Dehydroepiandrosterone Treatment of Women With Mild-to-Moderate Systemic Lupus Erythematosus

A Multicenter Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. To evaluate the efficacy and tolerability of dehydroepiandrosterone (DHEA) at a dosage of 200 mg/day in adult women with active systemic lupus erythematosus (SLE).

Methods. In a multicenter randomized, double-blind, placebo-controlled trial, 120 adult women with active SLE received oral DHEA (200 mg/day; n = 61) or placebo (n = 59) for 24 weeks. The primary end point was the mean change from baseline in the Systemic Lupus Activity Measure (SLAM) score at 24 weeks of therapy. Secondary end points included time to first flare, change in SLE Disease Activity Index (SLEDAI) score, and physician’s and patient’s global assessment scores at week 24.

Results. The two groups were well balanced for baseline characteristics. Mean reductions in SLAM scores from baseline were similar and were not statistically significantly different between treatment groups (DHEA -2.6 ± 3.4 versus placebo -2.0 ± 3.8, mean ± SD). The number of patients with flares was decreased by 16% in the DHEA group (18.3% of DHEA-treated patients versus 33.9% of placebo-treated patients; P = 0.044, based on time to first flare). The mean change in the patient’s global assessment was statistically signifi-

Systemic lupus erythematosus (SLE) is a multi-system autoimmune inflammatory disease with diverse clinical and laboratory manifestations and with a variable course and prognosis. Although the etiology of SLE is unknown, hormonal influences may play a key role in disease development and progression.

The adrenal steroid dehydroepiandrosterone (DHEA) is secreted primarily as its sulfated metabolite DHEAS. Although the biologic function of DHEA in humans has not been ascertained, it has mild intrinsic androgenic properties, and in peripheral tissues, both DHEA and DHEAS can be converted to various other androgens as well as aromatized to estrogenic steroids (1). The potential for using DHEA in the treatment of SLE was suggested by such observations as the female predominance of SLE, the low circulating levels of DHEA and DHEAS in patients with active disease (2), the immunomodulatory effects of DHEA (3), and the delayed onset of and reduced mortality from SLE in NZB × NZW mice that were fed DHEA (4).

The present study was designed to evaluate the safety and efficacy of DHEA treatment in female pa-
tients with mild-to-moderate SLE disease activity. Our findings are presented herein.

**PATIENTS AND METHODS**

**Study design.** This study was a randomized, double-blind, placebo-controlled trial conducted at 4 medical centers in Taiwan using the same protocol. Adult Chinese women with SLE according to the American College of Rheumatology criteria (5) who were receiving a dosage of 0–10 mg/day of prednisone (or its equivalent) at study entry were enrolled. Patients had active SLE, which was originally defined as a Systemic Lupus Activity Measure (SLAM) score ≥7 (6). This was subsequently amended to also require a baseline SLE Disease Activity Index (SLEDAI) score >2 (7). In patients treated with hydroxychloroquine, azathioprine, methotrexate, or cyclophosphamide, either alone or in combination, the regimen had to have been stable, with no changes in the dosage or drug combination, for at least 6 weeks prior to study entry. This regimen was to remain unchanged throughout the study. Patients who were receiving androgens, immunoglobulins, cyclosporin A, or immunosuppressive agents other than those noted above were excluded.

After a 10-day screening and qualifying baseline period, patients were assigned by predetermined randomization code to receive DHEA at a dosage of 200 mg/day or placebo for 24 weeks. Scheduled evaluations at baseline and at weeks 4, 12, and 24 included a physical examination, routine laboratory determinations, the SLAM score, and patient’s and physician’s global assessments (using a 100-mm visual analog scale [VAS]). The SLEDAI score was measured at baseline and at weeks 12 and 24 only. Serum levels of sex hormones and DHEAS were measured at baseline and at the last visit.

The protocol was approved by the Institutional Review Board at each center. All patients gave their written informed consent.

**Efficacy end point.** The primary end point was the mean change in the SLAM score at 24 weeks of therapy compared with baseline. Secondary end points included SLE flare, change in SLEDAI score, and physician’s and patient’s VAS scores at 24 weeks. Our definition of disease flare was similar to that of the ongoing SELENA (Safety of Estrogens in Lupus Erythematosus: National Assessment) study (8), except that we included an increase in glucocorticoid dosage of ≥2.5 mg for at least 7 days for SLE-related reasons as a component.

**Safety variables.** Adverse events were coded according to the COSTART system. The variables were summarized by treatment group and body system.

**Laboratory measurements.** Laboratory assessments included a urinalysis, a Westergren erythrocyte sedimentation rate (ESR), and routine serum biochemistries. Anti-double-stranded DNA (anti-dsDNA) antibody, C3 and C4 complement, serum 17β-estradiol, total testosterone, and DHEAS levels were also measured.

**Statistical analysis.** All statistical tests were 2-sided and evaluated at the 0.05 level of significance. Continuous variables were analyzed using an analysis of variance model. Categorical variables were analyzed using chi-square test.

### RESULTS

**Characteristics of the study patients.** A total of 120 patients were randomized into the study and received treatment as follows: 61 patients received DHEA 200 mg/day and 59 patients received placebo. The two treatment groups were well balanced with regard to baseline characteristics. The patients were of similar age and menopause status, and their prednisone dosage/use, use of cytotoxic agents, use of antimalarials, and scores on the SLE activity instruments were similar at baseline.

Patients were evaluated for 24 weeks or until early termination of the study drug. Fifty-eight patients in the DHEA group (95.1%) and 55 patients in the placebo group (93.2%) completed the study. There was no significant difference in the mean duration of exposure between the two groups (164 ± 26.6 days in DHEA group and 163.7 ± 23.5 in placebo group; P = 0.986); the median duration of exposure was identical (169.0 days).

**Efficacy of DHEA.** The primary end point was the change in SLAM scores from baseline. No significant difference in SLAM scores between the two treatment groups was detected (P = 0.355) (Table 1). As shown in Table 2 and Figure 1, significantly fewer patients in the DHEA group had disease flares.

The DHEA group showed significantly greater improvement in patient’s VAS scores compared with the placebo group. Patient’s VAS scores decreased by 5.5 from a baseline score of 37.0 in the DHEA group and

### Table 1. Efficacy variables in the study patients, by treatment group*

<table>
<thead>
<tr>
<th></th>
<th>DHEA-treated patients (n = 61)</th>
<th>Placebo-treated patients (n = 59)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLAM score Baseline</td>
<td>10.3 ± 2.8</td>
<td>10.4 ± 2.6</td>
<td>0.355</td>
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<tr>
<td>Mean change</td>
<td>−2.6 ± 3.4</td>
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<tr>
<td>SLEDAI score Baseline</td>
<td>8.2 ± 4.9</td>
<td>6.6 ± 3.4</td>
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<tr>
<td>Mean change</td>
<td>−1.2 ± 5.4</td>
<td>−1.4 ± 4.6</td>
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<tr>
<td>Patient’s VAS score</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>37.0 ± 18.8</td>
<td>33.7 ± 17.9</td>
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<tr>
<td>Mean change</td>
<td>−5.5 ± 20.0</td>
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</tr>
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<td>Physician’s VAS score</td>
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<tr>
<td>Baseline</td>
<td>31.0 ± 11.3</td>
<td>31.4 ± 14.0</td>
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<tr>
<td>Mean change</td>
<td>−9.2 ± 13.9</td>
<td>−6.3 ± 16.9</td>
<td>0.104</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD baseline scores and the mean ± SD change in scores at the last visit in the intent-to-treat population. DHEA = dehydroepiandrosterone; SLAM = Systemic Lupus Activity Measure; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; VAS = visual analog scale.

† P values were determined by analysis of variance, with treatment, center, and treatment by center interaction as factors.
increased by 5.4 from a baseline score of 33.7 in the placebo group (P = 0.005) (Table 1).

Safety of DHEA. DHEA was well tolerated in these study patients. Expected androgenic effects, including increased testosterone levels and increased incidence of acne, were observed. No life-threatening reactions or serious safety issues were identified during this study.

Adverse events. Adverse events that were assessed by the investigators as being serious were reported in a significantly higher proportion of patients in the placebo group than in the DHEA group. One or more serious adverse events were reported for 7 of 61 patients treated with DHEA (11.5%) and for 18 of 59 patients treated with placebo (30.5%); the difference was statistically significant (P = 0.010 by chi-square test). In most cases, the types of serious adverse events reported were consistent with SLE flares or hospitalization for manifestations of SLE, rather than being adverse effects of the study drug.

Findings of clinical laboratory evaluations. For all standard laboratory tests of safety, the two groups appeared to be well matched at baseline. There were no overall trends in the results of hematologic, biochemical, or lipid tests that would be suggestive of an adverse effect of DHEA treatment. Levels of triglycerides decreased in the DHEA group compared with the placebo group (P < 0.05).

Estradiol levels decreased in both groups. The median decrease was slightly larger for the DHEA group (39.3 pg/ml versus 31.5 pg/ml in the placebo group). Mean and median testosterone levels increased in the DHEA group and decreased in the placebo group (46.6 and 39.5 pg/ml versus −6.6 and −6.5 pg/ml, respectively; P < 0.05).

The mean and median levels of C3 and C4 serum complement decreased in patients in the DHEA group, whereas a small increase or no change was noted in patients in the placebo group (P < 0.05). Anti-dsDNA antibody titers decreased in both treatment groups, but the mean and median decreases were greater in the placebo group. In both treatment groups, the majority of patients had abnormally high anti-dsDNA titers at the baseline visit and at the final visit. The ESR was comparable in the two treatment groups at baseline. Small decreases in the median ESR values at each visit were observed in both treatment groups.

Most patients in both treatment groups had DHEAS levels of 0–200 μg/dl at baseline. At the assessments after baseline, ~60% of patients in the DHEA group had DHEAS levels >1,000 μg/dl. The levels in the remaining patients were distributed over each of the lower 200-μg/dl incremental ranges. There was no evidence of elevated DHEAS levels in the placebo group at baseline or at subsequent visits.

DISCUSSION

In this double-blind study evaluating the efficacy and safety of DHEA for the treatment of mild-to-moderate SLE in women, we found significant reductions in the time to disease flare and serious lupus-related adverse events, as well as improvement in patient’s global assessment in the DHEA-treated group compared with the placebo-treated group. This is of particular interest since almost all patients were already receiving treatment with standard medications, including glucocorticoids and other immunosuppressive agents. While the planned primary analysis, change in SLAM score from baseline to last visit, did not demonstrate significant differences between the two treatment groups, it is important to recognize that this study was of relatively short duration (6 months), and there are as yet
no fully validated end points for therapeutic interventions in lupus trials. Given the multiple end points of this study, its findings should be confirmed in a trial of longer duration.

Multiple mechanisms could be mediating these effects, including favorable changes in inflammatory cytokines such as interleukin-6 (IL-6), which is increased in patients with active SLE (9). DHEA has been reported to reduce the release of IL-6 from human mononuclear cells in vitro (3,10). Decreases in complement levels without SLE flare during DHEA treatment were observed in this study as well as in two other clinical studies (11,12). A presumed reduction in IL-6 production during DHEA administration might be associated with a reduction in the levels of C3, which is an acute-phase reactant (13).

DHEA was well tolerated by the patients in this study, with no evidence of unexpected or serious adverse effects of the drug. Most of the serious adverse events reported in this study appeared to be related to SLE flares or to hospitalization for manifestations of SLE, rather than to adverse study drug effects. The proportion of patients experiencing serious adverse events was statistically significantly higher in the placebo group. This finding is consistent with the reduction in SLE flares observed in the efficacy analysis of this study.

A double-blind study conducted at Stanford University suggested that DHEA at a dosage of 200 mg/day was well tolerated and may have steroid-sparing effects and reduce the number of flares in patients with mild-to-moderate SLE (14). Furthermore, in two subsequent multicenter studies, DHEA treatment at a dosage of 200 mg/day allowed for a reduction in the prednisone dosage to near-physiologic levels in a significantly greater proportion of patients than did placebo (11), and it stabilized or improved the SLE activity and its symptoms and prevented bone loss (12).

In summary, in this 24-week study of adult Chinese women with mild-to-moderate SLE, treatment with DHEA at a dosage of 200 mg once a day resulted in a stabilization of the overall lupus activity, with fewer flares and fewer hospitalizations and without serious or unexpected adverse effects. Concurrent use of DHEA will offer meaningful benefit, especially for steroids-dependent lupus patients. Confirmation in a larger study of longer duration will be necessary to further define the role of DHEA in SLE.

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REFERENCES