Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Experience with alendronate treatment for four years among Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
3 December 2010
Number of times this article has been viewed

Jun Iwamoto[1]
Yoshihiro Sato[2]
Mitsuyoshi Uzawa[3]
Tsuyoshi Takeda[1]
Hideo Matsumoto[1]

[1]Institute for Integrated Sports Medicine, Keio University School of Medicine, Tokyo; [2]Department of Neurology, Mitate Hospital, Fukuoka; [3]Department of Orthopaedic Surgery, Keiyu Orthopaedic Hospital, Gunma, Japan

Purpose: A retrospective study based on a conventional medical practice was performed to evaluate the outcome of alendronate treatment for four years in Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures.

Methods: Twenty-nine Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures (mean age at baseline 67.0 years) who had been treated with alendronate for over four years in our outpatient clinic were studied. Lumbar spine or total hip bone mineral density (BMD) was measured using dual energy x-ray absorptiometry, and urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) and serum levels of bone-specific alkaline phosphatase were monitored during the four-year treatment period.

Results: Urinary NTX and serum bone-specific alkaline phosphatase levels decreased (−44.4% at three months and −62.2% at four years, respectively) and lumbar spine and total hip BMD increased (+13.9% and +9.7% at four years, respectively), compared with baseline values. No serious adverse events were observed, including osteonecrosis of the jaw, femoral diaphysis atypical fractures, or atrial fibrillation.

Conclusion: To our knowledge, this is the first report of the outcome of alendronate treatment for four years in Japanese men with an increased risk for fractures. Alendronate suppressed bone turnover and increased lumbar spine and total hip BMD from baseline over the course of the four-year treatment period without causing any severe adverse events in Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures.

Keywords: alendronate, bone mineral density, fracture risk, men, osteoporosis, osteopenia

Introduction

Osteoporosis most commonly affects postmenopausal women, placing them at a significant risk for fractures. Alendronate is widely used for the treatment of postmenopausal osteoporosis. The Fracture Intervention Trial demonstrated the antifracture efficacy of alendronate for vertebral, nonvertebral, hip, and wrist fractures in postmenopausal women with osteoporosis.[1,2] A recent systematic review analyzing 11 randomized controlled trials including 12,068 women confirmed both clinically important and statistically significant reductions in vertebral, nonvertebral, hip, and wrist fractures for secondary prevention, ie, gold level evidence.[3] Alendronate is regarded as a first-line drug for the treatment of osteoporosis in Japan.

Because increasing longevity has increased the public health burden of osteoporotic fractures in men, considerable attention has been paid to osteoporosis in this group. Alendronate has been approved by the US Food and Drug Administration for the treatment of osteoporosis in men. However, the efficacy of alendronate for osteoporosis

Correspondence: Jun Iwamoto
Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
Tel +81 333 531 211
Fax +81 333 529 467
Email jiwamoto@sc.itc.keio.ac.jp

submit your manuscript | www.dovepress.com
Dovepress
DOI: 10.2147/TCRM.S15812

in men is not as firmly established as it is in women, because only a few strictly conducted randomized controlled trials have been performed examining the efficacy of alendronate in men with osteoporosis.[4,5]

Several studies have reported the effects (over 1–3 years) of alendronate or risedronate on bone mineral density (BMD) and bone turnover in men with osteoporosis.[4–9] However, to our knowledge, no data showing the long-term (more than three years) effects of alendronate on BMD and bone turnover in Japanese men with osteoporosis have been reported. Thus, a retrospective study based on a conventional medical practice was performed to evaluate the outcome of alendronate treatment for four years in Japanese men with an increased risk for fractures. The primary endpoint was BMD, and the secondary endpoints were biochemical markers. Adverse events, such as osteonecrosis of the jaw, femoral atypical diaphysis fractures, and atrial fibrillation,[10–12] as well as incident osteoporotic fractures (at the vertebrae, hip, wrist, and proximal humerus, were assessed). We believe that the data presented in this paper may provide physicians who treat patients in Asia with useful information, because there are no reports showing the long-term effect of alendronate treatment on BMD and bone turnover in Asian men with an increased risk for fractures.

Methods and materials

Subjects

Twenty-nine men with osteoporosis or osteopenia and clinical risk factors for fractures (mean age 61.0 years at the beginning of treatment) who had been treated with alendronate (5 mg daily or 35 mg weekly) for over four years were recruited at the outpatient clinic of Seiyu Orthopaedic Hospital, Gunma, Japan, during a three-month period between July 1 and September 30, 2010. Patients whose data were missing or incomplete were excluded. The doses indicated in parentheses are the doses used in Japan for treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective.[13,14] The effects of daily and weekly alendronate on BMD and bone turnover markers, as well as the incidence of side effects, were reported to be similar in postmenopausal Japanese women with osteoporosis.[14] Daily alendronate was available throughout the study period, but weekly alendronate only became available after October 2006. The patients were treated with daily alendronate (5 mg daily) before October 2006 and with weekly alendronate (35 mg weekly) after October 2006. The subjects did not receive either elementary calcium or natural vitamin D supplements.

According to the Japanese diagnostic criteria,[15,16] patients with a BMD < 70% of the young adult mean or 70%–80% of the young adult mean along with a history of osteoporotic fractures should be diagnosed as having osteoporosis. Patients with a BMD of 70%–80% of the young adult mean without any history of osteoporotic fractures are diagnosed as having osteopenia. Patients with osteoporosis or osteopenia and clinical risk factors for fractures, such as current smoking, alcohol abuse (≥2 U/day), a history of steroid use, or a maternal family history of hip fracture, are treated with drugs.[17] One alcohol unit is measured as 20 g pure alcohol. This equals a unit (180 mL) of Japanese wine (alcohol by volume [ABV] 15%), a bottle (500 mL) of Japanese beer (ABV 5%), a quarter (180 mL) of a bottle of red wine (ABV 14%), one 60 mL double measure of whisky (ABV 43%), or 0.6 unit (110 mL) of shochu (a clear liquor, ABV 25%). Lumbar spine or total hip BMD was used for diagnosis of osteoporosis. BMD was able to be evaluated only at one skeletal site among the lumbar spine, hip, distal radius, and calcaneus because of medical insurance regulations in Japan. Dual-energy x-ray absorptiometry at our facility was used to measure BMD of the lumbar spine and total hip, both of which are clinically important skeletal sites in the treatment of osteoporosis. BMD was measured at the lumbar spine before December 2004 because the spine was considered to be an important skeletal site in the treatment of osteoporosis, based on a report that showed a higher incidence of vertebral fractures in Japanese than in Caucasians.[18] However, BMD was measured at the total hip after January 2005 because hip BMD had been paid attention to as a result of a report suggesting use of the proximal femur with dual-energy x-ray absorptiometry (as the recommended site) for diagnosis in the assessment of fracture risk.[19] All patients in the present study had been diagnosed as having osteoporosis or osteopenia and had at least one of the aforementioned clinical risk factors for fractures.

Preliminary screening included a medical history, physical examination, plain x-rays of the thoracic and lumbar spine, lumbar spine (n = 15) or total hip (n = 14) BMD measurement, and blood and urinary biochemical tests including serum calcium, phosphorus, and bone-specific alkaline phosphatase as a bone formation marker and urinary cross-linked N-terminal telopeptides of type I collagen (NTX) as a bone resorption marker. Subjects with a history of reflux esophagitis or gastric or duodenal ulcers were excluded. None of the subjects had ever taken medication for treatment of osteoporosis prior to the present study.

The measurement of urinary NTX levels is permitted only twice (just before and within six months after the start of medication) in Japan because of medical insurance regulations. Thus, we evaluated urinary NTX at three months after the start of treatment, because a urinary NTX measurement performed at this stage provides important information and is sufficient to monitor the effects of treatment for osteoporosis.[20] Serum levels of calcium, phosphorus, and bone-specific alkaline phosphatase, and lumbar spine or total hip BMD, were measured every six months after the start of treatment. After four years of treatment, plain x-rays of the thoracic and lumbar spine were taken to assess incident vertebral fractures. Incident clinical fractures were also assessed. The outcome of alendronate treatment for four years was then evaluated. The present study was approved by the Ethics Committee of Keiyu Orthopaedic Hospital.

Vertebral fractures

Plain lateral x-ray films of the thoracic and lumbar spine were obtained at baseline to detect evidence of morphometric vertebral fractures. According to the Japanese criteria, a vertebral fracture was defined according to vertebral height on lateral x-ray films.[15,16] Briefly, vertebral height was measured at the anterior (A), central (C), and posterior (P) heights of the vertebral body, and the presence of a vertebral fracture was confirmed when: a reduction in the vertebral height of more than 20% (A, C, and P) compared with the height of the adjacent vertebrae was observed; the C/A ratio or C/P ratio was less than 0.8; or the A/P was less than 0.7. Assessment for vertebral fractures was performed at the T4–L4 level.

Lumbar spine or total hip BMD

BMD at the lumbar spine (L1–L4) or the left total hip in the AP view was measured using dual-energy x-ray absorptiometry (with Hologic QDR 1500W apparatus, Bedford, MA). The coefficient of variation (100 × standard deviation [SD]/mean) of five measurements with repositioning within 72 hours each time was less than 1.2% for three persons.

Serum calcium, phosphorus, bone-specific alkaline phosphatase, and urinary NTX

Serum calcium and phosphorus levels were measured using standard laboratory techniques (normal range 8.4–10.2 mg/dL, 2.5–4.5 mg/dL, and 135–310 IU/L, respectively). Serum bone-specific alkaline phosphatase levels were measured using an enzyme immunoassay. Urinary NTX levels were measured using an enzyme-linked immunosorbent assay. Normal ranges of urinary NTX and serum bone-specific alkaline phosphatase in men were not established in Japan.

Statistical analysis

Data were expressed as the mean ± SD. The unpaired *t*-test or Fisher's Exact test was used to compare data between the two groups. Analysis of variance (ANOVA) with Fisher's protected least significant difference (PLSD) test was used to compare data among the time points (post hoc analysis). One-way ANOVA with repeated measurements was used to determine the significance of longitudinal changes in BMD and biochemical markers. Two-way ANOVA with repeated measurements was used to compare longitudinal changes in BMD and biochemical markers between the lumbar spine and total hip groups. All statistical analyses were performed using the Stat View J 5.0 program on a Windows computer. A significance level of $P < 0.05$ was used for all the comparisons.

Results

Baseline characteristics of study subjects

Table 1 shows the characteristics of the study subjects at the start of alendronate treatment. The mean age was 61.0 years.

Table 1 Characteristics of study subjects at the start of treatment

	Mean ± SD	Range
Number of subjects	29	
Age (years)	61.0 ± 13.1	34–80
Height (m)	1.63 ± 0.08	1.50–1.79
Body weight (kg)	57.1 ± 10.1	38–75
Body mass index (kg/m^2)	21.4 ± 3.0	16.8–6.9
Current smoking [n (%)]	13 (44.8)	
Alcohol abuse [≧2 units/day, n (%)]	6 (20.7)	
History of steroid use [n (%)]	4 (13.8)	
Maternal family history of hip fracture [n (%)]	1 (3.4)	
Lumbar spine BMD (g/cm^2)	0.679 ± 0.110	0.446–0.804
%YAM of lumbar spine BMD (%)	65.7 ± 10.8	43–78
Total hip BMD (g/cm^2)	0.674 ± 0.098	0.486–0.768
%YAM of total hip BMD (%)	68.3 ± 7.8	51–72
Urinary NTX (nM BCE/mM Cr)	61.3 ± 26.1	32.2–144.5
Serum calcium (mg/dL)	9.4 ± 0.5	8.7–10.3
Serum phosphorus (ng/dL)	3.1 ± 0.7	2.2–5.6
Serum BSAP (U/L)	31.0 ± 10.2	13.6–50.9
Number (%) of patients with vertebral fracture	13 (44.8)	
Number of vertebral fracture/patient	1.28 ± 2.10	0–9

Note: The BMD was measured at the lumbar spine for 15 patients and at the hip for 14 patients.

Abbreviations: SD, standard deviation; BMD, bone mineral density; YAM, young adult mean; NTX, cross-linked N-terminal telopeptides of type I collagen; BCE, bone collagen equivalent; BSAP, bone-specific alkaline phosphatase.

Thirteen subjects (44.8%) were current smokers, six (20.7%) were alcohol abusers (≥2 U/day), four (29%) had a history of steroid use, and one (3.4%) had a maternal family history of hip fracture. Mean lumbar spine and total hip BMD were 0.679 g/cm^2 (65.7% of the young adult mean) and 0.674 g/cm^2 (68.3% of the young adult mean), respectively. Twenty subjects (69.0%) were diagnosed as having osteoporosis, and nine (31.0%) were diagnosed as having osteopenia in addition to clinical risk factors for fractures. Mean urinary NTX level was 61.3 nM BCE/mM Cr, and mean serum level of bone-specific alkaline phosphatase was 31.0 U/L. Thirteen subjects (44.8%) had prevalent vertebral fractures, and the mean number of prevalent vertebral fractures per subject was 1.28.

The past histories of subjects that could affect bone metabolism were steroid use (hearing loss [n = 1], nephritis [n = 1], subacute thyroiditis [n = 1], and Vogt-Koyanagi-Harada disease [n = 1]), diabetes mellitus (n = 1), hepatitis (n = 1), gastrectomy (n = 1), and cerebrovascular disease with no apparent hemiplegia (n = 1). Urinary NTX levels and serum bone-specific alkaline phosphatase levels at baseline were similar in those with and those without such illnesses (according to the unpaired *t*-test).

Table 2 shows the characteristics of the study subjects at the start of alendronate treatment divided by the BMD measurement site. Body weight and body mass index were significantly greater in the total hip group than in the lumbar spine group (according to the unpaired *t*-test). However, there were no significant differences in other characteristics between the two groups (according to the unpaired *t*-test or Fisher's Exact test).

Table 2 Characteristics of study subjects at the start of treatment divided by BMD measurement site

	Lumbar spine	Total hip	*P* values
Number of subjects	15	14	
Age (years)	59.6 ± 11.6	62.7 ± 14.6	NS
Height (m)	1.64 ± 0.08	1.62 ± 0.08	NS
Body weight (kg)	61.5 ± 8.7	53.1 ± 10.1	<0.05
Body mass index (kg/m^2)	22.6 ± 3.3	20.1 ± 2.1	<0.05
Current smoking [n (%)]	6 (40.0)	7 (50.0)	NS
Alcohol abuse [≧2 units/day, n (%)]	3 (20.0)	3 (21.4)	NS
History of steroid use [n (%)]	2 (13.3)	[illegible]	NS
Maternal family history of hip fracture [n (%)]	1 (6.7)	0 (0.0)	NS
Urinary NTX (nM BCE/mM Cr)	53.[illegible] ± 13.8	68.9 ± 33.0	NS
Serum calcium (mg/dL)	9.4 ± 0.5	9.[illegible]	NS
Serum phosphorus (ng/dL)	2.8 ± [illegible]	3.2 ± 0.5	NS
Serum BSAP (U/L)	[illegible] ± 9.7	1.7 ± 11.0	NS
Number (%) of patients with vertebral fracture	3 ([illegible]0)	10 (71.4)	NS
Number of vertebral fracture/	1.86 ± 2.45	0.73 ± 1.62	NS

Note: Data are expressed as means ± standard deviation. The unpaired *t*-test or Fisher exact test was used to compare data between the two groups.
Abbreviations: BMD, bone mineral density; NTX, cross-linked N-terminal telopeptides of type I collagen; BCE, bone collagen equivalent; BSAP, bone-specific alkaline phosphatase; NS, not significant.

Lumbar or total hip BMD and biochemical markers

Figure 1 shows a continuous increase in lumbar spine and total hip BMD over the four-year study period. Table 3 and Figure 2 show the rates of increase for lumbar BMD after years 1, 2, 3, and 4 of treatment compared with baseline values were 8.0%, +[illegible]%, +11.4%, and +13.9%, respectively, while the rates of increase for the total hip BMD compared with baseline values were +3.8%, +4.7%, 6.8%, and +9.2%, respectively. The post hoc analysis (ANOVA with Fisher's PLSD test) showed significant increases in lumbar spine BMD at 42 and 48 months compared with baseline values, but did not show any significant increases in total hip BMD at any time points compared with baseline values. However, one-way ANOVA with repeated measurements detected significant increases in both lumbar spine and total hip BMD (Table 3).

Figure 3 shows the changes in biochemical markers. Urinary NTX levels decreased after three months of treatment and serum bone-specific alkaline phosphatase levels decreased after six months of treatment and continued to decrease thereafter. Table 3 shows that the mean change in urinary NTX levels after three months of treatment compared with baseline values was –44.4%. Mean change in serum bone-specific alkaline phosphatase levels after one year of treatment compared with baseline values was –42.5%, and this effect continued to decrease gradually over the course of the four-year treatment period (–48.0% at two years, –55.5% at three years, and –61.2% at four years). The post hoc analysis (ANOVA with Fisher's PLSD test) showed a significant decrease in urinary NTX levels at three months compared with baseline values, and significant decreases in serum bone-specific alkaline phosphatase levels at all time points compared with baseline values. One-way ANOVA with repeated measurements detected significant decreases in both urinary NTX and serum bone-specific alkaline phosphatase levels (Table 3).

The post hoc analysis showed a significant decrease in serum calcium levels at 30, 42, and 48 months compared with baseline values, but did not show any significant decreases in serum phosphorus levels at any time points compared with baseline values. One-way ANOVA with repeated

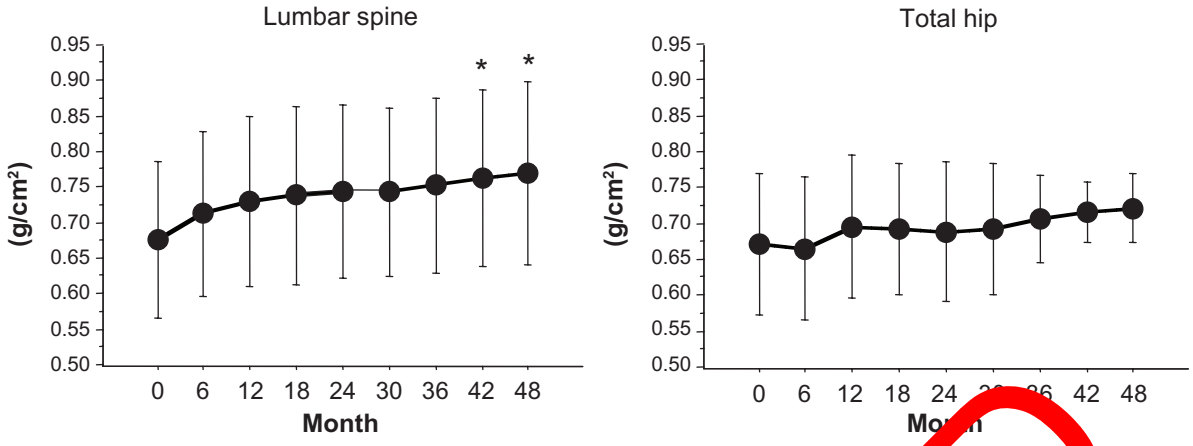

Figure 1 Changes in bone mineral density. The BMD was measured at the lumbar spine for 15 patients and at the hip for [illegible] patients. Data were expressed as the mean ± standard deviation. Post hoc analysis showed significant increases in lumbar spine BMD at 42 and 48 months compared with baseline values, but did not show any significant increases in total hip BMD at any time points compared with baseline values. However, one-way ANOVA with repeated measurements detected significant increases in both lumbar spine and total hip BMD.
Note: *$P < 0.05$ versus baseline values by ANOVA with Fisher's PLSD test.
Abbreviations: BMD, bone mineral density; ANOVA, analysis of variance; PLSD, protected least significant difference.

measurements did not detect any significant changes in either serum calcium and phosphorus levels (Table 3).

Longitudinal changes in BMD and biochemical markers, such as urinary NTX, serum bone-specific alkaline phosphatase, calcium, and phosphorus did not differ significantly between the lumbar spine and total hip groups (by two-way ANOVA with repeated measurements).

Incident fractures

During the four-year treatment period, two patients experienced vertebral fractures. One patient experienced fractures at T10 and T11 and another at L1. The BMD of the former patient was evaluated at the lumbar spine, and that of the latter patient at the hip. However, none of the patients experienced hip, wrist, or proximal humerus fractures. The incidence of vertebral fractures was 6.9%.

Adverse events

No serious adverse events, including osteonecrosis of the jaw, femoral atypical diaphysis fractures, or atrial fibrillation, were observed.

Table 3 Percent changes in BMD and bone turnover markers compared with baseline values

	3 mos	1 yr	2 yrs	3 yrs	4 yrs	*P* values
Lumbar spine BMD		+8.0	+10.0	+11.4	+13.9	<0.0001
Total hip BMD		+3.8	+4.7	+6.8	+9.2	<0.001
Urinary NTX	−44.4					<0.0001
Serum BSAP		−42.5	−48.0	−55.5	−61.2	<0.0001

Note: One-way ANOVA with repeated measurements was used to determine the significance of changes in BMD and bone turnover markers.
Abbreviations: BMD, bone mineral density; NTX, cross-linked N-terminal telopeptides of type I collagen; ANOVA, analysis of variance.

Discussion

The present study confirmed that alendronate suppressed bone turnover and increased lumbar spine or total hip BMD, compared with baseline values, over a four-year treatment period without causing any severe adverse events, including osteonecrosis of the jaw, femoral atypical diaphysis fractures, or atrial fibrillation.

The higher risk of osteoporotic fractures in men is considered to accrue from a lower peak volumetric BMD and greater bone loss with aging, particularly among those subjects with risk factors, hypogonadism, or underlying illness.[21] Bone formation, as reflected by bone formation markers, likely decreases with aging and in the presence of fractures in men.[21] On the other hand, bone resorption, as reflected by bone resorption markers, may increase late in life, probably reflecting an increase in bone turnover associated with secondary hyperparathyroidism.[21] However, whether osteoporosis in men is caused mainly by increased bone resorption remains controversial, even though increased or decreased bone turnover has been reported in men with vertebral fractures.[22,23] In the present study, eight patients (27.6%) had some illness that could affect bone metabolism. However, urinary NTX levels and serum bone-specific alkaline phosphatase levels at baseline were similar in both those with and those without such illnesses. In total, 44.8% of the subjects had prevalent vertebral fractures (mean number 1.28). The efficacy of antiresorptive drugs, such as alendronate, can be expected in our subjects with an increased risk for fractures.

Studies have shown that alendronate decreases urinary NTX (−42% at three months) and serum bone-specific alkaline phosphatase (about −33% at six months) levels and

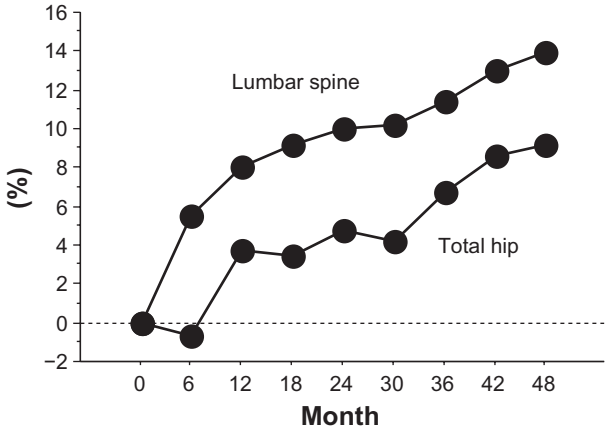

Figure 2 Mean percent changes in bone mineral density from baseline. The BMD was measured at the lumbar spine for 15 patients and at the hip for 14 patients. Rates of increase for the lumbar BMD after treatment years 1, 2, 3, and 4 compared with baseline values were +8.0%, +10.0%, +11.4%, and +13.9%, respectively, while the rates of increase for the total hip BMD compared with baseline values were +3.8%, +4.7%, +6.8% and +9.2%, respectively.
Abbreviation: BMD, bone mineral density.

increases the lumbar spine, femoral neck, and total hip BMD (+8.8%–11.5%, 4.2%–5.8%, and 3.9%, respectively, at three years) in men with osteoporosis.[5–7] In the present study, urinary NTX and serum BAP levels decreased (−44.4% at three months and −61.2% at four years, respectively) and lumbar spine and total hip BMD increased (+13.9% and +9.2% at four years, respectively), compared with baseline values. Reduction in serum bone-specific alkaline phosphatase and increase in BMD were greater in our subjects than in Western men with osteoporosis, probably because of higher bone turnover at baseline according to the normal ranges of urinary NTX and serum bone-specific alkaline phosphatase in healthy premenopausal women (9.3–5[illegible] nM BCE/mM Cr and 7.9–29.0 U/L, respectively).[24] Normal ranges for these bone turnover parameters in men were not established in Japan. Our previous study showed that urinary NTX levels were not higher in men with osteoporosis than in postmenopausal women with osteoporosis.[25]

Serum bone-specific alkaline phosphatase levels decreased after 3 months of treatment and continued to decrease thereafter. The mean change in serum bone-specific alkaline phosphatase levels after four year of treatment compared with baseline values was −61.2%. Postmenopausal women treated with alendronate with the greatest percent reduction in bone-specific alkaline phosphatase have the lowest risk of hip fractures, while those with the smallest reduction in bone-specific alkaline phosphatase have the highest risk.[26] Alendronate-treated postmenopausal women with a reduction in bone-specific alkaline phosphatase of at least 30% have a 74% lower risk of hip fractures, compared with those having a less than 30% reduction.[26] Although the efficacy of alendronate against vertebral fractures seems to have been established in men with osteoporosis,[27] the efficacy of alendronate with regard to reduction in risk of hip fractures remains to be established, probably because of the insufficient sample sizes for randomized controlled trials. Thus, the improvement of surrogate markers, such as hip BMD and bone turnover markers, is thought to be important for preventing hip fractures in men with an increased risk of fractures.

A cohort study in Japan revealed that the incidence (per 1000 person-years) of vertebral fractures in female atomic bomb survivors aged 60–69 years in Hiroshima and Nagasaki was 6.5 in the absence of prevalent vertebral fractures and 31.5 in the presence of prevalent vertebral fractures. Namely, the respective incidences of vertebral fractures during a four-year period was considered to be 2.6% and 12.6% (average 7.6%).[18] The incidence of vertebral fractures at four years was 6.9% in our study subjects (mean age 61.0 years, and 44.8% subjects had prevalent vertebral fractures), suggesting a relatively high incidence of vertebral fractures despite receiving alendronate therapy. One possible explanation for this result might be the higher proportion of patients with prevalent vertebral fractures in terms of the higher risk of incident fractures at baseline. Another possibility might be the existence of subclinical osteomalacia on a background of significantly decreased serum calcium levels because of lack of calcium and vitamin D supplementation.

The strength of the present study is that it is the first report of the outcome of alendronate treatment for four years in Japanese men with an increased risk for fractures. However, the present study has some notable limitations. First, it was a retrospective study with a small sample size based on a conventional medical practice. Second, we confirmed that there were no severe adverse events, including osteonecrosis of the jaw, femoral atypical diaphysis fractures, and atrial fibrillation in patients who were treated with alendronate over four years. However, because we were not able to recruit patients who dropped out from alendronate treatment, the true incidence of adverse events with alendronate treatment remains uncertain. Third, the subjects did not receive either elementary calcium or natural vitamin D supplementation, which is not prevalent in Japan. This circumstance makes it difficult to compare the present study with others, because most other studies have involved men with osteoporosis who have taken calcium and vitamin D supplements. Prospective studies with a large number of subjects are needed to establish the long-term efficacy and

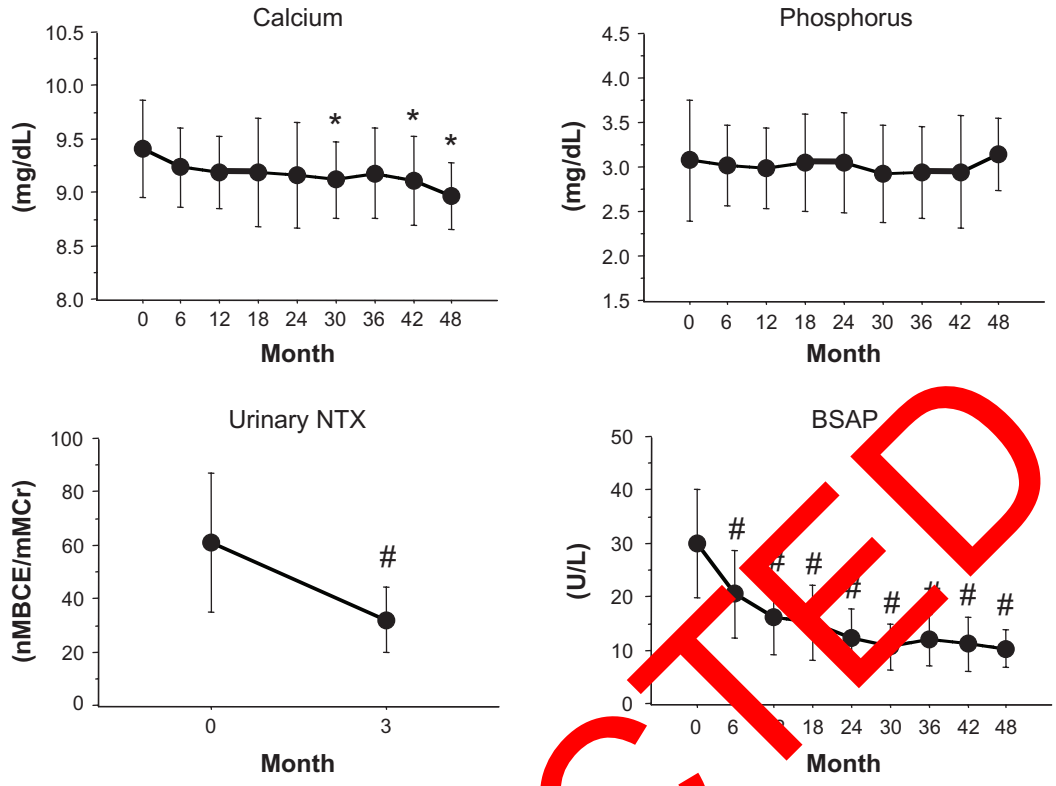

Figure 3 Changes in biochemical markers. Data were expressed as the mean ± standard deviation. Post hoc analysis showed a significant decrease in urinary NTX levels at three months compared with baseline values, and significant decreases in serum bone-specific alkaline phosphatase levels at all time points compared with baseline values. One-way ANOVA with repeated measurements detected significant decreases in both urinary NTX and serum bone-specific alkaline phosphatase levels. Post hoc analysis showed a significant decrease in serum calcium levels at 30, 42, and 48 months compared with baseline values, but did not show any significant decreases in serum phosphorus levels at any time points compared with baseline values. One-way ANOVA with repeated measurements did not detect any significant changes in both serum calcium and phosphorus levels.

Notes: *$P < 0.05$; #$P < 0.001$ versus baseline values by ANOVA with Fisher's PLSD test.

Abbreviations: NTX, cross-linked N-terminal telopeptide of type I collagen; BSAP, bone-specific alkaline phosphatase; ANOVA, analysis of variance; PLSD, protected least significant difference.

safety of alendronate treatment in combination with calcium and vitamin D supplementation in Japanese men with an increased risk for fractures.

In conclusion, the present study confirmed that alendronate suppressed bone turnover and increased lumbar spine and total hip BMD from baseline over the course of a four-year treatment period without causing any severe adverse events in Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures.

Disclosure

The authors report no funding sources or conflict of interest in this work.

References

1. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet*. 1996;348:1535–1541.
2. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial. *JAMA*. 1998;280:2077–2082.
3. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst Rev*. 2008;23:CD001155.
4. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med*. 2000;343:604–610.
5. Miller PD, Schnitzer T, Emkey R, et al. Weekly oral alendronic acid in male osteoporosis. *Clin Drug Investig*. 2004;24:333–341.
6. Ringe JD, Dorst A, Faber H, et al. Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. *Rheumatol Int*. 2004;24:110–113.
7. Gonnelli S, Cepollaro C, Montagnani A, et al. Alendronate treatment in men with primary osteoporosis: A three-year longitudinal study. *Calcif Tissue Int*. 2003;73:133–139.
8. Ringe JD, Faber H, Farahmand P, et al. Efficacy of risedronate in men with primary and secondary osteoporosis: Results of a 1-year study. *Rheumatol Int*. 2006;26:427–431.
9. Majima T, Shimatsu A, Komatsu Y, et al. Effects of risedronate or alfacalcidol on bone mineral density, bone turnover, back pain, and fractures in Japanese men with primary osteoporosis: Results of a two-year strict observational study. *J Bone Miner Metab*. 2009;27:168–174.
10. Ruggiero SL, Dodson TB, Assael LA, et al. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws – 2009 update. *J Oral Maxillofac Surg*. 2009;67:2–12.

11. Lenart BA, Lorich DG, Lane JM. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N Engl J Med*. 2008;358:1304–1306.
12. Heckbert SR, Li G, Cummings SR, et al. Use of alendronate and risk of incident atrial fibrillation in women. *Arch Intern Med*. 2008;168: 826–831.
13. Shiraki M, Kushida K, Fukunaga M, et al. A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. *Osteoporos Int*. 1999;10: 183–192.
14. Uchida S, Taniguchi T, Shimizu T, et al. Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: A double-blind, randomized study. *J Bone Miner Metab*. 2005;23:382–388.
15. Orimo H, Sugioka Y, Fukunaga M, et al. Diagnostic criteria of primary osteoporosis. *J Bone Miner Metab*. 1998;16:139–150.
16. Orimo H, Hayashi Y, Fukunaga M, et al. Diagnostic criteria for primary osteoporosis: Year 2000 revision. *J Bone Miner Metab*. 2001;19: 331–337.
17. Kanis JA, Borsgtrom F, de Laet C, et al. Assessment of fracture risk. *Osteoporos Int*. 2005;16:581–589.
18. Fujiwara S, Kasagi F, Masunari N, et al. Fracture prediction from bone mineral density in Japanese men and women. *J Bone Miner Res*. 2003; 18:1547–1553.
19. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet*. 2002;359:1929–1936.
20. Iwamoto J, Takeda T, Sato Y, et al. Early changes in urinary cross-linked N-terminal telopeptides of type I collagen level correlate with one-year response of lumbar bone mineral density to alendronate in Japanese postmenopausal women with osteoporosis. *J Bone Miner Metab*. 2005;23:238–242.
21. Seeman E. Unresolved issues in osteoporosis in men. *Rev Endocr Metab Disord*. 2001;2:45–64.
22. Resch H, Pietschmann P, Woloszczuk W, et al. Bone mass and biochemical parameters of bone metabolism in men with spinal osteoporosis. *Eur J Clin Invest*. 1992;22:542–545.
23. Sharp CA, Worsfold M, Rowlands PR, et al. Accurate prediction of spinal osteoporosis in men using a biochemical measure of collagen balance. *Bone*. 1994;15:243.
24. Nishizawa Y, Nakamura T, Ohta H, et al. Guidelines for the use of biochemical markers of bone turnover in osteoporosis (2004). *J Bone Miner Metab*. 2005;23:97–104.
25. Iwamoto J, Takeda T, Sato Y, et al. Comparison of the effect of alendronate on lumbar bone mineral density and bone turnover in men and postmenopausal women with osteoporosis. *Clin Rheumatol*. 2007;26: 161–167.
26. Bauer DC, Black DM, Garnero P, et al. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: The Fracture Intervention Trial. *J Bone Miner Res*. 2004;19: 1250–1258.
27. Ringe JD, Orth J, Daifotis A, et al. Treatment of male osteoporosis: Recent advances with alendronate. *Osteoporos Int*. 2002;13:195–199.