Efficacy and safety of topical and systemic medications: a systematic literature review informing the EULAR recommendations for the management of Sjögren’s syndrome

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ABSTRACT

Objective To evaluate current evidence on the efficacy and safety of topical and systemic medications in patients with primary Sjögren syndrome (SJS) to inform European League Against Rheumatism treatment recommendations.

Methods The MEDLINE, EMBASE and Cochrane databases were searched for case-control/prospective cohort studies, randomised controlled trials (RCTs) and systematic reviews.

Results Current evidence in primary SJS patients fulfilling the 2002 criteria is based on the data from 9 RCTs, 18 prospective cohort studies and 5 case-control studies. Two Cochrane systematic literature reviews (SLRs) have reported that topical treatments for dry mouth and dry eye are safe and effective. Ocular cyclosporine A was safe and effective in two RCTs including 1039 patients with dry eye syndrome. Two Cochrane SLRs on serum tear drops and plugs showed inconsistency in possible benefits, both for symptoms and objective measures. Five RCTs reported significant improvements in oral dryness and salivary flow rates for pilocarpine and cevimeline. An RCT showed no significant improvements in oral dryness and salivary flow rates for pilocarpine and cevimeline. An RCT showed no significant placebo-differences for hydroxychloroquine 400 mg/day for the primary outcome (visual analogue scale (VAS) composite of dryness, fatigue and pain). We identified seven RCTs carried out in primary SJS patients. RCTs using infliximab, anakinra and baminercept found no placebo-differences for the primary outcomes. The two largest RCTs randomised 255 patients to receive rituximab or placebo and reported no significant results in the primary outcome (VAS composite), while prospective studies suggested efficacy in systemic disease.

Conclusion The current evidence supporting the use of the main topical therapeutic options of primary SJS is solid, while limited data from RCTs are available to guide systemic therapies.

INTRODUCTION

Sjögren’s syndrome (SJS), a chronic, systemic autoimmune disease, has no cure. Although it was identified as a disease more than a century ago,1 the therapeutic management has not changed significantly in recent decades.2 The specific pathogenic basis of a disease that targets the exocrine glands has led to a very specific type of therapy (agents locally applied to the mucosal surfaces involved) as one of the key approaches. In contrast, the systemic element of SJS has traditionally been tackled using glucocorticoids (GCs) and immunosuppressive agents, due to their use in similar systemic diseases such as systemic lupus erythematosus or vasculitis.

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During the first decade of this century, Food and Drug Administration (FDA) approval of muscarinic agents and topical cyclosporine A (CyA) for oral and ocular dryness in SjS patients, respectively, and the first studies testing biological agents were considered the first signs of a new, game-changing therapeutic scenario for primary SjS patients. Despite this, the first specific systematic literature review (SLR) of SjS therapy, published in 2010, found that evidence remained very limited, without solid results that could change the disease management. Since 2010, there have been significant advances, including the accurate characterisation and scoring of the disease burden, the patient-centred therapeutic response and the publication of large, well-designed therapeutic studies.7

The aim of this review was to inform the new EULAR recommendations on the main topical and systemic therapies used in SjS.

METHODS

A MEDLINE SLR was carried out by PB-Z and SR using the MeSH term ‘Sjögren’s syndrome’ combined with each therapeutic intervention proposed by the Task Force (see ‘Intervention’ section of the Population, Intervention, Comparison, Outcomes and Study design (PICOS) strategy) with the following restrictions: date (1 January 1986 to 31 December 2017), studies (humans) and age (adults). Additional databases, such as EMBASE and Cochrane Central Library, were also checked. The SLR strategy followed prespecific PICOS definitions agreed by the Steering Committee members: (a) Population: in order to collect evidence from an aetio-pathogenically homogeneous population, data was retrieved from studies including adult primary SjS patients fulfilling the 2002 criteria (stated in the manuscript as ‘primary-2002 patients’) or the 2016 ACR/EULAR criteria; (b) Intervention: using the data from a 2010 SLR as a starting point, interventions were classified as topical or systemic medications; (c) Comparison: therapeutic interventions were compared with placebo (PLA) or other therapeutic interventions; (d) Outcomes: eligible studies had to contain sufficient, clear information on the effect of the therapeutic intervention (efficacy) and on the safety profile; (e) Study design: we included randomised controlled trials (RCTs), cohort studies (prospective non-PLA-controlled, non-randomised studies and those with quasi-experimental designs), case-control studies (comparing therapeutic options) and meta-analyses, according to the definitions proposed by the Oxford Centre for Evidence-Based Medicine (CEBM), while case series (descriptive/retrospective therapeutic studies) were considered in the absence of other studies; narrative reviews, experimental animal studies, duplicate publications and isolated case reports were excluded. In the absence of evidence on the target population, extrapolation of results from studies including SjS populations that differed from the definition in the PICOS strategy was allowed. Figure 1 summarises the SLR results. Summary-of-finding tables were generated for RCTs (table 1), prospective cohort studies (table 2) and case-control studies (table 3). For RCTs, the risk of bias (RoB) was assessed using the Cochrane RoB assessment tool (Cochrane Handbook for Systematic Reviews of Interventions V.5.1.0 March 2011 (available from: http://handbook.cochrane.org/)), and for uncontrolled studies, we used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist. The few RCTs available for each therapeutic intervention, together with the heterogeneity in the methodology of the studies included, such as differing participant characteristics, comparative interventions, the small size of the populations studied and the differences in follow-up intervals and outcomes measured, made it impossible to pool data in a meta-analysis.

RESULTS

Ocular topical therapies

Saliva substitutes

We identified five studies that evaluated gels/saliva substitutes in SjS patients, of which only one was carried in primary-2002 patients. Alpöz et al found that Xialine (a saliva substitute containing polysaccharide xanthan gum plus sodium fluoride) and plain water plus diluted tea (serving as PLA) were equally effective in most VAS scoring for specific oral symptoms, with the only between-group differences being an increased preference for Xialine at the end of the study (p=0.011). A Cochrane SLR evaluated the effectiveness of topical treatments for any-cause dry mouth (including SjS) in parallel and cross-over RCTs using lozenges, sprays, mouth rinses, gels, oils, chewing gum and/or toothpastes and found no strong evidence supporting any one specific topical therapy as more effective in treating dry mouth.

Interferon alpha

Three studies have evaluated the use of interferon alpha per the oromucosal route in SjS patients fulfilling the 1993 criteria, including a large RCT of nearly 500 patients that found significant improvement only in unstimulated salivary flow (uSF), with a higher percentage of gastrointestinal adverse events in comparison with PLA.

Artificial tear drops

Seven studies testing artificial tears (ATs) in patients with SjS were identified, all of which found significant improvements with respect to baseline in both VAS ocular dryness and diagnostic tests (except in one study) with no reported side effects. Only one study, comparing the use of AT with plug insertion, was carried out in primary-2002 patients: no significant between-group differences were reported and, after 8 weeks of treatment, patients treated with AT showed significant improvement in all ocular diagnostic tests performed (p<0.001). A recent
Sjögren syndrome

Figure 1 Flow chart of the systematic literature review. PICOs, Population, Intervention, Comparison, Outcomes and Study design; RCTs, randomised controlled trials; SjS, Sjögren’s syndrome; SLRs, systematic literature reviews.

Cochrane review of AT drops for dry eye syndrome concluded that ATs are safe and effective.44

Non-steroidal anti-inflammatory drugs/GC-based tear drops

Evidence is overwhelmingly limited to studies including patients with associated SjS or non-2002 SjS patients. Only one study40 was carried out in primary-2002 patients, and this compared topical 0.1% fluorometholone (FML) with topical CyA: although no significant differences were detected between groups for the main efficacy parameters (except for tear breakup time (BUT)), with better results in the FML group, although patients treated with topical 0.1% FML showed significant improvements with respect to baseline in the Corneal Fluorescein Staining score (p<0.001), BUT (p<0.001) and Ocular Surface Disease Index (p<0.001) after 8 weeks of therapy, but not for the Schirmer test; no serious side effects were reported: the mean intraocular pressure change at 8 weeks was +0.4 mm Hg in the FML group versus −1.15 mm Hg in the CyA group (p=0.389).

Cyclosporine-based tear drops

In December 2002, an ophthalmic formulation containing 0.05% CyA was approved by the US FDA to treat dry eye disease at a recommended two times per day dose, based on the results of two RCTs that included 1039 patients with keratoconjunctivitis sicca (SjS patients were included in varying proportions).3 Since then, a summary of the results reported until now shows that most studies only demonstrated within-group improvements, and
Table 1 Summary-of-findings table generated for RCTs in primary-2002 patients with Sjögren syndrome

| Author (year) | No. patients | RoB | Arms (patients) | Primary outcome (drug vs PLA arms, p value) | Secondary outcomes (p value) | SAEs (% of patients in each arm) | Infections | Deaths |
|---------------|--------------|-----|-----------------|---------------------------------------------|-----------------------------|---------------------------------|------------|--------|
| Mariette et al (2004) | 103 | Low | INF (n=54) PLA (n=49) | Improvement 30% joint pain, fatigue, dryness VAS at 22 w (20.4% vs 16.7%, p = 0.62) | Gammaglobulin (0.05), IgM (0.001) Salivary flow rate, mL/min (p = 0.24), Schirmer test (p = 0.75), swollen joint count (p = 0.75), tender joint count (p = 0.97), ESR (p = 0.97), CRP (p = 0.96), IgA (p = 0.56). | INF (n=6) vs PLA (n=1) Not detailed | None |
| Dass et al (2008) | 17 | Unclear comparative presentation of results | Rituximab (n=8), PLA (n=8) | Improvement >20% VAS fatigue at 6 months (87% vs 56%, p = 0.36) | SF-36: social functioning (0.01) NS: Immunoglobulin levels, titres or positivity for other antibodies, glandular manifestations of pSS, Schirmer’s test score, uSF rate. | RTX (n=2) vs PLA (n=0) Not detailed | None |
| Meijer et al (2010) | 30 | Unclear (arms not balanced for baseline SF) | Rituximab (n=20) PLA (n=10) | Improvement of SWSF rate at 48 weeks (p>0.05) | VAS oral dryness (p<0.05), VAS ocular dryness (p<0.05) | Not classified as SAEs | RTX 12 in 11 patients vs PLA 7 in 4 patients | None |
| Norheim et al (2012) | 26 | Moderate (27% men, required 2 phases separated 2 years) | Anakinra (n=13), PLA (n=13) | Group-wise comparison of fatigue scores at week 4 (p=0.19) | Improvement >50% fatigue VAS (0.03) NS W48: Lacrimal gland function, Schirmer’s test, mm/5 min, tear breakup time, seconds 3, 2; SF-36 total score, MFI, general fatigue. W 24 Raynaud’s phenomenon (p=0.057), tendomyalgia (p=0.074), arthralgia (p=0.058) | AKR (n=1) vs PLA (n=0) None | None |
| Devauchelle-Pensec et al (2014) | 122 | Low | Rituximab 1 g/15 days (n=63), PLA (n=57) | 30 mm or greater improvement at week 24 on at least 2 of 4 VAS scores—dryness, fatigue, pain, global (23% vs 22%, p = 0.91) | IgG (0.003), IgA (0.028), IgM (0.004) ESSDAI score (p = 0.60), systemic signs score (p = 0.089), salivary flow rate, mL/min (p = 0.80), Schirmer test result, mm (p = 0.054), ESR, mm/h (p = 0.84), serum CRP level, mg/L (p = 0.95), C4 complement level, g/L (p = 0.32), B2-Microglobulin level, g/L (p = 0.35), SF-36 score: PCS (p = 0.36), MCS (p = 0.35). | RTX 20.6% vs PLA 14% RTX 52.4% vs PLA 52.6% | None |

Continued
| Author (year)                  | No. patients | RoB | Arms (patients)                                      | Primary outcome (drug vs PLA arms, p value)                                                                 | Secondary outcomes (p value)                                                                 | SAEs (% of patients in each arm) | Infections | Deaths          |
|-------------------------------|--------------|-----|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------|-------------|-----------------|
| Gottenberg et al (2014)       | 120          | Low | HCQ 400 mg/day (n=56) vs PLA (n=64)                 | 30% or greater reduction at week 24 in 2 of 3 VAS scores—dryness, fatigue, pain (17.6% vs 17.3%, p=0.96) | ESR (<0.001), CRP (0.03), IgM (0.004), ESSPRI (p=0.87), ESSDAI (p=0.63), cardinal signs (pain, fatigue, dryness) evaluated by practitioner (p=0.76), systemic signs evaluated by practitioner (p=0.49), SF-36, physical health component (p=0.85), SF-36, mental health component (p=0.23), HAD-anxiety (p=0.54), HAD-depression (p=0.26), Schirmer test (p=0.42), uSF, mL/min (p=0.45), serum IgG, g/L (p=0.13), serum IgA, g/L (p=0.85).                                          | HCQ 3.6% vs PLA 4.7% ND | ND          | Pneumococcal meningitis (PLA group) |
| Ho Yoon et al (2016)          | 26           | High (primary outcome undefined)                  | HCQ 300 mg/day (n=11), PLA (n=15)                                                                       | Not defined                                                                                       | Fluorescein staining score (p=0.524), Schirmer test score (p=0.958), OSDI (p=0.292), TBUT (p=0.746), ESR (p=0.620), serum IL-6 (p=0.991), serum and tear BAFF (NA), Th17 cells (p=0.566). | Not classified as SAEs | None        | None            |
| Bowman et al (2017)           | 133          | Low | Rituximab 1 g/15 days (n=67), PLA (n=66)           | Reduction ≥30% at week 48 of either fatigue or oral VAS dryness (39.3% vs 36.8%, p=0.76)                  | uSF (0.0015), ESSPRI (p=0.1087), ESSDAI scores (p=0.0721), mean lacrimal flow (p=0.3698), SF-36 physical component (p=0.5246), SF-36 mental component (p=0.9485). | RTX n=9 vs PLA n=9              | RTX n=2 vs PLA n=2 | None            |
| St Clair et al (2018)         | 52           | Unclear (study enrolment was terminated early because of expiration of study drug) | BAM (n=33), PLA (n=19)                                                                                 | Change in the SWSF rate at week 24 (+0.07 vs –0.01, p=0.33)                                         | Schirmer test right eye (0.036), Unstimulated WSF (p=0.881), ESSDAI (p=0.104), physician global assessment (p=0.646), subject global assessment (p=0.587), overall dryness (p=0.744), fatigue (p=0.737), joint pain (p=0.797), Schirmer I test (mm) Left eye (p=0.662) Total ocular scoring (p=0.603), SF-36 Physical aggregate score (p=0.163), Mental aggregate score (p=0.885), BAFF (pg/mL) (p=0.523), LIGHT (pg/mL) (p=0.840), IP-10 (pg/mL) (p=0.907). | BAM 15% vs PLA 5% | BAM 24.2% vs PLA 15.8% | None            |

AKR, anakinra; BAFF, B-Cell Activating Factor; BAM, baminercept; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ESSDAI, EULAR Sjögren’s syndrome disease activity index; ESSPRI, EULAR Sjögren’s Syndrome Patient Reported Index; HAD, Hospital Anxiety and Depression Scale; HCQ, hydroxychloroquine; IL-6, interleukin 6; IFN, interferon; MCS, Mental Health Composite Score; MR, Multidimensional Fatigue Inventory; ND, not detailed; NS, not significant; OSDI, Ocular Surface Disease Index; PCS, Physical Health Composite Score; PLA, placebo; PRO-FAD-SSI, Profile of Fatigue and Discomfort-Sjögren Syndrome Inventory; pSS, primary Sjögren syndrome; RCT, randomised controlled trial; RoB, risk of bias; RTX, rituximab; SAEs, serious adverse events; SF-36, Short Form-36 Health Survey; SWSF, stimulated whole salivary flow; TBUT, Tear breakup time; uSF, unstimulated salivary flow; VAS, visual analogue scale; W, week; WSF, whole salivary flow.
| Author (year)   | Patients | Design (duration) | Intervention, dose (patients) | Comparison (patients) | Efficacy parameters (p<0.05) | Non-significant associations (p>0.05) | Safety profile |
|----------------|----------|-------------------|-------------------------------|-----------------------|----------------------------|--------------------------------------|----------------|
| Kedor et al (2016) | 30       | Prospective (16w) | Oral cyclosporine A, approx 2mg/kg/day (n=30) | None                  | Tender joint count (<0.001), swollen joint count (<0.001), DAS28 (<0.001), ESSDAI (<0.001), gammaglobulin (0.009), anti-La (0.048) | Patient's disease activity (p=0.249), pain (p=0.094), fatigue (p=0.350), SF-36 total (p=0.259), HAQ-DI (p=0.372), CRP mean (p=0.780), ESR mean (p=0.268), IgG mean (p=0.360), Schirmer's test (p=0.820), Saxon's test (p=0.925), anti-Ro (SSA) 60kDa (p=0.786), anti-Ro (SSA) 52kDa (p=0.400), RF (p=0.099) | All had experienced at least one adverse event (AE): gastrointestinal (70%), muscle cramps (67%), nervous system (53%), skin (53%); infections (30%) of mild or moderate severity occurred 13 times in 10 patients; drop-out 6/28 (21%) |
| Egrilmez et al (2011) | 22       | Prospective (12m) | Plug (n=22)                  | None                  | Schirmer test (0.006), BUT (<0.001) | Visual acuity levels (p=0.608), lissamine green staining scores (p=0.958) | Pyogenic granuloma (n=1) |
| Aragona et al (2006) | 15       | Prospective       | Pilocarpine                  | NA                    | Dry mouth (<0.001) | VARS for systemic symptoms (NS): skin dryness, vagina dryness. | Sweating in 6 (40%), chill in 3 (20%), nausea in 2 (13%), oversalivation in 2 (13%), gastritis in 1 (7%) |
|                 |           |                   |                              |                       | Ocular burning, foreign body (<0.02) | VARS for ocular symptoms (NS): itching, mucus secretion, photophobia, hyperaemia, tearing. | |
|                 |           |                   |                              |                       |                                | Ocular tests results (NS): corneal fluorescein stain, Schirmer's I, test basal secretion test | |
| Yamada et al (2007) | 13       | Prospective       | Cevimeline 30 mg             | No                    | No information about overall efficacy | Groups according to positive or negative findings of: ▶ sialography: age (p=0.700), ▶ labial minor salivary gland biopsy: age (p=0.623), pretreatment WSS (p=0.906), post-WSS (p=0.073) ▶ anti-Ro/SSA antibodies: age (p=0.446), pretreatment WSS (p=0.268), post-WSS (p=0.165), increment rate (p=0.683) ▶ anti-La/SSB: age (p=0.561), pretreatment WSS (p=0.914), post-WSS (p=0.116), increment rate (p=0.018) ▶ Disease duration (months): age (p=0.917), pretreatment WSS (p=0.934), post-WSS (p=0.950), increment rate (p=1.000) | No serious adverse effects |
|                 |           |                   |                              |                       |                                |                                                                      | |

Continued
Table 2 Continued

| Author (year) | Patients | Design (duration) | Intervention, dose (patients) | Comparison (patients) | Efficacy parameters (p<0.05) | Significant associations (p<0.05) | Non-significant associations (p>0.05) | Safety profile |
|---------------|----------|-------------------|-------------------------------|-----------------------|-----------------------------|-----------------------------------|-------------------------------------|----------------|
| Yavuz et al (2011) | 32 | Prospective | HCQ 6.5mg/kg/day (>2 years) | No | Symptom severity score (<0.001) | OSDI (NS), Schirmer's test (mm) NS, Schirmer's test with anaesthesia (mm) NS, average tear drop/day NS, NEI-VFQ-25 questionnaire (NS) | Not detailed |
| (12w) | | | | | Tear BUT (0.001) corneal fluorescein (0.01) | | |
| Cankaya et al (2010) | 30 | Prospective | HCQ 400 mg/day | No | Mean uSFR (<0.05) | Dry mouth (p=0.292), burning oral mucosa (p=0.11), difficulty in mastication (p=0.969) | Not detailed |
| (30w) | | | | | Oxford score (0.003) | | |
| van Woerkom et al (2007) | 15 | Prospective | Leflunomide 20 mg/24 hours | No | MFI (0.034) | VAS general health (p=0.529), VAS dry eyes (p=0.361), VAS sandy feeling (p=0.343), VAS dry mouth (p=0.098), VAS sleep disturbance due to dryness (p=0.484), Zung depression score (p=0.726), RAND (SF-36) mental component (p=0.790), ESR (p=0.200), CRP (p=0.453), Schirmer test (p=0.138), sialometry (p=0.632) | All 15 patients suffered AEs; not classified as SAEs |
| (24w) | | | | | SF-36 physical component (0.026) | Diarrhoea 7, GI discomfort 6, hair loss 7, weight loss >2 kg 5 |
| | | | | | Reduced serum IgA (0.023), IgG (0.006) and IgM (0.005) | Headache 5, LE skin lesions 5, anaemia 5, leucopa 4, dizziness 4 |
| | | | | | Reduced RF levels (0.045) | TAS 3, rashes 4 (different patients of LE rashes) | |
### Table 2  Continued

| Author (year)          | Patients | Design (duration) | Intervention, dose (patients) | Comparison (patients) | Significant associations (p<0.05) | Non-significant associations (p>0.05) | Safety profile |
|------------------------|----------|-------------------|-------------------------------|-----------------------|----------------------------------|--------------------------------------|----------------|
| Willeke et al (2007)   | 11       | Prospective       | Mycophenolic acid             | No                    | VAS sicca (<0.02)                | Schirmer’s test (millimetres per 5 min), whole saliva (grams per 5 min), VAS arthralgia, VAS fatigue, Health Assessment Questionnaire score, erythrocyte sedimentation rate (mm/hour), IgG (mg/dL), IgA (mg/dL), anti-SSA antibodies, anti-SSB antibodies. No changes in the 28-swollen/tender joint count or in the number of tender points were observed (data not shown). No significant changes concerning the Raynaud syndrome were observed. |
| Zandbelt et al (2004)  | 12       | Prospective       | Etanercept 25 mg twice per week | No                    | CRP (<0.05)                      | ESR (p=0.058), gammaglobulin (p<0.05), Schirmer-I tests (p<0.05), SL/SM salivary (p>0.05), flow measurements (p>0.05), BUT or rose bengal staining (NS, data not shown). Post-treatment LFS (p=0.101) and IgA% (p=0.621). Raynaud syndrome (NS). |

(24 w) Increased dose

| (360 mg to 1440 mg daily) | Reduct gammaglobulins, C3 and C4 levels (<0.02) | GI discomfort=5, herpes=1, common cold=2 |
|---------------------------|-----------------------------------------------|---------------------------------------|
|                           | Reduct IgM, RF (<0.05)                        | Dose reduction in 2                   |
|                           | Increased leucocytes (<0.05)                  |                                       |
|                           | General health, role emotional SF-36 domains  |                                       |
|                           | (<0.05)                                       |                                       |

12 w (n=15)

| General fatigue scale within the MFI (p=0.018) | VAS score for perceived disease activity (p=0.045) | Three withdrawals (one pneumonia) |

Continued
| Author (year)          | Patients | Design (duration) | Intervention, dose (patients) | Comparison (patients) | Efficacy parameters (p<0.05) | Safety profile |
|-----------------------|----------|-------------------|-------------------------------|----------------------|-----------------------------|-----------------|
| Pijpe et al (2005)    | 15       | Prospective (12w) | Rituximab 375mg/m² No         | Only in the subset ‘early’: rose bengal, BUT, MFI, SF-36 PF, V, HC (<0.05) | Either group of patients: levels of IgG, IgA, IgM, and 2-microglobulin did not change. Patients with MALT/primary SS: No changes in T-cell subsets All patients (>0.05): whole saliva, stimulated submandibular/sublingual salivary secretion. Schirmer’s test. Patients with MALT/primary SS: rose bengal, BUT, MFI, SF-36 PF, V, HC (>0.05) | Infusion-related (n=2), Herpes zoster (n=1), HACAs: 4/8 of early SS, 0/7 in MALT group, serum sickness (n=3), all HACA+ |
| Devauchelle-Pensec et al (2007) | 16 | Prospective (36w) | Rituximab 375mg/m² No         | Global VAS (0.03), pain VAS (0.006), fatigue VAS (0.006), dryness VAS (0.006), tender point count (0.027), tender joint count (0.017), IgA-RF (0.04) | Ocular and oral dryness (p=0.05), swollen joint count (p=0.15), salivary flow rate, ml/min (p=0.86), Schirmer test (p=0.79), anti-SSA (p=0.25), ESR (p=0.6), Latex test (p=0.1), IgA (p=0.7), IgG (p=0.2), IgM (p=0.2) | Infusion-related (n=2), lymphoma (n=1), delayed reactions (n=8), serum sickness (n=4) |
| St Clair et al (2013) | 12       | Prospective (26w) | Rituximab 375mg/m² No         | Global VAS physician (0.012) and patient (0.009), VAS tongue dryness (0.007), level of thirst (0.005), oral discomfort (0.02), fatigue (0.042) | Joint pain (p=0.077), unstimulated white blood cell count (p=0.287) or stimulated (p=0.718), whole salivary flow, RF (p=0.109) p≥0.05: Tear production, Schirmer’s test, ocular surface dryness (von Bisterveld scoring system), SF-36 for physical and mental functioning between week 0 and week 26. | Severe AE reaction to pneumococcal vaccine (n=1); non-severe (n=2), squamous cell carcinoma (+301 d) |
| Carubbi et al (2013)  | 41       | Case control (120w) | Rituximab 1g/15 d (n=22) DMARD treatment (n=19) | ESSDAI reduction RTX vs DMARD (<0.05) | Unstimulated salivary flow and the Schirmer’s I test were not affected in the DMARD treatment group. | No adverse events |
| Mariette et al (2015) | 30       | Prospective (28w) | Belimumab 10mg/kg No           | Dryness VAS (0.0021), ESSPRI (0.0174), ESSDAI (0.0015) | Unstimulated whole salivary flow (p=0.027) or Schirmer’s test (p=0.51), even in SF-36 physical health and mental health component (p=0.71) The focus score of the lymphoid labial salivary gland (LSG) infiltrate (p=0.57). Mean baseline BAFF level (p=0.57) Decrease of three points or more of ESSDAI (p=0.44). | Pneumococcal meningitis (n=1), breast cancer (n=1), scleroderma (n=1), pneumonia (n=1), headache (n=9), sinusitis (n=1), neutropenia (n=5), Rhinitis/pharyngitis (n=7), oral aphthosis (n=1), bronchitis (n=1), Herpes labialis (n=1), urinary tract infection (n=2), gastroenteritis/diarrhoea (n=2) | No withdrawals |
| Author (year) | Patients | Design (duration) | Intervention, dose (patients) | Comparison (patients) | Efficacy parameters (p<0.05) | Safety profile |
|---------------|----------|------------------|------------------------------|----------------------|----------------------------|----------------|
| De Vita et al (2015) | 19 | Prospective extension (52 w) | Belimumab 10mg/kg | No | Physician VAS (0.04), RF (0.048), IgM (<0.01) Glandular domain (p=0.0078) Articular domain (p=0.0313) Biologic domain (p=0.0078) | VAS dryness score (p=1.0), VAS fatigue (p=0.14) VAS pain (p=0.71), biologic improvement (p=1.0) at W28 and W52. VAS score of disease systemic activity by the physician at W28 (p=0.65), p>0.05: SF-36 physical health, mental health component uSFR (p=0.6), Schirmer’s I test (p=0.3) Focus score of labial salivary gland biopsy (p=0.9) |
| Steinfled et al (2006) | 16 | Prospective (18w) | Epratuzumab 360mg/m² | No | VAS fatigue (<0.05), patient assessment (<0.05), physician assessment (<0.05), tender joints (<0.05) | p>0.05: CRP; ESR; Ig, pain, changes from baseline in T cells |
| Meiners et al (2014) | 15 | Prospective (48w) | Abatacept 10 mg/kg | No | ESSDAI (<0.05), ESSPRI (<0.05), Patient’s GDA (<0.05), Physician’s GDA (<0.05), RF (kIU/L) (<0.05), IgG (g/L) (<0.05) ESSDAI at W48 from baseline (p=0.137) ESSPRI post-treatment (p=0.151) Unstimulated whole saliva, parotid flow rate and lacrimal gland function, patient’s GDA, parotid saliva, stimulated (mL/min), Schirmer (mm5min): NS. | No SAEs occurred, and no patients withdrew from the study due to AEs. |

Mild infusion reaction (n=1); mild acute AEs - dizziness, hypotension- (17 events in 6 patients)

18 self-reported infections (18 infections in 10 patients), the most common being upper respiratory tract infections. No infection required hospitalisation.
### Table 2  Continued

| Author (year) | Patients | Design (duration) | Intervention, dose (patients) | Comparison (patients) | Efficacy parameters (p<0.05) | Non-significant associations (p>0.05) | Safety profile |
|---------------|----------|-------------------|-------------------------------|-----------------------|----------------------------|----------------------------------------|----------------|
| Adler et al (2013) | 11 Prospective (108 w) | Abatacept 500–750mg | No | Numbers of lymphocytic foci decreased (0.041), numbers of local FoxP3, T cells decreased (0.037), peripheral blood, B cells increased (0.038), expansion of the naive B cell pool (0.034) | Histology (NS): Lymphocytic foci/mm², No serious adverse events, no CD20 B cells, CD3 T cells, mm², CD20 B cells, CD3 T cells, CD4 T cells, CD8 T cells. | No infusion reactions | |
| | | | | | | | |
| | | | | | | Total lymphocytes increase (0.044) and for CD4 cells (0.009) | Serum (NS): IgG, g/L | Transient increase in liver enzymes (concomitant rifampin) (n=1) |
| | | | | | | Gamma globulins decreased (0.005) | Peripheral blood cells (NS): lymphocytes, CD3 T cells, CD4 T cells, CD8 T cells, memory B cells, switched memory B cells, non-switched memory B cells | Diverticulitis (n=1) |
| | | | | | | Saliva production increased (0.029) | | Lupus-like skin lesions (n=1) |

AEs, serious adverse events; ANA, antinuclear antibody; AT, artificial tears; BAFF, B-Cell Activating Factor; BUT, tear breakup time; bx, biopsy; CRP, C-reactive protein; DAS, disease activity score; DMARD, Disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; ESSDAI, EULAR Sjögren’s syndrome disease activity index; ESSPRI, EULAR Sjögren’s Syndrome Patient Reported Index; GDA, global disease activity; GI, gastrointestinal; HACA, human antichimeric antibodies; HAQ-DI, Health assessment questionnaire disability index; HC, health change; HCQ, hydroxychloroquine; LE, lupus erythematosus; LFS, lymphocyte focus score; m, month; MALT, mucosa-associated lymphoid tissue-type lymphom; MFI, Multidimensional Fatigue Inventory; ND, not detailed; NEI-VFQ-25, National Eye Institute-Visual Function Questionnaire-25; NS, not significant; OSDI, Ocular Surface Disease Index; PF, physical functioning; RF, rheumatoid factor; RTX, rituximab; SAEs, serious adverse events; SF-36, Short Form-36 Health Survey; SL/SM salivary, sublingual/submandibular gland; TAS, taste; uSF-I, unstimulated salivary flow rate; V, vitality; VARS, Visual analogue rating scales; VAS, visual analogue scale; w, week; WSS, Whole stimulated saliometry.
### Table 3 Summary-of-findings table generated for case-control studies in primary-2002 patients with Sjögren syndrome

| Author (year)          | Patients | Design (duration) | Intervention, dose (patients) | Comparison (patients) | Differences between-groups (p value) | Differences within-groups (p value) | Safety profile                                      |
|------------------------|----------|-------------------|-------------------------------|-----------------------|--------------------------------------|------------------------------------|------------------------------------------|
| Alpöz et al (2008)     | 38       | Case control      | Xialine (n=29)                | Water (n=29)          | Relief xerostomia complaints (0.06)  | p values not detailed               | Not detailed                        |
|                        |          |                   |                               |                       | VAS improvement for Xialine group in mastication (0.06), swallowing (0.027), daily liquid consumption (0.019), mouth burning (0.025), the need to sip liquids to aid swallowing (0.023), difficulty in speaking (0.004) | | |
|                        |          |                   |                               |                       | VAS satisfaction better for Xialine (0.011) | | |
| Qiu et al (2013)       | 40       | Case control      | Plug (n=21)                   | Artificial tears (AT) (n=19) | OSDI score, BUT, Schirmer I, corneal staining score (p<0.05) | Plug group: better OSDI score, BUT, Schirmer I, corneal staining score (p<0.001) | Not detailed                        |
| Lin et al (2015)       | 40       | Case control      | 0.1% fluorometholone (FML) (n=20) | Topical cyclosporine A (n=20) | CFS score (>0.05), OSDI score (>0.05), Schirmer (>0.05), conjunctival goblet cell density (p<0.001) | FML group: better CFS score (<0.001), BUT (<0.001), OSDI score (<0.001), Schirmer (>0.05), conjunctival goblet cell density (ns), conjunctival congestion at week 4 (p=0.035) | No serious or severe adverse effects occurred |
| Li J et al (2015)      | 37       | Comparative       | Autologous serum (AS) (n=18) | Bandage contact lens (BCL) (n=19) | BUT (>0.05), corneal staining (>0.05), Schirmer (>0.05), BCVA (>0.05) | AS group: BUT (0.001), corneal staining (0.001), Schirmer (>0.05), BCVA (>0.05) | No adverse events                   |
| Noaeh et al (2014)     | 118      | Case control      | Pilocarpine first line (n=59) | Cevimeline first line (n=59) | Failure rates among first-time users: Cevimeline vs pilocarpine 27% vs 47% (p=0.02) | ANA (+) was associated with failure: 59% vs 38% (p=0.03) | Pilocarpine first line: 28 patients (47%) discontinued treatment due to AE. |

Continued
Table 3 Continued

| Author (year) Patients Design (duration) | Intervention, dose (patients) | Comparison (patients) | Differences between-groups (p value) | Differences within-groups (p value) | Safety profile |
|----------------------------------------|------------------------------|-----------------------|-------------------------------------|-------------------------------------|---------------|
| (2.8 y) Pilocarpine second line (n=13) | Cevimeline second line (n=32) | Failure rates among all users: Cevimeline vs pilocarpine 32% vs 61% (p<0.001). | | | |
| | | Cevimeline (first-time users) had lower failure rates due to AE vs pilocarpine (p=0.02) | | | |
| | | Previously failed one secretagogue were less likely to discontinue treatment with the other agent, 52% of first-time users vs 27% of second-time users (p=0.004). | | | |
| | | 11 patients (19%) discontinued therapy due to lack of efficacy | | | |
| | | Cevimeline first line: 16 patients (27%) discontinued due to AE: | | | |
| | | Sweating (n=8), nausea, dyspepsia and vomiting (n=5), flushing/hot flashes (n=1), headaches (n=1) and breast swelling (n=1) | | | |
| | | 6 patients (10%) due to lack of efficacy | | | |
| | | Pilocarpine second line: 3 patients (23%) developed AE requiring discontinuation | | | |
| | | Sweating (n=1), dyspepsia (1) and flushing/hot flashes (1) | | | |
| | | Two patients stopped treatment due to lack of efficacy | | | |
| | | Cevimeline second line: 7 (22%) developed AE requiring discontinuation | | | |
| | | Sweating (n=2), dyspepsia (1), flushing flushing/ hot flashes (1), diarrhoea (1), parotid swelling (1) and postnasal drip (1) | | | |
| | | None stopped treatment due to lack of efficacy | | | |
| | | Severe sweating more frequently in pilocarpine (25%) than cevimeline (11%) users (p=0.02) | | | |

ANA, antinuclear antibody; AT, artificial tears; BCVA, best-corrected visual acuity; BUT, tear breakup time; CFS, Corneal Fluorescein Staining; CyA, cyclosporine A; CyA, cyclosporine A; FML, fluorometholone; IOP, intraocular pressure; OSDI, Ocular Surface Disease Index; VAS, visual analogue scale; w, week.
those that reported significant between-group differences (drug and vehicle) found improvement in only one to two of the four to eight ocular outcomes evaluated. In addition, a study extension trial found no additional improvement in subjective and objective measurements after 6 months of therapy. With respect to adverse events, the largest RCT found that most events were mild-to-moderate and transient, with a significantly higher percentage of burning eye in comparison with PLA (15% vs 6% in PLA), and only 2% of patients discontinued because of burning and stinging.

There are no specific RCTs in primary-2002 patients, with only one case-control study, the above-mentioned study by Lin and Gong, which showed no significant differences with topical 0.1% FML and with a higher frequency of moderate-to-severe transient burning sensation in patients receiving CyA.

**Tacrolimus-based tear drops**

A recent small RCT using 0.03% tacrolimus tear drops in 24 SjS 2002 patients found significant improvements in the Schirmer test and corneal staining (fluorescein, rose Bengal) after 3 months of therapy in comparison with drops that included only the vehicle. Nearly 80% of those receiving tacrolimus experienced a burning sensation after instillation.

**Serum tear drops**

Autologous serum (AS) has been tested in six small (<30 patients) uncontrolled studies in SjS patients and has shown inconsistent benefits (improvement in some but not all ocular tests performed). Only one study was carried out in primary-2002 patients, which showed a significant improvement with respect to baseline in three out of five ocular outcomes. A recent Cochrane review of AS for dry eye syndrome confirmed inconsistency in the possible benefits of AS for both symptoms and objective measures, with no evidence of an effect after 2 weeks of treatment.

**Insertion of lachrymal plugs**

Of the nine studies identified in SjS patients, only two were carried out in primary-2002 patients. Qiu et al. compared the insertion of plugs with ATs in 40 patients: both treatments improved all ocular outcomes (subjective and objective) without statistically significant between-group differences. In a prospective study, Egrilmez et al. reported improvement in two out of four ocular tests with respect to baseline 12 months after inserting plugs. A recent Cochrane SLR reviewed the use of plugs for dry eye syndrome and found that the evidence was very limited and improvements in symptoms and ocular tests were inconclusive.

**Diquafosol**

In 2004, an ophthalmic formulation of diquafosol (an agonist of the purinergic P2Y receptor) was tested by Tauber et al. in an RCT including 527 patients with dry eye (only 76 had SjS), which reported statistically significant differences between groups in only one of the two defined primary outcomes, with no further studies being reported, making it impossible to recommend their use.

**Oral muscarinic agonists**

Two muscarinic agonists (pilocarpine and cevimeline) were licensed by the FDA in 1998 and 2000, respectively, for the treatment of oral dryness in SjS patients; these agents stimulate the M1 and M3 receptors present on salivary glands, leading to increased secretory function.

**Pilocarpine**

The two pivotal RCTs included 629 SjS patients (fulfilling the 1993 criteria and including both primary and associated cases) and found significant improvements in oral dryness VAS and salivary flow rates at doses of 5 and 7.5 mg/6 hours in comparison with the PLA arm. The RCTs showed a high frequency of adverse events, including sweating (43%), increased urinary frequency (10%) and flushing (10%). In a dose-escalating RCT, nearly a quarter of patients reduced from 7.5 to 5 mg/6 hours in a second 6-week period of therapy. Only two studies have been carried out in primary-2002 patients, and only one assessed efficacy. In a prospective study, Aragona et al. reported a significant improvement with respect to baseline in oral dryness VAS (p<0.001) after 2 months of therapy with pilocarpine 5 mg/6 hours.

**Cevimeline**

Three RCTs including 332 SjS patients (fulfilling the 1993/Japanese criteria, both primary and associated cases) tested the use of cevimeline using dosages ranging between 15 and 60 mg/8 hours. The best results were achieved with a dose of 30 mg/8 hours, including significant improvements in dry mouth and salivary flow rates, with a significantly higher frequency of nausea (relative risk 1.68) and sweating (relative risk 2.16) in comparison with PLA. There is only one study carried out in primary-2002 patients, but there was no information detailed about overall efficacy and safety. Only one study has compared cevimeline with pilocarpine but only assessed the safety profile. Noaiseh et al. retrospectively analysed 118 primary-2002 patients and found a lower failure rate of cevimeline both in first-time (27% vs 47%, p=0.02) and all (32% vs 61%, p<0.001) users in comparison with pilocarpine. Severe sweating was the main reason for therapy cessation and occurred more frequently in pilocarpine users (25% vs 11%, p=0.02).

**Hydroxychloroquine**

We identified 12 studies that assessed hydroxychloroquine in SjS patients, with only 4 (2 prospective and 2 RCTs) carried out in primary-2002 patients. Yavuz et al. prospectively enrolled 32 patients treated with hydroxychloroquine for at least 2 years (no data on mean length or cumulative dose) and reported, in a further 12-week control study, a significant improvement in four out of eight ocular outcomes with respect to baseline, with no...
information on concomitant ocular therapies. Çankaya et al25 prospectively evaluated 30 women who started on 400 mg/day of hydroxchloroquine and reported a significant improvement in uSF rate (0.212 vs 0.162 baseline, p<0.05) but not stimulated salivary flow rate at 30 weeks, with improvement in only two of the five subjective oral VAS scores. Yoon et al17 carried out a small RCT in 26 patients and found no significant differences in dry eye in comparison with PLA, but with no definition of the primary outcome. The pivotal RCT was carried out by Gottenberg et al46 in 120 patients with primary-2002 SjS who were randomised to receive 400 mg/day of hydroxychloroquine (n=56) or PLA (n=64): the primary outcome was defined as a ≥30% reduction in two out of three VAS scores—dryness, fatigue, pain—without significant PLA differences at week 24 (17.6% vs 17.3%, p=0.96). For one of the secondary outcomes, hydroxchloroquine was associated with a statistical trend to improved pain (p values between 0.06 and 0.10 at 12, 24 and 48 weeks) although it was not superior to PLA for articular involvement; with respect to fatigue, no statistical differences were found.16 No cases of retinal toxicity or severe adverse events were reported in any of these studies.

**Oral GCs**

The frequent use of GCs in clinical practice in primary SjS patients is not supported by reliable scientific evidence. In the absence of controlled studies in 2002 patients, we briefly analysed the data in other SjS populations.3 The first study was a very small RCT (eight patients per arm) comparing prednisone 30 mg/day with piroxicam 20 mg/day and PLA, which found significant differences in subjective symptoms but not in objective tests.52 However, a prospective study of 60 patients followed for a mean of nearly 4 years found that corticosteroids did not influence the progressive decrease in salivary flow rates.53 No controlled studies are published in primary-2002 patients, and only prospective studies have reported the use of GCs for systemic disease,24 with a high rate of GC-related adverse events, including increased appetite and weight gain,52 a two-fold higher frequency of diabetes mellitus55,56 and Cushing in up to 80% of patients.56

**Immunosuppressive agents**

Seven studies have tested immunosuppressive agents in SjS patients (two studies using leflunomide and cyclophosphamide, respectively, and one study each for azathioprine, methotrexate and mycophenolate), of which only two were carried out in primary-2002 patients. van Woerkom et al47 carried out a prospective study using 20 mg/day of leflunomide, which showed significant improvement in 5 out of 16 efficacy parameters tested after 24 weeks of therapy (2 were components of quality of life (QoL) questionnaires and 3 analytical parameters); all 15 patients experienced adverse events (between 4 and 8 per patient), principally gastrointestinal (67%), cytopenias (47%) and lupus-like cutaneous lesions (33%). Willeke et al48 tested the use of micophenolic acid 1440 mg/day, reporting significant improvement in 8 out of 16 efficacy parameters after 24 weeks of therapy, including VAS for sicca features (p<0.02) and mean AT use (p<0.02) (other parameters that improved included components of QoL questionnaires and analytical parameters); adverse events were reported in 72% of patients.

**Biological therapies**

Of the 34 studies in which biological agents have been tested in SjS patients, we identified 6 RCTs (using infliximab (INF), anakinra and rituximab) and 10 prospective cohort studies (using etanercept, abatacept, epratuzumab, rituximab and belimumab) carried out in primary-2002 patients. A summary of the results of the efficacy parameters is provided in table 4.

**Abatacept**

Two small prospective cohort studies have tested abatacept in primary-2002 patients. The first enrolled 15 patients with early active disease who received eight intravenous abatacept infusions49 and reported that ESSDAI, EULAR Sjogren’s Syndrome Patient Reported Index (ESSPRI), rheumatoid factor and IgG levels decreased significantly at 48 weeks; fatigue and health-related quality of life parameters improved significantly, while salivary and lacrimal gland function did not change; 6 (40%) patients experienced mild acute adverse events and 10 (67%) self-reported infections. The second study included 11 patients and reported increased saliva production (1.74 vs 1.61 g/2 min baseline, p=0.029) after 24 weeks of therapy and decreased lymphocytic foci in total (but not lymphocytic foci per mm²); one patient developed lupus-like cutaneous lesions.25

**Anakinra**

A small RCT that randomised 26 patients (13 to anakinra and 13 to PLA) found no significant reduction in fatigue in the primary endpoint4 (comparison of fatigue scores at week 4, p=0.19); 2 patients experienced severe side effects (injection site reaction and gastroenteritis, respectively), 2 had a transient episode of neutropenia and 7 (54%) mild injection site reactions.

**Baminercept**

St Clair et al8 have recently reported on the clinical efficacy and safety of baminercept in 52 patients with primary-2002 randomised in a 2:1 ratio to receive subcutaneous injections of 100 mg of baminercept every week for 24 weeks or matching PLA. The primary end point was the change between screening and week 24 in the stimulated whole salivary flow (SWSF) rate. The change from baseline to week 24 in the SWSF rate did not differ significantly between the baminercept and the PLA groups (baseline-adjusted mean change −0.01 vs 0.07 mL/min; p=0.332). Baminercept was associated with a higher incidence of liver toxicity, including two serious adverse events.
Table 4  Summary of the outcomes evaluated in RCTs including primary-2002 patients with Sjögren syndrome

| Author (year) | Patients | Weeks | Drug, dose | Global/composite | Dryness | Pain | Fatigue | HRQoL | Salivary flows | Ocular tests | ESSDAI |
|---------------|----------|-------|------------|------------------|---------|------|---------|-------|---------------|-------------|--------|
| Mariette et al (2004) | 103 | 22 | Infliximab, 5mg/kg | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |
| Sankar et al (2004) | 28 | 12 | Etanercept, 25 mg | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |
| Dass et al (2008) | 17 | 24 | RTX, 1g/15 days | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |
| Meijer et al (2010) | 30 | 48 | RTX, 1g/15 days | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |
| Norheim et al (2012) | 26 | 4 | Anakinra, 100 mg/day | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |
| Devauchelle-Pensec et al (2014) | 122 | 24 | RTX, 1g/15 days | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |
| Bowman et al (2017) | 133 | 48 | RTX, 1g/15 dys | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |
| St Clair et al (2018) | 52 | 24 | Baminercept, 100 mg weekly | VAS | VAS | VAS | VAS | SF-36* | SFR | Schir | |

Grey cells=primary outcome. *Statistically significant. BDI, Beck Depression Inventory; ESSDAI, EULAR Sjögren’s syndrome disease activity index; ESSPRI, EULAR Sjögren’s Syndrome Patient Reported Index; HRQoL, health-related quality of life; MFI, Multidimensional Fatigue Inventory; RCT, randomised controlled trial; RTX, rituximab; Schir, schirmer; SF-36, Short Form-36 Health Survey; SFR, salivary flow rate; SFR, salivary flow rate; UWS, unstimulated whole saliva; VAS, visual analogue scale.

The results reported by the Efficacy and Safety of Belimumab in Subjects with Primary Sjögren’s Syndrome (BELISS) open-label trial 57 in 30 primary-2002 patients (all with systemic complications, early disease and/or abnormal biomarkers) showed that belimumab 10 mg/kg (weeks 0, 2 and 4, and then every 4 weeks until week 24) was associated with a higher rate of improvement in the composite outcome (improvement of at least two of the following items: ≥30% reduction in VAS for dryness, fatigue, musculoskeletal pain and physician systemic activity, and ≥25% reduction in any of the B-cell activation biomarkers) in patients with early disease in comparison with those with systemic disease (73% vs 47%); the mean ESSDAI score decreased from 8.8 to 5.59 (p<0.0001) and the ESSPRI score from 6.44 to 5.56 (p=0.01). In the 19 patients who completed 1 year of treatment, a significant improvement in some ESSDAI involvements (glandular, lymphadenopathy and articular) was maintained. With respect to the safety profile, only one serious adverse event was reported (pneumococcal meningitis) after six drug infusions. Pratuzumab

In 2006, a small prospective study including 15 patients with primary-2002 SJS 23 reported a beneficial effect on VAS fatigue (<0.05), patient assessment (<0.05), physician assessment (<0.05), tender joints (<0.05); five patients experienced severe adverse events (acute infusion reactions and infection).

Epratuzumab

Two studies (one RCT, one prospective) have been carried out in SJS patients: only the prospective study included primary-2002 patients and showed no significant improvements in the main SjS signs and symptoms. 59

Etnaximab

An open-label, single-arm study in 16 patients found significant improvements in subjective and objective measures after the administration of INF, although recently the authors have retracted the manuscript. 58 In 2004, Mariette et al 12 conducted an RCT including 103 patients and found no significant differences in the primary outcome, defined as improvement in at least 30% of the joint pain, fatigue and dryness VAS at 22 weeks (INF 20.4% vs PLA 16.7%, p=0.62), or in the majority of secondary outcomes (symptoms, salivary flow rates, ocular tests, QoL and all the analitical parameters in comparison with PLA and pain/tender point count). 58 No significant improvements in subjective and objective measures were reported after the administration of INF, although recently the authors have retracted the manuscript. 58
improvements were reported for objective oral and ocular tests (except in the study by Pijpe et al. in a subset of patients). In the case-control study, Carubbi et al. compared the therapeutic effect of rituximab (n=22) and conventional immunosuppressive therapy (n=19) and found a significant improvement in patients treated with rituximab in the ESSDAI (<0.05), global VAS (<0.05), fatigue VAS (<0.01), dryness VAS (<0.01), physician VAS (<0.05), uSF (<0.01) and Schirmer test (<0.05) at the end of follow-up (120 weeks); the authors reported a complete lack of reported adverse events in either of the two arms in spite of the long-term nature of the study. With respect to the two small RCTs, Dass et al. randomised 17 primary-2002 patients to receive rituximab (n=8) or PLA (n=9) and found no significant results in the primary outcome (improvement >20% VAS fatigue at 6 months, rituximab 87% vs PLA 56%, p=0.36), while Meijer et al. randomised 30 primary-2002 patients to receive rituximab (n=20) or PLA (n=10) with no significant results for the primary outcome (improvement in SWSF rate at 48 weeks, p>0.05). Two large RCTs have recently been reported. In 2014, Devauchelle-Pensec et al. randomised 122 primary-2002 patients to receive rituximab (n=63) or PLA (n=57) and found no significant results in the primary outcome (≥30 mm improvement at week 24 on at least 2 out of 4 VAS scores—dryness, fatigue, pain, global, 22% vs 22%, p=0.91), while Bowman et al. randomised 133 primary-2002 patients to receive rituximab (n=67) or PLA (n=66) and found no significant results in the primary outcome (reduction ≥30% at week 48 in either fatigue or oral dryness VAS, rituximab 39.3% vs PLA 36.8%, p=0.76).

Two recent meta-analyses including the four RCTs have confirmed the lack of significant between-group differences in mean improvements between baseline and week 24 values for fatigue VAS, oral dryness VAS, salivary flow rate and Schirmer test, and no significant difference between groups for the main adverse events.\textsuperscript{59,60}

\textbf{DISCUSSION}

Current evidence on the therapeutic management of primary-2002 SJS patients is based on 9 RCTs (only four including ≥100 patients randomised to drug/PLA), 18 prospective cohort studies (all including ≤30 patients per study) and 5 case-control studies. For oral topical therapies, available evidence is limited to five studies carried out in SJS patients (only one in primary-2002 patients) and one Cochrane SLR that assessed the management of dry mouth. Xerostomia is a subjective symptom with wide interindividual variation, and a satisfactory output of unstimulated whole saliva in one patient may lead another to complain of symptoms of dry mouth. All studies have shown significant within-group improvement in comparison with baseline subjective oral outcomes. Mechanical stimulation (chewing gum) was associated with increased saliva production in patients with residual capacity, but there is no evidence that gum may have more or less efficacy than saliva substitutes in reducing dry mouth symptoms. Due to the wide range of interventions, small trials (mean of 45 participants per trial), the RoB and the range of outcome measures for oral dryness, there is no strong evidence to support any specific intervention over another, and the conclusion is that, in the absence of an effective topical treatment, we recommend that the treatment of xerostomia should be directed towards improving patients’ complaints rather than increasing saliva production, including improvements in tooth health and the prevention of oral infections. The cost of long-term topical therapy is another important consideration, but there are no available studies on this issue. Other therapeutic interventions are under investigation. A recent double-blind, cross-over-design study has evaluated the effects of intraoral electrostimulation,\textsuperscript{61} and further studies in primary-2002 patients are required to make a specific recommendation on its use.

For ocular topical therapies, among the 43 studies in SJS patients, only 6 (14%) were carried out in primary-2002 patients, while there are 4 SLRs on the management of dry eye using ATs, AS and plugs.\textsuperscript{44,49,50,62} The Cochrane SLR on AT showed that the AT formulations tested improved the signs and symptoms over the course of the studies included, although they found no consistent between-group differences when conducting head-to-head AT comparisons. The authors concluded that, given the large number of AT formulations compared and the wide variety of outcomes, it was difficult to propose that one over the counter AT formulation is superior to another for the treatment of dry eye syndrome. However, AT consistently improved ocular symptoms over the course of the trials included, based on within-group analyses, and three of four PLA-controlled trials consistently found that AT improved ocular symptoms compared with PLA (saline or vehicle), with a similar trend for many of the secondary outcomes. This review also found that the use of ATs is relatively safe, with the most common adverse events being blurred vision, ocular discomfort and foreign body sensation. It is important to consider that most outcomes were subjective measures of patient-reported outcomes rather than objective outcomes.\textsuperscript{44} With respect to non-steroidal anti-inflammatory drug (NSAID)/GC-based ocular tears, evidence not including primary-2002 SJS patients suggests careful use of tears containing NSAIDs or GCs due to the side effects associated with prolonged use.\textsuperscript{63} In these patients, ocular topical NSAIDs or corticosteroids may be a short-term therapeutic approach prescribed by ophthalmologists for the minimum time necessary (maximum 2–4 weeks).\textsuperscript{63}

With respect to topical CyA, the pivotal study (a combination of two trials including 877 patients—270 fulfilled the 1993 SJS criteria, not detailed how many were primary or associated) evaluated 14 efficacy outcomes (4 objective, 10 subjective) with no definition of which were primary or secondary and found statistically significant differences between groups only in 4 (2 subjective and 2 objective). In spite of this, the FDA approved their
use. In addition, a review of the results of all reported studies shows that most studies only demonstrated within-group improvements, and those that reported significant between-group differences (drug and vehicle) found improvement in only 20%–30% of the outcomes evaluated. In addition, a study extension trial found no additional improvement in subjective and objective measurements in patients treated for >6 months. Although SjS patients were included in variable proportions in the above-mentioned RCTs, there are no RCTs specifically in primary-2002 patients. Only one recent prospective study was made in primary-2002 patients, which found no significant differences between topical CyA and topical 0.1% FML. A recent small RCT using 0.03% tacrolimus tear drops found significant improvements in 24 primary-2002 patients, the lack of definition of the population included (unclear whether they were primary or associated cases), the high rate of side effects and, especially, the limited number of cases does not support their widespread use in primary SjS patients, although they could be considered as a rescue therapy for CyA non-responders/intolerant patients.

With respect to AS and plug insertion, in addition to the very limited evidence available for primary-2002 patients, the two Cochrane SLRs found significant limitations in the quality of trials (incomplete descriptive statistics for reported treatment outcomes, sample sizes with too few participants, quasi-randomisation methods, complete masking may not have been feasible, short-term evaluation of efficacy, lack of details on adverse outcomes and tolerance). For AS, the Cochrane SLR concluded that current evidence suggests that 20% AS might provide some benefit in improving patient-reported symptoms over the short term (2 weeks), but longer periods of follow-up provide no evidence of improvement over longer periods, while no clear effects were found for objective clinical measures of the ocular surface. For punctal occlusion, the certainty of the evidence ranged from moderate to very low (frequently downgrading the level of evidence due to the high RoB or imprecision in effect estimates), and it was concluded that current evidence suggests that punctal plugs are a modestly effective means of treating dry eye. For all these reasons, the use of AS and plugs in primary SjS has been considered as a rescue therapeutic option, always under prescription by an ophthalmologist. A combination of AS and plugs has recently been evaluated in 28 SjS patients (primary and associated, criteria not detailed). Ophthalmologists play a key role in prescribing topical and systemic therapies for ocular dryness, always with a close multidisciplinary follow-up.

The two pivotal trials of pilocarpine included 629 patients with primary/associated SjS fulfilling the 1993 criteria and reported statistically significant differences between groups for the two primary VAS outcomes defined. With respect to cevimeline, the two pivotal trials included 272 patients with primary/associated SjS fulfilling the 1993 criteria and reported statistically significant differences between groups for the primary VAS outcomes. There is very limited evidence to support the use of these drugs in the treatment of oral dryness in primary-2002 patients (only one study using pilocarpine). It would seem appropriate to offer patients a trial of the drug, assuming there are no contraindications (ie, uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease, uncontrolled cardiorenal syndrome, acute iritis, pregnancy, breast feeding) to the use of the drug. The trial should be prolonged, since the response can be delayed (up to 12 weeks), with a recommended dose of 5 mg three times a day to keep side effects to a minimum, since the adverse effects are dose dependent. Additional studies are required to clarify the role of muscarinic agonists in the treatment of xerostomia in primary SjS patients.

With respect to systemic synthetic immunosuppressive drugs, there are no new studies specifically assessing GCs in primary SjS in the last 20 years. For immunosuppressive agents, all reported studies (all including <20 patients) were principally centred on the efficacy in sicca features (with limited benefits) and laboratory parameters, with no specific analysis of the outcomes recommended in the guidelines (efficacy in systemic disease) and with an unacceptable rate of adverse events (41%–100%). In addition, there is a lack of head-to-head studies comparing the efficacy and safety profile of the different immunosuppressive agents.

The emergence of biological therapies has increased the therapeutic armamentarium available to treat SjS, but their use is limited by the lack of licensing. Available evidence is principally supported by the studies testing rituximab in primary SjS, making this drug the most frequently tested in these patients. There are six additional prospective cohort studies including ≤30 patients (one for etanercept, two—one extension—for belimumab, one for efalizumab and two for abatacept), one small study (<30 patients) using anakinra, one medium-sized study (n=52) using baminercept and one large trial (>100 patients) using INF.

The results of trials on the efficacy of rituximab in the outcomes evaluated are summarised in the SLR published by Leteif et al. There were no statistically significant differences between groups for the primary outcomes based on subjective VAS dryness. The quality of evidence according to the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach was low for oral dryness, salivary flow rates, fatigue, mental health and ESSDAI meta-analysis and moderate for the Schirmer test meta-analysis. All studies included reported adverse effects, but with no significant differences between groups; the meta-analysis presented low-quality evidence according to the GRADE approach. The promising results obtained in small uncontrolled studies for the use of belimumab and abatacept should be confirmed in large RCTs before a solid therapeutic recommendation for use in primary SjS patients in standard clinical practice can be made. Limited data have been obtained from controlled trials to guide systemic treatment, although prospective studies using rituximab...
have suggested efficacy in systemic disease, especially in cryoglobulinemic vasculitis, as reported in unselected cryoglobulinemic patients.66 The current evidence supporting the efficacy and safety of the main topical therapeutic options for the treatment of sicca symptoms of primary SjS is solid but is extrapolated from the results of RCTs carried out in mixed populations of patients with dryness caused by SjS and other aetiologies. The overall low level of evidence from therapeutic studies specifically carried out in primary SjS patients fulfilling the current classification criteria underscores the need for considerably larger trials. In addition, there is no information on the differential efficacy and safety of the main systemic therapeutic options available and treatment-by-treatment choices will remain challenging in clinical practice.

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REFERENCES
1. Brito-Zerón P, Baldini C, Bootsmà H, et al. Sjögren syndrome. Nat Rev Dis Primers 2016;2.
2. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, et al. Topical and systemic medications for the treatment of primary Sjögren’s syndrome. Nat Rev Rheumatol 2012;8:399–411.
3. Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjögren syndrome: a systematic review. JAMA 2010;304:452–60.
4. Seror R, Theander E, Brun JO, et al. Validation of EULAR primary Sjögren’s syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis 2015;74:859–66.
5. Seror R, Ravaud P, Mariette X, et al. EULAR Sjögren’s syndrome patient reported index (ESSPRI); development of a consensus patient index for primary Sjögren’s syndrome. Ann Rheum Dis 2011;70:968–72.
6. Seror R, Bootsmà H, Saraux A, et al. Defining disease activity states and clinically meaningful improvement in primary Sjögren’s syndrome with rituximab: results of a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2016;75:382–9.
7. Brito-Zerón P, Retamozo S, Ghelisì H, et al. Treating the underlying pathophysiology of primary Sjögren’s syndrome: recent advances and future prospects. Drugs 2016;76:1601–23.
8. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren’s syndrome: a revised version of the European criteria proposed by the American-European consensus group. Ann Rheum Dis 2002;61:554–8.
9. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League against rheumatism classification criteria for primary Sjögren’s syndrome: a consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis 2017;76:9–16.
10. Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren’s syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960–8.
11. OCEBM. Levels of evidence Working group OC for E-B, 2011. The Oxford 2011 levels of evidence, 2011. Available: http://www.cebm.net/%7Ea/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.
12. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren’s syndrome: results of the randomized, controlled trial of etanercept in primary Sjögren’s syndrome (TRIPS). Arthritis Rheum 2004;50:1270–6.
13. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541–4.
14. Norheim KB, Harboe E, Graønssøg LG, et al. Interleukin-1 inhibition and fatigue in primary Sjögren’s syndrome—a double blind, randomised clinical trial. PLoS One 2012;7:e30123.
15. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. *Ann Intern Med* 2014;160:233–42.

16. Gottenberg J-E, Ravaud P, Puéchal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. *JAMA* 2014;312:249–58.

17. Yoon CH, Lee HJ, Lee EY, et al. Effect of hydroxychloroquine treatment on dry eyes in subjects with primary Sjögren’s syndrome: a double-blind, randomised controlled study. *J Korean Med Sci* 2016;31:1127–35.

18. Protzen MM, Vissink A, Kroese FGM, et al. Abatacept treatment reduces disease activity in early primary Sjögren’s syndrome (open-label proof of concept ASAP study). *Ann Rheum Dis* 2014;73:1393–6.

19. van Woerden RM, van der Loos HFM, et al. Efficacy and safety of leflunomide in primary Sjögren’s syndrome: a phase II pilot study. *Arthritis Res Ther* 2013;15:R129–11.

20. van Woerden RM, van der Loos HFM, et al. Safety and efficacy of leflunomide in primary Sjögren’s syndrome: a phase II pilot study. *Ann Rheum Dis* 2007;66:1026–32.

21. Kerst J. Rituximab for Sjögren’s syndrome: a phase II pilot study. *Arthritis Res Ther* 2013;15:R129–11.

22. Lilleike P, Schlüter B, Becker H, et al. Mycophenolate sodium treatment in patients with primary Sjögren syndrome: a pilot trial. *Arthritis Res Ther* 2011;13:1045–9.

23. van Woerden RM, van der Loos HFM, et al. Efficacy and safety of leflunomide in primary Sjögren’s syndrome: the BELLIS open-label phase II study. *Rheumatology* 2015;54:2249–56.

24. Steinfeld SD, Taub Feuerstein GR, et al. Eptinezumab (humanised anti-CD22 antibody) in primary Sjögren’s syndrome: an open-label phase II/I study. *Arthritis Res Ther* 2006;8:R129–11.

25. Meiners PM, Vissink A, Kroese FGM, et al. Abatacept treatment reduces disease activity in early primary Sjögren’s syndrome (open-label proof of concept ASAP study). *Ann Rheum Dis* 2014;73:1393–6.

26. Adler S, Körner M, Förger F, et al. Evaluation of histologic, serologic, and clinical changes in response to abatacept treatment of primary Sjögren’s syndrome: a pilot study. *Arthritis Care Res (Hoboken)* 2013;65:1097–106.

27. Conroy JT, Korteweg V, et al. Efficacy and safety of rituximab in patients with primary Sjögren’s syndrome: one-year followup’. *Arthritis Rheumatol* 2013;65:1097–106.

28. Mariette X, Seror R, Quertodoz L, et al. Efficacy and safety of belimumab in patients with primary Sjögren’s syndrome: results of the BELISS open-label phase II trial. *Ann Rheum Dis* 2015;74:526–31.

29. Liu W, Liao Z, Luo M, et al. Treatment of primary Sjögren’s syndrome with belimumab: a multicenter, randomized controlled trial. *Arthritis Rheumatol* 2013;65:1097–106.

30. Conroy JT, Korteweg V, et al. Efficacy and safety of rituximab in patients with primary Sjögren’s syndrome: a prospective, multi-center, follow-up study. *Arthritis Res Ther* 2013;15:R172.

31. Mariette X, Seror R, Quertodoz L, et al. Efficacy and safety of rituximab in patients with primary Sjögren’s syndrome: results of the BELISS open-label phase II study. *Ann Rheum Dis* 2015;74:526–31.

32. Dicker GC, Gwinner K, et al. The efficacy of Xaline in patients with Sjögren’s syndrome: a single-blind, cross-over study. *Clin Oral Investig* 2008;12:165–72.

33. Saheb K, Kopp T, et al. Punctal plugs versus artificial tears for treating primary Sjögren’s syndrome with keratoconjunctivitis SICCA: a comparative observation of their effects on visual function. *Rheumatol Int* 2013;33:2543–8.

34. Liu Y, Gong L. Topical thalidomide treatment for ocular dryness in patients with Sjögren syndrome: a randomized clinical trial in China. *Medicine* 2015;94:e551.

35. Li J, Zheng X, Zheng Q, et al. Comparative evaluation of silicone hydrogel contact lenses and autologous serum for management of Sjögren syndrome-associated dry eye. *Cornea* 2015;34:1072–8.

36. Naleah G, Baker JF, Vivino FB. Comparison of the discontinuation rates and side-effect profiles of pilocarpine and cevimeline for xerostomia in patients with Sjögren’s syndrome. *Clin Exp Rheumatol* 2014;32:575–7.

37. Furness S, Blyth F, McMillan R, et al. Interventions for the management of dry mouth: non-pharmaceutical interventions. *Cochrane Database Syst Rev* 2013;CD009603.

38. Pacher AD, Ng SM, Nichols JJ, et al. Over the counter (OTC) artificial tear drops for dry eye syndrome. *Cochrane Database Syst Rev* 2015;2:CD009729.

39. Schwartz LM, Woolshin S. A Clear-eyed view of Restasis and chronic dry eye disease. *JAMA Intern Med* 2018;178:181–2.

40. Barber LD, Pfulfelder SC, Tauber J, et al. Phase III safety evaluation of cyclopamine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. *Ophthalmology* 2005;112:1790–4.

41. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclopamine ORTH2004 on ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The cyclopamine a phase 2 study, ORTH2004. *Ophthalmology* 2000;107:967–74.

42. Moscovici B, Holzchuh R, Sasaki-Sawada-Naves FE, et al. Treatment of Sjögren’s syndrome dry eye using 0.03% tacrolimus eye drop: Prospective double-blind randomized study. *Cont Lens Anterior Eye* 2015;38:373–8.

43. Pan O, Angelina A, Marrone M, et al. Autologous serum eye drops for dry eye. *Cochrane Database Syst Rev* 2017;252.

44. Ervin A-M, Law A, Pucker AD, et al. Punctal occlusion for dry eye syndrome. *Cochrane Database Syst Rev* 2017;140.

45. Tauber J, Davitt W, Bokosky JE, et al. Double-Masked, placebo-controlled safety and efficacy trial of diquafosol tetrasodium (INS365) ophthalmic solution for the treatment of dry eye. *Cornea* 2004;23:784–92.

46. Fox PC, Datiles M, Atkinson JC, et al. Prednisone and piroxicam for treatment of primary Sjogren’s syndrome. *Clin Exp Rheumatol* 1993;11:149–56.

47. Pipke J, Kalk WW, Bootstra H, et al. Progression of salivary gland dysfunction in patients with Sjogren’s syndrome. *Ann Rheum Dis* 2007;66:107–12.

48. Gheithasi H, Kostov B, Solans R, et al. How are we treating our systemic patients with primary Sjögren syndrome? analysis of 1120 patients. *Int Immunopharmacol* 2015;27:194–9.

49. Pérez-De-Lis M, Akasbi M, Sisó A, et al. Cardiovascular risk factors in primary Sjögren’s syndrome: a case-control study in 624 patients. *Lupus* 2010;19:941–8.

50. Shen Y, Xia J, Lin L, et al. Combination Cyclosporine/hydrated Glucocoicoids provide better tolerability and outcomes versus glucocorticoids alone in patients with Sjogren’s associated chronic interstitial nephritis. *Am J Nephrol* 2017;48:473–80.

51. Mariette X, Seror R, Quertodoz L, et al. Efficacy and safety of belimumab in primary Sjögren’s syndrome: results of the BELISS open-label phase II study. *Ann Rheum Dis* 2015;74:526–31.

52. Steinfeld SD, Demos P, Salimn I, et al. Notice of retraction of two articles ‘(infliximab in patients with primary Sjögren’s syndrome: a pilot study’ and ‘(infliximab in patients with primary Sjögren’s syndrome: one-year followup’), *Arthritis Rheumat* 2013;65.

53. Letaief H, Lukas C, Barneche T, et al. Efficacy and safety of biological DMARDs modulating B cells in primary Sjögren’s syndrome: systematic review and meta-analysis. *Joint Bone Spine* 2018;85:15–22.

54. Chu LL, Cui K, Pope JE. A meta-analysis of treatment for primary Sjögren’s syndrome. *Arthritis Care Res (Hoboken)* 2019. doi:10.1002/acr.23917. [Epub ahead of print: 06 May 2019].

55. Strietzel FP, Lafaurie GI, Mendoza GRB, et al. Efficacy and safety of an intralacrital electrostimulation device for xerostomia relief: a multicenter, randomized trial. *Arthritis Rheumat* 2011;63:180–90.

56. Shih KC, Lunt CN, Jhanji V, et al. Systematic review of randomized controlled trials in the treatment of dry eye disease in Sjogren syndrome. *J Inflamm (Lond)* 2017;14:26.

57. Fowler GN, Forost SL, Donshek PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. *Ocul Surf* 2015;13:118–32.
64. Sacchetti M, Mantelli F, Lambiase A, et al. Systematic review of randomised clinical trials on topical ciclosporin a for the treatment of dry eye disease. *Br J Ophthalmol* 2014;98:1016–22.
65. Liu Y, Hirayama M, Cui X, et al. Effectiveness of autologous serum eye drops combined with punctal plugs for the treatment of Sjögren syndrome-related dry eye. *Cornea* 2015;34:1214–20.
66. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012;64:843–53.
67. Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjögren’s syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. *Arthritis Rheum* 2004;50:2240–5.