Etidronate Prevents High Dose Glucocorticoid Induced Bone Loss in Premenopausal Individuals with Systemic Autoimmune Diseases

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ABSTRACT. ***Objective.*** To assess the efficacy of etidronate and alfacalcidol in preventing glucocorticoid induced bone loss in premenopausal women and men starting high dose glucocorticoid therapy.

Methods. Premenopausal women (n = 16) and men (n = 5) who had just developed autoimmune diseases, and who agreed to use high dose glucocorticoid therapy for the first time, were randomized to receive alfacalcidol (1 µg/day) alone (alfacalcidol group, n = 11); or alfacalcidol (1 µg/day) and intermittent cyclical etidronate (200 mg/day for 14 days), given for 4 cycles (combined group, n = 10). They were treated with these medications as well as high dose glucocorticoids for 12 months.

Results. In the alfacalcidol group the percentage changes in bone mineral density (BMD) of the lumbar spine after 6 and 12 mo of therapy were –9.6 ± 0.6% and –10.3 ± 1.0%, respectively. However, in the combined group the percentage changes in lumbar spine BMD after 6 and 12 mo were –3.8 ± 1.3% and –4.5 ± 2.1%. The percentage lumbar spine bone loss rate in the combined group was significantly lower than in the alfacalcidol group at both 6 and 12 mo. After 12 mo the percentage change in femoral neck BMD was increased 2.3 ± 1.5% in the combined group and was decreased 2.5 ± 2.4% in the alfacalcidol group; this difference was also statistically significant. There were no significant differences in metabolic bone markers between the groups during the study.

Conclusion. The results suggest that etidronate could prevent high dose glucocorticoid induced bone loss in premenopausal individuals with systemic autoimmune diseases. (J Rheumatol 2004; 31:163–6)

Key Indexing Terms:
AUTOIMMUNE DISEASE ETIDRONATE GLUCOCORTICOID OSTEOPOROSIS

High dose glucocorticoid therapy is prescribed to patients with severe autoimmune disease and posttransplantation, but could cause secondary osteoporosis. The amount of bone loss depends on the cumulative steroid dose, and the rate of bone loss is highest in the first 3 to 6 months of therapy[1,2]. Further, the incidence of vertebral fracture in glucocorticoid induced osteoporosis, even if loss of bone density is minimal, is higher than in primary osteoporosis[3]. Although recent studies indicate that bisphosphonates prevent glucocorticoid induced osteoporosis[4], the subjects of these studies consisted of patients who had already received glucocorticoids[2,5,6]. Although most physicians recognize that postmenopausal women have a greater risk of fracture during glucocorticoid treatment, most patients with autoimmune disease requiring high dose glucocorticoids are premenopausal. However, there is little information on the primary prevention of bone loss induced by high dose glucocorticoid therapy in premenopausal women. We performed this preliminary study to determine the effects of concomitant intermittent cyclical use of etidronate, a bisphosphonate available in Japan, and alfacalcidol in patients with normal bone density starting high dose glucocorticoid therapy in preventing glucocorticoid induced bone loss.

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MATERIALS AND METHODS

Subjects. The inclusion criteria required that premenopausal women or men (aged 17–50 yrs) had a systemic autoimmune disease requiring treatment with high dose glucocorticoids (minimum starting dose 30 mg/day prednisolone or equivalent dose of a methylprednisolone derivative), and that this treatment be expected to continue for at least 12 months, with the daily dose after 6 months being not less than 7.5 mg/day. In this study no patient had taken glucocorticoids in the past. Patients with rheumatoid arthritis or renal dysfunction, or who were pregnant, nursing or of childbearing potential, or who had been receiving drugs known to affect bone metabolism were excluded. This was a 12-month, single-center, prospective open controlled study to evaluate the efficacy and safety of etidronate and alfacalcidol for preventing bone loss by high dose glucocorticoid therapy. The study was approved by the ethics committee of the University of Occupational and Environmental Health. This study was performed between 1999 and 2002.

Procedures. Premenopausal women (n = 16) and men (n = 5) who had just developed autoimmune diseases such as systemic lupus erythematosus

(SLE), and who agreed to use high dose glucocorticoid therapy (30–60 mg/day) including steroid pulse therapy for the first time were recruited to the study. They were assigned randomly into 2 groups: those given alfacalcidol (1 µg/day) alone (the alfacalcidol group; 9 women and 2 men); and those given alfacalcidol (1 µg/day) and intermittent cyclical etidronate (200 mg/day for 14 days), given for 4 cycles (the combined group; 7 women and 3 men). Assignment to each group was by a simple randomization. After patients were numbered in order, the odd and even numbers were assigned to the alfacalcidol group and the combined group, respectively. Each patient received a calcium supplement (600 mg/day). The alfacalcidol group comprised 9 women and 2 men, 7 of whom were being treated for SLE, 2 for mixed connective tissue disease (MCTD), one for Sjögren's syndrome, and one for hypersensitivity vasculitis. The combined group comprised 7 women and 3 men, 7 being treated for SLE, 2 for dermatomyositis, and one for MCTD.

We chose etidronate because it was the only bisphosphonate permitted at that time in Japan. We advised premenopausal women to practice birth control in consideration of exacerbation of disease at delivery. They were not allowed to use birth control medication during the study.

Bone mineral density (BMD) of the lumbar spine (L2–L4) and femoral neck was measured by dual energy radiograph absorptiometry (DEXA) using a Hologic QDR 2000 (Hologic, Bedford, MA, USA) at baseline and after 6 and 12 months of the therapy. The presence of vertebral fractures was evaluated by lateral radiograph of thoracic and lumbar spine. Early morning blood and 2 hour fasting urine samples were collected for metabolic bone markers at baseline and after 6 and 12 months of therapy. Serum bone-specific alkaline phosphatase (bone-ALP), a marker of bone formation, was measured by an enzyme immunoassay (Osteolinks, Sumitomo Pharmaceuticals, Tokyo, Japan). Urinary deoxypyridinoline, a sensitive marker of bone resorption, was measured by high performance liquid chromatography (Mitsubishi Kagaku Bio-Clinical Laboratories, Tokyo, Japan). All samples were stored at –80°C until assayed; measurements were made simultaneously. The DEXA and radiographs and metabolic bone markers were evaluated by assessors who were blinded to the treatment group. We evaluated differences between the 2 groups 6 and 12 months later, including the presence of vertebral fractures, BMD of lumbar spine (L2–L4) and femoral neck, metabolic bone markers, and clinical features.

Statistical analysis. The primary efficacy criteria were the percentage changes in BMD and metabolic bone markers after 6 and 12 months of therapy compared with baseline in the 2 groups. The baseline value was considered as 100% BMD and metabolic bone markers for each patient. All results were expressed as the mean ± standard error. Differences between the 2 groups were analyzed by Mann-Whitney U test. A p value < 0.05 was considered significant.

RESULTS

Of the 21 patients who were randomized to treatment, one from the alfacalcidol group died from the underlying disease. The subjects' baseline characteristics, including age, height, weight, BMD of lumbar spine and femoral neck, and various metabolic bone markers, were not significantly different between the 2 groups (Table 1). The BMD measures of lumbar spine and femoral neck were all within the normal range at baseline. Table 2 shows the equivalent glucocorticoid dose at baseline and after 6 and 12 months. There was no significant difference between the groups in the glucocorticoid dose at any time point during the study. No patient in either group developed vertebral fracture during the 12 month study. The percentage changes in BMD of the lumbar spine and femoral neck at 6 and 12 months are shown in Figure 1. During the first 6 months of therapy, the mean lumbar spine BMD in the alfacalcidol group decreased markedly from an initial value of 0.99 g/cm^2 to 0.89 g/cm^2, a decrease of 9.6 ± 0.6% from baseline. In contrast, the decrease of lumbar spine BMD in the combined group amounted to only 3.8 ± 1.3%. The percentage change in lumbar spine BMD after 12 months of therapy was –10.3 ± 1.0% in the alfacalcidol group compared with –4.5 ± 2.1% in the combined group. The difference in the lumbar spine bone loss rate between the groups was statistically significant at both 6 and 12 months. Further, the mean femoral neck BMD increased after 6 and 12 months of treatment in the combined group, whereas it decreased in the alfacalcidol group. After 12 months the percentage change in femoral neck BMD was increased 2.3 ± 1.5% in the combined group, and was decreased 2.5 ± 2.4% in the alfacalcidol group, a statistically significant difference.

On the other hand, there were no significant differences in the metabolic bone markers between the 2 groups. Although not significant, the concentration of serum bone-ALP had a tendency to increase after 6 and 12 months of treatment in both groups, compared with baseline. The percentage increase in serum bone-ALP from the respective baseline value in the combined group was lower than in the alfacalcidol group (Figure 2). Although not significant, the level of urinary deoxypyridinoline showed a tendency to increase after both 6 and 12 months of treatment in the alfacalcidol group, whereas it decreased in the combined group (Figure 2).

Table 1. Baseline characteristics of the patients. Data are mean ± SE.

Characteristic	Alfacalcidol, n = 11	Alfacalcidol + Etidronate, n = 10	p
Age, yrs	30.6 ± 3.8	33.8 ± 3.2	0.76
Height, cm	159.4 ± 2.0	162.8 ± 2.4	0.50
Weight, kg	50.0 ± 1.8	56.4 ± 4.1	0.16
BMD, g/cm^2			
Lumbar spine (L2–L4)	0.99 ± 0.04	1.01 ± 0.04	0.50
Femoral neck	0.75 ± 0.02	0.82 ± 0.04	0.15
Serum bone alkaline phosphatase, U/L	12.9 ± 1.1	14.0 ± 2.0	0.97
Urinary deoxypyridinoline, nmol/mmol creatinine	7.0 ± 1.4	6.8 ± 1.1	0.91

BMD: bone mineral density.

Table 2. Equivalent prednisolone dose (mg/day) over the period of the study.

	Alfacalcidol, n = 11	Alfacalcidol + Etidronate, n = 10	p
Baseline			
Mean ± SE	39.0 ± 4.6	48.0 ± 3.9	0.12
Range	30.0–60.0	30.0–60.0	
Median	30.0	50.0	
6 months			
Mean ± SE	30.4 ± 1.7	43.1 ± 6.6	0.17
Range	25.0–40.0	15.0–60.0	
Median	27.5	37.5	
12 months			
Mean ± SE	23.2 ± 1.6	28.0 ± 3.9	0.48
Range	7.5–30.0	10.0–45.0	
Median	22.5	25.0	

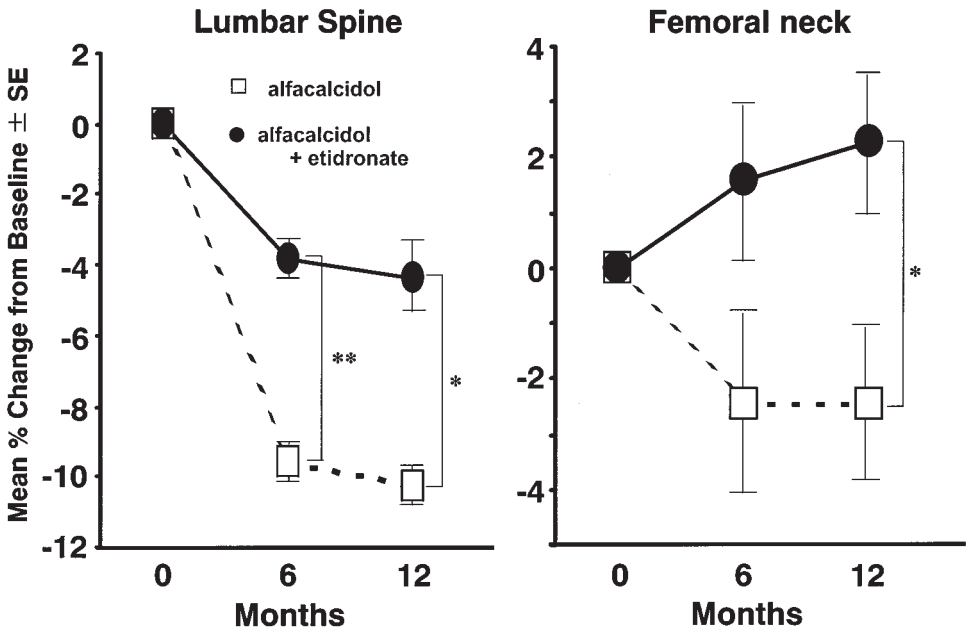

Figure 1. Mean (± SEM) percentage changes relative to baseline in BMD in patients treated with alfacalcidol or alfacalcidol and etidronate combination. *p < 0.05, **p < 0.001.

No adverse events related to etidronate or alfacalcidol treatment were reported from either group.

DISCUSSION

Although glucocorticoids are used to treat various autoimmune and allergic diseases, they often induce bone loss and are high risk for bone fractures. Recent studies indicate that bisphosphonates are effective against glucocorticoid induced osteoporosis, but little is known about the initial preventive effects of bisphosphonates in premenopausal individuals with high dose glucocorticoid therapy.

We documented the following 4 effects for alfacalcidol and etidronate. First, despite supplementation with an activated form of vitamin D with commencement of high dose glucocorticoid therapy, the marked bone loss occurred very rapidly — within the first 6 months in premenopausal women and men with systemic autoimmune diseases such as SLE. Further, the vitamin D supplement was not helpful at this dosage, yet it is one of the recommendations for people starting steroids. Unfortunately, there are still physicians who are unaware that men and premenopausal women are at great risk for glucocorticoid induced osteoporosis[7].

Second, intermittent administration of etidronate with the commencement of high dose glucocorticoid was well tolerated and primarily prevented glucocorticoid induced bone loss. Although this study was not powered to assess the effect of etidronate on fracture rate, a progressive and marked decrease of BMD with time was observed in

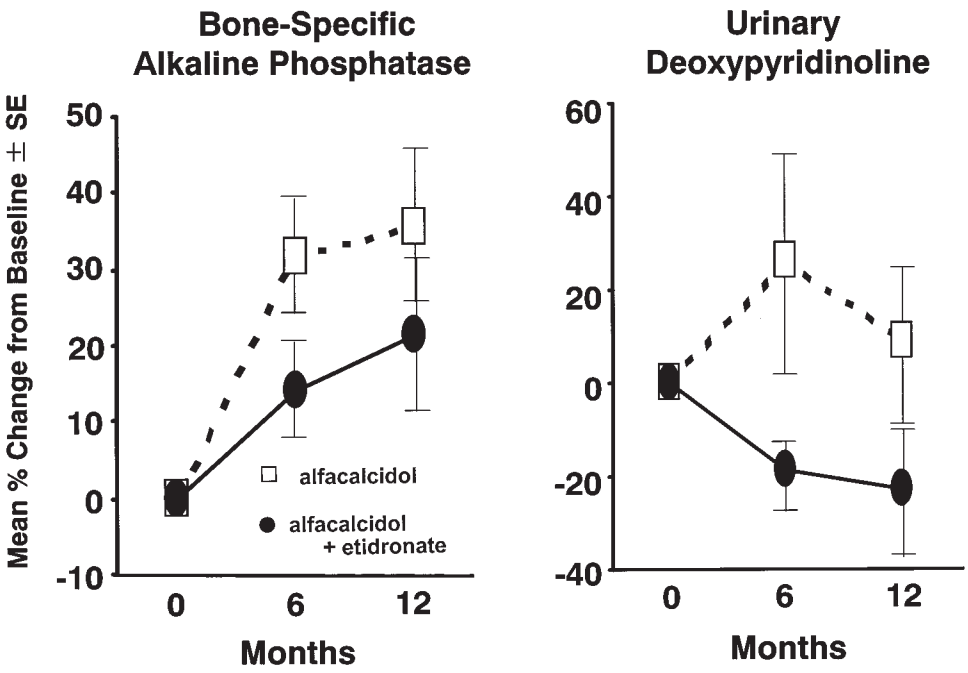

Figure 2. Mean (± SEM) percentage changes relative to baseline in serum bone-specific ALP and urinary deoxypyridinoline in patients treated with alfacalcidol or alfacalcidol and etidronate combination.

patients treated with alfacalcidol only. Although not significantly different, there was a trend to increased dose of glucocorticoid in the combined group, suggesting that the real benefit might be greater in the combination. Moreover, longterm continued high dose glucocorticoid therapy could further increase the risk of fracture over time. In this study, because the majority of patients were young women of premenopausal age and their BMD was within the normal range before glucocorticoid therapy, prevention of glucocorticoid induced bone loss is extremely important. We therefore propose that preventive therapy using bisphosphonates should be considered for patients commencing high dose glucocorticoid therapy even in those with normal bone density.

Third, both serum bone-ALP and urinary deoxypyridinoline levels were markedly increased relative to baseline values in patients treated with high dose glucocorticoids and alfacalcidol, whereas the increases in these values were suppressed by administration of etidronate. The results suggest that bisphosphonates could prevent glucocorticoid induced osteoporosis by inhibiting bone loss with high bone turnover.

Fourth, we chose etidronate, which is a first-generation bisphosphonate, in this study, because it was the only bisphosphonate permitted at that time in Japan. The dose of etidronate (200 mg cyclically) we used in this study was less than that used by physicians in other countries. This lower dose of etidronate was helpful — perhaps more cost-effective than the second-generation — but also perhaps still suboptimal for lumbar spine.

Further studies with more patients and longterm followup are necessary to establish the effects of bisphosphonate on high dose glucocorticoid induced osteoporosis and risk of fractures in premenopausal individuals. Our preliminary findings may have implications for the design of future treatments using these bisphosphonates, especially for high dose glucocorticoid induced osteoporosis, aimed at prevention of reduced BMD by inhibiting high bone turnover.

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