Osteoporosis International
https://doi.org/10.1007/s00198-025-07386-4

ORIGINAL ARTICLE

Impact of switching from bisphosphonates to denosumab, teriparatide, or romosozumab in patients with postmenopausal osteoporosis: a case–control study

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Received: 5 November 2024 / Accepted: 30 December 2024

Abstract

Summary This case-control study investigated the impact of switching from bisphosphonates to denosumab, teriparatide, or romosozumab in postmenopausal osteoporosis. Romosozumab demonstrated the most significant improvements in bone mineral density, particularly in the lumbar spine and total hip, by reducing bone resorption and increasing bone formation markers.

Purpose To investigate the impact of switching from bisphosphonates (BP) to denosumab (DMAb), teriparatide (TPTD), or romosozumab (ROMO) in postmenopausal osteoporosis.

Methods This retrospective, case-controlled, multicenter study included 389 patients who switched from BP to DMAb, TPTD, or ROMO due to treatment inefficacy. Propensity score matching was used to align patient backgrounds, resulting in 45 patients per group. Baseline characteristics included a mean age of 73.8 years, prior BP treatment duration of 37.1 months, and bone mineral density (BMD) T-scores of -2.8 in the lumbar spine (LS), -2.5 in the total hip (TH), and -2.7 in femoral neck (FN). BMD and bone turnover markers were assessed over 12 months.

Results Following the switch from BP, the ROMO group demonstrated a dual effect of decreased bone resorption and increased bone formation markers. The TPTD group exhibited the highest increases in both markers, while the DMAb group suppressed both. After 12 months, the ROMO group demonstrated significantly greater BMD increases in the LS (11.4%) compared to the DMAb (6.3%; $p < 0.001$) and TPTD (5.9%; $p < 0.001$) groups. Additionally, the ROMO group showed greater increases in the TH (3.3%) than TPTD group (0.8%; $p < 0.01$). Only the ROMO group showed a significant BMD increase in the FN (2.0%; $p < 0.01$ from baseline).

Conclusion Significant BMD increases were observed in the LS for all groups, in the TH for the ROMO and DMAb groups, and in the FN for the ROMO group. ROMO showed the most substantial BMD improvements following BP therapy.

Keywords Bone mineral density · Bisphosphonates · Denosumab · Teriparatide · Romosozumab

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Published online: 16 January 2025

Introduction

Treatment strategies for osteoporosis have evolved significantly in recent years, allowing for personalized treatment plans tailored to individual patient needs. With the introduction of new therapies, understanding the effectiveness of sequential treatments, such as transitioning from bisphosphonates (BP) to newer agents like denosumab (DMAb), teriparatide (TPTD), or romosozumab (ROMO), has become increasingly crucial. BP have traditionally been the mainstay of osteoporosis treatment due to their ability to inhibit bone resorption, increase bone mineral density (BMD), and reduce fracture risk [1]. However, the BMD increase achieved with BP therapy typically plateaus after 4–5 years [2], and long-term use can pose risks, such as osteonecrosis of the jaw and atypical femoral fractures, prompting exploration of alternative therapies [3]. When the therapeutic effect of BP is deemed inadequate, switching to more potent anti-resorptive agents, or to bone anabolic agents is recommended [4]. Recent studies have shown the effectiveness of transitioning from BP to DMAb, an anti-receptor activator of nuclear factor kappa-B ligand antibody [5], or to daily TPTD, a bone anabolic agent that stimulates bone formation [6]. By inhibiting sclerostin, ROMO stimulates bone formation through activating Wnt signaling in osteoblasts, and indirectly reduces bone resorption by enhancing osteoprotegerin production in both osteoblasts and osteocytes [7], resulting in a broader anabolic window compared to other osteoporosis treatments [8]. In patients with treatment-naïve postmenopausal osteoporosis, ROMO has demonstrated superior improvements in BMD compared to alendronate [9], DMAb [10], and TPTD [11]. However, in clinical practice, switching from BP is the most common scenario. To date, no studies have compared the efficacy of switching BP to DMAb, TPTD, or ROMO with matched patient backgrounds. This study aimed to assess differences in changes in bone turnover markers (BTMs) and BMD between the groups as the primary endpoint, while the secondary endpoint aimed to identify factors associated with these BMD increases.

Material and methods

Study design and subjects

This multicenter, case-controlled, retrospective study was conducted across seven medical centers and included 389 patients who were receiving intravenous or oral BP in accordance with the Japanese 2011 guidelines for the prevention and treatment of osteoporosis [12]. Patients were transitioned to DMAb (n = 118), TPTD (n = 57), or ROMO (n = 214) due to treatment inefficacy. Inefficacy was primarily defined as insufficient improvement or a decline in bone mineral density (BMD), or the occurrence of fragility fractures as previously described [4]. These decisions were made at the discretion of individual physicians and patient preferences (Fig. 1). Treatment with TPTD or ROMO was initiated for patients identified as having a high fracture risk, as per the World Health Organization's 1998 criteria or the Japanese 2011 Guidelines for Prevention and Treatment of Osteoporosis [12]. Criteria for high fracture risk included (1) BMD T-score of less than −2.5 with at least one fragility fracture, (2) lumbar spine (LS) BMD T-score of less than −3.3, (3) two or more vertebral fractures, or (4) semiquantitative Grade 3 vertebral fracture [13]. Calcium (200–1200 mg/day) and vitamin D (active form; 0.125–1 μg/day, native form; 400–1500 IU/day) supplements were provided, and dosing was adjusted according to the attending physician's decision. Patients with contraindications to DMAb, TPTD, or ROMO (i.e. those with major cardiovascular events within the past year), patients with bone metabolism disorders such as thyroid or parathyroid disorders, individuals receiving hormone replacement therapy, individuals with cancer undergoing skeletal radiation therapy, patients with osteomalacia, patients with severe renal impairment (estimated glomerular filtration rate less than 30 ml/min/1.73 m^2), or patients lacking BMD data were excluded.

To account for potential clinical factors that could influence bone metabolism, a 1:1 optimal propensity score matching without replacement was implemented, considering variables such as age, body mass index, and BMD T-scores at the LS, total hip (TH), and femoral neck (FN), as previously described [14]. Initially, matching was performed between individuals receiving DMAb and those receiving ROMO, resulting in a sample size of 73 for each group. Subsequently, matching was conducted between the extracted ROMO and TPTD cases. Finally, the corresponding DMAb cases were extracted from the initial matching process to align patient backgrounds, resulting in a final sample size of 45 for each group. The sample size was confirmed based on a previous study [15], considering the difference and standard deviation of the increase in LS BMD at 12 months. The statistical power (1—β) was set at 80%, and the significance level (α error) was set at 0.05.

Bone mineral density assessment

The BMD values of the LS (L2–L4), TH, and FN were assessed using dual-energy X-ray absorptiometry equipment (Horizon; Hologic, Inc., Marlborough, MA, USA/PRODIGY; GE Healthcare, Madison, WI, USA). The

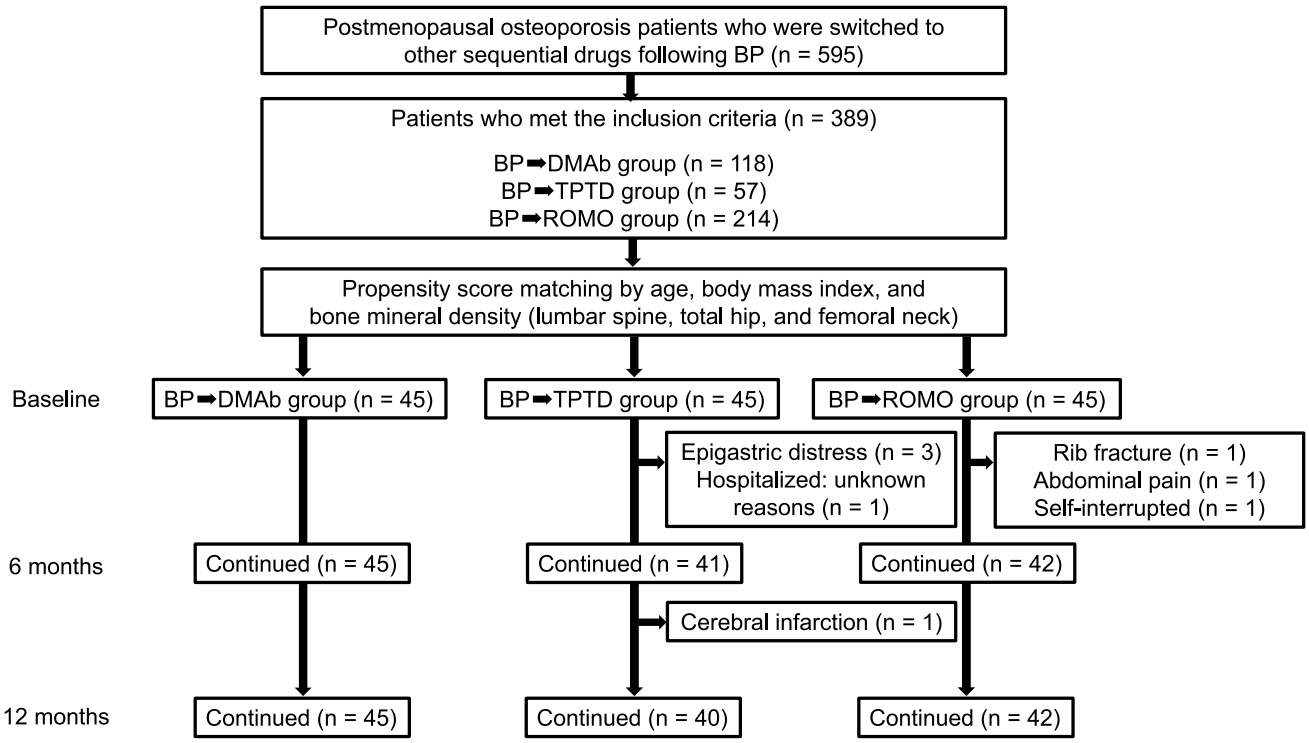

Fig. 1 Study design and patient flow. BP, bisphosphonates; DMAb, denosumab; TPTD, teriparatide; ROMO, romosozumab

percent coefficient of variation for L2-L4 was 0.63% with Horizon and 0.41% with PRODIGY. Measurements were taken at baseline and every 6 months following the initiation of the sequential therapy. BMD data were standardized using reference values from the Japanese population for each dual-energy X-ray absorptiometry device, following the correction method recommended by the Japan Osteoporosis Society and the International Society for Clinical Densitometry Guidance [16]. Regions with severe sclerosis, degenerative spine conditions, vertebral fractures, and surgical sites were excluded from the BMD measurements [17].

Biochemical markers of bone turnover

BTMs were assessed at baseline, 6 months, and 12 months during sequential therapy following the switch from BP. Total N-terminal type I procollagen propeptide (PINP) was used as a bone formation marker, with an inter-assay coefficient of variation ≤ 5.0% (Roche Diagnostics, Basel, Switzerland). Tartrate-resistant acid phosphatase isoform 5b (TRACP-5b) was measured as a marker of osteoclast activity, with an inter-assay coefficient of variation ≤ 9.0% (Nittobo Medical Co. Ltd., Tokyo, Japan). Serum 25-hydroxycholecalciferol [25(OH)D] levels were assessed using electrochemiluminescence with the Elecsys system (Roche Diagnostics, Basel, Switzerland).

Radiographs

Spinal radiographs were obtained at baseline and every 6 months following drug initiation. Vertebral fractures with grades of 1 or higher were identified using the semiquantitative method [13]. For patients exhibiting symptoms of incidental clinical, vertebral, or nonvertebral fractures, unscheduled radiographs were evaluated by attending investigators.

Statistical analysis

Changes in BMD and BTM levels were assessed by calculating the percentage change from baseline. The study groups were compared using the Kruskal–Wallis test and the Mann–Whitney *U* test for continuous variables, and the chi-square test for categorical variables. Changes in BMD and BTM levels within each group from baseline to specific time points were assessed using the Wilcoxon signed-rank test. Multiple regression analysis was conducted to identify factors associated with 12-month BMD changes, considering variables known to influence BMD (baseline BMD T-score, BTM, and treatment difference) [14]. The number of variables included in the regression analysis was determined based on a previously reported methodology, which suggested dividing the number of cases by 10 to 15 [14]. Statistical analyses were conducted 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) [18]. *P*-values less than 0.05 were considered statistically significant.

Ethical statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the institutional ethical review board of Osaka University Graduate School of Medicine (approval no. 18258) and each participating institute. Informed consent was obtained from all patients, and opt-out information was made available on the hospital's homepage.

Results

Patient disposition and characteristics

The patient flow is illustrated in the Consolidated Standards of Reporting Trials diagram (Fig. 1). Out of the 595 patients with postmenopausal osteoporosis who switched from BP to other treatments, 389 met the inclusion criteria. These patients were categorized into three groups: the DMAb-switched group ($n=118$), the TPTD-switched group ($n=57$), and the ROMO-switched group ($n=214$). After propensity score matching, 45 patients were selected from each group. Table 1 presents the clinical characteristics of the propensity score-matched patients when switching from BP to other drugs. No significant differences were observed

Table 1 Patients' clinical characteristics at baseline after propensity score matching

Variable	DMAb group ($n=45$)	TPTD group ($n=45$)	ROMO group ($n=45$)	*P*-value
Age (years)	73.3 ± 10.6	73.2 ± 10.0	74.9 ± 9.4	0.67
Body mass index (kg/m^2)	20.5 ± 2.9	20.8 ± 2.8	20.9 ± 3.4	0.82
Prior vertebral fracture (%)	48.8	72.7	53.3	0.054
Prior nonvertebral fracture (%)	15.6	20.5	20.0	0.16
Duration of prior BP treatment (months)	46.1 ± 34.3	40.2 ± 35.6	25.2 ± 20.7	0.007
Prior BP usage (%)	MIN: 46.7 ALN: 33.3 RIS: 17.8 IBN: 2.2	RIS: 38.1 ALN: 23.8 MIN: 19.1 IBN: 14.3 ZLD: 4.8	ALN: 44.4 RIS: 40.0 MIN: 15.6	NA
Combined active vitamin D (%)	55.6	22.3	64.5	< 0.001
Combined active vitamin D (μg/day)	0.84 ± 0.23	0.65 ± 0.24	0.66 ± 0.17	0.003
Combined native vitamin D (%)	37.8	0	2.2	< 0.001
Combined native vitamin D (IU/day)	1018.8 ± 563.6	0	1500 ± 0	< 0.001
Combined calcium (%)	62.2	0	31.1	< 0.001
Combined calcium (mg/day)	606.4 ± 133.4	0	642.9 ± 393.6	< 0.001
Lumbar spine BMD (g/cm^2)	0.767 ± 0.119	0.747 ± 0.116	0.732 ± 0.149	0.42
Lumbar spine BMD (T-score)	−2.6 ± 1.0	−2.9 ± 1.0	−2.8 ± 1.3	0.45
Total hip BMD (g/cm^2)	0.628 ± 0.116	0.611 ± 0.113	0.601 ± 0.119	0.5
Total hip BMD (T-score)	−2.4 ± 1.1	−2.7 ± 1.1	−2.5 ± 0.9	0.43
Femoral neck BMD (g/cm^2)	0.558 ± 0.129	0.595 ± 0.128	0.556 ± 0.122	0.20
Femoral neck BMD (T-score)	−2.6 ± 0.8	−2.8 ± 0.8	−2.7 ± 0.9	0.53
Corrected serum Ca (mg/dL)	9.2 ± 0.4	9.2 ± 0.3	9.1 ± 0.4	0.46
eGFR (ml/min/1.73 m^2)	73.8 ± 21.0	73.1 ± 18.3	70.7 ± 18.1	0.72
PINP (μg/L)	33.9 ± 16.7	38.1 ± 17.7	33.1 ± 20.0	0.38
TRACP-5b before starting BP (mU/dL)	414.7 ± 155.8	438.7 ± 154.7	422.1 ± 159.6	0.84
TRACP-5b (mU/dL)	332.4 ± 194.1	380.0 ± 183.8	329.4 ± 160.9	0.34
25(OH)D (ng/mL)	23.5 ± 11.4	19.0 ± 8.3	17.5 ± 7.8	0.057

Mean ± SD. % = number of patients with measurements/total number of patients

Differences between the groups were determined using Kruskal–Wallis test and the chi-square test

NA not applicable, *DMAb* denosumab, *TPTD* teriparatide, *ROMO* romosozumab, *BP* bisphosphonates, *MIN* minodronate, *ALN* alendronate, *RIS* risedronate, *IBN* ibandronate, *ZLD* zoledronate, *BMD* bone mineral density, *Ca* calcium, *eGFR* estimated glomerular filtration rate, *PINP* type I collagen N-terminal propeptide, *TRACP-5b* tartrate-resistant acid phosphatase isoform 5b; 25(OH)D, 25-hydroxycholecalciferol

among the groups, except for the rates and doses of combined use of vitamin D and calcium supplements, and the duration of prior BP treatment. The clinical characteristics of the non-matched patients are presented in Supplementary Table 1. In the TPTD group, treatment was discontinued due to epigastric distress ($n=3$) and unknown reasons for hospitalization ($n=1$) within the first 6 months and due to cerebral infarction ($n=1$) between 6 and 12 months. In the ROMO group, treatment was discontinued because of rib fracture ($n=1$), abdominal pain ($n=1$), and self-interruption ($n=1$) within the first 6 months (Fig. 1).

Bone turnover markers

Figures 2a and 2b show the percentage change in serum PINP and TRACP-5b levels (mean ± standard error), respectively. The ROMO group demonstrated a dual effect with a decrease in TRACP-5b (−15.5 ± 6.0%) and an increase in PINP (65.7 ± 16.2%) levels after 12 months. In contrast, the TPTD group showed the highest increases in both TRACP-5b (79.0 ± 17.0%) and PINP (280.0 ± 46.5%) levels, while the DMAb group suppressed both TRACP-5b (−29.7 ± 4.6%) and PINP (−27.9 ± 5.4%) levels.

Changes in the BMD

Regarding the percent change in BMD at the LS (Fig. 3a), all groups exhibited a significant increase from baseline at 6 to 12 months. The increase (mean ± standard error) at 12 months was significantly greater in the ROMO group (11.4 ± 1.1%) than in the DMAb (6.3 ± 0.9%; $p<0.001$) and TPTD (5.9 ± 1.0%; $p<0.001$) groups.

For TH BMD (Fig. 3b), both the ROMO and DMAb groups showed a significant increase from baseline at 6 to 12 months, while the TPTD group did not show a significant difference. The increase at 12 months was significantly greater in the ROMO group (3.3 ± 0.7%) than in the TPTD group (0.8 ± 0.9%; $p=0.008$), with no significant difference observed versus the DMAb group (1.8 ± 0.6%; $p=0.16$).

For FN BMD (Fig. 3c), only the ROMO group demonstrated a significant increase from baseline, with a 2.0 ± 0.7% rise at 12 months ($p=0.008$). No significant changes were observed in the TPTD group (1.9 ± 0.9%; $p=0.09$) and DMAb (1.1 ± 1.0%; $p=0.54$) groups, with no significant differences found between the groups.

Finally, a multiple regression analysis was conducted, combining all three groups to investigate the association between potential factors and BMD increases in the LS or TH at 12 months (Table 2). The background factors included baseline LS and TH BMD T-scores, baseline absolute values of PINP and TRACP-5b, and the treatment groups. The increase in LS BMD was significantly associated with the ROMO treatment compared to that in DMAb (β: 0.33, 95% confidence interval [CI]: 1.82 – 7.66, $p=0.002$) and TPTD (β: 0.84, 95% CI: 2.90 – 8.99, $p<0.001$).

For the TH, BMD increase was negatively associated with the baseline TH T-score (β: −0.23, 95% CI: −2.33 −0.19, $p=0.02$) and positively associated with the baseline PINP levels (β: 0.25, 95% CI: 0.01 – 0.14, $p=0.03$). In addition, TH BMD increase tended to correlate negatively with baseline

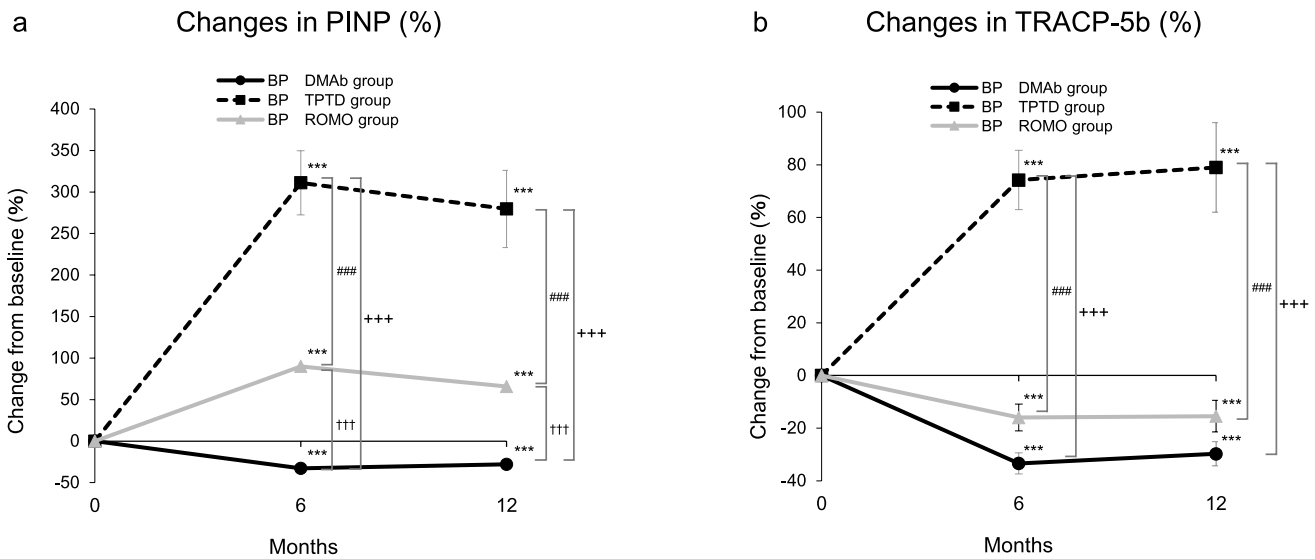

Fig. 2 Percentage change in the serum N-terminal type I procollagen propeptide (PINP) (**a**) and tartrate-resistant acid phosphatase isoform 5b (TRACP-5b) (**b**) levels. PINP, N-terminal type I procollagen propeptide; TRACP-5b, tartrate-resistant acid phosphatase isoform 5b; BP, bisphosphonates; DMAb, denosumab; TPTD, teriparatide; ROMO, romosozumab. Bars indicate mean ± standard error. $^{***}P<0.001$, *vs.* baseline. $^{+++}P<0.001$, DMAb *vs.* TPTD. $^{\dagger\dagger\dagger}P<0.001$ DMAb *vs.* ROMO. $^{\#\#\#}P<0.001$, TPTD *vs.* ROMO

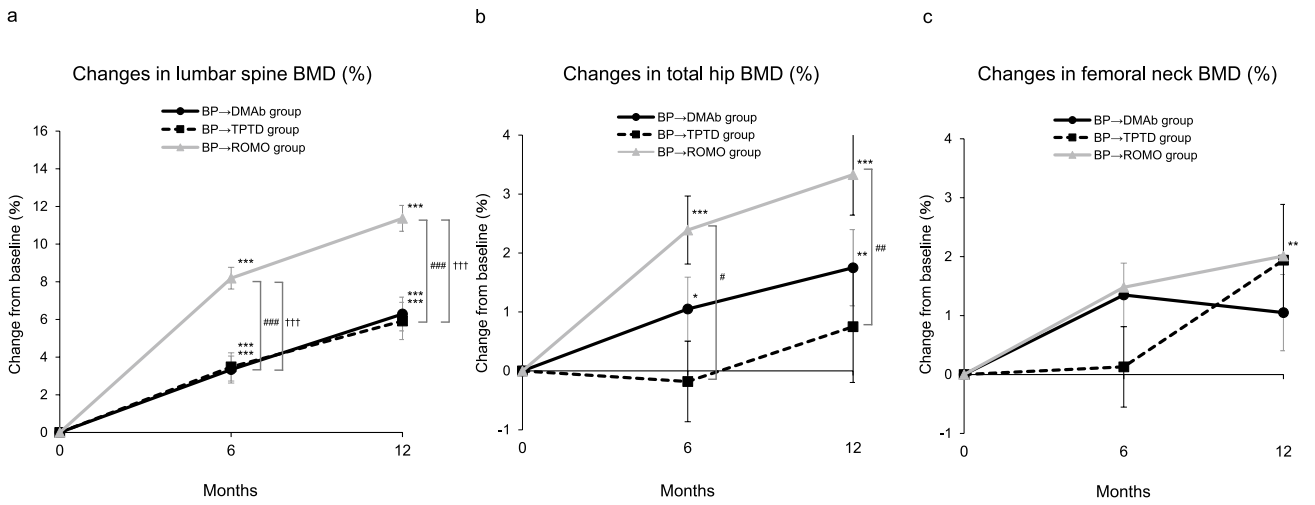

Fig. 3 Percentage change in bone mineral density (BMD) in the lumbar spine (**a**), total hip (**b**), and femoral neck (**c**). BMD, bone mineral density; BP, bisphosphonates; DMAb, denosumab; TPTD, teriparatide; ROMO, romosozumab. Bars indicate mean ± standard errors. $^{*}P<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, *vs*. baseline. $^{\dagger\dagger\dagger}P<0.001$, DMAb *vs*. ROMO. $^{\#}P<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$, TPTD *vs*. ROMO

Table 2 Multiple regression analysis of factors associated with 12-month lumbar spine and total hip bone mineral density increases

	Explanatory variables	β (95% CI)	*P*-value
Lumbar spine	Lumbar spine T-score	−0.13 (−2.12 – 0.40)	0.18
	PINP	0.10 (−0.05 – 0.13)	0.38
	TRACP-5b	0.17 (−0.00 – 0.02)	0.14
	Treatment groups (ROMO *vs*. DMAb)	0.33 (1.82 – 7.66)	0.002
	Treatment groups (ROMO *vs*. TPTD)	0.84 (2.90 – 8.99)	< 0.001
Total hip	Total hip T-score	−0.23 (−2.33 – −0.19)	0.02
	PINP	0.25 (0.01 – 0.14)	0.03
	TRACP-5b	−0.21 (−0.01 – 0.00)	0.08
	Treatment groups (ROMO *vs*. DMAb)	0.12 (−0.93 – 3.47)	0.26
	Treatment groups (ROMO *vs*. TPTD)	0.42 (−0.17 – 4.49)	0.07

β standardized coefficient, *CI* confidence interval, *PINP* type I collagen N-terminal propeptide, *TRACP-5b* tartrate-resistant acid phosphatase isoform 5b, *DMAb* denosumab, *ROMO* romosozumab, *TPTD* teriparatide

TRACP-5b levels (β: −0.21, 95% CI: −0.01 − 0.00, $p=0.08$) and positively with ROMO treatment compared to that with TPTD treatment (β: 0.42, 95% CI: −0.17 − 4.49, $p=0.07$).

Incidence of fragility fractures

No vertebral fractures were observed in any of the treatment groups during the observation period. A rib fracture due to fall was observed in one patient in the ROMO group.

Discussion

To the best of our knowledge, this study is the first to directly compare the effects of sequential therapy following BP treatment, specifically switching to DMAb, TPTD, or ROMO over a 12-month period. Previous studies have demonstrated that transitioning from BP to DMAb in patients with postmenopausal osteoporosis resulted in a 3.2% increase in LS BMD [19], while switching to TPTD led to a 5.4% increase [20]. A more substantial 9.8% increase was observed after switching to ROMO over 12 months [20]. The findings of our study are consistent with these findings, confirming the relative efficacy of each treatment.

In terms of the difference between BP and DMAb, DMAb has been shown to be more effective in suppressing intracortical bone remodeling compared to alendronate in humans [21]. A previous human study demonstrated that when switching from BP to either zoledronate or DMAb, DMAb offers superior efficacy in increasing BMD and down-regulating both bone resorption and bone formation marker levels [19]. These mechanisms may lead to a diminished

anabolic window, potentially resulting in a lesser BMD increase compared to ROMO with its 'dual effect'.

When switching from BP to TPTD, an increase in bone remodeling with cortical and/or intra-trabecular resorption was observed as early as 1 week [22]. This mechanism may explain the temporary decrease in TH BMD at 6 months followed by an increase at 12 months when switching from BP to TPTD in humans [23, 24]. Consequently, due to this remodeling process, BMD increases at the femur are less pronounced at 6 months, which may explain why outcomes in the early phase did not reach those achieved with ROMO.

Regarding the switch from BP to ROMO, previous reports indicate that prior BP treatment, even within a short period of one year, may attenuate both the serum PINP increase and BMD gains following ROMO therapy [25]. However, a randomized Phase 3 trial demonstrated that in postmenopausal patients transitioning from oral BP, ROMO treatment resulted in a smaller increase in PINP and C-telopeptides of type I collagen but a greater BMD increase compared to TPTD [20]. However, this study did not include DMAb treatment. Taken together, while prior BP treatment may diminish the effects of ROMO, its remaining 'dual effect' may lead to a superior BMD increase compared to DMAb and TPTD.

This study has several limitations. The observational, non-randomized design may introduce selection bias since treatment choices were made at the discretion of attending physicians. Additionally, the 12-month follow-up period may be insufficient to fully assess the long-term effects of these therapies on BMD and fracture risk. Despite these limitations, a significant strength of this study is the use of propensity score matching and multiple regression analysis to minimize variations and control for confounding factors across the groups. Although the duration of prior treatment was shorter in the ROMO group after propensity score matching, there were no significant differences in TRACP-5b levels before BP administration ($P=0.84$) or in the TRACP-5b reduction rate at the time of drug transition ($P=0.78$). These findings suggest that bone resorption was similarly suppressed across all groups, regardless of variations in BP formulation or treatment duration.

In Japan, under the public health insurance, the co-administration of vitamin D is permitted as follows: DMAb can be used with both active and native vitamin D, while ROMO can be used with the active form. On the other hand, concurrent use with TPTD and active vitamin D and calcium supplements is cautioned due to an increased risk of hypercalcemia caused by drug interactions. Although not covered by public health insurance, native vitamin D can be purchased as a supplement and is sometimes used at the discretion of the attending physician. As a results, the rates and doses of combined use of vitamin D and calcium supplements varied among the groups, which should be taken into account when interpreting the results. To the best of our knowledge, this is the first study to compare the efficacy of switching from BP to DMAb, TPTD, or ROMO with matched patient backgrounds.

In conclusion, the superior efficacy of ROMO in increasing BMD, particularly in the LS and TH, highlights its potential as a preferred treatment option following BP therapy. The results indicate that ROMO's dual action in promoting bone formation and inhibiting bone resorption provides substantial benefits, particularly in mitigating the lingering effects of previous BP treatment. These findings emphasize the significance of individualized treatment strategies to enhance patient outcomes in osteoporosis management.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07386-4.

Acknowledgements The authors would like to thank Kaoru Nagai, Yukio Nakamura, and all the medical staff for their excellent cooperation in the conduct of this study.

Authors' contributions Study design: KE and TY. Study conduct: KE, TY, and TK. Data collection: KE, TY, YE, TN, and TK. Data analysis: KE and TY. Data interpretation: KE, TY, and TK. Drafting the manuscript: KE and TY. Supervision: KE, Shin-ichiro O, KN, and Seiji O. Approval of the final version of the manuscript: KE, TY, YE, TN, Shin-ichiro O, KN, Seiji O, and TK. KE takes responsibility for the integrity of the data analysis.

Funding Open Access funding provided by Osaka University. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

Declarations

Conflict of interest KE has received research grants from Asahi Kasei, Eisai, and Teijin Pharma and speaker fees from Amgen, Asahi Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Ono Pharmaceutical, Pfizer, Taisho and UCB Japan. KE is affiliated with the Department of Sports Medical Biomechanics, Osaka University Graduate School of Medicine, supported by Asahi Kasei. YE received research grants and/or speaker fees from Asahi Kasei, Eisai, Eli Lilly, Ono Pharmaceuticals, and Taisho. YE is affiliated with the Department of Sports Medical Biomechanics, Osaka University Graduate School of Medicine, supported by Asahi Kasei. KN received a research grant from Astellas and supervises the Department of Sports Medical Biomechanics, Osaka University Graduate School of Medicine, supported by Asahi Kasei. TK has received payments for lectures from AbbVie, Amgen, Asahi Kasei, Astellas, Daiichi Sankyo, Eisai, Eli Lilly, Tanabe-Mitsubishi, Teijin Pharma, and Janssen Pharmaceutical K.K.. TY, TN, Shin-ichiro O, and Seiji O declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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