Short Communication

Effects of prior osteoporosis treatment on the treatment response of romosozumab followed by denosumab in patients with postmenopausal osteoporosis

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Abstract

Purpose:

To investigate the effects of prior osteoporosis treatment on the response to treatment with romosozumab (ROMO) followed by denosumab (DMAb) in patients with postmenopausal osteoporosis.

Methods:

In this prospective, observational, multicenter study, treatment naïve patients (Naïve; n = 55) or patients previously treated with bisphosphonates (BP; n = 37), DMAb (DMAb; n = 45), or teriparatide (TPTD; n = 17) (mean age, 74.6 years; T-scores of the lumbar spine [LS] −3.2 and total hip [TH] −2.6) were switched to ROMO for 12 months, followed by DMAb for 12 months. Bone mineral density (BMD) and serum bone turnover markers were evaluated for 24 months.

Results:

BMD increase was observed at 12 and 24 months in the following patients: Naïve (18.2% and 22.0%), BP (10.2% and 12.1%), DMAb (6.6% and 9.7%), and TPTD (10.8% and 15.0%) ($P < 0.001$ between the groups at both 12 and 24 months) in LS and Naïve (5.5% and 8.3%), BP (2.9% and 4.1%), DMAb (0.6% and 2.2%), and TPTD (4.3% and 5.4%) ($P < 0.01$ between the groups at 12 months and $P < 0.001$ at 24 months) in TH, respectively. BMD increase in LS from 12 to 24 months was negatively associated with the levels of bone resorption marker at 24 months. Incidences of major fragility fractures for the respective groups were as follows: Naïve (5.5%), BP (16.2%), DMAb (11.1%), and TPTD (5.9%).

Conclusions:

Previous treatment affected the BMD increase of following treatment with ROMO, although didn't affect that of following treatment with DMAb after ROMO.

Keywords: bone mineral density; bone turnover marker; denosumab; prior treatment; postmenopausal osteoporosis; romosozumab

Mini Abstract

In patients with postmenopausal osteoporosis, prior osteoporosis treatment affected the bone mineral density increase of following treatment with 12 months of romosozumab, although did not affect that of following treatment with 12 months of denosumab after romosozumab.

1. Introduction

For long-term osteoporosis management, sequential treatment starting with a bone-forming agent followed by an antiresorptive agent has been shown to provide better clinical outcomes and enable the rapid reduction of fracture risk in patients with severe osteoporosis and high risk of fractures [1].

Romosozumab (ROMO), a monoclonal anti-sclerostin antibody, is a novel osteoporosis agent, which promotes Wnt signaling by blocking sclerostin [2]. ROMO directly promotes bone formation by osteoblasts and indirectly inhibits bone resorption by osteoclasts by promoting the production of osteoprotegerin (*in vivo* decoy of receptor activator of nuclear factor–kappa B [RANK] ligand [RANKL]) by osteoblasts and osteocytes [3].

Patients who are administered bone-forming agents (such as teriparatide [TPTD] or ROMO) should be given follow-on therapy with an antiresorptive agent to maintain bone mineral density (BMD) because of their reversible effects. It has been reported that treatment with ROMO followed by that with alendronate (ALN) [4] or denosumab (DMAb) [5] further increased BMD, both of which seemed effective.

On the other hand, the effects of prior treatment on bone anabolic agents have been investigated. The prior use of DMAb [6] or bisphosphonates (BP) [7] has been shown to diminish the increase in BMD if follow-on treatment with TPTD is administered. We previously reported that the prior use of DMAb or BP diminished the increase in BMD if follow-on treatment with ROMO is administered [8,9]. However, the effects of prior treatment when ROMO is followed with DMAb are not known. In this study, we aimed to investigate the effects of prior treatment on treatment response in patients with postmenopausal osteoporosis treated with ROMO followed by DMAb for 12 months each.

2. Methods

2.1 Study design and patients

This prospective, observational, nonrandomized study was conducted in six centers. Treatment with ROMO was initiated in patients with high fracture risk according to the definition of the World Health Organization 1998 or the Japanese Guidelines for Prevention and Treatment of Osteoporosis 2011 [10]: patients with 1) BMD T-score < -2.5 and ≥ 1 fragility fracture, 2) lumbar spine (LS) BMD T-score < -3.3, 3) ≥ 2 vertebral fractures, or 4) semiquantitative (SQ) grade 3 vertebral fracture [11]. Patients with diseases affecting bone metabolism, such as thyroid or parathyroid diseases, those undergoing hormone replacement therapy, those with cancer undergoing radiation therapy involving the skeleton, those with

osteomalacia, or those with severely impaired renal function [estimated glomerular filtration rate (eGFR) < 30 (mL/min/1.73 m^2)] were excluded. A total of 154 postmenopausal patients with osteoporosis who were treatment naïve (Naïve; n = 55) or treated previously with BP (n = 37), DMAb (n = 45), or TPTD (n = 17) were switched to 12 months of ROMO. Subsequently, patients were recommended to undergo treatment with DMAb for 12 months to avoid excessive increase in bone turnover markers and obtain continuous BMD increase according to a previous report [5] by each attending physician. The detailed patient flow is presented in the CONSORT flow diagram (Supplementary Fig. 1).

2.2 BMD assessment

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

2.3 Biochemical markers of bone turnover

Bone turnover markers were measured every 6 months relative to the baseline and also 1 month after ROMO induction. Isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b; Nittobo Medical Co. Ltd., Tokyo, Japan) was measured as a bone resorption marker, and total N-terminal type I procollagen propeptide (PINP; Roche Diagnostics, Basel, Switzerland) was used as a bone formation marker (a previous report demonstrated that TRACP-5b is a useful

bone resorption marker with higher clinical sensitivity and signal-to-noise ratio compared with serum cross-linked C-telopeptide of type I collagen [CTX] [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 and every 6 months after ROMO induction. Vertebral fractures of grades ≥ 1 were defined by the SQ method [11]. For patients with symptoms of incidental clinical, vertebral, or nonvertebral fractures, each attending investigator assessed unscheduled radiographs.

2.5 Statistical analysis

The changes in BMD and bone turnover markers were evaluated based on the percentage change from baseline. The differences between study groups were assessed using analysis of variance (between four groups) for continuous variables and 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 Wilcoxon signed-rank test. Multivariate logistic regression analysis was performed to identify the factors significantly associated with the BMD increase from 12 to 24 months. The variables used in the regression analysis were selected by referring to a previous report [15] (age, body mass index, difference in prior treatment before ROMO, bone turnover markers and BMD at baseline and 12 months, and change in bone turnover markers from baseline to 24 months and from 12 to 24 months) that possibly influence the effects of BMD increased by DMAb after treatment with bone-forming agent. All statistical analyses were conducted using EZR

software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16]. *P* values < 0.05 were considered to indicate statistical significance.

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 of the institutes involved. Informed consent was obtained from the patients, and opt-out information was posted on the hospital's homepage.

3. Results

Table 1 presents the clinical background of the patients at the time of ROMO induction. No significant differences were observed among the groups in terms of baseline age, body mass index, prior vertebral and nonvertebral fracture incidence ratio, combined vitamin D and calcium ratio, eGFR, and 25(OH)D levels. Significant differences were observed in the duration of prior treatment ($P < 0.001$), interval from final prior treatment prescription ($P < 0.001$) (ROMO induction was performed 6.2 [on average] months after last DMAb administration in DMAb group patients), LS BMD (g/cm^2; $P = 0.024$), TH BMD (g/cm^2; $P = 0.022$), FN BMD (g/cm^2; $P = 0.002$), T-score ($P = 0.0047$), and serum levels of PINP ($P < 0.001$) and TRACP-5b ($P < 0.001$).

3.1 Bone turnover markers

The serum PINP level (Fig. 1a) and its percentage change (Fig. 1b) as well as TRACP-5b level (Fig. 1c) and its percentage change (Fig. 1d) are shown.

In general, PINP level reached its highest value at 1 month after ROMO induction, followed by a gradual decrease 6 months onwards. The peak response of serum PINP at 1 month was greatest in the Naïve group, followed by the TPTD group, and the BP group. The transition in the BP group was similar to that observed in the Naïve group, although its absolute value remained in a smaller range. Only the DMAb group maintained its high value until 12 months. After DMAb transition, PINP levels of all groups converged to similar levels within the reference range.

Regarding TRACP-5b, the Naïve and TPTD groups showed marked decrease 1 month onwards. This tendency was similar in the BP group, although the rate of decrease in this group was lower than that observed in the Naïve and TPTD groups. The DMAb group showed a gradual increase from 1 to 12 months. After DMAb transition, TRACP-5b levels of all groups converged to similar levels within the reference range.

3.2 Changes in BMD

Regarding the change in LS BMD (Fig. 1e), the increase (mean ± standard error; *P* value compared with baseline) observed at 12 months was highest in the Naïve group (18.2% ± 1.0%; $P < 0.001$), followed by TPTD (10.8% ± 1.3%; $P < 0.001$), BP (10.2% ± 1.1%; $P < 0.001$), and DMAb (6.6% ± 0.7%; $P < 0.001$) groups. BMD at 24 months remained highest in the Naïve group (22.0% ± 1.1%; $P < 0.001$), followed by TPTD (15.0% ± 1.2%; $P < 0.001$), BP (12.1% ± 1.1%; $P < 0.001$), and DMAb (9.7% ± 1.0%; $P < 0.001$) groups ($P < 0.001$ between the groups at both 12 and 24 months). There were no significant differences in the changes in LS BMD from 12 to 24 months between the groups ($P = 0.28$).

Regarding the change in TH BMD (Fig. 1f), the increase observed at 12 months was highest in the Naïve group (5.5% ± 0.9%; $P < 0.001$), followed by TPTD (4.3% ± 1.1%; $P = 0.0012$), BP (2.9% ± 0.5%; $P < 0.001$), and DMAb (0.6% ± 0.9%; $P = 0.83$) groups ($P = 0.0015$ between the groups at 12 months). BMD at 24 months remained highest in the Naïve group (8.3% ± 0.9%; $P < 0.001$), followed by TPTD (5.4% ± 1.0%; $P < 0.001$), BP (4.1% ± 0.6%; $P < 0.001$), and DMAb (2.2% ± 0.8%; $P = 0.024$) groups ($P < 0.001$ between the groups at 24 months). There were no significant differences in the changes in TH BMD from 12 to 24 months between the groups ($P = 0.11$).

Regarding the change in FN BMD (data not shown), the increase at 12 months was highest in the Naïve group (5.1% ± 1.0%; $P < 0.001$), followed by TPTD (3.4% ± 1.1%; $P = 0.017$), BP (3.0% ± 0.7%; $P = 0.0028$), and DMAb (0.7% ± 0.8%; $P = 0.16$) groups ($P = 0.028$ between the groups at 12 months). BMD at 24 months remained highest in the Naïve group (7.4% ± 1.0%; $P < 0.001$), followed by TPTD (5.6% ± 1.9%; $P = 0.016$), BP (3.8% ± 1.0%; $P = 0.0053$), and DMAb (2.9% ± 0.9%; $P = 0.0071$) groups ($P = 0.054$ between the groups at 24 months). There were no significant differences in the changes in FN BMD from 12 to 24 months between the groups ($P = 0.36$).

Multivariate logistic regression analysis showed that the significant factors indicating LS BMD increase from 12 to 24 months were the absolute level of TRACP-5b at 24 months ($P = 0.029$) and the percentage change in TRACP-5b from baseline to 24 months ($P = 0.012$) (Supplementary Table 1). TH BMD increase from 12 to 24 months was significantly associated with the absolute level of TRACP-5b at 12 months ($P = 0.027$) (data not shown).

3.3 Incidence of fragility fractures

Fifteen patients (n = 15/154; 9.7%) suffered major fragility fractures (including fractures of the spine, femur, tibia, patella, humerus, forearm, and rib) during the observation period. In the Naïve group, two vertebral fractures and one distal humerus fracture were observed (n = 3/55; 5.5%). In the BP group, one fracture each was observed for the proximal humerus, distal radius, proximal tibia, and patella in addition to two vertebral fractures (n = 6/37; 16.2%). In the DMAb group, one fracture each was observed for the femoral neck, proximal humerus, and rib in addition to multiple vertebral fractures (n = 5/45; 11.1%). In the TPTD group, one vertebral fracture was observed (n = 1/17; 5.9%).

3.4 Incidence of treatment discontinuation

During the observation period, 23 patients (14.9%) discontinued the treatment. Eight patients were lost to follow-up, including change of hospitals. Two patients each discontinued the treatment because of injection pain, dizziness, blood pressure elevation, and death due to unknown reasons. One patient each discontinued the treatment due to subarachnoid hemorrhage attributed to previously indicated aneurysm rupture (Naïve group; 3 weeks after first ROMO administration), cerebral hemorrhage (DMAb group; without history of cerebral or cardiovascular diseases; 7 months after switching from ROMO to DMAb), decreased blood pressure, facial flush, herpes zoster, oral lichen planus, and surgery for valvular disease.

4. Discussion

To the best of our knowledge, this is the first study that demonstrates the effects of prior osteoporosis treatment on response to treatment with ROMO followed by DMAb in patients with postmenopausal osteoporosis.

With respect to follow-on treatment after ROMO, a previous study showed that in patients with postmenopausal osteoporosis who were not previously treated for osteoporosis, switching from ROMO to ALN (70 mg orally every week) resulted in a BMD increase of 15.2% in LS and 7.1% in TH at 24 months compared with baseline (12 months after ALN transition) [4]. The FRAME extension study demonstrated that switching from ROMO to DMAb increased BMD by 16.6% in LS and 8.5% in TH among patients world-wide [5] and 21.5% in LS and 7.9% in TH among Japanese patients [17] at 24 months compared with baseline (12 months after DMAb transition). Taken together, in Japanese patients, sequential treatment with ROMO and then DMAb may be similar to or even more promising and effective than switching to ALN. Indeed, the Naïve group exhibited a BMD increase of 22.0% in LS and 8.3% in TH at 24 months in the present study, which is comparable to a previous Japanese study [17].

On the other hand, although there were marked differences in bone turnover levels at 12 months between the groups, they all converged to similar levels after the DMAb transition. We previously reported that in patients who were transitioned from TPTD to DMAb or BP, the subsequent BMD increase was significantly associated with the rates of decrease of PINP and TRACP-5b [18]. Indeed, in the present study, the increase in LS BMD from 12 to 24 months due to DMAb was significantly associated with the absolute level of TRACP-5b at 24 months and the percentage change in TRACP-5b from baseline to 24 months. These data suggest that the BMD increase observed by treatment with an anti-bone-resorptive agent after a bone-forming agent treatment may depend on the degree of final bone turnover inhibition. Consequently, the increased rate of BMD after transition to DMAb was similar between the groups, although the differences in response to ROMO that we observed between treatment-naïve and previously treated patients persisted during the subsequent 12 months of DMAb therapy.

This study has several limitations. The statistical power of the results might be weakened because of the small number of patients included. In line with the purpose of the study, this was not a randomized study, and there may be some selection bias and differences in the baseline patient backgrounds (particularly in BMD and bone turnover marker levels) between the groups, which may have affected the results. The contents of prior treatment were not uniform within the BP and TPTD groups. We evaluated serum TRACP-5b as a bone resorption marker, but serum CTX data were not available. Most patients had vitamin D deficiency [serum 25(OH)D < 20 ng/ml] at baseline, which may have affected the results even though combined with active vitamin D3. The fracture incidence rates tended to be lower in the Naïve (5.5%) and TPTD (5.9%) groups than in the BP (16.2%) and DMAb (11.1%) groups, but these results should be confirmed in a larger cohort. However, the significance of this study is that it is the first study to demonstrate the effects of prior treatment on the response to sequential treatment with ROMO followed by DMAb in a real-world setting.

In conclusion, the effects of treatment with ROMO for 12 months and follow-on treatment with DMAb for 12 months on BMD increase were significantly affected by prior osteoporosis treatment. However, the corresponding BMD increase after switching from ROMO to DMAb was similar. The insights gained from this study may facilitate the development of a more effective treatment regimen wherein ROMO is followed by DMAb.

Statements and Declarations

Authors' roles

Study design: KE, YE, HT, and MK. Study conduct: KE, YE, MH, and MK. Data collection: KE, HT, YN, MK, AM, YK, GO, and TN. Data analysis: KE and YE. Data interpretation:

KE, YE, MK, MH, KT, AG, TM, YF, and TK. Drafting the manuscript: KE and YE. Supervise: SO and KN. Approving the final version of the manuscript: KE, YE, HT, YN, MK, AM, YK, MH, GO, TN, KT, AG, TM, YF, TK, SO, and KN. KE takes responsibility for the integrity of the data analysis.

Conflict 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 Amgen, Asahi-Kasei, Astellas, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, and Ono. KE has received payments for lectures from Amgen, 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. YE, AM, YK, GO, TN, KT, AG, TM, YF, TK, 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 manuscript preparation.

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.

Figure legends

Fig. 1 Serum PINP level (a) and its percentage change (b); serum TRACP-5b level (c) and its percentage change (d); percentage change in BMD in the lumbar spine (e) and total hip (f)

PINP, N-terminal type I procollagen propeptide; TRACP-5b, isoform 5b of tartrate-resistant acid phosphatase; ROMO, romosozumab; BP, bisphosphonate; DMAb, denosumab; TPTD, teriparatide; BMD, bone mineral density; LS, lumbar spine; TH, total hip.

Bars indicate mean ± standard error. **P* < 0.05, ***P* < 0.01, ****P* < 0.001; change within each treatment group compared with baseline.

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Table 1. Clinical characteristics of the patients at baseline

Variable	Naïve group (n = 55)	BP group (n = 37)	DMAb group (n = 45)	TPTD group (n = 17)	*P* value
Age (years)	73.2 ± 7.8	74.7 ± 7.1	76.1 ± 7.7	75.1 ± 6.7	0.29
Body mass index (kg/m^2)	20.6 ± 2.9	20.5 ± 3.7	20.2 ± 2.7	19.5 ± 2.4	0.60
Prior vertebral fracture (%)	41.8	43.2	53.3	58.8	0.49
Prior nonvertebral fracture (%)	25.5	18.9	15.6	23.5	0.65
Prior osteoporosis treatment	None	ALN (weekly p.o. n = 10/monthly i.v. n = 1) RIS (weekly and monthly p.o. n = 17) IBN (monthly p.o. n = 2/ monthly i.v. n = 2) MIN (monthly p.o. n = 3) ZOL (yearly i.v. n = 2)	DMAb 60 mg (every 6 months s.c. n = 45)	Daily TPTD 20μg (s.c. n = 13) Weekly TPTD 56.5 μg (s.c. n = 4)	N.A.
Duration of prior treatment (months)	0	28.1 ± 23.3	24.1 ± 15.8	12.0 ± 7.9	<0.001
Interval from final prior treatment prescription (months)	0	3.6 ± 5.3	6.2 ± 1.3	1.7 ± 1.0	<0.001
Combined VD, % (n/N)	94.5 (52/55) ALF (n = 18) ELD (n = 34)	94.6 (35/37) ALF (n = 13) ELD (n = 22)	100.0 (45/45) ALF (n = 18) ELD (n = 27)	94.2 (16/17) ALF (n = 2) ELD (n = 14)	0.24
Combined ALF, μg/day	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.39

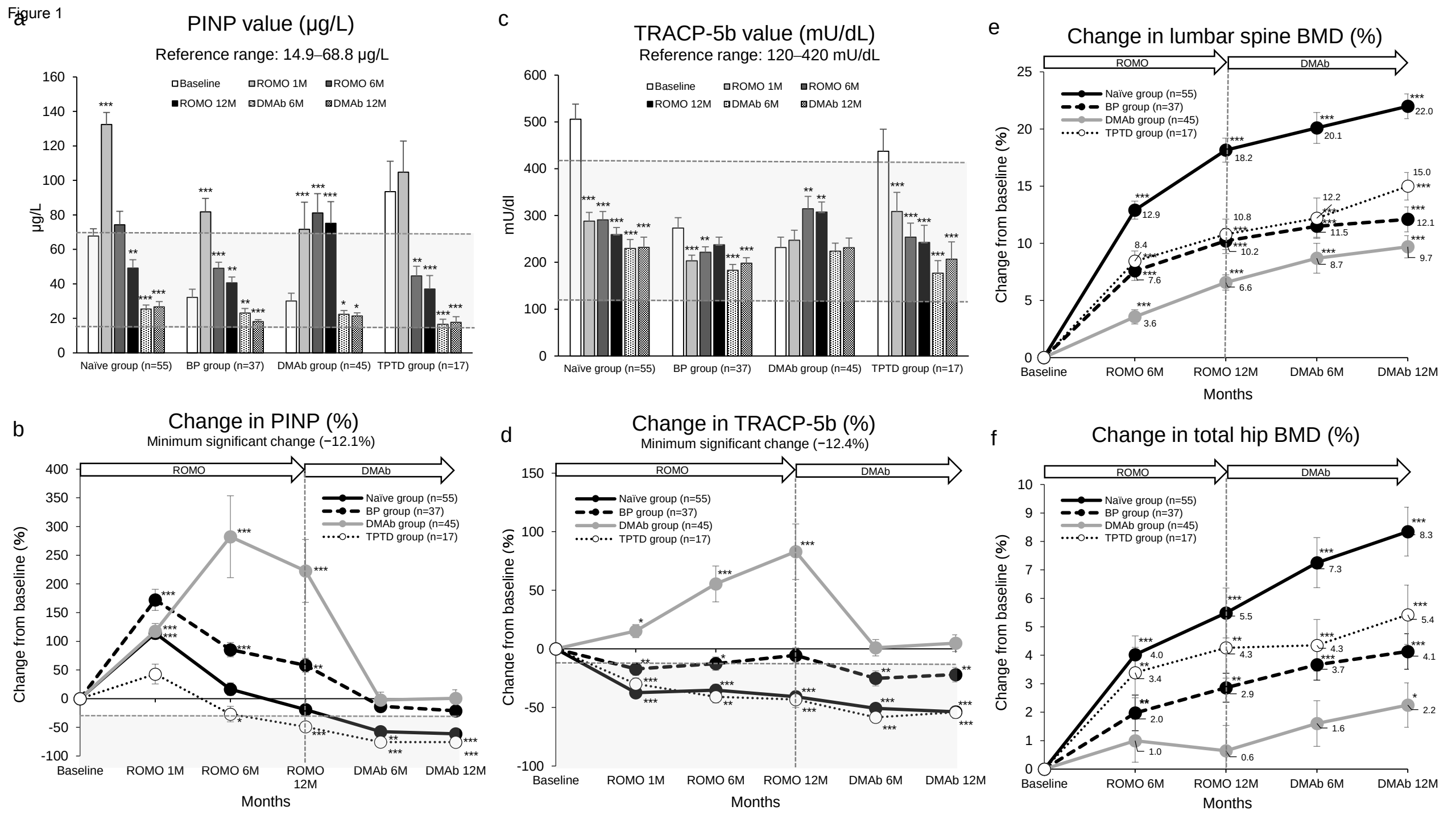
Combined ELD, μg/day	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.42
Combined Ca, % (n/N)	78.2 (43/55)	62.2 (23/37)	77.8 (35/45)	88.2 (15/17)	0.17
Combined Ca, mg/day	438.1 ± 238.9	617.4 ± 390.4	788.6 ± 561.4	407.3 ± 289.7	<0.001
Lumbar spine BMD (g/cm^2)	0.648 ± 0.128	0.732 ± 0.116	0.702 ± 0.141	0.682 ± 0.123	0.024
Lumbar spine BMD (T-score)	−3.4 ± 1.0	−2.9 ± 0.9	−3.0 ± 1.3	−3.3 ± 1.0	0.087
Total hip BMD (g/cm^2)	0.603 ± 0.079	0.635 ± 0.082	0.573 ± 0.087	0.617 ± 0.094	0.022
Total hip BMD (T-score)	−2.7 ± 0.7	−2.4 ± 0.7	−2.7 ± 0.9	−2.6 ± 0.8	0.12
Femoral neck BMD (g/cm^2)	0.512 ± 0.087	0.572 ± 0.109	0.484 ± 0.087	0.546 ± 0.093	0.002
Femoral neck BMD (T-score)	−3.3 ± 0.7	−2.7 ± 0.8	−3.1 ± 0.8	−2.9 ± 0.8	0.0047
Corrected serum Ca (mg/dl)	9.3 ± 0.4	9.5 ± 0.4	9.5 ± 0.5	9.5 ± 0.3	0.033
eGFR (ml/min/1.73 m^2)	70.9 ± 15.7	71.7 ± 17.9	65.1 ± 20.4	72.5 ± 17.6	0.35
PINP (μg/l)	67.7 ± 31.3	32.2 ± 28.8	30.4 ± 30.9	93.5 ± 72.7	<0.001
TRACP-5b (mU/dl)	505.9 ± 238.2	273.4 ± 133.6	220.3 ± 142.9	437.4 ± 193.8	<0.001
25(OH)D (ng/ml)	14.9 ± 4.6	16.3 ± 5.3	15.4 ± 7.0	14.2 ± 4.7	0.50

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

Differences between the groups were determined by analysis of variance or Fisher's exact tests.

N.A., not applicable; BP, bisphosphonates; DMAb, denosumab; TPTD, teriparatide; p.o., oral administration; i.v., intravenous; s.c., subcutaneous injection; 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.

Figure 1


a
PINP value (μg/L)
Reference range: 14.9–68.8 μg/L
Baseline
ROMO 1M
ROMO 6M
ROMO 12M
DMAb 6M
DMAb 12M
μg/L
Naïve group (n=55)
BP group (n=37)
DMAb group (n=45)
TPTD group (n=17)
c
TRACP-5b value (mU/dL)
Reference range: 120–420 mU/dL
mU/dl
e
Change in lumbar spine BMD (%)
ROMO
DMAb
Change from baseline (%)
Months
b
Change in PINP (%)
Minimum significant change (−12.1%)
d
Change in TRACP-5b (%)
Minimum significant change (−12.4%)
f
Change in total hip BMD (%)

Supplementary Table 1

Journal: Osteoporosis International

Title: Effects of prior osteoporosis treatment on the treatment response of romosozumab followed by denosumab in patients with postmenopausal osteoporosis

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Supplementary Table 1. Univariate and multivariate logistic regression analysis of the factors associated with the increase in lumbar spine bone mineral density after switching from 12-month romosozumab to 12-month denosumab

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (years)	−0.05 (−0.19, 0.08)	0.44	0.06 (−0.12, 0.25)	0.49
Body mass index (kg/m^2)	0.04 (−0.27, 0.35)	0.78	−0.01 (−0.38, 0.36)	0.98
Prior treatment (Naïve = 1, TPTD = 2, BP = 3, DMAb = 4)	0.36 (−0.38, 1.11)	0.97	0.63 (−0.93, 2.19)	0.42
PINP (at baseline)	0.003 (−0.02, 0.02)	0.73	0.01 (−0.02, 0.05)	0.42
TRACP-5b (at baseline)	−0.004 (−0.008, 0.0003)	0.07	0.01 (−0.004, 0.02)	0.23
PINP (at 12 months)	0.0002 (−0.02, 0.02)	0.98	0.03 (−0.09, 0.15)	0.63
TRACP-5b (at 12 months)	−0.005 (−0.01, 0.001)	0.12	0.01 (−0.02, 0.04)	0.47
PINP (at 24 months)	−0.11 (−0.17, −0.05)	<0.001	−0.07 (−0.35, 0.21)	0.63
TRACP-5b (at 24 months)	−0.01 (−0.02, −0.004)	0.002	−0.03 (−0.06, −0.004)	0.029
Change in PINP from baseline to 24 months (%)	−0.02 (−0.04, −0.007)	0.003	−0.05 (−0.10, 0.0003)	0.051
Change in TRACP-5b from baseline to 24 months (%)	−0.0004 (−0.02, 0.02)	0.97	−0.08 (−0.14, −0.02)	0.012

Change in PINP from 12 to 24 months (%)	−0.03 (−0.05, −0.009)	0.006	0.06 (−0.05, 0.17)	0.30
Change in TRACP-5b from 12 to 24 months (%)	−0.02 (−0.04, −0.002)	0.03	0.007 (−0.07, 0.08)	0.84
Lumbar spine BMD (T-score; at baseline)	0.15 (−0.73, 1.03)	0.74	0.41 (−3.21, 4.04)	0.82
Lumbar spine BMD (T-score; at 12 months)	−0.17 (−1.04, 0.69)	0.69	−0.60 (−4.11, 2.92)	0.73

OR = odds ratio CI = confidence interval.

TPTD, teriparatide; BP, bisphosphonates; DMAb, denosumab; PINP, type I collagen N-terminal propeptide; TRAP-5b, isoform 5b of tartrate-resistant acid phosphatase; BMD, bone mineral density.

Supplementary Figure 1

Journal: Osteoporosis International

Title:

Effects of prior osteoporosis treatment on the treatment response of romosozumab followed by denosumab in patients with postmenopausal osteoporosis

Authors:

Kosuke Ebina, MD, PhD*, Yuki Etani, MD, PhD, Hideki Tsuboi, MD, PhD, Yoshio Nagayama, MD, Masafumi Kashii, MD, PhD, Akira Miyama, MD, PhD, Yasuo Kunugiza, MD, PhD, Makoto Hirao, MD, PhD, Gensuke Okamura, MD, PhD, Takaaki Noguchi, MD, PhD, Kenji Takami, MD, Atsushi Goshima, MD, Taihei Miura, MD, Yuji Fukuda, MD, Takuya Kurihara, MD, Seiji Okada, MD, PhD, and Ken Nakata, MD, PhD

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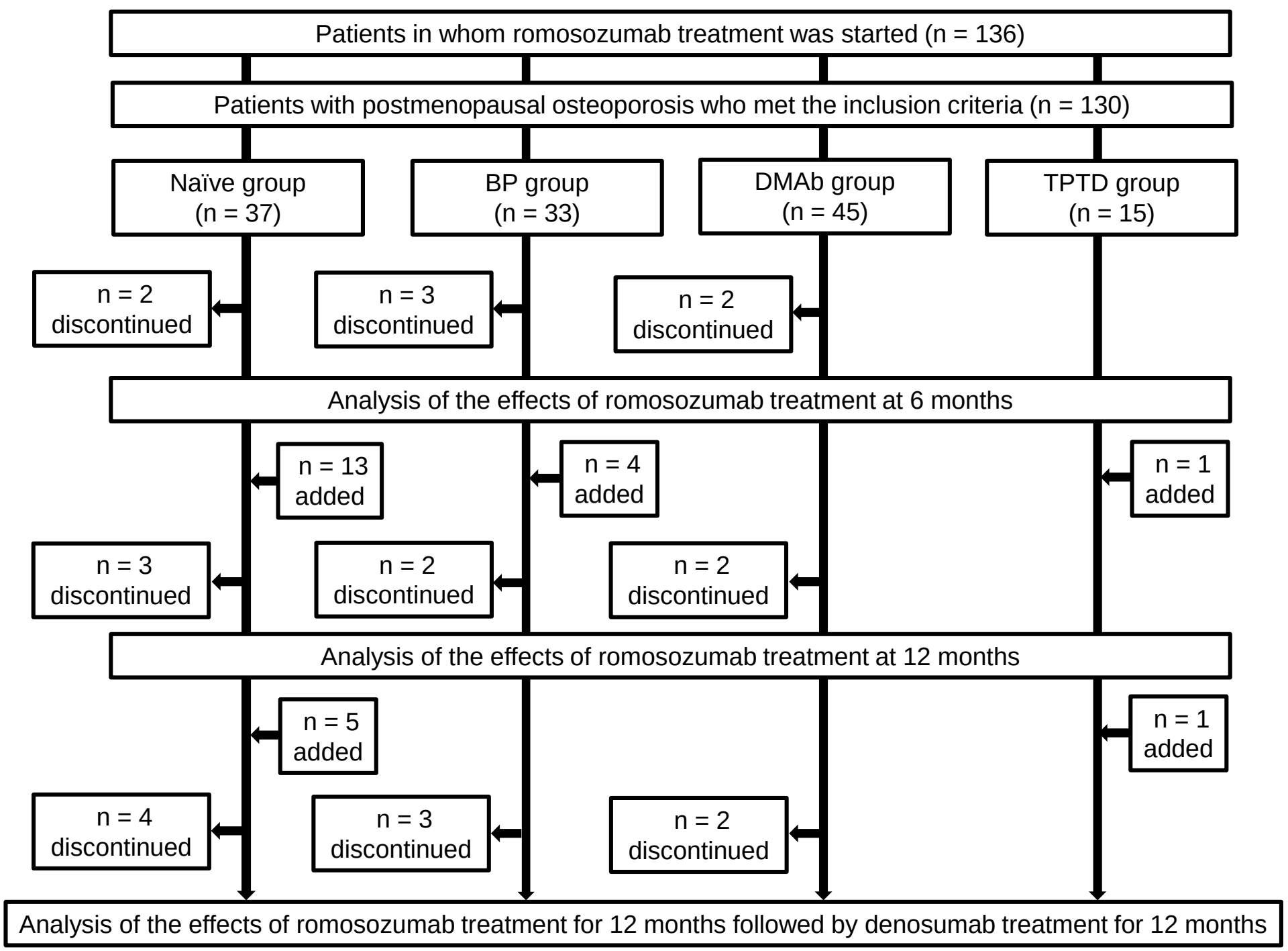
Patients in whom romosozumab treatment was started (n = 136)
Patients with postmenopausal osteoporosis who met the inclusion criteria (n = 130)
Naïve group (n = 37)
BP group (n = 33)
DMAb group (n = 45)
TPTD group (n = 15)
n = 2 discontinued
n = 3 discontinued
n = 2 discontinued
Analysis of the effects of romosozumab treatment at 6 months
n = 13 added
n = 4 added
n = 1 added
n = 3 discontinued
n = 2 discontinued
n = 2 discontinued
Analysis of the effects of romosozumab treatment at 12 months
n = 5 added
n = 1 added
n = 4 discontinued
n = 3 discontinued
n = 2 discontinued
Analysis of the effects of romosozumab treatment for 12 months followed by denosumab treatment for 12 months