ORIGINAL ARTICLE

Pilot Clinical Trial of Dehydroepiandrosterone (DHEA) Versus Placebo for Sjögren's Syndrome

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Objective. To screen for potential efficacy and assess feasibility and safety of dehydroepiandrosterone (DHEA) as a treatment for Sjögren's syndrome (SS).

Methods. A 24-week randomized, double-blinded, pilot trial of oral DHEA (200 mg/day) versus placebo was conducted. The primary comparison was to a hypothesized 20% placebo response rate. If 14 consecutive subjects on DHEA did not respond, a Phase III trial would be considered futile. A placebo group of 14 subjects was planned to verify placebo response rate and estimate sample size required for a definitive trial. Response criteria required 20% improvement in at least 2 of 3 domains. Analysis of covariance was used to adjust for baseline differences and for stratified randomization. Outcome measures included visual analog scale questionnaires for dry eye and dry mouth symptoms, lissamine green ocular dye staining and Schirmer I tests, stimulated salivary flow, IgG, and erythrocyte sedimentation rate (ESR).

Results. Randomization resulted in 14 DHEA and 14 placebo group subjects. At baseline, mean ± SD for DHEA versus placebo groups were Schirmer I tests 4.5 ± 4.5 versus 5.4 ± 6.1 mm/5 minutes; Van Bijsterveld score 5.3 ± 2.1 versus 5.5 ± 2.2; unstimulated saliva 0.03 ± 0.05 versus 0.04 ± 0.10 ml/minute; IgG 1,699 ± 749 versus 1,712 ± 621 g/dl; and ESR 40 ± 31 versus 44 ± 28 mm/hour. Apart from changes over the trial in dry mouth symptoms, no significant differences were noted between the DHEA and placebo groups for dry eye symptoms, objective measures of ocular dryness, stimulated salivary flow; IgG, or ESR. Four DHEA and one placebo group patient dropped out because of adverse effects. Although 7 subjects met response criteria in the DHEA group, 5 met the criteria in the placebo group, and there was no significant difference between groups.

Conclusion. DHEA showed no evidence of efficacy in SS. Without evidence for efficacy, patients with SS should avoid using unregulated DHEA supplements, since long-term adverse consequences of exposure to this hormone are unknown.

KEY WORDS. Dehydroepiandrosterone; Sjögren's Syndrome; Clinical trial.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disorder that predominantly affects women. SS is characterized by symptoms of dry mouth and dry eyes, lymphocytic infiltration of exocrine and other epithelial tissues, autoantibody production, and increased serum immunoglobulin levels. The prevalence of SS varies from 0.05% to 4.8% (1).

Low levels of serum dehydroepiandrosterone (DHEA) have been noted in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and SS, suggesting a possible role for this steroid hormone in these autoimmune disorders (2). In addition, trials of DHEA suggest that it may be beneficial in the treatment of SLE (3). We noticed that several of our SS patients were taking DHEA in the form of dietary supplements, which are not subject to the rigorous testing for efficacy and safety that is required for therapeutic agents in the United States. These supplements are widely available in supermarkets, pharmacies, health food stores, and through Internet sources. The lack of safety and efficacy data for DHEA in SS, the apparent use by some affected with the disease, and the suggestion that levels of metabolites of this hormone may

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be low in SS (4) prompted us to study this interesting agent.

We designed a 24-week, randomized, double-blinded, placebo-controlled, pilot clinical trial to screen for potential efficacy and to evaluate the safety and potential adverse effects of DHEA in primary SS.

Patients and methods

A double-blind, randomized, placebo-controlled, pilot study of DHEA was planned for 28 patients. Patients were randomized to receive oral DHEA 200 mg or placebo for 24 weeks. Highly purified pharmaceutical-grade DHEA was obtained from Diosynth, Inc. (Chicago, IL); DHEA and placebo capsules were produced by Pharmaceutical Development Services, Clinical Center Pharmacy, National Institutes of Health. The study was performed under Investigational New Drug application number 52,639, which was filed with the Food and Drug Administration.

Baseline evaluations included a history and physical examination, electrocardiogram, chest radiograph, acute care, hepatic and mineral panels, complete blood count with differential, Westergren erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factor, quantitative immunoglobulins, urinalysis, pregnancy test, ocular dye staining (lissamine green), and Schirmer I test.

Entry criteria included primary SS by the criteria of Fox et al (5) as well as symptoms and complaints consistent with oral and ocular dryness. Patients also met the American European criteria for SS (6). Exclusion criteria were women with known hypersensitivity to DHEA; a history of breast or uterine cancer or a family history of premenopausal breast cancer or bilateral breast cancer in a first-degree relative; confounding medical illnesses or abnormal laboratory test results; and use of an experimental drug 30 days or less prior to protocol entry. Men were excluded.

Clinical assessments of disease activity were planned for study entry and at 4, 12, and 24 weeks. A 28-week visit was planned to evaluate patients 4 weeks after discontinuing the study drug.

The primary outcome measure was meaningful improvement across 2 of 3 Sjögren's syndrome disease domains: oral, ocular, and laboratory tests. Oral improvement was defined as ≥20% improvement in patient's assessment of dry mouth by visual analog scale (VAS) or 20% improvement in total stimulated salivary flow. Ocular improvement was defined as ≥20% improvement in patient's assessment of dry eyes by VAS or ocular dye test scored according to the method of van Bijsterveld or Schirmer I without anesthetic. Laboratory improvement was defined as ≥20% improvement in serum IgG level or ESR.

The study design followed a method proposed by Pillemer et al for screening for antirheumatic agents (7). The method assumes a response rate of 20% in a single-armed study. If there are no responders, there is a 95% chance that further investigation will not reveal efficacy. However, if 1 or more individuals respond, 16 more patients would be treated; for 3 or more responders of these first 30 patients, the treatment would be further investigated in a

Table 1. Demographics and disease measures at baseline*			
Variable	**Placebo**	**DHEA**	**P**
N	14	14	-
Age, years	55.3 (3.30)	52.5 (3.58)	0.57
Female	14	14	-
Ethnicity			
White	11	10	-
Black	1	1	-
Hispanic	0	1	-
Asian	2	2	-
American Indian	-	-	-
Dry mouth?	22.6 (7.4)	25.4 (7.4)	0.79
Dry eyes?	36.9 (8.9)	36.3 (8.9)	0.96
Schirmer I test	5.4 (1.5)	4.5 (1.5)	0.69
Van Bijsterveld	5.5 (0.6)	5.3 (0.6)	0.80
Salivary flow, unstim	0.04 (0.02)	0.03 (0.02)	0.82
Salivary flow, stim	0.73 (0.22)	0.54 (0.23)	0.54
Focus score	7.9 (3.67)	8.1 (3.68)	0.98
IgG, mg/dl	1,713 (183.9)	1,699 (183.9)	0.96
ESR, mm/hour	44 (8.2)	40 (7.9)	0.70

* Data given for sex and ethnicity represent number of individuals. The other values for measures in the placebo and DHEA treatment groups are given as mean (standard error mean). Visual analog scale (100 mm) questionnaires for dry mouth and dry eyes at baseline visit: "How dry does your mouth feel most of the time? (dry as a desert . . . not at all)." "How dry do your eyes feel most of the time? (very dry . . . not dry at all)." Schirmer I test is tear flow in mm per 5 minutes. Lissamine green test yields the van Bijsterveld score. Stimulated (stim) and unstimulated (unstim) total salivary flow values are given in ml/minute. DHEA = dehydroepiandrosterone; ESR = erythrocyte sedimentation rate.

phase III trial. A placebo group of equal size was included because the placebo response rate is unknown.

The protocol was approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research. Safety was monitored in interviews at each monthly visit as well as in monthly telephone calls for possible adverse effects. Significant adverse effects required the investigators to discontinue the study medication. Reported adverse reactions to DHEA include decreased menstrual blood flow, acneiform dermatitis, and mild hirsutism (8). The effects of DHEA on proliferation of breast and uterine tissue are currently unknown, hence the exclusion of patients with a history or family history of breast or uterine cancer. In addition, since the effects of DHEA on oral contraceptives are unknown, patients were instructed not to rely exclusively on this method of contraception during the trial. Compliance was monitored at each safety call and clinic visit. Capsule counts for DHEA or placebo were done at each visit.

Comparisons between the 2 treatment groups were performed using t-tests and Fisher's exact test. Analysis of covariance was performed to adjust for baseline differences. The analyses for efficacy were based on intent to treat using the last observation carried forward.

Results

There were no significant baseline differences between the treatment groups (Table 1; all P > 0.54).

As shown in Table 2, the mean changes in outcome

Table 2. Changes in measures at the final visit compared with baseline*

Measure	Placebo	DHEA	*P*
Dry mouth?	−10 (5.5)	9 (5.5)	0.02
Dry eyes?	−12 (5.6)	−4 (5.6)	0.32
Schirmer I test	0.1 (1.3)	−1.9 (1.3)	0.28
Van Bijsterveld	0.7 (0.6)	1.1 (0.6)	0.64
Stim sal flow	−0.09 (0.09)	0.086 (0.09)	0.17
IgG, mg/dl	26.1 (44.9)	103.3 (44.9)	0.23
ESR, mm/hour	0.6 (2.9)	−3.1 (2.8)	0.37

* Values for measures in the placebo and DHEA treatment groups are given as mean (standard error mean). Changes in 100-mm visual analog scale questionnaires for dry mouth and dry eyes for final minus baseline visit: "How dry does your mouth feel most of the time? (dry as a desert . . . not at all)." "How dry do your eyes feel most of the time? (very dry . . . not dry at all)." Schirmer I test is tear flow in mm per 5 minutes. Change in stimulated total salivary flow (stim sal flow) is given in ml/minute. DHEA = dehydroepiandrosterone; ESR = erythrocyte sedimentation rate.

variables were not significantly different between the groups at the time of termination of the study drug, apart from the statistically significant improvement in dry mouth symptoms. However, this improvement was not clinically meaningful. There were no significant differences between the 2 groups for changes in final minus baseline values for symptoms reported in VAS questionnaires addressing dry eyes and mouth, oral discomfort, difficulty swallowing, difficulty speaking, energy level, joint pain, myalgia, appetite, dry nose or throat, and sleep (data not shown).

Applying the response criteria for the trial, 7 of the patients receiving DHEA and 5 of the placebo patients experienced clinical improvement. The difference between the 2 groups was not significant (*P* = 0.2, Fisher's exact test).

Five patients dropped out of the study because of adverse effects, and 1 of these patients was in the placebo group (Table 3). The patient in the placebo group was hospitalized during her first month of taking the study drug and found at surgery to have a perforated peptic ulcer. This patient had a long history of recurrent upper gastrointestinal pain in the past, which had been attributed to multiple gallstones. The study medication was discontinued without breaking the code until all patients

Table 3. Reasons for dropping out of the study*

Reason	Treatment
Acne; job related stress	DHEA
Eye exam too painful; concerned about facial hirsutism (not found on exam)	DHEA
Post-dose chills, arthralgia, nausea, abdominal discomfort, nervousness, irritability	DHEA
Disseminated streptococcal infection; acute abdomen	DHEA
Perforated peptic ulcer; *H. pylori* positive	Placebo

* DHEA = dehydroepiandrosterone; *H. pylori* = *Helicobacter pylori*.

had completed the trial and was not resumed because of the serious nature of the potential adverse event. A literature search at the time did not suggest any convincing association between DHEA and peptic ulcers.

Discussion

In this trial of DHEA compared with placebo, adverse effects were mild, apart from 1 patient with disseminated streptococcal infection that appears unlikely to be related to the medication. Despite evidence to suggest that DHEA may have a role in the treatment of autoimmune diseases, there was no evidence in this trial to support potential efficacy in the treatment of SS.

In terms of the primary outcome measure for the trial, there was no significant difference between the DHEA and the placebo groups. Comparisons of changes in the outcome measures showed only a statistically significant improvement in the dry mouth symptoms on VAS for the DHEA group compared with the placebo group. However, the improvement in the DHEA group represented only 9 mm on a 100-mm scale, i.e., 9% improvement, which by the definition used in our study is not clinically meaningful. The placebo group showed a worsening of dryness of 10%. We defined at least 20% improvement as clinically meaningful, in keeping with that used for symptoms in rheumatoid arthritis clinical trials (9). However, an isolated effect of DHEA on symptoms of dry mouth cannot be ruled out.

The adverse events seen in the trial were generally mild, mostly minor acne. However, one patient experienced a severe recurrence of preexisting acne and dropped out of the trial and another patient developed disseminated sepsis, which followed an upper respiratory infection with *Streptococcus*. The patient presented with acute abdominal pain suspected initially to be appendicitis or possibly diverticulitis. However, *Streptococcus* was cultured from the patient's throat, blood, and stools. No evidence was found in the literature to support a role for DHEA in enhancing susceptibility to streptococcal infections. Animal studies suggested that treatment with DHEA may decrease susceptibility to bacterial and viral infections (10). From this study, DHEA administration over a 6-month period appears to be safe. However, the potential for long-term complications of administration of a steroid hormone, such as DHEA, cannot be excluded.

Evidence suggested that DHEA sulfate levels may be decreased in SS, and DHEA levels may be decreased in SLE and RA (4,11,12). This raised the possibility that normalizing DHEA levels might result in an improvement in RA and SLE. Subsequent studies have provided evidence for a beneficial effect of DHEA in SLE (2,13). However, in a recent study of SS patients, no evidence was found to support the existence of decreased levels of either DHEA or DHEA sulfate (14). In 1988, a small, randomized, double-blind trial of another mild steroid androgen, nandrolone decanoate, showed some evidence of subjective, but not objective, improvement in primary SS (15).

A response was seen in the primary outcome measure for the DHEA group. In terms of the study design, potential efficacy could not be ruled out with 95% confidence if 1 or

more of 14 consecutive patients in the treatment group responded. However, the occurrence of responders in the placebo group violated the assumption of a ≤20% probability of response in the placebo group. Thus, the screening method for an uncontrolled active treatment group (DHEA) could not be applied. However, none of the oral and ocular objective tests and the serologic measures was significantly different between the 2 treatment groups. In addition, differences in oral symptoms, although statistically significant, were not clinically meaningful. The trial therefore provided no evidence of potential efficacy.

In conclusion, there is no evidence to support the potential efficacy of DHEA as a treatment for SS. Although the adverse effects related to DHEA were generally mild in this study of short duration, the long-term consequences of treatment with this steroid hormone have yet to be determined. Therefore, DHEA should not be used as a dietary supplement nor should it be prescribed as a treatment for SS until there is clear evidence for efficacy. However, DHEA may be considered in patients with SLE or other indications for which there is supportive evidence.

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