Alendronate Protects Premenopausal Women from Bone Loss and Fracture Associated with High-dose Glucocorticoid Therapy

YOSUKE OKADA, MASAO NAWATA, SHINGO NAKAYAMADA, KAZUYOSHI SAITO, and YOSHIYA TANAKA

ABSTRACT. ***Objective.*** We assessed the efficacy of bisphosphonate in premenopausal women (n = 47) commencing high-dose glucocorticoid (GC) therapy in protection against induced bone loss and bone fracture.

Methods. Subjects had just developed systemic autoimmune diseases and were randomized to be treated with 1 mg/kg/day prednisolone and alfacalcidol 1 μg/day alone (alfacalcidol group; n = 22), or prednisolone and alfacalcidol 1 μg/day with alendronate 5 mg/day (alendronate group; n = 25), each for 18 months.

Results. The percentage changes in lumbar spine bone mineral density (BMD) after 6 months of the therapy were –10.5% ± 0.8% in the alfacalcidol group, but only –2.1% ± 1.2% in the combined group. The rate of bone loss in the lumbar spine was significantly lower in the combined group than in the alfacalcidol group at 6 months. At 12 months of treatment, the percentage change in lumbar spine BMD was increased by 1.7% ± 1.4% in the combined group, but decreased by 9.9% ± 1.9% in the alfacalcidol group; the difference was significant. Bone fracture occurred at 12 months or later in 4 patients of the alfacalcidol groups, but not in the combined group, even at up to 18 months.

Conclusion. Our results indicate that alendronate with alfacalcidol can maintain BMD and protects against high-dose GC-induced bone loss and bone fracture. (First Release Oct 1 2008; J Rheumatol 2008;35:2249–54; doi:10.3899/jrheum.080168)

Key Indexing Terms:
AUTOIMMUNE DISEASE ALENDRONATE GLUCOCORTICOID
OSTEOPOROSIS WOMEN

Glucocorticoid (GC) has potent antiinflammatory and inhibitory actions on immune cells, and is widely used for treatment of various diseases. Despite the benefits of GC treatment of systemic connective tissue diseases, including improvement in prognosis, there is increased awareness of the many adverse effects of longterm use of GC. Administration of synthetic GC induces an imbalance in internal cortisol levels and leads to significant side effects, including diabetes, weight gain, hyperlipidemia, skin thinning, opportunistic infection, cataract, hypertension, psychoses, and osteoporosis. Among these complications, osteoporosis is an unavoidable, serious side effect of GC and is particularly harmful in postmenopausal women[1].

GC-induced osteoporosis progresses more rapidly and more markedly than postmenopausal osteoporosis, and its associated bone fracture rate is very high[2-6]. The bone fracture risk excluding the vertebrae increases sharply in patients taking ≥ 20 mg/day oral prednisolone[7,8]. Since bone mass decreases rapidly in a dose-dependent manner in response to GC administered in patients with connective tissue diseases and develops even in young patients, guidelines for primary prevention of this problem are needed[2-6,9,10]. Although a therapeutic policy is included in the guidelines for GC-induced osteoporosis published in each country, evidence for the therapeutic effect and primary prevention of high-dose GC-induced osteoporosis by bisphosphonate is not sufficient. We have reported the protective effects of etidronate against GC-induced osteoporosis in patients with first onset of systemic connective tissue diseases[11].

In this study, we administered alfacalcidol (active form of vitamin D_3), with or without alendronate, concomitantly with the initiation of GC therapy in patients who were scheduled for massive-dose GC treatment, and investigated prophylactic effects of alendronate on loss of bone mass and bone fracture, compared to subjects taking alfacalcidol alone.

MATERIALS AND METHODS

Subjects. The inclusion criteria stipulated that premenopausal women (aged 17–47 yrs) must be GC-naive and have a systemic autoimmune disease requiring treatment with high-dose GC (starting dose of prednisolone ≥ 1 mg/kg/day), and that this treatment was expected to continue for at least 12 months with the daily dose after 6 months being not less than 7.5 mg/day.

From the First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan.

Y. Okada, MD; M. Nawata, MD; S. Nakayamada, MD; K. Saito, MD; Y. Tanaka, MD, First Department of Internal Medicine.

Address reprint requests to Dr. Y. Tanaka, First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka Yahatanishi-ku, Kitakyushu, 807-8555 Japan. E-mail: tanaka@med.uoeh-u.ac.jp

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Patients with rheumatoid arthritis, renal dysfunction, pregnancy, lactation, or of childbearing potential or those who were taking medications known to affect bone metabolism were excluded. This was an 18-month, single-center, prospective, open-controlled study to evaluate the efficacy and safety of alendronate combined with alfacalcidol in prevention of bone loss caused by high-dose GC therapy. The study was approved by the ethics committee of the University of Occupational and Environmental Health, Japan, and each patient provided a signed consent form.

Methods. Premenopausal women (n = 47) who had just been diagnosed with autoimmune disease such as systemic lupus erythematosus, and who agreed to use high-dose GC therapy (> 1 mg/kg/day) for the first time were recruited to the study. They were assigned randomly into one of 2 groups: alfacalcidol (1 mg/day) alone (alfacalcidol group; 22 women); or combination of alfacalcidol (1 mg/day) and alendronate (5 mg/day) (alendronate group; 25 women). Assignment to each group was based on simple randomization. Each patient received a calcium supplement (600 mg/day) during the study. Autoimmune diseases in the 2 groups are described in Table 1. We advised premenopausal women to practice birth control based on possible exacerbation of disease at delivery, and part of the consent agreement included refraining from the use of birth control pills during the study.

The bone mineral density (BMD) of the lumbar spine (L2–L4) was measured by dual-energy radiograph absorptiometry (DEXA) using a Hologic QDR 2000 instrument (Hologic, Bedford, MA, USA) at baseline and after 6, 12, and 18 months of therapy. The presence of vertebral fractures was evaluated by lateral radiographs of the thoracic and lumbar spine every 6 months and every time fracture was suspected. Early morning blood and 2-hour fasting urine samples were collected for metabolic bone markers at baseline and after 6, 12, and 18 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 with 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, radiographs, and metabolic bone markers were evaluated by investigators blinded to the treatment group. The 2 groups were compared at 6, 12, and 18 months after initiation of treatment, with respect to clinical features, incidence of vertebral fractures, BMD of the lumbar spine (L2–L4), and metabolic bone markers.

Statistical analysis. The primary treatment efficacy criterion was the percentage change in BMD and metabolic bone markers after 6, 12, and 18 months of therapy compared with the baseline. Baseline (pretreatment) values of BMD and metabolic bone markers of each patient were considered 100% and the values at the indicated time periods as percentages of the baseline. All results were expressed as mean ± SEM. Differences between 2 groups were analyzed by the Mann-Whitney U test. A p value < 0.05 was considered significant.

Table 1. Autoimmune disease in 2 treatment groups.

Alfacalcidol group, n = 22	
SLE	17
MCTD	4
Other	1
Alendronate group, n = 25	
SLE	16
Dermatomyositis	5
MCTD	3
Other	1

SLE: systemic lupus erythematosus, MCTD: mixed connective tissue disease.

RESULTS

The 47 women patients enrolled in this study had a mean age of 34.3 ± 3.5 years (range 17–47) and were randomized to treatment. Thirty-three patients were treated daily with prednisolone and alfacalcidol with or without alendronate for a period of 18 months. Four patients in the alfacalcidol group were excluded during the 18 months because of bone fractures. Ten patients were withdrawn, including 2 patients who died from the underlying disease, and 8 patients discontinued treatment due to adverse effects, mainly digestive symptoms in the alendronate group.

Patients' baseline characteristics including age, height, body weight, baseline lumbar BMD values, and various metabolic bone markers were not significantly different between the 2 groups (Table 2). BMD measures of lumbar spine and bone metabolism markers were all within normal ranges before GC administration in the 2 groups. Of course, there were no patients with prevalent fractures. For all subjects, the mean dose of prednisolone was ≥ 40 mg/day at the initiation phase, ≥ 20 mg/day after 6 months, and ≥ 10 mg/day after 12 months. There was no significant difference between the groups in the GC dose at any timepoint during the study (Table 3).

The percentage changes in BMD of the lumbar spine at 6, 12 and 18 months are shown in Figure 1. During the first

Table 2. Baseline characteristics of patients. There were no significant differences in baseline characteristics between the 2 groups. Data are mean ± SEM.

Characteristic	Alfacalcidol	Alfacalcidol + Alendronate
n	22	25
Age, yrs	31.4 ± 1.8	32.5 ± 1.3
Height, cm	158.6 ± 1.2	157.0 ± 1.3
Weight, kg	52.1 ± 0.9	53.4 ± 1.2
Baseline lumbar BMD (L2-L4), g/cm^2	1.01 ± 0.02	1.00 ± 0.02
Baseline bone ALP, U/I	14.2 ± 0.6	14.6 ± 0.5
Baseline urinary deoxypyridinoline, nmol/mmol creatinine	7.7 ± 0.4	7.8 ± 0.3
Prevalent fracture	0	0
Parental history of fracture	2	3

BMD: bone mineral density, ALP: alkaline phosphatase.

Table 3. The mean (± SE) daily steroid dose (prednisolone), mg/day. There were no significant differences in the mean daily steroid dose between the 2 groups.

	Alfacalcidol, n = 16	Alfacalcidol + Alendronate, n = 17
Start	42.3 ± 2.9	44.0 ± 2.5
6 months	23.2 ± 1.6	24.6 ± 1.5
12 months	11.8 ± 1.1	13.4 ± 1.1
18 months	8.6 ± 1.4	8.2 ± 0.9

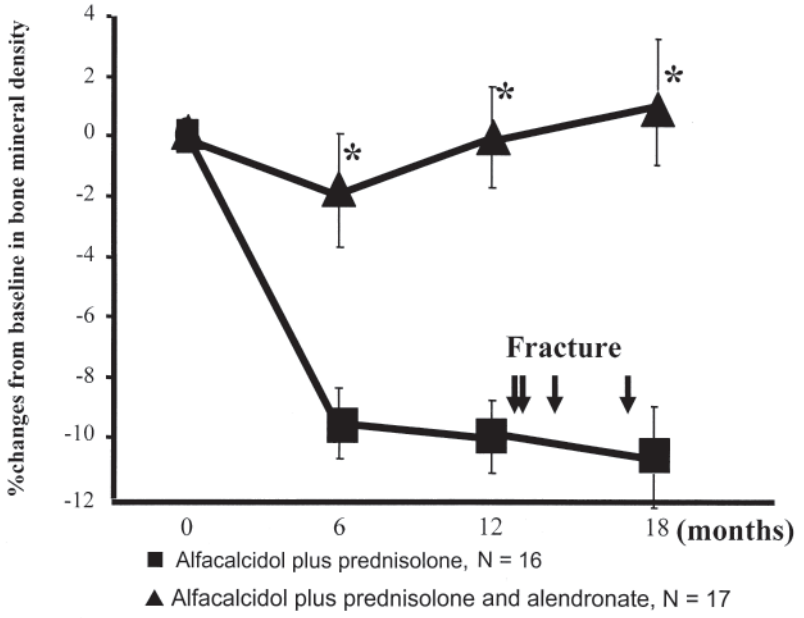

Figure 1. Mean (± SEM) percentage changes in BMD relative to baseline in patients treated with alfacalcidol plus prednisolone (N = 16), or alfacalcidol plus prednisolone and alendronate (N = 17). Arrows indicate bone fractures in 4 patients in the alfacalcidol group. *p < 0.001, compared with alfacalcidol plus prednisolone group.

6 months of therapy, although the lumbar spine BMD in the alfacalcidol group decreased markedly from an initial value, BMD values in the alfacalcidol with alendronate group decreased only slightly. The percentage changes in lumbar spine BMD after 6 months of therapy were –10.5% ± 0.8% in alfacalcidol group, but only –2.1% ± 1.2% in the combined treatment group. Further, the mean lumbar BMD appeared to increase after 6 and 18 months of treatment in the combined group, whereas it decreased in the alfacalcidol group. At 12 months of treatment, the percentage change in lumbar spine BMD was increased by 1.7% ± 1.4% in the combined group but decreased by 9.9% ± 1.9% in alfacalcidol group. The difference in the lumbar spine bone loss rate between the groups was statistically significant at 6, 12, and 18 months.

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 12 and 18 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 that in the alfacalcidol group (Figure 2). Although not significant, the level of urinary deoxypyridinoline showed a tendency to increase after 6, 12, and 18 months of treatment in the alfacalcidol group, whereas it decreased in the combined group (Figure 2).

Four patients developed vertebral fracture during the 12–18 month period in the alfacalcidol group, as diagnosed by spinal radiographs (Figure 1 and Table 4). However, no fractures were noted up to 18 months in the alendronate group. Table 4 shows patient profiles of the bone fractures; all fractures occurred after 13 months of treatment in the alfacalcidol group and were observed in women with an average age of 38.5 ± 3.0 years and with lumbar BMD of 0.81 ± 0.02 g/cm^2.

To investigate the background factors associated with bone fracture (Table 5), we compared the age, lumbar BMD, and bone metabolism markers after 12 months of treatment in patients with (n = 4) and without fracture (n = 33 patients). Significant differences were noted in lumbar BMD and percentage changes in lumbar BMD between the 2 groups. Lumbar BMD at 12 months of GC therapy was 0.81 ± 0.02 g/cm^2 in the fracture group, which was within the normal range. However, the value was significantly lower than that of patients without fracture (0.93 ± 0.03 g/cm^2). Further, the percentage change in lumbar BMD from baseline to 12 months after GC therapy was –12.8% ± 1.7% (range –8.5% to –16.4%) and –4.7% ± 0.9% (range –2.2% to –11.3%) for the groups with and without fracture, respectively, showing a significant acute decrease in bone mass in the group with fracture. Also, it is noteworthy that 6 of 33 patients in the nonfracture group had a parental history of fracture, whereas none of 4 in the fracture group did.

Finally, the lumbar BMD measures were followed up until 18 months in 3 patients who discontinued alendronate due to digestive symptoms after 6 months of treatment, as shown in Figure 3. Interestingly, the patients maintained above-normal lumbar BMD values and had no fractures by 18 months after the therapy. These results suggest that the

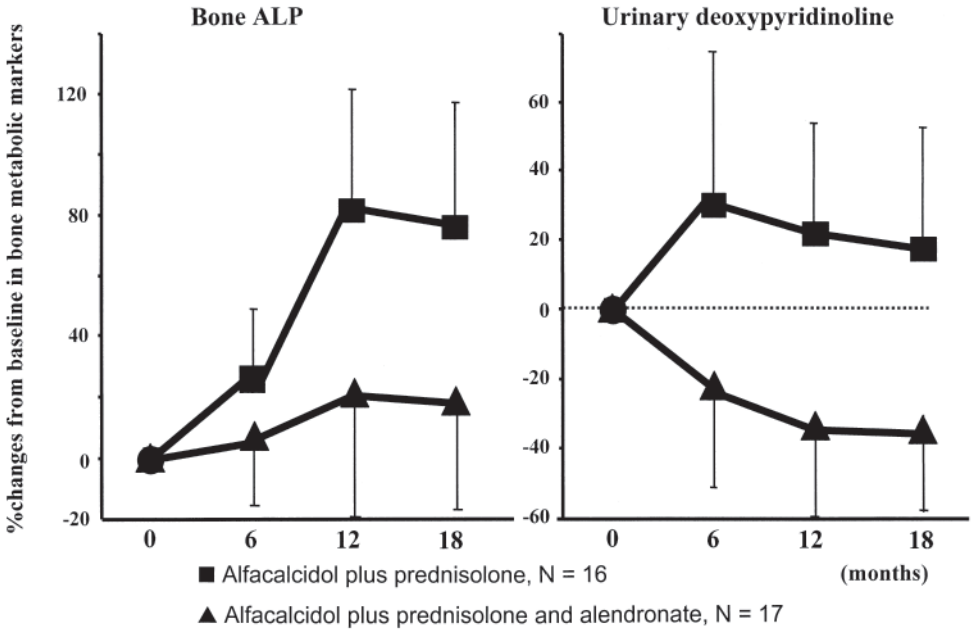

Figure 2. Mean (± SEM) percentage changes relative to baseline in serum bone-specific alkaline phosphatase (ALP) and urinary deoxypyridinoline in patients treated with alfacalcidol plus prednisolone (N = 16), or alfacalcidol plus prednisolone and alendronate (N = 17).

Table 4. Four women in the alfacalcidol group experienced fracture after 12 months with steroid therapy.

Age, yrs	Time to Fracture, mo	Location	Lumbar BMD	Bone ALP	Urine DPD
34	13	L1	0.85	20.1	27.2
38	13	Th12	0.77	19.3	16.8
35	14	L1, 2	0.83	17.8	15.2
47	17	Th12, L1	0.79	22.6	24.1
Mean ± SD 38.5 ± 3.0	14.3 ± 0.9		0.81 ± 0.02	19.8 ± 1.1	20.8 ± 2.9

BMD: bone mineral density, ALP: alkaline phosphatase, DPD: deoxypyridinoline.

Table 5. Characteristics of patients who did and did not develop bone fracture during the study. Data are mean ± SEM.

Characteristic	Fracture	Nonfracture
n	4	33
Age, yrs	38.5 ± 3.0	37.2 ± 2.3
Lumbar BMD, g/cm^2	0.81 ± 0.02	0.93 ± 0.03*
Change in lumbar BMD, % change	–12.8 ± 1.7	-4.7 ± 0.9*
Bone ALP, U/I	19.8 ± 1.1	14.4 ± 3.7
Change in bone ALP, % change	89.2 ± 0.6	40.8 ± 9.6
Urinary deoxypyridinoline, nmol/mmol creatinine	20.8 ± 2.9	11.4 ± 8.3
Change of urinary deoxypyridinoline, % change	21.3 ± 3.8	12.8 ± 4.5
Parental history of fracture	0	6

*p < 0.05 compared with the fracture group. BMD: bone mineral density, ALP: alkaline phosphatase.

combined use of alendronate and alfacalcidol for at least the initial 6 months, commencing with high-dose GC, could have a prophylactic efficacy for the GC-induced bone loss and fracture risk, even though this was a very small study.

DISCUSSION

The clinical features of GC-induced osteoporosis are as follows: (1) reduction of bone mass is dependent on the GC dose, and is especially marked during the early phase of

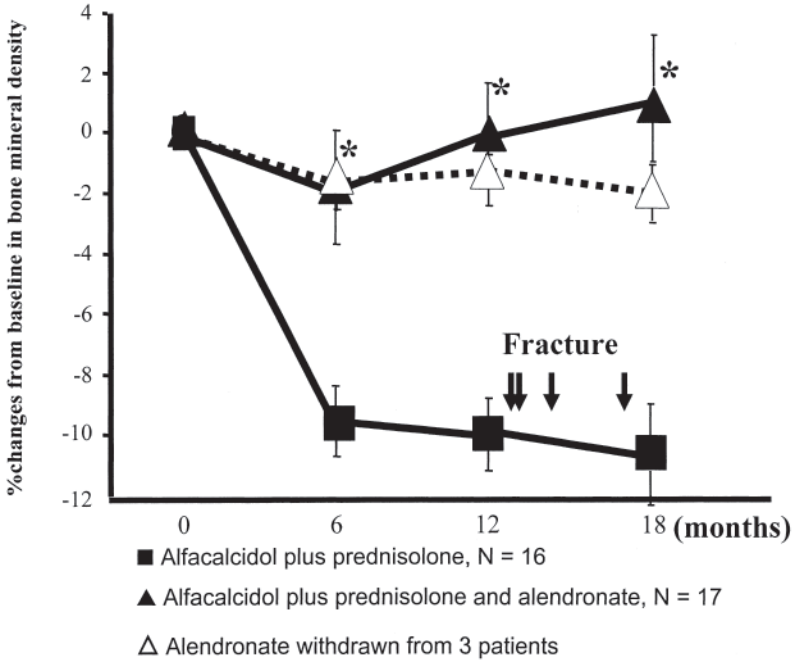

Figure 3. Mean (± SEM) percentage changes in BMD relative to baseline in patients treated with alfacalcidol plus prednisolone (N = 16), or alfacalcidol plus prednisolone and alendronate. Patients were treated with alfacalcidol plus prednisolone and alendronate for 18 months (N = 17). Alendronate was withdrawn from 3 patients at Month 6, but they were followed for 12 more months. Arrows indicate bone fractures in 4 patients. *$p < 0.001$ compared with alfacalcidol plus prednisolone group.

treatment (3–6 months); (2) secondary osteoporosis is inevitable when a large dose of GC is used, and the bone mass decreases most rapidly in the vertebral bodies and femoral neck within 1 year after initiation of therapy; (3) although the decrease in BMD is minimal, the risk of vertebral-body fracture is markedly higher than in primary osteoporosis; and (4) the fracture-preventive effect of bisphosphonate is more pronounced than that for postmenopausal osteoporosis[2-7]. Further, the mean age of patients with GC-induced osteoporosis is often lower than that of patients with postmenopausal osteoporosis, and the incidence of new vertebral-body fracture is high despite the high bone mass in this age group[12-14]. Based on our results, the combined use of alendronate with alfacalcidol has a prophylactic efficacy on GC-induced osteoporosis, especially in patients who are scheduled to be treated with high-dose GC, by maintaining bone mass and perhaps decreasing bone turnover during GC-induced bone metabolism.

Despite supplementation with an activated form of vitamin D at the commencement of high-dose GC therapy, bone loss developed rapidly within the first 6 months in "premenopausal" women with systemic autoimmune diseases in our study. Many studies and reviews have indicated that supplementation with vitamin D and calcium is not sufficient to retard loss of bone mass and fracture in GC-induced osteoporosis, compared to use of amino-bisphosphonate, although Reginster, *et al* reported that alfacalcidol could prevent GC-induced bone loss from the lumbar spine[15-19]. With regard to the higher rate of bone loss in the alfacalcidol group in our study, we consider that the rate of bone loss observed in the alfacalcidol group in the 6 months of this study depends upon the high dose of GC for the following reasons: (1) we used a higher dose of GC (1 mg/kg/day) for the treatment of systemic connective tissue diseases in the first 6 months than that used in previous studies; (2) it is well known that bone loss induced by GC is correlated with the dose of GC; (3) since the baseline value of BMD was within a normal range due to the premenopausal women in this study, the rate of bone loss might be greater than that in previous reports.

In this study, 4 patients developed vertebral fracture during the 12–18 month period in the alfacalcidol group, whereas no fractures were noted in the alendronate with alfacalcidol group. The lumbar BMD at 12 months of GC therapy was higher in the fracture group (0.81 ± 0.02 g/cm^2) than in the nonfracture group (0.93 ± 0.03 g/cm^2), but the values were still within the normal range. In contrast, the percentage change in the lumbar BMD from baseline was significantly higher in the fracture group (–12.8% ± 1.7%, range –8.5 to –16.4) than that in the group without fracture (–4.7% ± 0.9%, range –2.2 to –11.3), implying that a decrease in the lumbar BMD could be associated with bone fracture in persons with GC-induced osteoporosis, even though their BMD was within normal ranges.

However, the risk of bone fracture is determined not only by a decrease in bone mass but also by decreases in bone quality and architecture. Bone metabolism markers are used as indirect indices of bone quality. The serum bone-ALP appeared to rise in the alfacalcidol group, and the percentage increase in serum bone-ALP from baseline in the combined group was less than that in the alfacalcidol group, suggesting that alfacalcidol might stimulate osteoblast-mediated bone formation. Alternatively, because enrolled patients were young and premenopausal, osteoblasts could effectively respond to alfacalcidol in the condition described above. On the other hand, the level of urinary deoxypyridinoline, a resorption marker, decreased after 6, 12, and 18 months of treatment with alendronate, whereas it tended to increase in the alfacalcidol group. We therefore assumed that alendronate, but not alfacalcidol, could efficiently reduce osteoclast-mediated bone resorption during high turnover in bone metabolism induced by GC. Together with our current results that alfacalcidol alone was not sufficient to retard loss of bone mass and fracture in GC-induced osteoporosis, compared to combined use with alendronate, alendronate could be the key effective agent to prevent GC-induced osteoporosis, by inhibiting bone loss with high bone turnover, especially in patients treated with high-dose GC.

There is general agreement that GC therapy can induce osteoporosis, and that osteoporosis induced by longterm GC therapy does not improve even after discontinuation of treatment. A longterm policy should be established with full consideration of the use of GC to avoid unnecessary use of these drugs. The potential development of GC-induced osteoporosis should require active primary and secondary prevention with effective drugs.

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