

Towards Small Molecules in the Treatment of Sjögren's Syndrome: Current Therapy and Future Directions

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I. Abstract

Sjögren's syndrome (SS) is usually described as having "benign symptoms" (dryness of mouth and eyes), and *extraglandular* (systemic) manifestations (such as joint, neurologic, lung, cardiac, kidney, skin, gastrointestinal, neurologic and hematologic/mainly lymphoproliferative). The "benign symptoms" also include the "fibromyalgia" symptoms often associated with neurocognitive dysfunction.

Clinical trials have generally failed because the vast majority of enrolled patients had only "benign" symptoms at time of enrollment which did not significantly respond to the study medication, even though their extraglandular symptoms might have shown improvement. Since only a minority of enrolled pSS patients had extraglandular symptoms, the overall trial failed to meet its end point. Therapy for some extraglandular manifestations are particularly difficult to treat, such as peripheral and central neuropathies..

A number of hypothesis on the pathogenesis of pSS have been put forward, including 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, as well as for the fatigue and cognitive deficits.

This chapter reviews current small molecules used in the benign and extraglandular manifestations of SS. As a result of the repeated failures of trials in recent years, we suggest new directions that concentrate on collaboration with neurochemists who have brought new therapies to conditions such as multiple sclerosis and migraine.

In addition, we wish to provide a convenient site for both expert opinion guidelines and references that are required for successful drug development. Given the inadequacies and limitations of current treatment options, it suggests that innovative directions involving interactions with neuroscientists and neuropsychiatrists together or combined with new immune targeting may be hold promise for better treating Sjögren's.

II. Introduction

This chapter will first review the **current guidelines of the British and American Rheumatology Societies** for therapy of both *"benign"* and *"extraglandular"* symptoms.

The search for a "golden bullet" or "holy grail" that will improve the benign symptoms that afflict the vast majority of patients with Sjögren's syndrome has not yet been achieved. As a result, the expense of treating SS patients is second only to Rheumatoid Arthritis (RA), 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 on improving associated Sjögren's.

Guidelines from the Sjogren's Syndrome Foundation for American rheumatologists by Carsons et al [1] <https://www.sjogrens.org/files/research/RheumatologyCPG.pdf> as well as guidelines to topical therapy as recognized by the British Society of Rheumatology [2] have been published and can be accessed online:

<https://adademic.oup.com/rheumatology/article-abstract/56/10/e24/3895127>.

A European initiative [2] is also in line with these recommendations.

These guidelines include treatment guidelines for dry eyes, Meibomian gland dysfunction (MGD), 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 EMA is oral pilocarpine and by the United States Federal Drug Administration (FDA) are **oral pilocarpine** and *cevimeline*. For **ocular** topical use *cyclosporine* and *liftegrast* 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 [3]."

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 [4-6] or in particular areas of the brain cortex [7, 8].

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, Sjögren's 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 [9].

Based on these introductory remarks, this chapter will review the value of small molecules used in therapy of extraglandular manifestations pSS. It is worth noting that these have generally not arrived at late stage of development including seek for approval, but some hold promise to change the life of our pSS patients. Here, **we will look to the future of small molecules through the lens of unmet needs which concern 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) where the molecular basis of symptoms and therapeutic trials are being developed further.

III. Why Clinical Trials have Failed in Sjogren's Syndrome

A recent review article [10] entitled "*Why Clinical Trials Fail in Sjogren's*" outlines several basic points that may be overlooked in regular review articles. This article reviewed that past 20 trials in Sjögren's following the same basic clinical guidelines for recruitment and endpoints.

There is reason to be believe that it is time to change or shift this paradigm.

- **Either the patient recruitment subgroups have to be better defined, strictly using the new ACR/EULAR criteria [11] with defined disease activity [12].**
- **or more appropriate endpoints for success, such as ESSDAI and ESSPRI have been recently more widely used as validated instruments [12].**

Regarding systemic complications, a number of new insights of cytokine abnormalities in Sjögren's need to be considered. A recent study, Bodewes et al [13] 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 correlated 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 IFNN inactive patients. 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. [14] assessed the IFN type I signature by SIGLEC1 (CD169) and IFN- γ -inducible protein-10 (IP-10) profiles. Activated type I IFN was detected in 64.5% by SIGLEC-1 and 78.9% for IP-10 in pSS. SIGLEC1 expression was especially correlated with extraglandular manifestations (16/16, 100%) compared to 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 interest 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.

IV. Efficacy of Specific Therapeutic Agents in Current Clinical Use

So far not a single immunosuppressive agent has been approved for patients with Sjögren's syndrome. 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 for glandular enlargement - but not for sicca symptoms - may be observed, in our experience. Usually short-term use of GC permit control over glandular enlargements. In a small randomized trial, treatment with neither prednisolone (30 mg every other day) nor piroxicam (20 mg/day), compared with placebo, resulted in substantial changes after six months in salivary and lacrimal gland function or salivary gland histopathology [15]. Long-term use of glucocorticoids in pSS should be avoided due to potential side effects, including osteoporosis, hyperglycemia, 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 dose [16, 17].

Glucocorticoids are sometimes used to treat systemic manifestations of pSS in a manner similar to that in other systemic rheumatic and autoimmune diseases [18]. In an analysis of 1120 Spanish patients with primary SS, low-dose glucocorticoids (equivalent of prednisolone ≤ 20 mg/day) were used for this purpose in 19 percent of patients [19]. As long as there is no valid benefit/risk evaluation for GC in pSS, the use of GC should be limited in dose and duration and if possible avoided.

Conventional immunosuppressive drugs and (nonbiologic) synthetic DMARDs — Synthetic disease-modifying antirheumatic drugs (sDMARDs) are primarily used to treat specific organ manifestations in a manner similar to systemic lupus erythematosus (SLE), particularly to taper

or replace 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 various organ manifestations, available data are very limited. Briefly, clinical trials of these agents have included the following:

- **Hydroxychloroquine** – Therapy with hydroxychloroquine (HCQ) is largely based upon its efficacy in SLE [20]. In particular, the Canadian cohort study was a “withdrawal” study in which the number of flares increased after removing HCQ in a blinded trial was small but significant. The symptoms and signs improved on reintroduction of HCQ.

Also, HCQ had been shown effective in “subacute lupus” (annular erythema) [21] which is now recognized as a SS manifestation.

Small, open-label trials and observational studies have found improvement in arthralgias, myalgias, when acute phase reactants and hypergammaglobulinemia were present [22]. However, a randomized placebo-controlled trial involving SS patients did not show benefit on dryness, pain and fatigue at 6 months [22]. The apparent discrepancy in these results of HCQ is most likely due to the size and clinical characteristics of patients in each study. The longterm benefit of HCQ in pSS, regarding prevention of systemic complications and lymphomas remains to be studied. Of note, in SLE, use of HCQ has been reported to result in increased survival [23]. Clinical experience mandate HCQ as the DMARD of choice in pSS in the absence of other more potent options, also given its tolerability by the patients and known, manageable safety profile.

- **Methotrexate**– A one-year pilot study of methotrexate (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 [24]. However, no improvement in objective parameters of dry eyes and dry mouth was observed [24]. A retrospective case review of articular manifestations in a large French cohort also reported benefit in 11 of 12 SS patients treated with methotrexate for musculoskeletal pain[25, 26].
- **Azathioprine** – In a randomized trial of low-dose azathioprine (1 mg/kg/day) in 25 patients with primary SS, there was no significant change in disease activity over a period of six months [27]. However, azathioprine is commonly used in the management of specific extraglandular involvement, such as interstitial pneumonitis, myelopathy, and chronic active autoimmune hepatitis[28].

- **Leflunomide**– In an open-label pilot study, leflunomide (20 mg/day) provided only modest benefits for 15 patients with early and active primary SS [29]. 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, leflunomide 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 [30].
- **Mycophenolic Acid** – In an open-label pilot study of 11 patients with primary SS, mycophenolate in doses up to 1440 mg/day for six months did not improve objective measures of ocular or oral dryness, but did lead to significant reductions in hypergammaglobulinemia and rheumatoid factor (RF), and an increase in complement and white blood count levels [31].
- **Cyclosporine A**– Two randomized controlled trials have been reported in pSS. In one randomized trial, cyclosporine (5 mg/kg/day) resulted in symptomatic improvement of dry mouth at six months, compared with placebo, but no change in dry eye symptoms or objective parameters of ocular and oral dryness [32]. In an open-label extension, labial gland histopathology worsened at 12 months in cyclosporine-treated patients [32]. Another phase II open study with 30 pSS patients focused on the articular involvement and CyA [33]. Here treatment consisted of approximately 2 mg/kg of CyA. The primary endpoint was defined as a reduction in the number of painful and/or swollen joints at end of treatment. The mean number of swollen joints (66 counts) was reduced from 3.2 (\pm 3.3) at BL 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 the 68/66 joint counts. The disease activity score (DAS28) showed a statistically and clinically meaningful decrease over the 16-week period of treatment. Treatment was well tolerated, and adverse events were consistent with the known safety profile of CyA (e.g., hypertension, headache). This study arrived at the conclusion that CyA treatment is an efficacious option for articular involvements in pSS.

V. **Biologic Agents have been shown efficacious for use in extraglandular manifestations**

Several **biologic agents** are recommended for pSS in the treatment guidelines from both the British and American Rheumatology groups as well as the European Consensus group in certain clinical situations. They are briefly reviewed below since SS patients may show benefit 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 [34]. 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 [35] 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 [36] [37], although the suitability of these outcome measures has been questioned. As noted above, the drug has been reported to be of benefit for specific extraglandular manifestations in retrospective case series and registry analyses [38, 39], and 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 decrease in ESSDAI at 28 weeks [40, 41]. Saliva flow, Schirmer’s testing, and salivary biopsy focus score results did not change. However, there was improvement in nonmalignant parotid enlargement, arthritis/arthritis, and in B-cell biomarker values, including serum immunoglobulin and RF levels. Of particular note, responding patients showed further improvement over a subsequent 6 months, in particular for fatigue [31]. This may support the idea that longterm anti-cytokine therapy may have an effect on neuroimmune abnormalities in Sjögren’s.
- 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 Sjögren’s (Dörner T. et al. ACR 2016, Washington, DC, oral presentation). A single infusion showed improvements in several domains of ESSPRI including patients’ VAS. This drug is currently evaluated in a larger multicenter RCTs.
- **Abatacept (Orencia®) (CTLA fusion protein)**– CTLA4 is a negative regulator of T-cell function and one polymorphic SNP (single nucleotide polymorphism) has been associated with extraglandular manifestations[42]. An open-label pilot study of 11 patients has shown improvement in salivary gland biopsy and extraglandular manifestations, and a good safety profile [43]. Abatacept was found to improve saliva flow in a small cohort of treated RA patients[44]. Thompson et al [44] showed the possible synergy of tacrolimus and abatacept in lymphocytic interstitial pneumonitis, indicating a future direction of combining biologics with small molecules [44]. Another open-label study of 15 SS patients showed improvement in ESSDAI and biomarkers but no change

in tear flow or subjective symptoms [45]. Overall the use of CTLA4 antibodies holds promise in pSS based on these initial open studies while further RCT data are awaited.

- A non-depleting **anti-CD40 antibody (CFZ533)**[46] recently has shown significant improvement in SS patients with high extraglandular activity with improved ESSDAI [47] in a randomized placebo controlled trial and modest improvement in saliva.

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

VI. Toward the Future: Other Areas of 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 also to win-win situations for both disciplines [48]. Although the era of biologic treatment modalities have not led to any approval for pSS, the arrival of Jak inhibitors in RA (tofacitinib and baricitinib) with additional compounds at late stage/close to approval (upadacitinib, filgotinib) as well as other target molecules (BTK, Syk, Tyk, Akt etc.) in the RA space generates new hope for immunomodulation in Sjögren's syndrome.

Below we will briefly discuss potential candidates considered that may have the potential 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.

- a. **Fingolimod** that affects sphingosine pathways [49] and its derivatives such as ozanimod [50], since the S1P receptor is present on salivary and lacrimal glands. It is also important to retract lymphocytes within germinal center structures and as such prevents spreading of autoimmune responses. Interesting data of ozanimod in MS show [51] promising effects in preventing MRI lesions. A critical question is how brain-selective S1P1 inhibition is while the glandular effects require detailed assessment in pSS.
- b. **Sirtuin agonist or inhibitors** (silent information regulators) that affect epigenetic regulation of rDNA and NFK-B pathways [52] that play a role in diabetic neurologic dysfunction including their dryness symptoms.

- c. **NLRP3 (pyrin domain) inhibitors such as MCC950** that have proven effective in the mouse NOD model of SS[53]
- d. **A series of miRNA and modulators of NFK-B** [54] that have benefit in murine models of SS [55]. In this context, next generation antagomir therapy may be useful for targets in pSS. However, target validation is still at early stages and requires comprehensive analysis on the genetic, epigenetic as well as proteomic, immunomic level. Taking the rather low prevalence of pSS and various organ manifestations into account, international collaborative efforts are required in order to arrive at compelling and conclusive data.
- e. **mTOR and AKT inhibitors** that influence small molecule kinases [56]; Here *rapamycin* has shown benefit in SS patients and murine models [57-61] but still further target validation is required.
- f. **PI3K/AKT signalling pathway** [62, 63]; these agents may need to be used in combination with other agents. Upstream of Akt, the regulatory kinase is PI3K with at least 4 different catalytic units (alpha, beta, gamma, delta). Recent data of 30 pSS patients studying a PI3Kdelta inhibitor (*leniolisib*) showed good bioactivity as measured by reduced pAkt but clinical outcome as captured by ESSPRI and ESSDAI did not differentiate between 20 patients on active drug versus 10 placebo treated patients. Notably, the active arm had substantially more patients with skin rashes (Dörner T, EULAR 2018, Amsterdam oral presentation).
- g. **Pathways that involve interferon signatures** that involve sialic acid lectins and IFN inducible protein 10 [14]. 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 signaling by Jak/Tyk inhibitors has potential value to study in pSS [64]. 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.
- h. **Agents such as modafinil (Provigil®)** that have proven effective in improving fatigue in multiple sclerosis [65] and could have the potential to improve fatigue in pSS, too.
- i. 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 [66]. While there is a possibility that abnormal vagus activity could be involved in pSS, compelling clinical evidence is currently not available.

VII. Recommendations and Summary

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

In patients with moderate to severe involvement, systemic medical therapy may be indicated on the background of antimalarials, including the use of immunosuppressives and biologic agents, depending upon clinical manifestations and organ system affected. The value of rituximab in pSS is limited to severe organ manifestations, such as cryoglobulinemia-related complications and vasculitis. Various sDMARDs are in use for **Musculoskeletal pain** (*hydroxychloroquine* or low-dose weekly *methotrexate*, *azathioprine*, *leflunomide*). **Fibromyalgia** is treated with physical therapy and agents with strong anticholinergic properties. In patients with fatigue, treatment comprises initially with a low-impact aerobic exercise program. In patients with fatigue refractory to exercise and other lifestyle changes, neuropsychometric testing may help define subsets where factors such as depression, anxiety or conditions such as attention deficit disorder (ADD) may be treated. Sleep apnea syndrome should also be 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 (xeroderma due to affected sebaceous glands by SS infiltrates) and possible neuropathy are important causes. 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 systemic sclerosis mainly using high dose GC often combined with cyclophosphamide or mycophenolate mofetil. Rituximab may also be considered.

Management of glomerulonephritis (GN) and **Interstitial Nephritis with renal tubular acidosis (RTA)**: After excluding that GN is not due to SLE or amyloid, the use of corticosteroids, DMARDs discussed above and/or *rituximab* may be used in GN. After excluding 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 antiphospholipid syndrome (APS)

in SS is according 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., celiac disease or primary biliary cholangitis [cirrhosis]) should be identified and treated as in patients without SS. **Neurologic manifestations** – 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)- related neuropathy may require glucocorticoids and immunosuppressive therapies (rituximab). The majority of patients with leukopenia do not require specific therapy. Immune thrombocytopenic purpura is treated as in other rheumatic diseases. We evaluate monoclonal proteins according to guidelines recommended for monoclonal gammopathy of undetermined significance and monitor relevant laboratory studies on an annual basis unless specific symptoms arise suggesting the development of a hematologic malignancy. Treatment of **lymphomas** seen 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 is a large variety of different treatments that mainly follow experiences in other disciplines or entities. As such, there has been no approval for a new therapeutic for pSS for the last decades. However, new principles became and become available for rational testing in pSS. A main obstacle is related to new insight into pSS pathogenesis where glandular, extraglandular dysfunction with fatigue may merge in a node of interaction at the interface of immunoneurology or neuroimmunology. This also 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 signaling pathways in the hope that we tackle key node of interaction of both systems.

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