A Comparison of Calcium, Calcitriol, and Alendronate in Corticosteroid-Treated Premenopausal Patients with Systemic Lupus Erythematosus

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ABSTRACT. Objective. To assess bone mineral density (BMD) changes in patients with systemic lupus erythematosus (SLE) undergoing longterm therapy with corticosteroids (CS) while taking calcium, calcitriol, or alendronate. The primary endpoint was BMD changes at 2 years.

Methods. Premenopausal SLE patients were randomized into 3 groups according to medication: calcium carbonate 500 mg bd (calcium alone), calcitriol 0.25 μg bd plus calcium carbonate 500 mg bd (calcitriol + calcium), and alendronate 70 mg/week plus calcium carbonate 500 mg bd (alendronate + calcium). BMD was measured at baseline and at the end of the first and second years.

Results. Ninety-eight patients were recruited. There were 33 patients taking calcium alone, 33 calcitriol + calcium, and 32 alendronate + calcium. On randomization, median duration of CS use was 2.5 years (range 0–20 yrs). Seventy-seven patients (78.6%) completed the study (23 taking calcium alone, 27 calcitriol + calcium, 27 alendronate + calcium). There were no significant differences in mean CS dosages among the 3 groups at the time of BMD measurements. After 2 years, there were no significant changes in BMD in the calcium-alone and calcitriol + calcium groups, apart from a 0.93% ($p < 0.001$) reduction in total hip BMD in the calcium-alone group. In contrast, the alendronate + calcium group showed significant increases in BMD of 2.69% ($p < 0.001$) in the lumbar spine and 1.41% ($p < 0.001$) in total hip.

Conclusion. Both calcium alone and calcitriol + calcium preserved lumbar spine BMD in premenopausal patients with SLE taking longterm CS at 2 years, whereas alendronate + calcium led to increases in BMD in lumbar spine and total hip. Premenopausal women taking CS should be considered for osteoporosis prophylaxis. (First Release Nov 1 2008; J Rheumatol 2008;35:2344–7; doi:10.3899/jrheum.080634)

Key Indexing Terms:
OSTEOPOROSIS GLUCOCORTICOID SYSTEMIC LUPUS ERYTHEMATOSUS
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Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease of young women in the reproductive age group. The clinical course of the disease is characterized by periods of relapse and remission. Corticosteroids (CS) are widely used in the treatment of patients with SLE to control disease activity. Whether due to the CS treatment, or to the disease itself, osteoporosis is being increasingly recognized in patients with SLE and is an important cause of comorbidity.

CS are well known to affect the skeleton through multiple pathways. There is an initial rapid phase of increased bone resorption, followed by a slower, more progressive phase of reduced bone formation[1]. Longitudinal studies have shown that the most rapid rate of bone loss occurs in the first 6[2] to 12 months[3,4] of treatment and is similar at both the lumbar spine and femoral neck. This bone loss continues at a rate of 2 to 3 times greater than normal in patients undergoing longterm CS therapy[5], and is associated with an increased risk of both vertebral and nonvertebral fractures[6]. Hence, it is important to consider bone protection for patients on prolonged CS therapy.

Randomized trials have shown that calcium and vitamin D analogs[4,7,8] and bisphosphonates[9-11] can be used to prevent bone loss or improve bone mineral density (BMD) in patients taking CS. However, there have been very few head-to-head

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trials that compared the different therapeutic modalities[12,13], and none in Asian patients.

In this prospective, randomized controlled study, we compared the efficacy of calcium carbonate alone or combined with calcitriol or alendronate in the preservation of BMD in premenopausal patients with SLE taking CS. Our primary endpoint was to assess lumbar spine BMD after 2 years of treatment; the secondary endpoint was hip BMD after 2 years of treatment.

MATERIALS AND METHODS

Patient selection. Premenopausal SLE patients were recruited from outpatient clinics in 2 teaching hospitals in Kuala Lumpur, Malaysia. They all fulfilled American College of Rheumatology criteria for the diagnosis of SLE[14]. They were ambulant; they were taking and were expected to continue CS for the duration of the study, as part of their treatment for SLE. At entry, patients had to be taking at least 7.5 mg prednisolone daily.

The study was approved by the ethics committees of both centers and all patients gave informed consent.

Patients were excluded for the following conditions: postmenopausal, renal impairment (serum creatinine > 115 mol/l), known or past metabolic bone disorders, malabsorption, thyroid disease, immobilization, or taking other drugs affecting bone homeostasis (e.g., phenytoin, methotrexate, cyclosporine, oral contraceptive). Patients were also excluded if they had been taking calcitriol or alendronate previously, or any other medications for the treatment of osteoporosis. Patients were counselled against pregnancy and those who became pregnant during the study were withdrawn.

Assignment and treatment. Patients were assigned to their groups by means of 3-way block randomization. They were randomly allocated to one of 3 treatment arms: (1) calcium carbonate 500 mg twice daily (calcium alone); (2) calcitriol (Rocaltrol) 0.25 μg twice daily plus calcium carbonate 500 mg twice daily (calcitriol + calcium); or (3) alendronate (Fosamax®; provided by Merck & Co., Whitehouse Station, NJ, USA) 70 mg once a week plus calcium carbonate 500 mg twice daily (alendronate + calcium). Treatment arms were not blinded.

BMD measurement. BMD of lumbar spine (L2–L4) and left hip (femoral neck and total hip) were measured by dual-energy X-ray absorptiometry (DEXA) with a Lunar DPX-IQ or Norland XR36 densitometer. The precision of either machine is ± 2%. As we did not always use the same brand of DEXA machine, changes in BMD were measured as percentage changes compared with baseline (Δ%). The reference population used was the machine manufacturer's female Japanese population database. The densitometer technician was blinded to the treatment allocations. The study was not powered to examine fractures as an outcome.

Statistical analysis. SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were expressed as mean ± SD or median with range. Parametric tests (one-way ANOVA) and nonparametric tests (Kruskal-Wallis and median tests) were used to analyze differences between the groups and BMD changes. A p value < 0.05 was considered statistically significant.

RESULTS

Ninety-eight patients were recruited into the study: 54 (55.1%) Chinese, 35 (35.7%) Malay, and 9 (9.2%) Indian patients. All patients had premenopausal ranges of serum follicle-stimulating hormone and luteinizing hormone. Demographic and clinical characteristics of patients are shown in Table 1. We have shown that there was no correlation between BMD and race, score on the SLE Disease Activity Index (SLEDAI), smoking, and self-reported calcium intake or exercise in this group of patients at baseline[15]. At baseline, 6 patients (6.1%) had osteoporosis, 41 (41.8%) had osteopenia, and 51 (52.0%) had normal BMD. The number of patients with osteoporotic, osteopenic, and normal BMD was similar in both centers: 3, 15, 28 and 3, 26, 23, respectively. At baseline, there were no prevalent vertebral fractures on plain radiograph.

Table 1. Demographic and clinical characteristics of subjects at baseline.

Feature	Calcium, n = 33	Calcitriol, n = 33	Alendronate, n = 32
Age, yrs	28.09 ± 6.49	30.97 ± 7.44	31.13 ± 8.44
Duration SLE, mo	24.0	48.0	36.0*
Cumulative CS, g	11.40	10.35	5.90**
L2-L4 BMD	1.05 ± 0.16	1.06 ± 0.14	0.98 ± 0.41
L Femoral neck BMD	0.89 ± 0.16	0.87 ± 0.15	0.88 ± 0.13
L Total hip BMD	0.93 ± 0.14	0.91 ± 0.09	0.89 ± 0.17

Values are mean ± 1 SD or median. There were no significant differences between the groups (Kruskal-Wallis and median tests). * Kruskal Wallis p = 0.59; ** median test p = 0.163. CS: corticosteroid; BMD: bone mineral density; L: left.

Seventy-seven patients (78.6%) completed the study (23 calcium alone, 27 calcitriol + calcium, 27 alendronate + calcium). Reasons for withdrawal were as follows: 9 patients become pregnant, 3 died from infective complications of SLE, 3 moved away and were unavailable for followup, 3 developed renal impairment, 1 sustained an osteoporotic fracture of her right tibia and fibula, 1 had a right total hip replacement for avascular necrosis of the hip and started alendronate postoperatively, and 1 patient started cyclosporine treatment for severe thrombocytopenia. The patient with fracture was osteopenic at baseline (lumbar spine T score –1.8, femoral neck T score –1.2) and sustained her fracture 2 months after randomization into the calcium-alone group.

Four patients in the calcium-alone group became pregnant, of whom 3 had spontaneous vaginal deliveries (SVD) and 1 had an emergency cesarean section for severe preeclampsia. There were 3 pregnant patients in the calcitriol + calcium group; 2 had SVD and 1 had an emergency cesarean section for severe preeclampsia. There were 2 pregnant patients in the alendronate + calcium group, both of whom had SVD. None of the newborns had clinically detectable congenital abnormalities at birth.

The BMD changes at the lumbar spine, femoral neck, and total hip are shown in Table 2. Compared to baseline, there was a significant mean percentage increase in BMD in the alendronate + calcium group, at both the lumbar spine (+2.69%) and total hip (+1.41%). There was no difference between the calcium-alone and the calcitriol + calcium group in that they maintained BMD over 2 years compared to baseline. However, the calcium-alone group lost a mean of 0.93% BMD at total hip compared with baseline. After 2 years, there was a difference of +2.2% between the calcium-alone and

Table 2. Percentage BMD changes.

Location	Calcium	Calcitriol	Alendronate
Lumbar spine			
At 1 year	1.09 ± 5.98	–0.66 ± 5.48	2.24 ± 5.13*
2 years	0.49 ± 4.90	–0.07 ± 5.24	2.69 ± 5.35*
Femoral neck			
At 1 year	0.25 ± 4.81	–1.15 ± 5.73	0.62 + 4.14
2 years	–0.18 ± 3.88	–0.94 ± 6.72	0.24 ± 4.40
Total hip			
At 1 year	–0.97 ± 5.28	–0.49 ± 4.21	0.73 ± 5.13
2 years	–0.93 ± 2.88*	–0.71 ± 4.38	4.41 ± 4.04*

Values are given as mean ± 1 SD. * $p < 0.001$ vs baseline.

alendronate + calcium groups, and +2.76% between the calcitriol + calcium and alendronate + calcium groups in lumbar spine BMD. At the total hip, there was a difference of +2.34% between the calcium-alone and alendronate + calcium groups, +2.12% between the calcitriol + calcium and alendronate + calcium groups. There were no significant differences in the mean percentage BMD change between the calcium-alone and calcitriol + calcium groups. There were also no significant differences between the mean cumulative CS dosages among the 3 groups at the time of BMD measurements (ANOVA for 1 year, $p = 0.70$, for 2 years, $p = 0.95$; data not shown).

The study medications were well tolerated with relatively few side effects that required additional drug therapy or withdrawal of treatment. Four patients had 5 isolated episodes of hypercalcemia during the course of the 2 years, all of whom were in the calcitriol + calcium group. The hypercalcemia resolved by the following visit with no need for dose adjustment.

DISCUSSION

It is well recognized that patients with SLE can have low BMD and higher fracture risks compared to the healthy population[16]. One definite predisposing factor is premature menopause due to the use of cyclophosphamide in the treatment of the disease, especially severe lupus nephritis. Less clear is the effect of CS therapy and of the disease itself, which may lead to excessive bone loss. In studies that examined only premenopausal women with SLE, there have been conflicting results with regard to the effect of CS on BMD[15,17-25]. Some demonstrated an adverse effect of CS on BMD[15,19,21,22,24,25], whereas others showed no adverse effect[17,18,20,23]. Nevertheless, it is recommended that patients taking prednisolone ≥ 5 mg daily, and anticipated to be on treatment 3 months or longer, should take measures to protect their bones[26].

In patients taking CS, calcium has been used extensively as the control in previous studies. Overall, the data in these studies with both pre- and postmenopausal women (almost exclusively in Caucasian populations) suggest that calcium by itself is probably insufficient to prevent bone loss in patients starting CS, but may be of benefit as treatment in patients taking longterm chronic low-dose CS[27]. There have been few prospective studies in healthy premenopausal women, but a metaanalysis concluded that calcium intake > 1000 mg daily will prevent 1% bone loss per year[28]. In a study on premenopausal Chinese women with SLE taking CS, those using calcium supplementation of 1 g daily had higher BMD at the lumbar spine (8.4%) and hip (9.2%) compared to those not taking supplements[23]. However, that was a cross-sectional study only. In a prospective study comparing calcium, calcitriol, and calcitonin over 1 year, the calcium-alone group lost significantly more BMD at the lumbar spine (–4.3%) compared to the calcium and calcitriol group (–1.3%). Both the calcium-alone and calcium and calcitriol groups lost similar, although not statistically different, amounts of BMD at the hip (–2.9%, –2.8%, respectively) and wrist (–3.0%, +0.8%)[4]. Our study supports the results[23] obtained in the Hong Kong Chinese in that while taking CS, patients in the calcium group who received 1000 mg calcium carbonate daily managed to preserve their BMD at the lumbar spine and femoral neck over 2 years and at the total hip over 1 year. This is in contrast to studies in Caucasian populations and may suggest a possible difference in calcium-handling in the Asian populations that merits further investigation.

In a metaanalysis, active vitamin D3 analogs have been shown to preserve lumbar spine BMD in patients taking CS more effectively than no-treatment or calcium-alone, with a pooled effect size of 0.35 (95% CI 0.18, 0.52)[29]. There are fewer data for hip BMD. Our study confirms the protective effect of calcitriol + calcium on lumbar spine BMD, but, in contrast to the study by Sambrook and colleagues[4], we also observed some protection of hip BMD with the same regime.

Bisphosphonates in general are the class of agents most effective in improving lumbar spine BMD of patients taking CS compared with vitamin D or calcium alone[30]. Alendronate 10 mg daily was shown to increase lumbar spine and femoral neck BMD by 2.9% and 1%, respectively, compared to a decrease of 0.4% and 1.2%, respectively, in the placebo group over 48 weeks in patients receiving CS therapy[10]. There has been only one previous study of once-weekly alendronate in patients on CS treatment, and it was in children with a variety of chronic illnesses[31]. In that study, once-weekly alendronate led to an increase in volumetric bone density at the lumbar spine and suppressed bone resorption, as expected.

There have been very few comparative studies with different agents in CS-induced osteoporosis. Sambrook and colleagues compared calcitriol, vitamin D (ergocalciferol), and alendronate (10 mg daily) in a group of patients taking CS over 2 years[12]. They found a significant increase in lumbar spine BMD (+5.9%) in the alendronate group compared to the calcitriol and ergocalciferol groups. However, there was no difference of the femoral neck BMD measures among the 3 groups. Another study compared alfacalcidol, an active vitamin D3 analog, and alendronate 10 mg daily in patients start-

ing CS[13]. After 18 months, there was a 2.1% increase in lumbar spine BMD, 1.4% increase in femoral neck BMD, and 0.8% increase in total hip BMD compared to 1.9%, 2.0%, and 2.2% decreases, respectively, in the alfacalcidol groups. In both these studies, the majority of the female patients were postmenopausal. The diseases for which CS were given were also quite varied.

Our study is unique in several aspects. We studied only patients with SLE taking CS, which reduced the confounding effects of different diseases on BMD. In addition, they were all premenopausal, which eliminated the effect of accelerated postmenopausal bone loss. Finally, we used the once-weekly dose of alendronate, which had not previously been studied in CS-induced osteoporosis. Thus, in premenopausal SLE patients taking CS, once-weekly alendronate + calcium will significantly increase BMD compared to calcium alone or calcitrol + calcitriol over 2 years. However, both calcium alone and calcitriol + calcium preserved BMD in premenopausal patients with SLE, apart from a decrease in total hip BMD in the calcium-alone group at 2 years.

In summary, premenopausal women with SLE taking CS should be considered for osteoporosis prophylaxis.

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