Effects of Prasterone on Bone Mineral Density in Women with Active Systemic Lupus Erythematosus Receiving Chronic Glucocorticoid Therapy

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ABSTRACT. ***Objective***. To assess prevention of bone mineral density (BMD) loss and durability of the response during treatment with prasterone in women with systemic lupus erythematosus (SLE) receiving chronic glucocorticoids.

Methods. 155 patients with SLE received 200 mg/day prasterone or placebo for 6 months in a double-blind phase. Subsequently, 114 patients were re-randomized to receive 200 or 100 mg/day prasterone for 12 months in an open-label phase. Primary efficacy endpoints were changes in BMD at the lumbar spine (L-spine) from baseline to Month 6 and maintenance of BMD from Month 6 to 18 for patients who received prasterone during the double-blind phase.

Results. In the double-blind phase, there was a trend for a small gain in BMD at the L-spine for patients who received 200 mg/day prasterone for 6 months versus a loss in the placebo group (mean ± SD, 0.003 ± 0.035 vs –0.005 ± 0.053 g/cm^2, respectively; p = 0.293 between groups). In the open-label phase, there was dose-dependent increase in BMD at the L-spine at Month 18 between patients who received 200 versus 100 mg/day prasterone (p = 0.021). For patients who received 200 mg/day prasterone for 18 months, the L-spine BMD gain was 1.083 ± 0.512% (p = 0.042). There was no overall change in BMD at the total hip over 18 months with 200 mg/day prasterone treatment. The safety profile reflected the weak androgenic properties of prasterone.

Conclusion. This study suggests prasterone 200 mg/day may offer mild protection against bone loss in women with SLE receiving glucocorticoids. (ClinicalTrials.gov Identifiers NCT00053560 and NCT00082511) (First Release July 15 2008; J Rheumatol 2008;35:1567–75)

Key Indexing Terms:
DEHYDROEPIANDROSTERONE PRASTERONE OSTEOPOROSIS
SYSTEMIC LUPUS ERYTHEMATOSUS BONE MINERAL DENSITY

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Reduced bone mineral density (BMD) is present in over 50% of women with systemic lupus erythematosus (SLE)[1-3]. While often associated with glucocorticoid (GC) treatment, low BMD also occurs among women with SLE even prior to initiation of GC therapy, suggesting BMD is affected by the overall systemic inflammation associated with this disease[4-6]. As chronic treatment with even low dose prednisone is associated with increased risk of femoral and vertebral fracture[7], and SLE patients receiving treatment chronically with GC have been reported to be at a 5-fold increased risk in osteoporotic fractures[8], prevention of BMD loss is an important therapeutic goal early in the clinical course of this disease.

GC-induced bone loss is primarily due to decreased bone formation, as GC have direct effects on osteoblasts, including induction of osteoblastic apoptosis and reduced osteoblastic function[9]. GC adversely affect bone maintenance via other pathways as well, including gonadotropin suppression, reduced gastrointestinal calcium absorption by opposing the actions of vitamin D, suppression of adrenal androgen secretion, enhanced collagenase activity, and enhanced osteoclastogenesis and increased bone resorption[9-12].

The principal adrenal androgen is dehydroepiandrosterone (DHEA), which is secreted primarily in its sulfated form, DHEA-S[13]. DHEA and DHEA-S serve as precursors for conversion to androgens and estrogens on a tissue-specific basis, a process known as "intracrinology"[14]. Endogenous secretion of DHEA and DHEA-S may be important to maintenance of bone mass through localized conversion in bone to active androgens and/or estrogens[15,16] as well as possible effects on multiple pathways, including inflammatory cytokines and tissue growth factors[17-19]. Women with active SLE have low circulating levels of DHEA and DHEA-S[20], which are suppressed further by treatment with exogenous GC[21].

We hypothesized that treatment of SLE patients with prasterone (United States Adopted Names Council designation for the synthetic form of DHEA) would have a protective effect on BMD. An earlier investigation with 55 patients reported positive effects of 200 mg prasterone daily for 12 months on BMD in women with SLE receiving chronic GC[22]. We sought to further assess the effect of prasterone on prevention of bone loss and the durability of the effect. We describe results of a study consisting of a double-blind placebo-controlled phase (6 mo) and a subsequent open-label phase (12 mo) assessing BMD changes during up to 18 months of treatment with prasterone in female lupus patients receiving chronic GC therapy.

MATERIALS AND METHODS

Study population. Our study enrolled pre- and postmenopausal female patients 18 years or older who met the American College of Rheumatology classification for diagnosis of SLE[23], were receiving chronic therapy with prednisone dose (or equivalent) of > 5 mg/day, and had a baseline SLE Disease Activity Index (SLEDAI) score > 3[24]. This study excluded patients with a T-score at screening of less than -3.0 of the lumbar spine (L-spine) or total hip by dual energy x-ray absorptiometry (DXA) assessment, and patients who were receiving treatment with anti-resorptive agents such as hormone replacement therapy, bisphosphonates, and calcitonin.

Treatment and assessments. Our study was a randomized, multicenter, 18-month trial to assess safety, prevention of bone loss, and the durability of the response by treatment with prasterone in women with SLE who were receiving chronic GC treatment. The prevention of bone loss was first assessed during a 6-month double-blind, placebo-controlled phase and subsequently during a 12-month open-label phase. The 2 phases of the study were conducted in accord with the Declaration of Helsinki and were approved by the institutional review board at each center. All patients gave written informed consent.

Patients who met the selection criteria for the study were randomized to receive either 200 mg/day prasterone or placebo for 6 months in the double-blind phase, following which patients were re-randomized to enter the second phase and to receive either 200 mg/day or 100 mg/day prasterone in a 2 to 1 ratio. All patients received standard care of therapy for SLE including GC and calcium/vitamin D supplement.

Patients visited the clinic every 2 months during the double-blind phase and every 3 months for efficacy and routine safety assessments as well as SLEDAI determination, and patient's own self-assessment on a visual analog scale (VAS). BMD of the L-spine and total hip was measured in duplicate by DXA at screening (baseline), Month 6, Month 12, and Month 18 or at the time of early discontinuation of study medication.

Co-treatments. Patients received tablets providing calcium carbonate and vitamin D: premenopausal patients received 1000 mg elemental calcium and 400 IU vitamin D per day; postmenopausal patients received 1500 mg elemental calcium and 600 IU vitamin D per day.

Steroids and other SLE co-treatments were to be held at fixed dose during the double-blind phase and the first 6 months of the open-label phase. Steroids could be reduced in either treatment phase if deemed medically necessary, but only by the algorithms as shown in Table 1.

Statistical analysis. For the double-blind phase, the primary efficacy variable was the absolute change in L-spine BMD from baseline to Month 6 in all randomized patients (intent-to-treat population). Missing BMD data at the 6-month time point were imputed using the mean of completed patients from the opposite treatment group. Other efficacy analyses were based on patients in the randomized population with at least one post-baseline on-treatment efficacy assessment during the study.

Table 1. Prednisone tapering regimen.

Time Period	Daily Prednisone Dose	Maximum Dose Reduction per Month
Double-blind phase (baseline to Mo 6)[a]	≤ 10 mg	No reduction allowed
	> 10 mg to ≤ 20 mg	2.5 mg
	> 20 mg	At investigator discretion
Open-label phase (Mo 6 to Mo 12)[b]	5 mg	No reduction allowed
	> 5 mg to < 10 mg	1.0 mg
	≥ 10 mg to ≤ 20 mg	2.5 mg
	> 20 mg	At investigator discretion
Open-label phase (Mo 12 to Mo 18)[c]	< 10 mg	1.0 mg
	< 10 mg to ≤ 20 mg	2.5 mg
	> 20 mg	At investigator discretion

[a] Prednisone may be reduced if medically necessary but not to below 10 mg/day. [b] Prednisone may be reduced if medically necessary but not to below 5 mg/day. [c] Prednisone may be reduced if medically necessary but not to below 1 mg/day.

The analysis population for the open-label phase was those patients who underwent a DXA assessment at Month 6 of the double-blind phase and at least one post-Month 6 DXA scan at either Month 12 or Month 18. The primary efficacy variable was the mean percentage change in L-spine BMD from Month 6 to Month 18 or early termination. To assess the durability of longterm response, the BMD change from baseline to Month 18 was assessed in the group of patients treated with 200 mg/day prasterone in the double-blind phase who subsequently received 200 mg/day prasterone in the open-label phase.

Analysis of variance (ANOVA) method was used to compare treatment groups. Safety assessment for each phase of the study included all randomized patients who received at least one dose of study medication.

BMD and laboratory assessments. All patients underwent duplicate DXA scans of the L-spine and non-dominant total hip at specified clinical visits. At screening, lateral and AP radiographs of the L-spine and lateral radiographs of the thoracic spine were collected and reviewed to assess suitability of the L-spine (L1–L4) for DXA measurement. Quality control for the DXA measurements and vertebral x-ray data were evaluated with treatment assignments blinded by Synarc, Inc. [Portland, OR (DXA) and San Francisco, CA (X-ray)]. The routine clinical laboratory work was conducted by Quest Diagnostics, Inc. (Van Nuys, CA, USA), while serum and urine bone formation/resorption markers, 25-hydroxy vitamin D3 and 1,25-dihydroxy vitamin D3, and intact parathyroid (PTH) hormone levels were measured at Nichols Institute of Endocrinology (San Juan Capistrano, CA, USA).

RESULTS

Six month double-blind treatment phase. One hundred and fifty-five patients received either prasterone 200 mg (76 patients) or placebo (79 patients) daily for 6 months. Dosing compliance was high at 95.5 ± 7.7% and 95.0 ± 11.2% for patients in the prasterone and placebo groups, respectively.

There were 8 discontinuations from the placebo treatment group, 6 for reasons related to safety and 2 for administrative reasons. The safety withdrawals included 2 deaths (discussed below), and 4 withdrawals due to hematuria, ovarian cyst, excessive menstrual bleeding, and epigastric pain/increased memory loss/loss of balance. There were no premature discontinuations from the prasterone treatment group.

Demographics. The 2 treatment groups were well balanced, with no significant differences between the groups in any of the principal baseline demographic variables (Table 2).

BMD evaluation. In the double-blind phase of the study, 5 patients (1 prasterone and 4 placebo) did not undergo the Month 6 BMD assessment, so the individual missing values were imputed as the mean from the opposite treatment group. There was a trend of mean (± SD) gain from baseline in BMD at the L-spine in the prasterone group of 0.003 ± 0.035 g/cm^2 and a loss of 0.005 ± 0.053 g/cm^2 in the placebo group at Month 6 (p = 0.293 between groups). The corresponding mean percentage change from baseline in L-spine BMD was 0.268 ± 3.580% in the prasterone group and 0.197 ± 4.865% in the placebo group (p = 0.501 between groups).

Excluding the 5 patients without BMD data at Month 6 (n = 75 both groups), there was a gain of 0.251 ± 3.601% in the prasterone group versus a loss of 0.332 ± 2.988% in the placebo group (p = 0.282 between groups). For the hip, the gain was 0.163 ± 1.893% in the prasterone group versus a loss of 0.223 ± 1.746% in the placebo group (p = 0.197) (Figure 1A).

Nearly 60% of the patients in the study were postmenopausal and the median T-scores at both the L-spine and hip for this group were noticeably lower than those for the premenopausal group (Table 2). Postmenopausal patients who received prasterone showed higher mean gain of BMD at the L-spine than the premenopausal patients, while the premenopausal patients gained more BMD at the hip than the postmenopausal patients (Figure 1B).

Bone resorption and formation markers. Bone markers decreased at Month 6 compared to baseline for both the prasterone and placebo groups, but the decreases were greater in the prasterone group (Figure 2). Serum and urine N-telopeptide, markers of bone resorption, decreased in both treatment groups at Month 6, significantly so for the prasterone group (p < 0.001 from baseline). The decrease in serum N-telopeptide in the prasterone group was significantly more than the placebo group (p = 0.024). The decrease from baseline in serum bone-specific alkaline phosphatase, a marker of bone formation, declined significantly in both treatment groups, while the osteocalcin decrease was significant for the prasterone group only.

Serum intact PTH declined significantly in the placebo group at Month 6 (p = 0.009). There were small but significant increases in serum 25-hydroxy vitamin D3 in both treatment groups, while the levels of 1,25-dihydroxy vitamin D3 declined in both treatment groups.

SLE characteristics. SLEDAI scores decreased from baseline to Month 6 in both treatment groups, with mean ± SD/median changes from baseline of –2.1 ± 5.1/–2.0 for the prasterone group versus –1.6 ± 5.8/0.0 for the placebo group. Patient VAS scores did not change appreciably in either treatment group (data not shown).

12-month open-label extension phase. One hundred and fourteen patients were re-randomized to receive prasterone 200 or 100 mg/day in a 2:1 ratio, respectively, for an additional 12 months. There were 4 subgroups of patients defined by the treatment during the 2 phases of the study (double-blind → open-label): (1) 200 mg/day prasterone → 200 mg/day prasterone; (2) 200 mg/day prasterone → 100 mg/day prasterone; (3) placebo → 200 mg/day prasterone; and (4) placebo → 100 mg/day prasterone. The patients in subgroup 1 were of primary interest in assessing the durability of longterm treatment of 200 mg/day prasterone. Of these, 106 patients had at least one BMD measurement following the randomization.

The 200 mg → 200 mg group showed a mean percentage gain in BMD of 0.844 ± 0.525% in the L-spine from Month 6 to Month 18 of the study. Patients in the placebo → 200 mg group also showed mean percentage gain of 0.713 ± 0.537% in the L-spine BMD from Month 6 to Month 18. In

Table 2. Demographic and clinical characteristics of patients with SLE enrolled for the study.

Characteristic	Prasterone 200 mg, n = 76	Placebo, n = 79	p[d]
Age, yrs[a]	42.1 ± 11.8	41.4 ± 12.6	0.747
Race, n (%)			0.705
Caucasian	26 (34.2)	33 (41.8)	
African-American	15 (19.7)	16 (20.2)	
Asian	5 (6.6)	2 (2.5)	
Hispanic	28 (36.8)	26 (32.9)	
Other	2 (2.6)	2 (2.5)	
Premenopausal, n (%)	40 (52.6)	42 (53.2)	0.947
Current smoking status, n (%)	19 (25.0)	11 (13.9)	0.081
Alcohol use, n (%)	36 (47.4)	44 (55.7)	0.313
Duration of SLE disease, yrs[a]	8.6 ± 7.6	9.4 ± 8.2	0.521
Duration of glucocorticoid exposure, yrs[a]	7.6 ± 7.4	8.5 ± 7.3	0.521
Prednisone (or equivalent) at baseline, n (%)			0.736
> 10 mg/day	25 (32.9)	24 (30.4)	
5–10 mg/day	51 (67.1)	55 (69.6)	
Antimalarial, n (%)	45 (59.2)	55 (69.6)	0.176
Immunosuppressive, n (%)	57 (75.0)	56 (70.9)	0.565
Baseline glucocorticoid dose, mg/day[a]	13.3 ± 10.7	11.2 ± 6.6	0.139
Prior use of medication			
Estrogen (HRT or OC), n (%)	7 (9.2)	13 (16.4)	0.232[b]
Calcitonin, n (%)	1 (1.3)	2 (2.5)	1.000[b]
Prior bisphosphonate, n (%)	3 (3.9)	4 (5.1)	1.000[b]
Calcium supplements, n (%)	43 (56.6)	44 (55.7)	0.912
SLEDAI score[a]	9.2 ± 5.7	8.5 ± 5.3	0.409
Patient VAS score, 0–100 scale[a,c]	40.6 ± 26.0	36.3 ± 24.7	0.292
Osteopenia, n (%)	25 (32.9)	27 (34.2)	0.865
Osteoporosis, n (%)	7 (9.2)	6 (7.6)	0.716
L-spine BMD, g/cm^2, mean ± SD	1.039 ± 0.170	1.006 ± 0.160	0.212
Median	1.015	1.013	
Total hip BMD, gm/cm^2, mean ± SD	0.943 ± 0.164	0.917 ± 0.124	0.264
Median	0.921	0.926	
T-score L-spine, mean ± SD	–0.588 ± 1.342	–0.693 ± 1.267	0.617
Median	–0.608	–0.530	
Postmenopausal only, mean ± SD	–0.741 ± 1.647	–0.849 ± 1.533	
Median	–0.880	–0.980	
Premenopausal only, mean ± SD	–0.447 ± 1.007	–0.602 ± 0.976	
Median	–0.440	–0.482	
T-score total hip, mean ± SD	–0.203 ± 1.291	–0.341 ± 1.017	0.461
Median	–0.303	–0.150	
Postmenopausal only, mean ± SD	–0.356 ± 1.386	–0.337 ± 1.084	
Median	–0.420	–0.315	
Premenopausal only, mean ± SD	–0.060 ± 1.216	–0.334 ± 0.938	
Median	–0.215	-0.132	

[a] Values are mean ± SD. [b] Based on exact probability for limits on prior use of bone sparing agents. [c] 0: "no problems at all"; 100: "the worst I have ever felt." [d] p values for categorical variables are from the chi-square test. p values for continuous variables are from ANOVA with treatment as a factor.

contrast, 100 mg/day prasterone treatment during the 12-month open-label phase did not provide overall improvement for BMD as a group (Table 3).

A dose response was evident for BMD at the L-spine for patients who received 200 mg/day or 100 mg/day prasterone groups in the open-label phase (Figure 3), p = 0.021 between groups at Month 18.

BMD results after 18 months of treatment. A consistent increase in L-spine BMD was seen in the treatment group that received 200 mg/day prasterone continuously for 18 months (Figure 4) with an overall gain of 1.083 ± 0.512% at the L-spine (p = 0.042, change from baseline to Month 18). A switch from 200 to 100 mg/day prasterone was not protective, since the group mean BMD at the L-spine began to decline soon after the start of the 100 mg daily dose. The placebo → 200 mg/day prasterone treatment group also benefited by showing an increase of 0.795 ± 0.640% in the L-spine BMD at Month 18. The placebo → 100 mg/day prasterone group did not show any overall benefit of BMD gain over the 18 months of observation.

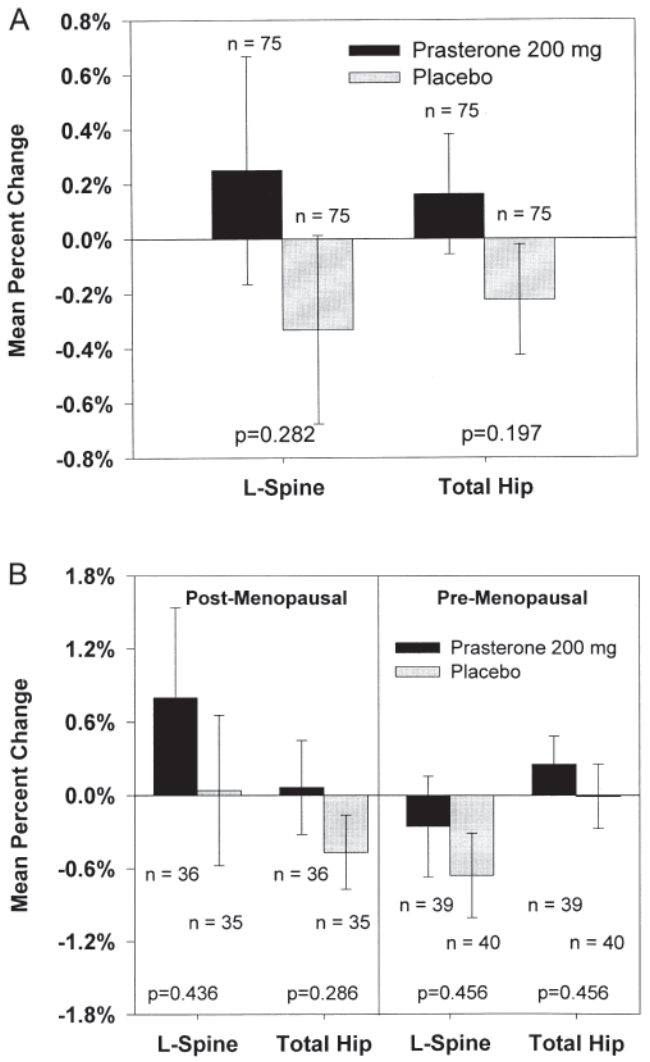

Figure 1. Mean percentage change in BMD at the L-spine and total hip after 6 months of treatment in women with active SLE. Results are presented as mean ± SEM for patients who underwent dual energy x-ray absorptiometry assessment at Month 6. 1A. All patients. 1B. Postmenopausal and premenopausal women presented separately.

The results for the total hip were less consistent than the L-spine. From the LOCF analysis, patients in all groups during the open-label phase lost BMD for the total hip, although the loss was generally less with patients on 200 mg/day. During the 18-month course of the study, BMD at the total hip was generally maintained with 200 mg/day prasterone while BMD reduction was seen with 100 mg/day prasterone.

Safety. Adverse events. In the double-blind phase, types of adverse events were similar in the prasterone and placebo treatment groups, except for acne and hirsutism, which, as expected, were more common in the prasterone group. Most reports of these androgenic events were mild in intensity and did not cause premature termination from the study. Adverse events reported as > 10% for either treatment group and rates of hirsutism are listed in Table 4. Additionally, a drug interaction between prasterone and warfarin, leading to an increase INR in 3 patients, required adjustment of the warfarin dose. There was no associated clinical bleeding.

There were 4 deaths in this study. Two occurred in the double-blind phase, both in placebo-treated patients (intracranial hemorrhage; abdominal sepsis/hepatic encephalopathy). There were also 2 deaths in the open-label phase of the study — one in a patient with pulmonary thromboembolism in the placebo → 100 mg/day group; the other in a patient in the 200 mg/day → 100 mg/day group. The patient had been in poor health for some time related to diabetes mellitus and its complications and the investigator believed the cause of death was probably due to atherosclerosis.

Serum testosterone, estradiol, and estrone increased in the prasterone treatment group. In premenopausal patients, the changes from baseline for serum estradiol and estrone were not clinically or statistically significant, while in postmenopausal patients, there were modest increases in estradiol and estrone levels, which were similar to those reported in a previous study in women with SLE treated with prasterone[25,26]. There were no differences between the treatment groups for adverse events that would be associated with estrogen exposure such as vaginal bleeding, which was reported with similar and low frequency in both treatment groups.

DISCUSSION

We postulated that prasterone treatment would be beneficial for maintenance of BMD in women with lupus treated with GC.

Three previous studies have addressed the effects of prasterone treatment on BMD in glucocorticoid-treated lupus patients[22,27,28]. Van Vollenhoven, *et al* reported a potential protective effect of prasterone 200 mg/day as compared to placebo with respect to glucocorticoid-induced bone loss at the L-spine in patients with severe SLE[27]. Mease, *et al* reported a mean BMD gain at the L-spine of 1.7% in the prasterone 200 mg/day group compared to a mean loss of 1.1% in the placebo group at 1 year[22]. Hartkamp, *et al* reported prasterone 200 mg/day for up to 1 year did not have a significant effect on BMD in the overall treatment group. However, most patients in their study were premenopausal or were receiving bone-protective co-treatments. Of the 9 postmenopausal patients not receiving bone-protecting agents, however, the mean change at the L-spine over 1 year was 3.22% with prasterone compared with –5.61% for placebo[28].

In our current study, the gain of BMD after 6 months of treatment with 200 mg/day prasterone did not achieve statistical significance, but there was continuous gain in BMD at the L-spine and maintenance of BMD at the total hip over the 18 months, suggesting 6 months may have been too short to observe a significant change in BMD in patients

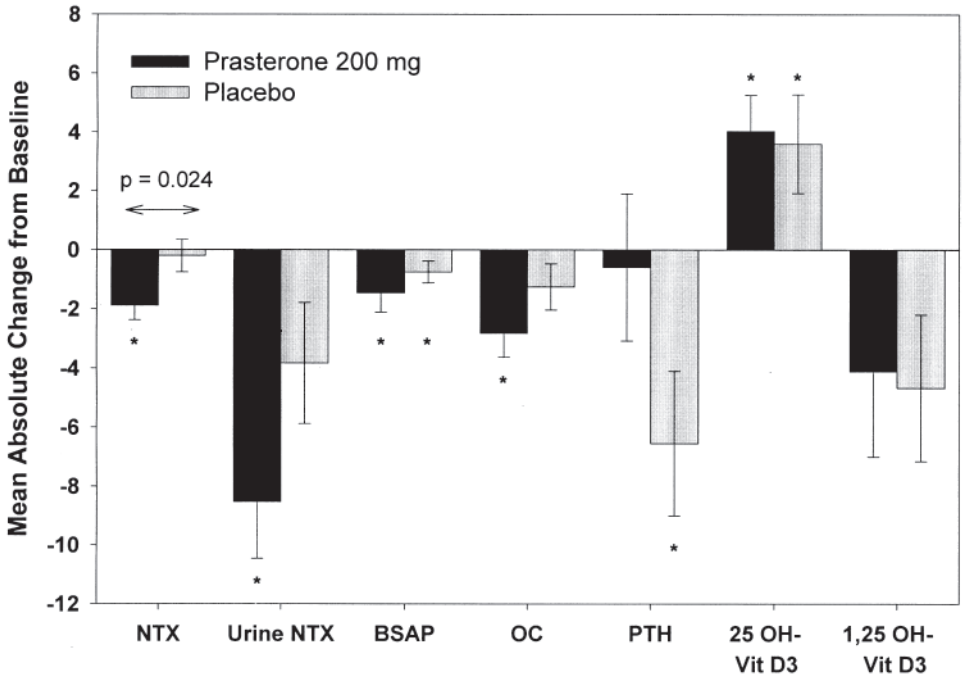

Figure 2. Mean absolute changes in bone markers and vitamin D metabolites from baseline to Month 6. The mean baseline levels and units of each of the markers for prasterone and placebo groups are: serum N-telopeptide (NTX) = 14 and 12 BCE/l; urine N-telopeptide (Urine NTX) = 36 and 36 nmol BCE/mmol creatine; serum bone specific alkaline phosphatase (BSAP) = 13 and 12 µg/l; osteocalcin (OC) = 16 and 15 ng/ml; serum intact PTH = 50 and 50 pg/ml; 25-hydroxy vitamin D3 (25VitD) = 32 and 32 ng/ml; 1,25-dihydroxy vitamin D3 (1,25VitD) = 46 and 45 pg/ml. Results are plotted as mean ± SEM. The asterisks (*) denote statistical significance within treatment group for change from baseline to Month 6. The mean change from baseline to Month 6 differed significantly between treatment groups for serum NTX (p = 0.024).

Table 3. Mean percentage change in BMD during the open-label phase from Mo 6 to Mo 18.

	Treatment Cohort[a]			
	200 mg → 200 mg, n = 37[b]	200 mg → 100 mg, n = 17[b]	Placebo → 200 mg, n = 34[b]	Placebo → 100 mg, n = 18[b]
L-spine, mean ± SD	0.844 ± 0.525	–1.174 ± 0.867	0.713 ± 0.537	–0.399 ± 0.748
Total hip, mean ± SD	–0.299 ± 0.479	–0.448 ± 0.554	–0.166 ± 0.383	–0.557 ± 0.469

[a] Patients who completed the double-blind phase and consented to participate in the open-label phase. Patients were re-randomized to receive either 200 mg/day or 100 mg/day prasterone in a 2 to 1 ratio during the open-labeled phase. [b] DXA data from the last visit was carried forward (LOCF analysis) for patients who discontinued study drug early.

who were receiving high doses of GC. The declines in bone formation and resorption markers in both treatment groups suggested that exogenous calcium supplementation may have reduced overall bone turnover, which in turn could have muted the overall gain in BMD during prasterone treatment. The decline in serum PTH levels in both treatment groups is consistent with this.

Among the limitations of the study were its short duration of 6 months for the double-blind phase, inclusion of patients with minimal BMD loss at baseline, the heterogeneous population of both pre- and postmenopausal patients, and the confounding effects of GC and other drugs used to control lupus in these patients. Despite exposure to chronic steroids for 7–8 years, there were only small reductions in BMD at baseline, which may reflect the current widespread use of calcium supplements in steroid-treated patients. Additionally, patients receiving co-treatments with bone-sparing agents such as bisphosphonates, hormone replacement therapy, and calcitonin were excluded, so the pool of patients from which to draw enrollment would have been likely to include only those with modest BMD loss. Not surprisingly, baseline T-scores were lowest for the postmenopausal group, and thus the overall gain in BMD at the L-spine was greatest and more evident for this group, while only modest effects were observed in the premenopausal group. The patients enrolled in this study were on standard

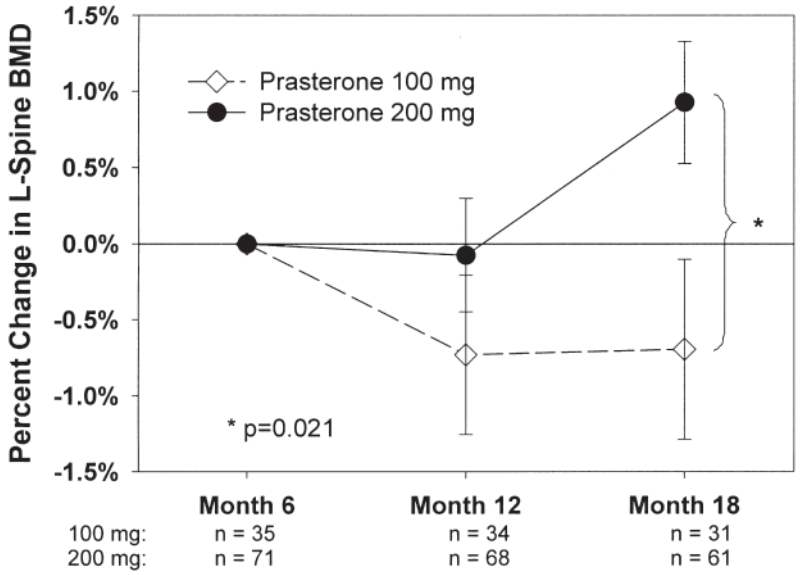

Figure 3. Mean percentage change in BMD at the L-spine during the open-label phase regardless of the treatment during the double-blind phase. All patients after re-randomization received prasterone at either 100 or 200 mg/day for 12 months. At Month 18, there was a significant dose response present (p = 0.021, prasterone 200 mg vs 100 mg). Results are plotted as mean ± SEM

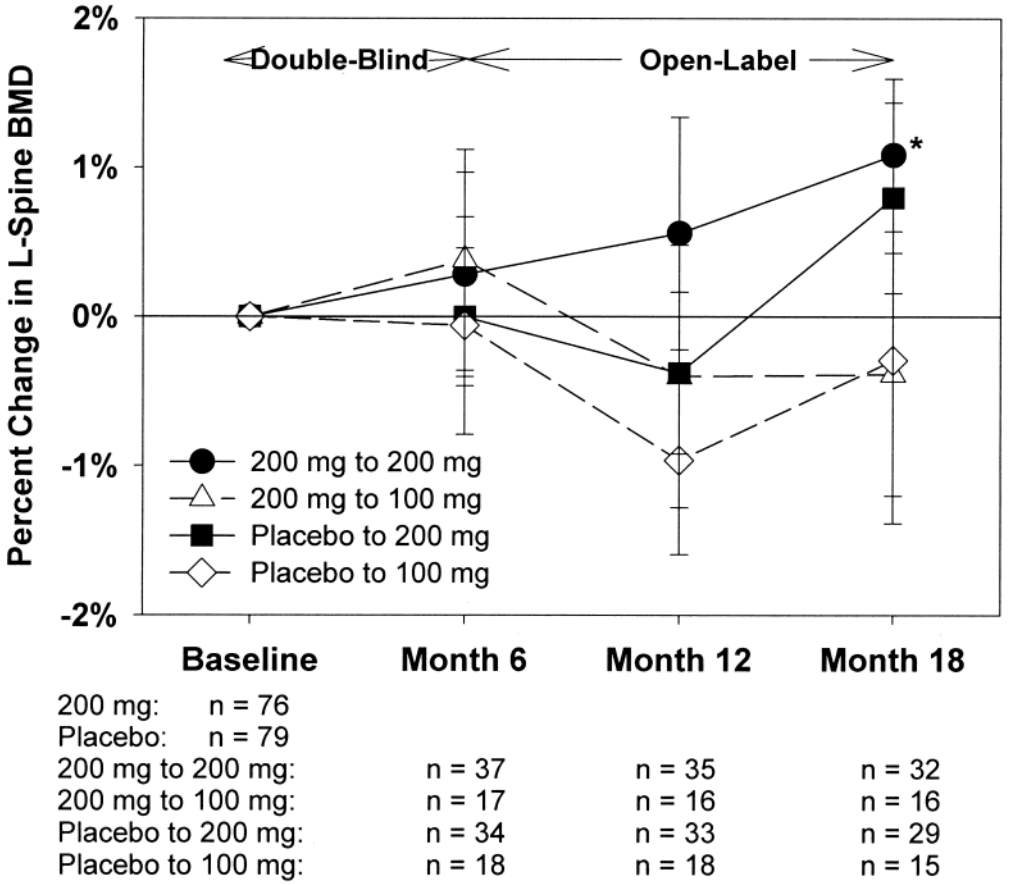

Figure 4. Mean percentage changes in BMD at the L-spine during 18 months of treatment. Both the 6 month placebo controlled double-blind phase and 12 month open-label extension phase are presented. The asterisks (*) denote statistical significance change from baseline to Month 18 (p = 0.042) in the group which received prasterone 200 mg/day for up to 18 months. Results are plotted as mean ± SEM.

Table 4. Adverse events during the 6 month double-blind phase in the ITT population*.

Adverse Event	Prasterone 200 mg, n = 76	Placebo, n = 79
Acne, n (%)	18 (23.7)	6 (7.6)
Discoid lupus erythematosus, n (%)	17 (22.4)	12 (15.2)
Asthenia, n (%)	9 (11.8)	12 (15.2)
Headache, n (%)	8 (10.5)	7 (8.9)
Pharyngitis, n (%)	6 (7.9)	16 (20.3)
Urinary tract infection, n (%)	6 (7.9)	13 (16.5)
Back pain, n (%)	6 (7.9)	8 (10.1)
Nausea, n (%)	6 (7.9)	8 (10.1)
Hirsutism, n (%)	6 (7.9)	2 (2.5)
Abdominal pain, n (%)	4 (5.3)	10 (12.7)
Myalgia, n (%)	4 (5.3)	9 (11.4)

* Table includes all adverse events ≥ 10% for either treatment group (except hirsutism).

of care medications for SLE, which is inherently heterogeneous. Nevertheless, randomization was shown to be effective in keeping the treatment groups well-balanced in baseline medications, i.e., glucocorticoid, immunosuppressives, antimalarials, and other clinical characteristics.

The increases in estradiol in postmenopausal patients were very similar to those reported previously during prasterone treatment[26] and to those observed during transdermal estrogen therapy[29], while there were no meaningful changes in serum estradiol and estrone in the premenopausal treatment group. The greater effects of prasterone on BMD in the postmenopausal patients might be mediated via its metabolism to androgenic or estrogenic steroids by bone cells[15-16], which could affect local production of growth factors, cytokines, and other regulatory pathways[12,17-19].

Finally, since this study was not designed to assess fracture incidence, it is not known whether these BMD findings of this study might translate into a reduction in longterm fracture risk.

In conclusion, the 6 month placebo controlled phase of our study demonstrated an overall mean gain in BMD relative to placebo at the L-spine while BMD at the hip was preserved. With continued dosing for 12 additional months, 200 mg/day of prasterone showed additional gain in BMD and was found to be protective against BMD loss at the L-spine, while 100 mg/day was not protective in patients with SLE receiving glucocorticoids.

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