

AN OPEN STUDY OF DEHYDROEPIANDROSTERONE IN SYSTEMIC LUPUS ERYTHEMATOSUS

RONALD F. VAN VOLLENHOVEN, EDGAR G. ENGLEMAN, and JAMES L. MCGUIRE

Objective. To determine if dehydroepiandrosterone (DHEA) has clinical benefits in patients with systemic lupus erythematosus (SLE).

Methods. Ten female patients with mild to moderate SLE and various disease manifestations were given DHEA (200 mg/day orally) for 3-6 months. The patients were given other medications as clinically indicated, and followed with respect to overall disease activity and specific outcome parameters.

Results. After 3-6 months of DHEA treatment, indices for overall SLE activity including the SLEDAI (SLE Disease Activity Index) score and physician's overall assessment were improved, and corticosteroid requirements were decreased. Of 3 patients with significant proteinuria, 2 showed marked and 1 modest reductions in protein excretion. DHEA was well tolerated, the only frequently noted side effect being mild acneiform dermatitis.

Conclusion. DHEA shows promise as a new therapeutic agent for the treatment of mild to moderate SLE. Further studies of DHEA in the treatment of SLE are warranted.

An etiologically important role of sex steroids in systemic lupus erythematosus (SLE) has been suggested both by observations of human patients and by manipulation of the sex hormone status of mice with lupus-like disease. Thus, SLE is seen predominantly

in women (1), tends to flare during pregnancy (2), and may correlate with the androgen/estrogen ratio (3). Female NZB × NZW mice develop lupus-like disease at a much higher frequency than do males; it has been shown that this can be ameliorated by administration of androgens (4-6). On the basis of these observations it has been suggested that administration of natural or synthetic androgens might benefit female SLE patients, were it not for troublesome masculinizing side effects.

Dehydroepiandrosterone (DHEA), an abundant adrenal hormone with only mild intrinsic androgenic activity (7), has been reported to ameliorate nephritis in NZB × NZW mice (8). Previous experience with DHEA supplementation in humans suggested overall good tolerance of this hormone (9-12). Here, we report the results of a clinical pilot study of the use of DHEA in SLE.

PATIENTS AND METHODS

Patients. Ten female patients with SLE according to the criteria of the American College of Rheumatology (13) consented to participate in an open-label, noncontrolled trial of DHEA. Their average age was 35.7 (range 27-68). Seven were Caucasian, one was black, one was Hispanic, and one was Filipino. Nine patients were premenopausal. As expected, the SLE manifestations were varied (Table 1). All patients had mild or moderate lupus. Renal disease was present in 3 patients, consisting of stable proteinuria without abnormalities in the urine sediment and without changes in serum creatinine or creatinine clearance. No overt central nervous system lupus was present in any of the patients, although mild, subjective cognitive impairment was noted by some, and "lupus headaches" were noted in 4.

DHEA protocol. After screening and documentation of baseline status, patients were given capsules of DHEA, 200 mg, to be taken once daily by mouth. They were followed up at monthly intervals by the rheumatologist carrying the primary responsibility for the patient, as well as by 1 of the investigators. Throughout the study period,

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Table 1. Disease characteristics of the study patients*

Patient	SLE duration	Previous manifestations	Manifestations at enrollment	Prednisone dose (mg/day)
1	4 yrs.	LCV, thrombocytopenia, arthritis, fatigue, pleuritis oral ulcers, FANA+	Thrombocytopenia, fatigue, vasculitic skin lesions	5
2	4 mos.	Myalgias, arthritis, malar rash, photosensitive rash, fatigue, FANA+, anti-DNA+	Arthritis, malar rash, myalgias, fatigue	0
3	3 yrs.	Malar rash, alopecia, arthritis, oral ulcers, fatigue, panniculitis, fever, headache, myalgia, leukocytopenia, FANA+, anti-DNA+	Arthritis, malar rash, fatigue, alopecia, headache, fever	37.5
4	10 yrs.	Membranous GN, LAN, s/p stroke, seizures, leukopenia, FANA+	LAN, proteinuria	0
5	21 mos.	Malar rash, oral ulcers, photosensitivity, RP, alopecia, vitiligo, arthritis, myalgia, SS, proteinuria, anemia, FANA+, SS-A+, anti-RNP+	Malar rash, oral ulcers, photosensitivity, RP, alopecia, vitiligo, arthritis, myalgia, SS, proteinuria	3.75
6	5 yrs.	Thrombocytopenia, pleurisy, arthritis, alopecia, ?CNS, hypocomplementemia, FANA+, anti-DNA+	Thrombocytopenia, arthritis, fatigue, HA, hypocomplementemia	10
7	9 yrs.	Vasculitis, malar rash, anemia, thrombocytopenia, oral ulcers, arthritis, alopecia, FANA+	Vasculitic skin lesions, arthritis, alopecia, oral ulcers	25
8	3 yrs.	Mesangial GN, nephrotic syndrome, arthritis, malar rash, fever, fatigue, FANA+	Nephrotic syndrome, pyuria, arthralgia, fatigue, hypocomplementemia	17.5
9	8 yrs.	Malar rash, LAN, fever, arthritis, SS, mesangial nephritis, proteinuria, CNS, FANA+	Arthritis, costochondritis, fever, fatigue, LAN, HA, proteinuria, pyuria, hematuria	10
10	5 yrs.	Malar rash, SS, arthritis, fever, myalgias, fatigue, FANA+	Arthralgias, myalgias, fatigue	7.5

* SLE = systemic lupus erythematosus; LCV = leukocytoclastic vasculitis; FANA = fluorescence antinuclear antibody; GN = glomerulonephritis; LAN = lymphadenopathy; s/p = status post; RP = Raynaud's phenomenon; SS = sicca syndrome; CNS = central nervous system; HA = lupus headache.

patients were treated based on clinical status, according to the discretion of the physician carrying the primary responsibility for the patient. Changes in medications were allowed, including changes in dosages or the addition of new medications.

DHEA powder was obtained from Sigma (St. Louis, MO), capsules of which were prepared by the Stanford University Hospital pharmacy.

Outcome parameters. The SLE Disease Activity Index (SLEDAI) score (14) was determined at each visit. Patients and physicians were asked to record their overall assessment of disease activity, on a scale of 1-100 (patients were given a visual analog scale). Other outcome measures were the medication profile and laboratory parameters.

Statistical analysis. Outcome measurements are given as the mean \pm SEM. Comparisons were made by Student's *t*-test and Wilcoxon sign rank test.

RESULTS

Serum androgen levels. Serum levels of DHEA and DHEA sulfate were determined at monthly intervals. There was a rise in DHEA sulfate levels over the course of the first month, followed by a plateau at a range of 439-1,659 μ g/dl. Levels of DHEA showed

similar increases, but were more variable, in keeping with the known marked circadian variation of this hormone (7). Serum testosterone levels increased in tandem with DHEA sulfate and DHEA. These results are shown in Figure 1. It is also noteworthy that the average baseline levels of DHEA and DHEA sulfate were low in these patients, and that steady-state levels were obtained slowly in some, but not all, patients (data not shown).

Effects of DHEA therapy on SLE activity parameters. All 10 patients completed 3 months of DHEA treatment. The SLEDAI score at the beginning of the study averaged 10.4 ± 2.4 (\pm SEM; range 0-24). After 3 months, the average SLEDAI score had decreased to 8.3 ± 2.1 (range 0-14; $P = 0.079$). Physician's overall assessment improved from 37.2 ± 7.0 to 27.2 ± 7.3 ($P = 0.040$), while the patient's overall assessment showed a statistically nonsignificant improvement. A summary of these outcome measures after 3 months of treatment is given in Table 2.

Eight of the 10 patients thought that DHEA

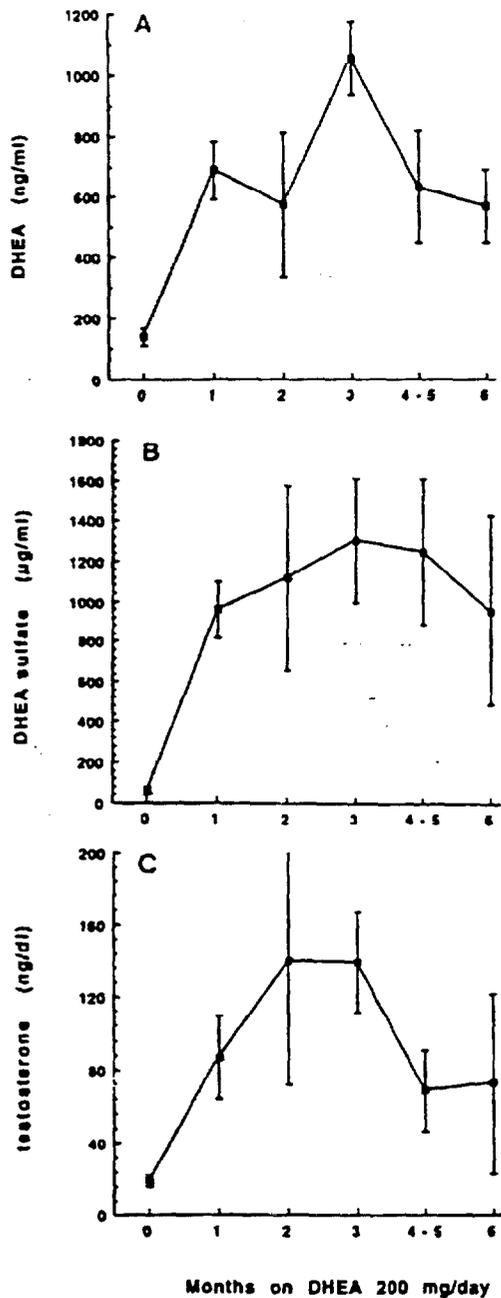


Figure 1. Serum levels of dehydroepiandrosterone (DHEA) (A), DHEA sulfate (B), and testosterone (C) were determined at baseline and after 1-6 months of treatment with DHEA, 200 mg/day, in women with mild to moderate systemic lupus erythematosus (SLE). Baseline DHEA and DHEA-sulfate levels in all 10 SLE patients ranged from 10 to 500 ng% and <10 to 250 µg%, respectively, with the plateau level ranging from 384 to 1,446 ng% and 439 to 1,659 µg%, respectively. Normal ranges were: DHEA 130-980 ng/ml, DHEA sulfate 12-379 µg/ml, and testosterone 0-70 ng/ml (for females). Values are the mean \pm SEM.

improved overall well-being, fatigue, energy, and/or other subjective aspects of their disease, and elected to continue for an additional 3 months. Figure 2 shows the results for these patients. After 6 months on DHEA therapy, the SLEDAI scores were significantly lower than at baseline (10.0 ± 2.9 versus 4.9 ± 1.7 ; $P = 0.040$) and the patient's overall assessment improved from 35.1 ± 8.0 to 14.1 ± 3.8 ($P = 0.015$).

Pretreatment levels of DHEA and DHEA sulfate did not predict a clinical response. There was no significant correlation between the changes in serum DHEA or DHEA sulfate levels and the lupus activity indices after 3 or 6 months by regression analysis (data not shown).

Effect of DHEA therapy on the dose of concurrently administered corticosteroids. Eight of the 10 patients were receiving daily corticosteroids at the beginning of the study. Dosages were changed as clinically indicated. Table 3 shows the corticosteroid dosages at study entry and after 3 and 6 months of treatment with DHEA. After 3 months, the average dose (prednisone equivalent per day) had decreased from 14.5 ± 4.1 to 9.4 ± 2.5 ($P = 0.028$). Of the patients who completed 6 months of DHEA treatment, 6 were taking corticosteroids at study entry, and a reduction in the average daily dose was seen in this small group as well (from 14.8 ± 5.5 to 5.6 ± 1.9 ; $P = 0.042$).

Six patients were taking antimalarials at study entry, and these remained unchanged. One patient (patient 5) who was taking azathioprine at the beginning of the study discontinued the drug during the study, while another patient (patient 7) was started on azathioprine therapy during the study.

Effect of DHEA on proteinuria. Three patients in this study had significant proteinuria. Their cases are described in more detail.

Patient 4. Proteinuria had been documented over 12 months prior to this study, with daily protein excretion ranging from 1 to 8 gm. Urine sediment was unremarkable, and creatinine clearance was consistently normal (>90 ml/minute). At the beginning of DHEA treatment, a 24-hour urine collection showed 1,197 mg of protein. After 3 months of treatment, this was 375 mg, and after 6 months 243 mg.

Patient 5. Proteinuria had been first noted 20 months prior to entering the study; 24-hour urine collections had been obtained on 6 occasions during this period, and showed proteinuria ranging from 1,700 to 8,640 mg/day. She had on several occasions developed nephrotic syndrome. The urinary sediment re-

Table 2. Global SLE activity parameters at study entry and after 3 months of treatment with DHEA*

	Baseline	At 3 months	Mean change	P
SLEDAI score (0-105)	10.4 ± 2.4	8.3 ± 2.1	-2.1 ± 1.06	0.079
Physician's overall assessment (1-100)	37.2 ± 7.03	27.2 ± 7.3	-10.0 ± 4.08	0.040
Patient's overall assessment (1-100)	32.3 ± 6.63	28.6 ± 6.52	-3.7 ± 7.21	0.62

* Values are the mean ± SEM for 10 women with mild to moderate systemic lupus erythematosus (SLE) who took dehydroepiandrosterone (DHEA; 200 mg/day). SLE Disease Activity Index (SLEDAI) score was determined as described in ref. 14. P determined by 2-sided, paired Student's *t*-test.

mained unremarkable throughout, and creatinine clearance was consistently normal and unchanged (>90 ml/minute). The patient declined renal biopsy on 2 occasions. Prior to DHEA treatment, prednisone (20 mg/day) had not appreciably changed the level of proteinuria. Moreover, a month-long attempt at reducing the proteinuria with 60 mg of prednisone daily was similarly unsuccessful. When DHEA treatment was initiated, a 24-hour collection of urine showed 4,000 mg of protein; after 6 months of treatment, this had decreased to 430 mg/day.

Patient 8. Proteinuria, 3,217 mg/day, and nephrotic syndrome developed 4 months prior to the study. A previous renal biopsy had shown membranous glomerulonephritis. Prednisone, 30 mg/day, and azathioprine, 150 mg/day, for 3 months did not significantly change the level of proteinuria. DHEA, 200 mg/day, was taken for 3 months concurrently with prednisone (which was tapered from 17.5 to 10 mg/day). After 3 months, proteinuria had decreased to 2,342 mg/day, and manifestations of the nephrotic syndrome were improved. Unfortunately, the patient had developed moderately severe acneiform dermatitis and opted to discontinue DHEA. She has since required a higher dosage of prednisone to control nonrenal manifestations of SLE, but has had no worsening of proteinuria.

Other laboratory parameters. Erythrocyte sedimentation rates (ESR) were abnormal in 7 patients. No meaningful changes were seen in 5 of them. One (patient 9) had an increase in ESR (from 12 to 41 mm/hour) without evidence of a lupus flare or disease progression, and one (patient 3) showed an increase in ESR (from 25 to 40 mm/hour) in the setting of marked improvement in clinical status. Complement levels were mildly abnormal in 3 patients and remained so during the study.

Side effects and safety. Four patients developed acneiform dermatitis, which was mild in 3 and moderate in 1. The latter patient decided to discontinue

DHEA for this reason; topical therapy was helpful in all other cases. Mild hirsutism was noted after 5-6 months of treatment in 2 patients who were receiving prednisone 10-20 mg/day as well as DHEA, and some patients reported a decrease in menstrual blood flow (without change in the cycle). No adverse effects were noted on physical examination or laboratory evaluation. Specifically, no elevations of fasting blood glucose and no changes in lipid profile were seen.

DISCUSSION

In this study, DHEA was taken by 10 female SLE patients for 3-6 months. DHEA was tolerated well, acneiform dermatitis being the most notable side effect. The use of DHEA coincided with subjective and objective improvement in the clinical status of

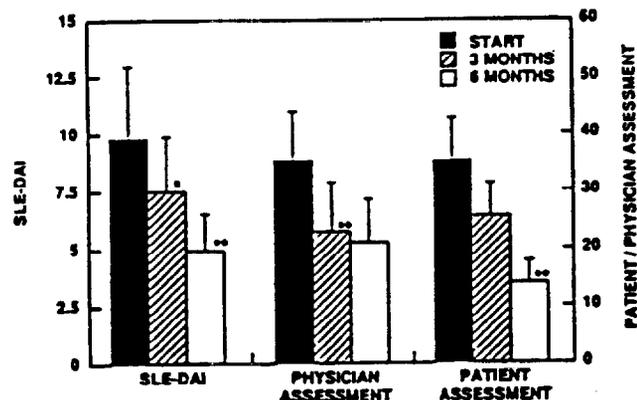


Figure 2. Eight of the 10 female patients with mild to moderate SLE received DHEA, 200 mg/day, for 6 months. The SLE Disease Activity Index (SLE-DAI) score (range 1-105) was determined based on clinical and laboratory criteria (14). Physicians were asked for overall numerical assessments (from 1-100). Patients were asked for overall assessments, using a visual analog scale (from 1-100). Values are the mean ± SEM for these 8 patients only. * = $P < 0.10$ and ** = $P < 0.05$, versus baseline, by 2-sided, paired Student's *t*-test (Wilcoxon's sign rank test yielded similar results). See Figure 1 for other definitions.

Table 3. Glucocorticoid dosages during the study period*

Group	Baseline	At 3 months	Mean change	P	At 6 months	Mean change	P
Patients who completed 3 months of DHEA (n = 8)	14.5 ± 4.1	9.4 ± 2.5	-5.1 ± 2.65	0.028	-	-	-
Patients who completed 6 months of DHEA (n = 6)	14.8 ± 5.5	9.3 ± 3.5	-5.5 ± 3.5	0.043	5.6 ± 1.9	-9.2 ± 4.1	0.042

* Values are the mean ± SEM mg of prednisone equivalent per day. Dosage changes were made as clinically indicated. P determined by Wilcoxon's sign rank test. DHEA = dehydroepiandrosterone.

most patients, and corticosteroid requirements decreased in most patients over the 3-6-month treatment period. From the patients' perspective, 8 of 10 thought the medication was helping them. Two of 3 patients with severe proteinuria of long duration, 1 of whom had not improved with high-dose prednisone, had dramatic improvement in the level of proteinuria. A third patient with proteinuria also improved, but to a lesser degree.

The mechanism of action of DHEA in SLE is unknown. Alteration of androgen/estrogen ratio may be implicated, and increased testosterone levels in treated patients were indeed documented. The mechanism whereby sex steroids affect SLE is, however, poorly understood. In one study, treatment with the semisynthetic androgen 19-nortestosterone did not improve SLE in female patients, and worsened the disease in male patients (15). In that study, however, testosterone levels were lower in the treated male patients, most likely due to feedback inhibition of pituitary follicle-stimulating hormone/luteinizing hormone secretion. Such negative feedback would not be expected from DHEA (7).

Another possible explanation for the apparent benefit of DHEA in SLE is the effect of this hormone on cytokine secretion. Decreased secretion of interleukin-2 (IL-2) has been reported in SLE, both in vitro and in vivo (16,17), and administration of IL-2 through gene transfer has been reported to ameliorate murine lupus (18). DHEA has been shown to increase secretion of IL-2 by stimulated T cells in both human (19) and murine (20) systems, and to normalize the excessive production of IL-4, IL-5, and IL-6 in aged mice (21). It is interesting that the latter cytokines all up-regulate B cell differentiation and/or antibody synthesis, and elevated levels of IL-6 have been reported in SLE (22). Inhibition of the production of these cytokines might therefore be associated with reduced autoantibody formation.

In summary, treatment with DHEA was asso-

ciated with improvement in a variety of outcome measures, reduction in corticosteroid dosage in most patients, and an acceptable toxicity profile. Although it is possible that our results might partly reflect the natural course of the disease and/or a placebo effect, the observed improvements appeared to be greater than what might be expected; all these patients, except for patient 2, had a pattern of lupus that was characterized by continuous, smouldering disease, with no true remissions interceding (particularly patients 3, 4, and 5). On the basis of these encouraging results, further studies of DHEA in the treatment of SLE are warranted.

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DEHYDROEPIANDROSTERONE IN SYSTEMIC LUPUS ERYTHEMATOSUS

Results of a Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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Objective. To determine if dehydroepiandrosterone (DHEA) is beneficial in the treatment of systemic lupus erythematosus (SLE).

Methods. In a double-blind, placebo-controlled, randomized trial, 28 female patients with mild to moderate SLE were given DHEA 200 mg/day or placebo for 3 months. Outcomes included the SLE Disease Activity Index (SLEDAI) score, patient's and physician's overall assessments of disease activity, and concurrent corticosteroid dosages (which were adjusted as clinically indicated).

Results. In the patients who were receiving DHEA, the SLEDAI score, patient's and physician's overall assessment of disease activity, and concurrent prednisone dosage decreased, while in the patients taking placebo, small increases were seen. The difference in patient's assessment between the groups was statistically significant ($P = 0.022$, adjusted). Lupus flares occurred more frequently in the placebo group ($P = 0.053$). Mild acne was a frequent side effect of DHEA.

Conclusion. DHEA may be useful as a therapeutic agent for the treatment of mild to moderate SLE. Further studies of DHEA in the treatment of SLE are warranted.

The epidemiology of systemic lupus erythematosus (SLE) suggests an important etiologic role of sex

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steroids in this multisystem, autoimmune disease. Thus, SLE is seen predominantly in women (1), tends to flare during pregnancy (2), and may correlate with the androgen:estrogen ratio (3). Murine studies have further supported this concept, in that female New Zealand black \times New Zealand white (NZB \times NZW) mice develop lupus-like disease at a much higher frequency than do males, and their disease can be ameliorated by administration of androgens (4-6). On the basis of these observations, it has been suggested that administration of natural or synthetic androgens might benefit female SLE patients, were it not for troublesome masculinizing side effects.

Dehydroepiandrosterone (DHEA), an abundant adrenal steroid with limited intrinsic androgenic activity (7), was shown to ameliorate nephritis in NZB \times NZW mice (8). Moreover, previous experience with DHEA supplementation in human subjects suggested overall good tolerance of this hormone (9-12).

On this basis, we previously completed an open-label trial of DHEA in female patients with mild to moderate SLE (13). The results of this study indicated a possible benefit and led us to undertake a double-blind, placebo-controlled, randomized clinical trial of DHEA in SLE. The results are presented here.

PATIENTS AND METHODS

Study protocol. The study protocol and informed consent document for this study were approved by the Administrative Panel on the Use of Human Subjects in Medical Research at Stanford University.

Thirty female patients with SLE according to the American College of Rheumatology criteria (14) consented to participate in a double-blind, randomized, placebo-controlled clinical trial of DHEA. All patients had mild or moderate lupus, as determined by the referring rheumatologist. Patients with severe renal disease requiring high-dose corticosteroids and/or cyclophosphamide were excluded.

Table 1. Demographics of the study population*

	DHEA group (n = 14)	Placebo group (n = 14)
Age, mean \pm SEM years	34.9 \pm 2.6	39.6 \pm 2.0
Ethnicity, no. (%)		
Caucasian	9 (64)	11 (79)
African-American	3 (36)	1 (7)
Other	0 (0)	2 (14)
Time since first SLE symptoms, mean \pm SEM years	11.1 \pm 2.2	8.5 \pm 1.8
Time since first diagnosis of SLE, mean \pm SEM years	8.1 \pm 2.4	6.2 \pm 1.2

* DHEA = dehydroepiandrosterone; SLE = systemic lupus erythematosus.

After screening and documentation of baseline status, the patients were given capsules containing 100 mg of DHEA or identical placebo capsules, to be taken once daily by mouth. The DHEA powder was obtained from Diosynth (Chicago, IL), and the capsules were prepared by the Stanford University Hospital pharmacy.

The patients were followed up at monthly intervals by the primary rheumatologist as well as by one of the investigators. After the 3-month double-blind period, patients were given the option of receiving DHEA 200 mg/day in an open-label manner.

Throughout the study period, patients were treated based on clinical status, according to the discretion of the physician carrying the primary responsibility for the patient. Changes in medications were allowed, including changes in dosages or the addition of new medications.

Outcome measures. The SLE Disease Activity Index (SLEDAI) score (15) was determined at each visit. Patients and physicians were asked to record their overall assessments of disease activity on a scale of 1-100 (patients were given a visual analog scale). Other outcome measures were the medication profile and laboratory parameters.

Lupus flares. Disease flares were assessed retrospectively, based solely on whether the term "flare" was used in

Table 2. SLE manifestations at the start of study*

	DHEA group (n = 14)	Placebo group (n = 14)
Malar rash	4	2
Alopecia	6	3
Mucosal ulcers	3	2
Arthritis	9	5
Pleurisy	1	1
Lupus headache	7	5
Organic brain syndrome	1	0
Fever	2	0
Hypocomplementemia	2	1
Rising anti-DNA	1	3
Leukopenia	1	0
Thrombocytopenia	0	1

* DHEA = dehydroepiandrosterone; SLE = systemic lupus erythematosus.

Table 3. SLE activity at baseline*

	DHEA group (n = 14)	Placebo group (n = 14)	P
SLEDAI score	9.8 \pm 1.7	6.1 \pm 1.3	0.056
Patient's overall assessment, 1-100	39.4 \pm 6.3	42.9 \pm 6.6	0.698
Physician's overall assessment, 1-100	21.4 \pm 4.6	21.4 \pm 4.0	1.000
Prednisone dose, mg/day	12.4 \pm 3.2	5.3 \pm 1.4	0.056
ESR, mm/hour	13.8 \pm 4.0	24.4 \pm 23.5	0.175
Anti-DNA titer	3.76 \pm 1.78	198.1 \pm 101.7	0.067
C3, mg%	90.7 \pm 9.3	102.0 \pm 12.0	0.456
C4, mg%	26.7 \pm 3.0	23.1 \pm 2.9	0.412
Platelets, $\times 1,000/\text{mm}^3$	319.7 \pm 21.5	251.5 \pm 26.2	0.055
Hematocrit, %	37.8 \pm 0.96	38.9 \pm 0.89	0.417

* Values are the mean \pm SEM. SLE = systemic lupus erythematosus; DHEA = dehydroepiandrosterone; SLEDAI = SLE Disease Activity Index; ESR = erythrocyte sedimentation rate.

the patient's chart by the primary rheumatologist, thus reflecting the subjective judgment of the treating rheumatologist. No strict definition of "flare" was used.

Statistical analysis. Outcome measurements are presented as the mean plus or minus the standard error of the mean. Each of the 4 variables—the SLEDAI score, corticosteroid dose (expressed in equivalent prednisone dose), and the physician's and patient's overall assessment of disease activity—were analyzed by two different statistical methods. First, a 2-sample *t*-test examined the between-group difference in the change from baseline for each of the 4 variables. The change-from-baseline measurements were assumed to have a normal distribution, with different unknown variances for the different treatment groups. The *P* values from this analysis are reported as unadjusted *P* values. Second, analysis of covariance was performed with treatment group as a factor and the baseline measurements for SLEDAI score, corticosteroid dose, and the respective variable as covariates, if applicable. Each covariate-by-treatment interaction term was also included in the analysis model. The *P* values from this analysis are reported as the adjusted *P* values. For comparison of the incidence of lupus flares, the chi-square test was used.

RESULTS

Twenty-eight patients completed 3 months of treatment. One patient in each group was lost to followup early in the study. The 2 groups were well matched demographically, as shown in Table 1. No significant differences were seen in the average age, duration of symptoms, or time since diagnosis. SLE manifestations were varied, as expected; these are listed in Table 2.

Disease parameters at baseline for the 2 groups are shown in Table 3. While patient's and physician's overall assessments were comparable, the average

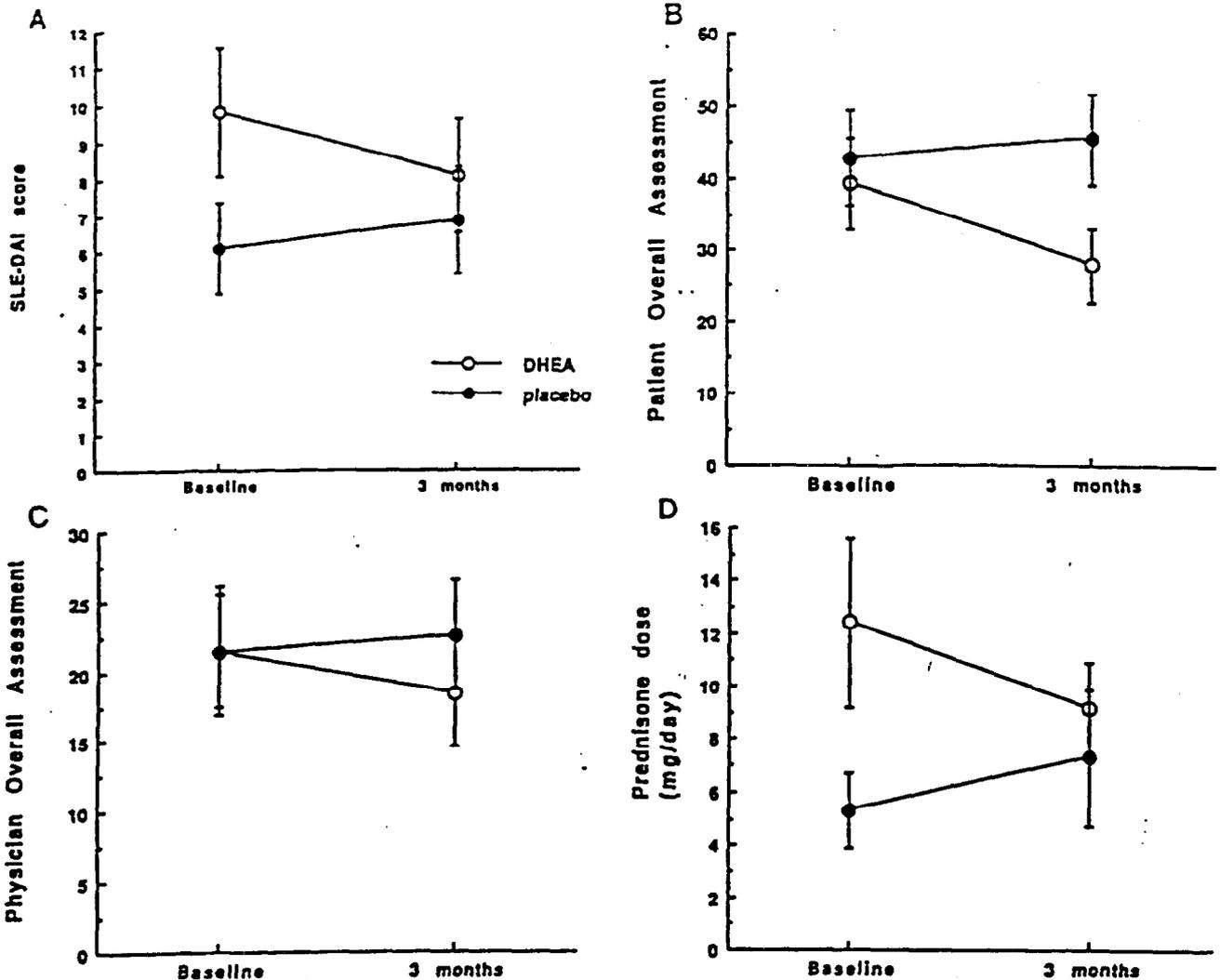


Figure 1. Changes in systemic lupus erythematosus (SLE) activity parameters during a 3-month double-blind trial of dehydroepiandrosterone (DHEA) 200 mg/day versus placebo. A, The SLE Disease Activity Index (SLE-DAI), as defined by Bombardier et al (15). B, Patient's overall assessment of disease activity, by visual analog scale of 1-100. C, Physician's overall assessment of disease activity, on a scale of 1-100. D, Prednisone dose, in mg/day. Values are the mean \pm SEM.

SLEDAI score and prednisone dose were higher in the patients who had been randomized to receive DHEA.

The results after 3 months of treatment with DHEA versus placebo are shown in Figure 1. In the patients treated with DHEA, the average SLEDAI score improved from a mean \pm SEM of 9.79 ± 1.74 to 8.07 ± 1.54 , the patient's overall assessment improved from 39.4 ± 6.3 to 27.9 ± 5.1 , and the physician's overall assessment improved from 21.4 ± 4.6 to 18.4 ± 3.8 . There were small increases in these same outcomes (i.e., worse disease) in the placebo group. After 3 months of treatment, the patient's overall assess-

ment was improved significantly more in the DHEA group than in the placebo group ($P = 0.138$ unadjusted; $P = 0.022$ adjusted).

Between-group comparisons of the changes from baseline are shown in Table 4. It is noteworthy that all of the principal outcome measures appeared to improve in the DHEA group, while worsening in the placebo group. For the SLEDAI score, the changes were -1.71 ± 1.18 in the DHEA-treated patients and 0.79 ± 0.75 in the placebo-treated patients ($P = 0.088$ unadjusted; $P = 0.158$ adjusted). If outcomes, rather than changes in outcomes, after 3 months were com-

Table 4. Effect of treatment with DHEA versus placebo on SLE activity indices, corticosteroid dosages, and lupus flares*

	DHEA group (n = 14)	Placebo group (n = 14)	P	
			Unadjusted	Adjusted
SLEDAI score	-1.71 ± 1.18	0.79 ± 0.75	0.088	0.158
Patient's overall assessment, 1-100	-11.5 ± 5.7	2.4 ± 7.0	0.138	0.022
Physician's overall assessment, 1-100	-3.1 ± 3.8	1.1 ± 4.2	0.470	0.278
Prednisone dose, mg/day	-3.2 ± 1.7	2.0 ± 2.6	0.107	0.306
Lupus "flares"	3	8	0.053	-
ESR, mm/hour	2.77 ± 2.60	1.91 ± 2.22	0.807	-
Anti-DNA titer	5.36 ± 5.63	-52.0 ± 45.4	0.221	-
C3, mg%	1.14 ± 19.12	-8.13 ± 6.89	0.639	-
C4, mg%	-6.75 ± 6.49	-0.11 ± 2.39	0.331	-
Platelets, ×1,000/mm ³	-25.0 ± 8.63	16.55 ± 8.76	0.003	-
Hematocrit, %	1.46 ± 0.53	0.18 ± 0.99	0.294	-

* Values are the mean ± SEM change from baseline. DHEA = dehydroepiandrosterone; SLE = systemic lupus erythematosus; SLEDAI = SLE Disease Activity Index; ESR = erythrocyte sedimentation rate.

pared, there were no significant differences between the groups' SLEDAI scores or prednisone dosages, but the patient's overall assessment of disease activity after 3 months was significantly lower in the DHEA group than in the placebo group (27.9 ± 5.1 versus 45.3 ± 6.4; $P < 0.05$).

Effects on the dosage of concurrently administered corticosteroids. Of the 28 study patients, 21 were receiving daily corticosteroids at the beginning of the study (11 in the DHEA group and 10 in the placebo group). During the study, the dosages were adjusted as clinically indicated. After 3 months, the average dose (expressed as the equivalent dose of prednisone in mg/day) had decreased in the DHEA group from a mean ± SEM of 12.4 ± 3.2 to 9.14 ± 2.33, while in the placebo group, the dose increased from 5.30 ± 1.37 to 7.30 ± 2.85. Intergroup comparison of the change is given in Table 4. Most patients were taking a stable dosage of hydroxychloroquine at the beginning of the study, and this remained unchanged. None of the patients were treated with immunosuppressive medications during the study.

Lupus flares. Lupus flares, as noted in the medical records of the patients in this study and ascertained retrospectively based solely on the use of the term "flare" by the primary rheumatologist, were noted in 11 patients: 8 in the placebo group, and 3 in the DHEA group ($P = 0.053$ by χ^2 test).

DHEA tolerance and safety. The side effects noted during this study are shown in Table 5. Acneiform dermatitis was the most frequently noted side-effect, seen in 8 patients taking DHEA and 1 taking placebo. Topical therapy was helpful in most cases.

No patients discontinued the double-blind study because of adverse reactions. However, after the 3-month trial, 1 patient elected not to continue with open-label DHEA because of acne. Mild hirsutism was noted more often in the placebo group. Other side effects were noted to a similar extent in the 2 groups. No adverse effects were noted by laboratory evaluation. Specifically, no elevations of fasting blood glucose levels and no significant changes in the lipid profile were seen.

Other laboratory parameters. Erythrocyte sedimentation rates, complement levels, and other laboratory parameters did not show significant changes during this study in patients with generally mild to moderate lupus (Table 4). The platelet count showed a small but statistically significant difference between the groups.

Open-label continuation. Following the 3-month controlled study, 21 patients elected to receive open-label treatment with DHEA at a dosage of 50-200 mg/day, for 3 months. The results are shown in Figure 2. The changes in the patients who had previously re-

Table 5. Side effects*

	DHEA group (n = 14)	Placebo group (n = 14)
Acneiform dermatitis	8 (57)	1 (7)
Hirsutism	2 (14)	4 (29)
Weight gain	2 (14)	1 (7)
Rash	0 (0)	2 (14)
Emotional change	1 (7)	0 (0)
Abnormal menses	1 (7)	2 (14)

* Values are the number (%) of patients.

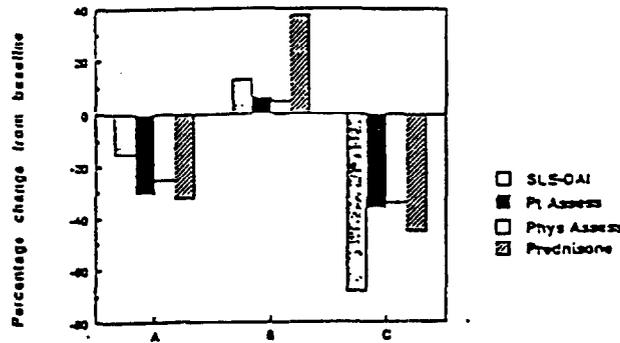


Figure 2. Change in systemic lupus erythematosus (SLE) activity indices (mean % change from baseline) during a 3-month double-blind trial of dehydroepiandrosterone (DHEA) 200 mg/day versus placebo, and during a 3-month, open-label, follow-through period during which all patients were given DHEA 200 mg/day. Data for 3-6 months are given only for those patients who elected to participate in this part of the study. SLE-DAI = SLE Disease Activity Index (see ref. 15); Pt Assess = patient's overall assessment of disease activity (1-100 by visual analog scale); Phys Assess = physician's overall assessment of disease activity (1-100 scale); Prednisone = prednisone dose in mg/day. A, DHEA group after 3 months. B, Placebo group after 3 months. C, Patients initially randomized to placebo and evaluated after a subsequent 3 months of DHEA.

ceived placebo were similar to those seen initially in the DHEA-treated group. Patients taking DHEA for 6 months experienced continued improvement (not shown).

To evaluate whether the presence of acne had "unblinded" some patients and thereby affected their outcome assessments, the outcomes after 3 months were analyzed separately for those patients in the treatment group who did and who did not develop acne. For the patient's global assessment, no difference was seen between those with and without acne (Figure 3). Similar results were obtained for the other outcomes (not shown).

DISCUSSION

In this study, 28 female patients with SLE received DHEA 200 mg/day versus placebo for 3 months in a double-blind manner. Although the duration of the study was relatively short, it is noteworthy that improvement was noted in all 4 of the outcome parameters defined prospectively: SLEDAI score, patient's self-assessment of disease activity, physician's assessment of disease activity, and prednisone dose. In contrast, these parameters were essentially unchanged in the patients who received placebo. "Lupus flares," as documented by the primary rheumatologist, who was blinded to the patient's study group,

were seen significantly more often in the placebo group. Moreover, improvement in most parameters continued in those DHEA-treated patients who elected to receive DHEA for another 3 months. In patients who elected to receive DHEA following 3 months of placebo treatment, improvement in all parameters was also noted. DHEA was tolerated well, acneiform dermatitis being the most noted side effect.

Some patients may have correctly identified their study group because of the development of acne in those taking DHEA. It is unlikely, however, that this resulted in a major bias in this study, for the following reasons. First, the majority of patients received glucocorticoids during this study, and could attribute their skin condition to this. Second, in most patients, improvement in subjective assessment of disease occurred prior to the onset of acne (data not shown). Third, the placebo-treated patients who developed side effects that were initially attributed to the study drug, in particular hirsutism, did not have better outcomes than those who did not. Fourth, when asked to guess whether they had received DHEA or placebo, 10 patients in the DHEA group, and 9 in the placebo group guessed they had received DHEA.

The mechanism of action of DHEA in SLE is unknown. Alteration of the androgen:estrogen ratio may be implicated, and elevated testosterone levels in DHEA-treated patients have been documented (13). The mechanism whereby sex steroids affect SLE is, however, poorly understood. Treatment with the semisynthetic androgen 19-nortestosterone did not improve SLE in female patients and worsened the disease in male patients (16). In that study, testosterone levels were lower in the treated patients, most likely due to feedback inhibition of pituitary follicle-

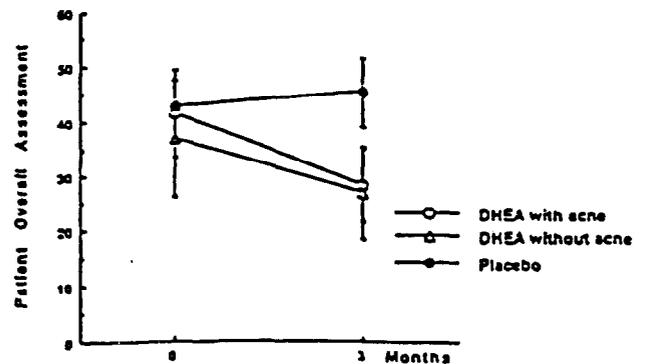


Figure 3. Changes in patient's overall assessment of disease activity in patients taking dehydroepiandrosterone (DHEA) who did or did not develop acneiform dermatitis versus those taking placebo, during a 3-month, double-blind trial. Values are the mean ± SD.

stimulating hormone/uteinizing hormone secretion. Such negative feedback would not be expected from DHEA (7), and indeed, increases in testosterone levels were seen.

Another possible explanation for the apparent benefit of DHEA in SLE is the effect of this hormone on cytokine secretion. Decreased secretion of interleukin-2 (IL-2) secretion has been reported in SLE, both in vitro and in vivo (17,18), and administration of IL-2 through gene transfer has been reported to ameliorate murine lupus (19). DHEA has been shown to increase the secretion of IL-2 by stimulated T cells in both murine (20) and human (21) systems, including healthy individuals (21) as well as patients with SLE (22), and to down-regulate the production of IL-4, IL-5, and IL-6 in mice (20,23). It is interesting that the latter cytokines tend to up-regulate B cell differentiation and/or antibody synthesis. Inhibition of their production might, therefore, be associated with reduced autoantibody formation. These possibilities await further study.

DHEA appeared to have a beneficial effect on overall wellbeing, fatigue, and energy levels. These features could be attributed to the DHEA itself, to increased levels of other androgens, or to improvement in immunologic dysfunction.

In summary, treatment with DHEA was associated with improvement in a variety of outcome measures, reduction in glucocorticoid dosage in most patients, decreased numbers of lupus flares, and a very acceptable toxicity profile. On the basis of these encouraging results, further studies of DHEA in the treatment of SLE are warranted.

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