Advances in the treatment of ocular dryness associated with Sjögren’s syndrome

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**Introduction:**

SS is a common autoimmune rheumatic condition, associated with localised symptoms of ocular and mouth dryness as a consequence of decreased lacrimal and salivary secretion due to the lymphocyte infiltration of the exocrine glands (1, 2). The incidence of pSS varies among different populations and depends on the classification criteria used for diagnosis (3, 4). A recent meta-analysis showed an incidence of 6.92 (95% CI 4.98 to 8.86) per 100 000 person-years and overall prevalence of 60.82 (95% CI 43.69 to 77.94) cases per 100 000 (5).

The pathogenesis of dry eye symptoms associated with SS remains uncertain (6, 7); lacrimal gland infiltration with B and T lymphocytes and epithelial cells activation driven by cytotoxic T cells, together with increased apoptosis, and expression of Ro and La antibodies on the surface of apoptotic cells are considered to be the main pathogenic events associated with glandular destruction in SS (8). More recently, it was found that abnormal apoptosis, cytokine and toll-like receptor (TLR) activation and perivascular lymphocytic infiltration are present in the glandular tissue even before the onset of clinical symptoms associated with SS (9). In contrast, the systemic features of SS seem to be more associated with B cell activation, autoantibody production and polyclonal hypergammaglobulinaemia, which is likely to be linked to the increased risk of lymphoma observed in these patients (10, 11).

Despite the recent efforts of ophthalmologists to define and classify the dry eye disease (12), very few publications have critically reviewed the evidence for treatment recommendations (13).

The ocular dryness is always associated with a localised inflammatory process and damage of the ocular surface, which is common to all underlying conditions (14). Although often labelled as a benign feature of SS, the eye dryness can lead to decreased quality of life and potentially severe complications (15). A recent study found no correlation between the perceived sicca symptoms and the tear secretion in pSS patients, despite good correlation
with age and disease activity (16). The incidence of dry eye is increased in the older population (17) and also after cataract and refractive surgery (18). Symptoms of ocular dryness are reported with different frequency by patients with rheumatic conditions (19, 20).

Methods:
We search PubMed (MEDLINE) and EMBASE electronic data bases from January 1994 to September 2014, aiming to identify reports about different therapies for dry ocular symptoms associated with SS, using the following MeSH terms: Sjogren’s syndrome treatment, dry eye treatment, sicca syndrome and keratoconjunctivitis sicca treatment. Using all these terms combined, we identified 458 articles. Only the articles in English, reporting on data about the effectiveness of treatment in SS were included in the review (n=163). We excluded case reports and animal model studies, and complemented the electronic search by a hand research of the references of the review articles related to this topic. Ultimately, 78 relevant articles were carefully reviewed.

Therapeutic strategies

The current therapeutic armamentarium comprises artificial tears, topical applications of immunosuppressant therapies, systemic immunosuppressant and immunomodulatory therapies, secretagogues and interventional treatments. We summarise below the main treatment options currently available for addressing of symptoms of dry eye associated with SS (Table 1).

Topical treatments

It is currently recognised that the ocular dryness is associated with a local inflammatory process. The efficacy of topical antiinflammatories was tested in two randomised controlled trials (RCT), one prospective, open label, using diclofenac 0.1% drops (21) and one controlled, parallel group study, comparing diclofenac 0.1% with indomethacin 0.1 % eye drops (22). Both studies showed improvement of the subjective symptoms in the NSAIDs
treatment arms, which was not maintained at day 28 in the first study, and was associated with significant worsening of the corneal staining in the diclofenac group in the second study. It is currently accepted that topical NSAIDs should be used with caution in patients with SS (22) (Table 1).

The use of topical corticosteroids was effective in one prospective trial of 53 SS patients, which used methylprednisolone, initially administered 4 times daily for the first two weeks, and tapered every 2 weeks. The treatment led to significantly improved tear break-up time (BUT) and Schirmer test results at the end of the treatment period and drug-free remission for a mean duration of 56.6 weeks and 20.8% recurrences. The clinical improvement was associated with an increased number of conjunctival goblet cells as assessed by impression cytology (23).

The use of topical applications with artificial tears was associated with statistically significant changes in contrast sensitivity over a 4 hour period of instillation of a variety of artificial tears in patients with SS in a randomised controlled trial (RCT). It was also observed that the more muco-adhesive artificial tears demonstrated a significantly greater effect (24). Both artificial tears and punctal plugs relieved dry eye symptoms, repaired corneal lesions, enhanced tear film stability, and improved contrast sensitivity in patients with pSS (25).

Instillations with 0.4% sodium hyaluronate were effective in achieving improvement in the rose bengal conjunctival stain starting from day 15 (p = 0.01) and for BUT and fluorescein corneal stain at day 90, but showed no improvement in the Schirmer’s test, according to another RCT involving patients with primary (pSS) and secondary SS (26).

Autologous serum (20%) topical applications were also associated with improvement in the Rose Bengal and fluorescein scores (p<0.01 and p<0.05, respectively) after 4 weeks (27). However, no significant change in BUT scores was observed, despite the improvement in the dryness sensation, as reported by 12 patients with pSS treated for 4 weeks. In another study, including 3 different groups of patients with ocular symptoms, autologous serum (concentration 100%) was associated with the best outcome in improving the sensation of dryness (p<0.01) and decrease of the corneal staining score in the SS group (p=0.041) after 12 weeks (28).
Several clinical trials investigated the efficacy of cyclosporine 0.05%, topical application, in patients with SS and dry eye symptoms (29-31). In a 24 week RCT using two different doses, 0.5% and 1%, there was evidence of improvement in several dry eye-related outcomes (Table 1); (32). Cyclosporine 0.05% was as effective as vitamin A (ocular instillations), and superior to carbomethylcellulose, in improving the symptoms of blurred vision and break time and Schirmer tests (p=0.05) (Table 1)(33).

Cyclosporine topical applications improved both, the mean corneal fluorescein staining scores (p ≤ 0.001) and global physician assessment of dry eye status (in 72.7% SS patients) in a prospective study (31).

**Oral treatments:**

Several oral treatments were used to assess their efficacy in controlling different symptoms associated with SS. Pilocarpine is a non-selective muscarinic acetylcholine receptor M3 agonist, known to stimulate the secretion of saliva and sweat, as established many years ago (34).

In a recent RCT, comparing the efficacy of pilocarpine 5 mg twice a day (n=29) with artificial tears (n=28) and inferior puncta occlusion (n=28), pilocarpine significantly improved the subjective global assessment of dry eyes compared with artificial tears (p<0.001) and inferior puncta occlusion (p<0.05). Furthermore, patients receiving oral pilocarpine also showed greater objective improvement, as measured by the Rose Bengal test (p<0.05), although the Schirmer test showed no differences between the treated groups (35). Another large RCT, placebo controlled, assessed the efficacy of pilocarpine 20-30 mg daily (dose adjustment study) vs. placebo in patients with SS. The pilocarpine group demonstrated both significant improvement in global assessment of dry eyes related symptoms (p≤0.0001) and relief in 6 of 8 dry-related symptoms as assessed using a patient questionnaire (p≤0.04) at 12 weeks (30 mg/daily) (36).

In another RCT, pilocarpine 5 mg, four times daily, was effective in improving the symptoms associated with dry mouth and dry eye (61% vs, 31%, p<0.001 and 42% vs. 26%, p=0.009) in comparison with placebo (37). The efficacy of cevimeline was confirmed in a prospective, double-blinded trial which followed up pSS patients for 4 weeks (20 mg t.d.s.) and in a 12
week RCT (30 mg t.d.s), which both showed statistically significant improvements in patient subjective global assessment of dry eyes and lacrimal flow rates, as measured by Schirmer's test (38, 39).

Hydroxychloroquine (HCQ) has been used in SS and found beneficial in controlling the symptoms of oral dryness and joint pain associated with SS (40).

The efficacy of HCQ in controlling symptoms of dry eye was confirmed in pSS patients in a prospective study where patients were assessed 3 months after stopping HCQ. However, a significant worsening was observed in, tear break up-time (TBUT) (P < 0.001), lissamine green (p < 0.01) and corneal fluorescein staining scores (p < 0.003). Improvement of subjective symptoms was also noted after 12 weeks treatment with HCQ (P < 0.007 and P < 0.003, respectively) (41). A clinical improvement in the symptoms of ocular dryness was associated with decrease in the tear BAFF levels (41). However, a recent RCT study showed no efficacy of HCQ in controlling the symptoms of dryness associated with SS after 24 weeks of treatment (42).

Methotrexate did not improve objective features of ocular dryness, despite being effective in improving the reported symptoms of dryness, as assessed by an open, one-year pilot study with weekly methotrexate (43). A small open-label study with leflunomide 20 mg daily, including 15 patients with pSS with early and active disease, found no statistical significant difference in terms of perceived ocular dryness of objective improvement in the Schirmer test (44). No significant improvement of the ocular dryness was reported in studies with azathioprine (45) or oral cyclosporine (46), and the use of thalidomide was associated with prominent side-effects (47).

Rebamipide, an amino acid derivative of 2-(1H)-quinolinone, was reported to be effective in increasing the secretion of both membrane-associated and secreted-type mucins through mucin production in the conjunctival goblet cells, and in the corneal epithelial cells (48). This mucin secretagogue, used as ocular suspension was more effective than sodium hyaluronate at relieving the symptoms of ocular dryness and improving the corneal and conjunctival staining tests in a RCT in 188 patients with dry eye (49). There are no studies available to assess its efficacy in patients with SS.
A large recent 6-week RCT, placebo controlled study, including 240 patients with SS and testing a Chinese traditional herbal medicine compound (granules) showed a significant improvement in the Schirmer test in both eyes, and also in the salivary flow, in the treatment arm compared with placebo (50).

The treatment of end-stage autoimmune dry eye associated disease with MICOF keratoprosthesis is considered to be one of the last resorts in the therapeutic armamentarium. Studies reported variable rates of success and additional treatment, comprising prophylactic autologous auricular cartilage implantation aiming to reinforce the anterior surface of recipient’s cornea was needed to preserve the ocular integrity following corneal melting (51). Despite the increasing experience with corneal transplants, there are no reports of this treatment being effective in the end-stage ocular disease associated with SS, suggesting that this condition is reasonably well controlled with conservative treatment.

**Table 1: Treatments for ocular dryness associated with SS**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design/patient characteristics/medication dose</th>
<th>Main results</th>
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<tbody>
<tr>
<td><strong>Topical NSAIDs</strong></td>
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<tr>
<td>Aragona et al, 2004 (22)</td>
<td>Controlled, single-blind, parallel, clinical study, 20 patients (8 with pSS and 12 with sSS), 0.1% indomethacin vs. 0.1 % diclofenac; 30 day study with a follow-up visit 7 days after the discontinuation of therapy.</td>
<td>Both groups showed at day 30 a statistically significant reduction of corneal sensitivity (p&lt;0.05). The ocular discomfort score was statistically significantly reduced in both groups starting from day 15 (p&lt;0.05).</td>
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<td>Zhang et al, 2013 (24)</td>
<td>10 SS patients were assessed over a 4-hour period after instillation of a variety of artificial tears.</td>
<td>Statistically significant changes in contrast sensitivity were measured over time after artificial tear instillation, with the greatest effect at 3 to 6 cycles.</td>
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<td><strong>Artificial tears and autologous serum</strong></td>
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<td>Tsubota et al, 1999 (27)</td>
<td>Case-control clinical trial, n= 12 patients with SS were treated with autologous</td>
<td>Subjective comfort evaluated using a questionnaire improved significantly at 2 and 4</td>
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<td>Study</td>
<td>Patients</td>
<td>Treatment</td>
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<td>Cho et al, 2013 (28).</td>
<td>Patients with SS, dry eye, and persistent epithelial defects were randomly treated with autologous serum eye drops for 12 weeks at different concentrations: 100% (AS100), 50% serum with normal saline, sodium hyaluronate or ceftazidime.</td>
<td>In the SS group, AS100 showed fewer symptoms all the other concentrations (all p &lt; 0.01) and was associated with decreased corneal staining at 12-week post-treatment (p = 0.041).</td>
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<td>Hong et al, 2007 (23).</td>
<td>Prospective trial, 53 SS patients treated with methylprednisolone, 4 times daily for the first two weeks, tapered off every 2 weeks.</td>
<td>Significantly improved tear break-up time (BUT) and Schirmer test results at the end of the treatment period and drug-free remission for a duration of 56.6 weeks and 20.8% recurrences. After the second pulse-therapy the drug-free remission period was 72.4 weeks.</td>
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<td>Deveci et al, 2014 (52).</td>
<td>Prospective study, 26 SS patients treated for 1 month with cyclosporine A 0.05% topical, vs. 20 SS patients treated with saline solution.</td>
<td>Improvement in subjective symptoms (burning-prickling sensation, light sensitivity, pain) and redness (p=0.0001) at 1 month. Improvement of the Shirmer test (p=0.0001) and tear BUT (p = 0.0001) at 1 month.</td>
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<td>Sall et al, 2000 (32).</td>
<td>RCT, 24 weeks, topical cyclosporine 0.05% (n=293) and 0.1% (n=292) vs. placebo (n=292).</td>
<td>0.05% vs. placebo: better corneal staining score (p =0.008), Schirmer test score (p&lt;0.007), better score for blurred vision (p&lt;0.01), and decrease in concomitant use of artificial tears (p&lt;.006). Cyclosporine 0.1% group had a better corneal staining score (p&lt;0.06), Schirmer test (p &lt;0.007) than the placebo group.</td>
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<td>Kim et al, 2009 (33).</td>
<td>RCT, 12 weeks, topical cyclosporine 0.05% (n=50) vs. vitamin A (n=50) vs. carboxymethylcellulose (CMC) (n=50).</td>
<td>Improvement of reported blurred vision (cyclosporine and vitamin A vs. CMC, p&lt;0.05), better break-up time (BUT) (cyclosporine and vitamin A vs. CMC, p&lt;0.05), better Schirmer test score (cyclosporine and vit A vs. CMC, p&lt;0.05).</td>
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<td>Study</td>
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<td>Roberts et al, 2007 (29)</td>
<td>RCT, 6 months, topical cyclosporine 0.05% (n=10) vs. cyclosporine 0.05% + punctal occlusion (PO) (n=10), PO only (n=10).</td>
<td>Cyclosporine and cyclosporine/PO groups vs. PO only group had no significant improvement in the Schirmer test score (3.0 and 3.9 vs. 3.8), but patient used less artificial tears in the cyclosporine/PO vs. PO groups (−3.9 vs. −2.1; p=0.01)</td>
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<td>Dastjerdi et al, 2009 (31)</td>
<td>Retrospective study, cohort of 22 patients (13 patients with ocular graft versus host disease and 9 patients with SS) treated with cyclosporine 0.05%</td>
<td>After a minimum of a 2-month course of treatment with a frequent dosing of cyclosporine 0.05%, overall dry eye symptoms were improved in 15 (68.2%) patients (9 patients with ocular graft versus host disease and 6 patients with SS).</td>
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<td>Oral muscarinic agonists</td>
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<td>Tsifetaki et al, 2013 (35)</td>
<td>A 12 week RCT, n=85, oral pilocarpine 5 mg twice a day (n=29) vs. artificial tears (n=28) vs. inferior puncta occlusion (n=28). Patients receiving oral pilocarpine and those with inferior puncta occlusion also received artificial tears.</td>
<td>Pilocarpine was more effective than artificial tears (p&lt;0.001) and inferior puncta occlusion (p&lt;0.05) in improving the subjective symptoms dry eyes as assessed using a VAS. Pilocarpine also was associated with more significant objective improvement of symptoms of dry eye, as measured by the Rose Bengal test (p&lt;0.05), while Schirmer’s-I test showed no differences between the treated groups.</td>
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<td>Papas et al, 2004 (36)</td>
<td>12 week RCT (n=256 patients), placebo-controlled, dose-adjustment study, oral pilocarpine (n=128) 20 mg to 30 mg daily vs. placebo (n=128).</td>
<td>The pilocarpine group demonstrated both significant improvement in global assessment of dry eyes (p≤0.0001) and dry eye relief as assessed by improvement of in 6 of 8 related symptoms (p≤0.04).</td>
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<td>Vivino et al, 1999 (37)</td>
<td>RCT, double blind, 12 weeks, oral pilocarpine 2.5 mg/6h (n=121) and 5 mg/6h (n=127) vs. placebo (n=125).</td>
<td>Primary outcomes met: improvement of dry mouth symptoms (5 mgx4/ daily vs. placebo) in 61% vs. 31% SS patients (p&lt;.001), and dry eye symptoms in 42% vs. 26%, (p=0.009);</td>
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<td>Conventional DMARDs</td>
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<td>Rihl et al, 2009 (40)</td>
<td>Retrospective analysis of 14 patients with pSS with vs. 21 patients with objective sicca symptoms were treated with HCQ for up to 6 months.</td>
<td>The sicca group showed a significant increase in tear production (p=0.001). There was a positive correlation between the α-fodrin IgA antibody titer and the Schirmer’s test at baseline (r=0.66; p=0.001) and after treatment (r=0.6; p=0.004) in this group.</td>
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<tr>
<td>Gottenberg et al.</td>
<td>RCT, n=120 SS patients receiving HCQ</td>
<td>Between weeks 0 and 24, the mean (SD)</td>
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<td>Reference</td>
<td>Study Design</td>
<td>Methods</td>
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<td>al., 2014 (42)</td>
<td>400 mg daily vs. placebo for 24 weeks and active medication from week 24 to 48.</td>
<td>Numeric analogue scale score for dryness changed from 6.38 (2.14) to 5.85 (2.57) in the placebo group and 6.53 (1.97) to 6.22 (1.87) in the HCQ group (p=0.55)</td>
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<td>Van Woerkom et al, 2007 (44)</td>
<td>Pilot study, 15 patients with early and active pSS received Leflunomide 20mg once daily for 24 weeks.</td>
<td>Schirmer test values didn't reach statistical significance. No changes were observed in the reported perceived ocular dryness.</td>
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<td><strong>Biologic treatments</strong></td>
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<td>Sankar et al, 2004 (53)</td>
<td>RCT, double-blind, 12 weeks, etanercept 25 mg (n=14) twice per week vs. placebo (n=14).</td>
<td>None of the primary and secondary outcomes were met at week 12. There was no statistical significant difference between the treated and placebo groups as far as the ocular dryness VAS (p=0.53) and Schirmer test (p=0.55), were concerned.</td>
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<td>Meijer et al, 2010 (54)</td>
<td>48 week, randomized, double-blind, placebo-controlled trial, rituximab (RTX) 1 g. twice at day 1 and 15 (n=20) vs. placebo (n=10).</td>
<td>The lissamine green test showed significant improvement in lacrimal gland function in the rituximab group from baseline to weeks 5–48. However the Schirmer’s test and BUT test revealed no significant changes in lacrimal gland function in either group.</td>
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<td>Carubbi et al, 2013 (55)</td>
<td>120 week, prospective, follow-up study, n=41 patients with early pSS and active disease, RTX 1 g/15 d (n=19) vs. DMARDs (n=22).</td>
<td>RTX treatment resulted in a faster and more pronounced decrease of ESSDAI (p&lt;0.001) from week 24. Both the unstimulated salivary flow and the Schirmer’s I test were significantly increased in the RTX group from week 12 (p&lt;0.001).</td>
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<td>Devauchelle-Pensec et al, 2014 (56)</td>
<td>24 week RCT including 120 patients with scores of 50 mm or greater on at least 2 of 4 VASs (global disease, pain, fatigue, and dryness) and recent-onset (&lt; 10 years) biologically active or systemic pSS treated with RTX (1 g twice) vs. placebo.</td>
<td>The proportion of patients with at least 30-mm decreases in at least two of the four VAS scores (assessing global disease, pain, fatigue, and dryness), was higher in the RTX group at week 6 (22.4% vs. 9.1%; P = 0.036)</td>
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<td>Meiners et al, 2014 (57)</td>
<td>48 week RCT, n=28 patients with SS, weekly subcutaneous administration of 125 mg abatacept.</td>
<td>Significant improvement in the lissamine green test from baseline to weeks 5–48 in the abatacept group. However the Schirmer’s and BUT tests did not change significantly in any of the groups</td>
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<td><strong>Steinfeld et al.</strong>&lt;br&gt; (58)</td>
<td><strong>6 months RCT, 4 i.v. infusions epratuzumab administered every two weeks vs. placebo</strong></td>
<td>Fifty-three percent achieved a clinical response (improvement of at least 20% of a composite score including 5 parameters, which one of them being the Schirmer’s tests) at 6 weeks, with 53%, 47%, and 67% responding at 10, 18, and 32 weeks, respectively.</td>
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<td><strong>Marriette et al., 2013</strong>&lt;br&gt; (59)</td>
<td><strong>52 week open label trial, 103 patients with SS, 10 mg/kg belimumab i.v., monthly.</strong></td>
<td>Improvement of the dryness as assessed by VAS from 7.8 (1.8) to 6.2 (2.9) (p=0.0021). No improvement in the Schirmer test at 6 months.</td>
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**Biologic treatments**

Increased interest in testing biologic therapies effect in SS patients is evident (60). Etanercept, a TNF receptor fusion protein licensed for use in rheumatoid arthritis and ankylosing spondylitis, was tested for efficacy in a 12-week, double blind RCT (53). None of the study outcomes were met as patients did not improve after 12 weeks of treatment. The negative results included objective and subjective assessment of ocular dryness (p=0.53 and p=0.55, respectively) (53).

The most encouraging results related to the use of biologic treatment in SS to address the symptoms of ocular dryness came from two RCT with rituximab (RTX). In a 48 week RCT of RTX vs. placebo, the lacrimal gland function assessed by the lissamine green test showed significant improvement in the rituximab group from baseline to weeks 5–48. However the Schirmer’s and BUT tests did not change significantly in any of the groups (54).

A prospective study which enrolled 41 patients with early pSS and active disease and followed for up to 120 weeks, demonstrated that RTX treatment results in a faster and more pronounced decrease of ESSDAI (p<0.001) from week 24. RTX treatment significantly increased the Schirmer tests from week 12 (p<0.001) (55).

A recently published RCT with RTX vs. placebo in patients with recent-onset or systemic pSS reported negative results as it did not reach the primary outcome, improvement of at least
30 mm in 2 of 4 VASs by week 24. However, there was a signal of efficacy of RTX at earlier time points as the proportion of patients with at least 30-mm decreases in at least two of the four VAS scores was higher in the RTX group at week 6 (22.4% vs. 9.1%; P = 0.036). (56).

There is only one open label pilot study of abatacept in pSS (n=15), which reported no improvement in the salivary and lacrimal function, despite the encouraging results suggesting improved disease activity, laboratory parameters, fatigue and HR-QoL at weeks 24 and 44 (57).

An open-label, phase I/II study investigated the safety and efficacy of epratuzumab, a humanised anti-CD22 monoclonal antibody, in the treatment of 16 patients with active pSS (58). The response to the treatment was assessed using a composite endpoint, including the Schirmer test. Fifty-three percent achieved a clinical response (at > or = 20% improvement level) evaluated by this composite endpoint at 6 weeks, with 53%, 47%, and 67% responding at 10, 18, and 32 weeks, respectively (58).

Another B cell targeted therapy, belimumab, which is a monoclonal antibody that inhibits B-cell activating factor (BAFF) was tested in patients with SS in a prospective 1-year open-label trial (59). The primary end-point was defined as improvement in two of five items: reduction in ≥30% in dryness score on a visual analogue scale (VAS), ≥30% in fatigue VAS score, ≥30% in VAS pain score, ≥30% in systemic activity VAS assessed by the physician and/or >25% improvement in any B cell activation biomarker values. The primary end-point was achieved in 18 (60%). The mean dryness assessed by VAS varied from 7.8 (1.8) to 6.2 (2.9) (p=0.0021) but the Schirmer test didn’t improve significantly after 6 months (59).

New biologic targets have emerged from in vivo and animal studies, such as Fas and CD 40 involved in the epithelial apoptosis associated with SS, which could represent the therapies of the future (61).

A proposed algorithm:
Based on the available evidence from the literature data and the current recommendations for the management of dry eye symptoms (62), we propose a following algorithm (Figure 1) of ocular dryness treatment in patients with SS.

**First line therapy**

- **Education**
  - Environmental and offending medication modification
  - Level of evidence III

- **Topical lubricants**
  - (Preserved artificial tear substitutes, gels and ointments)
  - Level of evidence Ia

**If not effective**

**Second line therapy**

- **Topical lubricants**
  - Non-preserved artificial tear substitutes, followed by autologous serum or umbilical cord serum.
  - Level of evidence Ia

- **Short-term topical immunomodulatory agents**
  - Corticosteroids (*level of evidence IIa*)
  - Cyclosporine - not licensed in the UK (*level of evidence Ia*)

**If not effective**

- **Secretagogues**
  - Pilocarpine and Cevimeline
  - *Level of evidence Ia*

- **B cell target therapy** (not licensed)
  - Rituximab - *level of evidence Ia*
  - Belimumab – *level of evidence Ia*
  - Epratuzumab – *level of evidence Ia*

- **Co-stimulatory inhibition** (not licensed)
  - Abatacept – *level of evidence Ib*
**Conclusions:**

Despite being one of the central symptoms of SS, associated with significant impact of the quality of life of these patients, the ocular dryness is usually managed with tear substitution or topical anti-inflammatory/immunomodulatory medication. There is no good evidence for the efficacy of conventional DMARDs in improving lacrimal gland secretion in SS patients, apart from methotrexate, which only improved the subjective symptoms of ocular dryness in a small study and hydroxychloroquine, which improved the tear secretion in small, non RCT studies. A recent RCT proved no efficacy of this treatment as assessed at week 24. In comparison, there is good evidence that both pilocarpin and cevimeline are useful in improving the ocular dryness in patients with SS. Interesting and exciting results have been provided by the RCT involving new biologic therapies, which have shown improvement in many of the patient reported outcome measures related to symptoms of dryness. There is also evidence, from a prospective study, that rituximab improved the lacrimal secretion and histologic scores as well. Epratuzumab also improved a composite score, including the Schirmer test, in an open label, early phase study. It was emphasized from previous studies, that the selection of patients with early disease and residual lacrimal and salivary function is pivotal in ensuring a functional response following treatment.
In conclusion, the therapeutic armamentarium available for the treatment of ocular dryness associated with SS has expanded significantly in the last decade, as new biologic therapies targeting specific cells and molecules in patients with early disease have emerged. Apart from the biologic treatments, no systemic therapies are effective in SS. The dry eye treatment approach in SS differs from the treatment of other symptoms associated with SS, proving that patients benefit from an interdisciplinary approach and ophthalmological periodic review.

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**References:**


