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Original Article

Effects of prior osteoporosis treatment on 12-month treatment response of romosozumab in patients with postmenopausal osteoporosis

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Abstract

Objectives:

To investigate the effects of prior treatment and determine the predictors of a 12-month treatment response of romosozumab (ROMO) in 148 patients with postmenopausal osteoporosis.

Methods:

In this prospective, observational, and multicenter study, treatment naïve patients (Naïve; n = 50) or patients previously treated with bisphosphonates (BP; n = 37) or denosumab (DMAb; n = 45) or teriparatide (TPTD; n = 16) (mean age, 75.0 years; T-scores of the lumbar spine [LS] −3.2 and total hip [TH] −2.6) were switched to ROMO due to insufficient effects of prior treatment. Bone mineral density (BMD) and serum bone turnover markers were evaluated for 12 months.

Results:

At 12 months, changes in LS BMD were Naïve (18.2%), BP (10.2%), DMAb (6.4%), and TPTD (11.2%) ($P < 0.001$ between groups) and changes in TH BMD were Naïve (5.6%), BP (3.3%), DMAb (0.6%), and TPTD (4.4%) ($P < 0.01$ between groups), respectively. In all groups, the LS BMD significantly increased from baseline at 6 and 12 months, although only the DMAb group failed to obtain a significant increase in TH BMD during 12-month treatment. Mean values of N-terminal type I procollagen propeptide (PINP; $\mu\text{g/L}$) from baseline \rightarrow 1 month \rightarrow 12 months were Naïve (67.9 \rightarrow 134.1 \rightarrow 51.0), BP (32.2 \rightarrow 81.7 \rightarrow 40.9), DMAb (30.4 \rightarrow 56.2 \rightarrow 75.3), and TPTD (97.4 \rightarrow 105.1 \rightarrow 37.1), and those of isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b; mU/dL) were Naïve (500.4 \rightarrow 283.8 \rightarrow 267.1), BP (273.4 \rightarrow 203.1 \rightarrow 242.0), DMAb (220.3 \rightarrow 246.1 \rightarrow 304.8), and TPTD

(446.6 → 305.1 → 235.7), respectively. Multiple regression analysis revealed that the significant predictors of BMD change at 12 months were difference of prior treatment ($r = -2.8$, $P < 0.001$) and value of PINP at 1 month ($r = 0.04$, $P < 0.01$) for LS, and difference of prior treatment ($r = -1.3$, $P < 0.05$) and percentage change of TRACP-5b at 1 month ($r = -0.06$, $P < 0.05$) for TH.

Conclusions:

The early effects of ROMO on LS and TH BMD increase at 12 months were significantly affected by the difference of prior treatment and are predicted by the early change in bone turnover markers.

Keywords

romosozumab; prior treatment; predictor; bone turnover marker; postmenopausal osteoporosis

Abbreviations

BMD; bone mineral density

BP; bisphosphonates

DMAb; denosumab

FN; femoral neck

LS; lumbar spine

N.S.; not significant

82 PINP; N-terminal type I procollagen propeptide

83 RANKL; receptor activator of nuclear factor–kappa B ligand

84 ROMO; romosozumab

85 TH; total hip

86 TPTD; teriparatide

87 TRACP-5b; isoform 5b of tartrate-resistant acid phosphatase

88

89 1. Introduction

90 Romosozumab (ROMO), a monoclonal anti-sclerostin antibody, is a novel osteoporosis agent
91 which promotes Wnt signaling by blocking sclerostin [1]. ROMO directly promotes bone
92 formation by osteoblasts, and also indirectly inhibits bone resorption by osteoclasts via
93 promoting production of osteoprotegerin (*in vivo* decoy of receptor activator of nuclear
94 factor–kappa B [RANK] ligand [RANKL]) from osteoblasts and osteocytes [2]. As a result of
95 this dual effect, the anabolic window (the difference between bone formation and bone
96 resorption), which determines the osteoporosis treatment effects, became larger with ROMO
97 than with other osteoporosis agents [3]. Especially, this anabolic window became largest
98 within 1 month after ROMO induction [1]. Consequently, ROMO showed superior increase
99 of bone mineral density (BMD) in postmenopausal women compared with alendronate or
100 teriparatide (TPTD) [1].

101 Previous researchers have investigated the effects of prior treatment on bone anabolic agents.
102 The prior use of denosumab (DMAb) before TPTD resulted in a transient decrease of BMD
103 associated with increase of bone resorption markers [4]. In addition, the prior use of

bisphosphonates (BP) diminished the increasing response of BMD to TPTD [5, 6]. In contrast, only a few studies have shown the effects of subsequent treatment of ROMO after alendronate [7] or DMAB [8], without direct comparison between other agents. Taking these findings into consideration, we hypothesized that prior antiresorptive treatment (such as BP or DMAB) might diminish the effects of sequential treatment by ROMO. In addition, no studies have directly compared the effects of ROMO between prior treatment-naïve cases, prior treatment by antiresorptive treatment (BP or DMAB) cases, or prior treatment by TPTD cases. In March 2019, Japan became the first country to approve the use of ROMO, and its clinical data based on real-world settings are of great interest. We recently reported that the early effects of ROMO on the increase of BMD at 6 months were significantly affected by the difference of prior treatment [9]. In addition, we also reported a case which suffered multiple spontaneous vertebral fractures after discontinuation of DMAB followed by delayed induction of ROMO [10]. In this study, we aim to clarify the effects of prior treatment and to determine the early predictors of the 12-month treatment response of ROMO in patients with postmenopausal osteoporosis by adding patients' number and longer follow-up periods to our previous study.

2. Methods

2.1 Study design and subjects

This prospective, observational, nonrandomized study was conducted in 6 centers in accordance with the Japanese Guidelines for Prevention and Treatment of Osteoporosis 2011 [11]. A total of 148 postmenopausal patients with osteoporosis who were treatment naïve

(Naïve; n = 50) or treated previously with BP (n = 37), DMAb (n = 45), or TPTD (n = 16) were switched to ROMO based on their physicians' decision due to an insufficient increase in BMD by the prior treatment [9]. Patients generally received vitamin D and calcium supplements (Table 1) and were followed up for 12 months. Figure 1 shows the study design, schedule, and patient flow.

2.2 BMD assessment

Areal BMD was assessed in the LS (L2–L4), total hip (TH), and femoral neck (FN) using dual-energy X-ray absorptiometry (Discovery, Hologic, Inc., Waltham, MA, USA) at baseline, 6 months, and 12 months after ROMO induction. BMD data were standardized by the correction method proposed by the Japan Osteoporosis Society in reference to the International Society for Clinical Densitometry Guidance [12]. Regions of severe sclerosis, vertebral fracture, and surgical sites were excluded from the BMD measurements, as previously described [13].

2.3 Biochemical markers of bone turnover

Bone turnover markers were measured at baseline, 1 month, 6 months, and 12 months after ROMO induction. From each patient, serum was obtained in the morning after an overnight fast. Using an enzyme-linked immunosorbent assay, we measured isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b; Nittobo Medical Co. Ltd., Tokyo, Japan) as a bone resorption marker, and N-terminal type I procollagen propeptide (PINP; Roche Diagnostics, Basel, Switzerland) as a bone formation marker. (A previous report demonstrated that the TRACP-5b level is a useful bone resorption marker that demonstrates

higher clinical sensitivity and signal-to-noise ratio compared with serum cross-linked C-telopeptide of type I collagen [CTX] levels [14].) Serum 25-hydroxycholecalciferol [25(OH)D] levels were measured by electrochemiluminescence using the Elecsys system (Roche Diagnostics, Basel, Switzerland).

2.4 Radiographs

Spinal radiographs were obtained routinely at baseline, 6 months, and 12 months after ROMO administration. For subjects who had symptoms of incidental clinical vertebral or nonvertebral fractures, each attending investigator assessed unscheduled radiographs.

2.5 Statistical analysis

The differences between study groups were assessed using analysis of variance (between four groups) and the Steel-Dwass test (between two groups) for continuous variables and using the Fisher's exact test (between four groups) for categorical variables. Changes in BMD and bone turnover marker levels from the baseline to the specified time points within each study group were assessed using the Wilcoxon signed-rank test. Spearman's correlation coefficients were calculated to identify significant indicators of change in LS or TH BMD ($P < 0.05$), and then they were submitted to multiple regression analysis to identify their significance. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [15]. A P value of < 0.05 was considered significant.

2.6 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; Osaka University, Graduate School of Medicine) and each institute. The board waived the requirement for patient informed consent by posting the opt-out information in the hospitals' homepage.

3. Results

Table 1 shows the clinical backgrounds of the patients at ROMO induction. No significant difference was observed among the groups in terms of baseline age, body mass index, prior vertebral and nonvertebral fracture incidence ratio, combined vitamin D and calcium dose or ratio or serum calcium, estimated glomerular filtration rate, and 25(OH)D levels. However, we observed a significant difference in the duration of prior treatment ($P < 0.001$), interval from final prior treatment prescription ($P < 0.001$), TH BMD (g/cm^2 ; $P < 0.05$), FN BMD (g/cm^2 ; $P < 0.01$), and T-score ($P < 0.05$) and in serum levels of PINP ($P < 0.001$) and TRACP-5b ($P < 0.001$).

3.1 Bone turnover markers

Figure 2 displays the serum PINP value (Fig. 2a) and its percentage change (Fig. 2b) as well as the TRACP-5b value (Fig. 2c) and its percentage change (Fig. 2d).

Regarding PINP value, the Naïve group reached its highest value compared with other groups at 1 month after ROMO induction, although only the DMAb group remained within the

reference range (14.9–68.8 µg/L) at 1 month. The tendency in the BP group was similar to that of the Naïve group, although the PINP value in the BP group remained in a smaller range. The TPTD group maintained its value at 1 month, which then markedly decreased from 6 to 12 months. The tendency of the percentage change of PINP was similar between the Naïve, BP, and TPTD groups, although only the DMAb group showed a continuous increase until 6 months, which then decreased at 12 months.

Regarding the TRACP-5b value and percentage change, the Naïve and TPTD groups showed marked decreases from 1 to 12 months. This tendency was similar in the BP group, although the decreasing rate of this group from 1 to 12 months was smaller than that of the Naïve and TPTD groups. On the other hand, the DMAb group showed a continuous increase from 1 to 12 months in both value and percentage change.

3.2 Changes in BMD

Regarding the change in LS BMD (Fig. 3a), the Naïve group had the highest increase (mean \pm standard errors; P value compared with baseline) ($12.9\% \pm 0.8\%$; $P < 0.001$), followed by TPTD ($8.4\% \pm 0.9\%$; $P < 0.001$), BP ($7.6\% \pm 1.0\%$; $P < 0.001$), and DMAb ($3.6\% \pm 0.6\%$; $P < 0.001$) at 6 months ($P < 0.001$ between groups). At 12 months, the Naïve group still demonstrated the highest increase ($18.2\% \pm 1.1\%$; $P < 0.001$), followed by the TPTD ($11.2\% \pm 1.4\%$; $P < 0.001$), BP ($10.2\% \pm 0.9\%$; $P < 0.001$), and DMAb ($6.4\% \pm 0.6\%$; $P < 0.001$) groups ($P < 0.001$ between groups).

Regarding the change in TH BMD (Fig. 3b), the Naïve group showed the highest increase ($4.1\% \pm 0.7\%$; $P < 0.001$), followed by the TPTD ($3.5\% \pm 1.0\%$; $P < 0.01$), BP ($2.0\% \pm 0.6\%$; $P < 0.01$), and DMAb ($1.0\% \pm 0.7\%$; $P = \text{not significant; N.S.}$) groups at 6 months (P

< 0.05 between groups). At 12 months, the Naïve group still had the highest increase ($5.6\% \pm 0.8\%$; $P < 0.001$), followed by the TPTD ($4.4\% \pm 1.2\%$; $P < 0.01$), BP ($3.3\% \pm 1.2\%$; $P < 0.01$), and DMAb ($0.6\% \pm 0.9\%$; $P = \text{N.S.}$) groups ($P < 0.01$ between groups).

Regarding the change in FN BMD (Fig. 3c), the Naïve group demonstrated the highest increase ($4.2\% \pm 1.2\%$; $P < 0.01$), followed by the TPTD ($2.2\% \pm 1.1\%$; $P = \text{N.S.}$), DMAb ($1.5\% \pm 1.0\%$; $P = \text{N.S.}$), and BP ($0.5\% \pm 1.0\%$; $P = \text{N.S.}$) groups at months ($P = \text{N.S.}$ between groups). At 12 months, the Naïve group still showed the highest increase ($4.9\% \pm 1.1\%$; $P < 0.001$), followed by the TPTD ($3.5\% \pm 1.2\%$; $P < 0.05$), BP ($3.1\% \pm 0.9\%$; $P < 0.01$), and DMAb ($0.7\% \pm 0.8\%$; $P = \text{N.S.}$) groups ($P < 0.05$ between groups).

Of note, only the DMAb group failed to obtain a significant increase in both TH and FN BMD during 12 months of ROMO treatment.

3.3 Significant predictor variables of the change in LS and TH BMD

To investigate the early predictor of BMD response at 12 months, confounders that showed a significant correlation with LS or TH BMD change at 12 months (including prior therapy before ROMO [categorized as Naïve (1), TPTD (2), BP (3), and DMAb (4)]; PINP [value of baseline and 1 month], TRACP-5b [value of baseline and percentage change at 1 month and 6 months], and baseline BMD [LS or TH T-score]) were subjected to stepwise multiple regression analysis.

Regarding the change in LS BMD at 12 months, significant predictors were the difference of prior therapy before ROMO (partial regression coefficient = -2.8 , $P < 0.001$), the value of PINP at 1 month (partial regression coefficient = 0.04 , $P < 0.01$), and the baseline LS BMD T-score (partial regression coefficient = -1.5 , $P < 0.05$).

Regarding the change in TH BMD, the significant predictors were the baseline TH BMD T-score (partial regression coefficient = -3.3 , $P < 0.001$), the baseline value of PINP (partial regression coefficient = 0.04 , $P < 0.01$), percentage change in TRACP-5b at 1 month (partial regression coefficient = -0.06 , $P < 0.05$) and 6 months (partial regression coefficient = -0.02 , $P < 0.05$), and difference of prior therapy before ROMO (partial regression coefficient = -1.3 , $P < 0.05$).

3.4 Incidence of fragility fracture

Nine patients (6.1%) suffered major fragility fractures during the observation period. In the Naïve group, one patient suffered a distal humerus fracture. In the BP group, we observed one each for proximal humerus fracture, distal radius fracture, proximal tibia fracture, patella fracture, and vertebral fracture. In the DMAb group, we noted one each for rib fracture, proximal humerus fracture, and multiple vertebral fracture [10]. In the TPTD group, no fracture incidence was observed.

3.5 Incidence of treatment discontinuation

During the observation period, 14 patients (9.5%) discontinued the treatment. Two patients discontinued because of injection pain, dizziness, blood pressure elevation, and lost follow-up. One patient discontinued due to subarachnoid hemorrhage attributed to aneurysm rupture, decreased blood pressure, facial flush, herpes zoster, oral lichen planus, and surgery for valvular disease.

4. Discussion

This study demonstrated that BMD increase by 12-month administration of ROMO were significantly affected by the difference of prior treatment, and are predicted by the early change in bone turnover markers.

Regarding BP, BMD gain after switching alendronate to ROMO was smaller than initial treatment by ROMO [16], which was similar to our results. A previous animal study showed that BP is absorbed not only by osteoclasts but also by osteoblasts, which leads to the suppression of bone modeling by lining osteoblasts [17]. In the present study, the BP group showed a smaller absolute value of PINP compared with the Naïve group at every time point, suggesting suppressed bone modeling by BP. On the other hand, the baseline value and percentage decrease of TRACP-5b were lower in the BP group compared with the Naïve group at every time point. This result suggests that the inhibited bone resorption by BP may diminish further suppression of bone resorption by ROMO, due to enhanced production of osteoprotegerin. Consequently, the narrowed anabolic window by BP may lead to a smaller increase in BMD compared with the Naïve group.

Regarding DMAb, a previous report showed that patients who received ROMO after DMAb demonstrated a continuous increase in bone turnover markers at 6 months, and BMD gain was smaller than initial treatment by ROMO [8], which was similar to our results. In addition, we recently reported that patients switched from DMAb to ROMO showed increased bone turnover and diminished BMD increase compared with the Naïve group at 6 months [9]. In the present study which was extended to 12 months, only the DMAb group showed a continuous increase in bone turnover and failed to obtain a significant increase in TH and FN BMD from baseline. Taking these findings together, it seems that increased bone turnover

from DMAb discontinuation (due to increased production of RANKL from osteocytes and osteoblasts) cannot be fully compensated by osteoprotegerin induced by ROMO.

Regarding TPTD, a previous animal study showed that TPTD stimulates not only bone remodeling (accounting for 70% of bone formation) but also bone modeling (accounting for 20%–30% of bone formation), which was particularly dominant within the first 2 months of treatment [18]. In human, TPTD strongly induced both bone remodeling and modeling at 3 months confirmed by iliac bone biopsies [19]. In the present study, the transition from TPTD to ROMO resulted in a maintained PINP level and a rapidly decreased TRACP-5b level at 1 month. Collectively, preceding treatment with TPTD may promote bone modeling in the early phase, and may leave little place for further bone modeling by ROMO. On the other hand, enhanced bone resorption by TPTD (due to enhanced production of RANKL by osteoblasts) may be suppressed by enhanced production of osteoprotegerin by ROMO. These findings resulted in both widening of anabolic window and increase in BMD second to the Naïve group.

Next, we investigated the early predictors of the BMD increase by ROMO. The anabolic window (increase in bone formation markers and decrease in bone resorption markers) became largest within 1 month after ROMO induction [1], which suggests that this early response may contribute to the BMD increase. Indeed, most of the patients who showed PINP increase more than 10 µg/L at 1 month from baseline showed good LS BMD increase (more than 3%) at 12 months [7]. However, they did not evaluate the correlation with bone resorption markers. Multiple regression analysis in the present study revealed that the 12-month treatment response of ROMO in BMD increase was associated with 1-month response of both bone formation marker (absolute value) for LS, and bone resorption marker

(percent change) for TH. Collectively, inhibition of bone resorption at early phase may also contribute to BMD increase by ROMO, which is a novel finding of the present study.

Regarding the order of the treatments, switching ROMO to DMAb led to a continuous increase in BMD [20]. However, our present study demonstrated that only the DMAb group failed to obtain a significant increase in TH and FN BMD during the 12-month of treatment. Taken together, preceding ROMO with DMAb may be more hopeful treatment strategy compared with preceding DMAb with ROMO.

This study has several limitations. The statistical power of the results might be attenuated because of the small number of included patients. Due to the purpose of the study, this was not a randomized study. Minor differences in the patients' backgrounds including diversity of prior treatment within the same group (both oral and intravenous agents, or different frequency regimens) and lack of fixed inclusion criteria might have potentially affected the physicians' treatment selection and subsequent effects. Difference of the production process between TRACP-5b (enzyme produced by bone resorbing osteoclasts) and CTX (C-terminal telopeptide of fibrillar collagens) [14] may lead to the difference between other studies using serum CTX. However, the strength of this study is that this is the first study which investigated the effects of prior treatment and the early predictors of the effects of 12-month treatment by ROMO in real-world settings.

In conclusion, in this 12-month follow-up study of postmenopausal patients with osteoporosis introduced to ROMO, the Naïve group demonstrated the highest treatment response compared with the other groups, as shown by the increase in BMD. Previous DMAb treatment may attenuate the treatment response, especially regarding the increase in TH and FN BMD. These results may contribute to the decision of adequate subsequent treatment strategy by ROMO.

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Authors' roles

Study design: KE, MH, HT, and MK. Study conduct: KE, MH, and MK. Data collection: KE, MH, HT, YN, MK, SK, AM, HN, YK. Data analysis: KE, MH, and MK. Data interpretation: KE, MH, MK, GO, YE, KT, AG, and TM. Drafting the manuscript: KE and MK. Supervise: KN and SO. Approving final version of the manuscript: KE, MH, HT, YN, MK, SK, AM, HN, YK, GO, YE, KT, AG, TM, KN, and SO. KE takes responsibility for the integrity of the data analysis.

Declaration of conflicting interests

KE is affiliated with the Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate School of Medicine, which is supported by Taisho. KE and MH have received research grants from Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. KE has received payments for lectures from Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Ono, and Pfizer. HT has received a research grant from Chugai and has received payments for lectures from Asahi-Kasei, Astellas, Chugai, Eisai, Eli Lilly, and Pfizer. YN has received payments for lectures from Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. MK has received payments for lectures from Asahi-Kasei and Astellas. KN has received a research grant from Astellas and supervises the Department of Musculoskeletal Regenerative Medicine, Osaka University, Graduate School of Medicine, which is supported by Taisho. SK, AM, HN, YK, GO, YE, KT, AG, TM, and SO declare that they have no conflicts of interest. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Figure legends

Figure 1. Study design, schedule, and patient flow.

ROMO, romosozumab; BP, bisphosphonate; ALN, alendronate; RIS, risedronate; IBN, ibandronate; MIN, minodronate; ZOL, zoledronate; DMAb, denosumab; TPTD, teriparatide; 25(OH)D, 25-hydroxycholecalciferol; LS, lumbar spine; TH, total hip; FN, femoral neck; TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; PINP, type I collagen N-terminal propeptide.

Figure 2. Serum PINP value (a) and its percentage change (b); serum TRACP-5b value (c) and its percentage change (d).

PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase; BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide. Bars indicate mean \pm standard errors. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; change from baseline within each treatment group.

Figure 3. Percentage change in BMD in the lumbar spine (a), total hip (b), and femoral neck (c).

BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; BMD, bone mineral density. Bars indicate mean \pm standard errors. # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$; difference between the two indicated groups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; change from baseline within each treatment group.

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1 **Table 1. Patients’ clinical characteristics at baseline**

Variable	Naïve group (n = 50)	BP group (n = 37)	DMAb group (n = 45)	TPTD group (n = 16)	<i>P</i> value
Age (years)	73.9 ± 6.7	74.7 ± 7.1	76.1 ± 7.7	75.9 ± 6.0	N.S.
Body mass index (kg/m ²)	20.5 ± 2.9	20.5 ± 3.7	19.7 ± 1.8	19.6 ± 2.4	N.S.
Prior vertebral fracture (%)	40.0	43.2	53.3	56.2	N.S.
Prior nonvertebral fracture (%)	26.0	18.9	15.6	25.0	N.S.
Prior osteoporosis treatment	None	ALN (weekly p.o. n = 10/monthly i.v. n = 1)		Daily TPTD 20µg	N.A.
		RIS (weekly and monthly p.o. n = 17)	DMAb 60 mg	(s.c. n = 12)	
		IBN (monthly p.o. n = 2/ monthly i.v. n = 2)	(every 6 months s.c. n = 45)	Weekly TPTD 56.5 µg	
		MIN (monthly p.o. n = 3)		(s.c. n = 4)	
		ZOL (yearly i.v. n = 2)			
Duration of prior treatment (months)	0	28.1 ± 23.3	24.1 ± 15.8	11.6 ± 8.0	<0.001
Interval from final prior treatment prescription (months)	0	3.6 ± 5.3	6.2 ± 1.3	1.6 ± 1.0	<0.001
	94.0 (47/50)	94.6 (35/37)	100.0 (45/45)	93.8 (15/16)	
Combined VD, % (n/N)	ALF (n = 16)	ALF (n = 13)	ALF (n = 18)	ALF (n = 2)	N.S.
	ELD (n = 31)	ELD (n = 22)	ELD (n = 27)	ELD (n = 13)	
Combined VD, µg/day	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	N.S.

Combined Ca, % (n/N)	76.0 (38/50)	62.2 (23/37)	77.8 (35/45)	87.5 (14/16)	N.S.
Combined Ca, mg/day	336.0 ± 289.8	383.8 ± 430.4	613.3 ± 594.5	356.9 ± 312.7	N.S.
Lumbar spine BMD (g/cm ²)	0.654 ± 0.133	0.732 ± 0.116	0.705 ± 0.138	0.698 ± 0.109	N.S.
Lumbar spine BMD (T-score)	-3.4 ± 1.0	-2.9 ± 0.9	-2.9 ± 1.2	-3.3 ± 0.9	N.S.
Total hip BMD (g/cm ²)	0.607 ± 0.079	0.635 ± 0.082	0.573 ± 0.087	0.614 ± 0.096	<0.05
Total hip BMD (T-score)	-2.7 ± 0.7	-2.4 ± 0.7	-2.7 ± 0.9	-2.6 ± 0.8	N.S.
Femoral neck BMD (g/cm ²)	0.519 ± 0.087	0.572 ± 0.109	0.484 ± 0.087	0.547 ± 0.096	<0.01
Femoral neck BMD (T-score)	-3.2 ± 0.7	-2.7 ± 0.8	-3.1 ± 0.8	-2.9 ± 0.8	<0.05
Corrected serum Ca (mg/dl)	9.3 ± 0.4	9.5 ± 0.4	9.6 ± 0.6	9.5 ± 0.3	N.S.
eGFR (ml/min/1.73 m ²)	71.0 ± 15.0	71.7 ± 17.9	65.1 ± 20.4	73.9 ± 17.1	N.S.
PINP (µg/l)	67.9 ± 32.0	32.2 ± 28.8	30.4 ± 30.9	97.4 ± 73.2	<0.001
TRACP-5b (mU/dl)	500.4 ± 246.1	273.4 ± 133.6	220.3 ± 142.9	446.6 ± 196.2	<0.001
25(OH)D (ng/ml)	15.0 ± 4.7	16.3 ± 5.3	15.3 ± 7.0	14.0 ± 4.9	N.S.

2 Mean ± standard deviation. % = number of patients with measurements/total number of patients.

3 Differences between the groups were determined by ANOVA or Fisher's exact test. N.S.= not significant.

4 ANOVA, analysis of variance; BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; p.o., oral
5 administration; i.v., intravenous; s.c., subcutaneous injection; ALN, alendronate; RIS, risedronate; MIN,
6 minodronate; ZOL, zoledronate; VD, vitamin D; ALF, alfacalcidol; ELD, eldecacitol; Ca, calcium; BMD, bone
7 mineral density; eGFR, estimated glomerular filtration rate; PINP, type I collagen N-terminal propeptide;
8 TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; 25(OH)D, 25-hydroxycholecalciferol.

Figure 1

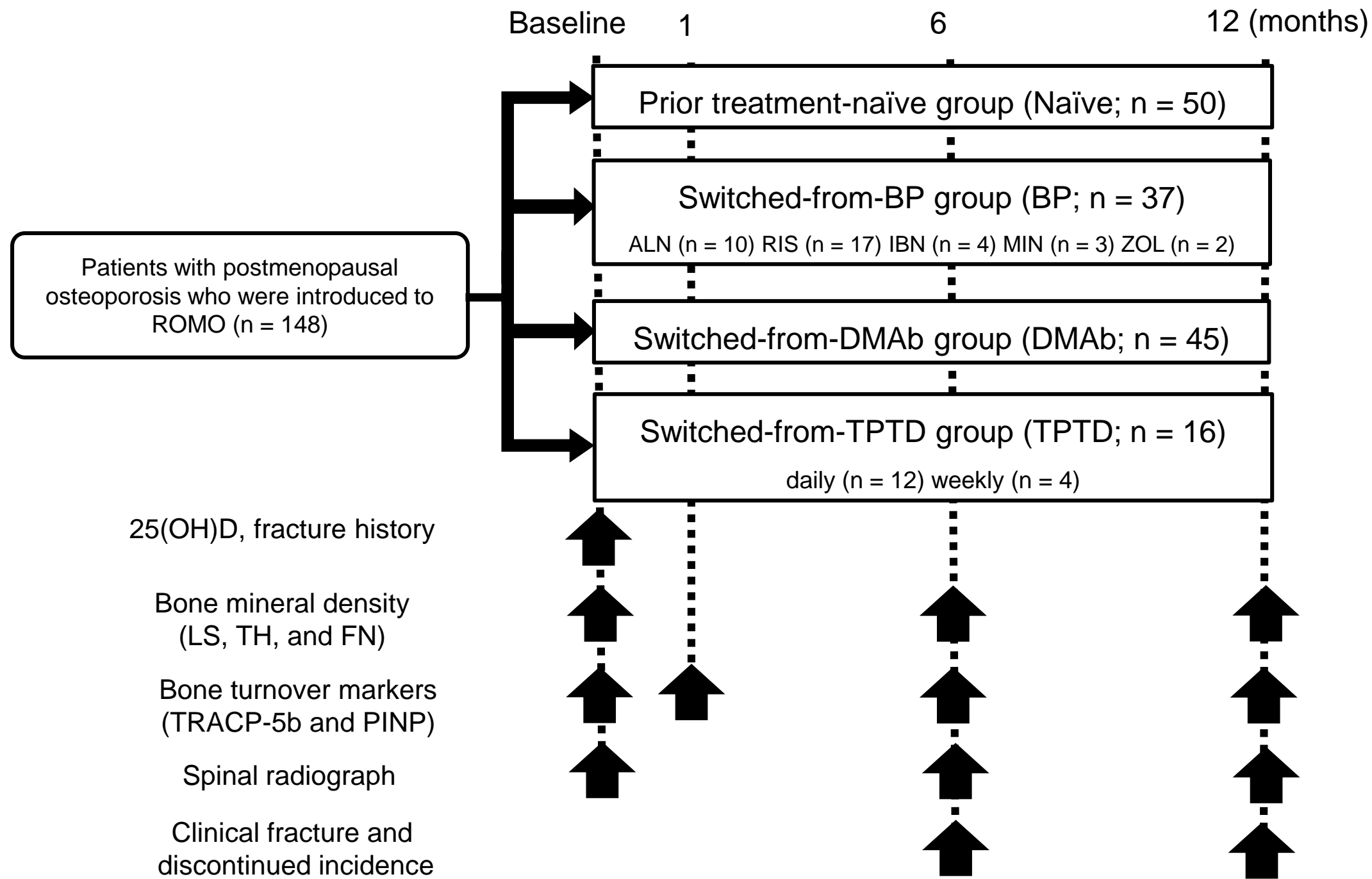


Figure 2

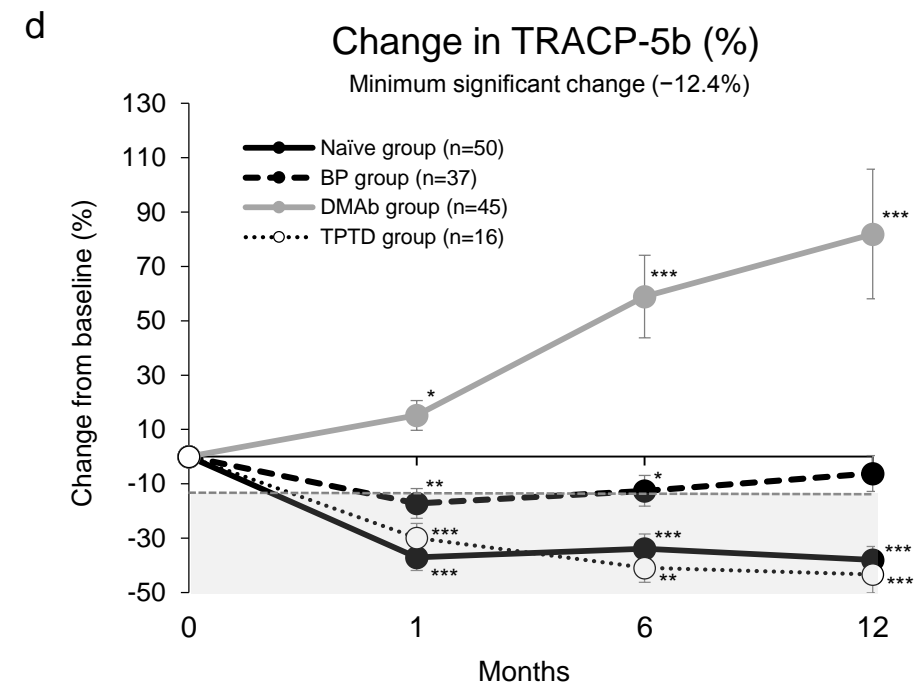
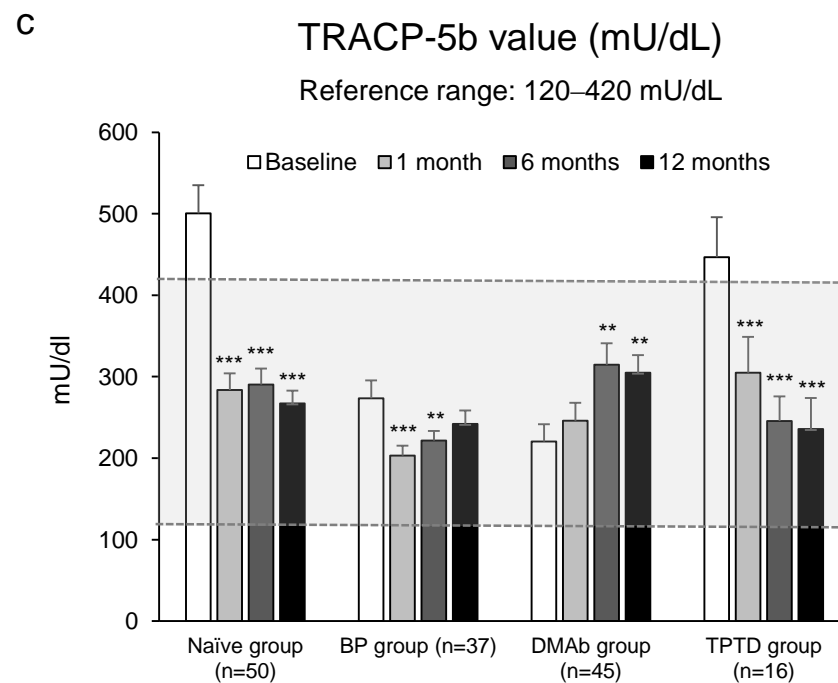
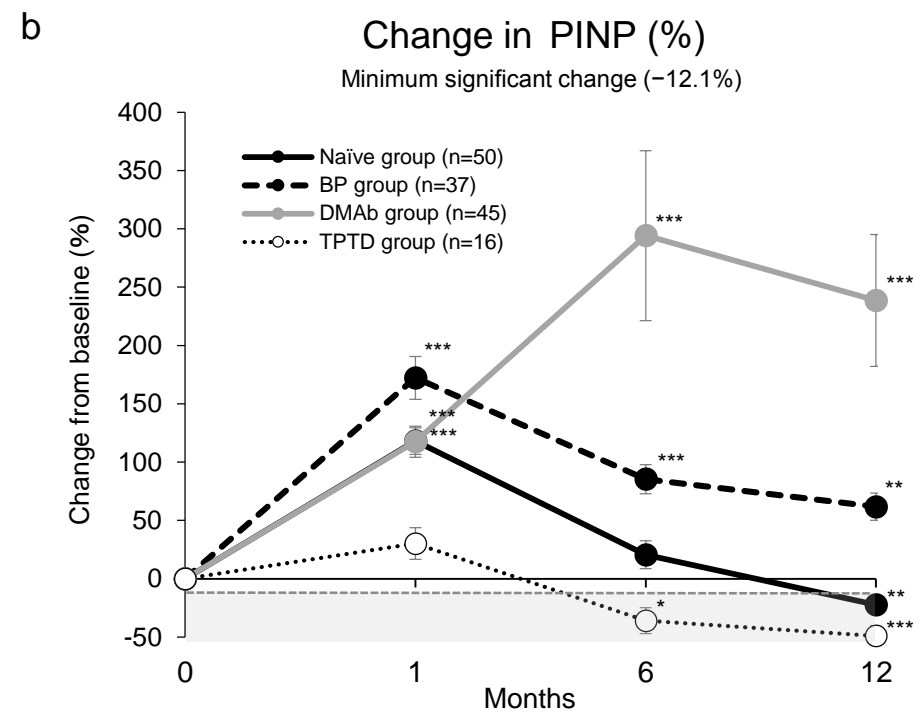
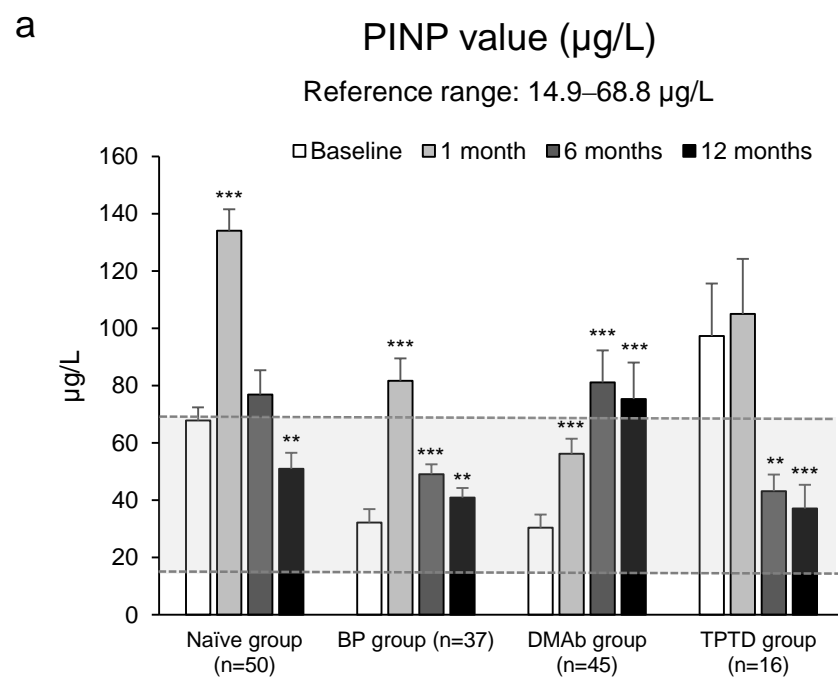
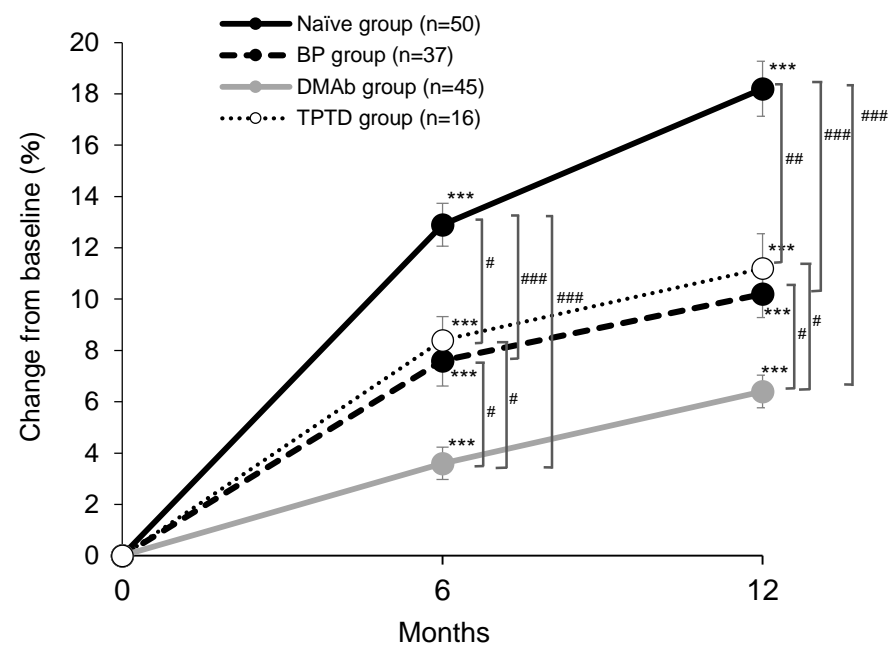


Figure 3

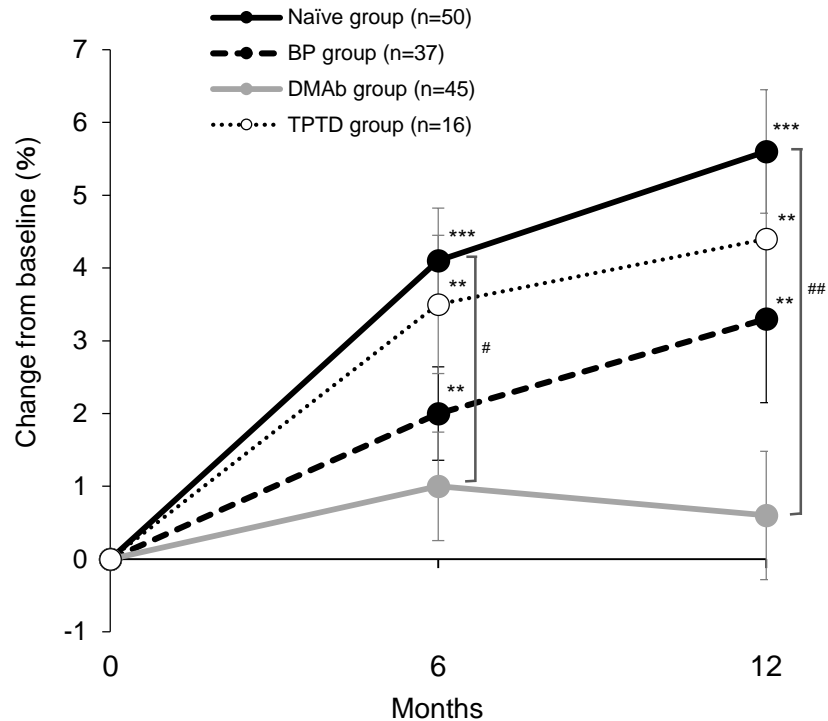
a

Change in lumbar spine BMD (%)



b

Change in total hip BMD (%)



c

Change in femoral neck BMD (%)

