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Effects of Prasterone on Corticosteroid Requirements of Women With Systemic Lupus Erythematosus

A Double-Blind, Randomized, Placebo-Controlled Trial

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Objective. **To evaluate whether treatment with prasterone (dehydroepiandrosterone [DHEA]) would allow the dosage of prednisone (or an equivalent corticosteroid) to be reduced to ≤7.5 mg/day for 2 months or longer while maintaining stable or reduced disease activity in steroid-dependent women with systemic lupus erythematosus (SLE).**

Methods. **In a double-blind, randomized trial, 191 female SLE patients receiving prednisone (10–30 mg/day) were treated daily with either placebo, 100 mg of oral prasterone (an adrenal androgen), or 200 mg of oral prasterone for 7–9-months. At monthly intervals, corticosteroid dosages were reduced by algorithm in patients whose SLE Disease Activity Index (SLEDAI) score was stable or improved. Patients for whom a sustained reduction in the dosage of prednisone (≤7.5 mg/day) was achieved for at least the last 2 months of the 7–9-month treatment period were classified as responders.**

Results. **Response rates were 41% in the placebo group, 44% in the 100-mg prasterone group, and 55% in the 200-mg group ($P = 0.110$, 200 mg versus placebo). Among the 137 subjects (45 in the placebo group, 47 in the 100-mg group, and 45 in the 200-mg group) who had active disease at baseline (defined as SLEDAI score >2), 29%, 38%, and 51%, respectively, were responders ($P = 0.031$ for 200 mg prasterone versus placebo). Acne was the most common adverse event but was generally mild. Clinical and laboratory changes primarily reflected androgenic effects of prasterone.**

Conclusion. **Among women with lupus disease activity, reducing the dosage of prednisone to ≤7.5 mg/day for a sustained period of time while maintaining stabilization or a reduction of disease activity was possible in a significantly greater proportion of patients treated with oral prasterone, 200 mg once daily, compared with patients treated with placebo.**

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disease of unknown etiology. After puberty, SLE is more common in women than in men, with a ratio of 9:1 (1). Abnormalities of both estrogen and androgen metabolism have been described in SLE patients, including enhanced formation of 16-α hydroxyestrone, an active metabolite of estradiol (2,3), and depressed blood androgen concentrations (4). Androgen treatment induces a delay in the appearance of anti-DNA antibodies and the onset of nephritis and decreases mortality in female (NZB × NZW)F_1 hybrid mice, a well-characterized animal model of SLE (5–7).

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Decreased secretion of interleukin-2 (IL-2) occurs in the murine model of SLE and in SLE patients (8–10). The adrenal hormone dehydroepiandrosterone (DHEA) has been reported to increase the secretion of IL-2 by stimulated murine (11) and human T cells (12). Additionally, circulating levels of the proinflammatory cytokine IL-6 are elevated in active SLE (13,14). DHEA has been reported to inhibit the release of IL-6 from human mononuclear cells in vitro (15).

Van Vollenhoven et al reported preliminary evidence of corticosteroid-sparing effects of prasterone (the United States Adopted Names Council designation for DHEA) in patients with mild to moderate SLE (16). In a subsequent double-blind, placebo-controlled assessment of prasterone (200 mg orally for 3 months) in patients with mild to moderate SLE, values for all 4 primary efficacy parameters (patient and physician overall assessments, SLE Disease Activity Index [SLEDAI] score, and glucocorticoid dose) improved in the prasterone group (17).

The current multicenter, double-blind, randomized, placebo-controlled trial was designed to determine whether treatment with prasterone would allow sustained reduction in corticosteroid doses while maintaining stable or reduced disease activity in women with corticosteroid-dependent SLE.

PATIENTS AND METHODS

Patients. The study group comprised women 18 years of age or older who had a history of fulfilling at least 4 of the American College of Rheumatology criteria for SLE (18). Women were eligible for entry into the study if they had been treated for at least 12 months with 10–30 mg/day of prednisone (or an equivalent corticosteroid), either as a single or divided dose, and were deemed corticosteroid-dependent by either of 2 criteria: 1) in the last 12 months an attempt to taper the prednisone dosage had failed, and the prednisone dosage had been stable for at least 6 weeks preceding the study, or 2) no attempt had been made during the past 12 months to taper the dosage of prednisone, but the patient had been on a stable dosage for at least 3 months preceding the study. Patients using an alternate-day dosing regimen were not included unless they had converted to daily dosing and the dosage had been stable for 6 weeks prior to the study. Use of nonsteroidal antiinflammatory drugs (NSAIDs) and/or hydroxychloroquine must have been constant, with no change in dosage for at least 1 month preceding the study. Patients who had been treated with adrenocorticotropic hormone, cyclophosphamide, azathioprine, other immunosuppressive agents, intravenous immunoglobulin, or androgens within the 3 months preceding study entry were excluded.

The study was approved by the institutional review boards for each of the participating institutions and investigators and all procedures were conducted in accordance with the Declaration of Helsinki.

Table 1. Algorithm for reducing the dosage of prednisone

Daily dose, mg	Dose reduction, mg
>0–5	1.0
>5–10	2.5
>10–30	5.0
>30	Taper at investigator's discretion

Baseline assessments. Study eligibility was determined at a screening visit and was confirmed at a qualifying visit 7–10 days later. Baseline assessments included a review of the medical history, physical examination, physician-scored SLEDAI (19), patient-scored assessment of health status by Short Form 36 (SF-36) Health Survey (20) and fatigue by the Krupp Fatigue Severity Questionnaire (21), patient and physician global assessments using a 10-cm visual analog scale (VAS), and the Systemic Lupus International Collaborating Clinic (SLICC) damage index (22). All investigators were trained in the use of the SLEDAI, the SLICC damage score, and VAS scoring, and evaluations of individual patients were conducted by the same physician.

Analytic measurements. Blood samples were drawn after an 8-hour fast but were not timed to prasterone administration. Laboratory assessments included anti–double-stranded DNA (anti-dsDNA) antibodies, C3 and C4, IgG and IgM anticardiolipin antibodies, serum lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, calculated low-density lipoprotein [LDL] cholesterol, and total triglycerides), routine serum chemistries, complete blood counts, urinalyses, 24-hour urine collections for creatinine clearance and protein quantitation, and serum levels of 17ß-estradiol, testosterone, follicle-stimulating hormone, luteinizing hormone, and DHEA-S (the sulfated ester of DHEA). To avoid unblinding, results from hormone assays were not returned to investigators or Genelabs study monitors until the study was complete. All blood and urine assays were conducted at a central laboratory (Covance Laboratories, Indianapolis, IN).

Treatments. After qualifying for the study, patients were randomly assigned to receive 1 of 3 treatments: placebo, 100 mg/day of prasterone (GL701, the Genelabs formulation for DHEA), or 200 mg/day of prasterone. All patients were to receive study medication (prasterone and/or placebo) for at least 7 months, administered as 4 capsules every morning. Patients returned at monthly intervals, at which time the clinical and laboratory assessments performed at baseline (except the SLICC) were repeated.

The goal of treatment was to achieve a sustained (defined as 2 consecutive months, including the last month on study) decrease in the dosage of prednisone, to ≤7.5 mg/day. The daily prednisone dose was reduced by algorithm if the patient's SLEDAI score was stable or had improved compared with the score from the previous monthly visit (Table 1). If the SLEDAI score had increased, signifying worsening of disease activity, the daily dose of prednisone could be increased at the investigator's discretion. If a patient's prednisone dosage had not been reduced to ≤7.5 mg/day at the end of 7 months, she was withdrawn from the study. If, however, at the end of 6 or

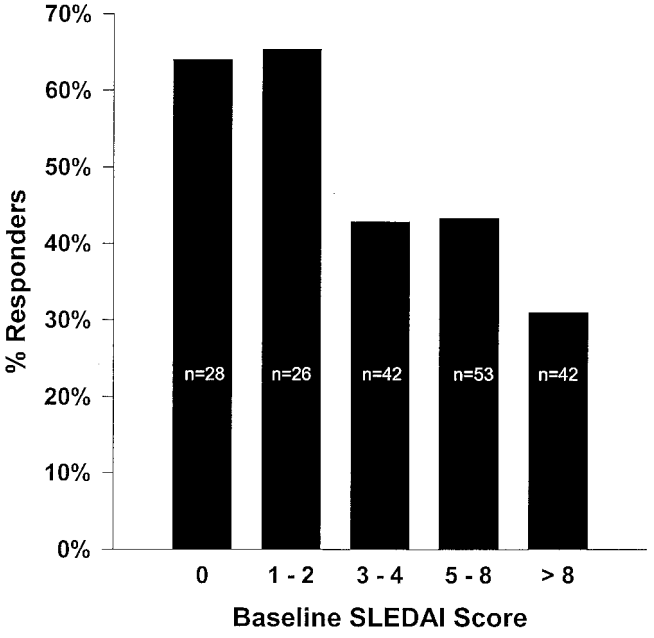

Figure 1. Responder rates prior to unblinding of data. All patients from all 3 treatment groups are included. SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

7 months of treatment, a patient's prednisone dosage had been reduced to ≤7.5 mg/day but had not yet been sustained for 2 months, she continued to receive study medication for 2 additional months (for a total of 8 or 9 months of treatment) or until the prednisone dosage was increased to >7.5 mg/day (whichever happened first).

Statistical analysis. The primary protocol-specified efficacy variable was achievement of a decrease in the dosage of prednisone to 7.5 mg/day or less for 2 consecutive months, including the last 2 months of the 7–9-month trial. Patients meeting this criterion were categorized as responders. Patients who received stress doses of hydrocortisone (or a corticosteroid equivalent) for acute (1–3 day), non–SLE-related events (e.g., minor surgery) were classified as nonresponders if the stress doses were administered during the last 2 months of the study period.

A substantial number of patients had low baseline SLEDAI scores, suggesting that their SLE was relatively inactive. Prior to unblinding, the overall response rate for all patients was analyzed according to baseline SLEDAI score. The response rate for patients with the mildest disease (SLEDAI score ≤2) was unexpectedly high (~65%), and the response rate decreased progressively and sharply as baseline SLEDAI scores increased (>2) (Figure 1). This suggested that patients with baseline SLEDAI scores ≤2 might represent a population different from the population of patients with baseline SLEDAI scores >2. Based on these observations, a subgroup was defined prospectively, prior to unblinding, that included patients with more active disease as reflected by a baseline SLEDAI score >2. Approximately 72% of patients (137 of 191) met this criterion.

The proportion of responders was determined by logistic regression analysis, with treatment group (prasterone or placebo) as a factor, and any statistically significant baseline variables were incorporated into statistical modeling procedures. The total number of days during which the prednisone dosage was ≤7.5 mg/day was assessed by one-way analysis of variance (ANOVA), with treatment as a factor. Treatment group comparisons for laboratory variables and adverse events were performed by either the Cochran-Mantel-Haenszel test or one-way ANOVA.

RESULTS

Participants and demographic characteristics. The study population comprised 191 women who met the entry criteria and were enrolled at 18 centers (see Appendix A). The treatment groups were well matched for baseline characteristics such as age, race, menopausal status, SLE disease activity, patient and physician global assessment scores (by VAS), and concomitant use

Table 2. Summary of demographic/medical history characteristics*

Parameter	Placebo (n = 64)	100 mg prasterone (n = 63)	200 mg prasterone (n = 64)
Age, mean (median) years	40.6 (39.0)	40.0 (39.0)	40.2 (41.0)
Caucasian, no. (%)	44 (69)	36 (57)	35 (55)
African American, no. (%)	17 (27)	16 (25)	17 (27)
Postmenopausal, no. (%)	16 (25)	17 (27)	7 (11)
Prednisone dosage, mg/day, mean (median)	15.2 (15.0)	13.7 (12.5)	13.7 (10.0)
Antimalarial use, no. (%)	33 (52)	27 (42.9)	33 (51.6)
SLEDAI score, mean (median)	6.4 (4.0)	5.5 (4.0)	5.9 (6.0)
Patient-scored global VAS, mean (median)	49.1 (48.5)	46.4 (47.0)	46.8 (47.5)
Physician-scored global VAS, mean (median)	28.0 (23.0)	26.0 (24.0)	23.3 (21.5)
Krupp Fatigue Score, mean (median)	5.3 (5.7)	5.1 (4.9)	5.4 (5.7)

* SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; VAS = visual analog scale.

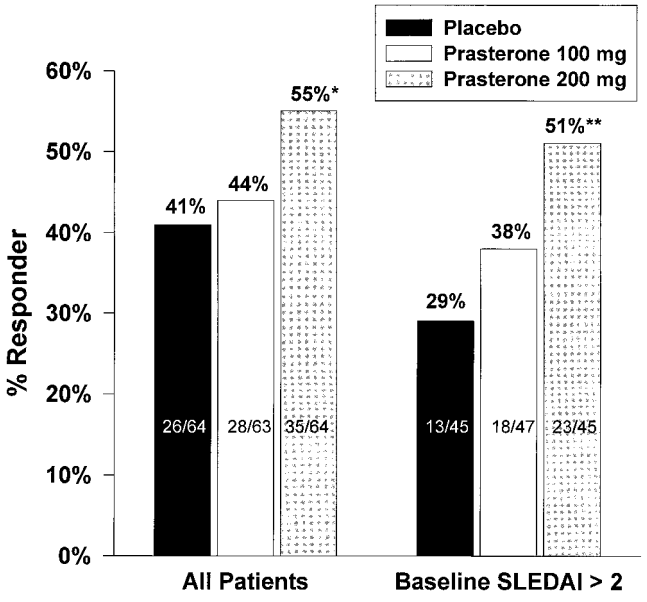

Figure 2. Percentage of responders in each treatment group according to baseline Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores. * = $P = 0.111$ versus placebo; ** = $P = 0.031$ versus placebo.

of medications for SLE (Table 2). There were no significant differences in baseline characteristics between treatment groups. However, in the subgroup of patients with a baseline SLEDAI score >2 (137 patients), an imbalance in the baseline dosage of prednisone reached statistical significance, with mean (median) dosages of placebo, 100-mg prasterone, and 200-mg prasterone of 15.7 (15.0), 13.6 (12.5), and 13.0 (10.0) mg/day, respectively ($P = 0.039$ for comparisons among the 3 treatment groups). The distribution of baseline prednisone dosages was skewed primarily toward the lower end for all treatment groups, however. For example, among patients with baseline SLEDAI scores >2, 30 of 45 in the placebo group, 39 of 47 in the 100-mg prasterone group, and 38 of 45 in the 200-mg prasterone group were treated with prednisone doses of 15 mg or less at baseline.

Efficacy. The proportion of responders was highest in the 200-mg prasterone group (55%) and lowest in the placebo group (41%; $P = 0.111$, prasterone 200 mg versus placebo) (Figure 2). For patients with active disease, defined as a baseline SLEDAI score >2, there was a dose-response relationship ($P = 0.033$ for linear trend), with responder rates of 13 of 45 (29%), 18 of 47 (38%), and 23 of 45 (51%) in the placebo, 100-mg prasterone, and 200-mg prasterone groups, respectively ($P = 0.031$, prasterone 200 mg versus placebo) (Figure 2).

The difference in the proportion of responders in the prasterone group and the placebo group was particularly evident among patients who had more severe disease at baseline (baseline SLEDAI scores of 3–4, 5–8, and >8) (Figure 3). The decline in pooled overall responder rates that was demonstrated with increasing SLEDAI scores, as shown in Figure 1, appeared to be primarily attributable to a decline in responder rates among patients in the placebo group whose SLEDAI scores increased from baseline. Thus, patients in the placebo group who had higher baseline SLEDAI scores tended to have lower response rates, while the response rate for patients in the 200-mg prasterone group and for each of the categorical groups with baseline SLEDAI scores >2 was maintained at ≥50% (Figure 3).

There were no significant differences between treatment groups in percentage change in the prednisone dosage from baseline to the last visit. The mean ± SD (median) percentage decreases in prednisone dosages were −36 ± 50% (−50%) for placebo, −14 ± 91% (−41%) for 100-mg prasterone, and −30 ± 74% (−53%) for 200-mg prasterone ($P = 0.094$ and $P = 0.672$ for 100 mg and 200 mg versus placebo, respectively). However, this end point compared only the prednisone dose on a single day (the last day of treatment) with that at baseline.

To further assess the durability of a reduction in the dosage of corticosteroids, the total number of days that the prednisone dosage was ≤7.5 mg/day was as-

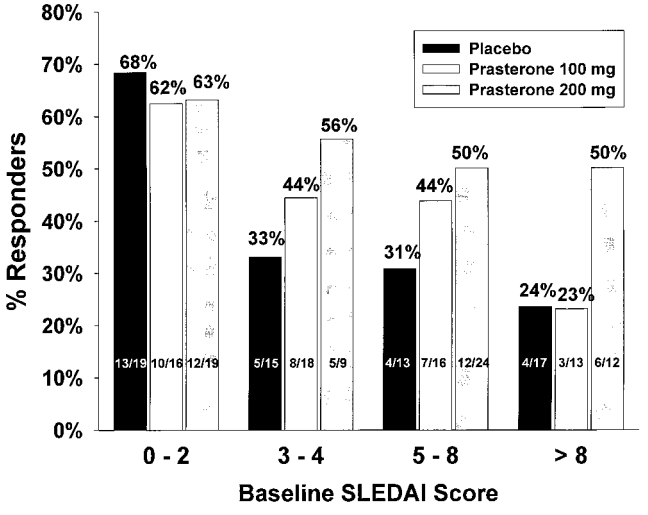

Figure 3. Responders by categorical baseline Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores.

Table 3. Number of days prednisone dosage was ≤7.5 mg/day

Treatment	All patients		Patients with baseline SLEDAI score >2*	
	n	Mean (median) no. of days	n	Mean (median) no. of days
Placebo	64	71.7 (66.5)	45	59.7 (28.0)
Prasterone, 100 mg	63	77.7 (81.0)	47	74.0 (55.0)
Prasterone, 200 mg	64	92.1 (111.5†)	45	93.4‡ (110.0§)

* SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.
† $P = 0.069$ versus placebo, by nonparametric Wilcoxon's rank sum test.
‡ $P = 0.015$ versus placebo, by parametric test.
§ $P = 0.013$ versus placebo, by nonparametric Wilcoxon's rank sum test.

sessed. Among patients whose baseline SLEDAI scores were >2, the number of days that the prednisone dosage was reduced to ≤7.5 mg/day was significantly higher in the 200-mg prasterone group compared with the placebo group ($P = 0.015$, prasterone 200 mg versus placebo) (Table 3).

Safety evaluation. Withdrawals due to adverse events occurred in 5% of the placebo group (3 patients), 6% of the 100-mg prasterone group (4 patients), and 9% of the 200-mg prasterone group (6 patients). No deaths in any treatment group occurred during the study, and only 2 events (both pneumonia) meeting Food and Drug Administration criteria for "serious and unexpected" occurred (1 each in the placebo and 200-mg prasterone groups). Overall, 142 of the 191 patients completed the study (49, 46, and 47 in the placebo, 100-mg prasterone, and 200-mg prasterone groups, respectively). Of these, 132 patients (46 in the placebo group, 43 in the 100-mg prasterone group, and 43 in the 200-mg prasterone group) elected to participate in a subsequent 1-year, open-label extension study.

Adverse events that were determined by the investigators as being probably or possibly related to the study drug are presented in Table 4. Acne was the most common adverse event in both prasterone groups and was reported by 41% of patients in each group, compared with 19% of patients in the placebo group ($P < 0.05$ for both comparisons). Hirsutism, another androgenic effect, was reported by 5% of patients treated with placebo and by 11% and 8% of patients treated with 100-mg prasterone and 200-mg prasterone, respectively (P not significant [NS]). Both side effects were generally mild, however, and only 1 patient each in the 100-mg and 200-mg prasterone treatment groups withdrew because of acne and/or hirsutism.

Menstrual abnormalities, including spotting or metrorrhagia, were reported by 8% of patients in the placebo group, 10% in the 100-mg prasterone group, and 13% in the 200-mg prasterone group (P NS). Menorrhagia was reported as an adverse event by 3% of patients in the placebo group, 2% in the 100-mg prasterone group, and 2% in the 200-mg prasterone group (P NS).

Adverse events grouped according to the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) (23) term "abdominal pain" occurred more frequently in the 200-mg prasterone group, but most of these events were transient, did not require discontinuation of the study drug, and resolved either spontaneously or with the use of H_2 receptor antagonists. These events were diverse and included abdominal tenderness, stomach cramps, or pain, and some of the patients had a preexisting history of abdominal pain or distress.

Serum concentrations of DHEA-S and testosterone increased significantly, and in a clear dose-related manner, in the 100-mg and 200-mg prasterone groups, but no change was demonstrated in the placebo group (Table 5). Among premenopausal patients, there were no significant differences between groups in serum estradiol levels before and after treatment (results not

Table 4. Adverse events occurring in ≥5% of patients*

Adverse event	Placebo (n = 64)	100 mg prasterone (n = 63)	200 mg prasterone (n = 64)
Acne	12 (19.0)	26 (41.0)†	26 (41.0)‡
Rash	3 (4.7)	3 (4.8)	7 (11.0)
Abdominal pain	0 (0.0)	3 (4.8)	5 (7.8)§
Hirsutism	3 (4.7)	7 (11.0)	5 (7.8)
Metrorrhagia	3 (4.7)	5 (7.9)	5 (7.8)
Headache	1 (1.6)	3 (4.8)	4 (6.3)
Asthenia	3 (4.7)	4 (6.3)	3 (4.7)
Insomnia	2 (3.1)	4 (6.3)	3 (4.7)

* Adverse events were assessed by investigators as being possibly or probably related to the study drug. Values are the number (%).
† $P = 0.007$ versus placebo, by Fisher's exact test.
‡ $P = 0.011$ versus placebo, by Fisher's exact test.
§ $P = 0.058$ versus placebo, by Fisher's exact test.

Table 5. Change in serum DHEA-S and testosterone*

Hormone, treatment group	Baseline	Change from baseline to last visit
DHEA-S, μg/dl		
Placebo (n = 60)	29.1 ± 29.6	12.8 ± 42.6
100 mg prasterone (n = 61)	28.9 ± 40.7	476.7 ± 489.2†
200 mg prasterone (n = 62)	66.2 ± 329.9	784.9 ± 1,029.9†
Testosterone, ng/dl		
Placebo (n = 59)	16.9 ± 16.0	0.47 ± 14.1
100 mg prasterone (n = 60)	16.7 ± 14.6	22.2 ± 35.1‡
200 mg prasterone (n = 57)	16.7 ± 13.2	56.9 ± 60.2§

* Only patients with baseline and at least 1 postbaseline measurement are included. DHEA-S = sulfated ester of dehydroepiandrosterone. Values are the mean ± SD.
† $P < 0.001$ versus placebo, by one-way analysis of variance (ANOVA).
‡ $P = 0.004$ versus placebo, by one-way ANOVA.
§ $P = 0.001$ versus placebo, by one-way ANOVA.

shown). Only 17 postmenopausal patients who received prasterone were not receiving exogenous hormone replacement therapy. Within this group, increases in serum estradiol to premenopausal levels (>120 pg/ml) were observed in 1 patient receiving 100 mg of prasterone and in 2 patients receiving 200 mg of prasterone. Both of the latter 2 patients were age 48 years, however, and in all likelihood were perimenopausal rather than truly postmenopausal. Consistent with hormone-related feedback on pituitary gonadotropin secretion, statistically significant dose-related reductions in serum luteinizing hormone and follicle-stimulating hormone were observed in postmenopausal patients receiving 200 mg of prasterone (data not shown).

A reduction in the level of HDL cholesterol occurred in the 200-mg prasterone group, with mean ± SD changes from baseline of −6.0 ± 11.8, −8.2 ± 14.8, and −13.5 ± 11.8 mg/dl for placebo, 100-mg prasterone, and 200-mg prasterone, respectively ($P = 0.002$, 200-mg prasterone versus placebo). Reductions in LDL cholesterol and total cholesterol levels occurred in all treatment groups, without a distinct pattern or any significant treatment differences. For the level of total triglycerides, mean changes from baseline were not significantly different between groups, with mean ± SD changes of 1.5 ± 53.9, −20.0 ± 60.1, and −2.2 ± 141.1 mg/dl for placebo, 100-mg prasterone, and 200-mg prasterone, respectively. Given the skewed distribution, however, median values are more meaningful, with demonstrated changes from baseline of 6, −21, and −19 mg/dl for placebo, 100-mg prasterone, and 200-mg prasterone, respectively.

The mean and median C3 and C4 levels at last visit in both prasterone treatment groups were lower than the values in the placebo group (Table 6). There were no significant differences between groups in changes in the levels of anti-dsDNA (Table 6) or in IgG or IgM anticardiolipin antibodies from baseline to the last visit (results not shown).

Table 6. Changes in serum C3 and C4 and anti-dsDNA levels*

	Placebo (n = 64)	100 mg prasterone (n = 63)	200 mg prasterone (n = 64)
C3, mg/dl			
Mean ± SD at baseline	100.5 ± 27.4	89.2 ± 33.5	100.3 ± 32.6
Median at baseline	99.0	91.0	95.0
Mean ± SD change from baseline to last visit	−2.7 ± 16.1	−8.8 ± 20.1†	−9.1 ± 19.2‡
Median change from baseline to last visit	−1.0	−8.0	−8.0
C4, mg/dl			
Mean ± SD at baseline	18.3 ± 7.4	17.5 ± 9.5	19.3 ± 12.6
Median at baseline	17.0	15.0	15.0
Mean ± SD change from baseline to last visit	−0.8 ± 4.2	−1.4 ± 5.3	−2.2 ± 6.4§
Median change from baseline to last visit	1.0	0.0	−1.0
Anti-dsDNA, IU/ml			
Mean ± SD at baseline	28.3 ± 77.6	87.9 ± 429.1	62.5 ± 169.7
Median at baseline	3.6	5.9	0.0
Mean ± SD change from baseline to last visit	33.4 ± 166.3	30.3 ± 145.5	−6.2 ± 186.1
Median change from baseline to last visit	0.2	0.0	0.0

* Only patients with baseline and at least 1 postbaseline measurement are included. Reference laboratory C3 normal range 85–193 mg/dl, C4 normal range 12–36 mg/dl. Normal anti–double-stranded DNA (anti-dsDNA) value <3.6 IU/ml.
† $P = 0.066$ versus placebo.
‡ $P = 0.052$ versus placebo.
§ $P = 0.030$ versus placebo.

DISCUSSION

Corticosteroids are one of the mainstays of treatment in SLE to suppress end-organ inflammation. Although administration of corticosteroids can be instrumental in controlling and/or preventing disease flares, corticosteroid toxicity contributes to the morbidity and perhaps even the mortality of SLE (24–26). Therefore, reducing the dosage of corticosteroids to the lowest possible level while maintaining stability of disease activity is paramount. In the current study, the end point of a sustained reduction in the dosage of prednisone to ≤7.5 mg/day was chosen because it is close to the replacement dosage used for patients with primary adrenal insufficiency (27).

In this study of women with SLE who were corticosteroid dependent, more patients in the 200-mg prasterone group than in the other 2 groups were able to reduce their dosage of prednisone to 7.5 mg/day without worsening of SLE. There was a strong trend favoring prasterone over placebo: the response rate in the placebo group was 41%, compared with 44% in the 100-mg prasterone group and 55% in the 200-mg prasterone group ($P = 0.111$, 200-mg prasterone versus placebo).

In patients with active SLE (defined before completion of the study and unblinding as a baseline SLEDAI score >2), there was a dose-response relationship ($P = 0.033$ for linear trend): 51% of patients in the 200-mg prasterone group were responders, compared with 38% in the 100-mg prasterone group and 29% in the placebo group ($P = 0.031$, 200-mg prasterone versus placebo).

SLEDAI descriptors for patients with baseline SLEDAI scores ≤2 suggested that disease was not active in this group. Of the 54 patients in this subgroup, 28 (52%) had a SLEDAI score of 0. Additionally, 20 (37%) had SLEDAI scores of 2, based only on serologic findings (i.e., increased DNA binding [n = 18] and low complement level [n = 2], which tend to remain positive regardless of disease activity) (28–30). The remaining 6 patients had mucosal ulcers (n = 2), alopecia (n = 1), new rash (n = 1), leukopenia (n = 1), and pleurisy (n = 1). Based on the results of this study, however, we now believe that in future trials, only patients with active disease should be enrolled.

Among patients with baseline SLEDAI scores >2, the differences between treatment groups in baseline prednisone dosages (mean 15.7, 13.6, and 13.0 mg/day for placebo, 100-mg prasterone, and 200-mg prasterone, respectively) were statistically significant. Importantly, patients starting at high dosages could still achieve the study end point, because the final visit had to be included in the evaluation. For example, compared with a patient who was receiving 10 mg of prednisone per day at entry, a patient who was receiving 15 mg per day at entry would require only 1 more month of treatment to achieve a daily prednisone dosage of 7.5 mg, according to the protocol-specified algorithm. Because the definition of responder required that the prednisone dosage of ≤7.5 mg/day be sustained for at least the last 2 months, *including* the termination visit, achieving this dosage earlier would not necessarily have improved an individual patient's chances of being a responder, because that patient's dosage would have to have been 7.5 mg/day for a longer duration.

According to the trial design, a reduction in the dosage of prednisone at protocol-specified visits was mandated when a patient's SLEDAI score was stable or had improved. As a result, the SLEDAI score and other secondary outcome measures (SF-36, Krupp Fatigue Severity Score, and physician and patient global assessments on a VAS) would not be expected to improve (data not shown), because at each monthly visit, only those patients with improved or stable SLE, as measured by SLEDAI, would have had their corticosteroid dose reduced by algorithm. Similarly, there were no statistically significant differences between treatment groups in changes in the level of anti-dsDNA at last visit.

Although there were no statistically significant differences in pairwise comparisons between treatment groups for percentage change in prednisone dosage from baseline to last visit, this end point assessed only the dose of prednisone on the last day of treatment rather than the durability of the reduction in prednisone dosage (i.e., the ability to maintain a sustained reduction of prednisone for at least 2 months). Because some patients experienced a disease flare during the reduction in the dosage of corticosteroids, and because an algorithm for increasing the dosage of prednisone was not stipulated in the protocol, an analysis of the prednisone dosage only on the last study day was of limited use in characterizing steroid reduction.

Acne was the adverse event that occurred most frequently during prasterone therapy and was probably related to the androgenic effects of prasterone. Although almost 20% of patients in the placebo group also reported acne (which was probably related to corticosteroid use), the rate of acne in the prasterone groups was double that in the placebo group. Acne was generally mild, however, and only 1 patient each in the 100-mg prasterone and the 200-mg prasterone groups withdrew because of this side effect.

The observed reductions in HDL cholesterol and total triglyceride levels were expected and may reflect androgenic stimulation of hepatic lipase and enhanced clearance of HDL cholesterol (31–33) as well as reduction in the dosage of prednisone, because prednisone treatment increases total HDL cholesterol (34). The reduction in C3 has also been demonstrated in other trials of prasterone in SLE (35,36). Although this reduction could reflect C3 consumption, the reduced steroid requirements shown in this study and the clinical improvement that occurred during trials of prasterone therapy in SLE are not consistent with this. Furthermore, a reduction in the level of C3 and C4 without signs of inflammation has been observed in men with Klinefelter syndrome during testosterone replacement therapy (37) and in normal female volunteers treated with 200 mg of DHEA for 28 days (Genelabs: unpublished observations), suggesting a physiologic effect. Consistent with this, the proinflammatory cytokine IL-6, the level of which is elevated in active SLE (13–14), is known to stimulate hepatic secretion of C3 as an acute-phase reactant (38). DHEA has been reported to inhibit IL-6 release from human mononuclear cells in vitro (15), and it is plausible that observed reductions in the level of C3 and C4 may reflect reduced tissue inflammation, reduction in circulating IL-6 levels, or a direct effect on hepatic complement synthesis.

Dose-related mean and median increases in the testosterone level were observed in both prasterone treatment groups, which is consistent with the known metabolism of DHEA (39). Serum estradiol levels also increased in some postmenopausal patients, in some cases to premenopausal levels, although the number of postmenopausal women in the study who were not receiving exogenous hormone replacement therapy was small (only 4 postmenopausal women in the 200-mg group were not receiving exogenous estrogens), and 3 of the 4 women were age 48–51 years and were probably perimenopausal.

Lowering the dosage of corticosteroids may lead to positive outcomes in terms of bone loss, cataracts, osteonecrosis, and other side effects of steroid use. Long-term evaluations will be required, however, to assess whether corticosteroid reduction can be sustained and achieves these goals. The potential benefits of corticosteroid reduction will need to be weighed against the possible long-term androgenic effects of prasterone use, including HDL reduction, which could increase cardiovascular risk (40). However, reduced HDL cholesterol and triglycerides, as noted earlier, may result from enhanced clearance of lipid particles, which could potentially be beneficial. Long-term studies will be needed to further characterize these effects.

It is important to note that only female SLE patients were enrolled in this study. Few men with SLE have been treated with androgens in the past. A prospective study to assess efficacy and safety of prasterone in male SLE patients is currently ongoing. Until data from this or other studies are available, any use of DHEA in men with SLE should occur in a carefully controlled investigative setting only.

Finally, to determine that the steroid-sparing effects of prasterone are caused not simply by changes in prednisone kinetics, a separate study was conducted (41). Prasterone was shown not to alter the kinetics, protein binding, or conversion of prednisone to prednisolone, its active metabolite (41). Several potential activities attributed to prasterone may perhaps enable steroid reduction in patients with active SLE, including enhanced secretion of IL-2 (11,12) and inhibition of release of inflammatory cytokines IL-1, IL-6, and tumor necrosis factor α (15,42–44).

In summary, this study presents evidence that prasterone has corticosteroid-sparing effects in SLE, especially among patients with active disease. Patients with SLE who are maintained for long periods of time on supraphysiologic doses of glucocorticoids may benefit from controlled tapering of glucocorticoids to physiologic doses, with consequent reduction of glucocorticoid toxicity, during treatment with prasterone.

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