ORIGINAL

Differences of therapeutic effects on regional bone mineral density and markers of bone mineral metabolism between alendronate and alfacalcidol in Japanese osteoporotic women

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Abstract : We studied the differences of therapeutic effects on regional bone mineral density (BMD) and markers of bone mineral metabolism between alendronate and alfacalcidol in Japanese osteoporotic women. Ninety-two Japanese women suffering from primary osteoporosis without osteoporotic fractures, aged 55 to 81 years, were divided into two groups : women treated orally with alendronate for one-year (5mg/day)(alendronate group, n=35) and women treated orally with alfacalcidol for one year (0.5μg/day) (alfacalcidol group, n=57). The mean BMD of the 2nd to 4th lumbar vertebrae (L2-4 BMD) and regional BMD were measured using dual energy X-ray absorptiometry. In the alendronate group, the percentage changes of L2-4BMD, lumbar spine BMD, thoracic spine BMD, pelvis BMD in the alendronate group were 106.3±4.6%, 104.2±6.6%, 107.1±10.4%, 107.1±10.5%, respectively. The percentage changes of L2-4BMD and regional BMD except for head BMD in the alendronate group were significantly greater than those in the alfacalcidol group. In the alfacalcidol group, L2-4BMD, thoracic spine BMD and lumbar spine BMD were maintained at respective pretreatment levels, whereas other regional BMD were decreased. Both serum bone-specific alkaline phosphatase and urinary type I collagen cross-linked N-telopeptide of the alendronate group were decreased, whereas these markers of bone mineral metabolism of alfacalcidol group were increased compared with the respective pre-treatment levels. The results suggest that one-year treatment with alendronate increased L2-4BMD, lumbar spine BMD, thoracic spine BMD and pelvis BMD, and that markers of both bone formation and bone resorption were decreased following one-year treatment with alendronate. J. Med. Invest. 54 : 35-40, February, 2007

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INTRODUCTION

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture (1). Osteoporotic fractures are one of significant

complications and an increasing health care burden in osteoporotic patients. As the population of elderly people increases, the incidence of osteoporotic fractures is expected to dramatically rise. At present, large number of postmenopausal women in Japan are at high risk for osteoporosis and its associated fractures, which is an issue of clinical importance. Therefore, in the treatment of osteoporosis, prevention of fractures is undoubtedly a major goal. Smith showed that bone mineral density (BMD) was accounted for approximately 75-80% of the variance in the bone strength (2). It is an undoubted fact that BMD is one of the important determinants of bone strength.

The purpose of this study was to clarify the difference of therapeutic effects of regional BMD and markers of bone mineral metabolism between one-year treatment of alendronate and that of alfacalcidol. Alendronate is a second-generation aminobisphosphonate. Bisphosphonate is an antiresorptive agent of bone and it increases BMD and bone mineral content resulting from inhibition of osteoclast-mediated bone resorption (3, 4), leading to prevention of osteoporotic fractures, hip fractures (5) and vertebral fractures (6). Alfacalcidol, 1 alfa-hydroxyvitamin D_3, is a prodrug of calcitriol, and is one of active vitamin D analog. Alfacalcidol has been widely used in the treatment of osteoporosis in Japan. Alfacalcidol stimulates intestinal calcium absorption, increases urinary Ca excretion and serum Ca levels, and suppresses parathyroid hormone secretion (5). Alfacalcidol is effective to increase BMD and reduces rate of vertebral fracture (7) or hip fracture (8).

MATERIALS AND METHODS

One hundred and three Japanese women suffering from primary osteoporosis without osteoporotic fractures, aged 55 to 81 years, were divided into two groups : women treated orally with alendronate for one year (5mg/day) (alendronate group, n=41) and women treated orally with alfacalcidol for one year (0.5μg/day) (alfacalcidol group, n=62). In the alendronate group, 35 of 41 women completed one-year treatment of alendronate. In contrast, 57 of 62 women in the alfacalcidol group completed one-year treatment of alfacalcidol. All the women had no osteoporotic fractures, no renal injury, no disease of the alimentary tract, no osteomalacia, and no primary or secondary neoplastic bone disease. None of them had received treatments affecting bone metabolism. All the women are allowed to continue their usual diets. Table 1 showed pre-treatment values of body mass index (BMI), age, L2-4BMD, total body BMD. No significant differences were found between the two groups with regard to BMI and age, L2-4BMD and total body BMD.

The mean BMD of the 2nd to 4th lumbar vertebrae (L2-4BMD), regional and total body BMD were measured by DXA using a Hologic QDR 2000 (Waltham, MA, USA). The coefficient of variation (CV) for DXA for total BMD and soft tissue mass was 0.5%-1.0% (9).

The regional BMD (g/cm^2) was measured in the head, arms, ribs, thoracic spine, lumbar spine, pelvis and legs (Figure 1). The regional BMD (g/cm^2) was measured in the head, arms, legs, ribs, thoracic spine, lumbar spine and pelvis. The horizontal line above the shoulders should be just below the chin. The vertical lines at the shoulders should be between the head of the humerus and scapula at the glenoid fossa. The vertical lines on either side of the spine should be moved close to the spine, angled to match the curvature if possible. The small horizontal line should be approximately at the level of L1-T12. The horizontal line above the pelvis should be just above the crest of

Table 1. Comparison of characteristics of alendronate and alfacalcidol groups.

	Alendronat group (n=35)	Alfacalcidol group (n=57)	*P* value
Age	65.2±4.0	66.0±4.5	0.3388
BMI (kg/m^2)	21.5±2.3	22.3±3.1	0.2233
L2-4 BMD (g/cm^2)	0.678±0.082	0.695±0.104	0.427
Total body BMD (g/cm^2)	0.824±0.066	0.836±0.064	0.4061

BMI, body mass index ; L2-4 BMD, the mean bone mineral density of the 2nd to 4th lumbar vertebrae

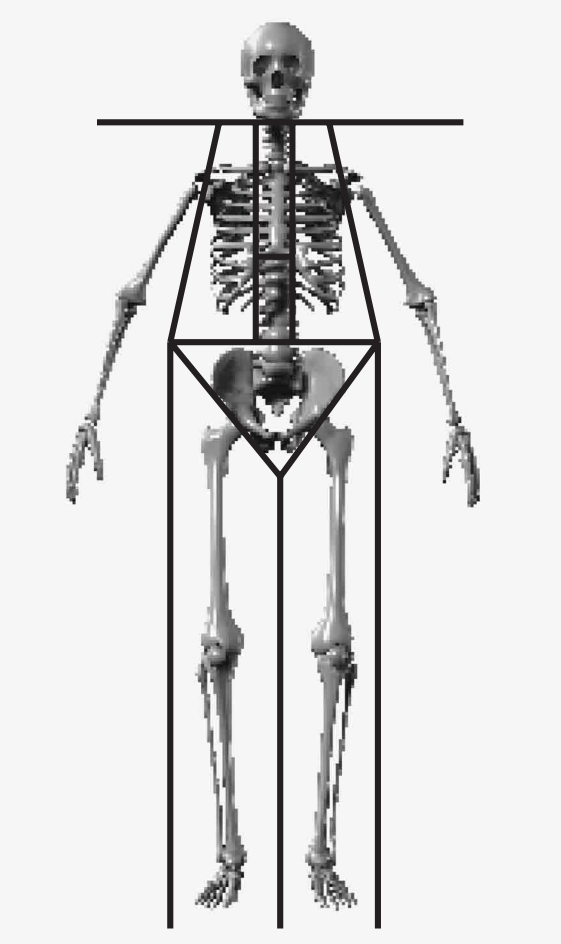

Figure 1. Screen display of total and regional BMD *in vivo*.

the ilium. This line can be extended out at the sides to include soft tissue in the chest and waist. If at all possible, soft tissue from the trunk should not be included with the arms. Due to patient size and placement of the hands, this may not always be possible. The angled lines below the pelvis should bisect both femoral necks. The vertical line between the legs should be adjusted to be between the feet. The vertical lines lateral to (outside of) the legs should be adjusted to include as much of the soft tissue in the thighs as possible.

STATISTICS

Results were expressed as the mean±standard deviation. Unpaired Student's t-test was used to evaluate the differences between the two groups. A P value of less than 0.05 was considered significant.

RESULTS

Fracture

After one-year treatment, 1 of 35 women in the alendronate group and 4 of 57 patients in the alfacalcidol group suffered vertebral fractures.

Regional and total body BMD (Table 2)

Percent change of pre-treatment level of L2-4 BMD and regional BMD of alendronate group were significantly greater than those of alfacalcidol

Table 2. Comparison of percent change of L2-4 BMD, BMD and BMC between alendronate and alfacalcidol groups.

	Alendronate group (n=35)	Alfacalcidol group (n=57)	*P* value
% L2-4 BMD (%)	106.3±4.6	100.7±6.8	< 0.0001
% Lt arm BMD (%)	101.2±4.0	98.7±3.4	0.0019
% Rt arm BMD (%)	100.4±3.4	97.7±3.4	0.0263
% Lt rib BMD (%)	103.2±6.7	98.9±5.5	0.0016
% Rt rib BMD (%)	102.2±4.2	99.6±5.3	0.017
% Thoracic spine BMD (%)	104.2±6.6	98.2±7.0	0.0001
% Lumbar spine BMD (%)	107.1±10.4	100.7±6.9	0.0007
% Pelvis BMD (%)	107.1±10.5	100.6±6.9	0.0013
% Lt leg BMD (%)	100.1±2.6	98.5±3.4	0.015
% Rt leg BMD (%)	100.4±2.2	98.8±3.4	0.0096
% Head BMD (%)	101.3±3.1	101.1±3.5	0.9228
% Total body BMD (%)	101.1±1.8	99.2±2.2	< 0.0001

BMD, bone mineral density ; L2-4 BMD, the mean BMD of the 2nd to 4th lumbar vertebrae.

group except for BMD of head. In the alendronate group, percentage change of L2-4BMD, lumbar spine BMD, thoracic spine BMD and pelvic BMD of alendronate group were greater than those of other regional BMD. There was no significant difference of the percent change of pre-treatment level of head BMD between the two groups.

L2-4BMD, lumbar spine BMD and thoracic spine BMD were maintained at respective pre-treatment levels, whereas other regional BMD were decreased following one-year treatment with alfacalcidol.

Markers of bone mineral metabolism (Table 3, Table 4)

There were no significant differences of pretreatmet levels of markers of bone mineral metabolism between these two groups (Table 3).

Percent change of urinary type I collagen cross-linked N-telopeptide (NTX) of the alendronate group was decreased to 55.1±30.5% of the pre-treatment level. In contrast, percent change of urinary NTX of alfacalcidol group was increased to 103.3±50.2% of the pre-treatment level. There was significant difference between the two groups (p=0.0002).

Percent change of serum alkaline phosphatase (AP) of alendronate group decreased to 77.4±18.0% of the pre-treatment level, whereas that of alfacalcidol group increased to 106.4±50.9% of the pre-treatment level, which was significantly different (p=0.0073). Percent change of serum bone-specific alkaline phosphatase (BAP) of alendronate group was decreased to 65.6±21.3% of the pre-treatment level, whereas that of alfacalcidol group was increased to 104.8±45.3% of the pre-treatment level. There was significantly difference between the two groups (p=0.0002) (Table 4).

Table 3. Comparison of markers of bone mineral metabolism before treatment.

	Alendronate group (n=35)	Alfacalcidol group (n=57)	*P* value
Urinary NTX (nMBCE/mMCr)	57.0±28.9	45.6±13.5	0.1121
Serum AP (IU/l)	268.3±97.6	281.4±67.8	0.619
Serum BAP (U/l)	36.5±11.9	29.8±14.4	0.0983
Serum Ca (mg/dl)	8.9±1.1	8.6±1.5	0.398
Serum P (mg/dl)	4.0±1.4	4.1±1.5	0.722

AP, alkaline phosphatase ; NTX, type I collagen cross-linked N-telopeptide ; BAP, bone-specific alkaline phosphatase

Table 4. Percent change of markers of bone mineral metabolism.

	Alendronate group (n=35)	Alfacalcidol group (n=57)	*P* value
% Urinary NTX (%)	55.1±30.5	103.3±50.2	0.0002
% Serum AP (%)	77.4±18.0	106.4±50.9	0.0073
% Serum BAP (%)	65.6±21.3	104.8±45.3	0.0002
% Serum Ca (%)	98.0±14.6	97.9±9.4	0.2968
% Serum P (%)	93.5±14.6	94.8±10.4	0.7502

AP, alkaline phosphatase ; NTX, type I collagen cross-linked N-telopeptide ; BAP, bone-specific alkaline phosphatase

DISCUSSION

One-year treatment with alendronate increased L2-4BMD, thoracic spine BMD, lumbar spine BMD and pelvic BMD, and maintained other regional BMD. In contrast, one-year treatment with alfacalcidol maintained L2-4BMD, lumbar spine BMD, pelvis BMD and head BMD, and decreased other regional BMD. Einhorn (10) showed that the relative content of trabecular bone varied among the different parts of the skeleton, and that the content of trabecular bone of vertebra was 66-90%, that of the hip at the intertrochanteric region was 50%, that of the hip at the femoral neck was 25%, that of the distal radius was 25%, that of the mid-radius was 1%, and that of the femoral shaft was 5%. As for bone metabolism, the trabecular bone is approximately eight times as metabolically active as cortical bones, because the surface of trabecular bone is larger than that of cortical bone, and the response to metabolic changes in trabecular bone is faster than that of cortical bone (11). Therefore, the great rate of increase in L2-4BMD, thoracic spine BMD, lumbar spine BMD and pelvis BMD after one-year treatment of alendronate may be due to the high content of trabecular bone compared with other regional bones.

In this study, one-year treatment of alendronate increased lumbar spine BMD, thoracic spine BMD and pelvis BMD. Smith showed that BMD was accounted for approximately 75-80% of the variance in the bone strength (2). In addition to BMD, bone quality is also one of important determinants of bone strength. Alendronate improves trabecular bone microarchitecture of the ileum (greater bone volume, trabecular thickness, decrease in trabecular spacing) (12). Based on these facts, one-year treatment of alendronate increases bone strength and prevents vertebral fracture and hip fracture in osteoporotic patients.

Urinary NTX of the alendronate group were decreased, whereas urinary NTX of the alfacalcidol group was increased. Urinary NTX is one of the markers of bone resorption. This fact showed that alendronate inhibits osteoclast-mediated bone resorption. In addition, one-year treatment with alendronate decreased serum BAP, whereas serum BAP in the alfacalcidol group was increased. Serum BAP is an index of bone turnover. This suggests that one-year treatment with alendronate normalizes bone turnover in patients with osteoporosis.

Previous studies have shown that combination therapy of alendronate and calcitriol are more effective to increase BMD in patients with osteoporosis than monotherapy with either calcitriol or alendronate (13, 14). Recker *et al.* (15) showed that alendronate provides efficacy of bone resorption as measured by serum BAP and urinary NTX, and that alendronate with cholecalciferol increases 25-hydroxyvitamin D (25-OH-D), whereas alendronate without cholecalciferol decreases 25-OH-D. Combination therapy of alfacalcidol and alendronate may be more effective to increase regional BMD and to reduce risk of osteoporotic fractures. Further studies are required to clarify the therapeutic effects of combination therapy of alfacalcidol and alendronate on prophylaxis of osteoporotic fractures.

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