Highlights

- Treatment response to romosozumab was evaluated by the change of bone mineral density and bone turnover markers
- Prior bone-resorption inhibitors' treatment attenuates early treatment response to romosozumab
- Early treatment response to romosozumab was highest in treatment-naïve cases
- Early treatment response to romosozumab was predicted by the early change of bone turnover markers

Rapid Communication

Effects of prior osteoporosis treatment on early treatment response of romosozumab in patients with postmenopausal osteoporosis

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Abstract

Purpose

To investigate the effects of prior treatment and the predictors of early treatment response to romosozumab (ROMO) in patients with postmenopausal osteoporosis.

Methods

In this prospective, observational, multicenter study, 130 treatment-naïve patients (Naïve; n = 37) or patients previously treated with bisphosphonates (BP; n = 33), denosumab (DMAb; n = 45), or teriparatide (TPTD; n = 15) (age, 75.0 years; T-scores of the lumbar spine [LS] −3.2 and femoral neck [FN] −2.9) were switched to ROMO based on their physician's decision. Bone mineral density (BMD) and serum bone turnover markers were evaluated for six months.

Results

At six months, LS BMD changes were 13.6%, 7.5%, 3.6%, and 8.7% ($P < 0.001$ between groups) and FN BMD changes were 4.2%, 0.4%, 1.6%, and 1.5% ($P = 0.16$ between groups) for Naïve, BP, DMAb, and TPTD groups, respectively. Changes in N-terminal type I procollagen propeptide (PINP; μg/L) levels from baseline→one month were 72.7→139.0, 33.5→85.4, 30.4→54.3, and 98.4→107.4, and those of isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b) (mU/dL) were 474.7→270.2, 277.3→203.7, 220.3→242.0, and 454.1→313.0 for Naïve, BP, DMAb, and TPTD groups, respectively. Multivariate regression analysis revealed that significant predictors of LS BMD change at six months were prior treatment difference ($r = −3.1$, $P = 0.0027$) and TRACP-5b percentage change ($r = −2.8$, $P = 0.0071$) and PINP value at one month ($r = 3.2$, $P = 0.0021$).

Conclusion

Early effects of ROMO on the increase in LS BMD are 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

Mini Abstract

Early effects of ROMO on the increase in LS BMD at six months is significantly affected by the difference of prior treatment and also predicted by the early change of bone turnover markers in patients with postmenopausal osteoporosis.

Introduction

With the advent of various novel anti-osteoporosis agents, goal-directed treatment for osteoporosis has been recommended to reduce imminent fracture risk [1]. One novel anabolic agent is romosozumab (ROMO), a monoclonal anti-sclerostin antibody that promotes bone formation and inhibits bone resorption [2]. Because of this unique dual effect, the anabolic window (i.e., the difference between bone formation and bone resorption), which determines the effects of osteoporosis treatment, is assumed to be

larger in ROMO than other osteoporosis treatments [3]. Indeed, in postmenopausal women, ROMO has shown superior effects in increasing lumbar spine (LS) bone mineral density (BMD) than alendronate or teriparatide (TPTD) [2]. In addition, the increase in the bone formation markers and decrease in the bone resorption markers become largest within a month after treatment induction [2], suggesting that this early bone turnover response may be beneficial in predicting early treatment response to ROMO.

The effects of prior treatment on bone anabolic agents have been reported. Prior antiresorptive treatment such as bisphosphonates (BP) blunted the hip BMD response to TPTD [4,5], and switching from denosumab (DMAb) to TPTD led to a transient increase in the bone resorption markers and a consequent decrease in BMD [6]. On the other hand, only a few studies have demonstrated the effects of subsequent treatment of ROMO after administration of other osteoporosis agents, such as alendronate [7] or DMAb [8]. We recently reported a case in which ROMO was not effective in preventing multiple spontaneous clinical vertebral fractures after DMAb discontinuation [9]. However, patients transitioned from oral BP to ROMO showed gains in hip BMD that were not observed with TPTD, suggesting the difference of sequential effects between these two agents [10].

Taken together, we hypothesized that prior antiresorptive treatment (such as BP or DMAb) may diminish the effects of ROMO, although may differ from that of TPTD. However, there has been no direct comparison between prior treatment-naïve cases or prior treatment by TPTD cases.

Japan was the first country to approve ROMO on March 2019, and its clinical data based on real-world settings is of great interest. This study aims to clarify the effects of prior treatment and determine predictors for early treatment response of ROMO in patients with postmenopausal osteoporosis.

Materials and methods

Study design and subjects

This prospective, observational, nonrandomized study was conducted in six centers in accordance with the Japanese Guidelines for Prevention and Treatment of Osteoporosis 2011 [11]. A total of 130 postmenopausal patients with osteoporosis who were treatment naïve (Naïve; n = 37) or previously treated by BP (n = 33), DMAb (n = 45), or TPTD (n = 15) were switched to ROMO based on the decision of the patients' physicians (mainly judged by insufficient increase of BMD associated with prior treatment). Patients were supplemented with vitamin D and calcium in principle (table 1), and followed up for six months.

BMD assessment

Areal BMD in the LS (L2–L4), total hip (TH), and femoral neck (FN) were assessed by dual-energy X-ray absorptiometry (Discovery, Hologic, Inc., Waltham, MA, USA) at baseline and six months after ROMO induction. We excluded regions of severe sclerosis, vertebral fracture, and surgical sites from BMD measurements, as previously described [12]. BMD data was standardized by correction method proposed by Japan

Osteoporosis Society in reference to the International Society for Clinical Densitometry Guidance [13].

Biochemical markers of bone turnover

Bone turnover markers were measured at baseline, one month, and six months after ROMO induction. Serum was obtained from each patient in the morning after an overnight fast. We measured the N-terminal type I procollagen propeptide (PINP; interassay coefficient of variation, 3.2%–5.2%; Intact UniQ assay; Orion Diagnostica, Espoo, Finland) as a bone formation marker and isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b; interassay coefficient of variation, 5.0%–9.0%; Immunodiagnostic Systems Ltd., Boldon, UK) as a bone resorption marker using enzyme-linked immunosorbent assay, as previously described [14]. (A previous report demonstrated that TRACP-5b levels are a useful bone resorption marker that demonstrates higher clinical sensitivity and signal-to-noise ratio as compared to serum CTX levels [15]). Serum 25-hydroxycholecalciferol [25(OH)D] levels were measured by electrochemiluminescence using the Elecsys system (Roche Diagnostics, Basel, Switzerland).

Radiographs

Spinal radiographs were obtained routinely at baseline and six months after ROMO administration as well as at unscheduled times if the subject had symptoms suggesting clinical vertebral fracture during follow-up. For subjects with symptoms of incidental nonvertebral fractures, radiographs were assessed by the investigator.

Statistical analysis

Differences between study groups were tested 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 baseline to the specified time points within each study group were compared using the Wilcoxon signed-rank test. Spearman's correlation coefficients were calculated, and multivariate logistic regression analysis with a forward stepwise procedure was performed to identify significant indicators of change in LS or FN BMD. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16]. A P value <0.05 was considered 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; 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' home page.

Results

Table 1 shows patient clinical backgrounds at ROMO induction. Among the groups, no significant difference was observed in baseline age, body mass index, prior vertebral and nonvertebral fracture incidence ratio, combined vitamin D and calcium dose or usage or serum calcium, estimated glomerular filtration rate, and 25(OH)D levels, whereas there was a significant difference in the duration of prior treatment ($P < 0.001$), LS BMD (g/cm^2; $P = 0.04$), FN BMD (g/cm^2; $P = 0.006$), T-score ($P = 0.03$), and serum levels of PINP ($P < 0.001$) and TRACP-5b ($P < 0.001$).

Bone turnover markers

Figure 1 shows the serum PINP level (Fig. 1a) and its percentage change (Fig. 1b) as well as the TRACP-5b value (Fig. 1c) and its percentage change (Fig. 1d).

Regarding PINP value, the Naïve group reached its highest value compared with other groups at one month after ROMO induction, although only the DMAb group remained within the reference range (14.9–68.8 μg/L) at one month and then continuously increased until six months. The tendency in the BP group was similar to that of the Naïve group, although the BP group's value remained in a smaller range. The TPTD group maintained its value at one month, which then markedly decreased at six months. The tendency of percentage change of PINP was similar between the Naïve, BP, and TPTD groups, although only the DMAb group showed a continuous increase during this period.

Regarding TRACP-5b value and percentage change, the Naïve and TPTD groups showed marked decreases from one month to six months. This tendency was similar in the BP group, although its decreasing rate was smaller than that of the other two groups

at six months. On the other hand, the DMAb group demonstrated a continuous increase from one month to six months.

Changes in BMD

Regarding the change in LS BMD (Fig. 2a), the Naïve group had the highest increase (mean ± standard errors; *P*-value compared with baseline; 13.6% ± 1.0%; $P < 0.001$), followed by TPTD (8.7% ± 1.0%; $P < 0.001$), BP (7.5% ± 1.0%; $P < 0.001$), and DMAb (3.6% ± 0.6%; $P < 0.001$). There was a significant difference between the groups ($P < 0.001$).

Regarding the change in TH BMD (Fig. 2b), the Naïve group had the highest increase (4.1% ± 0.8%; $P < 0.001$), followed by TPTD (2.7% ± 1.3%; $P = 0.031$), BP (2.1% ± 0.7%; $P = 0.032$), and DMAb (1.1% ± 0.8%; $P = 0.44$). There was a significant difference between the groups ($P = 0.033$).

Regarding the change in FN BMD (Fig. 2c), the Naïve group had the highest and most significant increase (4.2% ± 1.1%; $P = 0.002$), followed by DMAb (1.6% ± 1.1%; $P = 0.37$), TPTD (1.5% ± 1.4%; $P = 0.24$), and BP (0.4% ± 1.1%; $P = 0.43$). However, there was no significant difference between the groups ($P = 0.16$).

Significant predictor variables of the change in LS or FN BMD

Spearman's correlation coefficient revealed that the significant confounders ($P < 0.05$) of LS BMD change at six months were the PINP value at baseline ($r = 0.60$, $P < 0.001$) and at one month ($r = 0.67$, $P < 0.001$), TRACP-5b value at baseline ($r = 0.57$, $P <$

0.001) and its percentage change at one month (r = −0.55, P < 0.001) and six months (r = −0.57, P < 0.001), and baseline LS BMD T-score (r = −0.20, P = 0.039). Significant confounders of FN BMD change at six months were PINP value at baseline (r = 0.27, P = 0.004) and one month (r = 0.24, P = 0.014), TRACP-5b value at baseline (r = 0.22, P = 0.02) and its percentage change at one month (r = −0.19 P = 0.049) and six months (r = −0.25, P = 0.010), and baseline FN BMD T-score (r = −0.33, P < 0.001).

To investigate the early predictor of BMD response, the above significant confounders (including prior therapy before ROMO [categorized as Naïve (1), TPTD (2), BP (3), and DMAb (4)]; PINP [value of baseline and one month], TRACP-5b [value of baseline and percentage change at one month], and baseline BMD [LS or FN T-score]) were subjected to stepwise multivariable linear regression analysis.

Regarding the LS BMD change, the significant predictor was found to be the difference of prior therapy before ROMO (partial regression coefficient = −3.1, P = 0.0027), percentage change of TRACP-5b at one month (partial regression coefficient = −2.8, P = 0.0071), and value of PINP at one month (partial regression coefficient = 3.2, P = 0.0021). As for FN BMD change, the significant predictor was value of PINP at baseline (partial regression coefficient = 3.1, P = 0.0030).

Incidence of fragility fracture

During this period, a 74-year-old female patient who was switched from BP to ROMO suffered a proximal humerus fracture as a result of a fall. Another 59-year-old female patient who was switched from DMAb after a 9-month interval suffered multiple vertebral fractures [17].

Discussion

To the best of our knowledge, this is the first study to demonstrate the effects of prior treatment and predictors of ROMO in patients with postmenopausal osteoporosis. It has been reported that in addition to the apoptosis of osteoclasts by BP uptake, osteoblasts also uptake BP, and animal studies have demonstrated that BP suppress bone formation by the lining cells (i.e., bone modeling) [17]. Indeed, the BP group showed smaller percent decrease of TRACP-5b compared to the Naïve group. However, although the BP group tended to show smaller absolute value of PINP, percent increase of PINP at one month was similar to the Naïve group.

In a human clinical trial, patients receiving second-line treatment with ROMO after DMAb demonstrated a continuous increase in serum PINP and β-CTX levels, which was associated with a decreased or maintained BMD level at six months, and the BMD increase was relatively small compared with patients with treatment washout [8]. In addition, we have recently reported that a patient who was switched from DMAb to ROMO at nine months had increased bone turnover and multiple vertebral fractures [9]. Taken together, it seems that increased bone turnover from DMAb discontinuation cannot be fully compensated by ROMO in the early period. Regarding TPTD, Lindsay et al. demonstrated that TPTD was able to stimulate not only bone remodeling but also bone modeling [18]. In that report, 70% of bone formation by TPTD was based on remodeling, whereas 20%–30% was modeling-based (modeling was especially dominant within first two months after TPTD induction). In our study, switching from TPTD to ROMO led to a maintained PINP level and a rapidly decreasing TRACP-5b

level at one month. Taken together, prior treatment with TPTD may leave little room for further bone modeling by ROMO (as TPTD promotes bone modeling in relatively early phase), although enhanced bone resorption by TPTD can be suppressed by ROMO (as ROMO promotes osteoprotegerin production from both osteoblasts and osteocytes), which resulted in a significant increase in LS BMD second to the Naïve group.

Another point of interest is the identification of the early predictors of the effects of ROMO. It has been reported that both the increase in bone formation markers and the decrease in bone resorption markers are largest within one month after ROMO induction [2], suggesting that this early bone turnover response might be beneficial in widening the anabolic window and predicting the treatment response. Takada et al. reported that in patients with postmenopausal osteoporosis who were switched from BP to ROMO, 91% of patients showed more than 3% increase in LS BMD at 12 months when PINP increased more than 10 μg/L at 1 month [7]. This result suggests the usefulness of early PINP response in predicting LS BMD increase (PINP was not useful in predicting BMD increase of patients switched from BP to TPTD, suggesting the difference between ROMO and TPTD), although this study included only patients switched from BP and didn't evaluate the correlation with bone resorption markers. From this study's multivariable linear regression analysis results, the significant predictors of an increase in LS BMD at six months were the difference of prior treatment before ROMO, percentage change of TRACP-5b at one month, and value of PINP at one month. The significant predictor of FN BMD change was the value of PINP at baseline. These results indicate that an early treatment response of ROMO may be predicted by (1) difference of prior treatment, (2) bone turnover response at one month, and (3) baseline bone formation status. Concerning sequential treatment, Saag et

al. demonstrated that switching ROMO to alendronate lead to maintained BMD [19], while switching ROMO to DMAb lead to continuous BMD increase [20]. Taken together, preceding ROMO to DMAb may be more hopeful treatment strategy compared to preceding DMAb to ROMO.

There are several limitations to this study. Because of the small number of patients included, the statistical power of the results (especially for the TPTD group) might be attenuated. TPTD was treated for relatively short period (mean 10.7 months) with two regimens (daily and weekly), BP group was heterogeneous (including both oral and intravenous, with different frequency regimens), and relatively short duration of each prior treatment may affect the results. Some patients received a different treatment prior to the entry, although detailed information was unavailable. Because this was not a randomized study, differences in patients' backgrounds may potentially affect the physicians' treatment selection and subsequent effects. Larger randomized studies with longer follow-up periods should be conducted in the future.

In conclusion, in this short-term follow-up study of postmenopausal patients with osteoporosis who were introduced to ROMO, the Naïve group demonstrated the highest treatment response as compared to the other groups, as evaluated by the increase in LS and FN BMD. Prior antiresorptive treatment may attenuate the treatment response, and prior anabolic treatment may have a smaller influence as compared with antiresorptive treatment. These results may contribute to the selection of adequate subsequent treatment by ROMO, although further investigations are required.

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Conflicts of interest

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, and Ono. 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, and AG 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.

Availability of data and material

The dataset used or analyzed in the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Figure legend

Figure 1. 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 ± 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.

Figure 2. Percentage change of 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 ± 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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Table 1. Patients' clinical characteristics at baseline

Variable	Naïve group (n = 37)	BP group (n = 33)	DMAb group (n = 45)	TPTD group (n = 15)	P-value
Age (years)	74.2 ± 6.6	74.4 ± 7.4	76.1 ± 7.7	75.5 ± 6.0	0.64
Body mass index (kg/m^2)	19.1 ± 1.5	18.8 ± 1.7	19.7 ± 1.8	20.0 ± 2.6	0.14
Prior vertebral fracture (%)	48.6	45.5	53.3	60.0	0.79
Prior non-vertebral fracture (%)	24.3	21.2	15.6	26.7	0.67
Prior osteoporosis treatment	None	ALN (weekly p.o. n = 8/monthly i.v. n = 1) RIS (weekly and monthly p.o. n = 15) IBN (monthly p.o. n = 2/monthly i.v. n = 2) MIN (monthly p.o. n = 3) ZOL (yearly i.v. n = 2)	DMAb 60mg (every 6 months)	Daily TPTD 20μg (n = 11) Weekly TPTD 56.5μg (n = 4)	N.A.
Duration of prior treatment (months)	0	28.0 ± 23.9	24.1 ± 15.8	10.7 ± 7.4	<0.001
Interval from final prior treatment prescription (months)	0	2.6 ± 3.5	6.2 ± 1.3	1.4 ± 1.3	<0.001
Combined VD, (n)	None (n = 0) ALF (n = 15) ELD (n = 22)	None (n = 2) ALF (n = 10) ELD (n = 21)	None (n = 0) ALF (n = 18) ELD (n = 27)	None (n = 0) ALF (n = 2) ELD (n = 13)	0.16
Combined VD, μg/day	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.1	0.15
Combined Ca, % (n/N)	83.8 (31/37)	69.7 (23/33)	77.8 (35/45)	93.3 (14/15)	0.28
Combined Ca, mg/day	378.4 ± 304.7	430.3 ± 433.4	613.3 ± 594.5	380.7 ± 308.3	0.15
Lumbar spine BMD (g/cm^2)	0.652 ± 0.089	0.727 ± 0.121	0.705 ± 0.138	0.703 ± 0.109	0.04
Lumbar spine BMD (T-score)	−3.5 ± 0.8	−3.0 ± 0.9	−2.9 ± 1.2	−3.2 ± 0.9	0.09
Total hip BMD (g/cm^2)	0.615 ± 0.074	0.633 ± 0.081	0.573 ± 0.087	0.607 ± 0.095	0.03
Total hip BMD (T-score)	-2.5 ± 0.7	-2.4 ± 0.7	-2.7 ± 0.9	-2.6 ± 0.8	0.36
Femoral neck BMD (g/cm^2)	0.519 ± 0.076	0.568 ± 0.108	0.484 ± 0.087	0.539 ± 0.095	0.006

Femoral neck BMD (T-score)	−3.1 ± 0.6	−2.6 ± 0.7	−3.1 ± 0.8	−2.9 ± 0.9	0.03
Corrected serum Ca (mg/dl)	9.3 ± 0.4	9.5 ± 0.4	9.6 ± 0.6	9.5 ± 0.3	0.08
eGFR (ml/min/1.73 m^2)	70.8 ± 14.5	70.3 ± 18.3	65.1 ± 20.4	74.2 ± 17.6	0.34
PINP (μg/l)	72.7 ± 34.2	33.5 ± 30.1	30.4 ± 30.9	98.4 ± 75.7	<0.001
TRACP-5b (mU/dl)	474.7 ± 214.9	277.3 ± 140.7	220.3 ± 142.9	454.1 ± 200.7	<0.001
25(OH)D (ng/ml)	15.0 ± 4.4	16.1 ± 5.3	15.3 ± 7.0	14.2 ± 5.0	0.69

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

Differences between the groups were determined by ANOVA or the Fisher's exact test.

BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; p.o., oral administration; i.v, intravenous; ALN, alendronate; RIS, risedronate; MIN, minodronate; ZOL, zoledronate; VD, vitamin D; ALF, alfacalcidol; ELD, eldecalcitol; Ca, calcium; 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.

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Figure 1

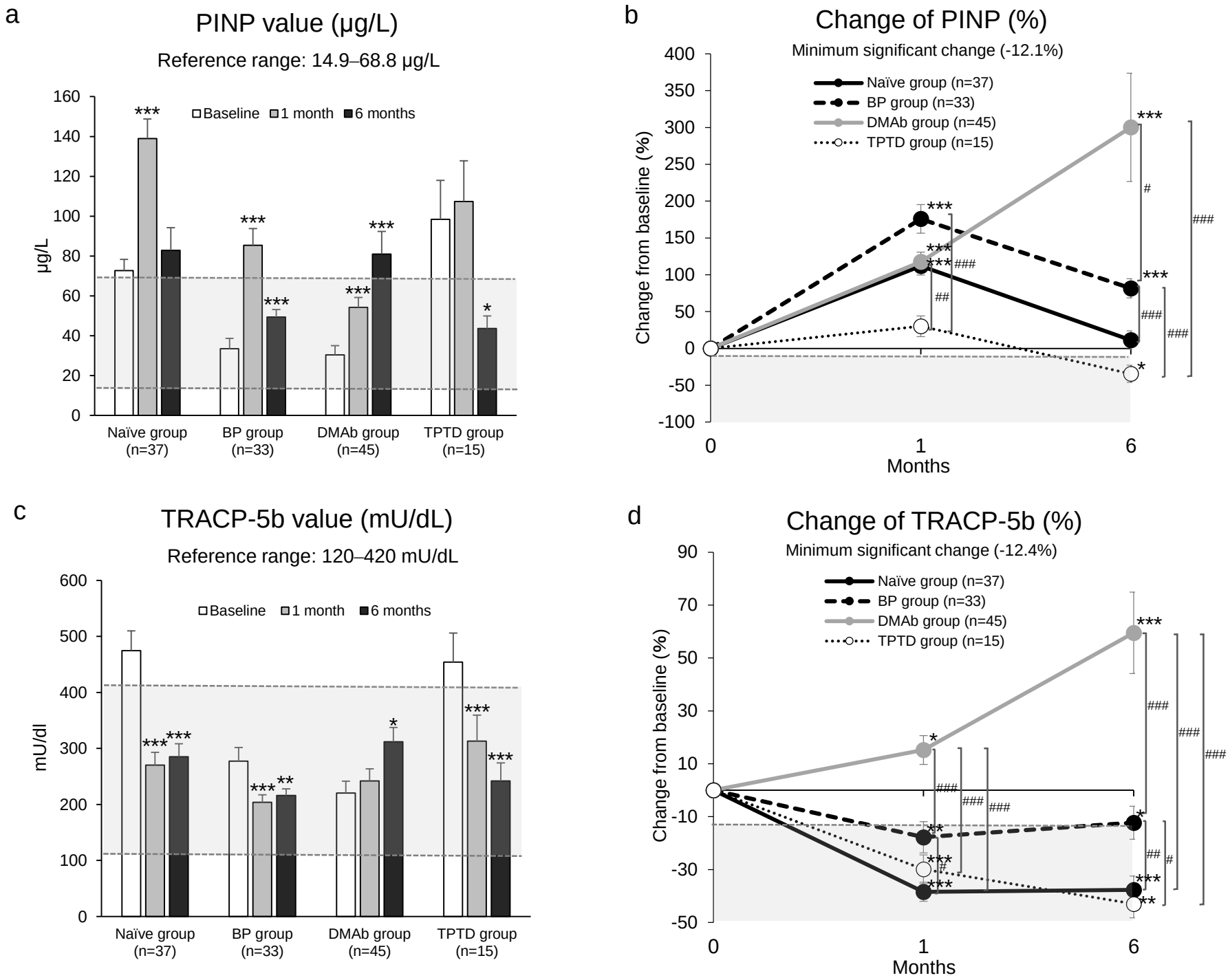
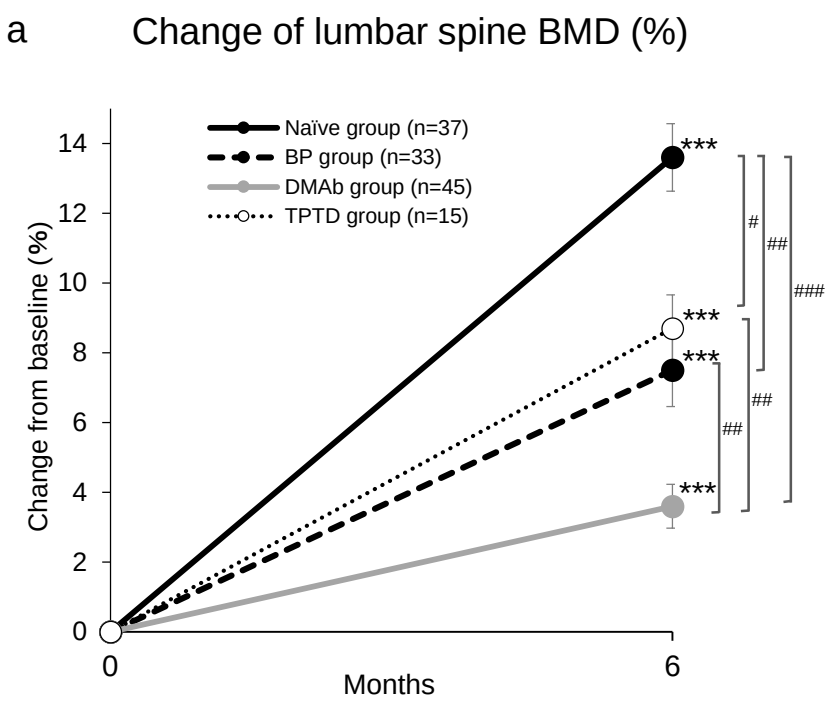

a
PINP value (μg/L)
Reference range: 14.9–68.8 μg/L
μg/L
Baseline
1 month
6 months
Naïve group (n=37)
BP group (n=33)
DMAb group (n=45)
TPTD group (n=15)
b
Change of PINP (%)
Minimum significant change (-12.1%)
Change from baseline (%)
Months
c
TRACP-5b value (mU/dL)
Reference range: 120–420 mU/dL
mU/dl
d
Change of TRACP-5b (%)
Minimum significant change (-12.4%)

Figure 2


a
Change of lumbar spine BMD (%)
Naïve group (n=37)
BP group (n=33)
DMAb group (n=45)
TPTD group (n=15)
Change from baseline (%)
Months
0
6
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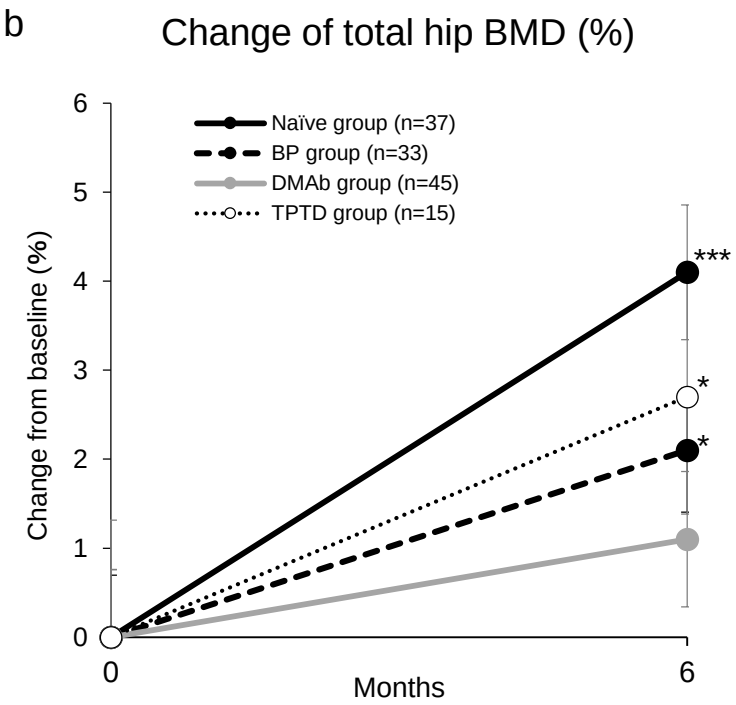
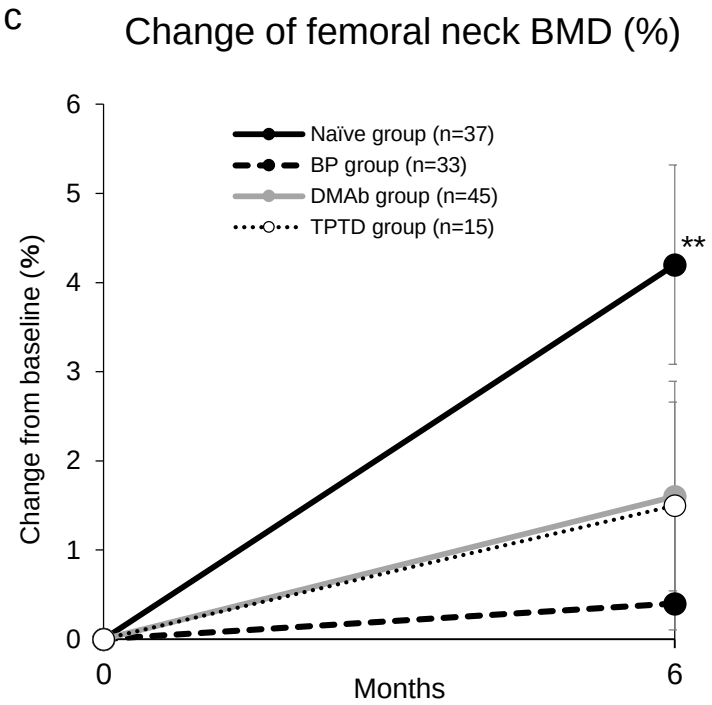

b
Change of total hip BMD (%)
Naïve group (n=37)
BP group (n=33)
DMAb group (n=45)
TPTD group (n=15)
Change from baseline (%)
Months
0
6
***
*
*


c
Change of femoral neck BMD (%)
Naïve group (n=37)
BP group (n=33)
DMAb group (n=45)
TPTD group (n=15)
Change from baseline (%)
Months
0
6
**

Credit Author Statement

Kosuke Ebina: Conceptualization, Data curation, Methodology, Validation, Visualization, Formal analysis, Investigation, Resources, Project administration, Funding acquisition, Writing – Original Draft, Writing – Review & Editing.

Makoto Hirao: Conceptualization, Project administration, Supervision.

Hideki Tsuboi: Data curation, Project administration, Supervision.

Yoshio Nagayama: Data curation, Project administration, Conceptualization.

Masafumi Kashii: Data curation, Conceptualization, Methodology, Writing – Review & Editing.

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