Clin Rheumatol (2016) 35:205–212
DOI 10.1007/s10067-014-2812-y

ORIGINAL ARTICLE

Experience with alendronate treatment for 7 years among Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures

Jun Iwamoto · Mitsuyoshi Uzawa

Received: 17 August 2014 / Revised: 1 October 2014 / Accepted: 12 October 2014 / Published online: 1 November 2014

Abstract A retrospective study was performed to evaluate the outcome of alendronate treatment for 7 years among Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures. Thirty-five Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures (mean age at baseline 58.2 years) who had been treated with alendronate for over 7 years in our outpatient clinic were analyzed. The lumbar spine or total hip bone mineral density (BMD) was measured using dual energy X-ray absorptiometry; the urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) and the serum levels of alkaline phosphatase (ALP) were monitored; the incidence of fractures during the 7-year treatment period was then assessed. The urinary NTX and serum ALP levels decreased (−46.1 % at 3 months and −21.1 % at 7 years, respectively) and the lumbar spine and total hip BMD increased (+14.2 and +10.1 % at 7 years, respectively), compared with the baseline values. Four patients (11.4 %) experienced vertebral fractures, and one patient (2.9 %) experienced a nonvertebral fracture. No serious adverse events were observed, including osteonecrosis of the jaw or atypical femoral fractures. These results suggested that alendronate suppressed bone turnover and increased the lumbar spine and total hip BMD from the baseline values over the course of the 7-year treatment period without causing any severe adverse events in Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures.

J. Iwamoto (✉)
Institute for Integrated Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: jiwamoto@a8.keio.jp

M. Uzawa
Department of Orthopaedic Surgery, Keiyu Orthopaedic Hospital, Gunma, Japan

Keywords Alendronate · Bone mineral density · Men · Osteoporosis · Osteopenia · Risk factor for fractures

Introduction

Osteoporosis most commonly affects postmenopausal women, placing them at a significant risk for fractures. Alendronate (ALN) is widely used for the treatment of postmenopausal osteoporosis. The Fracture Intervention Trial (FIT) has previously demonstrated the anti-fracture efficacy of ALN for vertebral, nonvertebral, hip, and wrist fractures in postmenopausal women with osteoporosis [1, 2]. Furthermore, a systematic review analyzing 11 randomized controlled trials (RCTs) representing 12,068 women has confirmed both clinically important and statistically significant reductions in vertebral, nonvertebral, hip, and wrist fractures for secondary prevention (gold level evidence) [3]. Thus, ALN is regarded as a first-line drug for the treatment of osteoporosis in Japan. The current Japanese 2011 guidelines for prevention and treatment of osteoporosis show that only ALN and risedronate therapies are strongly recommended for increasing bone mineral density (BMD) and reducing the risk of vertebral, nonvertebral, and hip fractures in patients (men and postmenopausal women) with primary osteoporosis [4].

Since increasing longevity has increased the public health burden of osteoporotic fractures in men, considerable attention has been paid to osteoporosis in men. ALN has been approved by the US Food and Drug Administration (US FDA) for the treatment of osteoporosis in men. However, the efficacy of ALN for osteoporosis in men is not as firmly established as it is in women because only a few strictly conducted RCTs have been performed examining the efficacy of ALN in men with osteoporosis [5, 6].

Several studies have reported the effects (1–3 years) of ALN or risedronate on BMD and bone turnover in men with

osteoporosis [5–10]. Recently, we reported that ALN successfully reduced bone turnover and increased the lumbar spine and total hip BMD for 4 years in Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures [11]. To our knowledge, however, no data showing the long-term (>5 years) effects of ALN on BMD and bone turnover in Japanese men with osteoporosis have been reported. The long-term efficacy of anti-osteoporosis medicines needs to be established. Thus, a retrospective study based on conventional medical practice was performed to evaluate the outcome of ALN treatment over a 7-year period among Japanese men with an increased risk for fractures. The primary end point was the BMD, and the secondary end points were the biochemical markers. Adverse events such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures [12, 13] as well as incident osteoporotic fractures (vertebral, hip, wrist, proximal humerus, pelvis, lower leg, and rib fractures) were also assessed.

Subjects and methods

Subjects

Thirty-five men with osteoporosis or osteopenia and clinical risk factors for fractures (mean age 58.2 years at the beginning of treatment) who had been treated with ALN (5 mg daily or 35 mg weekly) for over 7 years were recruited at the outpatient clinic of Keiyu Orthopaedic Hospital (Gunma, Japan) during a 1-year period between August 1, 2013, and July 31, 2014. The patients had been treated with ALN (5 mg daily or 35 mg weekly) for over 7 years. Patients whose data were missing or incomplete were excluded. The doses indicated in the parentheses (the half doses for Caucasians) are the doses used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective [14, 15]. The effects of daily and weekly ALN on the BMD and bone turnover markers as well as the incidence of side effects were reported to be similar in postmenopausal Japanese women with osteoporosis [15]. Daily ALN was available throughout the study period, but weekly ALN only became available after October 2006. The patients were treated with daily ALN (5 mg daily) before October 2006 and with weekly ALN (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 [16, 17], patients with a BMD <70 % of the young adult mean (YAM) or 70–80 % of the YAM along with a history of osteoporotic fractures should be diagnosed as having osteoporosis. Patients with a BMD of 70–80 % of the YAM without any history of osteoporotic fractures should be diagnosed as having osteopenia. Patients with osteoporosis or osteopenia and clinical risk factors for fractures, such as a current smoking habit, alcohol abuse (≧2 units a day), a history of steroid use, or a maternal family history of hip fracture, should be treated with drugs [18]. The lumbar spine or total hip BMD was used for the diagnosis of osteoporosis. The BMD can only be evaluated at one skeletal site (lumbar spine, hip, distal radius, or calcaneus) because of medical insurance regulations in Japan. Dual-energy X-ray absorptiometry (DXA), which was available in our facility, was used to measure the BMD of the lumbar spine and the total hip, both of which are clinically important skeletal sites in the treatment of osteoporosis. The BMD was measured at the lumbar spine before December 2004, since 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 among Japanese individuals than among Caucasians [19]. However, the BMD was measured at the total hip after January 2005 because the hip BMD had attracted attention based on a report recommending that the proximal femur be examined using DXA when assessing the risk of fractures [20]. All the patients in the present study had been diagnosed as having osteoporosis or osteopenia in addition to at least one of the abovementioned clinical risk factors for fractures.

The preliminary screening included a medical history, physical examination, plain X-rays of the thoracic and lumbar spine, BMD measurements at the lumbar spine (n=20) or total hip (n=15), and blood and urinary biochemical tests including measurements of the serum calcium, phosphorus, and alkaline phosphatase (ALP) levels and the urinary level of cross-linked N-terminal telopeptides of type I collagen (NTX). Subjects with a history of reflux esophagitis or gastric or duodenal ulcers were excluded. None of the subjects had ever taken medication for the treatment of osteoporosis prior to the present study.

The measurement of urinary NTX levels is permitted only twice (just before and within 6 months after the start of medication) in Japan because of medical insurance regulations. Thus, we evaluated urinary NTX at 3 months after the start of treatment, since a urinary NTX measurement performed at 3 months after the start of ALN treatment provides important information and is sufficient to monitor the effects of treatment for osteoporosis [21]. The serum levels of calcium, phosphorus, and ALP and the lumbar spine or total hip BMD were measured annually after the start of treatment. After 7 years of treatment, the serum bone-specific ALP and intact parathyroid hormone (PTH) levels were evaluated, and plain X-rays of the thoracic and lumbar spine were taken to assess the incidence of vertebral fractures. The incidence of clinical fractures was also assessed. The outcome of ALN treatment for 7 years was then evaluated. The present study was approved by the Ethics Committee of Keiyu Orthopaedic Hospital.

Assessment of 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 the vertebral height on lateral X-ray films [16, 17]. 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 (1) a reduction in the vertebral height of more than 20 % (A, C, and P) compared with the height of the adjacent vertebrae was observed, (2) the C/A or C/P was less than 0.8, or (3) the A/P was less than 0.75. The assessment for vertebral fractures was performed at the T4–L4 level.

Measurement of lumbar spine or total hip BMD

The BMD of the lumbar spine (L1–L4) or the left total hip in the anteroposterior view was measured using DXA with a Hologic QDR 1500W apparatus (Bedford, MA, USA). The coefficient of variation (100×standard deviation/mean) of five measurements with repositioning within 72 h each time was less than 1.2 % for three persons.

Measurements of serum calcium, phosphorus, ALP, bone-specific ALP, intact PTH, and urinary NTX

The serum calcium, phosphorus, and ALP levels were measured using a standard laboratory technique (normal range 8.4–10.2 mg/dL, 2.5–4.5 mg/dL, and 135–310 IU/L, respectively). The urinary NTX levels were measured using an enzyme immunoassay (normal range 9.3–54.3 nM bone collagen equivalent [BCE]/mM creatinine [Cr]). The serum bone-specific ALP levels were measured using a chemiluminescent enzyme immunoassay (normal range 3.7–20.9 U/L). The serum intact PTH levels were measured using an electrochemiluminescence immunoassay (normal range 10–65 pg/mL).

Statistical analysis

Data were expressed as the mean±standard deviation (SD) in the tables and figures. An unpaired *t* test or Fisher exact test was used to compare data between the two groups. An analysis of variance (ANOVA) with Fisher protected least significant difference (PLSD) test was used to compare data among the time points (post hoc analysis). A one-way ANOVA with repeated measurements was used to determine the significance of longitudinal changes in the BMD and biochemical markers. A two-way ANOVA with repeated measurements was used to compare the longitudinal changes in the BMD and biochemical markers between the lumbar spine and total hip groups. All the statistical analyses were performed using the Stat View-J5.0 program on a Windows computer. A significance level of $P<0.05$ was used for all the comparisons.

Results

Characteristics of study subjects at the start of treatment

Table 1 shows the characteristics of the study subjects at the start of ALN treatment. The mean age was 58.2 years. Fourteen subjects (40.0 %) were current smokers, 7 (20.0 %) were alcohol abusers (≧2 units/day), 7 (20.0 %) had a history of steroid use, and 1 (2.9 %) had a maternal family history of hip fracture. Nineteen subjects (54.3 %) had prevalent vertebral fractures, and the mean number of prevalent vertebral fractures per subject was 1.11. The mean lumbar spine and total hip BMD were 0.682 g/cm^2 (66.3 % of the YAM) and 0.641 g/cm^2 (66.9 % of the YAM), respectively. Thirty subjects (85.7 %) were diagnosed as having osteoporosis, and five (14.3 %) were diagnosed as having osteopenia in addition to clinical risk factors for fractures. The mean serum level of ALP was 267 IU/L, and the mean urinary NTX level was 52.4 nM BCE/mM Cr.

Table 1 Baseline characteristics of study subjects

	Mean±SD	Ranges
Age (years)	58.2±13.0	33–78
Height (m)	1.62±0.06	1.50–1.77
Body weight (kg)	57.1±9.3	43–75
Body mass index (kg/m^2)	21.6±3.3	16.8–29.9
Prevalence of vertebral fracture (%)	54.3	
Lumbar spine BMD (g/cm^2)	0.682±0.086	0.467–0.804
YAM of lumbar spine BMD (%)	66.3±8.4	45–78
Total hip BMD (g/cm^2)	0.641±0.085	0.499–0.768
YAM of total hip BMD (%)	66.9±8.9	52–79
Serum calcium (mg/dL)	9.3±0.5	8.4–10.2
Serum phosphorus (mg/dL)	3.0±0.6	1.9–4.6
Serum ALP (IU/L)	267±92	133–447
Urinary NTX (nmol BCE/mmol Cr)	52.4±16.5	21.5–113.0

Data are expressed as the mean±SD

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

The past histories of the subjects that could affect bone metabolism were steroid use (hearing loss [n=1], asthma [n=2], nephritis [n=1], subacute thyroiditis [n=1], psoriasis [n=1], and Vogt-Koyanagi-Harada disease [n=1]), diabetes mellitus (n=1), osteogenesis imperfecta (n=1), gastrectomy (n=5), and cerebrovascular disease with no apparent hemiplegia (n=1). The serum ALP levels and the urinary NTX levels at baseline were similar in those with and those without such illnesses (according to an unpaired t test).

When the characteristics of the study subjects at the start of ALN treatment were compared according to the BMD measurement site, no significant differences in any characteristics were found between the two groups (according to an unpaired t test or a Fisher exact test).

Changes in lumbar or total hip BMD and biochemical markers

Figure 1 shows an increase in the lumbar spine and total hip BMD over the 7-year study period. Table 2 shows that the rates of increase for the lumbar BMD after 1, 2, 3, 4, 5, 6, and 7 years of treatment, compared with the baseline values, were +7.4, +8.7, +10.9, +11.5, +12.4, +13.6, and +14.2 %, respectively, while the rates of increase for the total hip BMD, compared with the baseline values, were +2.3, +7.1, +6.4, +7.0, +10.5, +8.7, and +10.1 %, respectively. A post hoc analysis (ANOVA with Fisher PLSD test) showed significant increases in the lumbar spine BMD at 3, 4, 5, 6, and 7 years, compared with the baseline values, and significant increases in the

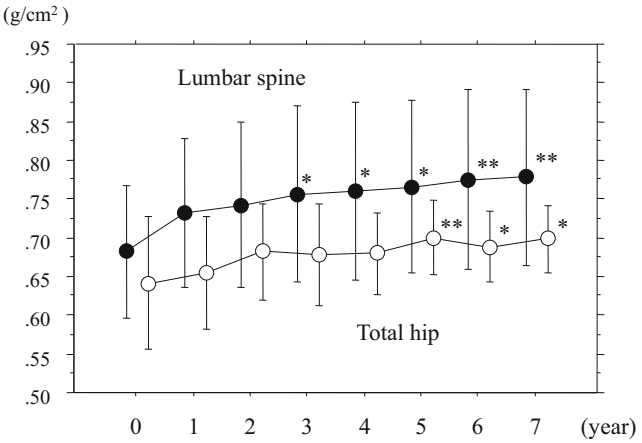

Fig. 1 Changes in BMD. The BMD was measured at the lumbar spine for 20 patients and at the hip for 15 patients. Data were expressed as the mean±SD. A post hoc analysis (ANOVA with Fisher PLSD test) showed significant increases in the lumbar spine BMD at 3, 4, 5, 6, and 7 years compared with the baseline values and significant increases in the total hip BMD at 5, 6, and 7 years compared with the baseline values. However, a one-way ANOVA with repeated measurements detected significant increases in both the lumbar spine and total hip BMD (Table 2). BMD, bone mineral density. *P<0.05, *P<0.01 vs. the baseline values by the ANOVA with Fisher PLSD test

Table 2 One-way ANOVA with repeated measurements

	Years							One-way ANOVA
	1	2	3	4	5	6	7	
Lumbar spine BMD	+7.4	+8.7	+10.9	+11.5	+12.4	+13.6	+14.2	<0.0001
Total hip BMD	+2.3	+7.1	+6.4	+7.0	+10.5	+8.7	+10.1	<0.0001
Serum calcium	−0.3	−1.6	−1.8	−1.2	−1.2	−3.1	−1.2	<0.05
Serum phosphorus	+0.4	−1.4	+4.5	+5.6	+6.6	+3.4	+4.8	NS
Serum ALP	−22.1	−21.1	−21.9	−21.6	−19.1	−21.8	−21.1	<0.0001
Urinary NTX	−46.1[a]							<0.0001

A one-way ANOVA with repeated measurements was used to analyze longitudinal changes in BMD and biochemical markers

BMD bone mineral density, *ALP* alkaline phosphatase, *NTX* cross-linked N-terminal telopeptides of type I collagen, *ANOVA* analysis of variance, *NS* not significant

[a] Changes in urinary NTX were evaluated after 3 months of treatment

total hip BMD at 5, 6, and 7 years, compared with the baseline values. A one-way ANOVA with repeated measurements also detected significant increases in both the lumbar spine and total hip BMD (Table 2).

Figure 2 shows the changes in the biochemical markers. The urinary NTX levels decreased after 3 months of treatment and the serum ALP levels decreased after 1 year of treatment and were maintained thereafter. Table 2 shows that the mean change in the urinary NTX levels after 3 months of treatment, compared with the baseline values, was −46.1 %. The mean change in the serum ALP levels after 1 year of treatment, compared with the baseline values, was −22.1 %, and this reduction was sustained over the course of the 7-year treatment period (−21.1 % after 7 years of treatment). A post hoc analysis (ANOVA with Fisher PLSD test) showed a significant decrease in the urinary NTX levels at 3 months, compared with the baseline values, and significant decreases in the serum ALP levels at all the time points, compared with the baseline values. A one-way ANOVA with repeated measurements detected significant decreases in both the urinary NTX and serum ALP levels (Table 2).

A post hoc analysis (ANOVA with Fisher PLSD test) did not show any significant changes in the serum calcium and phosphorus levels at any time points, compared with the baseline values. However, a one-way ANOVA with repeated measurements showed a significant decrease in the serum calcium levels but not in the serum phosphorus levels (Table 2).

The longitudinal changes in the BMD and biochemical markers, such as the urinary NTX and the serum ALP, calcium, and phosphorus levels, did not differ significantly between the lumbar spine and total hip groups (according to a two-way ANOVA with repeated measurements).

Serum bone-specific ALP and intact PTH levels after 7 years of ALN treatment

The serum bone-specific ALP and intact PTH levels after 7 years of treatment were 9.4±2.3 μg/L (normal range 3.7–20.9 U/L) and 27±12 pg/mL (normal range 10–65 pg/mL), respectively, both of which were within the normal ranges. No significant differences in these parameters were observed between the lumbar spine and total hip groups (according to an unpaired *t* test).

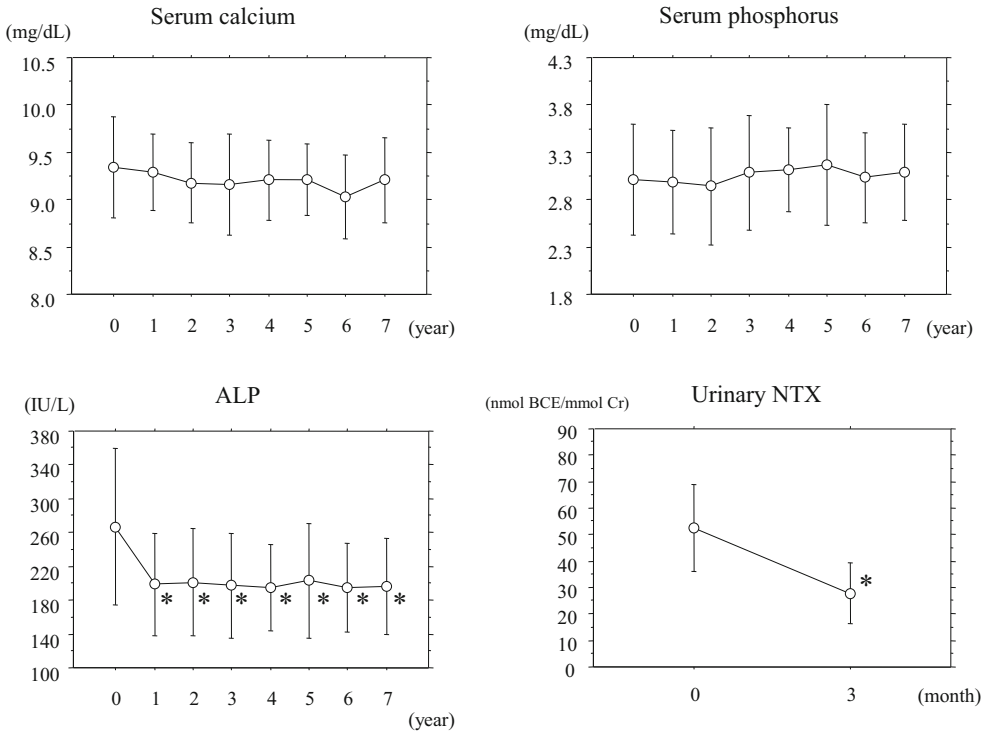

Fig. 2 Changes in biochemical markers. Data were expressed as the mean±SD. A post hoc analysis (ANOVA with Fisher PLSD test) showed a significant decrease in the urinary NTX levels at 3 months compared with the baseline values and significant decreases in the serum ALP levels at all time points compared with the baseline values, but did not show any significant changes in the serum calcium and phosphorus levels at any time points compared with the baseline values. A one-way ANOVA with repeated measurements detected significant decreases in both the urinary NTX and serum ALP levels and showed a significant decrease in the serum calcium levels, but not in the serum phosphorus levels (Table 2). *ALP* alkaline phosphatase, *NTX* cross-linked N-terminal telopeptides of type I collagen, *BCE* bone collagen equivalent. **P*<0.0001 vs. the baseline values by the ANOVA with Fisher PLSD test

Incident fractures

During the 7-year treatment period, four patients (11.4 %) experienced morphometric vertebral fractures and one patient (2.9 %) experienced a nonvertebral fracture (rib fracture).

Adverse events

No serious adverse events, including ONJ or atypical femoral fractures, were observed.

Discussion

The present study confirmed that ALN suppressed bone turnover and increased the lumbar spine or total hip BMD, compared with the baseline values, over a 7-year treatment period without causing any severe adverse events, including ONJ and atypical femoral fractures. To our knowledge, this is the first report showing the outcome of ALN treatment over a 7-year period among Japanese men with an increased risk for fractures.

The higher risk of osteoporotic fractures in men is considered to accrue from a lower peak volumetric BMD and a greater bone loss with aging, particularly among those subjects with risk factors, hypogonadism, or underlying illness [22]. Bone formation, as reflected by bone formation markers, likely decreases with aging and in the presence of fractures in men [22]. 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 [22]. However, whether osteoporosis in men is mainly caused by increased bone resorption remains controversial, even though increased or decreased bone turnover has been reported in men with vertebral fractures [23, 24]. In the present study, 15 patients (42.9 %) had some illness that could affect bone metabolism. However, the urinary NTX levels at baseline were 52.4 nM BCE/mM Cr, which were at the normal high level, and were similar in both those with and those without such illnesses. In total, 54.3 % of the subjects had prevalent vertebral fractures (mean number 1.11). The efficacy of antiresorptive drugs, such as ALN, can be expected in our subjects with an increased risk for fractures.

Previous studies have shown that ALN decreases the urinary NTX (−42 % at 3 months) and increases the lumbar spine, femoral neck, and total hip BMD (+8.8–11.5, +4.2–5.8, and +3.9 %, respectively, at 3 years) in men with osteoporosis [6–8]. In the present study, the urinary NTX levels decreased (−46.1 % at 3 months) and the lumbar spine and total hip BMD increased (+10.9 and +6.4 % at 3 years, respectively), compared with the baseline values. The changes in the urinary NTX and BMD during the 5 years were similar to those in our previous studies, because most of the subjects in our previous study were included in the present study [11]. The changes in the lumbar spine BMD might have been affected by the progression of spondylosis. The increase in the total hip BMD appeared to be greater in our subjects than in Western men with osteoporosis, probably because of the higher bone turnover at baseline.

Epidemiological studies in Japan and in other Asian countries demonstrated that prevalence of vertebral fractures was higher among Asians compared with Caucasians in the USA and Europe [25]. However, the prospective study in Japan revealed that BMD and prior fractures could predict fractures in Japanese as well as BMD did in the other cohorts in the USA and Europe with similar predictive ability [25]. A cohort study in Japan revealed that the incidence (per 1000 person-years) of vertebral fractures in atomic bomb male survivors (aged <60 years) in Hiroshima and Nagasaki was 2.5 in the absence of prevalent vertebral fractures and 19.4 in the presence of prevalent vertebral fractures [19]. Namely, the respective incidences of vertebral fractures during a 7-year period were considered to be 1.75 and 13.58 % (average 7.67 %) [19]. The incidence of vertebral fractures at 7 years was 11.4 % in our study subjects (mean age was 58.2 years, and 54.3 % of the subjects had prevalent vertebral fractures), suggesting a relatively high incidence of vertebral fractures despite receiving ALN treatment. 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 in a background of significantly decreased serum calcium levels caused by the lack of calcium and vitamin D supplementation.

The pharmacological management of osteoporosis involves consideration of the balance between the beneficial effects of treatment on outcome and the probability of adverse events [26]. The beneficial effects of ALN treatment in men with an increased risk for fractures are the efficacy against vertebral fractures [5], and its possible adverse events are gastrointestinal effects as well as ONJ and atypical femoral fractures [26]. However, ALN treatment is generally safe and well tolerated, although it is associated with a few very rare serious adverse reactions such as ONJ and atypical femoral fractures. While these are a cause of concern, the risk should be weighed against the benefits of ALN treatment itself, i.e., the prevention of fragility fractures [26].

How long patients with osteoporosis should continue ALN treatment is debatable. The prolonged or severe suppression of remodeling [27, 28] is associated with accumulation of microdamage, advanced glycation products, and increased tissue mineral density, while stopping treatment results in the re-emergence of remodeling [29]. Seeman inferred that stopping antiresorptive treatment was more likely to do net harm than continuing the treatment [29]. Compston et al. [30] also

suggest that the benefits and risks of both continuation and discontinuation must be considered in deciding the optimal duration of treatment. Long-term treatment is associated with fracture reduction but may increase the risk of rare adverse effects such as ONJ and atypical fractures, whereas discontinuation might reduce the risk of ONJ and atypical fractures but may also be associated with reduced protection against fractures [30]. An initial 5-year period of ALN treatment seems reasonable based on the results of the Fracture Intervention Trial Long-term Extension (FLEX) trial, which was conducted in postmenopausal women with osteoporosis [30, 31]. Nevertheless, the strength of evidence for fracture reduction in high-risk patients and the rarity of long-term adverse effects indicate that in the majority of individuals, the benefits of continued treatment outweigh the risks and suggest that treatment should be continued on a long-term basis in individuals who continue to have a high risk of fracture [30].

The Food and Drug Administration (FDA) analyzed the FLEX trial data [32] and revealed that the rates of vertebral and nonvertebral osteoporotic fractures were similar regardless of whether the participants continued to receive ALN for up to 10 years (17.7 %) or were switched to a placebo for the extended period (16.9 %). However, they also reported limitations in the post hoc analysis, statistical power, selection bias, and sample size. Thus, the optimal duration of ALN use has not been determined. However, patients with an increased risk for fractures may benefit even further from continued ALN treatment. In the present study, the patients were considered to have a high risk of fractures even after 5 years of ALN treatment because of a history of fracture, low BMD, or illness related to secondary osteoporosis; accordingly, ALN treatment was continued for over 7 years in these patients.

The present study had notable limitations. First, the study had a retrospective design and a relatively small sample size, and the data was collected based on conventional medical practices. Second, we confirmed the absence of severe adverse events, including ONJ and atypical femoral fractures, among the patients who had been treated with ALN for over 7 years. However, because we were unable to recruit patients who had dropped out from the ALN treatment, the true incidence of adverse events with ALN treatment remains uncertain. Third, the subjects did not receive either elementary calcium or natural vitamin D supplementation, although we instructed patients to consume 800 mg of calcium, 800 IU vitamin D, and 250 μg vitamin K [4] using brochures. Natural vitamin D supplementation is not prevalent in Japan. This circumstance makes it difficult to compare the present study with others, as most other studies have involved men with osteoporosis who have received calcium and vitamin D supplements. Prospective studies with a large number of subjects are needed to establish the long-term (possibly 10 years) efficacy and safety of ALN treatment in combination with calcium and vitamin D supplementation in Japanese men with an increased risk of fractures.

In conclusion, the present study confirmed that ALN suppressed bone turnover and increased the lumbar spine and total hip BMD from the baseline value over the course of the 7-year treatment period without causing any severe adverse events in Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures. We believe that the data presented in this paper may provide physicians who treat patients in Japan with useful information, as no other reports have shown the long-term (>5 years) effect of ALN treatment on the BMD and bone turnover in Japanese men with an increased risk of fractures. The value of this article is that the long-term efficacy and safety of ALN treatment based on a clinical practice in Japanese men with an increased risk of fractures were reported.

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

References

1. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 348:1535–1541
2. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 280:2077–2082
3. Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P (2008) Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 23(1), CD001155
4. Orimo H, Nakamura T, Hosoi T, Iki M, Uenishi K, Endo N, Ohta H, Shiraki M, Sugimoto T, Suzuki T, Soen S, Nishizawa Y, Hagino H, Fukunaga M, Fujiwara S (2012) Japanese 2011 guidelines for prevention and treatment of osteoporosis—executive summary. Arch Osteoporos 7:3–20
5. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A (2000) Alendronate for the treatment of osteoporosis in men. N Engl J Med 343:604–610
6. Miller PD, Schnitzer T, Emkey R, Orwoll E, Rosen C, Ettinger M, Vandormael K, Daifotis A (2004) Weekly oral alendronic acid in male osteoporosis. Clin Drug Investig 24:333–341
7. Ringe JD, Dorst A, Faber H, Ibach K (2004) Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. Rheumatol Int 24:110–113
8. Gonnelli S, Cepollaro C, Montagnani A, Bruni D, Caffarelli C, Breschi M, Gennari L, Gennari C, Nuti R (2003) Alendronate treatment in men with primary osteoporosis: a three-year longitudinal study. Calcif Tissue Int 73:133–139

9. Ringe JD, Faber H, Farahmand P, Dorst A (2006) Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. Rheumatol Int 26:427–431
10. Majima T, Shimatsu A, Komatsu Y, Satoh N, Fukao A, Ninomiya K, Matsumura T, Nakao K (2009) 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 27:168–174
11. Iwamoto J, Sato Y, Uzawa M, Takeda T, Matsumoto H (2010) Experience with alendronate treatment for four years among Japanese men with osteoporosis or osteopenia and clinical risk factors for fractures. Ther Clin Risk Manag 6:593–600
12. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B (2009) American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. J Oral Maxillofac Surg 67:2–12
13. Lenart BA, Lorich DG, Lane JM (2008) Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med 358:1304–1306
14. Shiraki M, Kushida K, Fukunaga M, Kishimoto H, Taga M, Nakamura T, Kaneda K, Minaguchi H, Inoue T, Morii H, Tomita A, Yamamoto K, Nagata Y, Nakashima M, Orimo H (1999) A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. Osteoporos Int 10:183–192
15. Uchida S, Taniguchi T, Shimizu T, Kakikawa T, Okuyama K, Okaniwa M, Arizono H, Nagata K, Santora AC, Shiraki M, Fukunaga M, Tomomitsu T, Ohashi Y, Nakamura T (2005) 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 23:382–388
16. Orimo H, Sugioka Y, Fukunaga M, Muto Y, Hotokebuchi T, Gorai I, Nakamura T, Kushida K, Tanaka H, Ikai T, Oh-hashi Y (1998) Diagnostic criteria of primary osteoporosis. J Bone Miner Metab 16:139–150
17. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19: 331–337
18. Kanis JA, Borsgtrom F, de Laet C, Johansson H, Johnell O, Jonsson B, Oden A, Zethraeus N, Pfleger B, Khaltaev N (2005) Assessment of fracture risk. Osteoporos Int 16:581–589
19. Fujiwara S, Kasagi F, Masunari N, Naito K, Suzuki G, Fukunaga M (2003) Fracture prediction from bone mineral density in Japanese men and women. J Bone Miner Res 18:1547–1553
20. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936
21. Iwamoto J, Takeda T, Sato Y, Uzawa M (2005) 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 23:238–242
22. Seeman E (2001) Unresolved issues in osteoporosis in men. Rev Endocr Metab Disord 2:45–64
23. Resch H, Pietschmann P, Woloszczuk W, Krexner E, Bernecker P, Willvonseder R (1992) Bone mass and biochemical parameters of bone metabolism in men with spinal osteoporosis. Eur J Clin Investig 22:542–545
24. Sharp CA, Worsfold M, Rowlands PR, Davie MW (1994) Accurate prediction of spinal osteoporosis in men using a biochemical measure of collagen balance. Bone 15:243
25. Fujiwara S (2005) Epidemiology of osteoporosis in Japan. J Bone Miner Metab 23(Suppl):81–83
26. Rizzoli R, Reginster JY, Boonen S, Bréart G, Diez-Perez A, Felsenberg D, Kaufman JM, Kanis JA, Cooper C (2011) Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. Calcif Tissue Int 89:91–104
27. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY (2005) Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 90:1294–1301
28. Imai K, Yamamoto S, Anamizu Y, Horiuchi T (2007) Pelvic insufficiency fracture associated with severe suppression of bone turnover by alendronate therapy. J Bone Miner Metab 25:333–336
29. Seeman E (2009) To stop or not to stop, that is the question. Osteoporos Int 20:187–195
30. Compston JE, Bilezikian JP (2012) Bisphosphonate therapy for osteoporosis: the long and short of it. J Bone Miner Res 27:240–242
31. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 296:2927–2938
32. Whitaker M, Guo J, Kehoe T, Benson G (2012) Bisphosphonates for osteoporosis—where do we go from here? N Engl J Med 366:2048–2051