Three-year outcome of alendronate treatment in older Japanese women with osteoporosis

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Abstract

The effects of alendronate (ALN) treatment on the bone mineral density (BMD), bone turnover markers, and fracture incidence remain to be established in older Japanese patients. The aim of the present study was to compare the outcome of ALN treatment for 3 years among postmenopausal osteoporotic Japanese women <80 years of age and those ≥80 years of age. One hundred ninety-eight postmenopausal osteoporotic women who had been treated with ALN for more than 3 years were analyzed. The 3-year outcome was compared between women <80 years of age (control group, n=167) and those ≥80 years of age (older group, n=31). During the 3-year treatment period, the urinary cross-linked N-terminal telopeptides of the type I collagen and serum alkaline phosphatase levels significantly decreased and the lumbar spine BMD significantly increased, compared with the baseline values, in manners that were similar in the control and older groups. However, the incidence of non-vertebral fractures, but not of vertebral fractures, was significantly higher in the older group than in the control group (16.1% *vs* 3.0%). These results suggested that the incidence of non-vertebral fractures was significantly higher among postmenopausal osteoporotic Japanese women ≥80 years of age who were treated with ALN than among those <80 years of age despite the similar effect of ALN treatment on surrogate markers.

Introduction

Osteoporosis most commonly affects postmenopausal women, placing them at a significant risk of fractures. Alendronate (ALN) is widely used for the treatment of postmenopausal osteoporosis. The fracture intervention trial (FIT) demonstrated the efficacy of ALN against vertebral, non-vertebral, hip, and wrist fractures in postmenopausal women with osteoporosis.[1,2] Furthermore, a recent systematic review analyzing 11 randomized controlled trials (RCTs) representing 12,068 women confirmed that ALN treatment resulted in both clinically important and statistically significant reductions in vertebral, non-vertebral, hip, and wrist fractures for secondary prevention (gold-level evidence).[3] An analysis of the FIT demonstrated that ALN treatment was effective for reducing the risk of symptomatic osteoporotic fractures including hip, clinical spine, and wrist fractures across a spectrum of ages (55 - 85 years), although the absolute risk reduction with ALN treatment increased with age because of the age-related increase in the fracture risk in the placebo group.[4]

RCTs in postmenopausal Japanese women with osteoporosis (mean ages: 63-72 years) also revealed that short-term (1-3 years) ALN treatment suppressed bone turnover, increased the bone mineral density (BMD), and reduced the incidence of vertebral fractures.[5-8] Clinical practice-based studies confirmed the long-term effect on surrogate markers and safety in postmenopausal Japanese women with osteoporosis or osteopenia and clinical risk factors for fractures (mean ages: 66-75 years).[9,10] ALN is regarded as a first-line drug for the treatment of osteoporosis in Japan. However, the effects of ALN treatment on the BMD, bone turnover markers, and fracture incidence remain to be established in older Japanese patients (≥80 years of age). The aim of the present study was to compare the outcome of ALN treatment for 3 years on the BMD, bone turnover markers, and incidence of osteoporotic fractures including morphometric vertebral fractures and clinical vertebral and non-vertebral fractures among postmenopausal osteoporotic Japanese women <80 years of age and those ≥80 years of age.

Materials and Methods

Subjects

One-hundred ninety-eight postmenopausal osteoporotic Japanese women who had been treated with ALN for more than 3 years were recruited at the outpatient clinic of Keiyu Orthopaedic Hospital (Gunma, Japan) during the 6-month period between October 1, 2010, and March 31, 2011. The inclusion criteria were postmenopausal women with osteoporosis at the start of treatment. The exclusion criteria were histories of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, renal failure, or bone diseases including cancer-induced bone loss because of aromatase inhibitors, primary hyperparathyroidism, hyperthyroidism, Cushing syndrome, multiple myeloma, Paget's disease of the bone, rheuma-

toid arthritis, and osteogenesis imperfecta.

All the patients had been diagnosed as having osteoporosis according to the Japanese diagnostic criteria.[11,12] Namely, patients with a BMD <70% of the young adult mean (YAM) or 70-80% of the YAM along with a history of osteoporotic fractures were diagnosed as having osteoporosis. The assessment prior to ALN treatment included a medical history, physical examination, plain X-rays of the thoracic and lumbar spine, lumbar spine BMD measurement, and blood and urinary biochemical tests including serum calcium, phosphorus, alkaline phosphatase (ALP), and urinary cross-linked N-terminal telopeptides of type I collagen (NTX). The patients had been treated with ALN (5 mg daily or 35 mg weekly) for more than 3 years. The doses indicated in the parentheses above are the doses used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective.[5-8] Daily ALN was available throughout the study period, but weekly ALN only became available after October 2006. All the patients who had been treated with daily ALN were switched to weekly ALN just after October 2006. The effects of daily and weekly ALN on the BMD and bone turnover markers as well as the incidence of side effects are reportedly similar in postmenopausal Japanese women with osteoporosis.[8]

The urinary NTX levels were measured at 3 months after the start of treatment. The serum levels of calcium, phosphorus, and ALP and the lumbar spine BMD were measured every 1 year after the start of treatment. The outcome of ALN treatment for 3 years was evaluated and

compared between women <80 years of age and women ≥80 years of age. The data presentation was approved by the Ethics Committee of Keiyu Orthopaedic Hospital.

Assessment of morphometric vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained to detect evidence of morphometric vertebral fractures. According to the Japanese criteria, a vertebral fracture was defined according to the vertebral height on lateral X-ray films.[11,12] Briefly, the vertebral height was measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body, and the presence of a vertebral fracture was confirmed when i) a reduction in the vertebral height of more than 20% (A, C, and P) compared with the height of the adjacent vertebrae was observed, ii) the C/A or C/P was less than 0.8, or iii) the A/P was less than 0.75. The assessment for vertebral fractures was performed at the T4-L4 level.

Assessment of clinical vertebral and non-vertebral fractures

Low-traumatic osteoporotic clinical fractures were assessed. Clinical vertebral fractures were determined based on clinical symptoms and radiographs or magnetic resonance images of the lumbar and thoracic spine. Non-vertebral fractures in terms of major osteoporotic fractures at the distal radius, proximal humerus, and hip were determined based on clinical symptoms and radiographs of the wrist, shoulder, and hip joints, respectively.

Measurement of serum calcium, phosphorus, alkaline phosphatase, and urinary cross linked N-terminal telopeptides of type I collagen

Serum and urine samples obtained from each patient were sent to Kotobiken Medical Laboratories, Inc. (Tatebayashi, Gunma, Japan) for the following biochemical analyses. The serum calcium and phosphorus levels were measured using the standard laboratory technique. The serum ALP levels were measured using the Japanese Society of Clinical Chemistry (JSCC) reference method. The coefficient of variation (CV = $100 \times$ standard deviation/mean) of two consecutive measurements within a day was less than 1.15% among 20 persons. The CV of two measurements at the same time point on two consecutive days was less than 4.08% among 6 persons. The urinary NTX levels were measured using the enzyme-linked immunosorbent assay (ELISA). The CV of two consecutive measurements within a day was less than 7.4% among 10 persons. The CV of two measurements at the same time point on two consecutive days was less than 15.0% among 24 persons.

Measurement of lumbar spine bone mineral densisty

The BMD of the lumbar spine (L1-L4) in the anteroposterior view was measured using dual-energy X-ray absorptiometry with a Hologic QDR 1500W apparatus (Bedford, MA, USA). The CV of five measurements with repositioning within 72 hours each time was less than 1.2% among 3 persons.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) in the tables and the mean ±95% confidence interval in the figures. An unpaired t-test or Fisher exact test was used to compare the characteristics of the study subjects between the two groups. A one-way analysis of variance (ANOVA) with repeated measurements was used to determine the significance of longitudinal changes in the BMD and biochemical markers in each group. A two-way ANOVA with repeated measurements was used to compare longitudinal changes in the BMD and biochemical markers between the two groups. An unpaired t-test was used to compare the percent changes in the BMD and biochemical markers at each time point between the two groups. A Fisher exact test was used to compare the incidence of osteoporotic fractures between the two groups. All the statistical analyses were performed using the Stat View-J5.0 program on a Windows computer. A significance level of P<0.01 was used for all the comparisons.

Results

Characteristics of the study subjects at the start of treatment

Thirty-one women were ≥80 years of age (older group), and 167 women were <80 years of age (control group). Table 1 shows the characteristics of the study subjects at the start of ALN treatment in the older and control groups. The age (mean ± SD) of all the subjects at the beginning of treatment was 68.7±9.5 years (range: 48-89 years). The age was significantly higher in the older group than in the control group (83.3±1.5 years and 66.0±7.7 years, respectively). Although the height and body weight were significantly lower in the older group than in the control group, the body mass index did not differ significantly between the two groups. The lumbar spine BMD and serum phosphorus and ALP levels did not differ significantly between the two groups. However, the serum calcium levels were significantly lower and the urinary NTX levels were significantly higher in the older group than in the control group. The mean levels of serum calcium, phosphorus, and ALP were within the normal ranges (8.4-10.2 mg/dL, 2.5-4.5 mg/dL, and 100-340 IU/L, respectively) in both groups. The mean urinary NTX level was higher than the normal range for Japanese women (9.3-54.3 nmol BCE/mmol Cr)[13] in both groups, indicating a high turnover characteristic of osteoporosis. The number of women with prevalent vertebral fractures did not differ sig-

Table 1. Characteristics of study subjects.

	Control group (n=167)	Older group (n=167)	P values
Age (years)	66.0±7.7	83.3±1.5	<0.0001
Height (m)	1.51±0.06	1.44±0.06	<0.0001
Body weight (kg)	48.4±6.7	43.3±5.6	<0.0001
Body mass index (kg/m²)	21.3±2.5	20.7±2.0	NS
Lumbar spine BMD (g/cm²)	0.653±0.095	0.650±0.074	NS
YAM of lumbar spine BMD (%)	64.0±9.3	63.8±7.2	NS
Serum calcium (mg/dL)	9.4±0.4	9.2±0.4	<0.01
Serum phosphorus (mg/dL)	3.4±0.5	3.4±0.5	NS
Serum ALP (IU/L)	243±81	284±125	NS
Urinary NTX (nmol BCE/mmol Cr)	67.2±24.2	80.2±30.3	<0.01
Number (%) of women with prevalent vertebral fractures	67 (40.1)	14 (45.2)	NS
Number (%) of women with history of non-vertebral fractures	8 (4.8)	1 (3.2)	NS

Data are expressed as means ± SD. Data comparisons between the two groups were performed using an unpaired t-test or a Fisher exact test. BMD, bone mineral density, YAM, young adult mean, ALP, alkaline phosphatase, NTX, cross linked N-terminal telopeptides of type I collagen, BCE, bone collagen equivalent, Cr, creatinine, NS, not significant.

nificantly between the two groups. The number of patients with a history of non-vertebral fractures (osteoporotic fractures at the distal radius, proximal humerus, and hip) also did not differ significantly between the two groups.

Changes in lumbar spine bone mineral density

Figure 1 shows that the lumbar spine BMD continued to increase for 3 years in both groups. A one-way ANOVA with repeated measurements showed significant longitudinal changes in the lumbar spine BMD (P<0.0001) in both groups (Table 2). A two-way ANOVA with repeated measurements showed no significant differences in longitudinal changes in the lumbar spine BMD between the two groups (Table 2).

The mean rates of change in the lumbar spine BMD after 1, 2, and 3 years of treatment were +4.87%, +6.77%, and +7.19%, respectively, in the older group and +5.55%, +7.56%, and +8.66%, respectively, in the control group. No significant differences in the percent changes in the lumbar spine BMD were observed at any time point between the two groups.

Changes in biochemical markers

Figure 2 shows the changes in the biochemical markers. The mean urinary NTX levels decreased to the normal range for Japanese women (9.3-54.3 nmol BCE/mmol Cr)[13] after 3 months of treatment, and the mean serum ALP levels decreased but remained within the normal range (135-310 IU/L) during the 3-year treatment period in both groups. A one-way ANOVA with repeated measurements showed significant longitudinal changes in the serum ALP and urinary NTX levels (both P<0.0001) in the older group and significant longitudinal changes in the serum calcium, ALP, and urinary NTX levels (all P<0.0001) in the control group (Table 2). No significant longitudinal changes in the serum phosphorus levels were observed in either group. A two-way ANOVA with repeated measurements showed no significant differences in longitudinal changes in the serum calcium, phosphorus, ALP, and urinary NTX levels between the two groups (Table 2). The mean rates of change in the urinary NTX levels after 3 months of treatment were -46.6% in the older group and -41.8% in the control group. The mean rates of change in the serum ALP levels after 1, 2, and 3 years of treatment were -23.7%, -23.9%, and -22.9%, respectively, in the older group and -17.7%, -24.3%, and -22.4%, respectively, in the control group. No significant differences in the percent changes in the urinary NTX and serum ALP levels as well as the serum calcium and phosphorus levels were observed at any time point between the two groups.

Incident fractures

Table 3 shows that during the 3-year treatment period, 4 patients experienced vertebral fractures (morphometric fracture in 2 patients and clinical fracture in 2 patients) in the older group and 22 patients experienced vertebral fractures (morphometric fracture in 16 patients and clinical fracture in 6 patients) in the control group. The incidence of morphometric vertebral fractures was 9.6% in the control group and 6.5% in the older group, and the respective incidence of clinical vertebral fractures was 3.6% and 6.5%. The incidence of morphometric and clinical vertebral fractures did not differ significantly between the two groups. Five patients experienced non-vertebral fractures (distal radius fracture in 3 patients, hip fracture in 1 patient, and proximal humerus fracture in 1 patient) in the older group and 5 patients experienced non-vertebral fractures (distal radius fracture in 4 patients and hip fracture in 1 patient) in the control group. All of these non-vertebral fractures occurred as a result of falls. The incidence of non-vertebral fractures was significantly higher in the older group than in the control group (16.1% vs 3.0%).
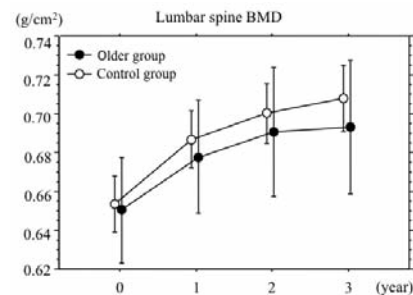

Figure 1. Changes in lumbar spine bone mineral density. Data were expressed as the mean ± 95% confidence interval. A one-way analysis of variance with repeated measurements showed significant longitudinal changes in the lumbar spine bone mineral density (P<0.0001) in the both groups. A two-way analysis of variance with repeated measurements showed no significant differences in longitudinal changes in the lumbar spine bone mineral density between the two groups. BMD, bone mineral density.

Table 2. Results of one- and two-way analysis of variance with repeated measurements.

	Group	One-way ANOVA	Two-way ANOVA (Control vs Older)
Lumbar spine BMD	Control	P<0.0001	NS
	Older	P<0.0001	
Serum calcium	Control	P<0.0001	NS
	Older	NS	
Serum phosphorus	Control	NS	NS
	Older	NS	
Serum ALP	Control	P<0.0001	NS
	Older	P<0.0001	
Urinary NTX	Control	P<0.0001	NS
	Older	P<0.0001	

A one-way analysis of variance (ANOVA) with repeated measurements was used to analyze the longitudinal changes in the BMD and biochemical markers within a group. A two-way ANOVA with repeated measurements was used to compare the longitudinal changes in the BMD and biochemical markers between the two groups. BMD, bone mineral density, ALP, alkaline phosphatase, NTX, cross linked N-terminal telopeptides of type I collagen; NS, not significant.

Table 3. Incidence of vertebral and non-vertebral fractures.

	Vertebral fractures			Non-vertebral fractures
	Morphometric	Clinical	Both	
Control group (n=167)	16 (9.6%)	6 (3.6%)	22 (13.2%)	5 (3.0%)
Older group (n=31)	2 (6.5%)	2 (6.5%)	4 (13.0%)	5 (16.1%)
P values	NS	NS	NS	P<0.01

The numbers of patients who suffered from fractures are shown. The numbers in parenthesis are the incidence of fractures. A Fisher exact test was used to compare the incidence of fractures. The incidence of non-vertebral fractures was significantly higher in the older group than in the control group. NS, not significant.

Adverse events

No serious adverse events, including osteonecrosis of the jaw, femoral diaphysis atypical fractures and atrial fibrillation, were observed.[14-24]

Discussion

In the control group (mean age: 66.0 years), ALN treatment increased the lumbar spine BMD (+8.66% at 3 years) subsequent to reductions in the urinary NTX level (-41.8% at 3 months) and the serum ALP level (-22.4% at 3 years). The urinary NTX levels were measured at 3 months after the start of ALN treatment because a urinary NTX measurement performed 3 months after the start of ALN treatment provides important information and is sufficient to monitor the effects of treatment for osteoporosis.[25] RCTs have shown that ALN (5 mg daily or 35 mg weekly) decreases the urinary NTX (-45% at 3 months) and serum ALP (about -20% at 3 years) levels and increases the lumbar spine BMD (+9.2% at 3 years) in postmenopausal Japanese women with osteoporosis (mean ages: 67-72 years).[6,8] The results of the present study are comparable with those of these previous studies.[6,8] Thus, ALN successfully suppressed bone turnover and increased the lumbar spine BMD, compared with the baseline values, over the course of a 3-year treatment period among postmenopausal osteoporotic Japanese women <80 years of age.

The incidence of morphometric vertebral fractures was 9.6% in the control group. A 3-year RCT in postmenopausal Japanese women with osteoporosis showed that the incidence of morphometric vertebral fractures was 7.8% for the ALN group and 18.8% for the active control (alfacalcidol) group without receiving either elementary calcium or natural vitamin D supplementation.[6] The higher incidence of morphometric vertebral fractures in the present study may be attributable to a higher proportion of frail patients who had a higher risk of incident fractures at baseline, since our exclusion criteria were not as strict as those used for the previous RCT.[6]

The serum calcium levels at baseline were significantly lower and urinary NTX levels at baseline were significantly higher in the older group (mean age: 83.3 years, range: 80-89 years) than in the control group (mean age: 66.0 years, range: 48-79 years). One possible explanation for these results might be attributable to the higher prevalence of vitamin D insufficiency and secondary hyperparathyroidism,[26] although we did not evaluate serum 25-hydroxyvitamin D and parathyroid hormone levels. Elderly patients may have vitamin D ins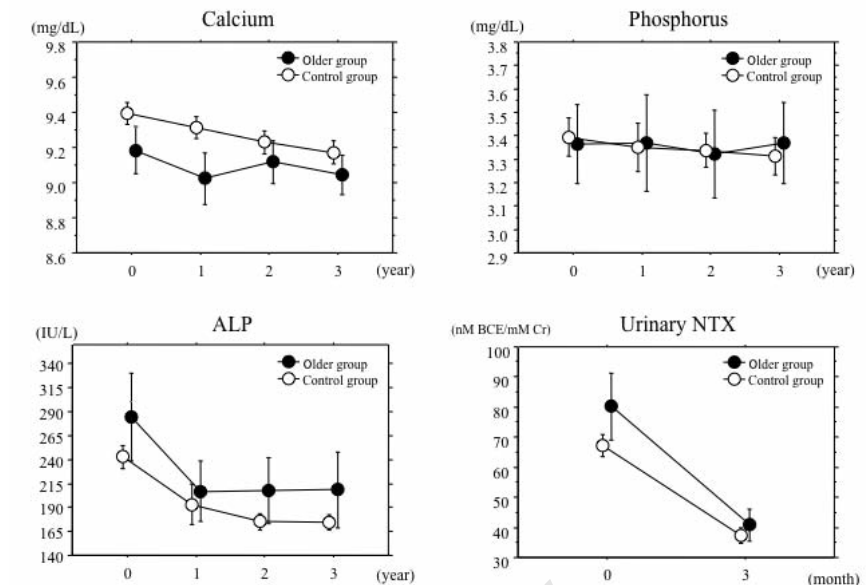ufficiency as a result of lower food intake as well as lower physical activity and, subsequently, inadequate sunlight exposure.[27] Secondary hyperparathyroidism may cause an increase in bone resorption.

In the older group, ALN treatment resulted in surrogate marker patterns similar to those observed in the control group. However, the incidence of non-vertebral fractures, all of which resulted from falls, during the 3-year ALN treatment period was significantly higher in the older group than in the control group. These results are consistent with the analysis of the FIT showing that the absolute risk reduction of symptomatic osteoporotic fractures with ALN treatment increased with age because of the age-related increase in the fracture risk.[4] The increased risk of fractures in osteoporotic older women was more likely to be caused by an increased risk of falls, compared with the risk in osteoporotic younger women.

Muscle tissue has highly specific nuclear receptors for 1,25-dihydroxyvitamin D.[28] Bischoff-Ferrari et al.[29,30] have shown that vitamin D supplementation appears to reduce the risk of falls as well as hip and all non-vertebral fractures in ambulatory or institutionalized elderly persons. Vitamin D increases muscle strength by ameliorating the atrophy of type II muscle fibers, an effect which could have decreased the risk of falls and hip fractures in disabled patients.[31] The conversion of calcidol (25-hydroxyvitamin D) to the most active metabolic form of vitamin D, calcitriol (1,25-dihydroxyvitamin D), is highly dependent on the renal function.[32,33] Thus, one possible explanation of the higher incidence of falls in the older group may be attributable to an age-related increase in the prevalence of renal dysfunction, although a secondary data analysis of women participating in the FIT demonstrated that ALN treatment increased BMD and decreased the relative risk, but not the absolute risk, of clinical fractures to a similar degree among women with and without reduced renal function.[34] Impairment of muscle strength and muscle power of the lower extremities, balance/postural control, and walking ability has been recognized as important risk factors for falls.[35] These parameters are known to become progressively more impaired with aging,[36] suggesting an increased risk for falls in the elderly. Another possible explanation may be due to the age-related impairment of physical function. Physicians may need to pay more attention to preventing falls even after the initiation of ALN treatment.

There are notable limitations in the present study. First, the quality of the present analyses may be relatively low because of the small sam-

Figure 2. Changes in biochemical markers. Data were expressed as the mean ± 95% confidence interval. A one-way analysis of variance with repeated measurements showed significant longitudinal changes in the serum alkaline phosphatase and urinary cross linked N-terminal telopeptides of type I collagen levels (both P<0.0001) in the older group, and significant longitudinal changes in the serum calcium, alkaline phosphatase, and urinary cross linked N-terminal telopeptides of type I collagen levels (all P<0.0001) in the control group. No significant longitudinal changes in the serum phosphorus levels were observed in the both groups. A two-way analysis of variance with repeated measurements showed no significant differences in longitudinal changes in the serum calcium, phosphorus, alkaline phosphatase, and urinary cross linked N-terminal telopeptides of type I collagen levels between the two groups. ALP, alkaline phosphatase, NTX, cross linked N-terminal telopeptides of type I collagen.

ple size, the absence of a statistical power for the fracture incidence, the retrospective nature of the analyses, and the limited number of patients ≥80 years of age. Second, the baseline biochemical marker levels of serum calcium and urinary NTX were not matched between the groups; the results of the present study might have differed if the above baseline data had been matched.

Conclusions

The present study showed that the incidence of non-vertebral fractures was significantly higher among postmenopausal osteoporotic Japanese women ≥80 years of age who were treated with ALN than among those <80 years of age despite the similar effect of ALN treatment on surrogate markers.

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