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

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Background: Patients with Sjögren syndrome (SS) experience slowly progressive infiltration of lacrimal and salivary glands by mononuclear cells. This leads to diminished secretions, with resultant symptoms of xerostomia and xerophthalmia. Although pilocarpine hydrochloride tablets are currently indicated for the treatment of radiation-induced xerostomia, their effects on dry mouth or dry eyes in patients with SS are unclear.

Objective: To assess the safety and efficacy of pilocarpine (Salagen) tablets as symptomatic treatment for dry mouth and dry eyes caused by SS in a multicenter, double-blind, placebo-controlled trial.

Methods: After providing written informed consent, 373 patients with primary or secondary SS and clinically significant dry mouth and dry eyes were randomized to receive 2.5-mg pilocarpine, 5-mg pilocarpine, or placebo tablets 4 times daily for 12 weeks. Symptoms were assessed by questionnaires with visual analog scales or categorical checkboxes. Whole-mouth salivary flow rates were measured.

Results: A significantly greater proportion of patients in the 5-mg pilocarpine group showed improvement compared with the placebo group (P < .01) in global assessments of dry mouth, dry eyes, and other symptoms of dryness (P < .05). Salivary flow was significantly increased 2- to 3-fold (P < .001) after administration of the first dose and was maintained throughout the 12-week study. The most common adverse effect was sweating, and no serious drug-related adverse experiences were reported.

Conclusion: Administration of 5-mg pilocarpine tablets 4 times daily (20 mg/d) was well tolerated and produced significant improvement in symptoms of dry mouth and dry eyes and other xeroses in patients with SS.

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PATIENTS AND METHODS

PATIENTS

Written of informed consent was obtained from all potential study participants as the first stage of screening and before admission to the study. Study patients were older than 18 years and had a diagnosis of primary or secondary SS consistent with the European Cooperative Community classification criteria for SS. The diagnosis of SS was confirmed at screening by positive test results for at least 1 of the following: marker autoantibodies against SS-A or SS-B, rheumatoid factor or antinuclear antibodies at a titer of 1:160 or greater (or equivalent), or a positive labial minor salivary gland biopsy sample. If a lip biopsy sample was used to support admission to the study, a representative slide of the biopsy sample was read by an external evaluator (T. E. Daniels, DDS, MS, Oral Pathology Laboratory, School of Dentistry, University of California, San Francisco). Positive biopsy samples required a focus score of greater than 1 focus per 4 mm² tissue area. The presence of clinically significant dry mouth and dry eye symptoms was confirmed by screening questionnaires. Patients who indicated mild symptoms by responding in the upper quartile of the screening questionnaire (100-mm visual analog scale [VAS]) did not qualify for entry. Patients were required to discontinue, at least 7 days before admission, taking any medication reported to produce significant dry mouth. To the positive on the right, and (2) 3-point categorical questions presented in 2 formats: (1) a 100-mm VAS, with responses ranging from the negative (0 mm = extremely dry) on the left to the positive on the right, and (2) 3-point categorical questions (increase in, no change, or decrease in symptoms). The presence of clinically significant dry mouth and dry eye symptoms was confirmed at screening by positive test results for at least 1 of the following: marker autoantibodies against SS-A or SS-B, rheumatoid factor or antinuclear antibodies at a titer of 1:160 or greater (or equivalent), or a positive labial minor salivary gland biopsy sample. If a lip biopsy sample was used to support admission to the study, a representative slide of the biopsy sample was read by an external evaluator (T. E. Daniels, DDS, MS, Oral Pathology Laboratory, School of Dentistry, University of California, San Francisco). Positive biopsy samples required a focus score of greater than 1 focus per 4 mm² tissue area. The presence of clinically significant dry mouth and dry eye symptoms was confirmed by screening questionnaires. Patients who indicated mild symptoms by responding in the upper quartile of the screening questionnaire (100-mm visual analog scale [VAS]) did not qualify for entry. Patients were required to discontinue, at least 7 days before admission, taking any medication reported to produce significant dry mouth. Patients were instructed to discontinue, at least 7 days before admission, taking any medication reported to produce significant dry mouth. Patients were instructed to discontinue, at least 7 days before admission, taking any medication reported to produce significant dry mouth. Patients were instructed to discontinue, at least 7 days before admission, taking any medication reported to produce significant dry mouth. Patients were instructed to discontinue, at least 7 days before admission, taking any medication reported to produce significant dry mouth.

Schirmer tear test results and Rose Bengal staining were also recorded during screening. A Schirmer score of 7 mm per 5 minutes and staining of 3 were each considered indicative of dry eyes. These screening requirements were modified from the European classification criteria for SS, which requires a patient to meet 4 of the following 6 criteria: ocular symptom, oral symptom, ocular sign, histopathologic feature, objective salivary gland involvement, and presence of autoantibodies.

Prospective patients were excluded if they had clinically significant cardiopulmonary, renal, or gastrointestinal tract disease; diabetes mellitus; multiple sclerosis; hypersensitivity to pilocarpine use; or clinically significant ocular disease, including narrow-angle glaucoma, peripheral retinopathies, or other conditions in which ocular (topical) pilocarpine use would be contraindicated. Female patients of childbearing potential were required to use medically acceptable contraceptive methods throughout the study.

TREATMENT PROTOCOL

At the admission visit, patients were randomly assigned to 1 of 3 treatment groups for the duration of the study: 2.5-mg pilocarpine, 5-mg pilocarpine, or placebo tablets. All tablets were identical in appearance and were supplied by MGI Pharma Inc, Minnetonka, Minn. Site personnel instructed patients to take 1 tablet of the study drug with water 4 times a day at mealtimes and bedtime, with a minimum of 3 hours between doses for the duration of the 12-week study. In addition, patients were instructed to record missed doses and adverse experiences in a diary. Patients recorded their responses to the dryness questionnaires before receiving the first dose of the test drug. At this visit, patients who took nothing by mouth for at least 90 minutes before the start of salivary procedures were given the first dose of test drug with 180 mL (6 oz) of water. They were then monitored for an additional 90 minutes, during which time saliva samples were obtained (see the “Methods” section). All baseline measurements were recorded for each patient before administration of this first dose of test drug. Patients returned to the study site at weeks 6 and 12 for efficacy and safety evaluations.

METHODS

Efficacy Assessment

Efficacy was evaluated at each visit by (1) response to questionnaires and (2) measurement of salivary flow. Primary variables were the global assessments of dry mouth and dry eyes at study end point. End point was defined as the last available postdose observation for each patient. In addition, specific symptoms associated with dry mouth and dry eyes were assessed, as was change in dryness associated with extraoral and extraocular symptoms, such as dryness of the skin, vagina, and nasal passages.

Questionnaires

Patients completed questionnaires at the admission (baseline), week 6, and week 12 visits. Questions were presented in 2 formats: (1) a 100-mm VAS, with responses ranging from the negative (0 mm = extremely dry) on the left to the positive on the right, and (2) 3-point categorical questions (increase in, no change, or decrease in symptoms). For assessment of primary measures of efficacy—global improvement of dry mouth and dry eyes—patients were asked at each week 6 and week 12 visit to indicate on
Of the 373 patients with SS enrolled in the study at 17 sites, 125 were randomized to the placebo group, 121 to the 2.5-mg pilocarpine group, and 127 to the 5-mg pilocarpine group. Demographic characteristics were similar among the treatment groups (Table 1). Patients with SS are predominantly female,11,17 which is consistent with enrollment in this study (95.7% women). Ninety-four per-

cent of patients met criteria similar to the European classification19 of SS (Table 2). Most patients (87%) completed this 3-month study (Table 3). Medications used by this patient population were monitored throughout the study. The most frequently used (≥10%) medications were consistent with those expected in this population, ie, analgesic or anti-inflammatory drugs (aspirin, ibuprofen, naproxen, acetaminophen, and prednisone), antirheumatic drugs (hydroxychloro-

Safety
Safety evaluations were based on results of laboratory tests (liver and kidney function tests, urinalysis, and complete blood cell counts with differential and platelet counts) conducted at each visit, results of electrocardiograms and physical examinations conducted before study admission and at the end of the study, and all adverse experience reports. An adverse experience was defined as any clinically significant change in physical signs or symptoms or a significant laboratory test result change occurring in any phase of the study regardless of its relationship to study drug. Safety assessment was done for any patient who withdrew from the study before week 12.

STATISTICAL ANALYSES
The sample of calculations was based on 1 of the 2 primary efficacy variables, particularly, response to treatment with respect to dryness of the mouth. A 2-sided \( \chi^2 \) test, with \( \alpha = .05 \), was used. Assuming a 30% response rate in the placebo group and a 50% response rate in the high-dose pilocarpine group, 100 persons per treatment would result in a power of 80% for this comparison. Efficacy results are presented for the intent-to-treat cohort. All patients who received at least 1 dose of the study drug and who had at least 1 efficacy assessment after administration of the first dose were included in this cohort. The safety cohort included all patients who took at least 1 dose of the study drug. Analyses were performed using the end-point observation, ie, the last-available postdose observation for a patient. Differences in the proportion of responders among treatment groups were evaluated using a logistic regression model.

Based on the pharmacokinetic profile for this drug,16 the peak salivary flow was anticipated to occur approximately 60 minutes after administration of a single 5-mg pilocarpine tablet. Therefore, the comparison of changes in salivary flow focused on the 60-minute postdose collection. Statistical significance was defined at \( P \leq .05 \) for the determination of an overall treatment effect. For analysis of symptomatic response, if there was an overall treatment effect, specific pairwise comparisons between the placebo and the 5-mg pilocarpine groups were made using a logistic regression model. For analysis of salivary flow, if there was an overall treatment effect, specific pairwise comparisons between placebo and 3-mg pilocarpine tablets, and comparison between placebo and 2.5-mg pilocarpine tablets, were made using a 2-sided \( t \) test.

The demographic and safety results are presented using overall comparisons for all 3 groups. Pairwise comparisons of the placebo group vs the 5-mg pilocarpine group are presented for efficacy results. A software program (SAS version 6.09 or greater, SAS Institute Inc, Cary, NC) was used for statistical analyses.

RESULTS

Of the 373 patients with SS enrolled in the study at 17 sites, 125 were randomized to the placebo group, 121 to the 2.5-mg pilocarpine group, and 127 to the 5-mg pilocarpine group. Demographic characteristics were similar among the treatment groups (Table 1). Patients with SS are predominantly female,11,17 which is consistent with enrollment in this study (95.7% women). Ninety-four per-
Supportive Outcomes—Dry Mouth and Dry Eyes

Additional questions assessed posttreatment benefits for specific symptoms associated with SS. Responses to 4 of the 5 dry mouth questions showed a statistically significant increase in the proportion of responders in favor of 5-mg pilocarpine tablets (Figure 1, right). In addition to improved mouth comfort (P≤.004) and mouth dryness (P≤.02), patients also experienced an improved ability to sleep because of reduced nocturnal fluid ingestion (P≤.04) and reduced use of saliva substitutes (P≤.02). The difference between the 5-mg pilocarpine group and the placebo group in the ability to speak without drinking water was not significant (P=.06). For ocular symptoms, a significantly greater proportion of patients taking 5-mg pilocarpine tablets also showed clinically significant improvement compared with those taking placebo for overall improvement in ocular problems (P≤.004), ability to focus their eyes during reading (P≤.04), and reduced severity of blurred vision (P≤.02). No benefit was observed for the remaining ocular symptoms (sensitivity to light, severity of itching, tiredness, redness, difficulty with night driving, discharge or draining, difficulty focusing in general, foreign body sensation, discomfort, reduced use of artificial tears, matting, and change in tear flow).

In addition to the responder analyses reported above, a statistical analysis of mean VAS scores in the placebo vs the 5-mg pilocarpine group indicated a significant benefit of pilocarpine treatment. Both primary end points—global improvement of dry mouth (P≤.001) and dry eyes (P≤.01)—were significant. In addition, for relief of specific dry mouth symptoms, both VAS questions (dryness of mouth and discomfort of mouth) were significant (P≤.01). For relief of dry eye symptoms, 2 of 3 VAS questions for specific dry eye symptoms (overall change in eye problems and severity of visual blurring) that were significant by the responder analyses were also significant (P≤.03) when measured by mean increase in VAS scores.

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Extraoral and Extraocular Symptoms of Dryness

A significantly higher proportion of patients in the 5-mg pilocarpine group showed a positive response to therapy compared with those in the placebo group for relief of symptoms of nasal dryness (P<.002), skin dryness (P<.01), ability to expectorate mucus (P<.02), and vaginal dryness (P<.02).

SALIVARY FUNCTION

The measure of salivary flow is presented in milliliters per minute. The change in predose salivary flow over time was evaluated to determine if there was a carryover effect of pilocarpine therapy. This was assessed by analyzing the mean predose salivary flow for each treatment group at each clinic visit. By the end of the study, there was no change in predose salivary flow rates (P<.10). Therefore, no adjustment to postdose flow rates was required for the remaining analyses. As early as administration of the first dose of test drug at the admission visit, the 5-mg pilocarpine group demonstrated a statistically significant increase (P<.001) in salivary flow at all postdose collections (30, 60, and 90 minutes) compared with the placebo group. This increase was maintained throughout the study. At admission, the mean (±SD) flow rates for placebo vs 5-mg pilocarpine therapy, respectively, were 0.11 (±0.14) vs 0.11 (±0.15) mL/min before dosing; 0.12 (±0.14) vs 0.34 (±0.53) mL/min 30 minutes after dosing; 0.13 (±0.15) vs 0.34 (±0.45) mL/min 60 minutes after dosing; and 0.13 (±0.15) vs 0.27 (±0.34) mL/min 90 minutes after dosing. Throughout the study, the mean salivary flow rate 60 minutes after dosing was 0.15 (±0.19) vs 0.33 (±0.41) mL/min (P<.001) at week 6, 0.17 (±0.13) vs 0.38 (±0.48) mL/min (P<.001) at week 12, and 0.17 (±0.19) vs 0.37 (±0.46) mL/min at end point (P<.001). Flow rates comparing the placebo and the 5-mg pilocarpine groups 60 minutes after dosing throughout the study are presented in Figure 2.

At study end point, there was no statistically significant difference between the 2.5-mg pilocarpine and the placebo groups in 60-minute postdose mean salivary flow.

ADVERSE EXPERIENCES

No serious drug-related adverse experiences were reported in this study. The most frequently reported adverse experiences (≥10% in any treatment group) are shown in Table 4. Sweating was the most frequently reported event. The assessment of a possible relationship between use of the study medication and the occurrence of an adverse experience was based on either the known pharmacologic properties of pilocarpine or a statistically significant increase in incidence in the 5-mg pi-
Table 4. Incidence of Adverse Experiences (≥10% in Any Treatment Group)*

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>Placebo Tablets (n = 125)</th>
<th>2.5 mg Pilocarpine Tablets (n = 121)</th>
<th>5 mg Pilocarpine Tablets (n = 127)</th>
<th>Overall P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating†</td>
<td>9 (7.2)</td>
<td>13 (10.7)</td>
<td>55 (43.3)</td>
<td>≤ .001</td>
</tr>
<tr>
<td>Headache</td>
<td>31 (24.8)</td>
<td>25 (20.7)</td>
<td>20 (15.8)</td>
<td>≤ .90</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>11 (8.8)</td>
<td>16 (13.2)</td>
<td>18 (14.2)</td>
<td>≤ .38</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (8.8)</td>
<td>15 (12.4)</td>
<td>15 (11.8)</td>
<td>≤ .62</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7 (5.6)</td>
<td>9 (7.4)</td>
<td>13 (10.2)</td>
<td>≤ .38</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (8.8)</td>
<td>6 (5.0)</td>
<td>13 (10.2)</td>
<td>≤ .29</td>
</tr>
<tr>
<td>Urinary frequency†</td>
<td>2 (1.6)</td>
<td>13 (10.7)</td>
<td>12 (9.5)</td>
<td>≤ .01</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage).
† Events with a probable relationship to pilocarpine use. Other events with a probable relationship to drug use but with <10% incidence are flushing (placebo group, 1.6%; 2.5-mg pilocarpine group, 1.7%; and 5-mg pilocarpine group, 9.5%) and increased salivation (0%, 0%, and 2.4%, respectively).

Saliva is a chemically complex fluid containing several organic and inorganic components, all of which play an essential role in maintaining oral health. Saliva functions not only required to preserve the dentition and mucosal surfaces but also to facilitate digestion, phonation, mastication, deglutition, and gustation. Therefore, the oral consequences of salivary gland hypofunction extend beyond those of a dry mouth. Common oral symptoms in SS can also include dysphonia, dysphagia, stomatopyrosis (burning mouth), dysgeusia (altered taste), oral ulcers, and sleep disruption caused by nocturnal fluid ingestion.

Two percent (5/248) of the patients taking pilocarpine tablets withdrew from the study because of 1 or more drug-related adverse experiences, ie, 1 patient receiving 2.5-mg pilocarpine tablets (urinary frequency) and 4 patients receiving 5-mg pilocarpine tablets (sweating, 4 patients; flushing, 1 patient; and hypersalivation, 1 patient). Of the total population, a comparable proportion of patients from each treatment group (5.6%-7.4%) withdrew because of adverse experiences, whether or not related to use of the study drug (Table 3). Of the remaining reasons for withdrawal, none differed among treatment groups by more than 1 patient. One patient, in the 2.5-mg pilocarpine group, died during the study because of complications of a probable pulmonary embolus and Clostridium difficile enterocolitis. The investigator and treating physician did not consider these events to have any relationship to use of the study drug.

Two VAS questions were asked to assess the potential adverse effects of pilocarpine tablets on vision after administration of the study drug: difficulty with night driving and difficulty reading (visual acuity). No exacerbation of these symptoms was noted during the study after use of 2.5- or 5-mg pilocarpine tablets (P = .64 and P = .63, respectively).

**COMMENT**

The medicinal properties of pilocarpine, including its ability to stimulate salivation, have been recognized for many centuries by the Tupi Indian tribe of northern Brazil, who named this indigenous shrub “jaborandi,” or the “slobber-mouth plant.” In 1888, a British physician described a 65-year-old woman with xerostomia and xerophthalmia who probably had SS and who responded symptomatically to treatment with tincture of jaborandi, administered orally and subcutaneously. The benefit of pilocarpine tablets for treatment of symptoms of dry mouth from various causes, including SS, has been previously suggested in smaller studies and case reports.

Data from the present multicenter trial indicate that the use of 5-mg pilocarpine tablets administered 4 times daily (20 mg/d) provides significant symptomatic relief of dry mouth caused by SS and significantly increases saliva production in measurable quantities. Regular use of pilocarpine tablets at this dosage significantly improves other specific symptoms of salivary gland hypofunction in patients with SS, such as oral discomfort, nocturnal fluid ingestion, and the need for saliva substitutes. Some benefit for dysphonia may also occur, as evidenced by the trend toward statistically

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significant improvement in the 5-mg pilocarpine group for this symptom.

Although the data show that pilocarpine-induced stimulation of salivary flow occurred within 30 minutes of ingestion of the first dose and was maintained through week 12, the onset of subjective benefit for various symptoms took 6 to 12 weeks. Because dry mouth develops rather insidiously in most patients with SS, it is not unreasonable to expect that improvement or reversal of symptoms after treatment would be delayed. This observation suggests that a patient's symptoms on a given day may reflect not only the quantity of saliva but also the cumulative effect of chronic tissue dehydration. For this reason, it seems that a prolonged treatment course with pilocarpine tablets (eg, 6-12 weeks) should be recommended to patients to allow sufficient time for symptomatic benefits to occur. In this study, the most dramatic response occurred in patients who took 5-mg pilocarpine tablets 4 times daily. Although salivary flow rates were measured during only the first 90 minutes of the dosing interval, results of previous studies in healthy participants indicate that the pilocarpine effect on flow rates lasts 3 to 5 hours. Optimal therapeutic benefit can therefore be best achieved through a 4-times-daily dosing regimen.

Results of this study also indicate symptomatic relief of dry eyes after use of 5-mg pilocarpine tablets 4 times daily. Significantly more patients reported improvement in their global assessment of dry eyes, blurred vision, ability to focus the eyes during reading, and ocular problems in the higher-dose (5-mg) treatment group compared with the placebo group. However, some ocular symptoms did not significantly change. This could be due to a differential degree of cholinergic stimulation by pilocarpine on the eyes compared with the mouth or could reflect the need for higher doses or a longer treatment period to achieve maximal benefit. As noted in a second study of pilocarpine tablet use for patients with SS, which used doses up to 30 mg/d, statistically significant response for relief of ocular symptoms was observed in 8 of 9 measures in the pilocarpine group compared with the placebo group.

As one could predict from pilocarpine's pharmacological effect, this investigation also suggests that pilocarpine tablets, at doses of 20 mg/d, can stimulate exocrine gland secretion in other organ systems besides the eyes and mouth. At study end point, statistically significant improvement was also observed in other sicca symptoms associated with SS, including nasal dryness, dry skin, vaginitis sicca, and the ability to expectorate. These data therefore suggest that treatment with pilocarpine tablets not only offers relief of symptoms of dry mouth and dry eyes but of whole-body dryness as well.

In this multicenter trial, the incidence of adverse effects related to the use of pilocarpine tablets reflected the cholinergic activity of this drug. The most common drug-related adverse experiences included sweating, urinary frequency, and flushing. Despite a relatively high incidence of sweating, this and other adverse effects were perceived as minor by most patients, and the withdrawal rate due to drug-related adverse experiences was low (2%). No significant differences between treatment groups were observed for alterations in blood pressure or heart rate, and no drug-related serious events were reported, including hematopoietic, renal, or hepatotoxic effects. No significant drug interactions were noted. This study did not demonstrate any pulmonary safety issues in this patient population. However, the package insert for Salagen tablets (oral pilocarpine) does note that pilocarpine should be administered with caution and under close supervision to patients with controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease requiring medical therapy.

From a physiologic standpoint, treatment of patients with SS with a systemic cholinergic agonist such as pilocarpine to stimulate the body's own multiorgan secretions not only is the most efficacious and cost-effective strategy to alleviate multiple symptoms but also offers the best potential treatment for prevention of long-term complications caused by severe dryness. Although the efficacy of long-term oral pilocarpine therapy for dental caries prophylaxis or prevention of oral infections in humans is not known, data from animal models suggest such a possible benefit. In a study of partially desalivated rats fed a cariogenic diet, treatment with pilocarpine reduced the incidence of sulcal cavities compared with nontreated controls. These findings did not significantly correlate with a lower incidence of infection by cariogenic bacteria (eg, Streptococcus sobrinus). However, in another study, the incidence of oral infection by S sobrinus in surgically desalivated rats was significantly reduced after pilocarpine treatment compared with untreated controls. Furthermore, stimulation of salivary flow by pilocarpine treatment can reportedly reverse sucrose-induced fissure caries in albino rats. Consequently, further studies to determine this treatment's ability to prevent complications (eg, dental caries) from dry mouth and other sicca symptoms from SS seem reasonable.

In conclusion, the administration of 5-mg pilocarpine tablets 4 times daily (20 mg/d in divided doses) produced significant benefits for the symptomatic treatment of dryness associated with SS that clearly outweighed adverse effects and risks in this 12-week study. Patients experienced improvement in symptoms of dry mouth and dry eyes, and improvement in dryness of the nose, skin, and vagina and the ability to expectorate. Treatment success with pilocarpine will most likely depend on existence of residual exocrine gland function. In SS, this may vary in different organs and cannot always be predicted based on the duration of symptoms. As data from the present study suggest, use of pilocarpine tablets offers a wide range of potential therapeutic effects for patients with SS. Therefore, at the present time, almost any patient with SS with some degree of exocrine gland function could potentially benefit from this treatment depending on therapeutic goals. As with other patient groups with rheumatic conditions, early diagnosis and treatment offer the best hope for a good outcome.

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REFERENCES


