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Treatment of Sjögren's syndrome: current therapy and future directions

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Abstract

SS is usually described as having severe fatigue, dryness, diffuse pain, glandular swelling, and various extraglandular (systemic) manifestations. Clinical trials have generally failed because the vast majority of enrolled patients had no extraglandular manifestations at the time of enrolment but suffered from fatigue, dryness and pain that did not significantly respond to the study medication. A number of hypotheses on the pathogenesis of pSS have been put forward, including disturbances of innate and adaptive immunity as well as abnormalities of the interface between immune disorders and the neuro-endocrine system related to lacrimal and secretory gland dysfunction. Thus, future therapies must be designed for improvement of the symptoms of dry eyes and dry mouth, extraglandular disease, and fatigue and cognitive deficits. Given the inadequacies and limitations of current treatment options, we suggest that innovative directions involving interactions with neuroscientists and neuropsychiatrists together or combined with new immune targeting may be hold promise for better treating pSS.

Key words: primary Sjögren's syndrome, treatment of primary Sjögren's syndrome, disease-modifying drugs, biologic therapies, cytokines and chemokines, neuroendocrine, neurokines

Rheumatology key messages

- The diagnosis of pSS is often met with a hopelessness that no cure is yet known.
- There is need for particular therapies that are effective in the treatment of extraglandular manifestations.
- Multidisciplinary efforts will be necessary to implement current therapies and develop new understanding of pSS patients' symptoms.

Introduction

This article will first review the current guidelines of the British and American Rheumatology Societies for therapy of both glandular and extraglandular symptoms.

The search for a golden bullet or holy grail that will improve disabling fatigue, dryness of all mucosa, and diffuse pain, which afflict the vast majority of patients with pSS, has not yet been achieved. As a result, the expense of treating SS patients is second only to that of treating RA patients, and the degree of patient/physician satisfaction with therapy is dismally lower. Notably, large studies in RA, SLE and other autoimmune diseases have not fully assessed the value of immune interventions in improving associated SS.

Guidelines from the Sjögren's Syndrome Foundation for American rheumatologists by Carson *et al.* [1] as well as guidelines for topical and systemic therapy as recognized by the British Society of Rheumatology [2] have been published and can be accessed online. A European initiative [3] is also in line with these recommendations.

These guidelines include treatment guidelines for dry eyes, Meibomian gland dysfunction, oral manifestations and secretagogues, including the quality grade of evidence supporting each study. The only agents that have actually been approved as secretagogue agents by the European Medicines Agency (EMA) is oral pilocarpine, and by the United States Federal Drug Administration are oral pilocarpine and cevimeline. For ocular topical use, ciclosporin and lifitegrast are approved. The other agents for ocular use (including topical 'soft steroids') are part of the general dry eye arsenal utilized by ophthalmologists, and include punctal occlusion or 'bandage contact lens' [4].

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Recent data and scientific perspectives have recognized that the symptoms of both eye and mouth symptoms are out of proportion to the objective tear flow, corneal surface observations or observations of the oral mucosa, consistent with the notion that severe dryness is not always related to substantial histologic changes. The conclusion deduced from this discrepancy of ocular/oral findings and ocular/objective signs is that signal processing of the afferent signals in the central nervous system is aberrant, and may be influenced by inflammation at locations such as the lacrimatory and salivatory nuclei regions in the midbrain [5–7] or in particular areas of the brain cortex [8, 9].

It needs to be emphasized that ocular and oral manifestations represent an immense economic burden on the health-care system (ocular discomfort and dryness is now the single leading cause of visits to ophthalmologists). Additionally, lost productivity at the workplace is enormous. Moreover, the social burden is remarkable. Dry mouth has led not only to increased dental decay and implant failure, but troublesome discomfort that interferes with eating, socialization, and even sleeping. Overall, PSs impacts on entire families that struggle to cope with the disease's significant corrosive quality of life impact, including the often severe fatigue and mood disorders in these patients [10].

Based on these introductory remarks, this article will review the value of small molecules used in therapy of extraglandular manifestations in pSS. It is worth noting that these have generally not arrived at a late stage of development, including seeking of approval, but some hold promise for changing the lives of our pSS patients. Here, we will also look to the future of small molecules through the lens of unmet needs, which concerns the most frequent and disabling symptoms: dryness and fatigue. We also take the opportunity to look at other multidisciplinary specialties such as Neurology (multiple sclerosis and idiopathic neuropathies) and Neuropsychiatry (anxiety, fatigue, and chronic pain), in which the molecular basis of symptoms and therapeutic trials are being developed further.

Why clinical trials have failed in pSS

A recent review article [11] entitled 'Why Clinical Trials Fail in Sjögren's' outlines several key points that may be overlooked in regular review articles. That article reviewed the past 20 trials in pSS.

We believe that it is time to change or shift this paradigm: the patient recruitment subgroups need to be better defined, using the new ACR/EULAR criteria more strictly [12]; disease activity needs to be clearly defined [13]; and/or more appropriate end points for success are needed, such as ESSDAI and ESSPRI, which have recently become more widely used as validated instruments [13]. Randomized trials targeted the wrong biologic pathway (such as TNF-alpha) and did not target the IFN-alpha pathway, which seems to play a pivotal pathogenic role.

Of note, anti-TNF therapies should not be used in any patient suffering from pSS, because two randomized trials have demonstrated their inefficacy; in addition, anti-TNF might increase the risk of lymphoma in pSS; moreover, TNF blockade increases the activation of the IFN alpha pathway and BAFF expression, which are considered drivers of pSS pathogenesis.

A recent study, Bodewes *et al.* [14] evaluated the relationship between systemic IFN type 1 and IFN type II gene signatures in whole blood RNA of 50 SS patients. The study was performed in two independent European cohorts and showed correlations with clinical features. Three groups could be stratified according to their systemic IFN activity: IFN inactive, IFN-1, and IFN I plus II. No patient had isolated IFN II activations. IgG levels were highest in patients with IFN I plus II, followed by IFN I and patients without IFN signature. The prevalence of antibodies to SSA/Ro was higher among those with increased IFN. Notably, there was no difference in EULAR SS Disease Activity Index (ESSDAI), fatigue or dryness between the groups, but the pain scores were lower in the IFN active groups. The systemic IFN-I, but not IFN I plus II activity, appeared to be relatively stable over time. Another study by Rose *et al.* [15] assessed the IFN type I signature by SIGLEC1 (CD169) and IFN-γ–inducible protein-10 (IP-10) profiles. Activated type I IFN was found in 64.5% by SIGLEC-1 and 78.9% for IP-10 in pSS. SIGLEC1 expression correlated with extraglandular manifestations (16/16, 100%) compared with patients with exclusively glandular involvement (4/15, 27%). Serum IP-10 levels neither differed significantly between glandular and extraglandular disease nor correlated with ESSDAI. These recent studies imply an important role for type I IFN in SS-related systemic complications and suggest the possibility of therapeutic targeting of type I IFN.

Regarding pathogenesis of dryness, it becomes obvious that the residual glandular acinar and ductal structures are present but dysfunctional. Currently available therapeutics, especially immunosuppressive agents, are not able to improve glandular functions, in contrast to adrenergic molecules, such as pilocarpine or cimeveline. This suggests that pathways of neural innervation of vascular and glandular secretion control need further investigation in pSS.

Efficacy of specific therapeutic agents in current clinical use

So far not a single immunosuppressive agent has been approved for patients with pSS. However, limited evidence and clinical experiences permit a clinical perspective (eminence based).

Glucocorticoids

There have been no large trials addressing the potential benefit of glucocorticoids for the glandular manifestations of SS. Some benefit in reducing glandular enlargement—but not sicca symptoms—may be observed consistent with our experience. Usually short-term use of glucocorticoids permits control over glandular enlargements. In a small randomized trial, neither treatment

with prednisolone (30 mg every other day) nor piroxicam (20 mg/day), compared with placebo, resulted in substantial changes after 6 months in salivary and lacrimal gland function or salivary gland histopathology [16]. Long-term use of glucocorticoids in pSS should be avoided due to potential side effects, including osteoporosis, hyperglycaemia, weight gain, agitation, damage accrual and increased risk of infections, as in other autoimmune diseases. In pSS patients, an increased risk of oral Candida and acceleration of dental decay further limit the prolonged use of glucocorticoids at higher doses [17, 18].

Glucocorticoids are sometimes used to treat systemic manifestations of pSS in a manner similar to that in other systemic rheumatic and autoimmune diseases [19]. In an analysis of 1120 Spanish patients with pSS, low-dose glucocorticoids (the equivalent of prednisolone $\leqslant$20 mg/day) were used for this purpose in 19% of patients [20]. As long as there is no valid benefit/risk evaluation for glucocorticoids in pSS, the use of them should be limited in dose and duration and if possible avoided.

Conventional immunosuppressive drugs and (non-biologic) synthetic DMARDs

Synthetic DMARDs are primarily used to treat specific organ manifestations in a manner similar to the treatment of SLE, particularly in the tapering or replacing of glucocorticoids. Their utility for the treatment of glandular manifestations of the disease has been disappointing. Since most trials assessed a very limited number of patients with heterogeneous organ manifestations, available data are very limited. Briefly, clinical trials of non-biologic synthetic DMARDs have included the following.

HCQ

Therapy with HCQ is largely based upon its efficacy in SLE [21]. In particular, the Canadian cohort study was a 'withdrawal' study: in SLE, the number of flares increased after removing HCQ in a blinded trial, and this increase was small but significant. The symptoms and signs improved on reintroduction of HCQ.

Also, HCQ had been shown to be effective in 'subacute lupus' (annular erythema) [22], which is now recognized as a SS manifestation.

Small, open-label trials and observational studies have found improvement in arthralgias and myalgias, when acute phase reactants and hypergammaglobulinemia were present [23]. However, a randomized placebo-controlled trial involving SS patients did not show reduction in dryness, pain and fatigue at 6 months [23]. The apparent discrepancy in these results for HCQ is most likely due to the size and clinical characteristics of the patients in each study. The long-term benefit of HCQ in pSS, regarding the prevention of systemic complications and lymphomas remains to be studied. Of note, in SLE, the use of HCQ has been reported to result in increased survival [24]. Clinical experience mandates HCQ as the DMARD of choice in pSS in the absence of other more potent options; it is generally well tolerated by patients, and has a known, manageable safety profile, including proper follow-up by opthalmologists.

MTX

A 1-year pilot study of MTX (0.2 mg/kg weekly) in 17 patients with primary SS showed improvement in dry mouth and eye symptoms, arthralgias, arthritis, and the frequency of parotid gland enlargement and purpura [25]. However, no improvement in the objective parameters of dry eyes or dry mouth was observed [25]. A retrospective case review of articular manifestations in a large French cohort also reported benefit in 11 of 12 SS patients treated with MTX for musculoskeletal pain [26, 27].

AZA

In a randomized trial of low-dose AZT (1 mg/kg/day) in 25 patients with pSS, there was no significant change in disease activity over a period of 6 months [28]. However, AZA is commonly used in the management of specific extraglandular involvement, such as interstitial pneumonitis, myelopathy, and chronic active autoimmune hepatitis [29].

LEF

In an open-label pilot study, LEF (20 mg/day) provided only modest benefits for 15 patients with early and active primary SS [30]. However, there was notable improvement in leukocytoclastic vasculitis in three patients. The treatment was associated with the development of lupus-like skin lesions in five patients. In a study of RA, LEF therapy was associated with worsening of ocular dryness in a group of 45 patients with RA with secondary SS, as compared with 30 without secondary SS [31].

Mycophenolic acid

In an open-label pilot study of 11 patients with pSS, mycophenolate in doses of up to 1440 mg/day for 6 months did not improve objective measures of ocular or oral dryness, but did lead to significant reductions in hypergammaglobulinemia and RF, and an increase in complement and white blood count levels [32].

CSA

Two randomized controlled trials have been reported in pSS. In one randomized trial, CSA (5 mg/kg/day) resulted in symptomatic improvement of dry mouth at 6 months, compared with placebo, but no change in dry eye symptoms or objective parameters of ocular and oral dryness [33]. In an open-label extension, labial gland histopathology worsened at 12 months in CSA-treated patients [32]. Another phase II open study with 30 pSS patients focused on the articular involvement and CSA [34]. Here treatment consisted of $\sim$2 mg/kg of CSA. The primary end point was defined as a reduction in the number of painful and/or swollen joints at the end of treatment. The mean number of swollen joints (66 counts) was reduced from 3.2 ($\pm$3.3) at baseline to 1.3 ($\pm$3.2) at 16 weeks ($P < 0.001$). Overall, 21 (70%) and 13 (43.3%) patients had a reduction of two or more tender and swollen joints, respectively, in their 68/66 joint counts. The DAS28 showed a statistically and clinically meaningful decrease over the 16-week period of treatment. This treatment was well tolerated, and adverse events were consistent with the known

safety profile of CSA (e.g. hypertension, headache). This study arrived at the conclusion that CSA treatment is an efficacious option for articular involvements in pSS.

Biologic agents have been shown to be efficacious for use in extraglandular manifestations

Several biologic agents are recommended for pSS in the treatment guidelines of both the British and American Rheumatology groups as well as the European Consensus group in certain clinical situations. They are briefly reviewed below, because SS patients may show benefit in terms of reduction in their extraglandular manifestations.

Rituximab (mabthera, rituxan)

A chimeric monoclonal antibody directed against the CD20 cell surface marker on B-cells and their precursors has been studied extensively as a treatment option [35]. The findings have been variable, as illustrated by a number of reports, including randomized trials, open-label studies, and retrospective case reports and series. It is hoped that a personalized medicine approach using biomarkers may identify the patients most likely to benefit [36] and then may explain the variable experiences. In the largest randomized trials of rituximab, the primary outcome measures, reduction of patient-reported dryness and fatigue, were not met [37, 38], although the suitability of these outcome measures has been questioned. Although experimental studies [39, 40] have suggested that resistance to B cell depletion by rituximab may be related to enhanced BAFF levels, the drug has been reported to be of benefit for specific extraglandular manifestations in retrospective case series and registry analyses [39, 40], and is reimbursed by certain health insurances based on the British and American guidelines described above.

Belimumab (benlysta)

A monoclonal antibody directed against B cell activating factor, was evaluated in an open-label trial of 30 primary SS patients (BELISS), which found a decrease in ESSDAI at 28 weeks [41, 42]. Saliva flow, Schirmer's testing, and salivary biopsy focus score results did not change. However, there was improvement in non-malignant parotid enlargement, arthritis/arthralgia, and in B cell biomarker values, including serum immunoglobulin and RF levels. Of particular note, responding patients showed further improvement over a subsequent 6 month period, in particular for fatigue [31]. This may support the idea that long-term anti-BLyS/BAFF therapy may have an effect on neuroimmune abnormalities in pSS.

Early experiences [43] of open treatment using belimumab followed by rituximab have been reported in patients with Sjögren's and coexistent MALT lymphoma and cryoglobulinemic vasculitis. Subsequently, a combination of rituximab and belimumab was recently evaluated in a randomized clinical trial (the results are not currently available). This combination could be of interest, given that B cell depletion results in BAFF upregulation, which may potentially lead to a more pronounced effect on pathogenic B cells.

A monoclonal antibody VAY736, targeting membrane-bound and soluble BAFF/Blys able to deplete simultaneously B cells even longer than RTX, has been studied in a phase Ib study in pSS [44]. A single infusion showed improvements in several domains of ESSPRI, including patients' Visual Analogue Scale. This drug is currently under investigation in a larger multicentre randomized phase IIb controlled trial.

Abatacept (orencia)

CTLA fusion protein (CTLA4) is a negative regulator of T cell function, and one polymorphic single nucleotide polymorphism (SNP) has been associated with extraglandular manifestations [45]. An open-label pilot study of 11 patients has shown improvement in salivary gland biopsy and extraglandular manifestations, and a good safety profile [46]. Abatacept was found to improve saliva flow in a small cohort of treated RA patients [47]. Thompson *et al.* [47] showed the possible synergy of tacrolimus and abatacept in lymphocytic interstitial pneumonitis, indicating a future direction of combining biologics with small molecules [44], and as such following a potentially promising multitarget therapy concept. Another open-label study of 15 SS patients showed improvement in ESSDAI and biomarkers, but no change in tear flow or subjective symptoms [48]. Overall, the use of CTLA4 antibodies holds promise in pSS based on these initial open studies, and further randomized controlled trial data are awaited.

A non-depleting anti-CD40 antibody (CFZ533) [49] has recently shown significant improvement in SS patients with high extraglandular activity, with improved ESSDAI and modest improvement in saliva [50], in a randomized placebo controlled trial.

Agents that have failed in clinical trials

A number of other therapeutic approaches have been evaluated and deemed treatment failures in SS. Further clinical testing was not pursued due to side effects or inefficacy for thalidomide, oral lozenges of interferon alfa, anakinra, baminercept and efalizumab.

Toward the future: selective small molecules

The occurrence of dryness in other conditions such as multiple sclerosis and diabetes mellitus suggests that further collaboration with neuro-endocrinologists and neuropharmacologists may be fruitful and lead to win–win situations for both disciplines [51]. Although the era of biologic treatment modalities has not led to any approvals for pSS, the arrival of Jak inhibitors in RA (tofacitinib and baricitinib), with additional compounds at late stage or close to approval (upadacitinib, filgotinib), suggests that the potential of these JAK inhibitors to target IFN pathways (at least partially type I and II IFN) is of particular interest in pSS.

Other target molecules (BTK, Syk, Tyk, etc.) being evaluated in RA and other inflammatory diseases are generating new hope for immunomodulation in pSS. BTK, which is involved in BCR and Fcγ receptor signal transduction, seems a relevant target, but this has to be confirmed by randomized trials. Mice that overexpress BTK in B cells develop salivary gland lymphocytic infiltrates. Of note, BTK protein was reported to be increased in B cells from a majority of patients with primary SS and correlated with serum RF levels and parotid gland T cell infiltration. Targeting T cell activation in patients with primary SS using abatacept restored BTK protein expression in B cells to normal levels.

Below, we will briefly discuss potential candidates that may be able to suppress inflammation and improve dryness symptoms or neurologic dysfunction, as suggested by data from multiple sclerosis or diabetes mellitus. It is important to note that these compounds have features beyond immunoactivity.

Fingolimod (which affects sphingosine pathways [52]) and its derivatives (such as ozanimod) [53] are further candidates, since the S1P receptor is present on salivary and lacrimal glands. It is also important to retract lymphocytes within germinal centre structures. Current thinking sees a potential for this in prevent spreading of autoimmune responses. Interesting data on the use of ozanimod in multiple sclerosis [54] are showing promising effects in preventing MRI lesions. A critical question is how brain-selective S1P1 inhibition is, and the glandular effects require detailed and further assessment in pSS.

Sirtuin agonist or inhibitors (silent information regulators) affect epigenetic regulation of rDNA and NFK-B pathways [55], which play a role in diabetic neurologic dysfunction, including their dryness symptoms. NLRP3 (pyrin domain) inhibitors such as MCC950 have proven effective in the mouse NOD model of SS [56].

A series of miRNA and modulators of NFK-B [57] have benefit in murine models of SS [58]. In this context, next generation antagomir therapy may be useful for targets in pSS. However, target validation is still in its early stages and requires comprehensive analysis on the genetic and epigenetic, as well as proteomic, transcriptome level. Taking the rather low prevalence of pSS and its various organ manifestations into account, international collaborative efforts are required in order to arrive at compelling and conclusive data.

mTOR and AKT inhibitors influence small molecule kinases involved in the regulation of cell survival programing as well as T cell activation [59]. Here rapamycin has shown benefit in SS patients and murine models [60–64], but still further target validation is required regarding human disease.

Agents in the PI3K/AKT signalling pathway [65, 66] may need to be used in combination with other agents. Upstream of AKT, the regulatory kinase is PI3K, which has at least four different catalytic units (alpha, beta, gamma and delta). Recent data for 30 pSS patients studying a PI3Kdelate inhibitor (leniolisib) showed good bioactivity, as measured by reduced pAKT, but the clinical outcome as captured by ESSPRI and ESSDAI did not differentiate between 20 patients on active drug and 10 placebo-treated patients. Notably, the active arm had substantially more patients with skin rashes [67].

Pathways that involve interferon signatures that involve sialic acid lectins and IFN inducible protein 10 [15] are another possibility for research. Based on the characteristic type I IFN signature, especially in patients with extraglandular disease, targeting this family of cytokines with the anti-type I IFN receptor monoclonal anifrolumab, but also other principles such as direct IFN-α blockade or interfering with pDC activity using anti-BDCA antibodies as well as blocking type I IFN signalling by Jak/Tyk inhibitors, has potential value to study in pSS [68]. Along these lines, ULK1 molecules (Beclin 1 and Ambra 1) involved in autophagy and the cycle that initiates both type 1 and type 2 IFN production could lead to reduced type IFN, with potential clinical improvements.

Agents such as modafinil (Provigil), which have proven effective in improving fatigue in multiple sclerosis [69], could have the potential to improve fatigue in pSS, too. An interesting observation over the last years is the interplay between vagal nerve stimulation and the immune system. Instrumental studies were reported after vagal nerve stimulation and denervation. Vagal stimulation and its variants that improve phantom pain are now approved for cluster headaches, with improved relief from ocular pain [70]. While there is a possibility that abnormal vagal activity could be involved in pSS, compelling clinical evidence is currently not available.

Recommendations and summary

Patients should undergo a thorough pretreatment evaluation to confirm the diagnosis and to determine the severity and extent of pSS (especially prevalent extraglandular disease), the disease subset, and the extent of fatigue. The approach to management is generally the same for primary (pSS) or associated (secondary) SS. Current recommendations comprise non-pharmacologic and preventive interventions, including patient education regarding self-care measures and the benefits of smoking cessation, counselling regarding diet and medication use, routine preventive care, immunizations, and pregnancy counselling. In addition to widely used substitution of tear drops and saliva, use of secretagogue (pilocarpine – or cimeveline in the USA and Japan) can be considered for certain patients.

In patients with moderate to severe involvement, systemic medical therapy may be indicated on a background of antimalarials, including the use of immunosuppressive and biologic agents, depending upon clinical manifestations and organ systems affected. The value of rituximab in pSS is limited to severe organ manifestations, such as cryoglobulinemia-related complications and vasculitis. Various DMARDs are in use for musculoskeletal pain (HCQ or low-dose weekly MTX, AZA or LEF). FM is treated with physical therapy and certain antidepressive agents, usually avoiding anticholinergic side effects that increase dryness. In patients with fatigue, treatment is comprised initially of a low-impact aerobic exercise program. In

patients with fatigue refractory to exercise and other lifestyle changes, neuropsychimetric testing may help define subsets of people with SS in whom factors such as depression, anxiety or conditions such as attention deficit disorder may be treated. Sleep apnea syndrome should also be excluded or investigated in these patients.

Certain organ manifestations require subtle approaches: cutaneous manifestations—treatment of cutaneous manifestations of SS varies by the condition. Pruritus is largely managed symptomatically. Attention to the role of skin dryness (xerodermia due to affected sebaceous glands by SS infiltrates) and possible neuropathy are important. The treatment of most cardiopulmonary manifestations, including interstitial lung disease, pulmonary hypertension, and myocarditis, is approached in the same way as in patients with other systemic rheumatic disorders, such as SLE or SSc, mainly using high-dose glucocorticoids, often combined with CYC or mycophenolate mofetil. Rituximab may also be considered.

Management of GN and Interstitial Nephritis with renal tubular acidosis (RTA): after confirming that GN is not due to SLE or amyloidosis, CSA, DMARDs discussed above and/or rituximab may be used in GN. After confirming that RTA is not due to other causes, bicarbonate is the main drug used to balance the urinary pH in RTA. Treatment of thrombotic glomerulopathy or microangiopathy caused by APS in SS is carried out according to APS protocols. Treatment of any of the various gastrointestinal disorders associated with SS requires a careful diagnostic evaluation and appropriate therapeutic interventions for the primary disorder (e.g. gastroesophageal reflux or dysmotility), and for aspects of the SS that may be contributing to the disorder (e.g. treatment with secretagogues to improve salivary flow). Associated conditions [e.g. caeliac disease or primary biliary cholangitis (cirrhosis)] should be identified and treated as in patients without SS. The treatment of neurologic manifestations differs depending upon the specific involvement, which may include several forms of peripheral neuropathy—especially sensory polyneuropathy, autonomic dysfunction, and central nervous system involvement. Symptomatic therapies for neuropathic pain should avoid the use of anticholinergic agents, which increase dryness. Vasculitis (cryoglobulinemia) and its related neuropathy may require glucocorticoids and immunosuppressive therapies (rituximab). The majority of patients with leukopenia do not require specific therapy. Immune thrombocytopaenic purpura is treated as in other rheumatic diseases. We evaluate monoclonal proteins according to the guidelines recommended for monoclonal gammopathy of undetermined significance and monitor relevant laboratory abnormalities (gradient, ß2 microglobuline level) on a regular basis, unless specific symptoms arise suggesting the development of a haematologic malignancy. Treatment of lymphomas in patients with SS uses the same regimens as in patients without SS, although the management of extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in SS requires particular attention.

There are a large variety of treatments for pSS patients that mainly follow the guidelines for other disciplines or entities. As such, there has been no approval for a new therapeutic for pSS in recent decades. However, new therapies are becoming available for rational testing in pSS. A main obstacle is related to a new insight into pSS pathogenesis: glandular and extraglandular dysfunction with fatigue may merge in a node of interaction at the interface of immunoneurology or neuroimmunology. This requires either new therapeutic combination strategies or identification of new targets. Meanwhile, we need to test promising immune interventions on the subcellular level, such as in signalling pathways, in the hope that we can identify the key nodes of interaction of these systems.

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