Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Pilocarpine Hydrochloride for the Treatment of Xerostomia in Patients with Sjögren’s Syndrome in Taiwan—A Double-blind, Placebo-controlled Trial

Cheng-Han Wu, Song-Chou Hsieh, Kuang-Lun Lee, Ko-Jen Li, Ming-Chi Lu, Chia-Li Yu*

Background/Purpose: Sjögren’s syndrome (SS) is characterized by diminished exocrine secretions with the resultant symptoms of dry mouth and dry eye. As genetic predisposition and ethnicity may alter the effectiveness of drug treatment, evaluation of the efficacy and safety of the secretagogue pilocarpine hydrochloride in the treatment of xerostomia in patients with SS in different populations is needed.

Methods: Forty-four patients with SS were enrolled in this double-blind, placebo-controlled trial. Patients were randomized to receive 5 mg pilocarpine (Salagen) or placebo tablet four times daily for 12 weeks. Global evaluation and subjective responses of patients were assessed by questionnaires with visual analog scales and categorical checkboxes. Saliva production was also measured by modified Saxon’s test.

Results: Pilocarpine treatment significantly improved global assessment of dry mouth, symptoms associated with dry mouth (mouth comfort, ability to sleep and ability to speak), and saliva production compared to placebo. The drug was well tolerated and the most common adverse effect was sweating (5/23, 21.7%) resulting from the muscarinic agonist action of the drug. No serious drug-related adverse effect was found in this study.

Conclusion: The results of this study suggest that therapy with 5 mg pilocarpine four times daily is effective, safe and well tolerated for the relief of oral symptoms in patients with SS in Taiwan. [J Formos Med Assoc 2006;105(10):796–803]

Key Words: pilocarpine, Sjögren’s syndrome, xerostomia

Sjögren’s syndrome (SS), a chronic autoimmune inflammatory exocrinopathy and epithelitis, is characterized by lymphocytic infiltration of different exocrine glands and epithelia, mostly notably the salivary and lacrimal glands. The involvement of exocrine glands in SS results in loss of functional epithelium and diminished exocrine secretory function leading to the typical features of sicca syndrome, such as keratoconjunctivitis sicca (dry eye), xerostomia (dry mouth) and dryness of other body parts. SS is one of the most common autoimmune disorders and can manifest either alone (primary SS) or in association with almost all of the systemic rheumatic diseases, most commonly rheumatoid arthritis and systemic lupus erythematosus. Treatment goals for SS include palliation of sicca symptoms, prevention of complications

©2006 Elsevier & Formosan Medical Association

Division of Immunology, Rheumatology and Allergy, Department of Internal Medicine, National Taiwan University Hospital, and
Division of Immunology, Rheumatology and Allergy, Buddhist Xindian Tzu Chi General Hospital, Taipei, Taiwan.

Received: December 30, 2005
Revised: January 26, 2006
Accepted: March 7, 2006

*Correspondence to: Dr Chia-Li Yu, Division of Immunology, Rheumatology and Allergy, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan. E-mail: clyu@ha.mc.ntu.edu.tw
and proper intervention of extraglandular manifestations. Although the awareness of its systemic nature and considerable morbidity has directed treatments toward disease modification, treatment of sicca symptoms with immunomodulatory drugs has been unsuccessful. In contrast, the use of tear or saliva substitutes may provide transient relief of sicca symptoms, but often fails to prevent ocular and dental complications. Hence, the use of secretagogues to stimulate secretion from exocrine glands represents a novel approach to alleviate the sicca symptoms of patients with SS.

Pilocarpine, a natural plant alkaloid derived from the South American shrub *Pilocarpus jaborandi*, is a cholinergic parasympathomimetic agonist that stimulates muscarinic-M3 receptors of various exocrine glands leading to increased secretory function. Indeed, pilocarpine hydrochloride (Salagen®; MGI Pharma, Inc., Bloomington, MN, USA) has been approved for the treatment of radiation-induced dry mouth and SS. In patients with primary or secondary SS, treatment with pilocarpine may alleviate sicca symptoms by increasing saliva flow. Controlled studies have also shown that pilocarpine is safe and well tolerated, with no serious adverse effect or drug interaction. As genetic predisposition and ethnicity affect the clinical manifestations and immunologic features of SS, differences in the treatment responses to pilocarpine require investigation in different populations. This double-blind, randomized, placebo-controlled trial investigated the clinical efficacy and safety of oral pilocarpine 5 mg four times daily for the improvement of oral symptoms in patients with SS in Taiwan.

**Methods**

**Patients**

Patients older than 18 years with a diagnosis of primary or secondary SS according to the 1993 American College of Rheumatology criteria were enrolled from rheumatology outpatient clinics of National Taiwan University Hospital (NTUH) between April 1, 2002 and November 13, 2002. Diagnosis of primary SS in patients without other rheumatic disorders required the presence of any four of the following six criteria: ocular symptoms, oral symptoms, ocular signs, objective salivary gland involvement, abnormal histopathologic feature of salivary glands, and the presence of antinuclear antibodies, rheumatoid factors, autoantibodies against Ro(SSA) or La(SSB) antigens. Diagnosis of secondary SS was based on the finding of a well-defined connective tissue disease with ocular or oral symptoms, and the presence of any two objective criteria among ocular signs, salivary gland involvement and histopathology.

Patients with a clinically significant history of cardiopulmonary, gastrointestinal, renal disease or diabetes mellitus were excluded. In addition, patients with clinically significant ocular disease, such as elevated intraocular pressure > 20 mmHg, glaucoma, uveitis or scleritis, preexisting retinopathy or retinal detachment, retrolubular neuritis, herpetic ulcer of cornea, or ocular cancer were excluded. Women of childbearing potential were required to use an acceptable method of contraception.

**Treatment protocol**

All participants underwent baseline medical and ophthalmologic history taking, physical examination and electrocardiography (ECG) at the screening visit. At the baseline visit (week 0), patients were randomly assigned to the pilocarpine or placebo group using sealed randomization envelopes. The placebo was made identical in appearance to the active drug, and all tablets were supplied by MGI Pharma Inc. Both investigators and participants were blinded to the treatment assignments. Participants were instructed to take one tablet of the study medication with water four times daily (qid) at mealtimes and bedtime for 12 weeks, and to record missed doses and adverse events in a diary. Participants returned to the study site at weeks 6 and 12 for efficacy and safety evaluations. At each visit, patients underwent vital signs measurement and clinical laboratory examinations (urinalysis, complete blood cell counts, electrolytes, liver and renal function tests),
and reported their responses in the questionnaires. Medications (prescription or over the counter) taken by study participants within 30 days prior to the screening date and changes in medication were also recorded. Saliva secretion was recorded at 60 minutes after taking the study medication. Physical examination and medical and ophthalmologic history taking were performed again at the end of the study. The study was approved by the institutional review board of the NTUH, and written informed consent was obtained from all study participants.

**Efficacy assessment**

Treatment efficacy was assessed based on the proportion of patients who indicated a beneficial response on questionnaires and had increased saliva production at weeks 6 and 12 compared to baseline. Efficacy was compared by intention-to-treat analysis using the last available postdose observation (i.e. end point) for each patient.

The primary outcome in this study was the global improvement of dry mouth. Participants were asked to indicate their overall condition of dry mouth on a 100 mm visual analog scale (VAS) at the week 6 and 12 visits compared with how they felt at the beginning of the study. Responses on the VAS were classified as follows: < 45 mm indicated nonresponder (worse); 45–55 mm indicated nonresponder (no change); and > 55 mm indicated responder (improvement). For assessment of other symptoms associated with dry mouth, six specific 100 mm VAS questions, including mouth dryness, discomfort of the mouth, ability to sleep, ability to speak without drinking liquids, ability to chew and swallow food, and ability to wear dentures, were also recorded at each visit. For these six questions regarding conditions that may interfere with a patient’s daily life, the response ranged from 0 mm (very dry, extremely uncomfortable and very difficult, respectively) on the left to 100 mm (not dry, comfortable and easy, respectively) on the right. An increase of 25 mm or more above the baseline score was defined as a response.

There were three questions that used a two-point categorical response (yes or no) format to assess the condition of dry mouth within the last 3 days prior to the visits at weeks 6 and 12. These questions evaluated whether study participants had a more comfortable mouth or less dry mouth, or felt that it was easier to speak without drinking at weeks 6 and 12 after starting the study medication. The extent of use of oral comfort agents was evaluated at the same time on the basis of three categories of response (improved, no change, or worse). For these categorical questions, patients with improvement in symptoms or an answer of “yes” were classified as responders, and those with no change or worsening of symptoms or an answer of “no” were classified as nonresponders.

Saxon’s test with some modifications was used to quantify saliva production. At each visit, subjects were first instructed to take nothing by mouth for at least 90 minutes and then to chew a piece of preweighed gauze for 5 minutes. The gauze was weighed again after chewing for 5 minutes. The change in the weight of the gauze represented the patient’s saliva production during this 5-minute period. After determination of the predose saliva production, the study medication was administered and the postdose saliva production was measured 60 minutes later. The effect of the study medication on saliva production was quantified by comparing the difference between postdose and predose saliva production.

**Safety**

Safety evaluations were based on the results of physical examinations and ECG conducted before study entry, clinical laboratory tests conducted at each visit and all reports of adverse experiences. Vital signs were measured before each dose and 1 hour after taking the study medication at each visit. During the 60-minute postdose period, adverse experiences and dose tolerability were queried. Adverse experiences were documented throughout the study at each visit.

**Statistical analysis**

Statistical analysis was performed with Stata/SE version 8.0 (Stata Corp., College Park, TX, USA) for Windows. Two-sided Fisher’s exact test was used to
Table 1. Demographic and disease characteristics of the study population*

|               | Placebo (n=21) | Pilocarpine (n=23) | p   |
|---------------|---------------|-------------------|-----|
| Age (yr)      | 56.4±12.5     | 57.1±11.9         | 0.74|
| Female gender | 17 (81.0)     | 22 (95.7)         | 0.18|
| Height (cm)   | 159.9±5.5     | 157.3±4.5         | 0.09|
| Weight (kg)   | 55.7±9.3      | 53.1±8.2          | 0.37|
| Rheumatic disease |         |                   | 1.00|
| Primary SS (%)| 15 (71.4)     | 17 (73.9)         |     |
| SLE (%)       | 2 (9.5)       | 2 (8.7)           |     |

*Data are presented as mean±standard deviation or n (%). SS = Sjögren’s syndrome; SLE = systemic lupus erythematosus.

Table 2. Patient disposition and reasons for discontinuation in study population*

|               | Placebo (n=21) | Pilocarpine (n=23) | p   |
|---------------|---------------|-------------------|-----|
| Completed study| 18 (85.7)     | 16 (69.6)         | 0.29|
| Lack of efficacy | 2 (9.5)    | 0 (0)             | 0.22|
| Adverse event† | 0 (0)         | 3 (13.0)          | 0.23|
| Lost to follow-up‡ | 1 (4.8)  | 4 (17.4)          | 0.35|

*Data are presented as n (%); †adverse event leading to dropout of three patients taking pilocarpine was marked sweating; ‡two of the four patients in the pilocarpine group withdrew during the period of severe acute respiratory syndrome (SARS) outbreak in Taiwan, and in the placebo group, the patient was lost to follow-up during the SARS outbreak period.

Results

Of 44 SS patients, 23 were randomized to the pilocarpine group and 21 to the placebo group. There was no significant difference in demographic variables or disease characteristics between the two groups (Table 1). The most frequently used (>10%) medications were hydroxychloroquine sulfate (200–400 mg/day), antacids, low dose prednisolone (2.5–10 mg/day) and nonsteroidal anti-inflammatory drugs. Use of these medications was similar between the pilocarpine and placebo groups. There was a similar dropout rate from the initial 44 patients, with 18 of 21 (85.7%) in the placebo group and 16 of 23 (69.6%) in the pilocarpine group completing the 3-month study (p=0.29; Table 2). In the placebo group, one patient (4.8%) was lost to follow-up during the period of severe acute respiratory syndrome (SARS) outbreak in Taiwan and two patients (9.6%) withdrew because of lack of efficacy. In contrast, none of the 23 patients in the pilocarpine group discontinued the study treatment due to lack of efficacy. In the pilocarpine group, three patients (13%) withdrew because of marked sweating and four (17.4%) were lost to follow-up. Of the four patients who were lost to follow-up, two withdrew during the SARS outbreak period. The reasons for discontinuation from the study were not significantly different between the pilocarpine and placebo groups (Table 2).

Global assessment of xerostomia showed that a significant proportion of patients in the pilocarpine group (69.6%) had improvement in the sensation of dry mouth compared to the placebo group (23.8%) in the intention-to-treat analysis (p=0.0032; Figure 1). Patients taking pilocarpine four times daily also showed significant improvement in xerostomia-related conditions, such as ability to sleep and ability to speak without...
drinking liquids (Figure 2). Borderline significance ($p=0.07$) in the ability to chew and swallow was observed in the pilocarpine group compared to the placebo group. Three patients in the placebo group and four in the pilocarpine group were denture wearers, but none of the patients in either group had significant improvement in the ability to wear dentures. However, analysis of VAS scores between the pilocarpine and placebo groups indicated a significant improvement ($p<0.01$) in the pilocarpine group in five of six specific dry mouth symptoms, including mouth dryness, mouth comfort, ability to sleep, ability to speak and ability to swallow food (all $p<0.01$) compared to baseline.

In addition to improved VAS scores, patients in the pilocarpine group also reported greater mouth comfort, less dryness and found it easier to speak compared to the placebo group (Figure 3). Although four patients in the pilocarpine group (17.4%) vs. placebo group (0%) experienced reduced use of oral comfort agents, the difference did not reach significance ($p=0.11$).

Saliva secretion was evaluated in the unit of g/minute and any increase in saliva flow more than baseline secretion was defined as a response.

**Figure 2.** Comparison of the percentage of patients with Sjögren’s syndrome showing clinical improvement in symptoms associated with dry mouth in questionnaire responses. The pilocarpine group demonstrated significant differences in symptomatic relief of oral symptoms in mouth dryness, mouth comfort, ability to sleep and ability to speak without drinking liquids. For the ability to chew and swallow food, a borderline significance was observed in the pilocarpine group compared with the placebo group. An increase of 25 mm or more above the baseline score of these 100 mm visual analog scale questions was defined as a response.

**Figure 3.** Percentage of Sjögren’s syndrome patients with a response in dry mouth symptoms and in saliva production at the end points. A greater proportion of patients in the pilocarpine group responded to therapy compared to the placebo group by the experience of more comfortable and less dry mouth, improved ability to speak and an increase in saliva production at the 60-minute postdose collection at the end of the study. No significant difference in decreased use of oral comfort agents between the two groups was observed.
At the end of the study, patients in the pilocarpine group exhibited a higher response (65.2%) in 60-minute postdose saliva production than the placebo group (28.6%) in the intention-to-treat analysis ($p=0.02$; Figure 3). The median increase in saliva production in the pilocarpine group was also significantly greater than that in the placebo group (0.05 g/minute vs. $–0.02$ g/minute, $p=0.0014$) at 12 weeks. A significant response in global assessment of xerostomia, symptoms associated with dry mouth and saliva secretion in the pilocarpine group was observed throughout the study period.

No serious adverse event was found during the study. Five patients (21.7%) in the pilocarpine group experienced perspiration and three of them withdrew from the study. Palpitation was reported in two patients, one (4.3%) in the pilocarpine group and the other (4.8%) in the placebo group. Most of the participants tolerated the study medication. No significant alterations in blood pressure, heart rate, hematopoietic, renal or hepatic profiles were noted during the study.

**Discussion**

This study demonstrated the clinical efficacy and safety of pilocarpine 5 mg four times daily for the treatment of dry mouth in patients with SS in Taiwan. As ethnicity can act as a predictor of the treatment outcome of a disease, separate clinical trials to determine the treatment response of patients with dry mouth to pilocarpine need to be performed in different races. In this study, patients with SS in Taiwan who received pilocarpine experienced global improvement of xerostomia, significant improvement in most of the symptoms associated with dry mouth including mouth dryness, mouth comfort, ability to sleep, ability to speak, and ability to swallow food, and an increase in saliva secretion from baseline without serious adverse effects and drug–drug interactions. Although the sample size was small, this study demonstrated the treatment benefits of pilocarpine in patients with SS in Taiwan. Further study with a larger sample size is needed. The lack of significant difference in improved ability to swallow and to wear dentures, and in decreased use of oral agents between the pilocarpine and placebo groups may be due to the relatively small sample size. These differences might become significant only with a higher case number.

In a fixed dose trial by Vivino et al and a dose titration study by PaPas et al, pilocarpine at doses of 20 mg/day or higher for 12 weeks resulted in significant global improvement in dry mouth as well as dry eyes. Furthermore, increase in saliva flow was also noted through the dosing interval at 60 minutes. We did not evaluate the clinical effect of pilocarpine on dry eyes because our purpose was to evaluate the efficacy and safety of pilocarpine for the treatment of xerostomia in patients with SS in Taiwan. It has been demonstrated that treatment with pilocarpine at doses of 20 mg/day or higher in patients with SS resulted not only in improvement in symptoms and signs of intraoral dryness but also alleviation of other sicca manifestations, such as dry eyes, dry skin, vaginal dryness and other xerothes.

Indeed, a recent randomized controlled study also confirmed the beneficial effect of 12-week oral pilocarpine on ocular symptoms in patients with SS. Ethnicity does not appear to affect the treatment efficacy of pilocarpine tablets on patients with SS among Caucasians, Orientals, Blacks and other origins, as this trial and other studies, all demonstrated that pilocarpine therapy benefited patients with SS by improving the symptoms of xerostomia.

In SS, the deficient secretory response of salivary and lacrimal glands leading to dry mouth and dry eyes is attributed to both a decrease in the number of secretory units and a dysfunction of the residual secretory units. Despite dysfunction, the residual glandular elements in these exocrine glands preserve their neural innervation and have upregulation of muscarinic receptors. Therefore, the excess of muscarinic receptors in the exocrine glands provides a target for the therapeutic use of a secretagogue to stimulate secretion from exocrine glands in patients with SS. It is conceivable that the physiologic roles and the protective functions
of saliva include lubrication, digestion, phonation, mastication, remineralization, maintenance of balance of oral microflora, buffer activity, and immunity and defense. Hence, the administration of a secretagogue like pilocarpine to stimulate saliva production is preferred to the use of a saliva substitute for the treatment of dry mouth in SS patients.\(^2\,12\,28\)

Pilocarpine is a cholinergic parasympathomimetic agonist that binds to muscarinic-M3 receptors of various exocrine glands for stimulation of secretory function.\(^13\) According to the pharmacokinetic profile of this drug, its effect on saliva flow is dose-dependent and time-related, with a peak effect at 1 hour and a duration of 3–5 hours.\(^29\)

Therefore, optimal benefit can be achieved with a four times daily dosing regimen. However, the cholinergic activity of this drug also contributes to its adverse effects in patients with SS, such as sweating, urinary frequency and flushing.\(^10\,12\,22\)

In fact, sweating is the most common drug-related adverse event (up to 43%) and could be a major reason for withdrawal from study.\(^2\) But in general, these adverse events tend to decrease over time and might be diminished by starting with a low dose (e.g. 5 mg once or twice daily), and then increasing the dose gradually until the maintenance dose of 5 mg four times daily is achieved.\(^2\,23\)

Due to the high efficacy and safety, stimulation of saliva flow with a secretagogue is now considered to be the treatment of choice for symptomatic relief of the sicca syndrome and has become the most effective medication to prevent dental and oral complications in patients with SS.\(^2\,3\,10\,12\)

In conclusion, the results of this study suggest that pilocarpine 5 mg four times daily for 12 weeks is effective, safe and well tolerated for the relief of oral symptoms in patients with SS in Taiwan. The most frequent adverse event was sweating, but it did not increase the treatment withdrawal rate.

References

1. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren’s syndrome.

2. Venables PJ. Sjögren’s syndrome. Best Pract Res Clin Rheumatol 2004;18:313–29.

3. Derk CT, Vivino FB. A primary care approach to Sjögren’s syndrome. Helping patients cope with sicca symptoms, extraglandular manifestations. Postgrad Med 2004;116:49–54, 59, 65.

4. Pillemer SR, Matteson EL, Jacobsson LT, et al. Incidence of physician-diagnosed primary Sjögren’s syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proc 2001;76:593–9.

5. Manousakis MN, Moutsopoulos HM. Sjögren’s syndrome: current concepts. Adv Intern Med 2001;47:191–217.

6. Andonopoulos AP, Drosos AA, Skopouli FN, et al. Secondary Sjögren’s syndrome in rheumatoid arthritis. J Rheumatol 1987;14:1098–103.

7. Andonopoulos AP, Skopouli FN, Dimou GS, et al. Sjögren’s syndrome in systemic lupus erythematosus. J Rheumatol 1990;17:201–4.

8. Fox RI. Sjögren’s syndrome. Lancet 2005;366:321–31.

9. Price EJ, Rigby SP, Clancy U, et al. A double blind placebo-controlled trial of azathioprine in the treatment of primary Sjögren’s syndrome. J Rheumatol 1998;25:896–9.

10. Vivino FB. The treatment of Sjögren’s syndrome patients with pilocarpine-tablets. Scand J Rheumatol 2001;(Suppl 115):1–13.

11. Daniels TE. Evaluation, differential diagnosis, and treatment of xerostomia. J Rheumatol 2000;27(Suppl 61):6–10.

12. 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’s syndrome: a randomized, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. Arch Intern Med 1999;159:174–81.

13. Fox RI, Konttinen Y, Fisher A. Use of muscarinic agonists in the treatment of Sjögren’s syndrome. Clin Immunol 2001;101:249–63.

14. LeVeque FG, Montgomery M, Potter D, et al. A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. J Clin Oncol 1993;11:1124–31.

15. Rieke JW, Hafermann MD, Johnson JT, et al. Oral pilocarpine for radiation-induced xerostomia: integrated efficacy and safety results from two prospective randomized clinical trials. Int J Radiat Oncol Biol Phys 1995;31:661–9.

16. Bell M, Askari A, Bookman A, et al. Sjögren’s syndrome: a critical review of clinical management. J Rheumatol 1999;26:2051–61.

17. Bolstad AI, Jonsson R. Genetic aspects of Sjögren’s syndrome. Arthritis Res 2002;4:353–9.

18. Kang HI, Fei HM, Saito I, et al. Comparison of HLA class II genes in Caucasoid, Chinese, and Japanese patients with primary Sjögren’s syndrome. J Immunol 1993;150:3615–23.
19. Nishikawa T, Provost TT. Differences in clinical, serologic, and immunogenetic features of white versus oriental anti-SS-A/ Ro-positive patients. *J Am Acad Dermatol* 1991;25:563–4.

20. Kohler PF, Winter ME. A quantitative test for xerostomia. The Saxon test, an oral equivalent of the Schirmer test. *Arthritis Rheum* 1985;28:1128–32.

21. Ho C, Murray N, Laskin J, et al. Asian ethnicity and adenocarcinoma histology continues to predict response to gefitinib in patients treated for advanced non-small cell carcinoma of the lung in North America. *Lung Cancer* 2005;49:225–31.

22. PaPas A, Charney M, Goden H, et al. The effectiveness of oral pilocarpine-HCL tablets for the treatment of dry mouth symptoms associated with Sjögren’s syndrome—a dose-titration study. *Arthritis Rheum* 1997;40(Suppl 9):S202.

23. 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;62:1204–7.

24. Solans R, Bosch JA, Selva A, et al. Usefulness of oral pilocarpine therapy in the treatment of xerostomia and xerophthalmia in patients with primary Sjögren’s syndrome. *Med Clin (Barc)* 2004;122:253–5.

25. Fox RI, Tornwall J, Michelson P. Current issues in the diagnosis and treatment of Sjögren’s syndrome. *Curr Opin Rheumatol* 1999;11:364–71.

26. Konttinen YT, Hukkanen M, Kemppinen P, et al. Peptide-containing nerves in labial salivary glands in Sjögren’s syndrome. *Arthritis Rheum* 1992;35:815–20.

27. Beroukas D, Goodfellow R, Hiscock J, et al. Up-regulation of M3-muscarinic receptors in labial salivary gland acini in primary Sjögren’s syndrome. *Lab Invest* 2002;82:203–10.

28. Soto-Rojas AE, Kraus A. The oral side of Sjögren’s syndrome. Diagnosis and treatment. A review. *Arch Med Res* 2002;33:95–106.

29. Salagen tablets. In: *Physician’s Desk Reference*, 51st edition. Montvale, NJ: Medical Economics Books, 1997: 1546–7.