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ORIGINAL ARTICLE

Effect of alendronate on glucocorticoid-induced osteoporosis in Japanese women with systemic autoimmune diseases: versus alfacalcidol

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Abstract Glucocorticoids-induced osteoporosis is a serious problem for patients with systemic autoimmune disease requiring relatively long-term glucocorticoid treatment. Effectiveness of alendronate for the prevention of glucocorticoids-induced osteoporosis was evaluated in comparison with that of alfacalcidol in Japanese women with autoimmune disease excluding rheumatoid arthritis. Loss of bone mass was evaluated with bone mineral density (BMD) of lumber vertebrae, bone resorption was with urinary N-telopeptide for type I collagen (NTX), and bone formation was with serum bone-specific alkaline phosphatase (B-ALP). A total of 33 patients who were treated with oral glucocorticoids (≥5 mg/day of prednisolone equivalence) for more than 6 months were randomized into two groups; alendronate group ($n = 17$) received 5 mg/day of alendronate, and alfacalcidol group ($n = 16$) received 1.0 μg/day of alfacalcidol for 24 months with glucocorticoids. The dose of alendronate was the maximal dose approved in Japan. BMD had tendency to decrease with alfacalcidol, while increase with alendronate. The difference in BMD change between the two groups was significant by 4.3% at 18 months and by 4.2% at 24 months (both $P < 0.05$). Bone resorption was significantly reduced only with alendronate; NTX was decreased by 28 to 35% at 6 to 24 months ($P < 0.05$), but not changed with alfacalcidol at 24 months. The bone formation was found to be unchanged according to the B-ALP measured between the two groups. In conclusion, the treatment of 5 mg alendronate daily is more effective than alfacalcidol for preventing the glucocorticoid-induced osteoporosis by the mechanism of reducing bone resorption in Japanese women with systemic autoimmune disease.

Keywords Glucocorticoid · Osteoporosis · Alendronate · Alfacalcidol · Bone mineral density

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Introduction

Glucocorticoid treatment is useful for the treatment of systemic autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. However, glucocorticoids produce osteoporosis and increase the risk of bone fracture as a side effect, which is a serious drawback for patients [1]. Since the complications of glucocorticoid therapy were recognized in 1996, several guidelines have been developed on the management of glucocorticoid-induced osteoporosis. In the guidelines, antiresorptive agents, e.g., calcium, vitamin D (plain or activated form), bisphosphonates or the combination were recommended to prevent bone loss in patients who begin the treatment with ≥5 mg/day of glucocorticoid (prednisolone equivalent) [2–7]. In the present clinical study, the efficacy of a bisphosphonate, alendronate, on the suppression of glucocorticoid-induced osteoporosis was investigated in comparison with that of activated form of vitamin D_3, alfacalcidol, in Japanese women who were treated with glucocorticoids for more than 6 months for autoimmune disease. The primary goal of the treatment is the prevention of bone fracture caused by glucocorticoid treatment. However, in the present study bone loss was monitored, for anti-fracture efficacy was demonstrated to be

strongly associated with prevention of bone loss and increased BMD [8]. This study was conducted before bisphosphonates were recommended for the management of glucocorticoid-induced osteoporosis in the guidelines of the Japanese Society for Bone and Mineral Research [9] in 2005. Patients with rheumatoid arthritis were excluded because the inflammation of rheumatoid arthritis independently causes bone resorption and bone loss [10]. Japanese women were specifically the basis of this study because systemic autoimmune disease is more prevalent in women, and more importantly, Asian women are known to have lower BMD than any other ethnic population [11].

Patients and methods

This is a prospective, open-labeled, randomized, comparative study conducted in Japanese women with systemic autoimmune disease excluding rheumatoid arthritis. The study included 33 patients who visited the section of nephrology and rheumatology, the department of internal medicine, Fukuoka University from April 2002 to April 2004 and who had been previously receiving 5 mg/day or more of oral glucocorticoids (prednisolone equivalent) for more than 6 months. They were allocated into two treatment groups: alendronate group ($n = 17$) receiving 5 mg/day of alendronate and alfacalcidol group ($n = 16$) receiving 1.0 μg/day of alfacalcidol, concomitantly with glucocorticoids. Calcium was not supplemented to either group. The underlying conditions of the patients included systemic lupus erythematosus in 21 patients, polymyositis/dermatomyositis in four patients, mixed connective tissue disease in four patients, progressive systemic sclerosis in three patients, Behçet's disease in one patient and Takayasu's arteritis in one patient.

Bone loss of the patients was monitored by bone mineral density (BMD) of the lumber vertebrae assessed with dual-energy X-ray absorptiometry (DXA) method (QDR4500, Hologic Co., Ltd.). Bone resorption was assessed by urinary N-telopeptide for type I collagen (NTX), and bone formation was assessed by serum levels of bone alkaline phosphatase (B-ALP). Both markers were assayed by enzyme-linked immunosorbent assay (ELISA) methods. Measurements were taken at pre-treatment period, and at 6, 12, 18, and 24 months of the treatment. The institutional ethics committee approved the protocol and written informed consents were given from all the study patients.

Statistical analysis

According to the previous US and European studies [12, 13], the mean percent changes in BMD of the lumber vertebra were $2.0 \pm 2.0\%$ after 12-month alendronate treatment (10 mg/day) and $0.5 \pm 2.0\%$ after 12-month alfacalcidol treatment (1.0 μg/day). A total of 40 patients (20 patients in each group) were estimated to be required to detect statistically significant differences with 80% power, $\alpha = 0.05$, and $P = 0.03$, assuming a 10% patient dropout.

Data is expressed as the mean ± SD. For baseline characteristics, differences in age, weight, height, BMD of the patients, and dose of glucocorticoids were evaluated between the two groups by unpaired *t*-test. Difference in the proportion of post-menopausal patients was evaluated by χ^2-test. Differences in BMD, NTX, and B-ALP values during the treatment period within each group were evaluated by ANOVA. If it is significant ($P < 0.05$), the difference in measured values between the two time points was evaluated by Dunnett's test. The Mann–Whitney *U*-test was used to examine the difference in percent changes of mean BMD, urinary NTX, and B-ALP between the two groups. Any difference with $P < 0.05$ was considered as statistically significant.

Results

Patient baseline characteristics of the alendronate group and the alfacalcidol group are summarized in Table 1. Both groups had similar baseline characteristics such as mean age, weight, height, BMD, NTX, and B-ALP, and received similar mean doses of glucocorticoids (prednisolone equivalent), 12.1 ± 6.6 mg/day for the alendronate group and 11.5 ± 10.5 mg/day for the alfacalcidol group.

Changes in BMD, NTX, and B-ALP at pretreatment, and 6, 12, 18, and 24 months were shown in Table 2. Patients treated with alfacalcidol had a tendency to have decreased BMD of lumber vertebrae from the baseline without significance at 18 and 24 months. On the other hand, patients treated with alendronate had a tendency to have increased BMD from the baseline without significance (Fig. 1). However, difference in percent change of BMD between the two groups was significant by 4.3 and 4.2% at 18 and 24 months, respectively (both $P < 0.05$) (Fig. 2).

Alfacalcidol treatment did not significantly change the level of NTX, demonstrating no effect on bone resorption, while alendronate treatment significantly reduced the level of NTX. The percent reduction was 34.8 ± 49.4 and $31.8 \pm 46.3\%$ at 18 and 24 months, respectively, demonstrating that alendronate markedly suppressed the bone resorption. The difference in percent change of NTX between the two groups was significant only at 6 months ($P < 0.05$).

Alendronate and alfacalcidol did not significantly affect the level of B-APL in percent change, demonstrating no effect on bone formation as shown in Fig. 3.

Table 1 Patient baseline characteristics

	Alendronate group $N = 17$	Alfacalcidol group $N = 16$	Differences between two groups
Post-menopause (%)	11 (64.7)	7 (43.8)	$P = 0.116$[a]
Age (year)	49.2 ± 14.6	45.0 ± 13.2	$P = 0.389$[b]
Weight (kg)	51.3 ± 8.7	49.9 ± 6.1	$P = 0.585$[b]
Height (cm)	155.7 ± 4.6	155.9 ± 8.7	$P = 0.906$[b]
Prednisolone equivalent (mg/day)	12.1 ± 6.6	11.5 ± 10.5	$P = 0.824$[c]
BMD (g/cm^2)	0.838 ± 0.153	0.893 ± 0.132	$P = 0.995$[b]
T-score	−1.19 ± 1.47	−1.06 ± 1.21	$P = 0.774$[c]
B-ALP (U/L)	20.1 ± 6.7	20.1 ± 9.1	$P = 0.792$[b]
NTX (nmolBCE/nmolCr)	52.0 ± 37.5	47.6 ± 27.0	$P = 0.638$[b]

Data was expressed with mean ± SD

BMD bone mineral density, *NTX* N-telopeptide for type I collagen, *B-ALP* bone alkaline phosphatase

[a] As determined by χ^2-test

[b] Determined by unpaired *t*-test

[c] Determined by Mann–Whitney *U*-test

Table 2 Changes in bone mineral density of lumber vertebrae and bone metabolism markers

	Group	Baseline	6 months	12 months	18 months	24 months	*P*-value by ANOVA
BMD (g/cm^2)	Alendronate	0.838 ± 0.153	0.844 ± 0.147	0.845 ± 0.155	0.854 ± 0.146	0.856 ± 0.142	0.997 (NS)
	Alfacalcidol	0.894 ± 0.133	0.880 ± 0.131	0.879 ± 0.123	0.874 ± 0.129	0.877 ± 0.128	0.994 (NS)
NTX (nmolBCE/nmolCr)	Alendronate	52.0 ± 37.5	27.5 ± 15.7**	29.6 ± 18.3**	26.4 ± 17.0**	28.9 ± 18.7**	0.015 ($P < 0.05$)
	Alfacalcidol	47.6 ± 27.0	39.9 ± 19.3	38.4 ± 20.2	32.2 ± 14.7	30.1 ± 12.5	0.098 (NS)
B-ALP (U/L)	Alendronate	20.1 ± 6.7	16.5 ± 5.3	17.3 ± 6.6	16.1 ± 5.4	15.9 ± 5.2	0.232 (NS)
	Alfacalcidol	20.1 ± 9.1	19.7 ± 10.0	23.0 ± 12.3	21.3 ± 10.2	20.2 ± 8.8	0.906 (NS)

Data was expressed with mean ± SD

BMD bone mineral density, *NTX* N-telopeptide for type I collagen, *B-ALP* bone alkaline phosphatase

** $P < 0.01$ versus baseline as determined by Dunnett's test

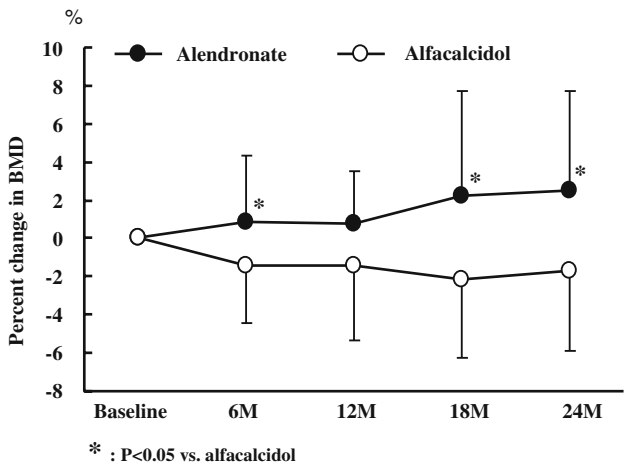

Fig. 1 Percent change in BMD from pre-treatment value. *Filled circle* alendronate group, *open circle* alfacalcidol group, *BMD* bone mineral density. There was a significant difference in percent change of BMD at either 6, 18, or 24 months between the two treatment groups. Mean ± SD. * $P < 0.05$ versus the alfacalcidol group as determined by Mann–Whitney *U*-test

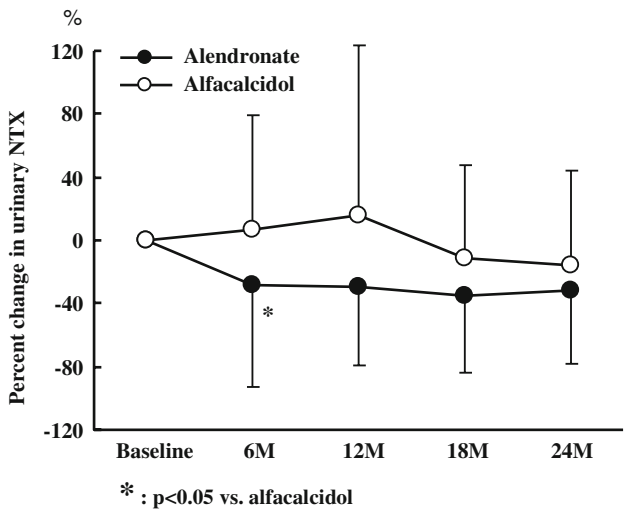

Fig. 2 Percent change in NTX from pre-treatment value. *Filled circle* alendronate group; *open circle* alfacalcidol group; *NTX* N-telopeptide for type I collagen. There was a significant difference in percent change of NTX at 6 months between the two treatment groups. Mean ± SD. * $P < 0.05$ versus the alfacalcidol group as determined by Mann–Whitney *U*-test

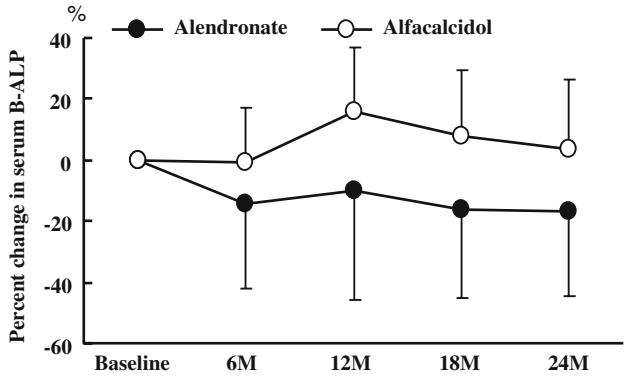

Fig. 3 Percent change in B-ALP from pre-treatment value. *Filled circle* alendronate group, *open circle* alfacalcidol group, *B-ALP* bone alkaline phosphatase. There was no significant difference in percent change of B-ALP between the two treatment groups

No patients had bone fracture of lumber vertebrae in this study.

Discussion

In this study of Japanese women who were treated with glucocorticoid (more than 5 mg of prednisolone equivalent) for more than 6 months for systemic autoimmune disease excluding rheumatoid arthritis, we found that patients treated with 5 mg/day of alendronate was significantly higher BMD of lumber vertebrae (4%) after 24-month treatment compared with those treated with 1.0 μg/day of alfacalcidol. Superior effectiveness of alendronate in suppressing osteoporosis progression was also demonstrated in 18-month study where 10 mg/day of alendronate was more effective compared to alfacalcidol in Caucasian patients who were started on glucocorticoid treatment of at least 7.5 mg/day [14, 15].

The mean daily doses of glucocorticoids administered were similar between the two groups; 11.5 ± 10.5 mg of prednisolone equivalent in the alfacalcidol group and 12.1 ± 6.6 mg in the alendronate group. Although the results on the association of a specific daily dose or cumulative glucocorticoid dose with bone loss or the risk of fractures were found to be inconsistent in several individual studies [16–19], the doses were consistent with those which produced bone loss in meta-analysis of 23 studies [20]. Treatment of glucocorticoid above 5 mg/day prednisolone equivalent found to reduce BMD and increase the risk of bone fracture. Patients in the present study had already been treated for 6 months with glucocorticoid. According to a study, 7.5 mg/day of glucocorticoids (prednisolone equivalent) produced 2% of significant reduction in BMD of lumber spine in 3-month studies in patients without rheumatoid arthritis [21].

The mean baseline BMD of lumber vertebrae in the alendronate group and the alfacalcidol group were above the cut-off value of BMD to separate fracture and non-fracture cases for Japanese, 0.820 mg/m^2, which was determined from the data of glucocorticoid-treated patients with clinical condition other than rheumatoid arthritis treated with more than 5.0 mg/day of glucocorticoids (prednisolone equivalent) [9]. Since the patients in the present study were younger (mean age 45 ± 15 in the alendronate group and 49 ± 13 in the alfacalcidol group versus 60), and post-menopausal women was only half of the group versus 85% compared with the study of de Nijs et al. [15], this may be the reason for higher level of BMD in the study patients of the present study although they had been previously treated with glucocorticoid for more than 6 months. In fact, the study patients had no bone fracture and vertebral deformity during 2 years of the study period in the both groups.

Alendronate 5 mg/day was recommended for premenopausal women and men, while alendronate 10 mg/day was recommended for post menopausal women for glucocorticoid-induced osteoporosis by American College of Rheumatology ad hoc committee [5]. However, 5 mg/day of alendronate is the maximum dose approved in Japan, which was effective as 10 mg/day in increasing BMD in the postmenopausal Japanese patients with osteoporosis in the 3-year study [22]. The effectiveness of 5 mg/day of alendronate was also shown in Japanese patients with primary osteoporosis [23] and in postmenopausal Japanese women [24] where 5 mg/day of alendronate increased lumber BMD by 4–6% of the baseline value after 12-month treatment in both studies. However, no study of glucocorticoids-induced osteoporosis treated with alendronate had been done in Japanese patients.

Although under the present study condition the effectiveness of 5 mg/day of alendronate was less, our findings are still consistent with the previous results on the usefulness of alendronate in prevention of osteoporosis demonstrated in the 12-month treatment [23, 24]. In the present study, the effect of alendronate was not potent as to recover BMD to the normal level (1.011 g/m^2 in Japanese) from the baseline level which once reduced by glucocorticoids treatment of more than 6 months, but alendronate prevented the BMD reduction in concomitant glucocorticoid therapy.

The changes in the levels of biomarkers of bone metabolism were shown to predict BMD change [25]. Previously, alendronate prevented bone loss and increased the BMD of lumber vertebrae by reducing both bone resorption and formation suppressing bone metabolism [15]. In ovarectomized primates, alendronate treatment reversed the effects of ovariectomy by reducing turnover of cancellous bone and increased bone mass and bone strength [26]. In the present study, only a marker for bone

resorption, urinary NTX, was significantly decreased with alendronate treatment. Although alendronate was also known to suppress bone formation [15, 23], we observed no significant change in a marker of bone formation. The reduction in bone resorption was a possible mechanism by which alendronate prevented vertebral BMD reduction in the present study condition. A study of alendronate treatment reported that the change in BMD was primarily associated with the change in bone resorption in postmenopausal osteoporosis [25].

The limitation of this study is that number of study subjects was small. Nonetheless, 5 mg/day of alendronate was demonstrated to be effective in Japanese patients. The finding of the present study is significantly important, because 5 mg/day is the maximum dose approved in Japan for alendronate, and the study was conducted in Asian women who are known to have lower BMD in general than other ethnic population [11]. However, a large-scale and long-term study is necessary in the near future.

In conclusion, alendronate prevents the progression of glucocorticoid-induced osteoporosis in Japanese women with systemic autoimmune disease excluding rheumatoid arthritis. Although alendronate brought only 4% recovery in BMD from the level reduced with alfacalcidol, this may still prevent future bone fracture. The effect of alfacalcidol to prevent progression of osteoporosis was not unequivocally demonstrated by this study results. Patients with systemic autoimmune disease under glucocorticoids treatment should be treated with alendronate rather than alfacalcidol.

Conflict of interest The authors of the present study have no financial conflict of interests.

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