Two-Year Outcomes of Daily and Twice-Weekly Teriparatide Treatment in Postmenopausal Women with Severe Osteoporosis: A Randomized Non-Blinded Prospective Study

Takeshi Mochizuki¹, Koichiro Yano², Katsunori Ikari², Ken Okazaki²

¹Department of Orthopaedic Surgery, Kamagaya General Hospital, Chiba; ²Department of Orthopaedic Surgery, Tokyo Women’s Medical University, Tokyo, Japan

Corresponding author
Takeshi Mochizuki
Department of Orthopaedic Surgery, Kamagaya General Hospital, 929-6 Hatsutomi, Kamagaya, Chiba 273-0121, Japan
Tel: +81-47-498-8111
Fax: +81-47-498-5050
E-mail: twmutamo@gmail.com

Received: March 10, 2024
Revised: April 22, 2024
Accepted: April 27, 2024

Background: The long-term effects of daily teriparatide (D-TPTD) and twice-weekly TPTD (W-TPTD) injections are compared among postmenopausal women with severe osteoporosis. Methods: A total of 102 patients were enrolled and randomly allocated into two groups for the administration of either D-TPTD or W-TPTD. Treatment efficacy was measured as the percentage change in bone mineral density (ΔBMD) from baseline in the lumbar spine, total hip, and femoral neck. The findings were compared between the two groups. Results: At 24 months after treatment, the persistence rates and medication possession ratios in the D-TPTD and W-TPTD groups were 68.6% and 56.9%, and 87.8% and 92.0%, respectively. The ΔBMD in the lumbar spine, total hip, and femoral neck were 15.6% ± 10.2%, 5.3% ± 6.3%, and 5.5% ± 6.2%, respectively, in the D-TPTD group; and 9.5% ± 7.9%, 2.3% ± 6.2%, and 3.1% ± 7.4%, respectively, in the W-TPTD group following 24 months of treatment. The ΔBMD of the lumbar spine (P = 0.008) at 24 months and total hip (P = 0.024) at 18 months differed significantly between the two groups. Conclusions: D-TPTD administration resulted in a significantly higher BMD in the lumbar spine and total hip, supporting this therapeutic regimen for postmenopausal women with severe osteoporosis.

Key Words: Bone mineral density · Daily · Osteoporosis · Teriparatide · Twice weekly

INTRODUCTION

Osteoporosis is a common disease in which reduced bone mass and poor bone quality lead to fragility fractures of the vertebral body and hip.[1,2] In Japan, self-administered once-daily teriparatide (D-TPTD) and twice-weekly TPTD (W-TPTD) are widely used to treat severe osteoporosis. D-TPTD and W-TPTD are anabolic agents that promote parathyroid hormone (PTH) and bone formation. Previous studies have reported that TPTD increases bone mineral density (BMD) in the lumbar spine and hip, and reduces the risk of vertebral and hip fractures.[3-7] D-TPTD and W-TPTD are classified as PTHs and bone-forming drugs, respectively. In Japan, self-administered D-TPTD and W-TPTD injections are used to treat severe osteoporosis. Long-term results concerning D-TPTD and W-TPTD outcomes
are needed for daily clinical practice, as studies reporting
two-year results following the use of W-TPTD are limited,
and no studies have compared two-year outcomes be-
tween D-TPTD and W-TPTD injections. Therefore, we com-
pared two-year outcomes of D-TPTD and W-TPTD injec-
tions in postmenopausal women with severe osteoporosis.

METHODS

This study included 102 postmenopausal women who
had been diagnosed with severe osteoporosis. Severe os-
teoporosis was defined as: a T-score ≤-2.5 at the lumbar
spine, total hip, or femoral neck and a history of fragility
fractures; a T-score ≤-3.3 at the lumbar spine; or at least
two vertebral fractures. The T-scores were measured using
dual energy X-ray absorptiometry (DXA).

Patients recruited between May 2020 and September
2021 were randomly assigned to either a D-TPTD (adminis-
tered 20 µg D-TPTD) or a W-TPTD (administered 28.2 µg W-
TPTD) group at a 1:1 ratio. Patients receiving treatment for
osteoporosis or glucocorticoids at the time of the study,
and those with a history of spine or hip surgery were ex-
cluded. The clinical research centers of the affiliated insti-
tutions allocated patients into groups. Medical staff blind-
ed to the group allocation summarized the clinical results
of the patients.

DXA (Prodigy System; GE Healthcare, Madison, WI, USA)
was used to measure the BMD in the lumbar spine, total
hip, and femoral neck. BMD of the lumbar spine was mea-
sured from the 1st to the 4th lumbar vertebrae. Vertebral
fractures were examined using plain radiography from the
8th thoracic vertebra to the lumbar spine. A new vertebral
fracture was defined as a deterioration of the grade, using
a semiquantitative grading scale, and a worsening fracture
was described as ≥ 20% loss of vertebral height.[8] Ortho-
pedic surgeons who were blinded to patient information
independently assessed the digital radiographs. Figure 1
illustrates the assessment conducted in this study.

The study was conducted in accordance with the princi-
ples of the Declaration of Helsinki. Written informed con-
sent was obtained from all study patients. This study was
approved by the Institutional Review Boards of the au-
thors’ affiliated institutions.

1. Statistical analysis

We determined and compared the BMD values using a
paired t-test. Intergroup comparisons were performed us-
ing the Wilcoxon rank-sum test. Statistical significance was
set at a P-value of less than 0.05. BMD and bone turnover marker (BTS) analyses were performed using observed cases. The power analysis result was 0.806 (α = 0.05; effect size = 0.5). Analyses were performed using the R Statistical Software (version 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline patient demographics and clinical data concerning both groups are shown in Table 1.

The persistence rates in the D-TPTD and W-TPTD groups at 24 months were 68.6% and 56.9%, respectively (P = 0.306). The medication possession ratios in the D-TPTD and W-TPTD groups were 87.8% and 92.0% (P = 0.211), respectively, 24 months after treatment. In the D-TPTD group, the adverse events due to discontinuation were injection site reaction (one patient), fatigue (one patient), and itching (one patient). Additionally, nine patients discontinued treatment because of hospital transfer, two patients discontinued treatment because of the onset of other diseases, and one patient discontinued treatment because of their wish to discontinue treatment (Fig. 2).

In the W-TPTD group, adverse events due to discontinuation were nausea (four patients), headache (two patients), appetite loss (one patient), trembling (one patient), and itching (one patient). Additionally, nine patients discontinued treatment because of hospital transfer, one patient discontinued treatment because of hospital transfer, two patients discontinued treatment because of the onset of other diseases, and one patient discontinued treatment because of an inability to perform self-injection. In the W-TPTD group, adverse events due to discontinuation were injection site reaction (one patient), fatigue (one patient), and itching (one patient). Additionally, nine patients discontinued treatment because of hospital transfer, two patients discontinued treatment because of the onset of other diseases, and one patient discontinued treatment because of their wish to discontinue treatment (Fig. 2).

The BMD values for the lumbar spine, total hip, and femoral neck in the D-TPTD and W-TPTD groups are shown in Figure 3. The BMD values of the lumbar spine in the D-TPTD group were significantly higher than those in the W-TPTD group at 6, 12, 18, and 24 months. The ΔBMDs in the

Table 1. Baseline demographics and clinical data of patients and comparison between patients received with daily and twice-weekly teriparatide

<table>
<thead>
<tr>
<th>Variables</th>
<th>D-TPTD group (N=51)</th>
<th>W-TPTD group (N=51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>76.2±6.5</td>
<td>77.8±6.1</td>
<td>0.141</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>49.5±8.1</td>
<td>47.4±8.7</td>
<td>0.284</td>
</tr>
<tr>
<td>Duration of postmenopausal status</td>
<td>26.4±6.2</td>
<td>27.9±5.7</td>
<td>0.211</td>
</tr>
<tr>
<td>Cr-eGFR (mL/min/1.73 m²)</td>
<td>70.0±14.7</td>
<td>67.1±13.3</td>
<td>0.252</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.4±0.3</td>
<td>9.4±0.4</td>
<td>0.470</td>
</tr>
<tr>
<td>Serum 25(OH)D (ng/mL)</td>
<td>16.3±6.3</td>
<td>18.0±16.0</td>
<td>0.785</td>
</tr>
<tr>
<td>Serum homocysteine (nmol/mL)</td>
<td>10.6±3.7</td>
<td>10.7±3.5</td>
<td>0.850</td>
</tr>
<tr>
<td>Skin AGE (AU)</td>
<td>2.49±0.53</td>
<td>2.47±0.6</td>
<td>0.545</td>
</tr>
<tr>
<td>Presence of vertebral fractures</td>
<td>45 (88.2)</td>
<td>41 (80.4)</td>
<td>0.415</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lumbar spine</th>
<th>BMD (g/cm²)</th>
<th>T-score</th>
<th>BMD (g/cm²)</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.828±0.149</td>
<td>-2.3±1.1</td>
<td>0.799±0.186</td>
<td>-2.5±1.3</td>
</tr>
<tr>
<td>Total hip</td>
<td>0.637±0.097</td>
<td>-2.5±0.8</td>
<td>0.638±0.124</td>
<td>-2.5±0.9</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.605±0.093</td>
<td>-2.9±0.8</td>
<td>0.608±0.109</td>
<td>-2.9±1.0</td>
</tr>
</tbody>
</table>

The data is presented as mean± standard deviation or N (%). D-TPTD, daily teriparatide; W-TPTD, twice-weekly teriparatide; Cr-eGFR, estimated glomerular filtration rate calculated using creatinine; 25(OH) D, 25-hydroxy-vitamin D; AGE, advanced glycation end product; AU, arbitrary unit; BMD, bone mineral density; P1NP, N-terminal propeptide of type I collagen; TRACP-5b, tartrate-resistant acid phosphatase 5b.

The ΔBTS at 6, 12, 18, and 24 months in the D-TPTD group than in the W-TPTD group.

The ΔBTS at 6, 12, 18, and 24 months in the D-TPTD group than in the W-TPTD group.
Teriparatide Treatment in Severe Osteoporosis

Enrolled patients in this study
D-TPTD (N=51), W-TPTD (N=51)

Complete at 2 years
D-TPTD (N=36), W-TPTD (N=31)

D-TPTD group: reasons of discontinuation
• Adverse events (N=3)
• Hospital transfer (N=9)
• Onset of other disease (N=2)
• Inability to self-injection (N=1)

W-TPTD group: reasons of discontinuation
• Adverse events (N=9)
• Hospital transfer (N=9)
• Onset of other disease (N=1)
• Patient’s hope (N=1)

DISCUSSION

This randomized clinical trial evaluated the effects of D-TPTD and W-TPTD on the BMD of the lumbar spine, total hip, and femoral neck. The BMD significantly increased at each location and time point in the D-TPTD group. In the W-TPTD group, the BMD of the lumbar spine increased significantly at 24 months. Obermayer-Pietsch et al.

Fig. 2. Patient flowchart. D-TPTD, daily teriparatide; W-TPTD, twice-weekly teriparatide.

Fig. 3. Percentage changes from baseline of bone mineral density in (A) lumbar spine, (B) total hip, and (C) femoral neck. D-TPTD, daily teriparatide; W-TPTD, twice-weekly teriparatide. a) P < 0.05, b) P < 0.01 (vs. baseline). c) P < 0.05, d) P < 0.01 (D-TPTD vs. W-TPTD).

and 61.7% ± 125.1%, respectively, in the procollagen type N-terminal propeptide of type I collagen (P1NP); and 25.2% ± 51.1%, 25.4% ± 56.7%, 19.0% ± 72.1%, and 8.8% ± 67.7%, respectively, in the tartrate-resistant acid phosphatase 5b (TRACP-5b). The ΔBTS values at 6, 12, 18, and 24 months in the W-TPTD group were 41.5% ± 55.2%, 28.6% ± 72.9%, 31.1% ± 97.0%, and 5.9% ± 59.1%, respectively, in the P1NP; and -6.3% ± 36.2%, -14.4% ± 32.7%, -18.8% ± 30.1%, and -24.3% ± 25.5%, respectively, in the TRACP-5b.

The incidence rates of new morphological vertebral fractures in the D- and W-TPTD groups at 24 months were 7.8% and 13.7%, respectively.
Takeshi Mochizuki, et al.

Table 2. Change in bone mineral density values in the lumbar spine and total hip for each osteoporosis treatment medication in previous reports

<table>
<thead>
<tr>
<th>Drugs</th>
<th>ΔBMD at lumbar spine</th>
<th>ΔBMD at hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>7.48%/2–4 yr</td>
<td>4.24%/2 yr</td>
</tr>
<tr>
<td>Risedronate</td>
<td>5.4%/1.5–3 yr</td>
<td>2.7%/1.5–3 yr</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>6.71%/3 yr</td>
<td>5.06%/–6.02%/3 yr</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>2.51%/2–3 yr</td>
<td>2.11%/2–3 yr</td>
</tr>
<tr>
<td>Denosumab</td>
<td>9.2%/3 yr</td>
<td>6.0%/3 yr</td>
</tr>
<tr>
<td>Daily teriparatide</td>
<td>9.7%/21 mon</td>
<td>2.6%/21 mon</td>
</tr>
<tr>
<td>Weekly teriparatide</td>
<td>6.7%/18 mon</td>
<td>2.9%/18 mon</td>
</tr>
</tbody>
</table>

ΔBMD, change in bone mineral density.

al. [3] reported that ΔBMD values in the lumbar spine, total hip, and femoral neck at 24 months were 13.1%, 3.8%, and 4.8%, respectively, after D-TPTD. Soen et al. [5] reported that ΔBMD values for the lumbar spine and total hip at 24 months were 17.2% and 7.9%, respectively, after D-TPTD. Tsuchie et al. [7] reported that ΔBMD values for the lumbar spine and femoral neck were 14.4% and 8.2%, respectively, after 24 months of W-TPTD. ΔBMD values in the lumbar spine were 12.0% after 18 months of D-TPTD, 8.5% after 18 months of W-TPTD, and 6.8% after 18 months of bisphosphonates, while those in the total hip were 3.0%, 2.1%, and 3.0%, respectively, in a previous study that reported significant differences between ΔBMD in the lumbar spine after D-TPTD and bisphosphate use.[9] In our study, ΔBMD values in the lumbar spine and total hip differed significantly between the two groups after 24 months. Based on previous studies, ΔBMD values in the lumbar spine and total hip considering each osteoporosis treatment medication are presented in Table 2.[10-16]

TPTD is an anabolic agent that activates the PTH1 receptor, induces bone formation, and results in transient signaling of intracellular cyclic adenosine monophosphate.[17] High-frequency TPTD administration in adult mice resulted in a higher number of TRACP-reactive osteoclasts and osteoblasts than low-frequency administration, leading to increased bone volume. High-frequency TPTD administration rapidly increases bone mass by accelerating bone remodeling. In contrast, low-frequency administration of TPTD causes trabecular formation through bone remodeling and mini-modeling.[18] Moreover, D-TPTD has a strong effect on trabecular bone, whereas W-TPTD has a moderate effect on trabecular bone, without decreasing cortical bone density.[9] In previous studies, changes in anabolic markers such as P1NP, TRACP-5b, and the C-terminal telopeptide of type 1 collagen differed between patients administered D-TPTD and W-TPTD.[6,8,9,19] Similarly, in our study, the BTS changes in both groups differed at 24 months. Therefore, the frequency of TPTD administration resulted in different BMD values.

No difference was observed in the frequency of new morphological vertebral fractures between the D-TPTD and W-TPTD groups. In previous studies, the rate of vertebral fracture at 18 months ranged from 1.8% to 5.0% in the D-TPTD group and 3.5% in the W-TPTD group.[4,15,20,21] Increased BMD and reduced fractures have been reported to be closely related.[22] The discrepancy between increased BMD and vertebral fracture frequency in this study may be explained in terms of bone quality and the observational period. Meta-analyses in a previous report revealed that the hazard ratio (HR) for vertebral fracture following D-TPTD versus placebo was 0.23 (95% confidence interval [CI], 0.16–0.32).[23] Romosozumab, which promotes bone formation and inhibits resorption by blocking sclerostin, increases BMD, improves bone strength, and reduces the risk of fractures.[24,25] Romosozumab differs from TPTD in its inhibitory effects on bone resorption. Following romosozumab treatment, the BMD values in the lumbar spine and total hip at 12 months were 13.3% and 6.8%, respectively. [26] The HR for vertebral fracture after romosozumab versus placebo was 0.27 (95% CI, 0.13–0.52).[23] The vertebral fracture suppression effect of D-TPTD was higher than that of other osteoporosis treatment medications.[23] However, in a previous study comparing romosozumab and TPTD in postmenopausal women with osteoporosis transitioning from oral bisphosphonate treatment, the ΔBMD in the lumbar spine was greater using romosozumab compared with TPTD (9.8% vs. 54%).[27] As the evidence of the differences in effectiveness between romosozumab and TPTD is insufficient, further clinical research is warranted.

Regarding the relationship between BMD and the incidence of vertebral fractures, 2% and 8% of BMD in the lumbar spine can be expected to result in a 28% and 62% reduction in the incidence of vertebral fractures.[22] We suggest that an increase in BMD can lead to a reduction in vertebral fractures.

This study has several limitations. First, the sample size was small; both groups had vitamin D insufficiency, which could have affected the efficacy of the agents; lifestyle fac-
tors, including exercise and nutrition, were not evaluated. Second, there were no statistical differences in the persistence rates or medication possession ratios between the two groups; however, it cannot be denied that these factors may have influenced the results. Finally, we did not evaluate nonvertebral fractures. Therefore, a prospective randomized study with a larger sample size that accounts for lifestyle confounders and non-vertebral fractures is needed to clarify the differences between the D-TPTD and W-TPTD groups. Thus, this study provides important insights for future research.

In conclusion, this randomized clinical trial is the first to compare two-year D-TPTD and W-TPTD outcomes. BMD values in the lumbar spine and total hip over 24 months differed significantly between the groups, suggesting that D-TPTD should be considered for the therapeutic management of postmenopausal women with severe osteoporosis.

DECLARATIONS

Funding
The authors received no financial support for this article.

Ethics approval and consent to participate
This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Soonchunhyang University Bucheon Hospital.

Conflict of interest
Some authors have received honoraria for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Hisamitsu, Janssen, Mochida, Takeda, Tanabe-Mitsubishi, Pfizer, and UCB. The sponsors were not involved in the study design; collection, analysis, interpretation of data; writing of the article; or the decision to submit the results for publication. No potential conflict of interest relevant to this article was reported.

ORCID
Takeshi Mochizuki https://orcid.org/0000-0002-8316-8671
Koichiro Yano https://orcid.org/0000-0002-9514-2719
Katsunori Ikari https://orcid.org/0000-0001-9066-2005
Ken Okazaki https://orcid.org/0000-0003-1274-8406

REFERENCES


