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ORIGINAL RESEARCH ARTICLE

Efficacy of Three Teriparatide Preparations and Romosozumab, Osteogenesis Promoters, in the Treatment of Fresh Vertebral Fractures: A Retrospective Observational Study

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Abstract

Background In Japan, daily, twice weekly, and weekly formulations of teriparatide (TPD) and monthly formulations of romosozumab (ROMO) are available as osteogenesis promoters for the treatment of osteoporosis with a high risk for fracture.

Objective To compare the effects of three TPD preparations and ROMO on fracture healing and low back pain after a fresh vertebral fracture.

Methods This was a retrospective observational study. Patients presenting with fresh osteoporotic vertebral fractures were treated subcutaneously with TPD daily (DTPD), twice weekly (2/WTPD), weekly (WTPD), or with ROMO monthly. Bone union, vertebral height changes, and low back pain in the injured vertebra were compared after 6 months of treatment.

Results Bone union and pain improvement were more frequent among those who received daily and twice weekly administration of TPD compared with those who received WTPD and ROMO administration. A comparison for multiplicity between the groups using the Steel–Dwass test showed significant differences between the DTPD and ROMO groups ($p = 0.0029$) and WTPD and ROMO groups ($p = 0.0490$), suggesting superior bone fusion in the DTPD and WTPD groups. Similarly, significant differences were noted between the DTPD and ROMO groups ($p = 0.0001$), WTPD and ROMO groups ($p = 0.0341$), and 2/WTPD and ROMO groups ($p = 0.0009$), indicating a higher degree of pain improvement in the DTPD, WTPD, and 2/WTPD groups compared with that in the ROMO group.

Conclusions Daily, weekly, and twice-weekly administration of TPD may be superior to ROMO for promoting fresh vertebral fracture healing.

Key Points

This is the first study to compare the efficacy of four osteogenic agents (three TPD formulations and ROMO) in patients with fresh vertebral fractures.

Daily, weekly, and twice-weekly TPD elicited greater bone union, with less deformity of vertebral bodies than that in ROMO.

Back pain also improved more in the TPD group, to the extent of no longer interfering with activities of daily living (ADLs).

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1 Introduction

Osteoporosis is known to increase the likelihood of fragility fractures, resulting in an increased need for nursing care and a higher rate of mortality [1, 2]. Patients with osteoporotic vertebral fractures are typically treated conservatively with rest and spinal orthosis; however, this often results in delayed bone healing and pseudarthrosis, leading to long-term physical deterioration [3, 4]. In addition, the risk for further vertebral or fragility fractures at other levels is increased following a fresh vertebral fracture [5], highlighting the importance of early pharmacotherapy for osteoporosis.

Teriparatide (TPD), a peptide corresponding to amino acids 1–34 of the human parathyroid hormone (PTH) is indicated for patients with osteoporosis at high risk for fracture, suggesting that it may also be useful as a treatment for osteoporosis after a fresh vertebral fracture [6–8]. In Japan, weekly and twice-weekly formulations of TPD are available, in addition to a daily formulation.

Romosozumab (ROMO), an antisclerostin antibody, has been shown to simultaneously promote bone formation and inhibit bone resorption, while also markedly increasing bone density [9]. Although some reports have demonstrated the usefulness of these osteogenesis promoters after fragility fractures, to the best of our knowledge, no reports have compared the efficacy of these four preparations in patients with fresh vertebral fractures. Therefore, in the present study, retrospective comparison was conducted on the effects of three formulations of TPD with different dosages and dosing frequency, as well as ROMO, on fracture healing and low back pain in the early phase of treatment after a fresh vertebral fracture.

The study was approved by the ethics committee of the Yoyogi Mental Clinic Research Ethics Committee on 4 October 2021. We conducted this study in accordance with the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" (enacted 23 March 2021; effective 30 June 2021).

2 Methods

2.1 Participants

Patients diagnosed with osteoporotic vertebral fractures according to the Justification Criteria for Vertebral Fractures 2012 version [10], who visited Hayashi Orthopedic Clinic between October 2010 and December 2020 based on medical record information stored at our hospital, were included in this study. These patients received TPD daily (DTPD), twice weekly (2/WTPD), weekly (WTPD), or ROMO subcutaneously once a month and were all followed up for 6 months after treatment.

The exclusion criteria were as follows:

(1) Patients who failed to complete 6 months of drug treatment
(2) Patients with bone loss caused by factors other than osteoporosis
(3) Patients who had received TPD or ROMO previously
(4) Patients who were considered ineligible for the study by the investigator or subinvestigator.

2.2 Study Design

This was a single-center, retrospective, observational study. All patients with fresh vertebral fractures were conservatively treated by placement in a simple cast for 1 week, followed by a hard bracelet. The selection of osteogenesis promoters depended on the time of treatment; that is, DTPD use began in 2010, until WTPD became the predominant treatment around 2013. Subsequently, ROMO was commonly used for a short period after its launch, but 2/WTPD started to be used with the launch of 2/WTPD. However, in this study, different osteogenesis-promoting agents were not used depending on the patient's condition. Preparations of TPD or ROMO were administered after 1 week, and active vitamin D3 (1αD3) preparations and calcium lactate were prescribed as concomitant medications for osteoporosis. Owing to differences in the risk for hypercalcemia between groups, the DTPD group was administered 0.25 μg/day, 2/WTPD and WTPD groups were administered 0.5 μg/day, and ROMO group was administered 1 μg/day of 1αD3. Calcium lactate was concomitantly administered at 2 g/day to all groups. Non-steroidal antiinflammatory drugs were rarely used because of concerns about their adverse effects on bone fusion; in cases of severe pain, acetaminophen was administered for the initial 1–2 months. At 6 months post-treatment, the degree of bone union was evaluated and categorized into three grades based on lateral radiographs and computed tomography (CT) evaluation. A single method was used for definitive diagnosis of vertebral fracture, and all imaging studies were performed by the principal investigator. The grades were measured by built-in electronic scales within the image viewer for CT and radiographic equipment and were divided as follows: healing with less than or equal to 50% deformity and more than 50% deformity compared with that at the initial examination, and pseudoarthrosis. Although the evaluation method of classifying by 50% has not been established, it is a guideline to determine the degree of crushing. Low back pain was also evaluated and classified into the following three grades: improved sufficiently and not interfering with activities of daily living (ADLs), slightly improved but still interfering with ADLs, and not notably different from the initial visit. Low-back pain was determined on the basis of patient complaints in medical records and not scored. The degree of bone union and low back pain were compared among these classification groups.

2.3 Statistical Analysis

Continuous variables were calculated as summary statistics, and the classification and ordinal variables were calculated by frequency distribution. Comparisons between treatment groups were made using Scheffe's multiple comparison test for continuous variables, Steel–Dwass test for ordinal variables, and Fisher's exact test for categorical variables, and Spearman's rank correlation coefficient was calculated for correlations. Statistical significance was set at two-sided $p < 0.05$.

2.4 Ethics Approval

This study was approved by the Yoyogi Mental Clinic Research Ethics Committee on 21 October 2021 (http://

www.yoyogimental.com/clinical-trial/index02.php) and conducted according to the Declaration of Helsinki. Ethics Committee approval was obtained for consent on an opt-out basis.

3 Results

3.1 Patient Background

Of the 144 patients enrolled in the study, 45 met the exclusion criteria and 99 (32, 23, 24, and 20 patients in the DTPD, 2/WTPD, WTPD, and ROMO groups, respectively) were included in the analysis. The most common reasons for patients who did not complete 6 months of treatment were complaints of adverse effects such as nausea and vomiting, which were slightly more common in the TPD group than those in the ROMO group, and the dropout rates were 21.7%, 17.9%, 35.6%, and 16.0% in the DTPD, 2/WTPD, WTPD, and ROMO groups, respectively, revealing slightly higher rates in the WTPD group. In some cases, patients requested drug changes to avoid incurring high drug costs. The other patients were regular outpatients without interruption and had good adherence.

3.2 Demographic Characteristics

Table 1 shows the patient demographic characteristics. Patient age ranged from 66 to 95 years (minimum–maximum), and there were 84 women and 15 men. There were no significant differences between the groups in terms of age or sex.

3.3 Assessment of Bone Union

Figure 1 shows the degree of bone union at 6 months after treatment. The percentage of patients with bone union and vertebral height maintained at ≥ 50% compared with that during the initial visit were 84.4%, 78.3%, 66.7%, and 40.0% in the DTPD, 2/WTPD, WTPD, and ROMO groups, respectively, with a lower percentage in the ROMO group compared with those of the other groups. At 6 months after drug administration, non-union was observed in two patients (6.7%) in the WTPD group and four patients (19.0%) in the ROMO group, while bone union was observed in all patients in the DTPD and 2/WTPD groups. A comparison for multiplicity between the groups using the Steel–Dwass test showed significant differences between the DTPD and ROMO groups and WTPD and ROMO groups, suggesting superior bone fusion in the DTPD and WTPD groups.

Table 1 Baseline demographics

	Total ($n = 99$)	DTPD group ($n = 32$)	2/WTPD group ($n = 23$)	WTPD group ($n = 24$)	ROMO group ($n = 20$)	p value
Age (years)						
Mean ± SD	82.3 ± 5.6	82.8 ± 4.3	82.3 ± 6.1	80.0 ± 6.9	84.4 ± 4.2	0.1349*
Median	83	82	84	81	84.5	
Min–max	66–95	75–95	71–93	66–95	77–91	
Sex						
Male	15 (15.2%)	3 (9.4%)	3 (13.0%)	6 (25.0%)	3 (15.0%)	0.4475**
Female	84 (84.8%)	29 (90.6%)	20 (87.0%)	18 (75.0%)	17 (85.0%)	
Number of fractures						
Mean ± SD	–	2.2 ± 2.1	1.5 ± 1.6	1.8 ± 2.0	1.1 ± 1.2	0.3340**
Genant classification of vertebral fractures						
0	14	3 (9.7%)	2 (8.7%)	3 (13.0)	6 (30.0%)	0.0418*
1	6	2 (6.5%)	1 (4.3%)	0 (0.0%)	3 (15.0%)	
2	32	8 (25.8%)	9 (39.1%)	9 (39.1%)	6 (30.0%)	
3	45	18 (58.1%)	11 (47.8%)	11 (47.8%)	5 (25.0%)	
Bone resorption inhibitor						
No	71	21 65.6%)	19 (82.6%)	15 (62.5%)	16 (80.0%)	0.3222**
Yes	28	11 (34.4%)	4 (17.4%)	9 (37.5%)	4 (20.0%)	
Glucocorticoid						
No	96	30	23	23	20	1.0000**
Yes	2	1	0	1	0	

*Kruskal–Wallis test, **Fisher's exact test

Patients with progressive crush compared with baseline were 75.0%, 82.6%, 91.7%, and 90.0% in DTPD, 2/WTPD, WTPD, and ROMO groups, respectively.

3.4 Improvement of Low-Back Pain

As shown in Fig. 2, the percentage of patients whose pain improved to the point where it no longer interfered with ADLs were 84.4%, 78.3%, 62.5%, and 25.0% in the DTPD, 2/WTPD, WTPD, and ROMO groups, respectively. Meanwhile, 3.1%, 0%, 8.3%, and 35.0% of patients in the DTPD, 2/WTPD, WTPD, and ROMO groups, respectively, reported pain levels of almost the same as those at the initial examination. A comparison for multiplicity between the groups using the Steel–Dwass test showed significant differences between the DTPD and ROMO groups, 2/WTPD and ROMO groups, and WTPD and ROMO groups, indicating that pain improvement was higher in the DTPD, 2/WTPD, and WTPD groups compared with that in the ROMO group. No patient developed a new fracture during the 6-month study period.

4 Discussion

Since the risk for a second vertebral fracture and further fragility fractures at other sites is greatly increased after a fresh vertebral fracture [5], treatment of osteoporosis with pharmacologic therapy is essential for preventing secondary fractures. There are several reports regarding the usefulness of bone formation-promoting drugs in conservative therapy after vertebral fractures. In a previous report, TPD was administered daily and alendronate (ALN) weekly to patients with osteoporotic vertebral compression fractures, with an average age of 76.7 years. The rate of bone union after 6 months improved with both treatments; however, the effect of TPD on promoting fracture healing was significantly greater than that of ALN [6]. Weekly administration of PTH to patients with acute osteoporotic vertebral fractures was also reported to suppress vertebral collapse and increase bone-union rate [7]. Furthermore, TPD increases lumbar vertebral bone density and improves postfracture pain and quality of life to a greater degree than ALN [8]. In addition, Tsuchie et al. [9] assessed patients with vertebral fractures treated with risedronate (RIS) administered once weekly and TPD administered daily and once weekly; the highest vertebral collapse rates were observed in the RIS group, followed by the WTPD and DTPD groups.

On the other hand, although there are several case reports [11, 12] that ROMO, an osteogenesis promoter similar to TPD, is effective for pseudoarthrosis of the radius and humerus, a double-blind placebo-controlled randomized, phase-II clinical trial [13] evaluated the effect of three doses of ROMO on proximal femoral fractures due to intertrochanteric or low energy injuries of the hip joint, demonstrating that none of the doses differed from placebos in terms of

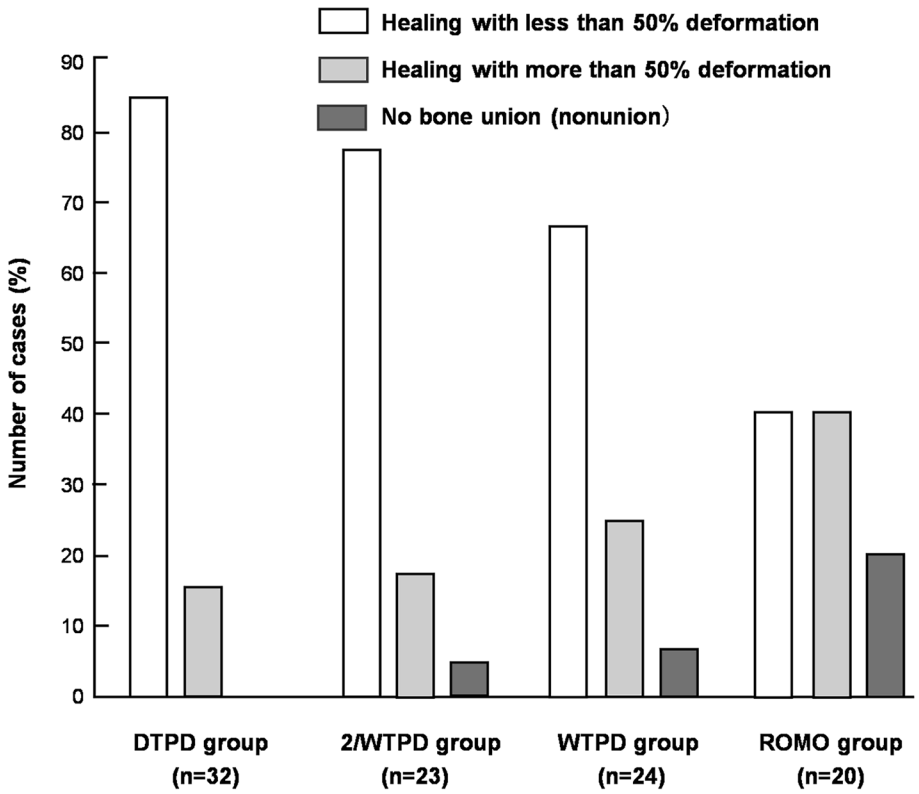

Fig. 1 Bone adhesion after 6 months of administration of TPD or ROMO. Fisher's exact test, $p = 0.0184$. Comparison between groups considering multiplicity (Steel–Dwass test). DTPD versus WTPD, $p = 0.9200$; DTPD versus 2/WTPD, $p = 0.3533$; DTPD versus ROMO, $p = 0.0029$; WTPD versus 2/WTPD, $p = 0.8060$; 2/WTPD versus ROMO, $p = 0.0490$, WTPD versus ROMO, $p = 0.2790$. Baseline vertebral height (mm) was as follows—DTPD: 12.14 ± 4.40 (mean ± SD), 2/WTPD: 13.48 ± 3.15, WTPD: 13.77 ± 4.81, ROMO: 16.22 ± 5.22

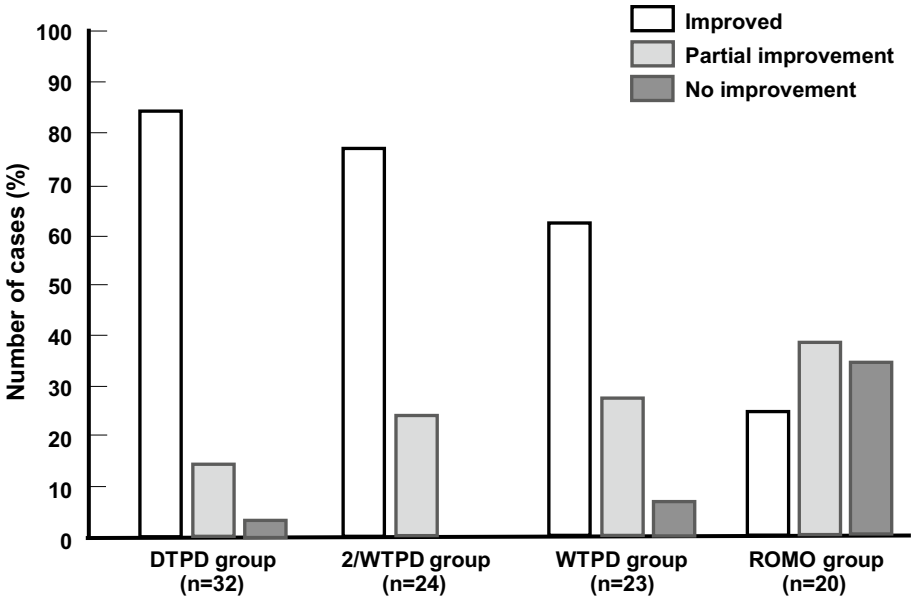

Fig. 2 Improvement in low-back pain after 6 months administration of TPD or ROMO. Fisher's exact test, $p = 0.0001$. Comparison between groups considering multiplicity (Steel–Dwass test). DTPD versus WTPD, $p = 0.2490$; DTPD versus 2/WTPD, $p = 0.9568$; DTPD versus ROMO, $p = 0.0001$; WTPD versus 2/WTPD, $p = 0.5675$; WTPD versus ROMO, $p = 0.0341$; 2/WTPD versus ROMO, $p = 0.0009$

fracture healing-related clinical and radiological outcomes. Bhandari et al. [14] also reported that the time to healing of femoral diaphyseal fractures was not significantly different between the ROMO and placebo groups and that ROMO did not accelerate healing. Regarding vertebral fractures, ROMO promoted bone union in a posterior lumbar interbody fusion (PLIF) of a rat model [15], but reports examining the effects of ROMO on vertebral fracture healing in a sufficiently large number of patients in clinical practice could not be found.

In Japan, three TPD preparations with different dosing frequencies and ROMO (which has a different osteogenesis-promoting mechanism to that of TPD) are available; these are indicated for osteoporosis with high fracture risk [16–18]. To the best of our knowledge, this was the first study to retrospectively compare the efficacy of the four osteogenesis promoters in patients with fresh vertebral fractures at the same institution. The mean age of the patients in this study was 82 years, which is higher than that in previous reports; this makes our report a useful reference for the treatment of vertebral body fractures in Japan, where super aging is increasing.

The osteogenesis promoter selection was not based on patient characteristics, but rather on the timing of each treatment launch. In addition, patient selection bias is considered to be small since treatment strategies other than pharmacotherapy of vertebral fractures did not change within the present observation period. At 6 months after vertebral fracture, the number of patients with pseudarthrosis was 0 for daily administrations of TPD. The proportion of patients with bone union with < 50% deformation from the initial fracture morphology was significantly higher in the DTPD and WTPD groups than that in the ROMO group. Furthermore, the percentage of patients whose low-back pain improved to a level where it no longer interfered with daily life was also significantly higher in the DTPD, WTPD, and 2/WTPD groups than that in the ROMO group. Our results also suggest that TPD promotes healing and pain improvement after vertebral fractures even in very elderly patients. On the other hand, ROMO is reported to have stronger bone density-increasing effects than TPD [19]; however, the percentage of patients with bone union and vertebral height maintained at ≥ 50% at 6 months relative to that at initial examination was lower in the ROMO group than that in all TPD treatment groups. Although the reason for this is unclear, adequate consolidation must be achieved as early as possible to counteract the local instability caused by the fracture and to achieve bone union with minimal deformity during conservative treatment after a vertebral fracture. Therefore, the TPD-predominant promotion of the remodeling effect may be more advantageous than the ROMO-induced promotion of the modeling effect in stimulating the healing of vertebral fractures. In the phase 3 study, Langdahl et al. [20] showed that ROMO has a superior effect on bone-mineral density compared with that by TPD. That is, the predominance of modeling-based bone formation in increasing bone-mineral density may make ROMO superior to TPD, which has a predominance of remodeling-based bone formation. On the other hand, the present study evaluated bone healing, not increased bone density; hence, this study demonstrated the superiority of TPD, which has a predominance of remodeling-based bone formation, over ROMO, which has a predominance of modeling-based bone formation.

The limitations of this study are that it was a retrospective observational study, the number of cases may not have

been sufficient to obtain significant differences, and the results were only evaluated using a three-stage assessment. In addition, some cases lacked detailed background information because the data were obtained from routine clinical practice, and therefore, background comparisons between groups were hindered and insufficient to potentially obtain significant differences. In addition, because the DXA system was changed from radius to whole-body during the observation period, comparisons between groups by baseline bone-mineral density and analysis of bone-mineral density changes over time were not possible. In the future, larger randomized controlled trials using more objective indicators will be required to confirm our findings.

This was the first study to compare the effectiveness of four types of osteogenesis promoters in patients with fresh vertebral fractures; the percentages of patients with good bone union and pain improvement were higher in the DTPD and 2/WTPD groups than those in the WTPD and ROMO groups. Though TPD and ROMO are in the same class of osteogenesis promoters, they may have different effects on the healing of fresh vertebral fractures.

5 Conclusion

DTPD, WTPD, and 2/WTPD formulations demonstrated greater improvement in bone union and less deformity of vertebral bodies than ROMO. Additionally, they showed better low-back pain improvement, almost to the point of no interference with ADLs. A similar trend was observed with the WTPD formulation; however, the difference was not significant compared with ROMO.

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Declarations

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Competing interests The author has no competing interests to declare that are relevant to the content of this article.

Ethics approval This study was approved by the Yoyogi Mental Clinic Research Ethics Committee (http://www.yoyogimental.com/clinical-trial/index02.php) on 21 October 2021 and conducted in accordance with the Declaration of Helsinki. Given the anonymity of the data, the informed consent requirement was waived.

Consent to participate The consent was opted out via in-clinic posting.

Consent to publish Not applicable.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Code availability Not applicable.

Author contributions The author contributed to the conception and design of the study. The statistical analysis and first draft of the manuscript were prepared by Accerise, Inc., and the author prepared the final manuscript for submission.

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