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ORIGINAL RESEARCH

Seven years' experience with alendronate in postmenopausal Japanese women with osteoporosis

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Abstract: A retrospective study was performed to evaluate the outcome of alendronate (ALN) treatment for seven years in postmenopausal Japanese women with osteoporosis. Forty-seven postmenopausal women with osteoporosis (mean age at baseline 65.7 years) treated with ALN for over seven years in our outpatient clinic were analyzed. Lumbar spine 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 alkaline phosphatase (ALP) were monitored during the seven-year treatment period. Urinary NTX and serum ALP levels decreased (–48.2% at three months and –15.7% at seven years, respectively) and lumbar spine BMD increased (+12.8% at seven years) compared with baseline values. No serious adverse events were observed, including osteonecrosis of jaw, atypical femoral diaphysis fractures, or atrial fibrillation. To our knowledge, this is the first report of the outcome of ALN treatment for seven years in Japanese patients with osteoporosis. ALN successfully suppressed bone turnover and increased lumbar spine BMD from the baseline value over the course of the seven-year treatment period without causing any severe adverse events.

Keywords: alendronate, osteoporosis, long-term treatment, bone mineral density, bone turnover

Background

Osteoporosis most commonly affects postmenopausal women, placing them at increased risk of fractures. Alendronate (ALN) is widely used for the treatment of postmenopausal osteoporosis. The Fracture Intervention Trial demonstrated the antifracture efficacy of ALN 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 has confirmed both clinically important and statistically significant reductions in vertebral, nonvertebral, hip, and wrist fractures for secondary prevention of osteoporosis (gold standard evidence).[3] ALN is regarded as a first-line drug for the treatment of osteoporosis in Japan.

The long-term efficacy of antifracture drugs needs to be established. Bone et al[4] reported their experience using ALN to treat postmenopausal Western women with osteoporosis for a period of 10 years. Ten years of ALN treatment produced an increase in bone mineral density (BMD) of 13.7% at the lumbar spine, 10.3% at the trochanter, 5.4% at the femoral neck, and 6.7% at the total proximal femur, compared with baseline values. Safety data, including fractures and stature, did not suggest that prolonged treatment resulted in any loss of benefit. Thus, the therapeutic effects of ALN were sustained, and the drug was well tolerated over a 10-year period.

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In Japan, results of randomized controlled trials testing the effects of short-term (1–3 years) ALN treatment on BMD, bone turnover, and fracture incidence have been reported in postmenopausal women with osteoporosis.[5–8] ALN reduces bone turnover, increases lumbar and hip BMD, and prevents vertebral fractures. Recently, we reported that ALN successfully reduced bone turnover and maintained metacarpal BMD for five years in older postmenopausal Japanese women with osteoporosis or osteopenia and clinical risk factors for fractures.[9] To our knowledge, however, the outcome of long-term (more than five years) ALN treatment has not been previously reported in Japanese patients. Therefore, a retrospective study was performed to evaluate the outcome of ALN treatment for seven years in postmenopausal Japanese women with osteoporosis. The primary endpoint was lumbar spine BMD, and the secondary endpoint was biochemical markers. Adverse events such as osteonecrosis of the jaw (ONJ), atypical femoral diaphysis fractures, and atrial fibrillation,[10–12] as well as incident osteoporotic fractures were also assessed.

Subjects and methods

Subjects

Forty-seven postmenopausal Japanese women (age range 52–83 years, mean age 65.7 years at the beginning of treatment) who had been treated with ALN for over seven years were recruited from the outpatient clinic at Keiyu Orthopaedic Hospital (Gunma, Japan) during the period between July 1 and December 30, 2009. Exclusion criteria were a history of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, or bone diseases secondary to primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome, multiple myeloma, rheumatoid arthritis, and osteogenesis imperfecta.

All the patients had been diagnosed as having osteoporosis according to the Japanese diagnostic criteria.[13,14] Namely, patients with a BMD $<$ 70% of the young adult mean (YAM) or a BMD 70%–80% of the YAM along with a history of osteoporotic fractures were diagnosed as having osteoporosis. Preliminary screening 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). Lumbar spine BMD was used for the diagnosis of osteoporosis.

The patients had been treated with ALN (5 mg daily or 35 mg weekly) over seven years. The doses indicated in 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.[7] Daily ALN was available throughout the study period, but weekly ALN only became available in October 2006. All the patients had been treated with daily ALN and then switched to weekly ALN just after October 2006. The effects of daily and weekly ALN on BMD and bone turnover markers, as well as incidence of side effects, were reported to be similar in postmenopausal Japanese women with osteoporosis.[8] The subjects did not receive any elementary calcium or natural vitamin D supplementation.

Urinary levels of NTX were measured three months after the start of treatment, based on the results of our previous study.[15] Serum levels of calcium, phosphorus, and ALP, and lumbar spine BMD were measured every year after the start of treatment. Serum bone-specific ALP levels were also measured at seven years after the start of treatment. The outcome of seven years of ALN treatment was 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.[13,14] Briefly, the vertebral height was measured at the anterior (A), central (C), and posterior (P) aspects of the vertebral body, and the presence of a vertebral fracture was confirmed when a reduction in vertebral height of more than 20% (A, C, and P) compared with the height of the adjacent vertebrae was observed, the C/A or C/P was less than 0.8, or the A/P was less than 0.5. The assessment for vertebral fractures was performed at the T4–L4 level.

Serum ALP, calcium, phosphorus, bone-specific ALP, and urinary NTX

Serum calcium, phosphorus, and ALP levels were measured by 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 ALP levels were measured by enzyme immunoassay (EIA, normal range for Japanese women 7.9–29.0 U/L).[16] Urinary NTX levels were measured by enzyme-linked immunosorbent assay (ELISA, normal range 9.3–54.3 nM bone collagen equivalent [BCE]/mM Cr).[16]

Measurement of lumbar spine BMD

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

Statistical analysis

Data were expressed as the mean ± standard deviation (SD) in the table and the mean ± 95% confidence interval (CI) for calcium, phosphorus, and ALP, and the median ± 95% CI for urinary NTX in the figures. The significance of longitudinal changes in the BMD and biochemical markers was determined using a one-way analysis of variance (ANOVA) with repeated measurements. All 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 subjects at start of treatment

Table 1 shows the baseline characteristics of the study subjects at the start of ALN treatment. The mean age was 65.7 years. The mean lumbar spine BMD was 0.638 g/cm^2 (62.7% of YAM). Twenty-three subjects (48.9%) had prevalent vertebral fractures, and the mean number of prevalent vertebral fractures per subject was 2.5. The mean level of urinary NTX was 73.3 nmol BCE/mmol Cr, indicating high turnover osteoporosis (normal range 9.3–54.3 nM BCE/mM Cr).[16]

Table 1 Characteristics of study subjects

	Mean ± SD	Range
Age (years)	65.7 ± 8.6	52–83
Height (m)	1.48 ± 0.07	1.35–1.62
Body weight (kg)	45.4 ± 6.6	32–59
Body mass index (kg/m^2)	20.5 ± 1.1	15.6–25.9
Lumbar spine BMD (g/cm^2)	0.638 ± 0.091	0.433–0.788
% YAM of lumbar spine BMD (%)	62.7 ± 9.0	42.6–77.4
Serum calcium (mg/dL)	9.4 ± 0.4	8.6–0.3
Serum phosphorus (mg/dL)	3.3 ± 0.5	2.3–4.3
Serum ALP (IU/L)	235 ± 62	132–398
Urinary NTX (nmol BCE/mmol Cr)	73.3 ± 21.2	30.6–135.1
Number (%) of women with prevalent vertebral fractures	23 (48.9)	
Number (%) of women with history of nonvertebral fractures	3 (6.4)	

Abbreviations: SD, standard deviation; 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.

Changes in biochemical markers and lumbar spine BMD

Figure 1 shows the changes in the biochemical markers. Urinary NTX levels decreased to the normal range (9.3–54.3 nmol BCE/mmol Cr)[16] after three months of treatment, and serum ALP levels decreased but remained within the normal range (135–310 IU/L) during the seven-year period. The mean change rate of the urinary NTX levels after three months of treatment was −48.2%. The mean change in serum ALP levels after two years of treatment was −24.1%, and this decrease continued gradually over the course of the seven-year treatment period (−23.9% at three years, −19.3% at five years and −15.7% at seven years). Serum calcium levels decreased after three years of treatment, and this effect was maintained. The mean change in serum calcium level after three months was −2.0%. However, the changes in the serum phosphorus levels were not significant during the course of the seven-year treatment period.

Figure 2 shows that the lumbar spine BMD continued to increase for seven years. Increase in lumbar BMD after three, five, and seven years of treatment was +6.1%, +9.4%, and +12.8%, respectively.

Adverse events

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

Incident fractures

Osteoporotic fractures including vertebral, hip, wrist, and proximal humeral fractures were assessed. During the seven-year treatment period, two patients experienced vertebral fractures and two patients experienced wrist fractures. The incidence of osteoporotic fractures was 8.6% and that of vertebral fractures was 4.3%.

Discussion

To our knowledge, this is the first report showing the outcome of ALN treatment for seven years in Japanese patients with osteoporosis. ALN successfully suppressed bone turnover and increased lumbar spine BMD compared with baseline values over the seven-year treatment period without causing any severe adverse events in postmenopausal Japanese women with osteoporosis. Of importance is the effect of ALN treatment for seven years on lumbar spine BMD and bone turnover, the necessity of long-term ALN treatment, and the

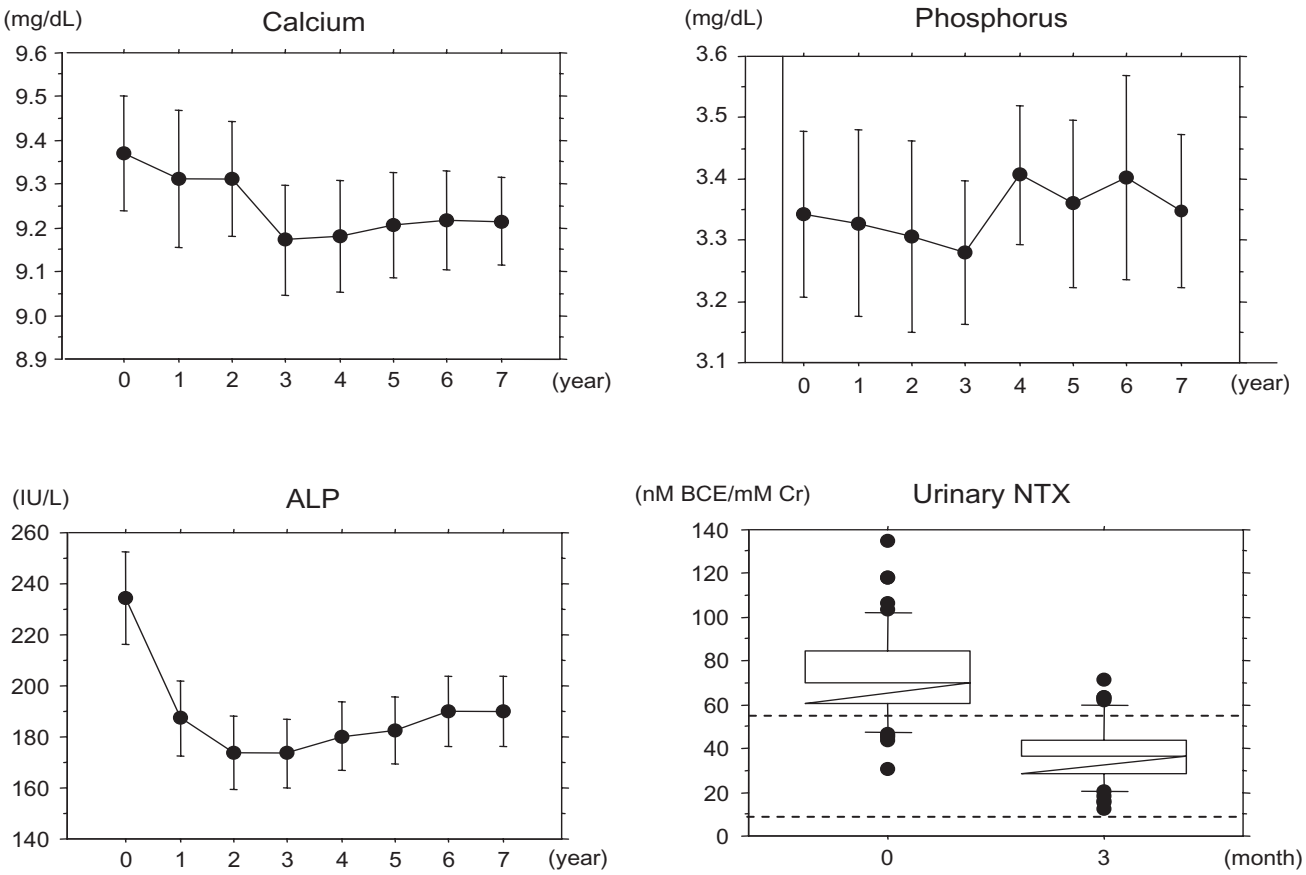

Figure 1 Changes in biochemical markers.
Data were expressed as the mean ± 95% confidence interval (CI) for calcium, phosphorus, and ALP and the median ± 95% CI for urinary NTX. One-way ANOVA with repeated measurements showed that changes in calcium and ALP, but not those in phosphorus, were significant ($P < 0.0001$ and $P = 0.0036$, respectively). Dashed lines are the upper (9.3 nM BCE/mM Cr) and lower (54.3 nM BCE/mM Cr) limits of urinary NTX levels. The normal range of serum ALP was 135–310 IU/L.
Abbreviations: ALP, alkaline phosphatase; NTX, cross-linked N-terminal telopeptides of type I collagen.

incidence of adverse events including ONJ, atypical femoral diaphysis fractures, and atrial fibrillation.

Studies have shown that ALN (5 mg daily or 35 mg weekly) decreases urinary NTX (–45% at three months) and serum ALP (about –20% at three years), and increases in lumbar BMD (+9.2% at three years) in postmenopausal Japanese women with osteoporosis.[6,8] Our previous study showed that ALN treatment for five years sustained metacarpal BMD following reductions in urinary levels of NTX (–43.6% at three months) and serum levels of ALP (–18.0% at five years). In the present study, ALN treatment increased lumbar spine BMD (6.1% at three years) subsequent to reductions in urinary levels of NTX (–48.2% at three months) and serum levels of ALP (–24.1% and –19.3% at three and five years, respectively). The results of the present study are comparable with those of previous studies.

Urinary NTX levels were reduced to within the normal range for Japanese women after three months of treatment, while serum ALP levels remained within the normal range throughout the seven-year treatment period. Measurement of urinary NTX levels was permitted only twice (just before and within six months after the start of medication) in Japan for medical insurance reason. Thus, we evaluated urinary NTX only at three months after the start of treatment, because a urinary NTX measurement performed at this time provides important information and is sufficient to monitor the effects of treatment for osteoporosis.[15] We failed to show urinary NTX data after seven years of ALN treatment. However, we evaluated serum bone-specific ALP levels (normal range for Japanese women 7.9–29.0 U/L)[16] after seven years of treatment. Serum levels of bone-specific ALP (mean ± SD) at seven years was 10.0 ± 2.0 U/L, suggesting a sustained effect of ALN treatment on bone turnover for seven years.

How long postmenopausal women with osteoporosis can continue ALN treatment is debatable. A survey of the effects of treatment discontinuation would provide valuable information on this issue. Several reports have demonstrated that discontinuation of ALN affects BMD and/or levels of bone resorption markers at 1–2 years of discontinuation after 1–2 years of treatment, two years of discontinuation after

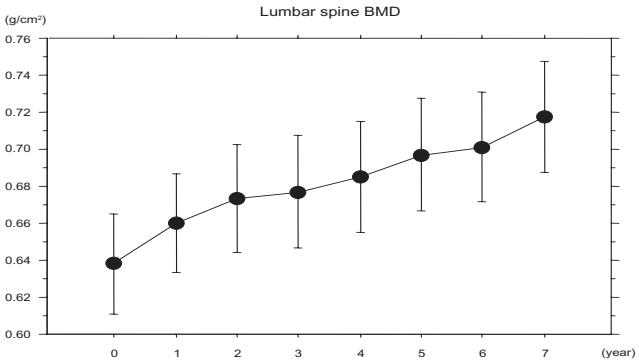

Figure 2 Changes in lumbar spine BMD.
Data were expressed as the mean ± 95% confidence interval (CI). One-way ANOVA with repeated measurements showed that changes in lumbar spine BMD were significant ($P < 0.0001$).
Abbreviation: BMD, bone mineral density.

two years of treatment, and 3–7 years of discontinuation after 2–6 years of treatment all decreased the BMD toward the baseline level.[17–19] Discontinuation of ALN treatment for five years after five years of treatment resulted in a gradual loss of its effects, as measured using BMD and biochemical markers of bone turnover,[4] and increased the risk of clinical vertebral fractures, compared with continuation of ALN treatment.[20] A recent study also showed that among women without any vertebral fractures after five years of ALN treatment, continuation of ALN treatment for another five years reduced the risk of nonvertebral fractures in women with a femoral neck BMD T-score ≤ -2.5 at five years, but not in women with a T-score > -2, compared with the discontinuation of ALN treatment for five years after five years of treatment.[21] These results suggest that continuous ALN treatment for 10 years is optimal for selected patients.

If patients are not considered to have a high risk of fractures, the discontinuation of ALN treatment could probably be considered after treatment for five years, with subsequent monitoring of BMD and bone turnover markers. The most important risk factor for fractures is considered to be BMD.[21] Other risk factors are low-trauma fractures after the age of 40 years, a maternal history of osteoporotic fractures after the age of 65 years, a thin body build, prolonged amenorrhea, early menopause, chronic corticosteroid use (>six months), and diseases predisposing an individual to osteoporosis.[22] In the present study, treatment was continued in all patients because they had BMD below 70% of the YAM or at least one of the aforementioned risk factors, as evaluated at the lumbar spine after five years of ALN treatment.

ONJ, atypical femoral diaphysis fractures, and atrial fibrillation have been reported as severe adverse events,[10–12] although whether these events are significantly related to ALN treatment remains uncertain. The efficacy and safety of ALN for 10 years has been established in postmenopausal Western women with osteoporosis.[4] However, adherence (persistence and compliance) of patients to treatment with oral bisphosphonates is very poor.[23] Because patients who withdrew from treatment were not followed up, the long-term safety of ALN remains uncertain in this patient group.

Once-yearly intravenous zoledronate has been reported to prevent morphometric vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis effectively (relative risk 0.30, 0.75, and 0.59, respectively)[24] and reduce mortality in patients who suffer a low-trauma hip fracture.[25] Because adherence to treatment with once-yearly intravenous zoledronate may be better than that with oral alendronate in clinical practice, zoledronate could be more useful in the prevention of osteoporotic fractures and reduce medical expenses related to treatment of hip fractures.

The incidence of vertebral fractures was 4.3% in the present study. A RCT of the two-year minodronate study showed that the incidence of vertebral and nonvertebral fractures in postmenopausal Japanese controls with established osteoporosis was 21.3% and 3.5%, respectively.[26] However, a three-year RCT of ALN showed that the incidence of vertebral fractures was 2% for the ALN group and 8% for the active control (alfacalcidol) group in postmenopausal Japanese women with osteoporosis.[6] One possible explanation for the higher incidence of vertebral fractures in the present study might be that there was a higher proportion of patients who had prevalent vertebral fractures in terms of higher risk of incident fractures at baseline as well as a comparatively long duration of observation. 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 present study confirmed the effect of ALN on lumbar spine BMD and bone turnover in postmenopausal Japanese women with osteoporosis who continued treatment for seven years. However, this study has notable limitations. First, it was a retrospective cohort study with a small sample size. Second, the subjects did not receive either elementary calcium or natural vitamin D supplementation. Natural vitamin D supplementation is not routinely given in Japan. This makes it difficult to compare our study with those of others, as most other studies have included postmenopausal women with osteoporosis taking calcium and vitamin D supplements. Moreover, performing a seven-year RCT with a sufficient number of subjects is difficult, but prospective studies with

a large number of subjects are needed to establish the long-term efficacy and safety of ALN treatment with calcium and vitamin D supplementation.

In conclusion, the present retrospective study showed that ALN successfully suppressed bone turnover and increased lumbar spine BMD, compared with baseline values, over the course of a seven-year treatment period without causing any severe adverse events in postmenopausal Japanese women with osteoporosis.

Disclosures

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

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