REVIEW

Short running header: Managing fatigue in patients with primary Sjögren's syndrome

Miyamoto et al

Title: Managing fatigue in patients with primary Sjögren's syndrome: challenges and solutions

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Abstract

Primary Sjögren's syndrome (pSS) patients identify fatigue as their most important symptom and the one most difficult to cope with, but there are still many challenges and few solutions to manage this debilitating symptom. Promising pharmacological treatments, such as rituximab, have failed in more stringent tests including randomized controlled trials (RCT) and meta-analysis. While non-pharmacological interventions may be safer, less costly, and address other common comorbidities, to date only aerobic exercise seems to be effective at reducing fatigue in pSS. All interventions, pharmacological or not, need to be tested in high-quality RCTs. The aim of this review is to provide an overview of fatigue management in pSS and discuss potential opportunities for future research.

Key words: primary Sjögren's syndrome, fatigue, treatment, review

Introduction

Fatigue is a hallmark of many rheumatologic conditions, including primary Sjögren's syndrome (pSS). A systemic autoimmune disease characterized by lymphocytic infiltration and progressive destruction of exocrine glands, 20-40% of pSS patients present with severe systemic manifestations.[1] Fatigue is reported in up to 70% of the pSS patients and most patients are also affected by dryness and pain.[2]

Fatigue is defined by Staud as "a subjective, unpleasant symptom that incorporates total body feelings ranging from tiredness to exhaustion, creating an unrelenting overall condition that interferes with individuals' ability to function in their normal capacity".[3] PSS patients often complain that it is their greatest problem and the most difficult to cope with.[4] They experience a heavy, resistant body and uncontrollable fluctuating fatigue.[5] Fatigue in pSS is chronic, persistent, and intractable.[6,7] In pSS its pathophysiology is unknown, and is likely to involve multiple factors.

Genetic factors have been postulated for the development of fatigue in pSS,[8,9] but there is a paucity of studies to confirm this link. Fatigue in pSS may be linked to inflammatory mechanisms. Hartkamp et al. did not find any association between the levels of fatigue and the serum levels of the inflammatory markers interleukin (IL)-1b, IL-2, IL-6, IL-10 and tumor necrosis factor alfa (TNF-α).[10] However, Howard et al. showed that lower levels of the pro-inflammatory cytokines inducible protein (IP)-10 and interferon-gamma (IFN-γ), together with pain and depression, were the most important predictors of fatigue[11]. Nonetheless, the evidence for an association between fatigue and disease activity - or any other inflammatory markers – remains controversial.[11–15]

Fatigue is known to be associated with lower aerobic capacity[16] and lower physical activity levels.[17,18] Wouters et al. have shown that pSS patients with lower physical activity, higher activity avoidance and greater somatic focus have more severe symptoms of fatigue.[19] Fatigue in pSS is associated with greater functional impairment.[20] It is possible that interventions to increase aerobic capacity and levels of physical activity may improve the symptoms of fatigue.

PSS patients also present a range of other manifestations associated with fatigue. These include sleep disturbances,[21–23] autonomic dysfunction,[24,25] depression,[11,13,15,26,27] dysfunctional or alexithymic psychological profile,[28] neuroticism and fibromyalgia.[15] These complex associations and comorbidities

require appropriate management in clinical practice based on a multi-disciplinary approach including rheumatologists and other health professionals.

A growing number of methods have been used to measure fatigue in pSS studies. Few of them used the specific instrument of the pSS, the Profile of Fatigue and Discomfort (PROFAD), whose fatigue component (Profile of Fatigue-ProF) measures the somatic (ProF-S) and mental (ProF-M) fatigue.[29,30] Instead, most studies have used a single-item instrument, the 10-cm visual analogue scale (VAS), or non-disease specific multi-item questionnaires.

Despite VAS popularity, it does not capture the multi-dimensional nature of fatigue; neither it is able to identify patients with major fatigue. However, another recent and specific disease instrument, the EULAR Sjögren's Syndrome Patients Reported Index (ESSPRI), also uses 0 to 10 numerical scales for the assessment of each of the 3 domains: dryness, fatigue and musculoskeletal pain.[4,31]

There are a range of multi-item questionnaires such as Multidimensional Fatigue Inventory (MFI)[32], Fatigue Severity Scale (FSS),[33] Functional Assessment of Cancer Therapy scale–fatigue (FACIT-fatigue),[34,35] Fatigue Impact Scale (FIS)[36] and Chalder Fatigue Scale (CFS).[37] Nevertheless, these instruments were designed initially to measure fatigue in other disorders and therefore may not necessarily be suitable for use in pSS.

Fatigue is inversely correlated with health-related quality of life[27,38,39] and with both the physical,[40,41] and the mental components of the SF-36.[41] While treatment of this disabling symptom is likely to improve patients' daily life, there is little evidence-based treatment of fatigue. This makes patient management a real challenge for rheumatologists and other health professionals. The aim of this review is to provide an overview on the management of fatigue in pSS and discuss potential targets for future research.

The main characteristics and outcomes of the selected studies are summarised in table 1.

Pharmacological treatment to treat fatigue in pSS: a real challenge

There is currently no evidence to support pharmacological treatment of fatigue in pSS. Both biological and non-biological treatments have been tried in pSS. Despite promising data from phase II studies,[42–44]

two phase III trials failed to demonstrate efficacy of rituximab (RTX) in improving fatigue in pSS.[45,46] It should be noted that for most of these clinical trials, fatigue is not the primary outcome. Instead it is often part of a composite outcome. This may reflect the substantial costs, potential adverse events, and the diversity of instruments and lack of standard, objective and validated measurements of fatigue in pSS. For other biological therapies, results from phase III trials are awaited. In addition, it is possible that biologic drugs potentially valuable to the treatment of pSS currently under investigation[47] may be effective for fatigue.

Non-biological therapies

Hydroxychloroquine (HCQ) is an antimalarial drug with an immunomodulatory effect widely prescribed in patients with pSS reporting extraglandular manifestations, such as fatigue, arthralgia, arthritis or myalgia. However, evidence supporting its efficacy in treating such symptoms are weak, and its use is based largely on clinical experience and expert recommendations.[48–51] A two year double blind crossover trial with only 19 patients[52] and a two year double blind randomized controlled trial (RCT) with 120 patients[53] did not demonstrate efficacy of HCQ for fatigue measured by its severity and VAS, respectively. These studies and one retrospective study including 50 patients who were taking hydroxychloroquine (6-7 mg/kg/day) for at least two years[54] were included in a recent meta-analysis. This concluded that effectiveness of HCQ was lower than placebo for fatigue and the most common adverse effects were gastrointestinal side effects.[55] Conversely, another multicentre retrospective study including 221 patients with at least 1 year of follow-up, showed that fatigue was less frequent in those on HCQ therapy than those in the non-treated group (16.7% vs 83.3%, $p < 0.001$).[56] Thus whether HCQ is effective for fatigue in pSS remains unclear and further research is needed.

Small open-label studies have shown improvement in general fatigue measured by MFI using leflunomide (LEF) 20 mg daily in 15 patients after 24 weeks,[57] and in fatigue VAS using zidovudine 250mg twice daily in a study including only seven patients.[58] In contrast, dehydroepiandrosterone,[59,60] gamma-linolenic acid, an essential omega-6 fatty acid,[61] and doxycycline[62] have shown no efficacy in reducing fatigue in

pSS RCTs. More recently, data from a phase II clinical trials of a combination therapy using both HCQ and LEF with 42 patients (28 active arm, 14 placebo) showed improvement in ESSPRI fatigue.[63]

There is an interesting case report of a 44-year-old pSS patient refractory to conventional treatment (prednisone, azathioprine and rituximab), presenting with severe clinical manifestations including uncontrollable fatigue, headache and hyperglobulinemic purpura, treated with bortezomib, a proteasome inhibitor licensed for the treatment of multiple myeloma. She showed a notable improvement of the general symptoms, particularly fatigue VAS, a decrease in serum globulin levels as well as in serum viscosity, and the return of the patient to her usual activities. More studies are needed to determine the safety and efficacy of this drug in patients with pSS.[64]

A recent Chinese multicentre RCT demonstrated the efficacy and safety of total glucosides of peony (TGP) in 320 patients with pSS who did not exhibit significant extra-glandular manifestations. TGP are extracted from the root of the *Paeonia lactiflora pall* and have been demonstrated to have immunomodulatory effects, such as inhibition of dendritic cell maturation and function. The results showed that ESSPRI scores improved dramatically, significantly alleviated some dryness symptoms, and improved fatigue VAS during the 24-week trial. The rate of adverse events in the TGP group was 10.9%; the main adverse event was diarrhoea at a rate of 4.8%.[65]

Biological therapies

The increasing evidence that B cells play a leading role in the pSS pathogenesis, indicates that rituximab (RTX), a chimeric anti-CD20 monoclonal antibody which acts through depletion of B cells, may be an exciting therapy. A small prospective open-label study with 16 patients receiving two low-dose RTX infusions (375mg/m^2)[42] and a RCT with 30 patients (2 infusions of 1000mg)[43] demonstrated an improvement in fatigue (VAS and MFI, respectively). However, a meta-analysis has shown that RTX is not able to reduce fatigue in pSS patients after 24 weeks.[66]

Improvement in fatigue is also observed in two other randomised controlled studies with two infusions (1000mg) of RTX. In the study by Devauchelle-Pensec et al. with 120 patients, reductions in fatigue VAS

were observed at week 6 and 16.[45] In the study by Dass et al. with 17 patients, fatigue VAS and PROFAD improvement was significantly higher than the placebo group.[44]

However, Bowman et al., in another larger RCT with 133 patients treated with two courses of RTX therapy (6 months apart), did not find significant differences in fatigue scores (VAS, ESSPRI and PROFAD) between the RTX and the placebo arms (MD 5.0, 95% CI -3.37 to 13.37).[46] Similarly, a more recent meta-analysis did not find significant differences between the RTX and placebo groups between baseline and week 24 in fatigue VAS (MD -3,24 95% CI -30,21 to 23,72).[67]

Belimumab, a monoclonal anti-BAFF antibody, is a promising biological drug to treat pSS, since 60% of the patients achieved the primary endpoint, including fatigue VAS and systemic activity, at week 28 in a prospective 1-year open-label study including 30 SS patients with systemic complications. Ten mg/kg of belimumab was administered at weeks 0, 2, and 4 and then every 4 weeks to week 24.[68,69]

Another small, open-label study including 16 pSS patients with active disease investigated the use of epratuzumab, a humanized anti-CD22 monoclonal antibody, over 4 infusions of 360 mg/m2 once every 2 weeks, with 6 months of follow-up, showing efficacy in fatigue VAS.[70]

Similarly, abatacept, a selective modulator of costimulation of T cells, seemed to be effective in improving MFI, as well EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and ESSPRI, in an open-label study including 15 patients. Eight intravenous abatacept infusions (10mg/kg) were administered over 24 weeks of treatment with a follow-up at weeks 36 and 48.[71]

TNFα blockers, however, did not improve fatigue. Infliximab showed no efficacy, including fatigue VAS, in a double-blind, placebo-RCT including 103 patients receiving infusions of 5 mg/kg at weeks 0, 2, and 6 and followed up after 22 weeks.[72]

Similarly, just four of the 15 pSS patients included in a pilot study using etanercept subcutaneously twice per week for 12 weeks, with follow up visits at 18 and 24 weeks reported reduction in MFI.[73]

Animal studies support IL-1 receptors as potential targets. Dantzer et al. report animal data demonstrating that sickness behaviour is signalled through IL-1 receptors in the brain.[74] In human studies, patients with pSS have higher levels of IL-1-RA in the cerebrospinal fluid with respect to controls, and its

concentration correlated with fatigue.[75] Norheim et al. designed a double-blind RCT including 26 patients to test anakira, a recombinant IL-1 receptor antagonist. However, while half of the patients in the active drug group reported a 50% reduction in fatigue VAS, compared to just one patient in the placebo group, there was no statistically significant reduction in the primary endpoint analysis using fatigue VAS. There were no significant changes in FSS scores between groups.[76]

May non-pharmacological interventions be potential treatments for fatigue in SSp?

Despite their potential, the only published non-pharmacological intervention that appears to be effective, but not with high quality evidence, is aerobic exercise. One problem is that complex interrelationships between physical activity, depression, sleep disturbances and pain in the pathophysiology of fatigue in pSS may make RCTs using fatigue as the primary outcome measure difficult to separate from confounding factors. However, in view of the possible adverse effects and substantial costs of biological therapies and the promising results of nonpharmacological studies from other rheumatic diseases, such interventions could be a great potential in the management of fatigue.

Exercise

While exercise is recommended for the treatment of fatigue in pSS in recent guidelines[48–51] and review studies,[77,78] this is based largely on a single, relatively small (training group=9; control group=10) non-randomized control study of aerobic exercise in pSS. This study reported improvements in fatigue VAS (but not in Profile of fatigue, Pro-F), aerobic capacity, depression and physical function. The training group performed a Nordic walking exercise three times a week for 12 weeks. The intensity of the prescribed exercise increased progressively over the training from 60-70% to a maximum of 70-80% of the age-predicted maximum heart rate (220 minus the age of the individual).[79] However, this study was not included in the systematic review of Hackett et al. on non-pharmacological treatment in pSS, as participants were not randomized.[80] Miyamoto et al., in a RCT with intention-to-treat analysis (training group=23; control group=22), demonstrated that a 16-week supervised walking program improves aerobic capacity, exercise tolerance, patient perception of improvement and fatigue measured by

Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) without exacerbating disease activity in women with pSS. Fatigue ESSPRI domain did not show a significant reduction. The intensity of the exercise was based on the heart rate at 80% of the maximum heart rate reached in the treadmill test. Increasing duration of exercise was made by time from 20 to 50 minutes of effective walking.[81]

Other interventions

Other non-pharmacological interventions are the subject of recent studies. Tarn et al. investigated the effect of a noninvasive vagus nerve stimulation device twice daily for a 26-day period in 15 female pSS patients finding a significant reduction in daytime sleepiness and Pro-F (but not in fatigue VAS). Authors suggest that the vagus nerve may play a role in the regulation of fatigue and immune responses in pSS. However, a RCT including a larger sample size is needed.[82]

Hackett et al., argue for a personalized, holistic approach, delivered by a multidisciplinary care team. This empowers patients by taking their health concerns seriously. Patients may be supported to self-managing aspects of their condition - especially their key symptoms of dryness, fatigue, pain, and poor sleep.[83] Data from 50 primary Sjögren's syndrome patients attended at the Newcastle CRESTA Fatigue clinic, a UK National Health Service multidisciplinary clinic, showed an improvement in fatigue VAS scores and were maintained at 6-12 months follow-up. After the medical review of fatigue (including autonomic dysfunction, untreated comorbidities and a medication review), therapy interventions are tailored according to the needs of the patient, and may include occupational therapy (activity management), physiotherapy (core strengthening exercises) and health psychology.[84]

One of the key interventions targeting self-management is patient education. This is defined as "planned organised learning experiences designed to support and enable people to manage life with their condition and optimise their health and well-being".[85] However, there is no study investigating the effect of a patient education program in pSS. In general chronic diseases, when compared to usual care, self-management programs have a small but statistically significant short-term improvement in fatigue, pain, disability, depression, health distress, self-rated health, and health-related quality of life, but not anxiety or depression.[86]

In addition to self-management and patient education, other psychosocial interventions have demonstrated a small benefit for managing fatigue in people with rheumatoid arthritis, such as cognitive behavioural therapy[87,88] and mindfulness.[87] But there is no study performed in pSS. Cognitive behavioural therapy (CBT) is well recognised for psychological conditions such as depression or anxiety. However, CBT is weakly recommended in the guidelines for the management of fibromyalgia,[89] and there is inconsistent to weak evidence to treat chronic fatigue syndrome.[90]

Mindfulness, a non-judgmental, present moment awareness meditation, has been shown to improve psychological well-being via improved cognitive and emotional reactivity.[91] There is only limited evidence that this and other multi-modal approaches are effective for improving patient-reported outcomes and emotional disturbances related to rheumatoid arthritis.[92]

Sleep management may be important. Current recommendations include sleeping at a regular bedtime, avoid oversleeping and schedule breaks at work or during day at home for management of fatigue.[93] Hackett et al. report an increased prevalence of sleep disturbances in pSS patients compared with controls[94] and suggest cognitive behaviour therapy for insomnia (CBT-I) may be an appropriate treatment.[23] This approach has not yet been tested in pSS, but there is evidence that it improves sleep, fatigue and other quality of life outcomes in fibromyalgia patients.[95] Usmani et al. reported a higher frequency of obstructive apneas and hypopneas detected by polysomnography in pSS. These were doubled in the pSS group compared with controls. Five patients identified as having severe sleep apnoea were treated with continuous positive airway pressure (CPAP) resulting in significant improvements in both daytime sleepiness and fatigue, but not depression or anxiety.[96]

Possible solutions

There is still a long way to go to find the solutions to manage fatigue in pSS. Certainly, the fragmented knowledge of the pathophysiological mechanisms of pSS, and especially of fatigue, is the main obstacle to find them. It is likely that basic research associated with therapeutic research may show more about the pathogenesis of SSp/fatigue and, consequently, define the most appropriate therapeutic approach. High-quality RCT for potential pharmacological and non-pharmacological interventions must be performed.

However, the recommendation for the best patient-reported outcome measures for fatigue in pSS through a systemic review with meta-analysis is an urgent and essential need to standardize the evaluation methods in the RCTs and to guarantee valid and reliable results.

New knowledge about the pathogenesis of autoimmune diseases may lead to a new therapeutic approach in pSS. It is known that Janus kinase–Signal Transducers and Activators of Transcription (JAK–STAT) pathway play a central role in the pathogenesis of autoimmune diseases.[97] Janus Kinases inhibitors (tofacitinib) have shown significant improvement in fatigue in rheumatoid arthritis,[98] but have yet to be tested in pSS. Sphingosine-1-phosphate (S1P) enhances proliferation and IFN-γ production by CD4+ T cells in pSS patients.[99] Sphingosine-1-phosphate receptor (S1PR) modulators (fingolimod and siponimod) might provide potential treatment for several autoimmune diseases[100] such as pSS.

Conclusion

Fatigue is a frequent and disabling symptom of pSS. The unknown pathophysiology of fatigue makes it difficult to determine a specific treatment for this symptom. Synthetic or biologic drugs have so far failed to show significant efficacy in improving fatigue. The role of HCQ remains unclear; RTX is questionable; leflunomide, zidovudine, bortezomib, total glucosides of peony, belimumab, epratuzumab, abatacept, etarnecept and anakira require further research. Other treatments such as dehydroepiandrosterone, gamma-linolenic acid, doxycycline, and infliximab are not effective based on available data.

Robust studies using non-pharmacological approaches are urgently needed. Non-pharmacological approaches are inherently attractive offering fewer adverse effects than drug treatments; and there is some data to support their use from other rheumatic diseases. Aerobic exercise seems to be effective and safe suggesting an important role for physical fitness in the pathogenesis of fatigue. Nonetheless long-term RCTs are needed and other types of exercise should be explored too. CPAP is considered the most efficacious method to treat sleep apnea[101]. However, the effect of CPAP or any other intervention for sleep disorders in pSS should be investigated by RCTs, as well as non-invasive vagus nerve stimulation, patient education programs or psychological techniques.

Much of the data comes from small trials, or the results of open-label studies that are not confirmed in RCTs, and there are few studies with long-term follow-up. One of the obstacles to trials in this area is the difficulties in measuring fatigue. Fatigue VAS scales may be of limited value. With the exception of PROFAD/ProF and ESSPRI fatigue domain, it is not possible to assume that the other instruments would have measures and practical properties of consistent measures in the population with pSS.

In addition, further studies exploring the pathogenesis of fatigue in pSS are crucial to guide therapeutic development. Certainly, in clinical practice, the multi-dimensional nature of fatigue suggests that effective management of pSS-associated fatigue may require a patient-centric, multidisciplinary approach.

Abbreviations

pSS: primary Sjögren's syndrome, IL: interleukin, TNF-α: tumor necrosis factor alfa, IP: inducible protein, IFN-γ: interferon-gamma, PROFAD: Profile of Fatigue and Discomfort, VAS: visual analogue scale, ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index, MFI: Multidimensional Fatigue Inventory, FSS: Fatigue Severity Scale, FACIT-fatigue: Functional Assessment of Cancer Therapy scale–fatigue, FIS: Fatigue Impact Scale, CFS: Chalder Fatigue Scale, RTX: rituximab, HCQ: hydroxychloroquine, RCT: randomized controlled trial, LEF: leflunomide, ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index, TGP: total glucosides of peony, CBT-I: cognitive behaviour therapy for insomnia, CPAP: continuous positive airway pressure, JAK–STAT: Janus kinase–Signal Transducers and Activators of Transcription, S1P: sphingosine-1-phosphate, S1PR: sphingosine-1-phosphate receptor

Disclosure

The authors report no conflicts of interest in this work.

Author's contributions

Study conception and design: STM; Acquisition of data: STM, DWL, WN and KLH; Writing: STM, DWL, WN, KLH and VV.

All authors have read and approved the manuscript.

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Table 1. Characteristics and outcomes of the studies.

Study	Country	Study design	Participants	Intervention	Follow-up	Primary outcome	Fatigue outcome measures	Fatigue improvement
Pharmacological interventions								
Non-biological therapies								
Kruize et al, 1993[52]	Netherlands	Cross-over	G1: 10 G2: 9	G1: hydroxychloroquine (400 mg/d) G2: placebo	24 months	NI	Presence and severity of fatigue	No
Gottenberg et al, 2014[53]	France	RCT	G1: 56 G2: 64	G1: hydroxychloroquine (400 mg/d) G2: placebo	48 weeks	Improvement on 2 of the VAS pain, fatigue and dryness	Fatigue VAS	No
Fox et al, 1996[54]	USA	Open-label	50	Hydroxychloroquine (6-7 mg/kg/day)	At least 24 months	NI	NI	No
Demarchi et al, 2017[56]	Argentina	Open-label	G1: 170 G2: 51	G1: hydroxychloroquine G2: non-treated	At least 3 months	NI	Presence of fatigue	Yes
van Woerkom et al, 2007[57]	Netherlands	Open-label	15	Leflunomide (20 mg/d)	3 months	Tolerability and safety	MFI	Yes (general fatigue)

Steinfeld et al, 1999[58]	Belgium	Open-label	7	Zidovudine (250mg b.i.d)	3 months	NI	Fatigue VAS	Yes
Hartkamp et al, 2008[59]	Netherlands	RCT	G1: 30 G2: 30	G1: Dehydroepiandrosterone (200 mg/d) G2: placebo	12 months	General fatigue, depressive mood, physical functioning, and mental well-being	MFI	No
Virkki et al, 2010[60]	Finland	Cross-over	G1:54 G2: 53	G1: Dehydroepiandrosterone (50mg/d) G2: placebo	9 months	General fatigue	MFI	No
Theander et al, 2002[61]	Sweden	RCT	G1: 57 G2: 30	G1: Gamma-linolenic acid (800 mg or 1600mg/d) G2: placebo	6 months	Fatigue	Fatigue VAS	No
[62](Seitsalo et al, 2007)	Finland	Cross-over	22	Doxycycline (20 mg b.i.d)	10 weeks	NI	Fatigue VAS	No
Radstake et al, 2018[63]	Netherlands	RCT	G1: 21 G2: 8	G1: leflunomide (20 mg/d) and hydroxychloroquine (400 mg b.i.d)	24 weeks	ESSDAI and stimulated whole saliva flow	MFI and ESSPRI	Yes (ESSPRI fatigue)

				G2: placebo				
Jakez-Ocampo et al, 2015[64]	Mexico	Case report	1	Bortezomib (1.3 mg/m^2, 10 days)	3 months	NI	Fatigue VAS	Yes
Liu et al, 2018[65]	China	RCT	G1: 211 G2: 103	Total glucosides of peony (600 mg t.i.d)	24 weeks	ESSPRI	Fatigue VAS	Yes
Biological therapies								
Devauchelle-Pensec et al, 2007[42]	France	Open-label	16	Rituximab (2 infusions 375 mg/m^2)	36 weeks	Safety and biologic effects	Fatigue VAS	Yes
Meijer et al, 2010[43]	Netherlands	RCT	G1: 20 G2: 10	G1: rituximab (2 infusions 1000 mg) G2: placebo	48 weeks	Stimulated whole saliva flow	MFI	Yes
Devauchelle-Pensec et al, 2014[45]	France	RCT	G1: 60 G2: 60	G1: rituximab (2 infusions 1000 mg) G2: placebo	24 weeks	Improvement on 2 of the VAS global disease, pain, fatigue and dryness	Fatigue VAS	Yes
Dass et al, 2008[44]	UK	RCT	G1: 8 G2: 9	G1: rituximab (2 infusions 1000 mg)	24 weeks	Fatigue VAS	FACIT-F, Fatigue VAS and	Yes (VAS and PROFAD)

				G2: placebo			PROFAD	
Bowman et al, 2017[46]	UK	RCT	G1: 67 G2: 66	G1: rituximab (4 infusions 1000 mg) G2: placebo	48 weeks	Fatigue and oral VAS	Fatigue VAS, ESSPRI and PROFAD	No
Mariette et al, 2015[68]; De Vita et al, 2015[69]	France/Italy	Open-label	30	Belimumab (8 infusions 10 mg/kg)	12 months	Improvement on 2 of the VAS dryness, fatigue, pain, systemic activity and C4 level.	Fatigue VAS	Yes
Steinfeld et al, 2006[70]	Belgium/ Germany	Open-label	16	Epratuzumab (4 infusions 360 mg/m2)	32 weeks	NI	Fatigue VAS	Yes
Meiners et al, 2014[71]	Netherlands	Open-label	15	Abatacept (8 infusions 10 mg/kg)	48 weeks	NI	ESSPRI and MFI	Yes
Mariette, 2004[72]	France/ Belgium	RCT	G1: 54 G2: 49	G1: Infliximab (3 infusions 5 mg/kg) G2: placebo	22 weeks	Improvement on 2 of the VAS pain, fatigue and dryness	Fatigue VAS	No
Zandbelt et al, 2004[73]	Netherlands	Open-label	15	Etanercept (25 mg b.i.d subcutaneously)	12 weeks	NI	MFI	No
Norheim et	Norway	RCT	G1: 26	G1: anakira (100 mg/d)	4 weeks	Fatigue VAS	FSS and Fatigue	No

al, 2012[76]			G2: 13	G2: placebo			VAS	
Non-pharmacological interventions								
Strömbeck et al, 2007[79]	Sweden	Non-randomized controlled trial	G1: 9 G2: 10	G1: Nordic walking (60-80% HR_{max}) G2: range of motion exercises (at home)	12 weeks	VO_{2max}	Pro-F and Fatigue VAS	Yes (Fatigue VAS)
Miyamoto et al, 2019[81]	Brazil	RCT	G1: 23 G2: 22	G1: supervised walking (80% HR_{max}) G2: no treatment	16 weeks	VO_{2max}	FACIT-F and ESSPRI	Yes (FACIT-F)
Tarn et al, 2018[82]	UK	Open-label	15	Non-invasive vagus nerve stimulation (90 sec/d)	26 days	NI	Pro-F and ESSPRI	Yes
Hacket et al, 2018[84]	UK	Open-label	50	Interdisciplinary care	12 months	NI	Fatigue VAS	Yes
Usmani et al, 2012[96]	Australia	Open-label	5	Continuous positive airway pressure (CPAP)	2-6 months	NI	FACIT-F	Yes

Abbreviations: G: group; NI: not informed; VAS: visual analogue scale; RCT: randomized controlled trial; USA: United States of America; MFI: Multidimensional Fatigue Inventory; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue; PROFAD: Profile of Fatigue and Discomfort; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; UK: United Kingdom; FSS: Fatigue Severity Scale; VO_{2max}: maximum oxygen uptake; PROF: