

# Treatment of Primary Sjögren Syndrome

## A Systematic Review

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**S**JÖGREN SYNDROME IS A SYSTEMIC autoimmune disease that presents with sicca symptomatology of mucosal surfaces,<sup>1</sup> mainly dry mouth and dry eyes. There is often systemic involvement (extraglandular manifestations) and lymphoma is a recognized complication.<sup>2</sup> Sjögren syndrome is one of the most prevalent autoimmune diseases (with an estimated 0.5 million to 3 million affected persons in the United States,<sup>3</sup> primarily perimenopausal women). When sicca symptoms appear in a previously healthy person, this is classified as primary Sjögren syndrome.<sup>4</sup>

Standard management focuses on controlling sicca features using substitute topical agents, and extraglandular features are managed with glucocorticoids and immunosuppressive drugs.<sup>5</sup> However, there are no evidence-based therapeutic guidelines for the management of primary Sjögren syndrome. Consequently, current therapeutic decisions are based on a mix of personal experience, expert opinion, and reported studies.

The purpose of this systematic review was to analyze and summarize the evidence on drug therapies (topical and systemic) for the main clinical mani-

**Context** A variety of topical and systemic drugs are available to treat primary Sjögren syndrome, although no evidence-based therapeutic guidelines are currently available.

**Objective** To summarize evidence on primary Sjögren syndrome drug therapy from randomized controlled trials.

**Data Sources** We searched MEDLINE and EMBASE for articles on drug therapy for primary Sjögren syndrome published between January 1, 1986, and April 30, 2010.

**Study Selection** Controlled trials of topical and systemic drugs including adult patients with primary Sjögren syndrome were selected as the primary information source.

**Results** The search strategy yielded 37 trials. A placebo-controlled trial found significant improvement in the Schirmer and corneal staining scores, blurred vision, and artificial tear use in patients treated with topical ocular 0.05% cyclosporine. Three placebo-controlled trials found that pilocarpine was associated with improvements in dry mouth (61%-70% vs 24%-31% in the placebo group) and dry eye (42%-53% vs 26%). Two placebo-controlled trials found that cevimeline was associated with improvement in dry mouth (66%-76% vs 35%-37% in the placebo group) and dry eye (39%-72% vs 24%-30%). Small trials (<20 patients) found no significant improvement in sicca outcomes for oral prednisone or hydroxychloroquine and limited benefits for immunosuppressive agents (azathioprine and cyclosporine). A large trial found limited benefits for oral interferon alfa-2a. Two placebo-controlled trials of infliximab and etanercept did not achieve the primary outcome (a composite visual analog scale measuring joint pain, fatigue, and dryness); neither did 2 small trials (<30 patients) testing rituximab, although significant results were observed in some secondary outcomes and improvement compared with baseline.

**Conclusions** In primary Sjögren syndrome, evidence from controlled trials suggests benefits for pilocarpine and cevimeline for sicca features and topical cyclosporine for moderate or severe dry eye. Anti-tumor necrosis factor agents have not shown clinical efficacy, and larger controlled trials are needed to establish the efficacy of rituximab.

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festations of primary Sjögren syndrome (sicca symptoms and extraglandular involvement) in adults.

### METHODS

We searched MEDLINE and EMBASE using the MeSH term *Sjögren's syndrome* and subheading *therapy* with these restrictions: language (English), date (January 1, 1986, to April 30, 2010), study participants (humans), and age (adults).

Studies were eligible when the study population included adults with primary Sjögren syndrome and the intervention consisted of a drug therapy

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CME available online at [www.jamaarchivescme.com](http://www.jamaarchivescme.com) and questions on p 478.

(nondrug therapeutic interventions were excluded) (eTable 1, available at <http://www.jama.com>). Eligible studies had to be randomized controlled trials or prospective cohort studies (reviews, experimental studies, duplicate publications, retrospective cohort studies, case-control studies, and case reports were excluded). Studies also had to contain sufficient, clear information on the effect of the drug on clinical outcomes to be included. The control intervention could include placebo or standard therapy.

Two of us (M.R.C. and A.S.) read the titles and abstracts (if available) identified by the search and selected potentially eligible studies. Three of us (M.R.C., A.S., X.B.) fully reviewed the selected studies to determine criteria fulfillment. Disagreements between the 3 authors were discussed with the other 2 authors (A.G. and J.S.) until consensus was reached. Study authors were contacted when necessary (M.R.C.). Reference lists of relevant articles were also searched.

Three of us (M.R.C., A.S., X.B.) extracted the data independently. The data were entered into a database (M.R.C.), and the remaining 4 authors checked it.

The following variables were abstracted: first author, year of publication, population studied, number of patients, mean age and range, sex, subpopulations included (primary or associated Sjögren syndrome, sicca syndrome), classification criteria for primary Sjögren syndrome, study design and duration, drug, control population, primary and secondary outcomes, statistical comparisons, and adverse events.

Three of us (M.R.C., A.S., X.B.) assessed methodological quality of the selected trials according to the Cochrane Collaboration tool for assessing risk of bias,<sup>6</sup> documenting the method of sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias such as baseline imbalance or sources of bias related to the specific study design. Disagreements between the 3 authors were discussed with the other 2 authors (A.G.

and J.S.). Assessment of study heterogeneity is detailed in eSupplement.

## RESULTS

The search strategy yielded 37 controlled trials (5 with a crossover, wash-out design)<sup>7-43</sup> and 19 prospective cohort studies (FIGURE).<sup>44-62</sup>

### Overall Description of Trials

Sixteen trials included only primary Sjögren syndrome patients; 12 included patients with primary or associated Sjögren syndrome (7 detailed the types of patients, 263 of whom were primary and 136 associated); and 9 trials included patients with dry eye disease (including Sjögren syndrome), of which only 3 detailed how many Sjögren syndrome patients were included (389 of 1566 patients). In 5 trials,<sup>13,23,24,33,43</sup> the epidemiological profile of participants was not typical of primary Sjögren syndrome (mean age, <50 years; female to male ratio, <8:1).

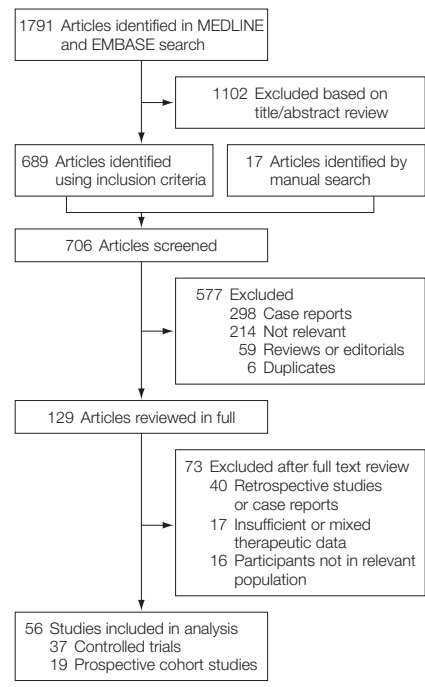
Six trials did not use a placebo,<sup>8,9,13-15,30</sup> and the drug tested was compared with standard therapy (artificial tears in 3 studies) or with other therapies (sucralfate, topical ocular diclofenac, punctal lachrymal occlusion). Therapies evaluated included eyedrops (topical nonsteroidal anti-inflammatory drugs [NSAIDs], glucocorticoids, or cyclosporine), oral sialogogues (pilocarpine or cevimeline), immunomodulatory and immunosuppressive drugs, and biologic therapies.

A variety of outcomes were defined (eTable 2). Primary and secondary outcomes were clearly specified in only 12 trials. The duration of included trials varied from 4 weeks to 1 year. When specific primary outcomes were not defined, we summarized the statistically significant results. A detailed evaluation of the methodological quality of trials is shown in eTable 3.

### Results of Individual Studies

**Eyedrops.** One controlled trial<sup>9</sup> compared 2 NSAIDs (0.1% diclofenac vs 0.1% indomethacin) and found a greater reduction in corneal sensitivity in the diclofenac group (43.5 mm vs 52.0 mm,

**Figure.** Flow Diagram of the MEDLINE and EMBASE Search



$P = .01$ ). Two controlled trials and 1 prospective study evaluated different topical glucocorticoids. The first trial<sup>8</sup> found that patients treated with fluorometholone had lower dry eye symptom severity scores in comparison with flurbiprofen ( $P = .03$ ) and artificial tears ( $P = .03$ ), and lower rose bengal and fluorescein staining scores in comparison with the flurbiprofen group ( $P = .046$  and  $P = .02$ , respectively). The second trial<sup>7</sup> found no significant differences between 0.5% loteprednol etabonate and placebo in the primary outcome of a combined corneal staining score (percent change at 4 weeks from baseline score,  $-5.9$  vs  $0.0$ ,  $P > .05$ ). The prospective study<sup>44</sup> found significant improvement in ocular tests scores with respect to baseline after treatment with topical 1% methylprednisolone, although severe dry eye symptoms recurred in 21% of patients.

Three placebo-controlled trials assessed topical cyclosporine in 1451 patients with moderate or severe dry eye disease (TABLE 1). The largest trial<sup>10</sup> tested 2 doses (0.05% and 0.1%) and

found significant improvement in Schirmer test scores for both groups ( $P < .007$ ) but improvement in corneal staining scores only in the 0.05% group ( $P = .008$ ;  $P = .06$  in the 0.1% group); the 0.05% group showed a significant improvement in 1 of 7 symptoms of ocular discomfort (blurred vision) evaluated using a 5-point scale ( $P < .01$ ) and a significant decrease in artificial tear use ( $P = .006$ ). A 12-month extension of this trial using the 0.1% dose found no additional improvement in these outcomes.<sup>11</sup> A con-

trolled trial<sup>12</sup> tested 4 doses (0.05%, 0.1%, 0.2%, and 0.4%) and found no linear dose-response results. The best results were obtained in the 0.1% and 0.05% groups.

Three controlled trials compared 0.05% cyclosporine with other therapies. Kim et al<sup>13</sup> found significant improvement in subjective evaluation of dry eye symptoms, tear film break-up time, and Schirmer test scores in 150 patients treated either with 0.05% cyclosporine or with 0.05% retinyl palmitate in comparison with artificial

tears. There were no differences between cyclosporine and retinyl palmitate. Sall et al<sup>14</sup> found a better dry eye symptom composite ( $P = .02$ ) and corneal staining scores ( $P = .005$ ) for the combination of cyclosporine and glycol-based tears compared with cyclosporine and standard artificial tears in 60 patients. Roberts et al<sup>15</sup> compared the use of 0.05% cyclosporine, punctal occlusion, and the 2 therapies combined in 30 patients; there were no differences between the cyclosporine/punctal occlusion combination and cyclospor-

**Table 1.** Trials Evaluating Topical Ocular Cyclosporine

Source	No. (F, No.)	Study Design (Duration)	Dose (Patients, No.)	Control (Patients, No.)	Results	Adverse Events
Sall et al, <sup>10</sup> 2000	877 (715)	RCT-d (24 wk)	0.05% (n = 293) and 0.1% (n = 292)	Placebo (n = 292)	0.05% vs placebo: better corneal staining score (NA, $P = .008$ ), conjunctival staining (NA, NS), better Schirmer test score (NA, $P < .007$ ), better score for blurred vision (NA, $P < .01$ ), other symptoms of dry eyes (NS), global response by physician assessment (35% vs 32%, NS), decrease in concomitant use of AT (NA, $P < .006$ ). 0.1% vs placebo: better corneal staining score (NA, $P = .06$ ), conjunctival staining (NA, NS), better Schirmer test score (NA, $P < .007$ ), symptoms of dry eyes (NS), global response by physician assessment (39% vs 32%, NS), decrease in concomitant use of AT (NS).	0.05% vs 0.1% vs placebo total: 25% and 29% vs 19% placebo ( $P < .001$ ); burning eye: 15% and 16% vs 6% placebo ( $P = .02$ )
Barber et al, <sup>11</sup> 2005	412 (331)	RCT-c 12-mo study extension (mean, 19.8 mo)	0.1%		Change from baseline at 12 mo: mean fluorescein corneal staining score (1.6 vs 1.2, NS), mean Schirmer test score, mm/5 min (5.8 vs 5.4, NS), mean OSDI (0.296 vs 0.282, NS), mean Facial Expression Subjective Scale score (2.5 vs 2.5, NS), scores for dry eye symptoms unchanged (NA).	Total: 91/412 (22%); AE >5%: burning eye, 11% (severe in 4 patients)
Stevenson et al, <sup>12</sup> 2000	162 (136)	RCT-d (12 wk)	0.05% (n = 31), 0.1% (n = 32), 0.2% (n = 34), 0.4% (n = 32)	Placebo (n = 33)	vs placebo: better temporal RB staining (0.1% and 0.05%, $P < .02$ ), superficial punctate keratitis score (NS), better sandy/gritty ocular feeling (0.05%, 0.1%, 0.2%, 0.4%), mean score for ocular dryness (NS), change in OSDI (NS), decrease in concomitant use of AT (NS).	0.05% vs 0.1% vs 0.2% vs 0.4% vs placebo total: 3%, 3%, 3%, 6% vs 9% placebo
Kim et al, <sup>13</sup> 2009	150 (86)	RCT (12 wk)	0.05% (n = 50)	Vit A (n = 50), CMC (n = 50)	Better blurred vision (cyclosporine and vit A vs CMC, $P < .05$ ), better break-up time (cyclosporine and vit A vs CMC, $P < .05$ ), better Schirmer test score (cyclosporine and vit A vs CMC, $P < .05$ ).	Burning eyes: 18% vs 14%, NA for CMC; stinging eyes: 10% vs 8%, NA for CMC
Sall et al, <sup>14</sup> 2006	60 (48)	RCT-s (24 wk)	0.05% + sys (n = 20)	0.05% + CMC (n = 20), sys alone (n = 20)	Cyclosporine/sys vs cyclosporine/CMC: better score dry eye symptoms ( $P = .02$ ); better corneal staining score ( $P = .005$ ); tear film break-up time (+1.56 vs +0.44, $P = .07$ ); better Schirmer test score (NS); less frequent ocular burning ( $P = .02$ ), grittiness ( $P = .01$ ), stinging ( $P = .03$ ), and scratchiness ( $P = .07$ ).	None
Roberts et al, <sup>15</sup> 2007	30 (25)	RCT (6 mo)	0.05% (n = 10)	0.05% + PO (n = 10), PO only (n = 10)	Cyclosporine and cyclosporine/PO vs PO only (change from baseline score): Schirmer test score (3.0 and 3.9 vs 3.8, NS), RB score (-0.9 and -1.0 vs -0.3, NS), AT uses/d (-3.2 and -3.9 vs -2.1; $P = .01$ cyclosporine/PO vs PO only).	1 withdrawal with cyclosporine (burning), 1 withdrawal with PO (discomfort), no other AE

Abbreviations: AE, adverse events; AT, artificial tears; c, crossover; CMC, carboxymethylcellulose (artificial tears); d, double-blind; F, female; NA, not available; NS, no significant differences; OSDI, Ocular Surface Disease Index; PO, punctal occlusion; RB, rose bengal staining; RCT, randomized controlled trial; s, single-blind; sys, polyethylene + propylene glycols; VAS, visual analog scale; vit A, retinyl palmitate 0.05%.

ine alone in Schirmer test (3.9 vs 3.0 mm over 3 minutes) and rose bengal staining scores (mean change, -1.0 vs 0.9) and less daily artificial tear use (3.9 vs 3.2 fewer uses per day).

A 6-month prospective study<sup>45</sup> showed statistically significant improvements from baseline in subjective and objective measures of dry eye ( $P < .001$ ) after treatment with topical 0.05% cyclosporine. The largest trial<sup>10</sup> found a significantly higher percentage of total adverse events in the 0.1% group (relative risk [RR], 1.28; 95% confidence interval [CI], 1.08-1.51) but not in the 0.05% group (RR, 1.17; 95% CI, 0.98-1.40) compared with placebo.

A placebo-controlled trial<sup>16</sup> evaluated 2 doses (1% and 2%) of topical ocular diquafosol, an agonist of the purinergic P2Y<sub>2</sub> receptor, in 527 patients and found better corneal staining scores (mean, 0.81 and 0.83, respectively, vs 0.94 in placebo;  $P < .05$ ) but not improved clearing of foreign body sensation.

**Sialogogues.** Three placebo-controlled trials evaluated oral pilocarpine in 673 patients (TABLE 2). The largest trial<sup>17</sup> evaluated 2 doses (2.5 and 5 mg every 6 hours) and found a higher frequency of improvement in dry mouth (61% vs 31%,  $P < .001$ ) and dry eye (42% vs 26%,  $P = .009$ ) in the 5-mg group but not in the 2.5-mg group. Papas et al<sup>18</sup> conducted a dose-escalating trial (from 5 to 7.5 mg every 6 hours) and also found a higher frequency of improvement in dry mouth (61% vs 31%,  $P < .001$ ) and dry eye (53% vs 26%,  $P < .001$ ), while Wu et al<sup>19</sup> found a similar improvement in dry mouth (70% vs 24%,  $P = .003$ ) using a dose of 5 mg every 6 hours. The largest trial<sup>17</sup> found a higher frequency of sweating (RR, 2.24; 95% CI, 1.82-2.76) and increased urinary frequency (RR, 1.77; 95% CI, 1.38-2.28) compared with placebo. In the dose-escalating trial,<sup>19</sup> 23% of patients switched from 7.5 to 5 mg every 6 hours because of adverse effects. A prospective study<sup>46</sup> used a lower dose (5 mg every 12 hours) and found greater improvement in subjective assessment of dry eye symptoms com-

pared with artificial tears ( $P = .001$ ) or punctal occlusion ( $P = .05$ ).

Four placebo-controlled trials evaluated oral cevimeline in 376 patients (Table 2). The largest trial<sup>20</sup> evaluated 2 doses (15 and 30 mg every 8 hours) and found a higher frequency of improvement in dry mouth (45% in the 15-mg group and 66% in the 30-mg group, vs 37% in the placebo group;  $P = .006$  and  $P < .001$ , respectively), dry eye (31% and 39% vs 24%,  $P > .05$  and  $P = .04$ , respectively), and overall dryness (32% and 66% vs 36%,  $P > .05$  and  $P < .001$ , respectively). The second trial<sup>21</sup> evaluated 2 doses (30 and 60 mg every 8 hours) and found a higher frequency of improvement in dry mouth (76% in the 30-mg group and 67% in the 60-mg group compared with 35% of patients in the placebo group,  $P = .004$  and  $P = .02$ , respectively), dry eye (72% and 52% vs 30%,  $P = .007$  and  $P = .10$ ), and overall dryness ( $P = .004$  and  $P = .03$ ). The third trial<sup>22</sup> found significant differences in subjective sicca symptoms in the 20-mg group but not in the 30-mg group, while the fourth trial, which tested 30 mg of cevimeline every 8 hours using a crossover design,<sup>23</sup> found no significant results.

The 2 latter trials included 104 patients compared with 272 included in the 2 larger trials. The 2 largest trials showed a significantly higher frequency of nausea (RR, 1.68; 95% CI, 1.18-2.40;  $P = .02$ ) and sweating (RR, 2.16; 95% CI, 1.65-2.82) in the 30-mg group compared with placebo,<sup>20</sup> and a higher frequency of nausea (RR, 2.77; 95% CI, 1.79-4.28), sweating (RR, 3.00; 95% CI, 1.70-5.28), and rigors (RR, 1.92; 95% CI, 1.28-2.87) in the 60-mg group in comparison with placebo.<sup>21</sup>

A prospective study<sup>47</sup> identified greater baseline stimulated whole saliva ( $P < .001$ ), lesser lymphocytic infiltration of salivary gland biopsy ( $P = .003$ ), and less-advanced sialography stage ( $P = .004$ ) as independent predictors of stimulated whole saliva after 4 weeks of cevimeline.

**Immunomodulatory or Immunosuppressive Drugs.** One controlled trial<sup>24</sup> compared oral prednisone (30 mg

per day) with piroxicam (20 mg per day) and placebo (8 patients each group). There was no difference between groups in salivary flow rate (SFR), Schirmer test, rose bengal staining score, or histopathological focus score. A prospective study<sup>48</sup> found that glucocorticoids did not influence progressive SFR worsening in 60 patients with primary Sjögren syndrome. However, another prospective study in 20 patients found that oral prednisone increased SFR.<sup>49</sup>

In 1993, Kruize et al<sup>25</sup> conducted a 2-year crossover trial using 400 mg of hydroxychloroquine per day in 19 patients and found no significant differences in hydroxychloroquine vs placebo for sicca symptoms, parotid enlargement, fatigue, myalgia, and arthralgia and no significant differences in ocular tests. A prospective study of hydroxychloroquine<sup>50</sup> in 14 patients found no effects on sicca symptoms and fatigue but significant differences in laboratory tests, including erythrocyte sedimentation rate (27.2 vs 43.1 mm per hour at baseline,  $P < .05$ ), C-reactive protein (2.1 vs 3.4 mg/dL,  $P < .05$ ), and IgG levels (1560 vs 2350 mg/dL,  $P < .05$ ). No retinal toxicity or severe adverse events were reported in either study.

Two placebo-controlled trials evaluated azathioprine<sup>26</sup> and oral cyclosporine<sup>27</sup> in 13 and 20 patients, respectively. The first trial<sup>26</sup> found no significant differences in any outcome. The second trial found a higher rate of improvement in xerostomia in patients treated with cyclosporine (80% vs 20%,  $P < .01$ ) without significant differences in the Schirmer test score (5.2 vs 5.0 mm) and SFR (1.14 vs 1.06 mL per 5 minutes). Three prospective studies evaluated the use of methotrexate,<sup>51</sup> leflunomide,<sup>52</sup> and mycophenolic acid<sup>53</sup> and found limited improvements in sicca symptoms. A common finding in all the studies was the high rate of adverse events (31% for azathioprine, 41% for methotrexate, 60% for cyclosporine, 63% for mycophenolic acid, and 100% for leflunomide). One controlled trial of thalidomide was stopped early because of an excess of adverse events.<sup>28</sup>

Three controlled studies evaluated oral interferon alfa-2a (150 IU daily). A small, controlled trial (12 patients) suggested a beneficial effect on unstimulated SFR and ocular or oral dryness,<sup>29</sup> while a single-blinded, sucral-fate-controlled trial<sup>30</sup> found a significant time-dependent increased production of whole saliva at 3 months but not at

**Table 2.** Trials Evaluating Oral Muscarinic Agonists (Pilocarpine and Cevimeline)

Source	No. (F, No.)	Study Design (Duration)	Drug (Patients, No.)	Control (Patients, No.)	Results	Adverse Events
Vivino et al, <sup>17</sup> 1999	373 (357)	RCT-d (12 wk)	Pilocarpine 2.5 mg/6 h (n = 121) and 5 mg/6 h (n = 127)	Placebo (n = 125)	Primary outcomes (5 mg vs placebo): higher % improving dry mouth (61% vs 31%, $P < .001$ ), higher % improving dry eyes (42% vs 26%, $P = .009$ ); figures NA for 2.5-mg group (NS). Secondary outcomes (5 mg vs placebo): better significant results in 4/5 dry mouth symptoms; better significant results in 3/15 dry eye symptoms; higher % improved nasal dryness ( $P < .002$ ), skin dryness ( $P < .01$ ), ability to expectorate mucus ( $P < .02$ ), and vaginal dryness ( $P < .02$ ); increased salivary flow, mL/min (0.17 vs 0.37, $P < .001$ ), figures NA for 2.5-mg group (NS).	5 mg vs 2.5 mg vs placebo: sweating, 43% vs 11% vs 7% ( $P = .001$ ); urinary frequency, 10% vs 11% vs 2% ( $P = .01$ )
Papas et al, <sup>18</sup> 2004	256 (242)	RCT-d (12 wk)	Pilocarpine (n = 128) 5 mg/6 h wk 0-6, 7.5 mg/6 h wk 6-12	Placebo (n = 128)	Primary outcomes: higher % improving dry mouth (61% vs 31%, $P < .001$ ), higher % improving dry eyes (53% vs 26%, $P < .001$ ). Secondary outcomes: better significant results in 5/7 dry mouth symptoms; better significant results in 6/8 dry eye symptoms; higher % with overall improvement in dryness (77% vs 41%, $P < .001$ ); higher % improved nasal dryness ( $P < .04$ ), skin dryness (NS), and vaginal dryness (NS); increased salivary flow (figures NA).	vs placebo: sweating, 64% vs 7% ( $P < .001$ ); urinary frequency, 15% vs 6% ( $P < .02$ ); flushing, 9% vs 3% ( $P = .003$ ); chills, 9% vs 1% ( $P = .004$ ); increased salivation, 7% vs 0% ( $P = .003$ )
Wu et al, <sup>19</sup> 2006	44 (39)	RCT-d (12 wk)	Pilocarpine 5 mg/6 h (n = 23)	Placebo (n = 21)	Higher % improved dry mouth (70% vs 24%, $P = .003$ ), mouth comfort ( $P = .04$ ), and ability to sleep ( $P = .009$ ), speak ( $P = .02$ ), and swallow ( $P = .07$ ); better significant results in 5/6 dry mouth VAS; higher mean increase in saliva production (0.05 vs -0.02, $P = .001$ ).	vs placebo: sweating, 22% vs 0% ( $P = .03$ ); no influence in vital signs
Petrone et al, <sup>20</sup> 2002	197 (187)	RCT-d (12 wk)	Cevimeline 15 mg/8 h (n = 65), 30 mg/8 h (n = 62)	Placebo (n = 70)	Primary outcomes (30 mg vs placebo): higher % improving dry mouth (66% vs 37%, $P < .001$ ), dry eyes (39% vs 24%, $P = .04$ ), and overall dryness (66% vs 36%, $P < .001$ ). Primary outcomes (15 mg vs placebo): higher % improving dry mouth (45% vs 37%, $P = .006$ ), dry eyes (31% vs 24%, NS), and overall dryness (32% vs 36%, NS). Secondary outcomes: increased lacrimal flow 15-mg vs placebo (95% CI, -0.14 to 1.22; $P = .03$ ), increased lacrimal flow 30-mg vs placebo (95% CI, 0.29 to 1.79; $P = .04$ ), data on salivary flow NA, VAS for sicca symptoms NA.	15 mg vs 30 mg vs placebo: nausea, 12% vs 21% vs 7% ( $P = .02$ ); sweating, 5% vs 18% vs 1% ( $P = .001$ )
Fife et al, <sup>21</sup> 2002	75 (65)	RCT-d (6 wk)	Cevimeline 30 mg/8 h (n = 25), 60 mg/8 h (n = 27)	Placebo (n = 23)	Primary outcomes (30 mg vs placebo): higher % improving dry mouth (76% vs 35%, $P < .004$ ), dry eyes (72% vs 30%, $P = .007$ ), and overall dryness (NA, $P = .004$ ). Primary outcomes (60 mg vs placebo): higher % improving dry mouth (67% vs 35%, $P = .02$ ), dry eyes (52% vs 30%, $P = .10$ ), and overall dryness (NA, $P = .03$ ). Secondary outcomes (30 mg vs placebo): better significant results in 2/6 dry mouth symptoms; better significant results in 2/3 dry eye symptoms; increased salivary flow, mL/min (0.19 vs 0.01, $P < .001$ ); increased lacrimal flow, mm/min (0.67 vs 0.71, NS); higher % reducing AT use (40% vs 44%, NS); higher % reducing saliva substitute use (4% vs 0%, NS). Secondary outcomes (60 mg vs placebo): better significant results in 2/6 dry mouth symptoms; better significant results in 1/3 dry eye symptoms; increased salivary flow, mL/min (0.26 vs 0.01, $P < .001$ ); increased lacrimal flow, mm/min (0.75 vs 0.71, NS); higher % reducing AT use (58% vs 44%, NS); higher % reducing saliva substitute use (19% vs 0%, $P = .07$ ).	30 mg vs 60 mg vs placebo: sweating, 16% vs 67% vs 9% ( $P < .001$ ); nausea, 20% vs 52% vs 0% ( $P < .001$ ); rigors, 4% vs 30% vs 4% ( $P = .03$ )

(continued)

**Table 2.** Trials Evaluating Oral Muscarinic Agonists (Pilocarpine and Cevimeline) (continued)

Source	No. (F, No.)	Study Design (Duration)	Drug (Patients, No.)	Control (Patients, No.)	Results	Adverse Events
Ono et al, <sup>22</sup> 2004	60 (57)	RCT-d (4 wk)	Cevimeline 20 mg/8 h (n = 18) 30 mg/8 h (n = 14)	Placebo (n = 17)	20 mg vs placebo: improved subjective symptoms (47% vs 17%, <i>P</i> = .05), corneconjunctival epithelium (42% vs 33%, <i>P</i> = .58), and tear dynamics (47% vs 12%, <i>P</i> = .03); overall improvement rating (32% vs 0%, <i>P</i> = .009); overall efficacy (24% vs 0%, <i>P</i> = .23). 30 mg vs placebo: improved subjective symptoms (47% vs 17%, <i>P</i> = .06), corneconjunctival epithelium (67% vs 33%, <i>P</i> = .06), and tear dynamics (27% vs 12%, <i>P</i> = .32); overall improvement rating (13% vs 0%, <i>P</i> = .11); overall efficacy (12% vs 0%, <i>P</i> = .12).	20 mg vs 30 mg vs placebo: diarrhea, 5% vs 28% vs 0% ( <i>P</i> = .04)
Leung et al, <sup>23</sup> 2008	44 (44)	RCT-c (10 wk, 4 wk washout, 10 wk)	Cevimeline 30 mg/8 h (n = 21)	Placebo (n = 23)	vs placebo: mean change in XI score (-2.6 vs -0.9, <i>P</i> = .20), mean change in GOHAI score (1.4 vs -0.1, <i>P</i> = .06), mean change whole salivary flow (0.04 vs -0.04, <i>P</i> = .56), mean change parotid salivary flow (0.03 vs 0, <i>P</i> = .27), mean change xerostomia tongue ( <i>P</i> = .39).	Cevimeline: sweating, 14%; gastrointestinal, 19%; palpitation, 24%; heat sensation, 10%

Abbreviations: AT, artificial tears; c, crossover; d, double-blind; F, female; GOHAI, General Oral Health Assessment Index; NA, not available; NS, no significant differences; RCT, randomized controlled trial; VAS, visual analog scale; XI, Xerostomia Inventory.

6 months. In contrast, a large placebo-controlled trial including 497 patients<sup>31</sup> found significant improvement in only 1 of 28 outcomes evaluated (unstimulated whole saliva, *P* = .01) and a higher percentage of adverse events (40% vs 25% in the placebo group, *P* < .001).

**Biologic Agents.** A placebo-controlled trial<sup>32</sup> evaluated infliximab in 103 patients and found no significant differences in the primary outcome ( $\geq 30\%$  improvement in 2 of 3 visual analog scales [VAS] measuring joint pain, fatigue, and dryness) (17% vs 20%, *P* = .62). No significant differences were found for the secondary outcomes (TABLE 3). In contrast, a previous prospective study in 16 patients found significant improvements in subjective and objective sicca measures.<sup>54</sup>

A placebo-controlled trial<sup>34</sup> evaluated etanercept in 28 patients and found no significant differences in the primary outcome ( $\geq 20\%$  improvement in the values on 2 of 3 domains: oral, ocular, and laboratory) (36% vs 21%, *P* = .20). No significant differences were found for the secondary outcomes. Similar negative results were found in a prospective study in 15 patients.<sup>58</sup>

Two placebo-controlled trials evaluated the use of rituximab (two 1000-mg doses 15 days apart) (Table 3). The first 48-week trial<sup>33</sup> included 30 patients with

stimulated SFR at 0.15 mL or greater per minute and achieved the primary outcome (improvement of stimulated SFR) at 12 weeks (0.87 vs 0.28 mL/minute in the placebo group, *P* = .04) but not at the end of the study. Only the VAS score for dry eye significantly improved at 48 weeks (46 vs 76, *P* < .05) while other secondary outcomes improved at different study time points but not at 48 weeks. The second trial<sup>35</sup> including 17 patients with a baseline fatigue VAS score greater than 50 did not achieve the primary outcome ( $\geq 20\%$  improvement in VAS fatigue score with respect to placebo) (87% vs 56%, *P* = .36). The 2 trials included a premedication dose of 100-mg methylprednisolone and a short course (<15 days) of high-dose oral prednisone in both the rituximab and placebo groups; concurrent medication such as immunosuppressive agents was only permitted in the second trial.<sup>35</sup> Two prospective studies found significant improvements in sicca and general symptoms compared with baseline values.<sup>56,57</sup>

A prospective study in 16 patients treated with epratuzumab found significant improvements in fatigue and subjective patient and physician assessments.<sup>55</sup>

**Miscellanea.** A placebo-controlled trial tested oral N-acetylcysteine in 26 patients and found significant improvement in the van Bijsterweld score and

dry eye and mouth symptoms compared with baseline, although specific results were not detailed.<sup>36</sup>

Several drugs have been tested in placebo-controlled trials (rebamipide, doxycycline, dehydroepiandrosterone, and lamivudine)<sup>37-43</sup> and prospective studies (nizatidine, zidovudine, mizoribine, and D-penicillamine)<sup>59-62</sup> without significant benefits.

## COMMENT

This systematic review reveals a very low level of evidence for the majority of drugs currently used in primary Sjögren syndrome. In addition, less than 10% of the studies were designed to compare different drugs in the same clinical scenario. However, some recommendations on drug therapy can be proposed for the management of the main symptoms.

## Xerophthalmia

Frequent use of preservative-free tear substitutes are recommended, while ocular lubricating ointments are usually reserved for nocturnal use.<sup>2,4,5</sup> Controlled trials support the use of topical 0.05% cyclosporine twice daily for patients with moderate to severe dry eye disease, although the largest trials did not include predominantly patients with primary Sjögren syndrome.<sup>10,12</sup> However, in one study, no further improvements were reported after 6 ad-

ditional months of treatment.<sup>11</sup> Patients with severe refractory ocular dryness may require the addition of topical NSAIDs or glucocorticoids, although these should only be prescribed by ophthalmologists for the minimum time necessary, because of adverse events associated with long-term use.<sup>63</sup>

### Xerostomia

Saliva replacement products and sugar-free chewing gums may be effective for mild to moderate dry mouth. Alcohol and smoking should be avoided and thorough oral hygiene is essential.<sup>2,4,5</sup> For patients with residual salivary gland function, oral pilocarpine and cevime-

line are the treatment of choice. However, the efficacy of the 2 drugs has not been compared. The doses that best balance efficacy and adverse effects are 5 mg every 6 hours for pilocarpine and 30 mg every 8 hours for cevimeline. In patients with contraindications or intolerance to muscarinic agonists, N-acetylcysteine may be an alternative.

### General Symptoms

No clear benefit from hydroxychloroquine for general symptoms (muscle and joint pain, fatigue) was reported by controlled and prospective studies (all had small sample sizes); its use is only supported by retrospective studies.<sup>64,65</sup> The

off-label use of biologic agents to treat general symptoms only, even when severe, is not warranted at present.

### Extraglandular Involvement

There is limited evidence on the use of glucocorticoids and immunosuppressive agents, since controlled and prospective studies were small and were specifically designed to evaluate sicca features. Rituximab has shown improvement in some extraglandular features in a recent controlled trial (vasculitis) and 3 uncontrolled studies (vasculitis, neuropathy, glomerulonephritis, and arthritis).<sup>66-68</sup> However, while awaiting the results of larger trials, rituximab may be considered as a res-

**Table 3.** Trials Evaluating Biologic Agents

Source	No. (F, No.)	Study Design (Duration)	Drug (Patients, No.)	Control (Patients, No.)	Results	Adverse Events
Mariette et al. <sup>32</sup> 2004	103 (NA)	RCT-d (22 wk)	Infliximab 5 mg/kg (n = 54) wk 0, 2, 6	Placebo (n = 49)	Primary outcome (vs placebo): % of patients with favorable response (17% vs 20%, <i>P</i> = .62). Secondary outcomes (vs placebo): patients with ≥30% decrease in pain VAS (20% vs 26%, <i>P</i> = .46), fatigue VAS (24% vs 24%, <i>P</i> = .96), and dryness VAS (17% vs 16%, <i>P</i> = .96); change in salivary flow rate, mL/min (0.03 vs 0.02, <i>P</i> = .24), Schirmer test, mm (0.9 vs 1.5, <i>P</i> = .75), swollen joint count (−0.4 vs −0.3, <i>P</i> = .75), tender joint count (−2.4 vs −2.3, <i>P</i> = .97), ESR, mm/h (−0.8 vs −0.9, <i>P</i> = .97), CRP, mg/L (−0.4 vs −0.5, <i>P</i> = .96), gamma globulins, g/L (0.78 vs 0.13, <i>P</i> = .05), IgG, g/L (0.74 vs 0.03, <i>P</i> = .24), IgA, g/L (0.16 vs 0.09, <i>P</i> = .56), and IgM, g/L (0.34 vs 0.04, <i>P</i> = .001).	Total vs placebo: 11% vs 2% ( <i>P</i> = .11); infliximab: 2 infusion reactions, 1 lupus-like rash, 1 autoimmune hepatitis, 1 pneumococcal septicemia, 1 breast cancer; placebo: 1 polyclonal lymph node enlargement
Meijer et al. <sup>33</sup> 2010	30 (29)	RCT-d (48 wk)	Rituximab 1 g/15 d (n = 20) wk 0 and 2	Placebo (n = 10)	Primary outcome (vs placebo): increased stimulated whole saliva, mL/min (0.66 vs 0.28, NS). Secondary outcomes (vs placebo): increased unstimulated whole saliva, mL/min (0.18 vs 0.05, NS), Schirmer test score, mm/5 min (10 vs 5, NS), lysamine green score (2 vs 4, NS), tear break-up time, sec (6 vs 4, NS), IgM-R, U/L (103 vs 225, NS), MFI general fatigue score (15 vs 14, NS), SF-36 total score (55 vs 62, NS), oral dryness VAS (50 vs 69, NS), dry eyes VAS (46 vs 76, <i>P</i> < .05).	Total vs placebo: NA; total infections vs placebo: 55% vs 40% ( <i>P</i> = .43); 12 infections in 11 rituximab patients, 7 infections in 4 placebo patients
Sankar et al. <sup>34</sup> 2004	28 (26)	RCT-d (12 wk)	Etanercept 25 mg (n = 14) twice per wk	Placebo (n = 14)	Primary outcome (vs placebo): % of patients with favorable response (36% vs 21%, <i>P</i> = .20). Secondary outcomes (vs placebo): change in dry mouth VAS (−2 vs 3, <i>P</i> = .44), dry eyes VAS (1 vs −0.5, <i>P</i> = .53), salivary flow rate, mL/min (−0.03 vs −0.22, <i>P</i> = .63), Schirmer test, mm/5 min (−0.75 vs −0.5, <i>P</i> = .55), van Bijsterveld score (0 vs −0.25, <i>P</i> = .96), IgG, mg/dL (10 vs −30, <i>P</i> = .82), and ESR, mm/h (−5.5 vs 1.5, <i>P</i> = .004).	Total vs placebo: 14% vs 7% ( <i>P</i> = .50); AE etanercept: 1 atypical injection-site reaction, 1 rapidly enlarging skin lesion; AE placebo: upper respiratory infection
Dass et al. <sup>35</sup> 2008	17 (NA)	RCT-d (6 mo)	Rituximab 1 g/15 d (n = 8) wk 0 and 2	Placebo (n = 9)	Primary outcome (vs placebo): patients with >20% improvement in fatigue VAS (87% vs 56%, <i>P</i> = .36). Secondary outcomes (vs placebo): social functioning SF-36 score (12 vs −25, <i>P</i> = .01), mental health SF-36 score (4 vs −24, <i>P</i> = .06), PROFAD differences NA, RF reduction (45 vs 0, <i>P</i> = .05), immunoglobulin levels (NS), Schirmer test, salivary flow rate (NS).	3 serious AE in 2 patients (delayed reaction with meningism, probable gastroenteritis, palpitations), 2 additional infusion reactions

Abbreviations: AE, adverse events; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; MFI, Multidimensional Fatigue Inventory; NA, not available; NS, no significant differences; PROFAD, Profile of Fatigue and Discomfort; RCT-d, double-blind randomized controlled trial; RF, rheumatoid factor; SF-36, 36-Item Short Form Health Survey; VAS, visual analog scale.

cue therapy in patients refractory to standard treatment.<sup>69</sup>

### Life-Threatening Situations

Treatment of severe, life-threatening involvement has rarely been detailed and at present, there are only a few retrospective studies and isolated case reports. However, this scanty evidence, taken together with expert review, suggests that methylprednisolone and cyclophosphamide pulses, possibly together with plasma exchanges, should be used in patients with rapidly progressing extraglandular features (glomerulonephritis, neuropathy, interstitial lung disease, or myelitis) or with severe systemic vasculitis.<sup>2,4,5</sup> Rituximab is increasingly used in life-threatening situations and cases of B-cell lymphoma.<sup>69</sup>

### CONCLUSION

In the last 3 decades, therapeutic approaches in primary Sjögren syndrome have been based on the use of substitute agents for sicca features and glucocorticoids and immunosuppressive agents for extraglandular involvement. The emergence of new immunosuppressive agents and biologic therapies has increased the therapeutic armamentarium available in the most severe situations, but their use is limited by the lack of specific licensing.

This systematic review highlights the limited evidence available for the drugs most frequently used in primary Sjögren syndrome and the difficulties of offering solid therapeutic recommendations. There is even less scientific evidence on the treatment of patients who do not respond to first-line therapies. International efforts are required to collect and characterize large multicenter cohorts of patients<sup>70</sup> and develop consensual end points for homogeneous evaluation of the main outcomes.<sup>71</sup> B-cell targeted agents seem to be the most promising future therapy, as suggested by recent preliminary studies,<sup>72,73</sup> especially rituximab, which has been used in more than 100 reported cases. However, 2 recent controlled trials did not achieve the primary outcome. Agents that

block BAFF (B cell-activating factor of the tumor necrosis factor family) may also be a promising therapy.<sup>74</sup> Advances in knowledge of the molecular mechanisms involved in the etiopathogenesis of primary Sjögren syndrome may allow the development of more effective, highly selective therapies without the adverse effects often associated with standard, less-selective drugs.

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### REFERENCES

1. Sjögren H. About keratoconjunctivitis sicca: keratitis filiformis with hypofunction of the lacrimal glands [in Dutch]. *Acta Ophthalmol (Copenh)*. 1933; 11(suppl 2):1-151.
2. Kassin SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med*. 2004;164(12):1275-1284.
3. Helmick CG, Felson DT, Lawrence RC, et al; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part I. *Arthritis Rheum*. 2008;58(1):15-25.
4. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. *Ann Rheum Dis*. 2005;64(3):347-354.
5. Ramos-Casals M, Font J. Primary Sjögren syndrome. In: Imboden J, Hellman D, Stone JH, eds. *Current Diagnosis and Treatment in Rheumatology*. New York, NY: McGraw-Hill; 2007:237-245.
6. Tetzlaff JM, Moher D, Sterne JAC, Altman DG, Weeks L, Turner L; Cochrane Bias Methods Group. About the Cochrane Collaboration (methods groups) [article No. CE000140]. <http://www.mrw.interscience.wiley.com/cochrane/dabout/articles/CE000140/sect0.html>. Accessed June 25, 2010.
7. Pflugfelder SC, Maskin SL, Anderson B, et al. A randomized, double-masked, placebo-controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5%, and placebo for treatment of

keratoconjunctivitis sicca in patients with delayed tear clearance. *Am J Ophthalmol*. 2004;138(3):444-457.

8. Avunduk AM, Avunduk MC, Varnell ED, Kaufman HE. The comparison of efficacies of topical corticosteroids and nonsteroidal anti-inflammatory drops on dry eye patients: a clinical and immunocytochemical study. *Am J Ophthalmol*. 2003;136(4):593-602.

9. Aragona P, Stilo A, Ferreri F, Mubrici M. Effects of the topical treatment with NSAIDs on corneal sensitivity and ocular surface of Sjögren's syndrome patients. *Eye (Lond)*. 2005;19(5):535-539.

10. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease: CsA Phase 3 Study Group. *Ophthalmology*. 2000;107(4):631-639.

11. Barber LD, Pflugfelder SC, Tauber J, Foulks GN. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. *Ophthalmology*. 2005;112(10):1790-1794.

12. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial: the Cyclosporin A Phase 2 Study Group. *Ophthalmology*. 2000;107(5):967-974.

13. Kim EC, Choi JS, Joo CK. A comparison of vitamin A and cyclosporine A 0.05% eye drops for treatment of dry eye syndrome. *Am J Ophthalmol*. 2009; 147(2):206-213, e3.

14. Sall KN, Cohen SM, Christensen MT, Stein JM. An evaluation of the efficacy of a cyclosporine-based dry eye therapy when used with marketed artificial tears as supportive therapy in dry eye. *Eye Contact Lens*. 2006;32(1):21-26.

15. Roberts CW, Carniglia PE, Brazzo BG. Comparison of topical cyclosporine, punctal occlusion, and a combination for the treatment of dry eye. *Cornea*. 2007;26(7):805-809.

16. Tauber J, Davitt WF, 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(8):784-792.

17. Vivino FB, Al-Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial: P92-01 Study Group. *Arch Intern Med*. 1999;159(2):174-181.

18. Papas AS, Sherrer YS, Charney M, et al. Successful treatment of dry mouth and dry eye symptoms in Sjögren's syndrome patients with oral pilocarpine: a randomized, placebo-controlled, dose-adjustment study. *J Clin Rheumatol*. 2004;10(4):169-177.

19. Wu CH, Hsieh SC, Lee KL, Li KJ, Lu MC, Yu CL. Pilocarpine hydrochloride for the treatment of xerostomia in patients with Sjögren's syndrome in Taiwan: a double-blind, placebo-controlled trial. *J Formos Med Assoc*. 2006;105(10):796-803.

20. Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum*. 2002;46(3):748-754.

21. Fife RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. *Arch Intern Med*. 2002; 162(11):1293-1300.

22. Ono M, Takamura E, Shinozaki K, et al. Therapeutic effect of cevimeline on dry eye in patients with Sjögren's syndrome: a randomized, double-blind clinical study. *Am J Ophthalmol*. 2004;138(1):6-17.

23. Leung KC, McMillan AC, Wong MC, Leung WK, Mok MY, Lau CS. The efficacy of cevimeline hydrochloride in the treatment of xerostomia in Sjögren's



- syndrome in southern Chinese patients: a randomised double-blind, placebo-controlled crossover study. *Clin Rheumatol*. 2008;27(4):429-436.
24. Fox PC, Datiles M, Atkinson JC, et al. Prednisone and piroxicam for treatment of primary Sjögren's syndrome. *Clin Exp Rheumatol*. 1993;11(2):149-156.
  25. Kruije AA, Hené RJ, Kallenberg CG, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. *Ann Rheum Dis*. 1993;52(5):360-364.
  26. Price EJ, Rigby SP, Clancy U, Venables PJ. A double blind placebo controlled trial of azathioprine in the treatment of primary Sjögren's syndrome. *J Rheumatol*. 1998;25(5):896-899.
  27. Drosos AA, Skopouli FN, Galanopoulou VK, Kitridou RC, Moutsopoulos HM. Cyclosporin A therapy in patients with primary Sjögren's syndrome: results at one year. *Scand J Rheumatol Suppl*. 1986;61:246-249.
  28. Pillemer SR, Leakan RA, Sankar V, et al. Prominent adverse effects of thalidomide in primary Sjögren's syndrome. *Arthritis Rheum*. 2004;51(3):505-506.
  29. Shiozawa S, Tanaka Y, Shiozawa K. Single-blinded controlled trial of low-dose oral IFN-alpha for the treatment of xerostomia in patients with Sjögren's syndrome. *J Interferon Cytokine Res*. 1998;18(4):255-262.
  30. Khurshudian AV. A pilot study to test the efficacy of oral administration of interferon-alpha lozenges to patients with Sjögren's syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;95(1):38-44.
  31. Cummins MJ, Papas A, Kammer GM, Fox PC. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. *Arthritis Rheum*. 2003;49(4):585-593.
  32. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum*. 2004;50(4):1270-1276.
  33. 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(4):960-968.
  34. 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(7):2240-2245.
  35. 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(11):1541-1544.
  36. Walters MT, Rubin CE, Keightley SJ, Ward CD, Cawley MI. A double-blind, cross-over, study of oral N-acetylcysteine in Sjögren's syndrome. *Scand J Rheumatol Suppl*. 1986;61:253-258.
  37. Sugai S, Takahashi H, Ohta S, et al. Efficacy and safety of rebamipide for the treatment of dry mouth symptoms in patients with Sjögren's syndrome: a double-blind placebo-controlled multicenter trial. *Mod Rheumatol*. 2009;19(2):114-124.
  38. Seitsalo H, Niemelä RK, Marinescu-Gava M, Vuotila T, Tjäderhane L, Salo T. Effectiveness of low-dose doxycycline (LDD) on clinical symptoms of Sjögren's syndrome: a randomized, double-blind, placebo controlled cross-over study. *J Negat Results Biomed*. 2007;6:11.
  39. Pillemer SR, Brennan MT, Sankar V, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjögren's syndrome. *Arthritis Rheum*. 2004;51(4):601-604.
  40. Hartkamp A, Geenen R, Godaert GL, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren syndrome: a randomised controlled trial. *Ann Rheum Dis*. 2008;67(1):91-97.
  41. Forsblad-d'Elia H, Carlsten H, Labrie F, Konttinen YT, Ohlsson C. Low serum levels of sex steroids are associated with disease characteristics in primary Sjögren's syndrome; supplementation with dehydroepiandrosterone restores the concentrations. *J Clin Endocrinol Metab*. 2009;94(6):2044-2051.
  42. Virkki LM, Porola P, Forsblad-d'Elia H, Valtysdottir S, Solovieva SA, Konttinen YT. Dehydroepiandrosterone (DHEA) substitution treatment for severe fatigue in DHEA-deficient patients with primary Sjögren's syndrome. *Arthritis Care Res (Hoboken)*. 2010;62(1):118-124.
  43. Gescuc B, Wu AJ, Whitcher JP, et al. Lamivudine is not effective in primary Sjögren's syndrome. *Ann Rheum Dis*. 2005;64(9):1326-1330.
  44. Hong S, Kim T, Chung SH, Kim EK, Seo KY. Recurrence after topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren's syndrome. *J Ocul Pharmacol Ther*. 2007;23(1):78-82.
  45. Toker E, Asfuroğlu E. Corneal and conjunctival sensitivity in patients with dry eye: the effect of topical cyclosporine therapy. *Cornea*. 2010;29(2):133-140.
  46. Tsifetaki N, Kitsos G, Paschides CA, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. *Ann Rheum Dis*. 2003;62(12):1204-1207.
  47. Yamada H, Nakagawa Y, Wakamatsu E, et al. Efficacy prediction of cevimeline in patients with Sjögren's syndrome. *Clin Rheumatol*. 2007;26(8):1320-1327.
  48. Pijpe J, Kalk WW, Bootsma H, Spijkervet FK, Kallenberg CG, Vissink A. Progression of salivary gland dysfunction in patients with Sjögren's syndrome. *Ann Rheum Dis*. 2007;66(1):107-112.
  49. Miyawaki S, Nishiyama S, Matoba K. Efficacy of low-dose prednisolone maintenance for saliva production and serological abnormalities in patients with primary Sjögren's syndrome. *Intern Med*. 1999;38(12):938-943.
  50. Tishler M, Yaron I, Shirazi I, Yaron M. Hydroxychloroquine treatment for primary Sjögren's syndrome: its effect on salivary and serum inflammatory markers. *Ann Rheum Dis*. 1999;58(4):253-256.
  51. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjögren's syndrome. *Clin Exp Rheumatol*. 1996;14(5):555-558.
  52. van Woerkom JM, Kruije AA, Geenen R, et al. Safety and efficacy of leflunomide in primary Sjögren's syndrome: a phase II pilot study. *Ann Rheum Dis*. 2007;66(8):1026-1032.
  53. Willeke P, Schlüter B, Becker H, Schotte H, Domschke W, Gaubitz M. Mycophenolate sodium treatment in patients with primary Sjögren syndrome: a pilot trial. *Arthritis Res Ther*. 2007;9(6):R115.
  54. Steinfeld SD, Demols P, Salmon I, Kiss R, Appelboom T. Infliximab in patients with primary Sjögren's syndrome: a pilot study. *Arthritis Rheum*. 2001;44(10):2371-2375.
  55. Steinfeld SD, Tant L, Burmester GR, et al. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phase I/II study. *Arthritis Res Ther*. 2006;8(4):R129.
  56. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). *Arthritis Rheum*. 2007;57(2):310-317.
  57. Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. *Arthritis Rheum*. 2005;52(9):2740-2750.
  58. Zandbelt MM, de Wilde P, van Damme P, Hoyng CB, van de Putte L, van den Hoogen F. Etanercept in the treatment of patients with primary Sjögren's syndrome: a pilot study. *J Rheumatol*. 2004;31(1):96-101.
  59. Nakayamada S, Saito K, Umehara H, et al. Efficacy and safety of mizoribine for the treatment of Sjögren's syndrome: a multicenter open-label clinical trial. *Mod Rheumatol*. 2007;17(6):464-469.
  60. Kasama T, Shiozawa F, Iozaki T, et al. Effect of the H2 receptor antagonist nizatidine on xerostomia in patients with primary Sjögren's syndrome. *Mod Rheumatol*. 2008;18(5):455-459.
  61. ter Borg EJ, Haanen HC, Haas FJ, et al. Treatment of primary Sjögren's syndrome with D-penicillamine: a pilot study. *Neth J Med*. 2002;60(10):402-406.
  62. Steinfeld SD, Demols P, Van Vooren JP, Cogan E, Appelboom T. Zidovudine in primary Sjögren's syndrome. *Rheumatology (Oxford)*. 1999;38(9):814-817.
  63. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjögren syndrome. *Ophthalmology*. 1999;106(4):811-816.
  64. Rihl M, Ulbricht K, Schmidt RE, Witte T. Treatment of sicca symptoms with hydroxychloroquine in patients with Sjögren's syndrome. *Rheumatology (Oxford)*. 2009;48(7):796-799.
  65. Fox RI, Dixon R, Guarrasi V, Krubel S. Treatment of primary Sjögren's syndrome with hydroxychloroquine: a retrospective, open-label study. *Lupus*. 1996;5(suppl 1):S31-S36.
  66. Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. *Ann Rheum Dis*. 2007;66(3):351-357.
  67. Gottenberg JE, Guillevin L, Lambotte O, et al; Club Rhumatismes et Inflammation (CRI). Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. *Ann Rheum Dis*. 2005;64(6):913-920.
  68. Ramos-Casals M, García-Hernández FJ, De Ramon E, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases [published online June 3, 2010]. *Clin Exp Rheumatol*.
  69. Ramos-Casals M, Brito-Zerón P, Muñoz S, Soto MJ; BIOGEAS STUDY Group. A systematic review of the off-label use of biological therapies in systemic autoimmune diseases. *Medicine (Baltimore)*. 2008;87(6):345-364.
  70. Ramos-Casals M, Solans R, Rosas J, et al; GEMESS Study Group. Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine (Baltimore)*. 2008;87(4):210-219.
  71. Seror R, Ravaud P, Bowman SJ, et al; EULAR Sjögren's Task Force. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis*. 2010;69(6):1103-1109.
  72. Pijpe J, Meijer JM, Bootsma H, et al. Clinical and histologic evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjögren's syndrome. *Arthritis Rheum*. 2009;60(11):3251-3256.
  73. Jousse-Joulin S, Devauchelle-Pensec V, Morvan J, et al. Ultrasound assessment of salivary glands in patients with primary Sjögren's syndrome treated with rituximab: quantitative and Doppler waveform analysis. *Biologics*. 2007;1(3):311-319.
  74. Pers JO, Devauchelle V, Daridon C, et al. BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjögren's syndrome. *Arthritis Rheum*. 2007;56(5):1464-1477.