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Original article

Impact of patient background factors on the treatment efficacy of once-weekly teriparatide

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ABSTRACT

Objectives: The impact of patient background factors on changes in bone mineral density (BMD) and bone metabolic markers after treatment with once-weekly teriparatide (W-TPTD) has not been fully elucidated. To clarify the impact, I performed stratified analysis in addition to the efficacy and safety assessments to analyze treatment data with W-TPTD.

Methods: The primary endpoint of the efficacy was the rate of change of the lumbar spine BMD at 18 months after treatment. In the exploratory analysis, bone metabolic markers at baseline were used to divide the patients into 3 groups, by the first tertile and the second tertile. The rate of change in the lumbar spine/femoral neck BMD and bone metabolic markers in each group were analyzed by stratification.

Results: The rate of change in the lumbar spine BMD at 18 months was 9.0%, which represented a significant increase. The rate of change in the lumbar spine/femoral neck BMD in each group classified into tertiles by their baseline bone metabolic markers significantly increased, regardless of the type of bone metabolic markers and baseline value. For markers, all groups remained within the range of reference values at 18 months after treatment.

Conclusions: I demonstrated that W-TPTD significantly increased the BMD of the lumbar spine and femur, regardless of baseline values of the bone metabolic markers. In addition, W-TPTD was able to normalize bone metabolic markers. I considered that W-TPTD would be useful, independent of bone metabolic markers in patients, as an agent to improve BMD, and be a useful option for the treatment of osteoporosis.

1. Introduction

Teriparatide agents used for the clinical treatment of osteoporosis include once-weekly teriparatide (W-TPTD) and daily self-injected teriparatide (D-TPTD). W-TPTD was shown to increase the bone mineral density (BMD) of the lumbar spine by 6.7% after 72 weeks in the Phase 3 Teriparatide Once Weekly Efficacy Research trial [1], whereas D-TPTD was reported to increase the lumbar spine BMD by 9.7% after 18 months in fracture prevention trials [2]. As for the effect on the prevention of the new onset of vertebral fractures, the relative risk of using W-TPTD was reported to be 0.20 in comparison with placebo [1], but 0.35 when using D-TPTD [2]. Although the results were not directly comparable, there was a similar preventive efficacy between W-TPTD and D-TPTD against the new onset of vertebral fractures, without any large differences in the increase in BMD between regimens.

With respect to the efficacy of teriparatide on pain, D-TPTD has significantly improved the visual analogue scale (VAS) score of back pain [3], and both D-TPTD and W-TPTD in patients with spinal fracture have significantly improved the VAS of low back pain compared with risedronate [4].

In clinical practice, BMD and VAS are important parameters for the evaluation of the therapeutic effect of osteoporosis [5]. Although improvements to BMD and VAS were also found after D-TPTD treatment, it was reported that such improvement was affected by patient background factors, including the baseline values of bone metabolic markers or pretreatment medications. Given the impact of BMD on the therapeutic effect of D-TPTD, the values of bone metabolic markers at baseline were classified into 3 categories to compare their respective lumbar spine BMD. In the

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group with higher values for bone metabolic markers, the lumbar spine BMD increased significantly [6]. In addition, D-TPTD attenuated the increase in the effect of BMD in case with pretreatment of bisphosphonates (BP) [7], whereas in patients with BP-naive or existing fractures, D-TPTD resulted in greater improvements in VAS [8,9]. However, the impact of baseline bone metabolic markers on bone metabolic markers and/or BMD in W-TPTD regimens has not yet reported, nor has the impact of patient background factors, such as pretreatment with BP or existing fractures, been considered on BMD and VAS.

To clarify the impact of patient background factors on these evaluation parameters in W-TPTD, it is important to appropriately determine the therapeutic efficacy. In this study, we performed a stratified analysis, in addition to the efficacy and safety assessments, of data from patients treated with W-TPTD accumulated in our hospital and clarified the impact of patient background factors on efficacy.

2. Methods

2.1. Study design

The study was designed as a single-center, retrospective study in Japan. I included only the existing data into the analysis; no new data were collected. Therefore, I adopted an opt-out policy for use of the existing data. After review and approval by the second Institutional Review Board in Adachi Kyosai Hospital (approval number: 2201), the research was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the "Ethical Guideline for Clinical Research Involving Humans".

2.2. Study subjects

Patients with osteoporosis starting the treatment using W-TPTD by August 2016 at Koenji Orthopedics Clinic (Tokyo, Japan), who met the required inclusion criteria and did not meet the exclusion criteria were enrolled in this study.

Inclusion criteria:

1. Postmenopausal women of ≥65 years of age
2. Patients diagnosed with primary osteoporosis

Exclusion criteria:

1. Patients diagnosed with secondary osteoporosis
2. Patients with a metabolic bone disease other than osteoporosis
3. Patients determined unsuitable by a physician, such as patients who failed to administer regularly W-TPTD

The safety assessment population included all subjects, and the efficacy assessment population included subjects that had received W-TPTD for 6 months or more and for which there were measurements of lumbar spine BMD both at baseline and after a minimum of one visit.

2.3. Evaluation

The primary endpoint for efficacy was the rate of change of the lumbar spine BMD measured by the Dual Energy X-Ray Absorptiometry (DXA) (Horizon C, Hologic, Inc., MA, USA) after 18 months. The secondary endpoints were the rate of change in the lumbar spine BMD after 6 and 12 months, and the rate of change in the femoral neck BMD after 6, 12, and 18 months. These parameters were measured by DXA. In addition, we evaluated the changes in type I procollagen N-terminal propeptide (P1NP) and tartrate-resistant acid phosphatase-5b (TRACP-5b) as bone metabolism markers after 6, 12, and 18 months, and the rate of change in VAS after 6, 12, and 18 months.

For the exploratory analysis, the following three items were evaluated.

1. The patients were divided into 3 groups by the first tertile and the second tertile based on P1NP or TRACP-5b values at baseline, and the rate of changes in the lumbar or femoral neck BMD and of bone metabolic markers in each group were analyzed by stratification at 6, 12, and 18 months of treatment.
2. The patients were stratified by the history of BP pretreatment, and the rate of changes in the lumbar spine/femoral neck BMD was compared in the intra- or inter-groups after 6, 12, and 18 months.
3. The patients were stratified by the history of BP pretreatment or existing fractures, and the rate of changes in VAS was compared in the intra- or inter-groups after 6, 12, and 18 months.

In this study, we evaluated subjects whose data was obtained at all observation point for primary and secondary endpoints. The safety assessment showed the number of cases and the incidence of adverse drug reaction observed within the 18 months after treatment. In addition, a list of symptoms was prepared, and the number of symptoms is shown.

2.4. Statistical analysis

The changes from baseline in each efficacy endpoint were assessed by using a paired *t*-test. VAS was assessed by using the Wilcoxon signed rank test. The treatment groups were compared by Student *t*-test, the Wilcoxon rank sum test, or analysis of variance (ANOVA).

When a significant difference was observed in ANOVA, multiple comparisons were performed by the Tukey-Kramer test. For the analysis of each parameter, the patients with all measurement values between baseline and 18 months were included. The continuous variables of patient background were presented as the mean ± standard deviation. All other continuous variables were presented as the mean values (lower limit of the 95% confidence interval [CI] – upper limit of the 95% CI), and nominal scales were the number of patients (%). The significance level of test was 2-sided 5%. R software version 3.4.0 (R Core Team, Vienna, Austria) was used for statistical analysis.

3. Results

The number of subjects in this study was 316, of which 193 were included in the efficacy assessment population. Among all subjects, 114 subjects did not receive W-TPTD administration for ≥6 months, 3 subjects received administration for an unknown period, 5 subjects had no measurement for baseline lumbar spine BMD, and 3 subjects had no measurement of their lumbar spine BMD at 6 months; all these subjects were excluded from the efficacy assessment population (reasons for exclusion may relate to the same subject).

The baseline subject demographics and characteristics are presented in Table 1. In our study, 130 subjects (41.1%) received pretreatment medications; of these, 81 subjects (25.6%) received BP as a pretreatment agent.

The rate of change in lumbar spine BMD after 18 months, the primary endpoint, was 9.0% (7.5%–10.4%), which represented a significant increase ($P < 0.001$). The rate of change in the lumbar spine BMD, a secondary endpoint, was 4.3% (3.3%–5.3%) ($P < 0.001$) at 6 months and 6.5% (5.3%–7.7%) ($P < 0.001$) at 12 months, which

Table 1
Patient demographics.

Variable	Value
Age, yr	78.5 ± 6.2 (316)
BMI, kg/m^2	21.7 ± 3.7 (167)
Lumbar spine BMD, g/cm^2	0.738 ± 0.168 (300)
Femoral neck BMD, g/cm^2	0.480 ± 0.091 (287)
P1NP, ng/mL	45.4 ± 23.3 (312)
TRACP-5b, mU/dL	417.4 ± 177.9 (299)
VAS, cm	5.4 ± 3.2 (37)
JOQOL total	70.2 ± 30.1 (37)
With pretreatment	130 (41.1)
BP	81 (25.6)
Others	49 (15.5)

Values are presented as mean ± standard deviation (number) or number (%).
BMI, body mass index; BMD, bone mineral density; P1NP, type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b; VAS, visual analogue scale; JOQOL, Japanese Osteoporosis Quality of Life Questionnaire; BP, bisphosphonate.

represented a significant increase after 6 months. The rate of change in femoral neck BMD was 1.4% (0.1%–2.6%) at 6 months, 3.2% (1.9%–4.4%) at 12 months, and 4.3% (2.8%–5.7%) at 18 months, with no significant difference after 6 months (P = 0.099), but a significant increase after 12 months (at 12 months: P < 0.001; at 18 months: P < 0.001). For the bone metabolic markers, a significant increase was observed in P1NP at 6 months (P = 0.011), but it was decreased significantly after 12 months (at 12 months: P = 0.045; at 18 months: P < 0.001) (Supplementary Fig. 1a). For TRACP-5b, a significant decrease was observed after 6 months (P < 0.001) and continued until 18 months (at 12 months: P < 0.001, at 18 months: P < 0.001) (Supplementary Fig. 1b).

The results of the stratified analysis of the changes in each marker, significant decreases were observed after 12 months in the high P1NP level group (53.7–99.4 ng/mL) (at 12 months: P < 0.001; at 18 months: P < 0.001). However, in the low P1NP level group (9.6–28.7 ng/mL), significant increases were observed after 6 months (at 6 months: P < 0.001; at 12 months: P < 0.001; at 18 months: P < 0.001). All groups remained within the range of reference values at 18 months (Fig. 1a). For TRACP-5b, significant decreases after 6 months were observed in the high level (473–1079 mU/dL) and medium level groups (309–472 mU/dL) (at 6 months: P < 0.001 [high], P < 0.001 [middle]; at 12 months: P < 0.001 [high], P < 0.001 [medium]; at 18 months: P < 0.001 [high], P < 0.001 [medium]) (Fig. 1b). Similarly, in TRACP-5b, all groups remained within the range of reference values at 18 months.

The rate of change in the lumbar spine/femoral neck BMD in each group classified by their baseline bone metabolic markers by tertile are shown in Figs. 2 and 3. In the lumbar spine BMD, regardless of the type of bone metabolic markers and baseline value, significant increases were observed in the rate of change at 6 months and later in all groups and continued to increase significantly until 18 months (at 6 months: P < 0.001 [in all groups]; at 12 months: P < 0.001 [in all groups]; at 18 months: P < 0.001 [in all groups]). Significant increases in the rate of change of the femoral neck BMD were observed in all groups, except for the TRACP-5b medium level group at 18 months (high group: P < 0.001 [P1NP], P < 0.001 [TRACP-5b]; medium group: P = 0.010 [P1NP], P = 0.080 [TRACP-5b]; low group: P = 0.033 [P1NP], P < 0.001 [TRACP-5b]). In the comparison between the 3 groups, no significant differences were recognized at all points in both lumbar spine and femoral neck BMDs (lumbar vertebra [P1NP]: $p = 0.318$ [at 6 months], P = 0.189 [at 12 months], P = 0.193 [at 18 months]; lumbar vertebra [TRACP-5b]: P = 0.374 [at 6 months], P = 0.351 [at 12 months], P = 0.180 [at 18 months]; femur [P1NP] P = 0.220 [at 6 months], P = 0.364 [at 12 months], P = 0.082 [at 18 months]; femur [TRACP-5b]: P = 0.125 [at 6 months], P = 0.052 [at 12 months], P = 0.158 [at 18 months]).

The rates of change in the lumbar spine/femoral neck BMD when stratified by BP pretreatment are shown in Fig. 4. In the lumbar spine BMD, the rate of changes in both groups were significantly greater after 6 months and continued to increase until 18 months (at 6 months: P < 0.001 [both groups]; at 12 months: P < 0.001 [both groups]; at 18 months: P < 0.001 [both groups]). However, in the femur, although significant increases were observed in both groups after 12 months (with BP pretreatment: P = 0.013; without BP pretreatment: P = 0.001), it was only observed in the group without BP pretreatment at 18 months (with BP pretreatment: P = 0.065, without BP pretreatment: P < 0.001). Meanwhile, in the comparison between groups, no significant differences were observed in the rate of change in BMD at all points for the lumbar spine and femur (at 6 months: P = 0.540 [lumbar spine]; P = 0.530 [femur]; at 12 months: P = 0.513 [lumbar spine] P = 0.789 [femur]; at 18 months: P = 0.472 [lumbar spine], P = 0.065 [femur]).

The extent of the changes in VAS when stratified by BP pretreatment are shown in Fig. 5. Significant improvement was observed after 6 months in both groups (with BP pretreatment:

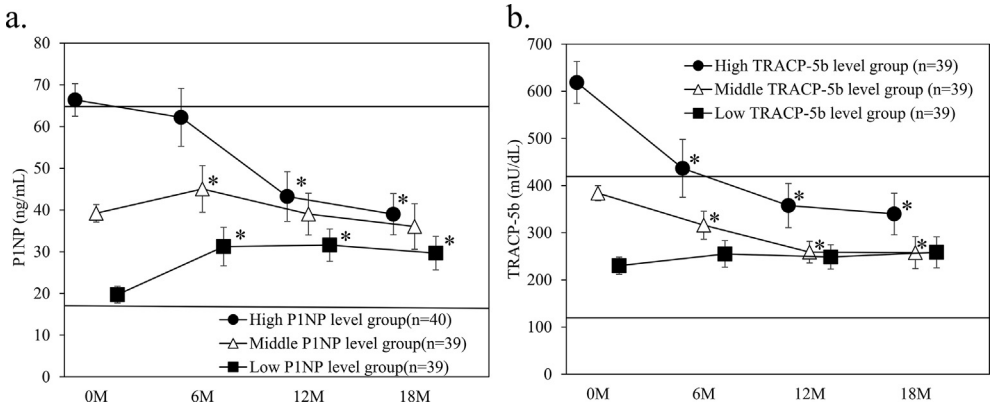

Fig. 1. Changes in bone metabolic markers after stratification of baseline bone metabolic markers by tertile. (a) P1NP. (b) TRACP-5b. The patients with baseline values equal or less than the first tertile were considered the low-level group, those with baseline values higher than the first tertile but equal or less than the second tertile were considered the medium level group, and those with baseline values higher than the second tertile were considered the high-level group. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. The horizontal lines in the graph indicate the upper and lower limits of the reference values. P1NP, type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b. (P1NP: 17.1–64.7 ng/mL, TRACP-5b: 120–420 mU/dL). *P < 0.05 vs. 0 M, paired t-test.

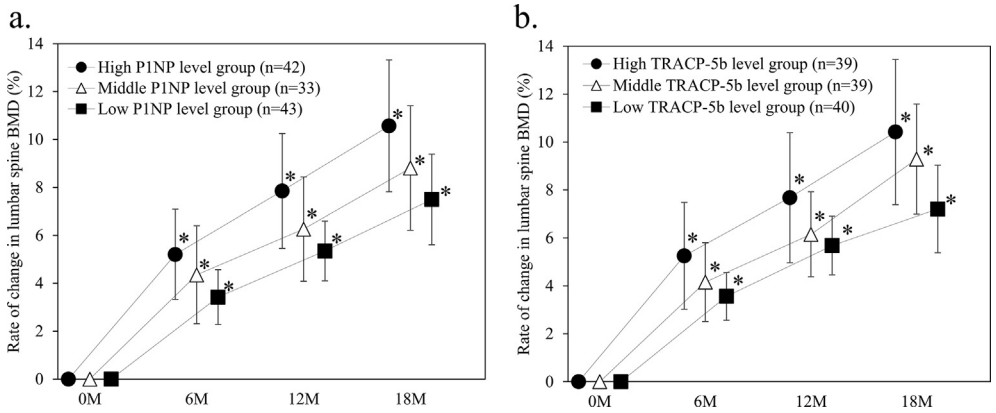

Fig. 2. The rate of changes in the lumbar spine bone mineral density (BMD) after stratification of baseline bone metabolic markers by tertile. (a) P1NP. (b) TRACP-5b. The patients with baseline values equal or less than the first tertile were considered the low-level group, those with baseline values higher than the first tertile but equal or less than the second tertile were considered the medium level group, and those with baseline values higher than the second tertile were considered the high-level group. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. P1NP, type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b. *P < 0.05 vs. 0 M, paired t-test. No significant difference was observed in the comparison between groups using analysis of variance.

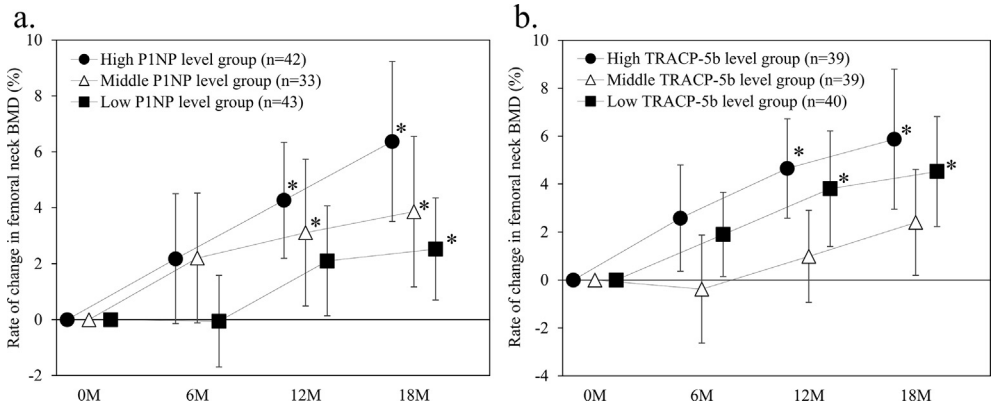

Fig. 3. The rate of changes in femoral neck BMD after stratification of baseline bone metabolic markers by tertile. (a) P1NP. (b) TRACP-5b. The patients with the baseline values equal or less than the first tertile were considered the low-level group, those with baseline values higher than the first tertile but equal or less than the second tertile were considered the medium level group, and those with baseline values higher than the second tertile were the high-level group. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. P1NP, type I procollagen N-terminal propeptide; TRACP-5b, tartrate-resistant acid phosphatase-5b. *P < 0.05 vs. 0 M, paired t-test. No significant difference was observed in the comparison between groups using analysis of variance.

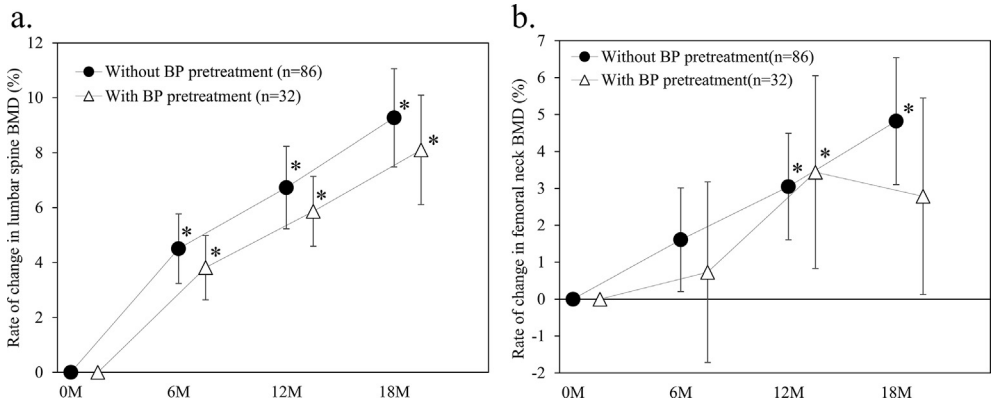

Fig. 4. The rate of changes in bone mineral density (BMD) by bisphosphonate (BP) pretreatment. (a) Rate of change in lumbar spine BMD. (b) Rate of change in femoral neck BMD. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. *P < 0.05 vs. 0 M, paired t-test. No significant difference was observed in the comparison between groups using Student t-test.

P = 0.002 [at 6 months], P = 0.002 [at 12 months], P = 0.002 [at 18 months]; without BP pretreatment: P < 0.001 [at 6 months], P < 0.001 [at 12 months], P < 0.001 [at 18 months]), but no significant difference was observed between the groups (at 6 months: P = 0.872; at 12 months: P = 0.673; at 18 months: P = 0.602).

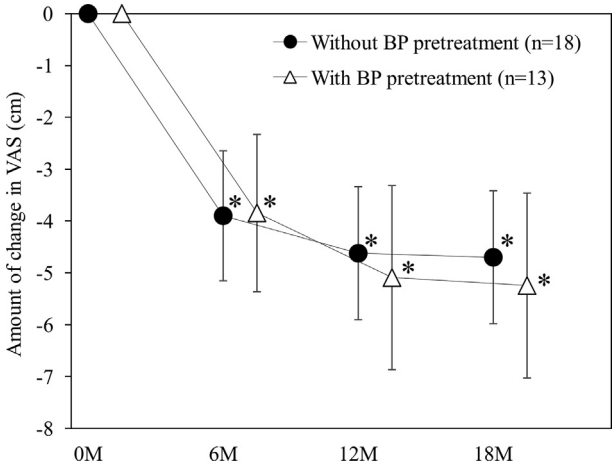

Fig. 5. Extent of changes in visual analogue scale (VAS) by bisphosphonate (BP) pretreatment. The values shown are the mean, and the error bars indicate the upper and lower limits of the 95% confidence interval. *P < 0.05 vs. 0 M. No significant difference was observed between groups using the Wilcoxon rank sum test.

The extent of the changes in VAS when stratified by the history of existing fractures revealed significant improvements after 6 months in both groups (with existing fractures: $P < 0.001$ [at 6 months], $P < 0.001$ [at 12 months], $P < 0.001$ [at 18 months]; without existing fractures: $P = 0.022$ [at 6 months], $P = 0.022$ [at 12 months], $P = 0.022$ [at 18 months]). In the comparison between groups, significant differences were recognized in the amount of change at 12 months and 18 months (at 6 months: $P = 0.142$, at 12 months: $P = 0.037$, at 18 months: $P = 0.037$), which revealed greater improvement of VAS with existing fractures (Supplementary Fig. 2).

The safety assessment revealed that the number of adverse drug reactions was 71, with an incidence of 22.5%. The most commonly observed event was nausea ($n = 52$). No serious adverse events were recorded (Supplementary Table 1).

4. Discussion

To clarify the impact of patient background factors, such as bone metabolic markers at baseline, the history of BP pretreatment, and the history of existing fractures, on the treatment effect, we evaluated the efficacy of W-TPTD on the lumbar spine and femur in clinical practice and analyzed the impact of these factors on BMD and VAS.

Significant improvements were observed in both the lumbar spine and the femur; as with the effect on BMD in the efficacy analysis, the improvement was not inferior to existing reports [1,10].

Based on the stratified analysis categorized by tertiles of baseline bone metabolic markers, W-TPTD resulted in an increase in BMD, regardless of baseline values of bone metabolic markers, without significant differences between groups. The results suggested the potential to improve BMD in a wide range of patients without limiting their baseline values of bone metabolic markers. In addition, as for bone metabolic markers, W-TPTD could be potentially used without exerting an excessive influence on physiological bone turnover, as the markers have demonstrated the potential to be normalized to within the range of reference values. Although the detailed mechanism by which the bone metabolic markers were normalized within the range of reference values is unknown, a simulation using a mathematical model identified the replacement of older bone with newer bone, leading to a decrease in the amount of bone on which teriparatide acts so that bone metabolic markers might converge [11]. In addition, the action of teriparatide, an exogenous parathyroid hormone, may affect the endogenous parathyroid hormones.

As with the pretreatment with BP, significant increases in BMD were observed in both the lumbar and femoral neck BMD, regardless of BP pretreatment, but no significant difference between groups was observed. In D-TPTD, the effect of increasing BMD was reduced with BP pretreatment [12]. Obermayer-Pietsch et al. [7] showed that treatment with teriparatide resulted in the resorption of highly calcified bone by long-term bisphosphonate treatment, reducing BMD soon after the teriparatide treatment was commenced, which indicated the impact of BP pretreatment history on the increase in BMD. However, the results of our study suggested that W-TPTD was able to increase BMD without being affected by BP pretreatment. Yamamoto et al. [13] showed that high-frequency TPTD administration seems to increase bone mass through accelerated bone remodeling in a mouse model. Alternatively, low-frequency TPTD administration leads to bone formation through bone remodeling and mini-modeling [13]. The impact of BP pretreatment history on the increase in BMD might be depend on difference in mechanism of action between these agents on bone formation.

The examination of the association between background factors, including history of BP pretreatment and existing fractures, and the improvement of VAS, did not yield a significant improvement of VAS with any factor. However, between groups, no significant difference in the degree of improvement was observed by the history of BP pretreatment, although a significant difference was found for existing fractures; greater improvements were found for patients with a history of existing fractures. In patients treated with D-TPTD, VAS was reported to lead to greater improvements in BP-naive patients or those with existing fractures [8,9]. However, in W-TPTD, there was no significant difference observed in the improvement of VAS by history of BP pretreatment. The absence of differences in the improvement of VAS after W-TPTD treatment, regardless of BP pretreatment, may indicate a possible therapeutic effect in patients, regardless of their history of BP pretreatment. In addition, in patients with a history of existing fractures, W-TPTD has improved VAS to a similar extent as D-TPTD. Langdahl et al. [14] reported that in the EUROFORS Study using D-TPTD, they observed a correlation between the reduction of low back pain by D-TPTD and a significant decrease in the rate of fractures. In animal experiments, the daily administration of teriparatide was reported to promote the healing of fractures [15]. Therefore, Genant et al. [16] hypothesized that the effect on fracture healing by D-TPTD reduced the risk of the development of low back pain and led to a significant improvement of VAS in the group with existing fractures. Thus, a similar hypothesis might be considered for W-TPTD.

4.1. Limitation

This study was conducted in single center. This is a retrospective study, stratified by tertiles of the bone metabolic markers at the baseline value only, and did not consider patient demographics. In addition, the analysis in the study included patients with all data after 6 months; therefore, effects on patients that discontinued the drug in the short-term cannot be concluded.

5. Conclusions

In this study, we demonstrated that W-TPTD significantly increased the lumbar and femur BMD, regardless of the baseline values of bone metabolic markers. In addition, W-TPTD was able to normalize bone metabolic markers. Even if the level of P1NP was

high, the value decreased and converged to normal value. Unlike D-TPTD, W-TPTD did not result in significant differences in the increase of BMD by BP pretreatment. The rate of change in VAS improvement was not significantly different by BP treatment. Therefore, we considered that W-TPTD should be used regardless of bone metabolic markers in patients, is a potentially valuable agent to produce BMD improvements, and is useful option for the treatment of osteoporosis.

Conflicts of interest

Fumitoshi Omura has received a research grant from Asahi Kasei Pharma Corporation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2019.04.001.

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