Efficacy of Switching From Teriparatide to Bisphosphonate or Denosumab: A Prospective, Randomized, Open-Label Trial

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ABSTRACT
There is no consensus on an optimal treatment after daily teriparatide (TPTD). We performed a prospective, randomized, open-label, 12-month trial to investigate the efficacy of follow-up treatment after daily TPTD treatment for Japanese patients. Three-hundred patients were enrolled in this study. Patients received oral bisphosphonate (BP) including alendronate (ALN; 35 mg/week) and minodoronate (MINO; 50 mg/month), or subcutaneous denosumab (60 mg/6 month). The primary efficacy measure was bone mineral density (BMD) responses in the lumbar spine (LS) and femoral neck (FN). Lumbar spine BMD increased by 1.3/6.1% in the ALN subgroups, 0.5/6.5% in the MINO subgroups, and 4.3/6.5% in the denosumab subgroups. Femoral neck BMD increased by 0.7/6.4% in the ALN subgroups, 0.2/6.4% in the MINO subgroups, and 1.4/6.4% in the denosumab subgroups. Lumbar spine BMD increases were significantly greater in the denosumab subgroup than the BP subgroups. There were no significant differences in FN BMD increases among the three subgroups. Lumbar spine BMD increases were significantly greater in the denosumab subgroup than the BP subgroups, whereas FN BMD increases were not significant. Denosumab treatment was more effective in increasing BMD and therefore has the potential benefit of fracture prevention. Further research is warranted to determine the optimal treatment after daily TPTD.

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Introduction

A daily teriparatide (TPTD) injection stimulates bone formation and remodeling,(1,2) which is beneficial to patients with osteoporosis. After completion of a 24-month TPTD regimen, patients generally require follow-up treatment because cessation of osteoporosis treatment causes a decrease in bone mineral density (BMD).(3) Therefore, follow-up treatment is essential: Almost all patients are treated with bisphosphonate (BP), denosumab, and selective estrogen receptor modulators during follow-up. Despite these therapeutic options, there is no consensus on an optimal therapeutic regimen after daily TPTD treatment. Ebina et al. recently reported that switching from daily TPTD to denosumab significantly increased BMD and decreased expression levels of bone resorption markers, as compared to switching to oral BP at 12 months.(4) However, there is currently limited clinical evidence to guide treatment strategies after a 24-month TPTD treatment regimen, and clinical prospective randomized trials are lacking.

Based on previous reports,(4–6) by switching from 24-month teriparatide to denosumab, alendronate, or minodoronate, more patients with denosumab would achieve better BMD responses. The primary objective of this trial was to investigate BMD responses by switching from daily teriparatide to denosumab versus alendronate or minodoronate. Secondary objectives were to compare effects of switching from daily teriparatide to alendronate versus minodoronate on BMD responses.

Here, the findings of a prospective, randomized, open-label, 12-month trial after TPTD treatment are reported. This study provides direct comparisons of the efficacy of oral BP with denosumab after TPTD treatment.

Patients and Methods

Study subjects

The cohort of this prospective, single-center, randomized (using block randomization—6 patients in each block), open-label 12-month trial included Japanese men (n = 35) and postmenopausal women (n = 265), with an average age of 78/6 8 years (mean ± SD), who received TPTD treatment for 24 months. We recommend all patients with 24-month TPTD treatment to...
adopt the treatment using bisphosphonate or denosumab described below. Therefore, the inclusion criterion for this study was patients who completed 24-month TPTD treatment. The exclusion criteria were patients with illnesses affecting the bone and calcium metabolism or bone disorders other than osteoporosis, and patients with serious cardiovascular, renal, or hepatic dysfunctions. Patients with a high serum calcium concentration (>11 mg/dL) at baseline were also excluded. Recruitment started in June 2013 and stopped in June 2016. A randomization sequence table was generated by an orthopedic surgeon who was involved in this trial. Outcome assessors were blinded to efficacy of switching from TPTD to BP or denosumab until all patients finished 12-month treatment. The longitudinal BMD responses in the lumbar spine (LS) and femoral neck (FN), as well as the longitudinal changes in serum total procollagen type I N-terminal propeptide (PINP) and urinary N-telopeptide (uNTX) levels were evaluated. Follow-up visits were scheduled at 1, 4, 8, and 12 months.

Our indication for the TPTD was patients at a high risk of fracture. A high risk of fracture was defined as (1) a BMD at the lumbar spine (LS; L1–4) of <80% of the young adult mean (YAM) of all subjects reported in the Japanese Normative Female Database, with a minimum of one prevalent fragility fracture; (2) a BMD at the LS (L1–4) of <70% of the YAM and being aged ≥65 years; (3) a BMD at the LS (L1–4) of <65% of the YAM and being aged ≥55 years; or (4) >3 previous fragility fractures.

Compliance
Patients received oral BP including alendronate (ALN; 35 mg/week), minodronate (MINO; 50 mg/month), or subcutaneous denosumab (60 mg/6 month). Patients treated with denosumab also received active or native vitamin D during the study period. Medication compliance was assessed at each visit, and participants were queried regarding the number of missed medication doses. Compliance was defined as usage of ≥85% of the study drug in case of oral BP. Otherwise, patients treated with denosumab received a subcutaneous injection every 6 months.

The study protocol was approved by the Ethics Committee of Tomidahama Hospital, and conducted in compliance with the ethical principles stated in the Declaration of Helsinki. Written informed consent was obtained from each patient.

Measurements
The BMD of the LS and FN were measured by dual-energy radiography absorptiometry (DXA) using a DPX-BRAVO instrument (GE Healthcare, Madison, WI, USA) at baseline and at every 4 months during the 12-month treatment period. The intraobserver coefficients of variation (%CV) for DXA in 60 healthy subjects with a mean age of 29 years (range, 21 to 39 years) were 0.5% for the LS and 1.0% for the FN. The interobserver %CV were 0.6% for the LS and 0.9% for the FN. The baseline PINP concentration (normal range, 26.4 to 98.2 μg/L in postmenopausal women and 18.1 to 74.1 μg/L in men) was measured using a radioimmunoassay (Orion Diagnostica, Ltd., Espoo, Finland). The intra- and interassay %CV for the PINP concentrations were 3.5% and 4.2%, respectively. uNTX (normal range, 14.3 to 89.0 nmol bone collagen equivalents (BCE)/mmol creatinine (Cr) in women and 13.0 to 66.2 nmolBCE/mmol Cr in men) was measured using an enzyme-linked immunosorbent assay (Alere Medical Co., Ltd., Tokyo, Japan). The intra- and interassay %CV for uNTX were 6.6% and 6.5%, respectively.

Statistical analysis
Data were analyzed by an intention-to-treat approach. Differences between measurements and subgroups were analyzed using the Kruskal–Wallis test. Longitudinal BMD changes in each group were analyzed using the paired t test. Longitudinal changes in the PINP concentration and uNTX excretion were assessed by the Wilcoxon signed-rank test. Differences in categorical variables were assessed by the χ² test and Fisher’s exact test. Differences in fracture incidences were assessed by Kaplan–Meier analysis and the log-rank test. Data are expressed as means ± SD. A probability (p) value of <0.05 was considered statistically significant. StatView, statistical software version 5.0 (SAS Institute, Inc., Cary, NC, USA), was used to perform all statistical analyses.

Results
Baseline characteristics
The age, sex, height, weight, body mass index, previous treatments, previous osteoporotic fractures, baseline BMD at the LS and FN, and baseline serum calcium, phosphorus, uric acid, estimated glomerular filtration rate, alkaline phosphatase, and PINP levels are presented in Table 1. There were significant differences in serum calcium levels among the three groups (p < 0.01). Twelve of 100 patients (12%) in the ALN subgroup, 19 of 100 (19%) in the MINO subgroup, and 8 of 100 (8%) in the denosumab subgroup discontinued treatment (Fig. 1). There were no significant differences in the completion rates among the three subgroups (p = 0.07; χ² test). There was no adverse event in any subgroup. Six patients died of unrelated causes to the osteoporosis treatment during their treatment.

BMD response to TPTD treatment
In the ALN subgroup, the percent LS BMD significantly increased at 4 months of ALN therapy (p < 0.05 vs. baseline, paired t test) and increased by 1.3 ± 5.1% at 12 months (p < 0.01 versus baseline, paired t test) (Fig. 2A). The percent FN BMD increased by 0.7 ± 4.6% at 12 months of ALN therapy, but this change was not significant (p = 0.32, paired t test), as compared with baseline (Fig. 2B).

In the MINO subgroup, the percent LS BMD increased by 0.5 ± 4.6% at 12 months, but this change was not significant (p = 0.08, paired t test), as compared with baseline (Fig. 2A). The percent FN BMD increased by 0.2 ± 4.6% at 12 months, but this change was not significant (p = 0.66, paired t test), as compared with baseline (Fig. 2B).

In the denosumab subgroup, the percent LS BMD significantly increased at 4 months (p < 0.01 versus baseline, paired t test) and increased by 4.3 ± 3.5% at 12 months (p < 0.01 versus baseline, paired t test) (Fig. 2A). The percent FN BMD significantly increased at 4 months (p = 0.03) and increased by 1.4 ± 3.4% at 12 months (p < 0.0, paired t test) (Fig. 2B).

There was a significant difference in the LS BMD increase at 4, 8, and 12 months among the three subgroups (all p < 0.01, Kruskal–Wallis test). There were no significant discrepancies in the LS BMD percent increase between the ALN and MINO subgroups at 4, 8, and 12 months (p = 0.11, 0.26, and 0.44, respectively, Mann–Whitney U test). The discrepancies in the LS BMD percent increase between the MINO and denosumab subgroups were significant (p < 0.01 at 4, 8, and 12 months, Mann–Whitney U test). The discrepancies in the LS BMD percent increase between the
Table 1. Demographics and Baseline Characteristics of Subjects

| Variable                              | Alendronate subgroup (n = 100) | Minodronate subgroup (n = 100) | Denosumab subgroup (n = 100) | p valuea |
|---------------------------------------|-------------------------------|-------------------------------|-------------------------------|----------|
| Age (years)                           | 78 ± 9 (43–97)                | 79 ± 7 (61–95)                | 78 ± 8 (53–92)               | 0.49     |
| Female sex                            | 91 (91)                       | 86 (86)                       | 88 (88)                      | 0.54     |
| Height (cm)                           | 150 ± 7 (134–165)             | 150 ± 8 (130–175)             | 151 ± 8 (130–173)            | 0.90     |
| Body weight (kg)                      | 48 ± 9 (31–77)                | 49 ± 9 (29–90)                | 48 ± 8 (31–76)               | 0.67     |
| BMI (kg/m²)                           | 21 ± 4 (14–35)                | 22 ± 4 (13–40)                | 21 ± 3 (15–32)               | 0.53     |
| Previous osteoporotic fractures, n (%)| 74 (74)                       | 78 (78)                       | 77 (77)                      | 0.79     |
| Vertebral body                        | 63 (63)                       | 65 (65)                       | 71 (71)                      | 0.46     |
| Proximal femur                        | 27 (27)                       | 17 (17)                       | 15 (15)                      | 0.06     |
| Distal radius                         | 5 (5)                         | 9 (9)                         | 6 (6)                        | 0.50     |
| Proximal humerus                      | 3 (3)                         | 1 (1)                         | 1 (1)                        | 0.44     |
| BMD                                   |                               |                               |                               |          |
| Lumbar spine (g/cm²), T-score         | 0.909 ± 0.146, −1.7 ± 1.2     | 0.943 ± 0.176, −1.5 ± 1.4     | 0.920 ± 0.190, −1.7 ± 1.6    | 0.37     |
| Femoral neck (g/cm²), T-score         | 0.629 ± 0.102, −2.3 ± 0.8     | 0.644 ± 0.117, −2.2 ± 0.9     | 0.633 ± 0.109, −2.2 ± 0.9    | 0.65     |
| Biochemistry                           |                               |                               |                               |          |
| Serum calcium (mg/dL)b                | 9.8 ± 6.0 (8.5–11.5)          | 9.7 ± 0.5 (8.2–11.2)          | 9.6 ± 0.5 (8.4–10.8)         | 0.01     |
| Serum phosphorus (mg/dL)c             | 3.4 ± 0.6 (2.2–5.0)           | 3.4 ± 0.6 (2.3–4.7)           | 3.5 ± 0.5 (2.3–4.5)          | 0.70     |
| Serum uric acid (mg/dL)d              | 5.8 ± 1.7 (0.9–10.3)          | 5.8 ± 1.7 (1.7–11.8)          | 5.6 ± 1.5 (2.2–9.4)          | 0.49     |
| Serum eGFR (mL/min)e                  | 62.0 ± 20.7 (23.2–147.0)      | 60.1 ± 18.0 (23.1–101.5)      | 63.1 ± 19.8 (21.9–134.3)     | 0.56     |
| Serum ALP (IU/L)f                     | 276 ± 101 (103–770)          | 292 ± 119 (129–1125)         | 267 ± 83 (78–541)           | 0.14     |
| Bone turnover markers                 |                               |                               |                               |          |
| Serum PINP (µg/L)f                    | 82.3 ± 79.8 (13.4–532.0)      | 80.3 ± 58.5 (13.7–256.0)      | 71.8 ± 48.5 (8.1–242.0)      | 0.46     |
| Urinary NTX (nmolBCE/mmol Cr)h        | 74.2 ± 83.2 (5.0–633.3)       | 65.0 ± 52.8 (15.5–323.3)      | 64.2 ± 44.7 (7.7–248.8)      | 0.49     |

Data are expressed as mean ± SD (range). Normal reference ranges.

BMI = body mass index; SERM = selective estrogen receptor modulator; BMD = bone mineral density; eGFR = estimated glomerular filtration rate;
ALP = alkaline phosphatase; PINP = procollagen type I N-terminal propeptide; NTX = N-telopeptide of type I collagen.

aKruskal-Wallis test, χ² test, Fisher’s exact test.
b8.5–10.2 mg/dl
c2.5–4.5 mg/dl
d2.5–7.5 mg/dl
e60 mL/min
f100–350 IU/L
g19.0–83.5 µg/L (men) and 21.9–71.9 µg/L (postmenopausal women)
h13.0–66.2 nmolBCE/mmol Cr (men) and 14.3–89.0 nmol BCE/mmol Cr (postmenopausal women).

denosumab and ALN subgroups were significant (p = 0.02 at 4 months and p < 0.01 at 8 and 12 months, Mann–Whitney U test).
Otherwise, there was no significant difference in the FN BMD increase at 4, 8, and 12 months (p = 0.14, 0.67, and 0.16, respectively, Kruskal–Wallis test).

Changes in the serum PINP and uNTX levels in response to treatment

Changes in serum PINP levels are shown in Fig. 3A. The serum PINP levels rapidly and significantly decreased at 4 months in the three subgroups and were continuously suppressed until month 12 of treatment. There were significant differences in serum PINP levels among three subgroups at 4, 8, and 12 months (p < 0.01 at 4 and 8 months, p = 0.01 at 12 months, Kruskal–Wallis test). Changes in uNTX levels are shown in Fig. 3B. The urinary NTX levels rapidly and significantly decreased at 4 months in the three subgroups and were continuously suppressed until month 12 of treatment. There were significant differences in urinary NTX levels among three subgroups at 4, 8, and 12 months (p < 0.01 at 4 and 8 months, p = 0.03 at 12 months, Kruskal–Wallis test).

Incidences of fracture during the 12-month treatment period among the three subgroups

There was one fracture (proximal femur fracture) in the ALN subgroup, yielding an accumulative incidence of 99% (Kaplan–Meier analysis). There was one vertebral fracture in the MINO subgroup, yielding an accumulative incidence of 99% (Kaplan–Meier analysis). There were two fractures (one vertebral fracture and one distal radius fracture) in the denosumab subgroup, yielding an accumulative incidence of 97% (Kaplan–Meier analysis). There were no significant differences in fracture incidence among three subgroups (p = 0.49, Log-rank test).

Discussion

The results of the present study showed that the LS BMD increases were significantly greater in the denosumab subgroup than the BP subgroups, whereas there were no significant differences in the FN BMD increases among three subgroups for Japanese subjects. In addition, the serum PINP and urinary NTX concentrations at 4, 8, and 12 months were significantly decreased in all subgroups.
Fig. 1. Study flow.

Fig. 2. Longitudinal changes in bone mineral density (BMD). Mean percent changes in (A) the lumbar spine (LS BMD) and (B) femoral neck bone mineral density (FN BMD) at 4, 8, and 12 months (\(^* p < 0.01, \,** p < 0.05\), not significant [n.s.] versus baseline, paired t test; \(# p < 0.01\) among three subgroups; Kruskal–Wallis test). Data are presented as means \(\pm\) standard deviations.
Teriparatide is the only available anabolic agent to increase BMD, especially in the LS. Teriparatide reduces the risk of spine and nonspine fractures. However, daily TPTD treatment is limited to 24 months and discontinuation results in a rapid decrease in BMD. Therefore, follow-up treatment is required. Adami et al. reported that 12-month raloxifene treatment after TPTD treatment prevented the rapid BMD decrease at LS and further increased FN BMD. The results—that the BMD decrease at LS was less in the raloxifene subgroup than the placebo subgroup—showed that raloxifene treatment after TPTD treatment was effective.

There were two important findings in this study. First, BMD increases were significantly greater in the denosumab subgroup than the BP subgroups. A 12-month observational study performed by Ebina et al. reported significant increases in the BMD of the LS, FN, and total hip, and bone turnover markers (BTMs) were significantly decreased in the denosumab subgroup, as compared with the BP subgroup, which are in agreement with the results of the present study. In this study, denosumab treatment was more effective in increasing BMD. Therefore, denosumab treatment would be the most important option after teriparatide treatment, although we could not evaluate the fracture risk reduction. Second, the increases in BMD were not as good in the BP subgroups. In regard to the BMD response of each drug in previous reports, Brown et al. compared denosumab with ALN and reported that LS BMD increased by 5.3% in the denosumab subgroup and 4.3% in the ALN subgroup (70 mg/week) after 12 months of treatment. They also reported that FN BMD increased by 2.4% in the denosumab subgroup, but only by 1.8% in the ALN subgroup, after 12 months of treatment. Another study performed by Hagino et al. reported that LS BMD increased by 5.9% in the MINO subgroup and by 6.3% in the ALN subgroup after 12 months of treatment. They also reported that total hip BMD increased by 3.5% in the MINO subgroup and by 3.3% in the ALN subgroup after 12 months of treatment. Leder et al. showed that 24 months of TPTD therapy followed by denosumab was associated with continuous BMD increases. After 24 months of denosumab therapy, the BMD of the LS and FN increased by 8.6% and 5.6%, respectively. Although the reason for the low BMD responses in the BP subgroups in this study remains unknown, the differences in patient characteristics or dosages may have had some influence. For example, the therapeutic dose of ALN is 70 mg/week in the United States and Europe, but is limited to 35 mg/week in Japan. Further analyses are required to interpret the results of this study.

The limitations of this study should be considered when interpreting our results. First, although BMD increases in the denosumab subgroup were superior to the BP subgroups, reductions in the fracture incidence were not assessed. For osteoporotic treatment, it must be considered that the efficacy of fracture prevention could not increase in proportion to BMD responses, especially in the comparison among different kinds of drugs. Therefore, these results are insufficient to identify the most beneficial treatment for patients after TPTD treatment in terms of fracture prevention. Second, BMD and BTM responses were evaluated for only 12 months. Third, serum vitamin D levels were not evaluated, which may have affected the results. Fourth, this clinical study was centered on Japanese subjects.

In conclusion, this study demonstrated that BMD increases in the LS were significantly greater in the denosumab subgroup as compared to the oral BP subgroups. In addition, the serum PINP concentration at 12 months was correlated with the LS BMD increase during the latter 12 months in a similar manner as that of the correlation of the baseline PINP concentration to the LS BMD increase during the first 12 months. These results should encourage clinicians to continue TPTD treatment if patients have blunt BMD increases and distinct BTM responses for the first 12 months of treatment. As it was not possible to identify factors associated with the BMD and BTM responses, especially the fracture risk, further studies are required.

Disclosures
All authors state that they have no conflicts of interest.

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