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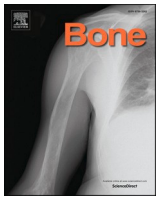

Full Length Article

Impact of prior teriparatide treatment on the effectiveness of romosozumab in patients with postmenopausal osteoporosis: A case-control study

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ABSTRACT

Purpose: To evaluate the impact of prior teriparatide (TPTD) treatment on the effectiveness of romosozumab (ROMO) in postmenopausal osteoporosis.
Methods: In this retrospective, case-controlled, multicenter study, 323 postmenopausal patients were initiated ROMO. Of these, 275 were treatment-naïve, and 48 were switched from TPTD, with uninterrupted ROMO treatment for 12 months. Propensity score matching was applied to ensure clinical comparability, yielding 44 patients in each group. Baseline characteristics included a mean age of 78.0 years, lumbar spine (LS) T-score of −3.6, and total hip (TH) T-score of −2.8. Bone mineral density (BMD) and serum bone turnover markers were evaluated over the 12-month period.
Results: The increasing rate in the bone formation marker PINP was significantly greater in the treatment-naïve group compared to the TPTD-switched group throughout the 1–12 month period. Conversely, the reduction in the bone resorption marker TRACP-5b was similar between the groups, indicating a diminished anabolic window in the TPTD-switched group. After 12 months, the TPTD-switched group showed lower BMD gains in the LS (10.3 % vs. 17.3 %; $P = 0.002$) and TH (3.1 % vs. 7.8 %; $P = 0.002$) compared to the treatment-naïve group. Multiple regression analysis revealed positive associations between the 12-month percentage BMD increases (LS; $\beta = 0.30$; 95 % CI = 0.85–11.61; $P = 0.024$ / TH; $\beta = 0.32$; 95 % CI = 0.51–8.56; $P = 0.028$) and being treatment-naïve compared to prior TPTD treatment.
Conclusions: Prior TPTD treatment may attenuate the effectiveness of ROMO, potentially due to diminished bone formation activation.

1. Introduction

Recent studies have highlighted the robust relationship between on-treatment bone mineral density (BMD) gain and reduced fracture risk, emphasizing the importance of BMD improvement in fracture prevention [1]. To stimulate new bone formation and achieve substantial BMD increases, osteoanabolic agents such as teriparatide (TPTD), abaloparatide (ABL), and romosozumab (ROMO) have been developed [2].

TPTD and ABL act as agonists of parathyroid hormone (PTH) receptor 1, primarily inducing remodeling-based bone formation by promoting stem cell differentiation into osteoblasts, enhancing osteoblast activity, and extending their lifespan [3]. Additionally, PTH reduces

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sclerostin expression, a key inhibitor of bone formation produced by osteocytes, further facilitating bone formation [4].

ROMO, a monoclonal antibody against sclerostin, enhances Wnt signaling by neutralizing sclerostin. ROMO stimulates bone formation by activating osteoblasts and lining cells, as well as promoting the proliferation and differentiation of osteoprogenitors [5]. Moreover, ROMO concurrently reduces the expression of RANKL by osteocytes and osteoblasts, thereby decreasing bone resorption and creating a "dual effect". Consequently, ROMO-induced bone formation primarily involves modeling-based mechanisms without concurrent bone resorption, resulting in rapid bone mass accrual [3].

We previously reported that baseline levels of the bone formation marker PINP were positively associated with femoral BMD increase following ROMO treatment in treatment-naive postmenopausal osteoporosis patients [6]. Conversely, we also observed that prior anti-resorptive agents, particularly denosumab (DMAb), attenuated BMD increases with ROMO, while prior TPTD treatment ($n = 16$) tended to maintain femoral BMD gains compared to prior anti-resorptive agents-treated patients [7,8]. However, these studies involved relatively small number of patients, and clinical backgrounds were not matched. Thus, it remains uncertain whether the absence of pre-treatment or prior osteoblast-lineage activation with TPTD affects subsequent ROMO efficacy. In this case-controlled study, the primary endpoint was to evaluate differences in bone turnover markers (BTMs) and BMD changes between the two groups, while the secondary endpoint aimed to elucidate factors contributing to BMD increases with ROMO in these groups.

2. Methods

2.1. Study design and patients

This retrospective, case-controlled study was conducted across six medical centers. Treatment with ROMO (administered subcutaneously at 210 mg monthly) was initiated between March 2019 and April 2022 for patients identified as having high fracture risk, as per the World Health Organization's 1998 criteria or the Japanese Guidelines for Prevention and Treatment of Osteoporosis (2011) [9]. Inclusion criteria encompassed postmenopausal osteoporosis patients with one or more of the following conditions: (1) BMD T-score ≤ -2.5 with at least one fragility fracture, (2) lumbar spine (LS) BMD T-score < -3.3, (3) two or more vertebral fractures, or (4) semiquantitative (SQ) grade 3 vertebral fracture [10].

Exclusion criteria included patients contraindicated for ROMO (e.g., those with major cardiovascular events within the past year), individuals with conditions affecting bone metabolism such as thyroid or parathyroid disorders, patients on hormone replacement therapy, cancer patients, and those with osteomalacia. Additionally, patients with severe renal impairment [estimated glomerular filtration rate (eGFR) $<$ 30 (mL/min/1.73 m^2)], missing BMD data, male patients, those concurrently using oral glucocorticoid use, autoimmune disease patients, or those who discontinued ROMO before completing 12 months of therapy were excluded [11].

The sample size was confirmed based on the previous study [12], using the difference and standard deviation of the increase in LS BMD at 12 months. The statistical power (1 - β) was set as 80 %, and the significance level (α error) was set as 0.05.

2.2. BMD assessment

BMD values for the LS (L2–L4), total hip (TH), and femoral neck (FN) were measured via dual-energy X-ray absorptiometry (DXA) using Horizon (Hologic, Inc., Marlborough, MA, USA) or PRODIGY (GE Healthcare, Tokyo, Japan) devices, at baseline and at 6-month intervals. The percentage coefficient of variation for L2-L4 was 0.63 % with Horizon and 0.41 % with PRODIGY. BMD data were standardized using Japanese population reference values and corrected according to the Japan Osteoporosis Society and the International Society for Clinical Densitometry Guidance [13]. Severe sclerosis, degenerative spine conditions, vertebral fractures, and surgical sites were excluded from BMD analysis [14].

2.3. Biochemical markers of bone turnover

Fasting blood samples were collected in the morning, and BTMs were measured at baseline and at 1, 6, and 12 months during ROMO treatment. Total N-terminal type I procollagen propeptide (PINP; interassay coefficient of variation $\leq$5.0 %; Roche Diagnostics, Basel, Switzerland) was measured as a bone formation marker, and Isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b; interassay coefficient of variation $\leq$9.0 %; Nittobo Medical Co. Ltd., Tokyo, Japan) as a bone resorption marker. TRACP-5b provides greater sensitivity and a superior signal-to-noise ratio compared to serum cross-linked C-telopeptide of type I collagen (CTX) [15]). Serum 25-hydroxycholecalciferol [25(OH) D] was measured using the Elecsys system (Roche Diagnostics, Basel, Switzerland).

2.4. Radiographs

Spinal radiographs were routinely obtained at baseline and at 6-month intervals after ROMO initiation [16]. Vertebral fractures with grades $\geq$1 were defined using the SQ method [10]. Unscheduled radiographs were assessed for patients presenting symptoms of incidental vertebral or nonvertebral fractures, with each investigator evaluating these radiographs.

2.5. Statistical analysis

Changes in BMD and BTMs levels were calculated as percentage change from baseline. The Mann–Whitney *U* test and Fisher exact test were used for between-group comparisons. Within-group changes from baseline were assessed using the Wilcoxon signed-rank test. Multiple regression analysis was performed to identify factors associated with 12-month BMD changes, incorporating variables previously suggested to influence BMD (age, body mass index [BMI], baseline T-score, baseline value and percentage change in BTMs at 1 month) [6,17,18]). The number of variables utilized in the multiple regression analysis was determined based on the number of cases divided by 10 to 15, as reported previously [19].

All analyses were condeucted using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [20]. *P* values $<$0.05 were considered statistically significant.

2.6. Propensity score matching

To align comparable clinical backgrounds potentially affecting bone metabolism, 1:1 optimal propensity score matching was applied without replacement. Matching variables included baseline age, BMI, BMD of LS, TH, and FN, concomitant calcium or vitamin D supplementation, and serum BTMs (PINP and TRACP-5b) as previously described [21].

2.7. Ethical statement

This observational study was conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study received approval from the institutional ethical review board of Osaka University Graduate School of Medicine (approval No. 18258) and all participating institutions. Informed consent was obtained from all patients, and opt-out information was made available on the hospital's websites.

3. Results

3.1. Patient disposition and characteristics

The detailed flow of patient inclusion is illustrated in the CONSORT diagram (Fig. 1). Out of 676 postmenopausal osteoporosis patients who initiated ROMO treatment, 323 met the inclusion criteria. These patients were categorized into two groups: the treatment-naïve group ($n = 275$) and the TPTD-switched group ($n = 48$). After propensity score matching, 44 patients were selected from each group.

Table 1 summarizes the clinical characteristics of the propensity score-matched patients at the initiation of ROMO therapy. No significant differences were observed between the groups, with the exception of corrected serum calcium levels. The baseline clinical characteristics of non-matched patients at the time of ROMO initiation are shown in Supplementary Table 1.

3.2. Bone turnover markers

Fig. 2a and b depict the percentage change (mean ± standard error; *P* value) in serum PINP and TRACP-5b levels, respectively. The Naive group showed a significantly greater increase in PINP compared to the TPTD-switched group at 1 month (117.6 ± 11.5 % vs. 52.9 ± 10.7 %; $P = 0.001$), 6 months (20.9 ± 8.7 % vs. -14.5 ± 8.6 %; $P = 0.005$), and 12 months (−11.4 ± 6.5 % vs. -30.6 ± 6.9 %; $P = 0.016$). Conversely, TRACP-5b levels decreased similarly in both the Naïve and TPTD-switched groups at 1 month (−36.1 ± 2.8 % vs. -31.9 ± 3.0 %; $P = 0.37$), 6 months (−29.5 ± 3.9 % vs. -33.0 ± 3.1 %; $P = 0.49$), and 12 months (−40.1 ± 3.9 % vs. -34.5 ± 4.0 %; $P = 0.32$). These findings suggest a reduced anabolic window in the TPTD-switched group compared to the Naïve group.

Then, we conducted a simple linear regression analysis to examine the relationship between the duration of prior TPTD treatment (in months) and the percentage change in PINP at 1 month. The regression coefficient estimate was $\beta = -2.57$ (95 % confidence interval [CI]: −4.79 to −0.35, $P = 0.024$). These findings indicate that, despite the relatively short average duration of prior TPTD treatment, a longer duration was associated with a diminished bone formation response to ROMO.

The percentage changes in serum PINP and TRACP-5b for the non-matched patients are provided in Supplementary Table 2, and the trends are consistent with the results observed in the matched cohort.

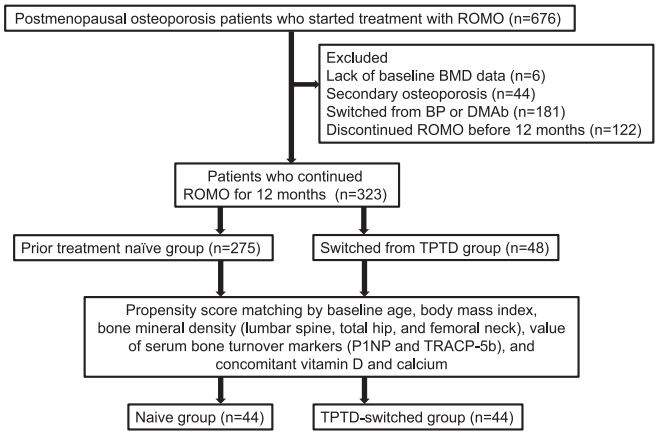

Fig. 1. Study design and patient flow.
ROMO, romosozumab; BMD, bone mineral density; BP, bisphosphonates; DMAb, denosumab; TPTD, teriparatide; PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase.

Table 1
Initial clinical characteristics of patients following propensity score matching.

Variable	Naive group ($n = 44$)	TPTD-switched group ($n = 44$)	*P* value
Age (years)	79.5 ± 7.6	76.6 ± 7.3	0.068
Body Mass Index (kg/m^2)	20.11 ± 3.0	19.7 ± 2.7	0.54
Prior vertebral fracture (%)	34.1	56.8	0.053
Prior nonvertebral fracture (%)	22.7	25.0	1.0
Lumbar spine BMD (g/cm^2)	0.66 ± 0.10	0.67 ± 0.12	0.53
Lumbar spine BMD (T-score)	−3.6 ± 0.8	−3.5 ± 0.9	0.67
Total hip BMD (g/cm^2)	0.59 ± 0.10	0.59 ± 0.10	0.84
Total hip BMD (T-score)	−2.8 ± 0.8	−2.8 ± 0.8	0.93
Femoral neck BMD (g/cm^2)	0.55 ± 0.10	0.55 ± 0.10	0.92
Femoral neck BMD (T-score)	−3.4 ± 0.8	−3.3 ± 0.9	0.49
Corrected serum calcium (mg/dl)	9.1 ± 0.4	9.4 ± 0.4	0.005
eGFR (ml/min/1.73 m^2)	71.0 ± 23.7	72.3 ± 17.9	0.78
PINP (μg/l)	87.4 ± 47.5	90.7 ± 57.5	0.77
TRACP-5b (mU/dl)	569.1 ± 217.9	587.6 ± 314.6	0.75
25(OH)D (ng/ml)	16.4 ± 6.2	18.4 ± 10.6	0.28
Prior osteoporosis treatment			
Daily TPTD (20 μg) (%)	N.A.	65.9	N.A.
Weekly TPTD (56.5 μg) (%)	N.A.	22.7	N.A.
Twice-weekly TPTD (28.2 μg) (%)	N.A.	11.4	N.A.
Treatment duration (months)	N.A.	14.0 ± 6.7	N.A.
Combined vitamin D (%)	72.7	75.0	1.0
Combined calcium (%)	38.6	52.3	0.28

Mean ± standard deviation. % = number of patients with measurements/total number of patients.
TPTD, teriparatide; N.A., not applicable; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; PINP, type I collagen N-terminal propeptide; TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; 25(OH)D, 25-hydroxycholecalciferol.

3.3. Changes in BMD

Regarding the percentage change in BMD at the LS (Fig. 3a), the increase (mean ± standard error; *P* value) at 12 months was significantly greater in the Naïve group compared to the TPTD-switched group (17.3 ± 1.8 % vs. 10.3 ± 1.1 %; $P = 0.002$). Similar trends were observed in the TH (Fig. 3b) (7.8 ± 1.1 % vs. 3.1 ± 1.0 %; $P = 0.002$) and FN (Fig. 3c) (6.0 ± 1.0 % vs. 3.2 ± 0.9 %; $P = 0.042$). The percentage changes in BMD for non-matched patients are presented in Supplementary Table 3, which were consistent with the results observed in the matched cohort.

Lastly, we performed a multiple regression analysis to assess the relationship between potential factors and BMD increases in the LS or TH at 12 months in the matched cohort ($n = 88$; Table 2). The increase in LS BMD was negatively correlated with the baseline LS T-score (standardized coefficient [β] = −0.35, 95 % CI = −7.86 to −0.80, $P = 0.017$) and positively correlated with the absence of prior treatment compared to prior TPTD therapy (β = 0.30, 95 % CI = 0.85–11.61, $P = 0.024$). The increase in TH BMD was positively correlated with BMI (β = 0.33, 95 % CI = 0.02–1.62, $P = 0.046$), baseline PINP (β = 0.44, 95 % CI = 0.00–0.12, $P = 0.046$), and the absence of prior treatment compared to prior TPTD therapy (β = 0.32, 95 % CI = 0.51–8.56, $P = 0.028$).

3.4. Incidence of fragility fractures

During the 12-month ROMO treatment period, two patients in the Naïve group experienced fragility fractures: one sustained a hip fracture, and another suffered a humerus fracture following a fall. No vertebral or non-vertebral fractures were observed in the TPTD-switched group.

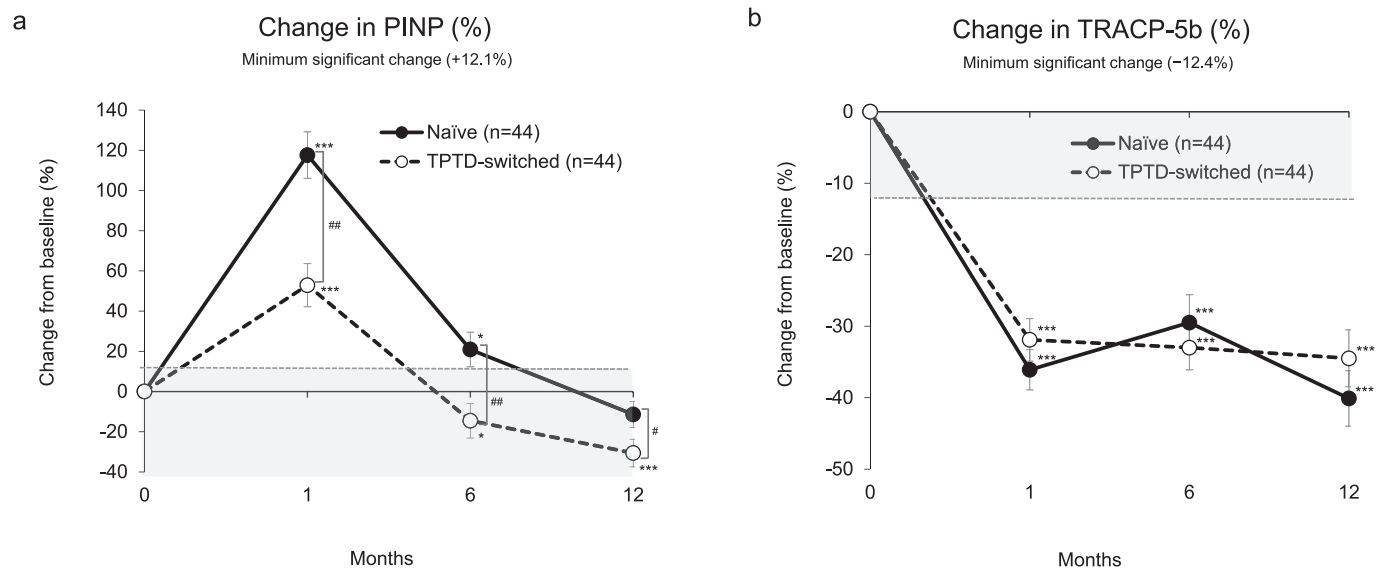

Fig. 2. Percentage change of serum PINP level (a) and TRACP-5b level (b).
PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase; TPTD, teriparatide.
Bars indicate mean ± standard error. $^{*}P < 0.05$, $^{***}P < 0.001$; change within each treatment group compared with baseline. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$; difference between the two indicated groups.

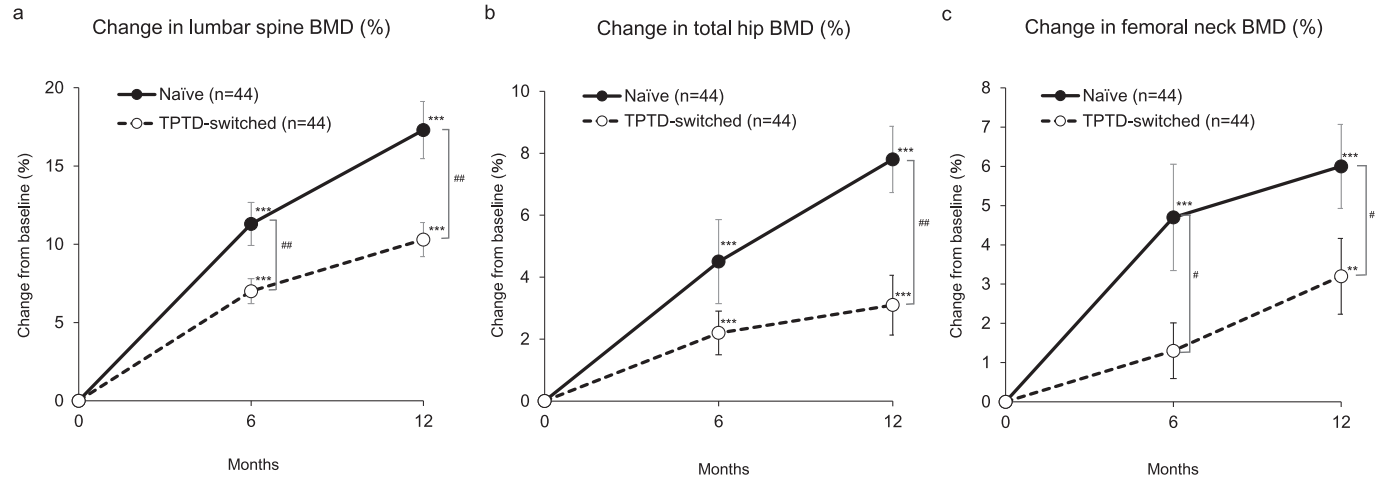

Fig. 3. Percentage change of BMD in the lumbar spine (a), total hip (b), and femoral neck (c).
BMD, bone mineral density; TPTD, teriparatide.
Bars indicate mean ± standard errors. $^{**}P < 0.01$, $^{***}P < 0.001$; change from baseline within each treatment group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$; difference between the two indicated groups.

4. Discussion

To the best of our knowledge, this study is the first to compare the effects of ROMO between postmenopausal osteoporosis patients who were treatment-naïve and those who were switched from TPTD. In patients switched from TPTD, the anabolic window appeared to be narrower due to a reduced increase in bone formation markers, resulting in smaller gains in BMD compared to treatment-naïve patients.

It has been reported that PTH analogs (such as TPTD and ABL) and PTH receptor 1 binding can form a complex with LRP6, and stimulates Wnt-ligand-independent, β-catenin-dependent Wnt signaling [3]. This pathway directly enhances the differentiation, proliferation, and survival of mesenchymal stromal cells, osteoblasts, and lining cells [3]. Additionally, TPTD suppresses the expression of sclerostin from osteocytes, indirectly promoting Wnt-ligand-dependent Wnt signaling, thereby facilitating bone modeling [3]. Indeed, animal studies have demonstrated that TPTD promotes both bone remodeling and modeling, with modeling being particularly dominant during the first two months of treatment [22]. In humans, iliac bone biopsies confirmed that TPTD strongly stimulates bone modeling at first three months [23].

On the other hand, PTH induces the expression of RANKL while suppressing osteoprotegerin, an endogenous anti-RANKL factor, from osteoblasts [24]. This suggests that TPTD may promote bone modeling through Wnt signaling activation, while simultaneously enhancing bone resorption by osteoclasts. Consequently, when switching from TPTD to ROMO, the potential for additional bone modeling may be diminished due to prior inhibition of sclerostin by TPTD. However, bone resorption suppression is expected to recover, as ROMO induces osteoprotegerin production. This hypothesis is supported by the diminished PINP increase following TPTD and comparable reductions in TRACP-5b levels observed in both groups in the present study, as well as in previous unmatched studies [7,8].

Table 2
Results of multiple regression analysis assessing the association between potential factors and the change in LS or TH BMD over 12 months in matched patients (n = 88).

Areas	Explanatory variables	β (95%CI)	*P* value
LS	Age	−0.15 (−0.54–0.12)	0.21
	BMI	−0.04 (−1.22–0.89)	0.75
	Baseline LS T-score	−0.35 (−7.86 to −0.80)	0.017
	Baseline PINP	0.11 (−0.06–0.11)	0.59
	Baseline TRACP-5b	0.26 (−0.01–0.03)	0.21
	% change of PINP at 1 month	0.08 (−0.03–0.05)	0.59
	% change of TRACP-5b at 1 month	0.10 (−0.07–0.18)	0.38
	Without prior treatment (vs. TPTD)	0.30 (0.85–11.61)	0.024
TH	Age	−0.05 (−0.31–0.22)	0.74
	BMI	0.33 (0.02–1.62)	0.046
	Baseline TH T-score	−0.22 (−4.54–0.58)	0.13
	Baseline PINP	0.44 (0.00–0.12)	0.046
	Baseline TRACP-5b	−0.18 (−0.02–0.01)	0.46
	% change of PINP at 1 month	0.25 (−0.01–0.05)	0.14
	% change of TRACP-5b at 1 month	−0.24 (−0.18–0.01)	0.076
	Without prior treatment (vs. TPTD)	0.32 (0.51–8.56)	0.028

LS, lumbar spine; TH, total hip; BMI, body mass index; BMD, bone mineral density; β, standardized coefficient; CI, confidence interval; PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase; TPTD, teriparatide.

Multiple regression analysis identified the absence of prior treatment (compared to prior TPTD usage) as a significant predictor of BMD increase in both the LS and TH. In the LS, a lower baseline BMD T-score was positively correlated with BMD gains, whereas baseline BTMs values and percentage changes in BTMs at 1 month showed no significant association. These findings suggest that prior TPTD therapy may exert a stronger influence on LS BMD increases than on bone turnover at early phase of ROMO initiation.

Furthermore, higher BMI and baseline PINP levels were positively correlated with increase in TH BMD, and the absence of prior treatment remained a significant predictor when compared to prior TPTD treatment. These results align with our previous studies, suggesting that femoral BMD increases with ROMO are associated with greater mechanical loading, which may decrease sclerostin expression from osteocytes [11], and higher baseline PINP levels, potentially indicative of osteoblastic cell activity [6].

Tominaga et al. reported that in patients undergoing ROMO treatment, prior BP or DMAb treatment resulted in reduced PINP increases and lower TRACP-5b values compared to treatment-naïve cases. This contrasts with cases switching from TPTD to ROMO, which showed a reduced PINP increase but similar TRACP-5b values relative to treatment-naïve cases [25]. Additionally, Adami et al. demonstrated that adding ROMO to ongoing DMAb treatment suppressed both PINP and CTX levels compared to ROMO monotherapy [26]. These findings suggest that the effects of prior BP or DMAb treatment on subsequent ROMO treatment differ from those of prior TPTD treatment, highlighting distinct mechanisms of action. However, these studies involved relatively small patient cohorts and did not adjust for differences in patient backgrounds, suggesting the need for further validation.

This study has several limitations. First, as a retrospective, case-controlled study, there may be selection bias in baseline characteristics, potentially influencing the results. Second, while most patients received daily TPTD (20 μg), some were treated with weekly (56.5 μg) or twice-weekly (28.2 μg) formulations, which are also approved in our country. The average duration of prior TPTD treatment was 14.0 months, as continuous 24-month TPTD therapy is not strictly enforced in our country. It was challenging to obtain comprehensive data on treatments preceding TPTD, and to calculate the BMD increase specifically limited to the TPTD treatment period due to its variability in treatment duration. Nevertheless, bone modeling via Wnt signaling activation is typically induced within 2–3 months of TPTD initiation [22,23], suggesting that 14.0 months of TPTD treatment is sufficient to activate this pathway. Third, we used serum TRACP-5b as a bone resorption marker which has been reported to provide greater sensitivity compared to serum CTX [22,23], but serum CTX data were not available. Fourth, the small sample size may limit the statistical power of our findings. Nonetheless, a notable strength of this study is the use of propensity score matching and multiple regression analysis to minimize confounding factors between the two patient groups.

5. Conclusion

The effectiveness of ROMO treatment may be attenuated in patients switched from TPTD compared to those who were treatment-naïve, likely due to reduced further activation of bone formation and subsequent BMD increases.

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CRediT authorship contribution statement

Kosuke Ebina: Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tomonori Kobayakawa:** Project administration, Investigation, Data curation, Conceptualization. **Yuki Etani:** Project administration, Conceptualization. **Takaaki Noguchi:** Investigation, Conceptualization. **Masafumi Kashii:** Investigation, Data curation, Conceptualization. **Gensuke Okamura:** Investigation, Data curation. **Yoshio Nagayama:** Investigation, Data curation. **Hideki Tsuboi:** Investigation, Data curation. **Akira Miyama:** Investigation, Data curation. **Makoto Hirao:** Investigation, Data curation. **Yuji Fukuda:** Investigation, Data curation. **Takuya Kurihara:** Investigation, Data curation. **Atsushi Sugimoto:** Investigation, Data curation. **Ken Nakata:** Supervision, Resources. **Seiji Okada:** Supervision, Resources.

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Declaration of competing interest

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TN, AM, MH, YF, TKurihara, AS, and SO declare that they have no conflicts of interest.

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Data availability

The data set used or analyzed in this study is available from the corresponding author upon reasonable request.

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