Comparative effect of alendronate and teriparatide on bone mineral density and bone turnover among Japanese postmenopausal women with history of fragility fractures: A clinical practice-based observational study

Jun Iwamoto, Hitoshi Kono, Mitsuyoshi Uzawa

Institute for Integrated Sports Medicine, Keio University School of Medicine, Tokyo, Japan
Department of Orthopaedic Surgery, Keiyu Orthopaedic Hospital, Gunma, Japan

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Abstract

A clinical practice-based observational study was performed to compare the outcome of alendronate (ALN) and teriparatide (TPTD) treatment among Japanese postmenopausal women with a history of fragility fractures. Sixty-one Japanese postmenopausal women with a history of fragility fractures were treated with ALN (35 mg weekly, n = 32) or TPTD (20 μg daily, n = 29) for 2 years in our outpatient clinic. Alfacalcidol (1 μg daily) was combined with ALN. The lumbar spine or total hip bone mineral density (BMD) was measured using dual energy X-ray absorptiometry, and bone turnover markers were monitored. ALN decreased the urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) (38.3% after 3 months) and the serum levels of alkaline phosphatase (ALP) (25.7% at 24 months), whereas TPTD increased the serum levels of intact procollagen type 1 N-terminal propeptide (P1NP) and ALP (79% and 14.1%, respectively at 24 months). Both ALN and TPTD increased the lumbar spine BMD (8.8% and 15.9%, respectively) and sustained the total hip BMD at 24 months. One patient treated with ALN experienced vertebral fractures, and one patient treated with TPTD experienced a nonvertebral fracture. These results confirmed the differential effects of ALN and TPTD on bone turnover and the greater effect of TPTD on the BMD among Japanese postmenopausal women with a history of fragility fractures.

Keywords: Alendronate; Teriparatide; Bone mineral density; Postmenopausal women; Fragility fracture

1. 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. ALN reduces the incidence of vertebral, hip, and wrist fractures in postmenopausal osteoporotic women with existing vertebral fractures and the incidence of vertebral fractures in postmenopausal women with low bone mineral density (BMD) but without vertebral fractures [1,2]. Teriparatide (TPTD) is used for postmenopausal women with osteoporosis at a high risk of fractures [3]. TPTD dramatically increases bone formation and the lumbar spine, hip, and total-body BMD and effectively reduces the incidence of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis [4]. Both medicines appear to be effective for reducing fragility fractures among postmenopausal women with established osteoporosis.

A randomized controlled trial (RCT) demonstrated the 1-year comparative effect of ALN and TPTD on the BMD and the incidence of nonvertebral fractures in postmenopausal women with osteoporosis [5]. TPTD is available for up to 2 years in Japan. To our knowledge, however, no data showing the 2-year comparative effect of ALN and TPTD on the BMD...
Sixty-one postmenopausal women with a history of fragility fractures (mean age: 70.8 years) were treated with ALN (35 mg orally, weekly) (n = 32) or TPTD (20 µg subcutaneously, daily) (n = 29) for 2 years at the outpatient clinic of Keiyu Orthopaedic Hospital (Gunma, Japan) between March 2011 and December 2014. Alfacalcidol (1 µg orally, daily) instead of vitamin D supplementation was combined with ALN, because an RCT clarified the efficacy of ALN (5 mg daily) plus alfacalcidol (1 µg daily) versus ALN (5 mg daily) alone in postmenopausal women with severe osteoporosis who were aged 70 years or older and had several risk factors for incident fractures [6]; the combination therapy with ALN and alfacalcidol was more effective for fracture prevention in patients with severe vertebral deformity (semi-quantitative method: grade 3), multiple prevalent vertebral fractures, and for nonvertebral weight-bearing bone fracture prevention. Fragility fractures included vertebral, distal radius, proximal humerus, hip, pelvis, rib or lower leg fractures along with low BMD (<80% of the young adult mean [YAM]). In Japan, the %YAM is used instead of the T score for the diagnosis of primary osteoporosis [7]. The doses indicated in the parentheses are the doses used in Japan for the treatment of postmenopausal women with osteoporosis and have been recognized as being safe and effective [8–10]. The inclusion criteria were postmenopausal osteoporosis, and the exclusion criteria were secondary osteoporosis and other diseases that decrease the BMD [7,11,12]. None of the subjects had ever taken medication for the treatment of osteoporosis prior to the present study. Patients selected the treatment (ALN or TPTD) by themselves after the method of administration and the prices of the medicines had been explained: the monthly cost of TPTD (daily subcutaneous injection) and ALN (weekly internal use) were approximately 52,000 yen and 2600 yen, respectively. Adverse events of TPTD were explained by doctors: nausea, headache, and dizziness, and those of ALN were explained by pharmacists: upper gastrointestinal adverse events. Patients whose data were missing or incomplete were excluded, because they were not followed up adequately.

The preliminary screening included a medical history, physical examination, plain X-rays of the thoracic and lumbar spine, BMD measurements at the lumbar spine or total hip, and blood and/or urinary biochemical tests. Dual-energy X-ray absorptiometry (DXA) was used to measure the BMD of the lumbar spine or the total hip. The BMD was primarily measured at the lumbar spine, but was done at the total hip in patients with severe spondylosis, callus formation after vertebral fractures, and severe aortic calcification, which were thought to significantly affect the lumbar spine BMD. Thus, the lumbar spine BMD was measured in 55 patients and the total hip BMD was measured in 6 patients. Biochemical tests included measurements of the serum levels of calcium, phosphorus, and alkaline phosphatase (ALP) in the ALN and TPTD groups. The urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) were measured in the ALN group, while the serum levels of intact procollagen type I N-terminal propeptide (P1NP) were measured in the TPTD group.

The serum levels of calcium, phosphorus, and ALP and the lumbar spine or total hip BMD were measured every 6 months after the start of treatment in both groups. 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 health insurance regulations. Thus, we evaluated urinary NTX at 3 months after the start of treatment in the ALN group [13]. The serum intact P1NP levels were measured every 6 months in the TPTD group. After 2 years of treatment, 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 and TPTD treatment for 2 years was then evaluated. The present study was approved by the Ethics Committee of Keiyu Orthopaedic Hospital.

2.2. 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 [11,12]. Briefly, the vertebral height was measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body, and the presence of a vertebral fracture was confirmed when (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.

2.3. Assessment of clinical fractures

Low-traumatic osteoporotic clinical fractures were assessed. In particular, nonvertebral fractures in terms of major osteoporotic fractures at the distal radius, proximal humerus, hip, pelvis, rib or lower leg were determined, if any, based on clinical symptoms and radiographs.

2.4. Measurement of lumbar spine or total hip BMD

The BMD of the lumbar spine or the left total hip in the anteroposterior view was measured using DXA with a Hologic QDR Explorer apparatus (Bedford, MA, USA). The inappropriate spine within the lumbar (L1–L4) spine for the BMD
measurements was not included in the analysis. 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.

2.5. Measurements of biochemical markers

The serum levels of calcium, phosphorus and ALP 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). The urinary NTX levels were measured using an enzyme immunoassay (normal range: 9.3–54.3 nM BCE/mM Cr). The serum intact P1NP levels were measured using a radioimmunoassay (normal range: 17.1–64.7 µg/L).

2.6. 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. A one-way analysis of variance (ANOVA) with repeated measurements was used to determine the significance of longitudinal changes in the BMD and biochemical markers. A two-way ANOVA with repeated measurements was used to compare the longitudinal changes in the BMD and biochemical markers between the two groups. The correlations between the increase in the serum intact P1NP levels after 6 months of treatment and the increase in the lumbar spine BMD after 12 and 24 months of treatment were examined using a single regression analysis. 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.

3. Results

3.1. Baseline characteristics of study subjects

Table 1 shows that the mean age of the study subjects was 70.9 years in the ALN group and 70.6 years in the TPTD group. There were no significant differences in the age, height, body weight, body mass index, prevalence of vertebral fractures, history of nonvertebral fractures, serum calcium, phosphorus, or ALP levels between the two groups. Although there was no significant difference in the total hip BMD because of the small sample size, the lumbar spine BMD was significantly lower in the TPTD group than in the ALN group (0.576 g/cm² vs. 0.652 g/cm²).

Twenty-eight patients (87.5%) in the ALN group and 28 patients (96.6%) in the TPTD group had prevalent vertebral fractures (morphometric vertebral fractures). In total, 52 vertebral fractures were found in the ALN group, and 72 vertebral fractures in the TPTD group. Thus, the average numbers of vertebral fractures per patient were 1.63 in the ALN group and 2.48 in the TPTD group. With regard to the fracture distribution, vertebral fractures were found at the T7 (n = 1), T8 (n = 3), T9 (n = 2), T10 (n = 1), T11 (n = 2), T12 (n = 13), L1 (n = 8), L2 (n = 11), L3 (n = 4), L4 (n = 5), and L5 (n = 2) in the ALN group, and at the T6 (n = 1), T7 (n = 3), T8 (n = 2), T9 (n = 3), T10 (n = 3), T11 (n = 3), T12 (n = 11), L1 (n = 9), L2 (n = 11), L3 (n = 10), L4 (n = 11), and L5 (n = 5) in the TPTD group.

3.2. Changes in lumbar spine or total hip BMD and biochemical markers

Fig. 1 shows the changes in the lumbar spine BMD. The increases in the lumbar spine BMD after 6, 12, 18, and 24 months of treatment, compared with the baseline values, were +4.1%, +6.1%, +7.0%, and +8.8%, respectively, in the ALN group, while the respective increases were +7.6%, +11.9%, +14.4%, and +15.9%, in the TPTD group. A one-way ANOVA with repeated measurements detected significant increases in the lumbar spine BMD in both groups (Table 2). The changes in the total hip BMD after 6, 12, 18, and 24 months of treatment, compared with the baseline values, were +1.3%, +1.8%, −1.5%, and +1.6%, respectively, in the ALN group, while the respective changes were +0.5%, +2.5%, +2.8%, and +2.0%, in the TPTD group. However, a one-way ANOVA with repeated measurements did not detect any significant increases in the total hip BMD in either group (Table 2).

A two-way ANOVA with repeated measurements detected a significant difference in increase in the lumbar spine BMD, but not total hip BMD, between the two groups (Table 2).

Fig. 1 also shows the changes in bone turnover markers. In the ALN group, the urinary NTX levels decreased (−38.3% compared with the baseline values) after 3 months of treatment and the serum ALP levels decreased after 6 months of treatment. The decreases in the serum ALP levels after 6, 12, 18, and 24 months of treatment, compared with the baseline values, were −23.4%, −29.9%, −26.2%, and −25.7%, respectively. A one-way ANOVA with repeated measurements

### Table 1

<table>
<thead>
<tr>
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<th>ALN (n = 32)</th>
<th>TPTD (n = 29)</th>
<th>P values</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>70.9 ± 8.1</td>
<td>70.6 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.50 ± 0.07</td>
<td>1.48 ± 0.04</td>
<td>NS</td>
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<tr>
<td>Body weight (kg)</td>
<td>49.8 ± 6.8</td>
<td>48.8 ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.2 ± 2.3</td>
<td>22.2 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Prevalence of vertebral fracture (%)</td>
<td>87.5</td>
<td>96.6</td>
<td>NS</td>
</tr>
<tr>
<td>History of nonvertebral fracture (%)</td>
<td>34.4</td>
<td>13.8</td>
<td>NS</td>
</tr>
<tr>
<td>Lumbar spine BMD (g/cm²)</td>
<td>0.652 ± 0.082</td>
<td>0.576 ± 0.123</td>
<td>&lt;0.01</td>
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<td>(n = 30)</td>
<td>(n = 25)</td>
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<tr>
<td>YAM of lumbar spine BMD (%)</td>
<td>65.4 ± 8.1</td>
<td>57.1 ± 12.3</td>
<td>&lt;0.01</td>
</tr>
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<td>Total hip BMD (g/cm²)</td>
<td>0.430 ± 0.046</td>
<td>0.619 ± 0.079</td>
<td>NS</td>
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<td>(n = 2)</td>
<td>(n = 4)</td>
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</tr>
<tr>
<td>YAM of total hip BMD (%)</td>
<td>52.0 ± 5.7</td>
<td>72.0 ± 18.9</td>
<td>NS</td>
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<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.3 ± 0.4</td>
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<td>NS</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>3.2 ± 0.4</td>
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<td>NS</td>
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<tr>
<td>Serum ALP (IU/L)</td>
<td>258 ± 80</td>
<td>258 ± 98</td>
<td>NS</td>
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<tr>
<td>Serum intact P1NP (ng/mL)</td>
<td>45.8 ± 14.2</td>
<td>62.6 ± 28.3</td>
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<tr>
<td>Urinary NTX (nmol BCE/mmol Cr)</td>
<td>53.8 ± 14.2</td>
<td></td>
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</table>

Data are expressed as the mean ± SD. BMD: bone mineral density, YAM: young adult mean, ALP: alkaline phosphatase, P1NP: procollagen type 1 N-terminal propeptide, NTX: cross-linked N-terminal telopeptides of type I collagen, BCE: bone collagen equivalent, Cr: creatinine.
detected significant decreases in the urinary NTX and serum ALP levels in the ALN group (Table 2). In the TPTD group, the serum intact P1NP and ALP levels increased after 6 months of treatment. The increases in the serum intact P1NP levels after 6, 12, 18, and 24 months of treatment, compared with the baseline values, were +121%, +137%, +132%, and +79%, respectively. The respective increases in the serum ALP levels were +19.4%, +24.9%, +26.0%, and +14.1%. A one-way ANOVA with repeated measurements detected significant increases in the serum intact P1NP and ALP levels in the TPTD group (Table 2). A two-way ANOVA with repeated measurements detected a significant difference in changes in the serum ALP levels between the two groups (Table 2). However, a one-way ANOVA with repeated measurements did not detect any significant differences in changes in the serum calcium and phosphorus levels between the two groups (Table 2).

3.3. Correlations between increases in serum intact P1NP levels and lumbar spine BMD

The increase in the serum intact P1NP levels after 6 months of treatment was not significantly correlated with the increases in the lumbar spine BMD after 12 and 24 months of treatment.

3.4. Incident fractures

During the 2-year treatment period, one patient experienced morphometric vertebral fractures and one patient experienced a nonvertebral fracture (rib fracture).

3.5. Adverse events

No severe adverse effects were observed among the patients who continued the treatment for 2 years in either group [10,14].
The present study confirmed that ALN suppressed bone turnover, thereby increasing the lumbar spine BMD (8.8%), while TPTD increased bone formation, thereby increasing the lumbar spine BMD (15.9%), compared with the baseline values, over a 2-year treatment period in postmenopausal women with a history of fragility fractures. The effect of TPTD on the lumbar spine BMD was greater than that of ALN. Since there was a significant difference in the baseline lumbar spine BMD between the two groups, the longitudinal changes, but not the percentage changes, in the lumbar spine were compared using a two-way ANOVA with repeated measurement.

RCTs have shown that ALN (5 mg daily or 35 mg weekly) decreases the urinary NTX (~45% after 3 months of treatment) and serum ALP (approximately −26% after 2 years of treatment) levels and increases the lumbar spine BMD (+6.9% after 2 years of treatment) when administered in combination with calcium and/or vitamin D supplementation in postmenopausal Japanese women with osteoporosis [8,15]. In the present study, alfacalcidol (1 µg daily) was combined with ALN, since an RCT clarified the efficacy of ALN plus alfacalcidol (1 µg daily) versus ALN alone in postmenopausal women with severe osteoporosis who were aged 70 years or older and had several risk factors for incident fractures [6]. ALN decreased the urinary NTX levels (38.3% after 3 months) and the serum ALP levels (25.7% at 24 months), thereby increasing the lumbar spine BMD (8.8% at 24 months). The results of the present study were comparable with those of previous studies [8,15]. Thus, ALN successfully suppressed bone turnover and increased the lumbar spine BMD, compared with the baseline values, over the course of a 2-year treatment period.

A phase III study has shown that TPTD increases the serum intact P1NP levels (+76.1% at 24 months), thereby increasing the lumbar spine BMD (+13.4% at 24 months) in postmenopausal women with osteoporosis [10]. The increases in the lumbar spine BMD (+7.6%, +11.9%, +14.4%, and +15.9% after 6, 12, 18, and 24 months of treatment, respectively) observed in the present study were consistent with those observed in an RCT of TPTD in Japanese patients [10]. However, the increases in the serum intact P1NP levels (+121%, +137%, +132%, and +79% after 6, 12, 18, and 24 months of treatment, respectively) observed in the present study were greater than those (+87% after one month of treatment) observed in an RCT of TPTD in Japanese patients [10]. The discrepancy remains uncertain. The large SDs of the percentage increases in the serum intact P1NP levels suggest that the response of this marker to TPTD treatment differed from patient to patient. A strong relationship has been reported between an early change in the serum intact P1NP levels (after 1 or 3 months of treatment) and later changes in the lumbar spine BMD (after 12 months of treatment) during TPTD therapy in Japanese patients with a high risk of fractures (r = 0.56, P < 0.01 and r = 0.36, P < 0.01, respectively) [16]. In the present study, however, an increase in the lumbar spine BMD after 12 months of treatment was not correlated with increases in the serum intact P1NP levels after 6 months of treatment. The serum intact P1NP levels should have been measured after 1 or 3 months of treatment to predict the increase in the lumbar spine BMD.

Calcium and vitamin D supplementation, after an evaluation of the serum 25-hydroxyvitamin D [25(OH)D] levels, is well-recognized to be important in the treatment of osteoporosis. In Japan, however, calcium and vitamin D supplements are not widely used, and the measurement of the serum 25(OH)D levels is not covered by health insurance. Epidemiological studies have indicated a high prevalence of vitamin D deficiency among postmenopausal Japanese women [17]. Although the vitamin D status was uncertain, the patients in the present study appeared to respond well to TPTD therapy, based on the increase in their serum P1NP levels. A post-hoc analysis of the Fracture Prevention Trial also demonstrated that the responses to TPTD did not differ significantly between women with baseline 25(OH)D insufficiency and those with baseline 25(OH)D sufficiency among postmenopausal women with osteoporosis and a normal intact parathyroid hormone [18].

An RCT demonstrated the 1-year comparative effect of ALN and TPTD on the BMD and bone turnover markers in postmenopausal women with osteoporosis [5]. TPTD
significantly increased the lumbar spine BMD by a greater value than that induced by ALN (TPTD: 12.2% vs. ALN: 5.6%). TPTD also increased the serum levels of bone-specific ALP (approximately 100% at 6 months), while ALN decreased the serum levels of bone-specific ALP and the urinary levels of NTX (both approximately 50% after 3 months). In the present study, the serum bone-specific ALP levels were not evaluated; however, the changes in the lumbar spine BMD and bone turnover markers were comparable between the previous studies and our present study. These results were supported by a 6-month lumbar spine quantitative computed tomography (finite element modeling) study and an 18-month bone histomorphometry (transiliac crest biopsy) study in postmenopausal women with osteoporosis [19,20]. The former study demonstrated that both TPTD and ALN increased the average volumetric density and strength in the trabecular bone, but that the median percentage increases for these parameters were 5-fold–20-fold greater for TPTD [19]. The latter confirmed the opposite mechanism of action of TPTD and ALN on bone remodeling and of TPTD on bone formation [20].

The strength of the present study was that the 2-year comparative effect of ALN and TPTD on the BMD and bone turnover in Japanese postmenopausal women with established osteoporosis was shown. The notable limitations were that the study had a clinical practice-based observational design (retrospective study) and a relatively small sample size, and that the data was collected based on conventional medical practices. Thus, selection bias might affect the results of the study. RCTs with a large number of subjects are needed to establish the efficacy and safety of ALN and TPTD in Japanese postmenopausal women with established osteoporosis.

In conclusion, the present study confirmed that ALN suppressed bone turnover, thereby increasing the lumbar spine BMD (8.8%), while TPTD increased bone formation, thereby increasing the lumbar spine BMD (15.9%), compared with the baseline values, over a 2-year treatment period in postmenopausal women with a history of fragility fractures. These results suggested that ALN and TPTD had differential effects on bone turnover and that TPTD had a greater effect on the BMD among Japanese postmenopausal women with a history of fragility fractures.

Conflict of interest

The authors report no funding sources in this work. Dr. Iwamoto reports grants from Eisai, Teijin, Taisho-Toyama, Chugai, Ono, Asahi-Kasei, MSD, and Takeda, honoraria from Eisai, Teijin, Taisho-Toyama, Chugai, Asahi-Kasei, Daiichi-Sankyo, and Astellas, and research grants from Asahi-Kasei.

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