depressive syndrome. Interestingly, among 120 pSS patients participating in a large therapeutic trial (Tolerance and Efficacy of Rituximab in pSS, TESSAR) who completed the Short Form 36 health survey (SF-36), cardinal symptoms of pSS (dryness, pain, and fatigue) were the most strongly associated with HRQoL impairment, best assessed using the ESSPRI. In particular, pain and fatigue were the primary contributors to decline in quality of life (98). Similarly, in 257 Korean patients, younger age, xerostomia, and pain assessed by Euro-QoL-5 (EQ-5D) were found to be the major determinants of fatigue (fatigue domain of the ESSPRI) (99). These data were strengthened in a large cross-sec-
tional study aimed at assessing HRQoL by SF-36 and physiologcal status by the Hospital Anxiety Depression Scale (HADS) in 304 Chinese women with pSS. In this study, significantly lower SF-36 scores were detected in patients in comparison to general population in all domains outlined in the score, suggesting a reduced QoL in these patients. Moreover, anxiety and depression scores of pSS patients were significantly higher in comparison to patients treated in the Internal Medicine Departments. Younger patient displayed greater anxiety level. Pain and fatigue levels were related to anxiety, whereas pain, fatigue and xeroderma were associated with depression, suggesting that pain and fatigue are the main contributing factors to lower QoL and increase anxiety and depression in these patients (100). Multiple still unexplored factors may contribute to the increased level of anxiety and depression characterising pSS patients in comparison to a matched control population. First of all, emotional status in pSS patients may be partly related to probable central nervous involvement and immune system activation and chronic inflammatory state may alter the neuroendocrine and central nervous system, inducing or worsening anxiety and depression status. Moreover, chronic joint and muscle pain, fatigue and xerosis are important contributing factors to anxiety and depression and the menopausal status in pSS women may contribute to enhance this phenomenon inducing a chronic depressive syndrome. Dryness may affect smell, taste and sexual function in pSS patients, further contributing to QoL impairment. A recent review of five studies involving more than 300 pSS patients demonstrated that smell and taste are significantly impaired in pSS patients in comparison to age- and gender-matched controls. In particular, 50% of subjects complained of hyposmia and 70% suffered from hypogeusia. Moreover, sexual function was significantly affected in pSS women and vaginal dryness has been demonstrated to significantly affect sexual function in these patients. Of consequence, impairment of taste and smell and of sexual function represent adjunctive factors contributing to impaired QoL in pSS patients (101).

In a recent paper, Lackner et al. developed a questionnaire for the specific assessment of HRQoL pSS (pSS-QoL). Construct validity of the questionnaire was assessed by correlating the score with the EULAR Sjögren’s Syndrome Patient Reported Index (ESSPRI), EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) and EQ-5D and consisted of 25 questions divided in two main categories: physical (discomfort and dryness) and psychosocial. Strong and moderate correlations were found between the PSS-QoL and ESSPRI and EQ-5D suggesting the potential value of this questionnaire as a novel PRO measure in clinical studies (102). To better characterise the needs and perspectives of patients and their preferences and difficulties in daily life, the same group performed a study aimed at evaluating perspectives and needs which may influence HRQoL in pSS patients. A small cohort of pSS patients was enrolled and three main domains were identified, including physical dimension, psychological and emotional challenges, social life and daily living. The study confirmed that complaints secondary to pain, dryness and fatigue are important to patients with pSS and significantly affect physical, psychological and social life components of HRQoL (103).

Finally, research attention focused on the evaluation of physical tiredness and activity in pSS. Physical tiredness, mental fatigue and ocular fatigue were assessed in a semi-structured qualitative interview in the Division of Psychology at Nottingham Trent University. Participants (n=20) linked their experience of fatigue to feelings of depression, frustration, irritation and anxiety. They also described an exacerbation of other ocular symptoms including pain, dryness and itching, which were compounded by fatigue (104).

Moreover, physical inactivity with consequent reduced aerobic exercise and muscle strength represent major determinants of impaired QoL in these patients. A recent study evaluated habitual physical activity (i.e. sedentary time and light and moderate-to-vigorous physical activity) in a small cohort of pSS patients with mild disease activity and the association between habitual physical activity level with physical capacity and function, fatigue, HRQoL and depression. In particular, 29 women with pSS were assessed for habitual physical activity levels and compared with 20 healthy women matched for physical activity level, body mass index and body fat percentage. In comparison to the healthy control group, pSS patients were characterised by reduced physical capacity and function, increased fatigue and pain, and reduced HRQoL. Interestingly, these differences were sustained when only more physically active participants were compared, indicating that minimum recommended levels of physical activity for the general population may not be sufficient to counteract pSS comorbidities (105). Similar results were detected in a cross-sectional study aimed at investigating self-reported levels of physical activity measured by the International Physical Activity Questionnaire-short form (IPAQ-SF) in 273 pSS patients in comparison to healthy controls matched for age, sex and body mass index. Interestingly, patients with pSS displayed significantly reduced levels of physical activity but similar levels of sedentary activity compared to healthy individuals. Moreover, a significant association between physical activity and fatigue, orthostatic intolerance, depressive symptoms and QoL was also found while sedentary activity did not correlate with fatigue. Symptoms of depression and daytime sleepiness were independent predictors of levels of physical activity (106).

Novel insights into treatment

Despite increasing knowledge on the pathophysiological events that lead to pSS, treatment of the disease has not greatly improved if compared to other autoimmune diseases and is mostly based on personal experience and expert opinion, rather than on strong scientific evidence. For these reasons and in consideration of the limited effectiveness of current treatments, considerable efforts are currently being made to identify novel drugs and to test ef-
fectiveness of medications which have proven useful in other autoimmune diseases. It is now well established that both T and B cells are involved in the pathogenesis of pSS, which are able to induce the formation of GC-like structures in salivary glands. This observation, along with other supportive data, such as the detection of specific auto-antibodies, the frequent development of hypergammaglobulinemia and the increased incidence of B-cell lymphoma in pSS patients, lead to a strong interest in the potential usefulness of targeting B and plasma cells with rituximab, a monoclonal anti-CD20 antibody. Verstappen et al. (107) made a very interesting observation on pSS patients treated with rituximab, showing that anti-CD20 therapy not only predictably reduces the number of circulating B-cells, but also affects levels of some subtypes of T cells, namely circulating T follicular helper (Tfh) cells, IL-21 and IL-17-producing CD4+ T cells. Although not surprising, the exact mechanism of such effect needs to be elucidated. Nonetheless, this study adds further suspicion that rituximab may be an effective treatment for glandular and systemic manifestations of pSS. The results of published human trials are contrasting, with some studies showing mild effectiveness and others failing to confirm this observation (TEARS study). In a recently published randomised controlled trial, the authors evaluated the efficacy of rituximab on fatigue and oral dryness after two courses of therapy, i.e., 12 months. Rituximab was not superior to placebo on fatigue and xerostomia improvement; likewise, no substantial benefits were achieved on secondary endpoints such as ESSDAI, ESSPRI, salivary and lacrimal flows and quality of life (108). Levels of circulating Tfh cells are also reduced after administration of the fusion protein abatacept which blocks co-stimulatory signals, thus inhibiting T cell activation by antigen presenting cells. Because Tfh cells are essential to orchestrate the formation of ectopic GCs in exocrine glands, this observation may explain the findings of the study by Haacke et al. who demonstrated a reduction of the presence of GCs in the parotid glands of pSS patients following treatment with abatacept (62, 109).

One of the most widely prescribed first-line medications for pSS is hydroxychloroquine (HCQ), especially to treat symptoms such as fatigue and arthralgia. This approach derives from the well-recognised effect on skin and articular manifestations in systemic lupus erythematosus. Studies performed on pSS show conflicting data. Results of a meta-analysis of four studies including a total of 215 SS patients suggests no effect of HCQ on fatigue, xerophthalmia, xerostomia and tear and saliva production (110). HCQ is also almost routinely prescribed in pSS female patients during pregnancy, owing to the absence of foetal toxicity. On the contrary, strong evidence in favour of potential beneficial effects is lacking, even though some studies suggest that HCQ is effective in reducing the incidence of congenital heart block (CHB), one of the most detrimental – albeit rare – obstetrical complications of anti-SSA/Ro+ patients. A recent case-control study on 54 pregnancies showed a positive effect of HCQ on pre-term delivery rate, although no conclusions can be drawn considering the low number of patients enrolled (111).

Such a paucity of evidence on the effectiveness of commonly prescribed medications – not limited to HCQ – underpins the importance of promoting further investigation on “old” molecules which may still serve as a valuable tool, even in the era of targeted agents and biologics. Xerostomia and xerophthalmia are unquestionably the most common manifestation of pSS. Although not particularly organ-threatening, they represent the main cause of distress for patients. Current treatments for dry eye and mouth consist of topical lubricants, topical immunosuppressants such as cyclosporine eye drops and systemic secretagogues like pilocarpine. These treatments provide only limited amelioration of discomfort and some are burdened by adverse effects which limit their use. Furthermore, establishing the actual effectiveness of these treatments is challenging as it is now well known that subjective and objective measures of oral and ocular dryness do not always well correlate with each other due to variability of pain sensitivity among individuals, presence of comorbidities such as fibromyalgia and of frequent confounding ocular sensations like burning pain and tired eye which may be referred erroneously. To try and overcome this limitation, especially in an experimental setting, a new method has been proposed, which aims to account for discrepancies between subjective symptoms and objective measures of dryness by means of a score ranging from -5 (asymptomatic with severe dryness) to +5 (severe symptoms despite normal tear and saliva production) (112).

Numerous studies performed on murine models and evaluating potential new topical treatments for ocular dryness have been recently published. Non-obese diabetic (NOD) mice, which spontaneously develop autoimmune dacryoadenitis and sialoadenitis, responded very well to a topical nano-encapsulated formulation of sirolimus, which helps to overcome limitations due to systemic toxicity and very low solubility. The treated mice showed a reduction of both histological lacrimal gland inflammation and corneal fluorescein staining score (113). Blockage of high mobility group box (HMGB)1 – a pleiotropic alarmin contributing to inflammation initiation – by subconjunctival injection of a specific antibody in NOD mice also appeared to be superior to placebo in terms of tear production and corneal staining score. Treated mice also showed increased amounts of IL-22-producing innate lymphoid cells (ILC3) in draining lymph nodes, indeed a very interesting observation worth further investigation (44). Another murine model that spontaneously develops ocular inflammation resembling pSS is thrombospondin-1 (TSP-1) deficient mouse. Contreras-Ruiz et al. demonstrated that TSP-peptide can induce T regulatory cells (Treg) binding to CD47; topical administration of this peptide in TSP-1 deficient mice reduced corneal fluorescein staining score, preserved tear quality and increased ex-
pression of FoxP3 mRNA in draining lymph nodes, compared to mice treated with a control peptide (114). Another interesting area of research is represented by the potentials of autologous products used to promote tissue regeneration. Mesenchymal stem cells are providing good results in in vitro and in vivo studies but have strong limitations (115), while other technologies may provide new therapeutic options in the near future. Plasma rich in growth factors (PRGF) eye drops can be produced from autologous plasma and have already shown to be effective for various ocular surface diseases. A retrospective analysis performed on primary and secondary SS patients demonstrated a significant improvement of symptoms related to xerophthalmia, even in those who had previously failed to respond to topical cyclosporine (116).

References


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