Etanercept in the Treatment of Patients with Primary Sjögren's Syndrome: A Pilot Study

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ABSTRACT. ***Objective.*** This pilot study evaluated the effect of anti-tumor necrosis factor-α antiinflammatory treatment with etanercept (Enbrel®) on sicca, systemic, and histological signs in patients with primary Sjögren's syndrome (SS).

Methods. Fifteen patients with well defined primary SS were treated with 25 mg etanercept subcutaneously twice per week during 12 weeks, with followup visits at Weeks 18 and 24. Evaluation measures included a Multidimensional Fatigue Inventory (MFI) questionnaire, serological monitoring, salivary flow tests, Schirmer test, rose bengal cornea staining, and tear film breakup time. A sublabial minor salivary gland biopsy was performed at baseline and at Week 12 and lymphocytic focus score and percentage IgA-containing plasma cells (IgA%) were assessed.

Results. No increase of salivary or lachrymal gland function was observed in any participant. In 4 patients a decrease of fatigue complaints was noted, which was also reflected by decreased scores in the MFI questionnaire. Reduced erythrocyte sedimentation rate was observed in 3 of 4 patients with reduced fatigue. No significant change of lymphocyte focus score or IgA% was observed. A repeated treatment up to 26 weeks showed the same results.

Conclusion. A 12-week or prolonged treatment of etanercept 25 mg twice weekly did not appear to reduce sicca symptoms and signs in SS. However, etanercept treatment may be beneficial in a small subgroup of SS patients with severe fatigue. Etanercept 25 mg twice weekly did not affect minor salivary gland biopsy results. (J Rheumatol 2004;31:96–101)

Key Indexing Terms:
SJÖGREN'S SYNDROME SALIVARY GLAND BIOPSY SICCA FATIGUE
ETANERCEPT ANTI-TUMOR NECROSIS FACTOR-ALPHA

Sjögren's syndrome (SS) is a chronic autoimmune exocrinopathy of unknown origin. As a consequence of exocrinopathy, patients present with sicca signs such as irritated eyes, a dry mouth, chronic cough, and dyspareunia. Other manifestations of SS include nonspecific systemic symptoms such as moderate to severe invalidating fatigue, arthralgia, myalgia, and intermitting fever[1]. Patients with SS have an increased risk to develop non-Hodgkin's lymphoma, which affects about 5% of these patients[2].

The diagnosis of SS is frequently guided by classification criteria sets. Within the recently proposed US/European consensus group classification criteria[3], objective items such as presence of anti-SSA or anti-SSB autoantibodies and minor salivary gland biopsy showing a lymphocytic focus score (LFS) > 1 are emphasized. In addition to the LFS, which describes the extent of a lymphocytic infiltrate, the composition of the infiltrate can also serve as a diagnostic tool. For example, the percentage IgA-containing plasma cells (IgA%) appears to have greater disease specificity and sensitivity than the LFS[4,5].

Apart from the discomfort patients with SS experience from sicca symptoms (e.g., sleep disturbance), the effect of systemic symptoms is often underestimated. Moderate to severe fatigue is a frequent complaint[6] that disables a subgroup of SS patients to such an extent that it leads to incapacity for work and limits social activities, leading to social isolation.

To date, no effective systemic treatment is available for SS. Disease modifying antirheumatic drugs (DMARD) that are successful in the treatment of several other rheumatic diseases did not turn out to be a successful overall approach in SS[7]. Treatment is therefore mainly symptomatic and consists of artificial eyedrops and saliva. Pilocarpine has been shown to enhance autologous production of both saliva and tears in patients with SS[8].

Although some efforts were undertaken to treat fatigue complaints using conventional or experimental drugs, none has been proven to effectively reduce fatigue in patients with SS[9,10]. Thus, while local symptoms like irritated eyes and dry mouth may be alleviated to some extent, there is

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neither a systemic nor a symptomatic treatment available to reduce moderate to severe incapacitating fatigue in SS.

Recently, biological agents inhibiting the proinflammatory cytokine tumor necrosis factor (TNF-α) have been approved for the treatment of rheumatoid arthritis (RA) and chronic juvenile arthritis[11,12]. Promising results have also been presented for the efficacy of anti-TNF-α treatment in psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and Wegener's granulomatosis[13-15].

Since enhanced TNF-α expression has been observed in exocrine glands of patients with SS[16,17], anti-TNF-α treatment might potentially suppress inflammation in SS with local and systemic effects. Further, although not well documented, RA patients in practice frequently report not only a beneficial effect of anti-TNF-α treatment on joint symptoms but also a marked improvement of perceived condition and energy.

A recent pilot study by Steinfeld and co-workers described treatment with infliximab, an intravenously administered monoclonal chimeric anti-TNF-α antibody, evaluated in 16 patients with SS. Both local (reduced sicca signs) and systemic (reduced fatigue) responses were reported[18].

Etanercept (Enbrel®), a soluble fully human TNF-α-p75-receptor fusion protein, also interferes with the inflammatory process by binding and inactivating the proinflammatory cytokine TNF-α[19]. Etanercept can be administered subcutaneously by the patients themselves. Our pilot study investigated the potential local and systemic therapeutic effects of etanercept in patients with primary SS.

From a diagnostic point of view, a secondary aim of the study was to evaluate whether etanercept treatment would influence minor salivary gland (MSG) biopsy scores. This hypothesis was based on our observation of a normalized LFS and IgA% following immunomodulatory treatment with high dose corticosteroids in a patient with SS[20].

MATERIALS AND METHODS

Patient selection. A total of 15 patients with primary SS fulfilling the US/European consensus group classification criteria[3] were included upon giving informed consent. Evidence of sublabial MSG involvement was present in all 15 patients, indicated by a LFS > 1. An IgA-containing plasma cells percentage (IgA%) < 70, shown to be strongly associated with SS[4], was present in all patients.

Patients did not use immunosuppressive agents such as corticosteroids or DMARD. Pilocarpine, which potentially increases salivary flow and tear production, was taken in a constant dosage throughout the study by one of the 15 participants.

At baseline, patients had to have experience of moderate to severe fatigue, which was the main outcome measure in this study. Table 1 shows the main baseline characteristics of all patients.

Intervention with etanercept. Patients were treated with etanercept in subcutaneous doses of 25 mg twice per week during 12 weeks of treatment. Followup visits were at 4, 8, and 12 weeks after the start of treatment, followed by post-treatment followup visits at Weeks 18 and 24.

Measurement of fatigue. Fatigue was quantified throughout the study using the Multidimensional Fatigue Inventory (MFI) questionnaire. The MFI has been validated for measuring fatigue in Dutch patients with SS[6]. At each visit the patients completed the MFI questionnaire and a visual analog scale (VAS) scale for perceived disease activity. The MFI consists of 20 questions in 5 scales revealing different dimensions of fatigue (i.e., general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity). Each scale score ranges from 4 to 20, a higher score indicating more severe fatigue[21]. A clinical response regarding perceived fatigue was predefined as a decrease of at least 6 points within a MFI scale [a decrease of 1 point on each item (range 1–5) would decrease a MFI scale score by 4 points].

Table 1. Baseline characteristics of patients with primary SS (n = 15). Values are the number (%) of patients, except where noted.

Male: Female	1:14
Mean age, yrs (range)	47.9 (21–80)
Mean disease duration, yrs (range)	3.6 (1–10)
Oral symptoms	15 (100)
Ocular symptoms	14 (93)
Other sicca symptoms	15 (100)
Oral signs	15 (100)
Ocular signs	13 (87)
Positive MSG biopsy	15 (100)
Anti-SSA positive	14 (93)
Anti-SSB positive	13 (87)
IgM-RF positive	14 (93)
Hypergammaglobulinemia	11 (73)
Fatigue	15 (100)
Recurrent fever episodes	7 (47)
Arthralgia	12 (80)
Myalgia	8 (53)

MSG: minor salivary glands, at least one positive biopsy (LFS > 1.0 and IgA % < 70). RF: rheumatoid factor.

Evaluation of salivary and lachrymal gland function. At baseline and at Weeks 4, 12, and 24 unstimulated and stimulated (2% citric acid) combined sublingual and submandibular (SL/SM) salivary flow was measured as recommended by Kalk, *et al*[22]. Unstimulated SL/SM flow and stimulated SL/SM flow was measured for 5 and 10 min, respectively, by manually aspirating saliva with a Monoject syringe. Parotid flow was blocked using Dry-tips™ absorption shields covering the opening of Stensen's ducts on either side. The weight of both the unstimulated and stimulated saliva collecting tubes was electronically measured before and after collection of saliva, including a third control tube that was not used for saliva collection. The latter enabled correction in case of changed circumstances (such as room temperature). At the same time points lachrymal gland function was evaluated using the Schirmer-1 test (i.e., without anesthetic droplets and with closed eyes for a 5 min period). Complete ophthalmologic examination including rose bengal cornea staining and tear film breakup time was performed at screening and at Week 12 by an ophthalmologist.

Serological and histological evaluation. Serological tests, apart from standard safety tests and gammaglobulin level measured at each visit, included anti-dsDNA and IgM rheumatoid factor measured at screening and at Week 12. All serological variables were assessed using routine standardized measurement procedures.

At baseline and at Week 12 patients underwent a sublabial MSG biopsy performed by an experienced oral and cranio-maxillofacial surgeon. The first biopsy was taken on the left and the second biopsy on the right side of the lower lip. Focus scores were assessed by an experienced pathologist, and computer-aided microscopy was used to quantify the IgA%.

Statistical analysis. An intention-to-treat (ITT) analysis was performed comparing scores at baseline and at Week 12. Because MFI scores and VAS scores (Table 2) decreased very rapidly after cessation of etanercept treatment these scores were compared during treatment (Week 8) versus base-

line scores. Data were analyzed by a paired t test using the SPSS 9.0 software package.

The pretreatment and post-treatment MSG biopsies (Tables 3 and 4) of the 10 subjects who underwent both biopsies were also compared using a paired t test. In this per-protocol statistical analysis one subject was excluded because her MSG biopsies were assigned the score of 12. Since this is an arbitrarily defined value describing a large confluent lymphocytic infiltrate that does not enable measurement of separate lymphocytic aggregates per area, and this value is not part of a continuous LFS scale, this score was excluded from group comparison. The post-treatment MSG biopsy of this subject, however, was again assigned a LFS of 12 by the pathologist, i.e., no change of the histological picture. Salivary and lachrymal gland function (Table 5) was not tested statistically because of extreme low values in a small study population and no clinical response.

RESULTS

Etanercept was well tolerated in all participating patients with SS. One patient, however, had to temporarily interrupt etanercept treatment at Week 7 because of a prolonged episode of parotitis, which quickly resolved with antibiotics after cessation of etanercept treatment. Due to this interruption, for this patient the data of subsequent scheduled visits were not acquired at the intended time points. Also, the parotitis episode considerably biased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values. For this patient it was therefore decided not to include the data acquired after the treatment interruption in the ITT analysis. Three other patients ended their participation before completing the protocol due to lack of efficacy of treatment and were therefore considered as dropouts. Therefore in the ITT statistical analysis the last observation of these 4 patients was carried forward to Week 12.

Systemic signs/symptoms. A persistent decrease of fatigue was reported by 4 of 15 patients, including the patient who had to temporarily interrupt anti-TNF-α treatment due to parotitis. This was also reflected in the fatigue scores of the MFI and the VAS scores (Table 2, data of responders

Table 2. Multidimensional Fatigue Inventory (MFI) scores. Values are mean (SD).

MFI scales	Baseline	Week 4	Week 8	Week 12	Week 18	Week 24
Total, n*	15	15	14	12	11	11
General fatigue	16.3 (3.6)	13.9 (3.4)	12.4 (4.7)†	13.1 (3.9)	13.5 (3.7)	13.6 (6.0)
Physical fatigue	15.2 (3.7)	13.2 (3.8)	12.1 (3.2)	13.0 (3.8)	12.5 (4.1)	13.0 (5.5)
Reduced activity	13.0 (3.3)	12.9 (4.4)	12.1 (4.1)	10.3 (3.1)	12.1 (2.9)	12.1 (5.2)
Reduced motivation	11.8 (3.9)	11.1 (3.4)	10.3 (3.2)	10.1 (3.0)	10.5 (3.5)	10.9 (4.7)
Mental fatigue	12.8 (4.4)	11.9 (3.7)	11.3 (4.7)	12.0 (4.5)	10.7 (4.4)	10.3 (4.7)
VAS, mm	70 (19)	61 (21)	50 (16)†	59 (17)	60 (13)	66 (20)
Responders only						
General fatigue	16.8 (3.0)	10.3 (1.5)	8.0 (2.0)	10.0 (3.5)	11.0 (3.6)	14.7 (9.2)
Physical fatigue	16.2 (3.6)	10.0 (2.0)	10.0 (2.6)	10.0 (1.7)	10.0 (4.0)	15.0 (8.7)
Reduced activity	12.8 (3.3)	8.7 (0.6)	11.3 (4.2)	8.0 (1.7)	11.0 (3.6)	13.7 (7.6)
Reduced motivation	10.2 (2.3)	7.0 (2.9)	7.7 (3.5)	8.0 (2.6)	7.3 (3.1)	10.0 (5.6)
Mental fatigue	15.3 (4.4)	13.7 (5.5)	11.7 (4.0)	14.3 (4.6)	11.0 (5.2)	12.3 (4.5)
VAS, mm	73 (16)	41 (20)	34 (10)	53 (22)	67 (14)	67 (32)

* Data of all patients, including the responders. † $p < 0.05$ vs baseline by paired t test. VAS: Visual analog scale for perceived disease activity.

Table 3. Serological and histological data. Values are mean (SD).

	Baseline	Week 4	Week 8	Week 12	Week 18	Week 24
Total, n	15	15	14	12	11	11
ESR, mm	24 (25.6)	24 (26.7)	18 (15.6)	13 (95)	18 (10.5)	20 (11.9)
CRP, mg/l	4.4 (3.8)	4.5 (4.4)	2.8 (1.8)	2.3 (1.6)†	3.2 (1.6)	3.4 (3.3)
Gammaglobulin, g/l	16 (7.1)	17 (8.0)	15 (4.2)	15 (4.8)	15 (4.6)	16 (4.3)
LFS	2.22 (1.5)			1.49 (1.0)		
IgA%	56.0 (9.3)			54.3 (8.3)		
IgM RF, U/l	85 (95)			80 (102)		
Responders only						
ESR, mm	19 (18.2)	15 (11.7)	14 (11.9)	12 (12.3)	16 (17.0)	15 (12.2)
CRP, mg/l	3.7 (2.3)	1.7 (0.6)	2.0 (1.0)	2.0 (1.0)	4.0 (2.8)	2.7 (2.1)
Gammaglobulin, g/l	16 (5.4)	16 (5.4)	15 (6.0)	16 (4.0)	15 (5.9)	18 (0.3)
LFS	2.62 (2.0)			2.08 (0.5)		
IgA%	56.1 (16.3)			54.7 (15.6)		
IgM RF, U/l	63 (17)			49 (23)		

† $p < 0.05$ versus baseline by paired t test. ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, LFS: lymphocytic focus score, IgA%: percentage IgA-containing plasma cells, IgM RF: IgM rheumatoid factor.

Table 4. Pre- versus post-treatment minor salivary gland (MSG) biopsy scores. (Only the data of double MSG biopsies are shown).

Patient	Time 0		Time 1	
	LFS	IgA%	LFS	IgA%
1	0.18	60.7	0.22	65.2
2	12	37.1	12	34.4
3	0.5	NA	0.34	62.7
4	3.39	61.0	2.85	54.9
5	4.9	58.2	2.47	65.7
6	1.91	58.4	1.73	59.3
7	2.68	64.0	2.35	48.4
8	1.44	38.8	1.69	43.6
9	0.62	62.5	0.15	49.0
10	2.11	44.2	1.61	48.6

Time 0: pretreatment biopsy, Time 1: post-treatment biopsy, LFS: lymphocytic focus score, IgA%: percentage IgA-containing plasma cells, NA: data not available (unreliable small tissue sample).

described separately at the bottom of the table). For the group as a whole a statistically significant decrease of the general fatigue scale within the MFI ($p = 0.018$) as well as the VAS score for perceived disease activity ($p = 0.045$) was observed. In the clinically responding patients the mean score on the general fatigue scale diminished from 16.8 to 8.0, and the score on the physical fatigue scale from 16.2 to 10.0, with the maximum effect reported at Week 8. The effect started after 2–4 weeks of treatment, and disappeared in 3 patients within 2 weeks after cessation of etanercept administration. In one patient the effect was prolonged, and disappeared after 8 weeks.

In 3 of the 4 responders ESR levels and the IgM rheumatoid factor level decreased during etanercept treatment. For the entire group the mean ESR decreased from 24 to 13 mm/h ($p = 0.058$), while the mean CRP values decreased from 4.4 to 2.3 mg/l ($p = 0.048$), although it should be noted that CRP values in general were already low at baseline. Gammaglobulin concentrations, however, were stable throughout the study in all participants (Table 3).

It is noteworthy that one patient appeared to undergo a "reverse" response: she felt worse during anti-TNF-α treatment and much better in the post-treatment followup phase without treatment. All 15 participants remained negative for anti-dsDNA antibody throughout the study.

Sicca signs/symptoms. An objective substantial improvement of salivary gland function and improvement of lachrymal gland function could not be established in any of the 15 patients. Both Schirmer-1 tests and SL/SM salivary flow measurements showed sustained low to extremely low scores throughout the study (Table 5). Also, no changes were observed in tear film breakup time or rose bengal staining (data not shown).

Subjective improvement of either irritation of eyes or dry mouth was also not reported in the majority of patients. One patient reported less vaginal dryness, leading to resolved dyspareunia complaints, and one patient reported less respiratory tract dryness. Two patients who frequently experienced severe blepharitis reported considerable alleviation of eye symptoms during etanercept treatment. However, once etanercept treatment was stopped, these patients again encountered ocular discomfort due to blepharitis.

Pre- and post-treatment salivary gland biopsy scores. The (immuno)histological pattern of the pre- versus post-treatment sublabial MSG biopsies interestingly showed a trend to decreased lymphocytic focus scores following etanercept treatment. Only one of 10 samples showed a slightly (0.25) increased post-treatment LFS, while in 7 of 10 samples a decrease varying from 0.2 to 2.4 points was observed in the post-treatment LFS (Table 4). However, the difference in post-treatment LFS ($p = 0.101$) and IgA% ($p = 0.621$) from baseline values was not statistically significant (Table 3). Thus, the (immuno)histological pattern was compatible with the clinical findings for sicca signs and symptoms. As well no noteworthy differences were observed in sublabial MSG biopsy scores from patients with decreased fatigue versus nonresponding patients.

Table 4 shows, surprisingly, that in 3 of 15 subjects a LFS < 1.0 was found at baseline. In all 3 patients a previous diagnostic MSG biopsy had shown a LFS > 1.0. Furthermore, in 2 of these 3 patients the IgA% at baseline was below 70, which has been shown to be a more disease-specific marker[4,5]. In the third patient a LFS could not reliably be assessed and IgA% could not be assessed at all due to a bad sample. The double MSG biopsies were well tolerated in this study population. One patient complained about post-biopsy numbness of the lip, while all other biopsies were taken without complications. Although in 9 of the 15 participants a previous diagnostic lower lip biopsy had preceded the 2 biopsies taken in this study, no difficulties were encountered assessing LFS and IgA% in the study samples.

Extension phase. After completing the study protocol including the 12 week post-treatment followup without etanercept, all 4 responding patients resumed etanercept treatment 25 mg twice a week. Again, fatigue symptoms decreased quickly (within 2–4 weeks), but as well, after prolonged treatment for up to 26 weeks, no effects on sicca signs or symptoms were noted. No adverse events occurred in patients who participated in this extension phase.

DISCUSSION

In this pilot study, subcutaneous administration of etanercept 25 mg twice weekly in patients with SS did not improve salivary or lachrymal gland function. However, in a small subgroup of patients, there was markedly reduced fatigue as well as reduced ESR level, which may indicate a possible systemic response. This study describes 4 of 15 patients who reported less fatigue during etanercept treatment. Although fatigue cannot be assessed objectively, and the numbers of participants in this pilot study were small, their reports were

Table 5. Salivary and lachrymal gland function tests. Values are mean (SD).

	Baseline	Week 4	Week 12	Week 24
Total, n	15	15	12	11
Schirmer-I, mm/5 min	5.0 (5.8)	5.9 (6.2)	5.8 (7.0)	5.6 (9.8)
U-SL/SM flow, ml/5 min	0.1	< 0.01	< 0.01	< 0.01
S-SL/SM flow, ml/10 min	0.4	0.3	0.4	< 0.01
Responders only				
Schirmer-I, mm/5 min	0.3 (0.6)	1.7 (0.6)	2.0 (1.7)	1.3 (1.5)
U-SL/SM flow, ml/5 min	< 0.01	< 0.01	< 0.01	< 0.01
S-SL/SM flow, ml/10 min	< 0.01	< 0.01	< 0.01	< 0.01

SL: sublingual, SM: submandibular, U: unstimulated, S: stimulated with 2% critic acid once per 2 minutes.

very consistent throughout and following the study. Fatigue scores worsened again in the post-treatment followup phase of the protocol, but after restarting etanercept treatment in the extension phase these patients again reported a quick decrease of perceived fatigue. In these patients the (immuno)histological pattern in the MSG biopsies did not differ from that of nonresponders in terms of fatigue. Indeed, although decreased LFS scores were observed, etanercept treatment did not lead to statistically significant changes in MSG biopsy scores in any patient in this study. In general, etanercept was well tolerated and appeared to be a safe drug for patients with SS.

These results contrast in part to observations of Steinfeld, *et al*, who reported a beneficial effect of anti-TNF-α treatment with infliximab on both fatigue complaints and sicca signs in a very similar open label pilot study[18]. This might be explained by differences in patient selection and chosen method of saliva collection, or result from different efficacy of infliximab versus etanercept in SS.

Although both anti-TNF-α agents have potent antiinflammatory effects in RA[11,23], some recent clinical studies in other autoimmune diseases indeed suggest different clinical efficacy of etanercept compared to infliximab. For example, the differing results of initial studies with infliximab and etanercept in Crohn's disease[15,24,25] are quite similar to our results compared to those of Steinfeld, *et al* in SS. One hypothesis drawn from an *in vitro* study is that while both antagonists block circulating TNF-α molecules, the blocking of membrane-bound TNF-α lasts longer in infliximab treatment compared to etanercept treatment, in which the receptor fusion protein appears to dissociate from the membrane-bound TNF-α some time after having bound to it[26]. As a consequence, a higher etanercept dosing regimen, or shorter dosing interval, might be needed to achieve comparable efficacy to infliximab in SS.

Although the exact characterization of systemic signs and symptoms in patients with SS is unknown, it is noteworthy in this respect that a subgroup of patients reported less fatigue during etanercept treatment yet none of these patients showed functional improvement of the glands. However, since measuring serum concentrations of TNF-α was not part of the study design, the hypothesis that circulating TNF-α levels might be associated to fatigue cannot be verified in this study.

For efficacy of anti-TNF-α treatment in SS, careful patient selection may be important as well, since reversibility of decreased glandular function in an advanced stage of the disease is questionable. To compensate for this issue in future studies, one might define a minimum glandular rest function at baseline or challenge patients with pilocarpine to test for potential reversibility of glandular function. This might increase the probability of successful etanercept intervention resulting in a functional response of the glands.

Measuring parotid flow next to sublingual and submandibular flow might have given additional information about the functional status of salivary glands. However, from the evidence that the majority of patients did not report improvement of dry mouth, and macroscopic inspection of the absorption shields that were used to block parotid flow into the oral cavity did not show improvement as well, it is unlikely that a clinically important improvement of salivary flow was overlooked by not measuring parotid flow.

In conclusion, etanercept administered subcutaneously in a conventional RA dosing regimen of 25 mg twice weekly did not lead to improvement of sicca signs and symptoms in 15 patients with primary SS. In a small subgroup of patients, however, a presumed systemic response was observed, indicated by a reduction of moderate to severe fatigue complaints in these patients. Since this etanercept dosing regimen did not result in statistically significant histological changes in sublabial MSG gland biopsies, there are no indications that diagnostic biopsies taken, for example, in patients with RA are biased by concomitant etanercept treatment.

Additional studies might elucidate the possible fatigue-reducing mechanism of anti-TNF-α treatment. The efficacy of etanercept treatment in reducing oral and ocular dryness in SS should be evaluated in studies with a higher dosage or shorter dosing intervals.

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