Treatment of Exocrine Gland Disease in pSS

Subjects: Rheumatology

Contributor: Weizhen Zeng , Xinyao Zhou , Sulan Yu , Ruihua Liu , Chrystie Wan Ning Quek , Haozhe Yu , Ryan Yong Kiat Tay , Yun Feng , Xiang Lin

Primary Sjögren's syndrome (pSS) is a chronic, systemic autoimmune disease defined by exocrine gland hypofunction resulting in dry eyes and dry mouth.

primary Sjögren's syndrome dryness fatigue

1. Introduction

Sjögren's syndrome is a chronic systemic autoimmune disorder characterized by the destruction and diminished function of exocrine glands, mainly salivary and lacrimal glands, resulting in dry eyes and dry mouth [1]. In primary or secondary form, the disease is characterized by the gradual infiltration of lymphocytic cells and atrophy of glandular and ductal cells.

Primary Sjögren's syndrome (pSS) has become increasingly common with a prevalence of 0.3%~3% among the public. Clinical manifestations of the disease are largely classified into exocrine gland and extraglandular disease features, which may be associated with widespread systemic complications involving the thyroid, lungs, kidneys, liver, and nervous system. A wide range of cognitive issues in pSS have also been reported, where persistent fatigue occurs in approximately 70% of pSS patients. The dryness and fatigue symptoms of pSS often impose detrimental effects on quality of life, as patients suffer from difficulties in eating, sleeping, and interacting with others [2].

Consensus on the cytokines and molecular entities involved in the initiation and maintenance of chronic immune activation in the disease remains difficult to elucidate [1][3]. Currently, the literature surrounding these therapies remains fragmented and no studies has been done to link the cytokines involved in pSS to the novel biological agents. Recent studies on novel drugs have shown promising results for the improvement of disease prognosis but unintended effects on the immune system, a variety of complications, and rising costs for patients [4]. In addition, ESSDAI (EULAR Sjögren's syndrome disease activity index), which is a primary outcome measure in most trials, does not include certain common symptoms such as vaginal dryness (occurring in up to 64% of female patients) [5] [6], fatigue (70% of patients) [7], and mental effects (over 30% of patients) [8].

2. Treatment of Exocrine Gland Disease in pSS

2.1. Dry Mouth (Xerostomia)

Salivary hypofunction leads to xerostomia in pSS patients. Dysphonia, dysphagia, stomatopyrosis (burning mouth), dysgeusia (altered taste), tooth erosion, and oral infections are common problems caused by xerostomia [9]. Current treatments include oral swabs, lip moisturizers, topical saliva substitutes, muscarinic agonists, scheduled use of ice water, electrostimulation, and acupuncture [10][11]. Though not life-threatening, dysphagia and awakening from sleep due to oral dryness are debilitating consequences of xerostomia [12], which beg the advancement of drug therapies beyond symptom relief [13].

Although type I interferon (IFN) is a pro-inflammatory cytokine, low-dose IFNα treatment was found to increase aquaporin-5 transcription and protein production in human parotid gland tissue, resulting in enhanced saliva and tear secretion. Administration of 150 IU of oral IFNα three times daily demonstrated the greatest potential in improving salivary output in one study [14]. However, multiple adverse effects were discovered, including a flu-like syndrome, chest pain and arthropathy, central nervous system depression, and myelosuppression [14][15]. Alternatively, 10–15 mg weekly dose of methotrexate resulted in increased salivary flow rate [16]. Eculizumab, a humanized mAb binding to complement protein C5, has been shown to ameliorate fatigue in myasthenia gravis and may be considered for the alleviation of fatigue in pSS [17].

2.2. Dry Eye

Dry-eye disease (DED) manifests as itching, grittiness, irritation, foreign body sensation, and blurry vision in pSS patients [18]. Anti-inflammatory therapies for pSS-DED include DMARDs (disease-modifying anti-rheumatic drugs) such as iguratimod and methotrexate, topical corticosteroids (1% methylprednisolone), antibiotics (azithromycin, doxycycline, and minocycline), and immunosuppressive agents (cyclosporine A and tacrolimus) [19]. The variety of systemic and topical drugs and the intricate titration of doses pose a challenge to developing treatment for dry-eye disease (DED). Mediators in driving the lacrimal pathology, and the latest drugs being trialed for the relief of pSS-DED are discussed.

Varieties of drugs targeting T cells have been considered in DED treatment. Abacept (NCT02067910, NCT04186871, NCT02915159) is a selective T cell costimulation inhibitor that may improving tear secretion in pSS by engaging CD28 and suppressing antigen-presenting cells. Baminercept, a lymphotoxin β receptor IgG fusion protein, inhibits differentiation and proliferation of T cells and decreases CXCL13 levels, which is associated with ectopic lymphocytic structures in the lacrimal and salivary glands of pSS patients [20]. However, the phase II trial failed to significantly improve either glandular or extraglandular pathology in pSS [21]. The combination of lulizumab (an anti-CD28 domain antibody antagonist) and BMS-986142 (a highly selective BTK inhibitor) is being trialed. Lastly, while hydroxychloroquine (HCQ) was recommended by the European League Against Rheumatism (EULAR) as an effective suppressor of effector T cells, it did not improve tear film break-up time and ocular surface disease index in a recent trial [22]. This was further supported by a meta-analysis, where the efficacy and efficiency of HCQ in relieving eye dryness was limited [23].

Other candidates for DED treatment are drugs targeting cysteine protease cathepsin S (CatS). CatS may play a crucial role in MHCII processing and T cell stimulation, as it was found to be elevated in the tears of pSS patients.

RO5459072, a CatS inhibitor, caused a dose-dependent downregulation of CatS/MHCII-mediated effect and may be a potential target for treatment [24].

There are also emerging biological agents targeting Th1/Th17 cytokines and B cell activating factor (BAFF) pathways. DMARDs such as leflunomide and anti-TNF, which ameliorate dryness symptoms in rheumatoid arthritis (RA) patients, may also be considered in pSS patients [25][26]. Topical use is preferred due to the side effects of these systemic immunosuppressants. Finally, 0.005%/0.01% lacripep and 0.05% cyclosporine eyedrops have also exhibited promising efficacy in relieving symptoms in pSS [27].

2.3. Vaginal Dryness and Dyspareunia

Women with pSS may suffer from vulvovaginal dryness, vulvar pruritus, and dyspareunia, partially similar to that in postmenopausal women. Histopathological assessment of vaginal mucosa biopsies displayed subepithelial inflammation, with lymphocytic infiltrations of CD45+, CD3+, and B cells occurring more frequently in pSS patients. It has been postulated that this is induced by IFN-mediated CXCL10 and/or JAK-STAT pathways [6]. Lymphocytic infiltration resulting in decreased transudation of serous fluid into the vaginal vault has also been hypothesized. Clinical trials of interest are those on parsaclisib and abatacept. The results are highly anticipated as possible future therapies for vaginal symptoms in pSS.

2.4. Fatigue in pSS

Current trials often neglect the treatment of extraglandular symptoms such as fatigue, depression, and anxiety. Approximately 70% of pSS patients claim persistent fatigue [28][29]. Evidently, fatigue has significant effects on quality of life, rendering it as one of the key issues in pSS clinical management. Despite being the most common symptom in pSS, the immunology behind fatigue has yet to be established. Currently, factors involved in mechanisms causing fatigue in pSS include IL-1, IL-36α, and humoral autoimmunity.

2.4.1. IL-1

IL-1 is a pro-inflammatory cytokine that exists in two biologically active forms: IL-1α and IL-1β [30][31]. Pharmacological experiments have shown that systemic administration of IL-1β to rats and mice induced a reduction in exercise activity, less food and water intake, social withdrawal, increase in slow wave sleep, and cognitive changes in a dose- and time-dependent manner that parallels human fatigue [32]. Studies have found that increased levels of IL-1 receptor antagonist (IL-1Ra) in the cerebrospinal fluid of pSS patients was associated with greater fatigue [33]. This was further supported by a cohort study (n = 49) that showed a higher association with serum IL-1β and hypocretin-1. Interestingly, hypocretin-1, the main regulator of sleep and wakefulness, is possibly driven by the IL-6/tumor necrosis factor α (TNF-α) axis, thus causing fatigue in pSS [34].

Treatment of fatigue in pSS has been challenging; however, inspiration may be drawn from a randomized study in which canakinumab, a human anti-IL-1β monoclonal antibody, improved the Short-Form Vitality 36 score from 12.0 to 48.3 in patients with gout [35]. Thus, targeting IL-1 may be an option for relieving fatigue in pSS.

2.4.2. IL-36α

As mentioned, IL-36α plays a role in pSS mechanisms. Interestingly, compared with pSS patients who did not experience fatigue, the expression of IL-36α was up-regulated in patients with fatigue [36]. Although there was no overt evidence for the function of IL-36α in causing fatigue in pSS, this possibility should be considered.

2.4.3. Immunoglobulins

It is speculated that the fatigue in pSS patients may be related to humoral autoimmunity. One study showed that the Fatigue Scale 14 in a sub-healthy population negatively correlated with their serum immunoglobulin A (IgA) and IgG levels. This was further corroborated by a cross-sectional study that demonstrated a positive correlation between increased IgG levels and risk of pSS-related fatigue [37].

2.4.4. Other Mediators

Recent studies found that the intensity of fatigue based on the Profile of Fatigue Questionnaire was negatively correlated with several pro-inflammatory cytokines, including IFN-γ, TNF-α, lymphotoxin α, and CXCL10 [38][39]. Analysis by logistic regression model revealed that lower levels of IFN-γ and CXCL10 with increases in reported pain and depression were the most important predictors of fatigue [38]. This constitutes an argument against the role of inflammation in the pathogenesis of fatigue in pSS; more research is needed given its prevalence and pervasiveness.

2.4.5. Alternative Medicine

The future of pSS therapy should consist of a blend of Western and alternative medicine, tapping their synergistic potential while maintaining a balance to minimize the risk of drug–drug interactions. Total glucosides of paeony (TGP), derived from the herb root of the Paeonia lactiflora pall, was approved by the Food and Drug Administration of China to enter the market as a DMARD since 1998. A multi-center study found that TGP improved fatigue VAS scores [40]. The mechanisms are based on the balancing of Th1/Th2 cytokines and reduction of IFN-γ, interleukin-4 (IL-4), Fas, and FasL expression, as revealed on serological assessment [41]. Acupuncture therapy is a well-recognized approach by the public for relieving fatigue. A protocol for a trial was published in 2017 [42], and ongoing study of acupuncture treatment in pSS may provide evidence for it ameliorating fatigue.

2.4.6. Anti-Inflammatory and Immunosuppressive Treatment for Fatigue

The therapies targeting IL-1, IL-36α, and immunoglobulins for pSS-related fatigue and current treatments, efficacies, and adverse effects are as follows, mainly including hydroxychloroquine (HCQ), rituximab, and TNF-α inhibitors.

A retrospective study of sham-needle-free group in 1996 reported that about one-third of systemic lupus erythematosus (SLE) patients with SS treated with HCQ had an improvement in fatigue [43]. Based on this, HCQ has been considered for the treatment of fatigue symptoms in pSS. Although a randomized experiment completed

in 2012 (NCT00632866) found that HCQ has limited efficacy in improving fatigue [44], the 2016 guidelines continue to support the use of HCQ in selected situations [45].

Rituximab is associated with better visual analogue scale (VAS) scores for fatigue in 17 pSS patients receiving 1000 mg rituximab for 6 months [46]. A larger trial (n = 120) had similar findings, where VAS scores for fatigue in patients treated with rituximab were also improved [47] due to the elimination of B cell-mediated immune response and immunoglobulin productions.

A pilot study reported that fatigue symptoms improved in pSS patients treated with infliximab as an inhibitor against TNF-α signaling [48]. A hypothesis from an in vitro study suggested that, apart from the blockage of circulating TNF-α molecules, infliximab also has the added function of inhibiting membrane-bound TNF-α. This may explain why infliximab-mediated interruption has a longer duration of action compared with etanercept, which does not improve fatigue because the receptor fusion protein detaches from membrane-bound TNF-α [49]. Similarly, there is a lack of evidence on whether the latest biological drugs, such as anakinra (NCT00683345) [50], abatacept (2009-015558-40) [51], belimumab [52], and epalizumab [53] could be applied for treating fatigue in patients with pSS.

Additionally, dehydroepiandrosterone (DHEA) has been proposed as a treatment for several autoimmune diseases. However, a trial suggested that there were no significant differences in fatigue between pSS patients treated with DHEA or placebo [54]. These findings were supported by another study (NCT00543166) that demonstrated that DHEA substitution treatment in DHEA-deficient and severely fatigued patients with pSS did not significantly improve fatigue compared to the placebo [55].

2.5. Depression and Anxiety in pSS

Psychological complications frequently disturb patients with fatigue and pain [56][57]. Depression and anxiety occurs in 36.9% and 33.8% of pSS patients in China [58]. In France, anxiety (pSS: 41.5%, non-pSS:39.5%) and depression (pSS: 28.3%, non-pSS: 26.7%) happen more frequently in pSS patients [59]. A study found that patients who experienced more pain, fatigue, worse oral hygiene, and swallowing disorders also had greater anxiety and depression. In female pSS patients, pain (β = 0.025, p = 0.028) and fatigue levels (β = 0.029, p = 0.004) were associated with anxiety, while pain (β = 0.022, p = 0.047), fatigue (β = 0.033, p = 0.001), and xeroderma scores (β = 0.030, p = 0.003) were strongly associated with depression [57]. Meanwhile, oral health (OR = 0.956, $p < 0.05$) and swallowing disorders (OR = 1.036, $p < 0.05$) were significantly associated with anxiety, while fatigue (OR = 0.587, $p < 0.05$) was positively correlated with depression in pSS [8][57].

To date, the underlying mechanisms of depression or anxiety in pSS remain unclear, although neurobiological factors are speculated. A recent hypothesis suggests that depression may be attributed to neuronal serotonergic and noradrenergic dysfunction, the change of dopamine and brain-derived neurotrophic factor (BDNF), and hyperactivity of hypothalamic–pituitary–adrenal (HPA) axis in the central nervous system. Additionally, gut microbe and amino acid metabolism and autoAbs against neuropeptides have also been considered to be involved in the pathological mechanisms of depression [60]. Early studies reported relatively higher serum autoAbs against α-

melanocyte-stimulating hormone (MSH) in pSS patients compared with health controls. This was highly correlated with anxiety states [61], which may result from dysregulation of melanocortin system. A study found an association between humoral autoimmunity and cytokines with depression [62]. While these findings were similar to those in animal models, greater information is needed about anxiety and depression in humans.

Interestingly, BAFF transgenic mice were established to research the mechanisms of anxiety, supporting the notion that humoral autoimmunity may partially be responsible for brain inflammation, impaired neurogenesis (stress-related brain responses), and hippocampal plasticity, leading to pSS-related anxiety [63]. Notably, using the same model, further studies suggested that dietary supplementation with *n*-3 polyunsaturated fatty acids could inhibit hippocampal microglial activation and increase hippocampal progenitor cell proliferation and plasticity [64], thus validating the effect of humoral autoimmunity-mediated neuroinflammation on depression. Given the possible role of BAFF in depression, it is worthwhile to explore the BAFF-targeted drugs mentioned above.

Except for regular drug options like serotonin selective reuptake inhibitors (SSRIs) [65], compelling evidence has suggested that traditional Chinese medicine can relieve anxiety and depression in pSS [66], including the influence of BAFF production and endocrine hormone levels. Additionally, in a randomized-controlled trial (*n* = 45) (NCT02370225), aerobic exercise greatly improved life quality by relieving fatigue and depression, further supported by studies showing supervised walking as beneficial for female pSS patients [67]. Additionally, acupuncture (NCT02691377) and dehydroepiandrosterone (NCT00391924) were also shown to have favorable effects on depression and anxiety, though the mechanisms remain unclear. Thus, a combination of neuroinflammation resolution and aerobic exercise may be considered as alternative approaches for treating pSS patients with depression or anxiety.

References

1. Mavragani, C.P. Mechanisms and New Strategies for Primary Sjögren's Syndrome. Annu. Rev. Med. 2017, 68, 331–343.
2. Perera, S.; Ma, L.; Punwaney, R.; Ramachandran, S. Clinical and Cost Burden of Primary Sjögren's Syndrome: Descriptive Analysis Using a US Administrative Claims Database. J. Health Econ. Outcomes Res. 2017, 5, 150–161.
3. Nocturne, G.; Mariette, X. B cells in the pathogenesis of primary Sjögren syndrome. Nat. Rev. Rheumatol. 2018, 14, 133–145.
4. Fox, R.I.; Fox, C.M.; Gottenberg, J.E.; Dörner, T. Treatment of Sjögren's syndrome: Current therapy and future directions. Rheumatology 2021, 60, 2066–2074.
5. Oliveira, F.R.; Valim, V.; Pasoto, S.G.; Fernandes, M.L.M.S.; Lopes, M.L.L.; de Magalhães Souza Fialho, S.C.; Pinheiro, A.C.; Dos Santos, L.C.; Appenzeller, S.; Fidelix, T.; et al. 2021

recommendations of the Brazilian Society of Rheumatology for the gynecological and obstetric care of patients with Sjogren's syndrome. Adv. Rheumatol. 2021, 61, 54.

6. van Nimwegen, J.F.; van der Tuuk, K.; Liefers, S.C.; Verstappen, G.M.; Visser, A.; Wijnsma, R.F.; Vissink, A.; Hollema, H.; Mourits, M.J.E.; Bootsma, H.; et al. Vaginal dryness in primary Sjögren's syndrome: A histopathological case-control study. Rheumatology 2020, 59, 2806–2815.
7. Mæland, E.; Miyamoto, S.T.; Hammenfors, D.; Valim, V.; Jonsson, M.V. Understanding Fatigue in Sjögren's Syndrome: Outcome Measures, Biomarkers and Possible Interventions. Front. Immunol. 2021, 12, 703079.
8. Cui, Y.; Xia, L.; Li, L.; Zhao, Q.; Chen, S.; Gu, Z. Anxiety and depression in primary Sjögren's syndrome: A cross-sectional study. BMC Psychiatry 2018, 18, 131.
9. Pinto, A. Management of xerostomia and other complications of Sjögren's syndrome. Oral Maxillofac. Surg. Clin. North Am. 2014, 26, 63–73.
10. Assy, Z.; Bikker, F.J.; Picauly, O.; Brand, H.S. The association between oral dryness and use of dry-mouth interventions in Sjögren's syndrome patients. Clin. Oral Investig. 2021, 26, 1465–1475.
11. Mariette, X. . La Rev. Med. Interne 2004, 25, 287–293.
12. Choi, J.; Kim, M.; Kho, H. Oral health-related quality of life and associated factors in patients with xerostomia. Int. J. Dent. Hyg. 2021, 19, 313–322.
13. Garlapati, K.; Kammari, A.; Badam, R.K.; Surekha, B.E.; Boringi, M.; Soni, P. Meta-analysis on pharmacological therapies in the management of xerostomia in patients with Sjogren's syndrome. Immunopharmacol. Immunotoxicol. 2019, 41, 312–318.
14. Ship, J.A.; Fox, P.C.; Michalek, J.E.; Cummins, M.J.; Richards, A.B. Treatment of primary Sjögren's syndrome with low-dose natural human interferon-alpha administered by the oral mucosal route: A phase II clinical trial. IFN Protocol Study Group. J. Interferon Cytokine Res. Off. J. Int. Soc. Interferon Cytokine Res. 1999, 19, 943–951.
15. Cummins, M.J.; Papas, A.; Kammer, G.M.; Fox, P.C. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: Combined phase III results. Arthritis Rheum. 2003, 49, 585–593.
16. Skopouli, F.N.; Jagiello, P.; Tsifetaki, N.; Moutsopoulos, H.M. Methotrexate in primary Sjögren's syndrome. Clin. Exp. Rheumatol. 1996, 14, 555–558.
17. Andersen, H.; Mantegazza, R.; Wang, J.J.; O'Brien, F.; Patra, K.; Howard, J.F. Eculizumab improves fatigue in refractory generalized myasthenia gravis. Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil. 2019, 28, 2247–2254.
18. Vivino, F.B.; Bunya, V.Y.; Massaro-Giordano, G.; Johr, C.R.; Giattino, S.L.; Schorpion, A.; Shafer, B.; Peck, A.; Sivils, K.; Rasmussen, A.; et al. Sjogren's syndrome: An update on disease

pathogenesis, clinical manifestations and treatment. Clin. Immunol. 2019, 203, 81–121.

19. Thulasi, P.; Djalilian, A.R. Update in Current Diagnostics and Therapeutics of Dry Eye Disease. Ophthalmology 2017, 124, S27–S33.
20. Haskett, S.; Ding, J.; Zhang, W.; Thai, A.; Cullen, P.; Xu, S.; Petersen, B.; Kuznetsov, G.; Jandreski, L.; Hamann, S.; et al. Identification of Novel CD4+ T Cell Subsets in the Target Tissue of Sjögren's Syndrome and Their Differential Regulation by the Lymphotoxin/LIGHT Signaling Axis. J. Immunol. 2016, 197, 3806–3819.
21. St Clair, E.W.; Baer, A.N.; Wei, C.; Noaiseh, G.; Parke, A.; Coca, A.; Utset, T.O.; Genovese, M.C.; Wallace, D.J.; McNamara, J.; et al. Clinical Efficacy and Safety of Baminercept, a Lymphotoxin β Receptor Fusion Protein, in Primary Sjögren's Syndrome: Results From a Phase II Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Rheumatol. 2018, 70, 1470–1480.
22. Yoon, C.H.; Lee, H.J.; Lee, E.Y.; Lee, E.B.; Lee, W.-W.; Kim, M.K.; Wee, W.R. Effect of Hydroxychloroquine Treatment on Dry Eyes in Subjects with Primary Sjögren's Syndrome: A Double-Blind Randomized Control Study. J. Korean Med. Sci. 2016, 31, 1127–1135.
23. Wang, S.-Q.; Zhang, L.-W.; Wei, P.; Hua, H. Is hydroxychloroquine effective in treating primary Sjogren's syndrome: A systematic review and meta-analysis. BMC Musculoskelet. Disord. 2017, 18, 186.
24. Hargreaves, P.; Daoudlarian, D.; Theron, M.; Kolb, F.A.; Young, M.M.; Reis, B.; Tiaden, A.; Bannert, B.; Kyburz, D.; Manigold, T. Differential effects of specific cathepsin S inhibition in biocompartments from patients with primary Sjögren syndrome. Arthritis Res. Ther. 2019, 21, 175.
25. Shahin, A.A.; El-Agha, S.; El-Azkalany, G.S. The effect of leflunomide on the eye dryness in secondary Sjögren's syndrome associated with rheumatoid arthritis and in rheumatoid arthritis patients. Clin. Rheumatol. 2014, 33, 925–930.
26. Usuba, F.S.; De Medeiros-Ribeiro, A.C.; Novaes, P.; Aikawa, N.E.; Bonfiglioli, K.; Santo, R.M.; Bonfa, E.; Alves, M.R. Dry eye in rheumatoid arthritis patients under TNF-inhibitors: Conjunctival goblet cell as an early ocular biomarker. Sci. Rep. 2020, 10, 14054.
27. Wan, K.H.; Chen, L.J.; Young, A.L. Efficacy and Safety of Topical 0.05% Cyclosporine Eye Drops in the Treatment of Dry Eye Syndrome: A Systematic Review and Meta-analysis. Ocul. Surf. 2015, 13, 213–225.
28. Ng, W.-F.; Bowman, S.J. Primary Sjogren's syndrome: Too dry and too tired. Rheumatology 2010, 49, 844–853.
29. Strömbeck, B.; Ekdahl, C.; Manthorpe, R.; Jacobsson, L.T. Physical capacity in women with primary Sjögren's syndrome: A controlled study. Arthritis Rheum. 2003, 49, 681–688.

30. Dinarello, C.A. The IL-1 family of cytokines and receptors in rheumatic diseases. Nat. Rev. Rheumatol. 2019, 15, 612–632.
31. Migliorini, P.; Italiani, P.; Pratesi, F.; Puxeddu, I.; Boraschi, D. The IL-1 family cytokines and receptors in autoimmune diseases. Autoimmun. Rev. 2020, 19, 102617.
32. Dantzer, R. Cytokine-induced sickness behavior: Where do we stand? Brain Behav. Immun. 2001, 15, 7–24.
33. Harboe, E.; Tjensvoll, A.B.; Vefring, H.K.; Gøransson, L.G.; Kvaløy, J.T.; Omdal, R. Fatigue in primary Sjögren's syndrome—A link to sickness behaviour in animals? Brain Behav. Immun. 2009, 23, 1104–1108.
34. Bårdsen, K.; Brede, C.; Kvivik, I.; Kvaløy, J.T.; Jonsdottir, K.; Tjensvoll, A.B.; Ruoff, P.; Omdal, R. Interleukin-1-related activity and hypocretin-1 in cerebrospinal fluid contribute to fatigue in primary Sjögren's syndrome. J. Neuroinflammation 2019, 16, 102.
35. Schlesinger, N.; De Meulemeester, M.; Pikhlak, A.; Yücel, A.E.; Richard, D.; Murphy, V.; Arulmani, U.; Sallstig, P.; So, A. Canakinumab relieves symptoms of acute flares and improves health-related quality of life in patients with difficult-to-treat Gouty Arthritis by suppressing inflammation: Results of a randomized, dose-ranging study. Arthritis Res. Ther. 2011, 13, R53.
36. Bodewes, I.L.A.; van der Spek, P.J.; Leon, L.G.; Wijkhuijs, A.J.M.; van Helden-Meeuwsen, C.G.; Tas, L.; Schreurs, M.W.J.; van Daele, P.L.A.; Katsikis, P.D.; Versnel, M.A. Fatigue in Sjögren's Syndrome: A Search for Biomarkers and Treatment Targets. Front. Immunol. 2019, 10, 312.
37. Vivino, F.B.; Carsons, S.E.; Foulks, G.; Daniels, T.E.; Parke, A.; Brennan, M.T.; Forstot, S.L.; Scofield, R.H.; Hammitt, K.M. New Treatment Guidelines for Sjögren's Disease. Rheum. Dis. Clin. N. Am. 2016, 42, 531–551.
38. Davies, K.; Registry, U.P.S.S.; Mirza, K.; Tarn, J.; Howard-Tripp, N.; Bowman, S.J.; Lendrem, D.; Ng, W.-F. Fatigue in primary Sjögren's syndrome (pSS) is associated with lower levels of proinflammatory cytokines: A validation study. Rheumatol. Int. 2019, 39, 1867–1873.
39. Howard Tripp, N.; Mirza, K.; Tarn, J.; Howard-Tripp, N.; Bowman, S.J.; Lendrem, D. Fatigue in primary Sjögren's syndrome is associated with lower levels of proinflammatory cytokines. RMD Open 2016, 2, e000282.
40. Liu, X.; Li, X.; Li, X.; Li, Z.; Zhao, D.; Liu, S.; Zhang, M.; Zhang, F.; Zhu, P.; Chen, J.; et al. The efficacy and safety of total glucosides of peony in the treatment of primary Sjögren's syndrome: A multi-center, randomized, double-blinded, placebo-controlled clinical trial. Clin. Rheumatol. 2019, 38, 657–664.
41. Wu, G.; Wu, N.; Li, T.; Lu, W.; Yu, G. Total glucosides of peony ameliorates Sjögren's syndrome by affecting Th1/Th2 cytokine balance. Exp. Ther. Med. 2016, 11, 1135–1141.

42. Jiang, Q.; Zhang, H.; Pang, R.; Chen, J.; Liu, Z.; Zhou, X. Acupuncture for Primary Sjögren Syndrome (pSS) on symptomatic improvements: Study protocol for a randomized controlled trial. BMC Complement. Altern. Med. 2017, 17, 61.

43. Fox, R.I.; Dixon, R.; Guarrasi, V.; Krubel, S. Treatment of primary Sjögren's syndrome with hydroxychloroquine: A retrospective, open-label study. Lupus 1996, 5 (Suppl. 1), S31–S36.

44. Gottenberg, J.-E.; Ravaud, P.; Puéchal, X.; Le Guern, V.; Sibilia, J.; Goeb, V.; Larroche, C.; Dubost, J.J.; Rist, S.; Saraux, A.; et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: The JOQUER randomized clinical trial. JAMA 2014, 312, 249–258.

45. Carsons, S.E.; Vivino, F.B.; Parke, A.; Carteron, N.; Sankar, V.; Brasington, R.; Brennan, M.T.; Ehlers, W.; Fox, R.; Scofield, H.; et al. Treatment Guidelines for Rheumatologic Manifestations of Sjögren's Syndrome: Use of Biologic Agents, Management of Fatigue, and Inflammatory Musculoskeletal Pain. Arthritis Care Res. 2017, 69, 517–527.

46. Dass, S.; Bowman, S.J.; Vital, E.M.; Ikeda, K.; Pease, C.T.; Hamburger, J.; Richards, A.; Rauz, S.; Emery, P. Reduction of fatigue in Sjögren syndrome with rituximab: Results of a randomised, double-blind, placebo-controlled pilot study. Ann. Rheum. Dis. 2008, 67, 1541–1544.

47. Devauchelle-Pensec, V.; Mariette, X.; Jousse-Joulin, S.; Berthelot, J.-M.; Perdriger, A.; Puéchal, X.; Le Guern, V.; Sibilia, J.; Gottenberg, J.-E.; Chiche, L.; et al. Treatment of primary Sjögren syndrome with rituximab: A randomized trial. Ann. Intern. Med. 2014, 160, 233–242.

48. Steinfeld, S.D.; Demols, P.; Salmon, I.; Kiss, R.; Appelboom, T. Infliximab in patients with primary Sjögren's syndrome: A pilot study. Arthritis Rheum. 2001, 44, 2371–2375.

49. Scallon, B.; Cai, A.; Solowski, N.; Rosenberg, A.; Song, X.-Y.; Shealy, D.; Wagner, C. Binding and Functional Comparisons of Two Types of Tumor Necrosis Factor Antagonists. J. Pharmacol. Exp. Ther. 2002, 301, 418–426.

50. Norheim, K.B.; Harboe, E.; Gøransson, L.G.; Omdal, R. Interleukin-1 inhibition and fatigue in primary Sjögren's syndrome—A double blind, randomised clinical trial. PLoS ONE 2012, 7, e30123.

51. Meiners, P.M.; Vissink, A.; Kroese, F.G.M.; Spijkervet, F.K.L.; Smitt-Kamminga, N.S.; Abdulahad, W.H.; Bulthuis-Kuiper, J.; Brouwer, E.; Arends, S.; Bootsma, H. Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). Ann. Rheum. Dis. 2014, 73, 1393–1396.

52. 63. Mariette, X.; Seror, R.; Quartuccio, L.; Baron, G.; Salvin, S.; Fabris, M.; Desmoulins, F.; Nocturne, G.; Ravaud, P.; De Vita, S. Efficacy and safety of belimumab in primary Sjögren's syndrome: Results of the BELISS open-label phase II study. Ann. Rheum. Dis. 2015, 74, 526–531.

53. Steinfeld, S.D.; Tant, L.; Burmester, G.R.; Teoh, N.K.W.; Wegener, W.A.; Goldenberg, D.M.; Pradier, O. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: An open-label phase I/II study. Arthritis Res. Ther. 2006, 8, R129.
54. Hartkamp, A.; Geenen, R.; Godaert, G.L.R.; Bootsma, H.; Kruize, A.A.; Bijlsma, J.W.J.; Derksen, R.H.W.M. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren syndrome: A randomised controlled trial. Ann. Rheum. Dis. 2008, 67, 91–97.
55. Virkki, L.M.; Porola, P.; Forsblad-d'Elia, H.; Valtysdottir, S.; Solovieva, S.A.; Konttinen, Y.T. Dehydroepiandrosterone (DHEA) substitution treatment for severe fatigue in DHEA-deficient patients with primary Sjögren's syndrome. Arthritis Care Res. 2010, 62, 118–124.
56. Milic, V.; Grujic, M.; Barisic, J.; Marinkovic-Eric, J.; Duisin, D.; Cirkovic, A.; Damjanov, N. Personality, depression and anxiety in primary Sjogren's syndrome—Association with sociodemographic factors and comorbidity. PLoS ONE 2019, 14, e0210466.
57. Liu, Z.; Dong, Z.; Liang, X.; Liu, J.; Xuan, L.; Wang, J.; Zhang, G.; Hao, W. Health-related quality of life and psychological status of women with primary Sjögren's syndrome: A cross-sectional study of 304 Chinese patients. Medicine 2017, 96, e9208.
58. Hsieh, M.-C.; Hsu, C.-W.; Lu, M.-C.; Koo, M. Increased risks of psychiatric disorders in patients with primary Sjögren's syndrome-a secondary cohort analysis of nationwide, population-based health claim data. Clin. Rheumatol. 2019, 38, 3195–3203.
59. Milin, M.; Cornec, D.; Chastaing, M.; Griner, V.; Berrouiguet, S.; Nowak, E.; Marhadour, T.; Saraux, A.; Devauchelle-Pensec, V. Sicca symptoms are associated with similar fatigue, anxiety, depression, and quality-of-life impairments in patients with and without primary Sjögren's syndrome. Jt. Bone Spine 2016, 83, 681–685.
60. Peng, G.-J.; Tian, J.-S.; Gao, X.-X.; Zhou, Y.-Z.; Qin, X.-M. Research on the Pathological Mechanism and Drug Treatment Mechanism of Depression. Curr. Neuropharmacol. 2015, 13, 514–523.
61. Karaiskos, D.; Mavragani, C.P.; Sinno, M.H.; Déchelotte, P.; Zintzaras, E.; Skopouli, F.N.; Fetissov, S.O.; Moutsopoulos, H.M. Psychopathological and personality features in primary Sjogren's syndrome—Associations with autoantibodies to neuropeptides. Rheumatology 2010, 49, 1762–1769.
62. Hammett, E.K.; Fernandez-Carbonell, C.; Crayne, C.; Boneparth, A.; Cron, R.Q.; Radhakrishna, S.M. Adolescent Sjogren's syndrome presenting as psychosis: A case series. Pediatr. Rheumatol. 2020, 18, 15.
63. Crupi, R.; Cambiaghi, M.; Spatz, L.; Hen, R.; Thorn, M.; Friedman, E.; Vita, G.; Battaglia, F. Reduced Adult Neurogenesis and Altered Emotional Behaviors in Autoimmune-Prone B-Cell

Activating Factor Transgenic Mice. Biol. Psychiatry 2010, 67, 558–566.

64. Crupi, R.; Cambiaghi, M.; Deckelbaum, R.; Hansen, I.; Mindes, J.; Spina, E.; Battaglia, F. n−3 fatty acids prevent impairment of neurogenesis and synaptic plasticity in B-cell activating factor (BAFF) transgenic mice. Prev. Med. 2012, 54, S103–S108.
65. Murrough, J.W.; Yaqubi, S.; Sayed, S.; Charney, D.S. Emerging drugs for the treatment of anxiety. Expert Opin. Emerg. Drugs 2015, 20, 393–406.
66. Wu, G.-L.; Li, T.-Y. Focus on Effects of Chinese Medicine on Improving Anxiety-Depression and Quality of Life of Patients with Primary Sjögren's Syndrome. Chin. J. Integr. Med. 2020, 26, 486–489.
67. Miyamoto, S.T.; Valim, V.; Carletti, L.; Ng, W.F.; Perez, A.J.; Lendrem, D.W.; Trennel, M.; Giovelli, R.A.; Dias, L.H.; Serrano, É.V.; et al. Supervised walking improves cardiorespiratory fitness, exercise tolerance, and fatigue in women with primary Sjögren's syndrome: A randomized-controlled trial. Rheumatol. Int. 2019, 39, 227–238.