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ORIGINAL ARTICLE

Early clinical effects, safety, and predictors of the effects of romosozumab treatment in osteoporosis patients: one-year study

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Abstract

Summary Romosozumab is an effective treatment for spine osteoporosis because it reduces the incidence of new fractures and significantly increases the percent change in the spine BMD at 12 months. The percent change in the spine BMD is higher in patients not previously treated with other anti-osteoporosis medications.

Introduction Romosozumab appeared as a new osteoporosis medication in Japan in 2019. It is an anti-sclerostin antibody, which increases bone formation and suppresses bone resorption. The aim of our study was to elucidate the clinical effects, safety, and predictors of the effects of one-year romosozumab treatment.

Methods This study was an observational study designed as a pre–post study in 262 patients. Romosozumab (210 mg) was administered subcutaneously once every 4 weeks during 12 months. We focused on incidence of new fractures, safety, bone mineral density (BMD) at the spine and total hip, and bone metabolism markers.

Results There were five cases of new fractures during one-year romosozumab treatment. There were no fatal adverse events. Percent changes from baseline in the spine and total hip BMD after 12 months of romosozumab treatment were 10.67% and 2.04%, respectively. Romosozumab had better effects in cases of severe osteoporosis with low spine BMD, high TRACP-5b, and high iP1NP at the start of romosozumab treatment. The percent change in the spine BMD at 12 months was significantly lower in the group transitioning from bisphosphonates than in the group not previously treated with other anti-osteoporosis medications.

Conclusion Romosozumab is an effective treatment for spine osteoporosis because it significantly increases the percent change in the spine BMD at 12 months. The percent change in the spine BMD is higher in patients not previously treated with other anti-osteoporosis medications.

Keywords Osteoporosis · Romosozumab · Anti-sclerostin antibody · BMD · Bone metabolism markers · Anti-osteoporosis drug

Introduction

The number of osteoporosis patients is increasing in developed countries due to population aging [1]. According to Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study, there were 6.4 million patients with lumbar spine osteoporosis and 17.3 million patients with hip osteoporosis in Japan in 2005 [1, 2]. New therapeutic agents for osteoporosis have recently appeared. Since introduction of romosozumab in Japan in 2019, there have been several papers on clinical use of romosozumab [3, 4]. Romosozumab is a humanized antibody against sclerostin. Sclerostin, a glycoprotein secreted by bone cells, inhibits the classical Wnt/β-catenin signaling to suppress bone formation [5]. Although Wnt/β-catenin signaling pathway is a systemically distributed pathway, sclerostin is specifically expressed in osteocytes. Romosozumab increases bone formation, but also suppresses bone resorption [6]. Such uncoupling phenomenon leads to an increase in bone density of the spine and hip and prevents new fractures [7–9]. This pathway is a specific pathway for bone metabolism [5]. Previous articles reported that romosozumab caused a significant increase in bone density compared with placebo, and some articles highlighted its effect on decreased incidence of new vertebral and femoral fractures compared with placebo [10]. It has been recently reported that anti-osteoporosis drugs used before the start of romosozumab

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treatment affected the therapeutic effect of romosozumab [3, 4]. However, there were some concerns about an increased incidence of cardiovascular and cerebrovascular events with romosozumab compared with alendronate preparations [11]. Previous studies [4] reported the rate of increase in bone mineral density (BMD) and the kinetics of bone metabolism markers during the first 6 months of romosozumab treatment, but the effects of 12 months of treatment with romosozumab have not yet been reported. The aim of the study was to further understand the effects of one-year romosozumab treatment by investigating its actual clinical effects, adverse effects, and factors influencing the effects of romosozumab treatment. Particular attention was paid to percent change in BMD from baseline as well as to the kinetics of bone metabolism markers during one-year treatment. We also aimed to elucidate the influence of anti-osteoporosis pretreatment on the effects of 12 months of romosozumab treatment.

Material and methods

This study was an observational study and included patients who were treated for osteoporosis at our hospital between March 2019 and August 2020. Patients who had either low spine BMD (BMD before starting romosozumab treatment ≤−2.5 standard deviations) or previous multiple fragility bone fractures were included in the study. The exclusion criteria encompassed presence of cardiovascular disease (CVD) and cerebrovascular disease (CeVD) events in the year before starting romosozumab treatment. Romosozumab (210 mg) was administered with a subcutaneous injection once every 4 weeks during 12 months. The study was designed as pre–post comparison of the study endpoints. We investigated the incidence of new fractures, safety, and side effects as primary endpoints. Furthermore, as secondary endpoints, we evaluated the changes in BMD and bone metabolism markers, and evaluated factors predicting or influencing the effects of romosozumab. All procedures 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. The study was approved by our institute Ethics Committee, number 5596. Informed consent was obtained from all participants included in the study.

Total number of included patients was 262 (35 men and 227 women). The patients' age ranged between 35 and 95 years (mean age 77.06 ± 9.31 years) (Table 1). Among the included patients, 201 patients (76.72%) had primary osteoporosis, whereas 61 patients (23.28%) had secondary osteoporosis due to glucocorticoids, diabetes mellitus, chronic renal failure, end stage renal failure, rheumatoid arthritis, cirrhosis, or multiple myeloma. The average BMD before starting treatment was 0.77 g/cm^2 (±0.011 g/cm^2) at the spine and 0.62 g/cm^2 (±0.007 g/cm^2) at the hip. More than 90% of the patients experienced fragility fractures before starting romosozumab. Among them, 188 patients (71.76%) had vertebral fractures (VFs). Mean number of VFs per individual was 1.65 ± 0.10. There were 33 cases of new fractures within 3 months before the start of romosozumab treatment. Fourteen patients received active vitamin D preparations during romosozumab treatment.

Table 1 Baseline characteristics. *SE*, standard error; *n*, number

Variable	Mean (SE), *n* (%)
Age (years)	77.06±9.31
Gender, *n* (%)	
Males	35 (13.36%)
Females	227 (86.64%)
Primary or secondary osteoporosis, *n* (%)	
Primary osteoporosis	201 (76.72%)
Secondary osteoporosis	61 (23.28%)
Pretreatment (some had multiple treatment), *n*	
Without pretreatment	115
Teriparatide	68
Denosumab	49
Bisphosphonates	79
Previous osteoporotic fracture n (%)	
Total osteoporotic fracture	249 (95.04%)
Vertebral body	188 (71.76%)
BMD	
Lumbar spine (L1-4) (g/cm^2)	0.77±0.011
Total hip (g/cm^2)	0.62±0.007

The presence of adverse effects was recorded from the interview every time before the injection was administered, and it was verified using Naranjo algorithm [12]. We performed dual-energy X-ray absorptiometry (DXA) to determine areal BMD at the spine (L1–L4 total) and total hip before romosozumab treatment (0 month), after 6 months (spine *n*=158; total hip *n*=153), and after 12 months (spine *n*=127; total hip *n*=116). We also screened for new vertebral fracture during the treatment by using X-ray before and after one-year romosozumab treatment, or when symptoms appeared. Bone densitometry equipment used in this study included Lunar iDXA (GE Healthcare, Chicago, USA) and Discovery (HOLOGIC, Marlborough, USA). Each patient always underwent bone densitometry using the same device. Serum analysis was performed before romosozumab treatment (0 month), as well as after 1, 3, 6, 9, and 12 months. Specifically, we measured the following parameters in the blood: corrected calcium level (Ca level), phosphate concentration (serum P level), total alkaline phosphatase (tALP), creatinine, serum cross-linked N-telopeptide of type 1 collagen (sNTX) and tartrate-resistant acid phosphatase 5b (TRACP-5b) as bone resorption markers [13, 14], and intact type I procollagen N-terminal propeptide (iP1NP) and bone alkaline

phosphatase (BAP) as bone formation markers [15, 16]. In addition, we measured intact parathyroid hormone (iPTH).

There were 115 patients without previous treatment (NON group), whereas the remaining patients had received previous anti-osteoporosis medication (teriparatide 68 patients; denosumab 49 patients; bisphosphonates 79 patients; some patients had multiple treatments). No wash-out term was set. The pretreatment groups were based on the most recent anti-osteoporosis pretreatment before starting romosozumab, and they included the following four groups: no pretreatment group (NON, n=115), change from teriparatide (TPD, n=47), change from denosumab (DMAB, n=46), and change from oral bisphosphonates (BIS, n=54). We investigated whether previous treatment affected the results of the current romosozumab treatment. In these groups, we evaluated percent change from baseline in spine and total hip BMD and bone metabolism markers (TRACP-5b and iP1NP).

The least significant (LSC) and the minimum significant change (MSC)

LSC of percent change from baseline is 2.77% and 4.16% for the spine and total hip BMD, respectively [17]. MSC of percent change from baseline of bone metabolism markers are as follows: 16.3% for sNTX, 12.4% for TRACP-5b, 12.1% for iP1NP, and 9% for BAP [18].

Statistical analysis

We performed statistical analysis using the GraphPad Prism 8 (GraphPad software, San Diego, USA). Outliers were identified by Smirnov–Grubbs test. Paired t test was used for pre–post comparisons of normally distributed data. Pearson correlation analysis and one-way analysis of variance (one-way ANOVA) with post hoc tests (Tukey test) were also performed. The cut-off value was calculated from the receiver operating characteristic curve (ROC) analysis. Estimation of the required sample size was based on the BMD at the spine; specifically, when the standard deviation was 0.07 and the effective value was 0.028 as LSC [17], the number of patients required was 103. The p-value of 0.05 or lower was considered statistically significant.

Results

Primary endpoint: Incidence of new fractures, compliance, safety, and adverse events during one-year romosozumab treatment

There were five cases of new fractures during administration of romosozumab (Table 2). Of these, three cases had VFs. The incidence rate of new fractures was 1.91%. None of the patients in this study showed symptoms of suspected CVD or CeVD. There were no romosozumab-related deaths. One case (0.38%) died, but he suffered from severe chronic obstructive pulmonary disease (COPD) and died of acute pneumonia. The Naranjo algorithm showed that his death was doubtful as an adverse drug reaction to romosozumab, which allowed us to consider it a non-romosozumab-related matter. In addition, there were no cases of atypical fracture or jaw bone necrosis during treatment with romosozumab. There were 59 cases (22.52%) in which treatment was unavoidably discontinued (see Table 2). The most distinctive feature was the interruption caused by COVID-19 (eight cases, 3.05%). Another noteworthy reason for the interruptions was the extension of prothrombin time-international normalized ratio (PT-INR) in patients using warfarin (two cases, 0.76%).

Secondary endpoint: Effects of romosozumab treatment on BMD at the spine and total hip

From baseline, the spine BMD increased by 6.38% ± 0.5% and 10.67% ±0.8% after six (n=158) and 12 months (n=127) of romosozumab therapy, respectively (Fig. 1a). Considering that the LSC of percent change from baseline in the spine BMD is 2.77% [17], the spine BMD showed significant changes beyond LSC both at 6 and 12 months of romosozumab therapy. On the other hand, the average percent change from baseline in the total hip BMD was 1.01 ± 0.5% and 2.04 ± 0.6% at six (n=153) and 12 months (n=116) of romosozumab therapy, respectively. Considering that the LSC

Table 2 Incidence of new fractures, compliance, safety, and adverse events. *CVD*, cardiovascular disease; *CeVD*, cerebrovascular disease; *PT-INR*, prothrombin time-international normalized ratio

Variable	*n* (%)
New fractures	5 (1.91)
Event	
Dead	1 (0.38)
CVD and CeVD symptoms	0 (0)
Atypical femoral fractures	0 (0)
Jaw osteonecrosis	0 (0)
Withdrawal due to complications n(%)	59 (22.52)
Due to COVID-19	8 (3.05)
Fever	3 (1.15)
Injection site pain	2 (0.76)
Hospitalization at another hospital	2 (0.76)
Extansion of PT-INR	2 (0.76)
Liver enzyme elevation	1 (0.38)
Pancreatic enzyme elevation	1 (0.38)
Vomiting	1 (0.38)
Dental treatment	1 (0.38)
Self-interruption of unknown cause	38 (14.5)

of the total hip BMD was 4.16% [17], neither six- nor 12-month treatment showed therapeutic effect higher than LSC.

We evaluated factors affecting the degree of percent change in BMD with romosozumab treatment. Factors showing significant association with percent change in BMD included the spine and total hip BMD values before starting romosozumab treatment (Fig. 1b), TRACP-5b value before the start of romosozumab treatment (Fig. 1c), and iP1NP value before starting romosozumab treatment (Fig. 1d). Spine BMD level at the start of treatment showed negative correlation with percent change in the spine BMD at six and 12 months (p=0.0364, p=0.0355, respectively). Total hip BMD level at the start of treatment showed negative correlation with percent change in the hip BMD at 12 months (p=0.0082). The cut-off value was below 0.682 g/cm^2 for the spine BMD and below 0.604 g/cm^2 for the total hip BMD. There was also a direct correlation between TRACP-5b level before the start of romosozumab treatment and percent change in the spine BMD at 12 months (p=0.004). The cut-off for TRACP-5b value was 297 mU/dL. There was also a positive correlation between iP1NP level before the start of treatment and percent change in the spine BMD at 12 months (p=0.0051). The cut-off iP1NP value was 29.5 mg/mL.

Secondary endpoint: Percent change from baseline in bone metabolism markers

Corrected Ca level percent change from baseline

Percent change from baseline in serum-corrected Ca levels is shown in Fig. 2a. Maximum decline in Ca level was recorded at the third month of romosozumab treatment. However, no special concomitant drug addiction was required, and the corrected Ca value returned to approximately baseline values.

P level percent change from baseline

Percent changes in serum P levels are shown in Fig. 2a. Maximum percent change from baseline was recorded at 6 and 9 months of treatment.

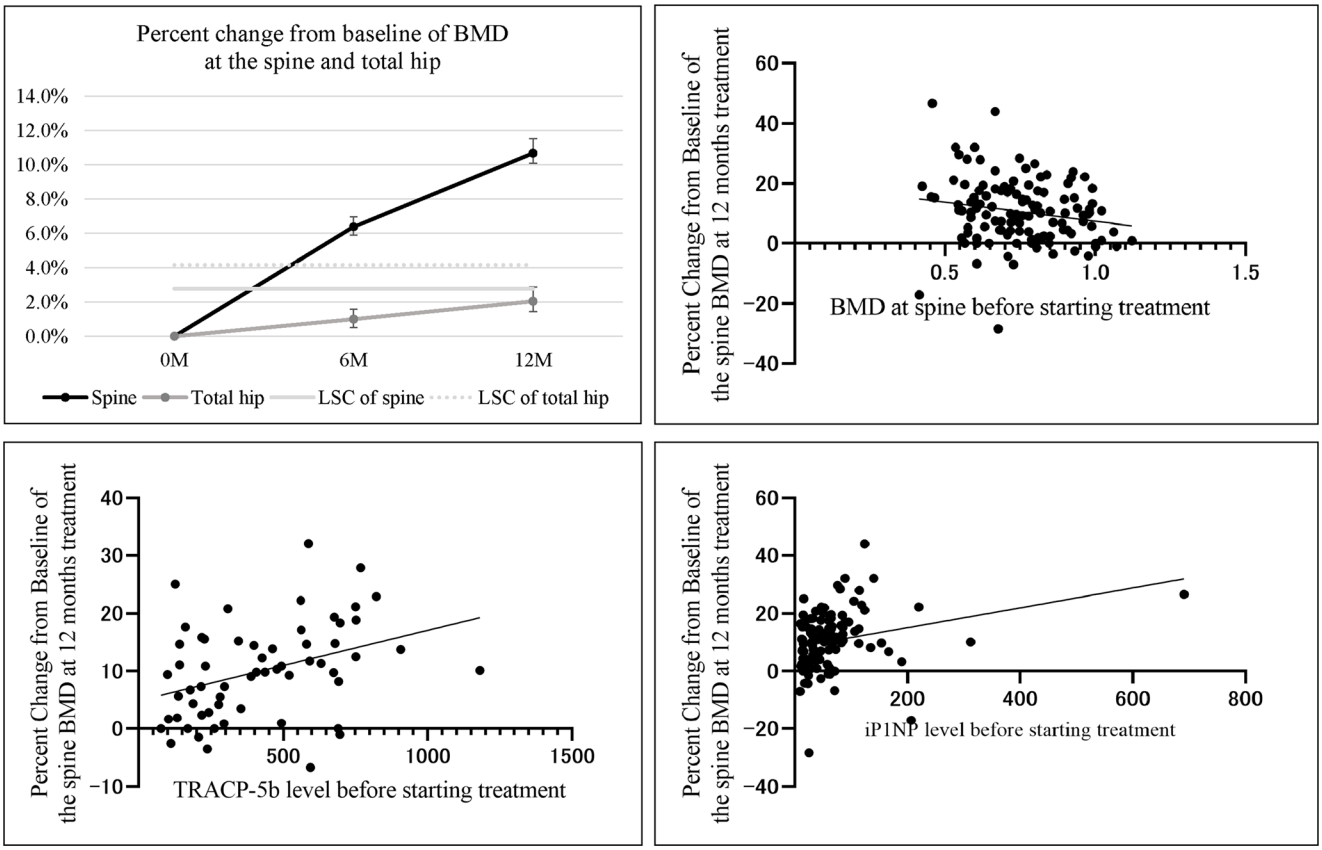
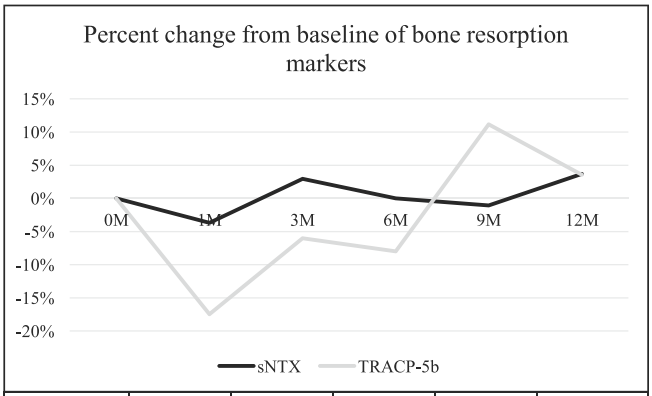
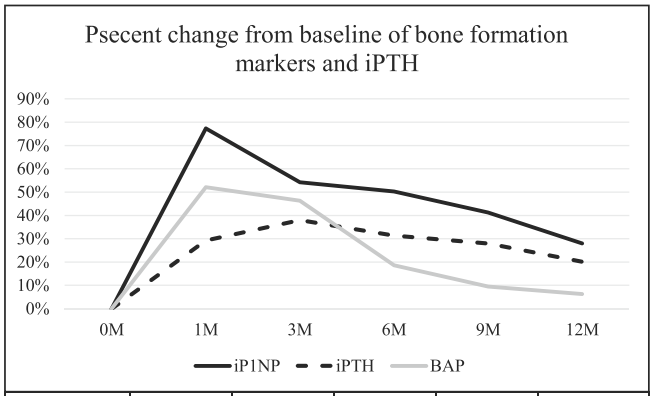


Fig. 1 **a** Percent change in the spine BMD increased above LSC at both the sixth and twelfth month whereas the percent change in the total hip BMD did not increase above LSC neither at the sixth or twelfth month of treatment. BMD (bone mineral density), LSC (least significant change). **b** The spine BMD before starting romosozumab treatment negatively correlated with percent change in the spine BMD at the twelfth month. **c** TRACP-5b value before starting romosozumab treatment positively correlated with percent change in the spine BMD at the twelfth month. **d** iP1NP value before starting romosozumab treatment positively correlated with percent change in the spine BMD at the twelfth month



	1M	3M	6M	9M	12M
Ca	-1.73%	-2.31%	-0.50%	-0.61%	-0.80%
P	-0.41%	1.71%	3.02%	2.28%	1.56%
sNTX	-3.70%	2.94%	0.01%	-1.07%	3.69%
TRACP-5b	-17.48%	-6.02%	-8.00%	11.17%	3.56%



	1M	3M	6M	9M	12M
iP1NP	77.34%	54.26%	50.23%	41.25%	27.96%
BAP	52.11%	46.35%	18.63%	9.45%	6.27%
iPTH	29.20%	38.01%	31.38%	27.90%	20.14%

Fig. 2 Results of serum parameters. **a** While SNTX did not show any changes beyond MSC, TRACP-5b showed changes beyond the MSC. **b** Both iP1NP and BAP showed changes over MSC. IPTH was elevated throughout 12 months of romosozumab treatment. Ca (calcium), P (phosphorus), sNXT (serum cross-linked N-telopeptide of type 1 collagen), TRACP-5b (tartrate-resistant acid phosphatase 5b), iP1NP (intact type I procollagen N-terminal propeptide), BAP (bone alkaline phosphatase), iPTH (intact parathyroid hormone), M (month)

Percent change from baseline in bone resorption markers

Percent changes from baseline in sNTX, a bone resorption marker, are shown in Fig. 2a. The MSC of sNTX was 16.3% [18], meaning that no significant change above the MSC was found during the 12-month period.

Compared with the baseline, TRACP-5b levels are shown in Fig. 2a. Evidently, compared with baseline, TRACP-5b decreased most at the first month and increased most at the ninth month. Since the MSC of TRACP-5b is 12.4% [18], TRACP-5b showed a significant change during romosozumab treatment. In addition, percent change from baseline in TRACP-5b at first month correlated negatively with percent change from baseline in the spine BMD at 12 months (p=0.0062). Also, there was a negative correlation between percent change in TRACP-5b at 12 months and percent change in the spine BMD at 12 months (p=0.0015).

Percent change from baseline in bone formation markers

Compared with the baseline, iP1NP levels are shown in Fig. 2b. Hence, iP1NP increased significantly at the first month, and it remained high during all 12 months, although with a downward trend. The MSC of iP1NP is 12.1% [18], meaning that the observed changes during romosozumab treatment were significant.

Compared with the baseline, BAP levels are shown in Fig. 2b. The maximum increase was observed at the first and third months, and the values decreased thereafter to the twelfth month. The MSC of BAP is 9% [18], indicating that the changes from the first to the ninth month were significant.

Percent change from baseline in iPTH level

Compared with the baseline, iPTH levels are shown in Fig. 2b. iPTH was elevated throughout 12 months of romosozumab treatment, but percent changes were moderate and nearly constant.

Examination of factors influencing the percent change in BMD

Results of cases with postmenopausal osteoporosis without pretreatment with anti-osteoporosis drugs

Considering that other studies often focused only on patients with postmenopausal osteoporosis [3, 19], we focused on cases of postmenopausal osteoporosis without previous osteoporosis treatment (n=71). Percent change from baseline in the spine BMD was 7.83 ± 1.35% and 14.61 ± 1.91% at six and 12 months, respectively, whereas percent change from baseline in the total hip BMD was −0.07 ± 1.12% (6 months) and 2.13 ± 1.34% (12 months). Percent changes in bone metabolism markers were as follows: compared with the baseline, TRACP-5b levels were −24.51% (±9.16%), −1.59% (±9.81%), 7.48% (±12.91%), 13.11% (±12.29%), and 12.92% (±11.28%) at the first, third, ninth, and twelfth months of therapy. iP1NP levels were 67.10% (±21.11%), 47.15% (±9.94%), 59.91% (±17.06%), 16.22% (±14.64%), and 4.79% (±16.77%) at the first, third, ninth, and twelfth months of therapy. Further analysis showed that percent change from baseline in the spine BMD at 12 months was inversely related to the spine BMD before starting romosozumab treatment. Percent change from baseline in the spine BMD showed a

direct correlation between iP1NP level before starting romosozumab treatment. The cut-off values were 0.656 g/cm^2 or less in the spine BMD and 62.90 mg/mL or more in iP1NP before starting romosozumab (p=0.0421, p=0.0133, respectively).

Comparison of non-pretreated group and pretreated group

Percent changes in BMD, TRACP-5b, and iP1NP were compared between the NON group (n=115), TPD group (n=47), DMAB group (n=46), and BIS group (n=54).

Percent changes in the spine BMD are shown in Fig. 3a. Between zero and 6 months, percent change from baseline in the spine BMD was greater than LSC in all four groups. Moreover, at six to 12 months of treatment, percent change from baseline in the spine BMD was greater than LSC in all four groups. Percent change in spine BMD was significantly higher in the NON than in DMAB group at 6 months (one-way ANOVA, p=0.0274) and BIS group at 12 months of treatment (one-way ANOVA, p=0.0358).

Percent changes in the total hip BMD are shown in Fig. 3b. Percent change from baseline in the total hip did not change above LSC between zero and 6 months, or between 6 and 12 months. There were no statistically significant differences in percent changes in the total hip BMD between the groups.

Percent changes from baseline in TRACP-5b are shown in Fig. 3c. TRACP-5b decreased in the NON, TPD, and BIS groups 1 month after starting romosozumab treatment, whereas in DMAB group, it increased immediately after starting the treatment. Percent change in TRACP-5b from 1 to 12 months was significantly higher in DMAB group compared with the NON, TPD, and BIS groups (one-way ANOVA and Tukey test, p=0.05).

In contrast, iP1NP increased in the NON, TPD, and BIS groups at the first month of romosozumab treatment, and decreased thereafter (Fig. 3d). However, DMAB group showed a continuous upward trend from 1 to 12 months. There was a significant difference between TPD and BIS group at the first month (one-way ANOVA and Tukey test, p=0.0003). There was a significant difference between the NON and DMAB group, TPD and DMAB group, and TPD and BIS group at the third month (one-way ANOVA and Tukey test, p=0.0015, p<0.0001, and p=0.0335). There were significant differences between DMAB and NON/TPD/BIS groups at 6 months (one-way ANOVA and Tukey test, p=0.001). However, no inter-group differences were observed at the ninth month. There were significant differences between DMAB group and NON/TPD/BIS groups (one-way ANOVA and Tukey test, p=0.0002) and between BIS group and NON/TPD groups at 12 months (one-way ANOVA and Tukey test, p=0.05).

Comparison of romosozumab effects depending on the presence or absence of new fracture within 3 months before starting romosozumab treatment

We compared cases with new fractures within 3 months before starting romosozumab treatment (new Fx(+), n=33) and those without (new Fx(-), n=229). Percent changes in the spine BMD in new Fx(+) and new Fx(-) are shown in Fig. 4a. Percent change in the spine BMD at 12 months was significantly higher in new Fx(+) group (p=0.0155). Percent changes in the total hip BMD in new Fx(+) and new Fx(-) are shown in Fig. 4b. There was no significant difference in percent change in the total hip BMD between new Fx(+) and new Fx(-). Percent changes from baseline in TRACP-5b and iP1NP are shown in Fig. 4c, d. Neither percent change in TRACP-5b nor in iP1NP showed significant difference between new Fx(+) and new Fx(-) patients.

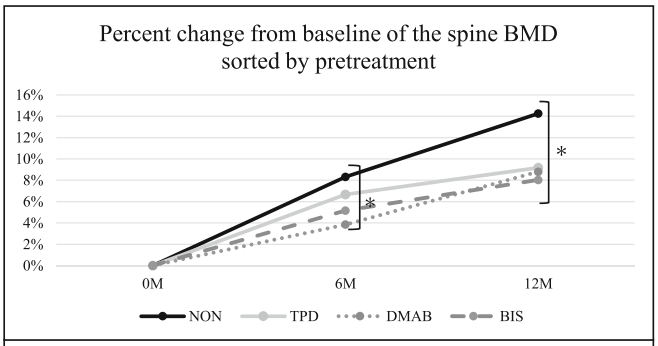
Discussion

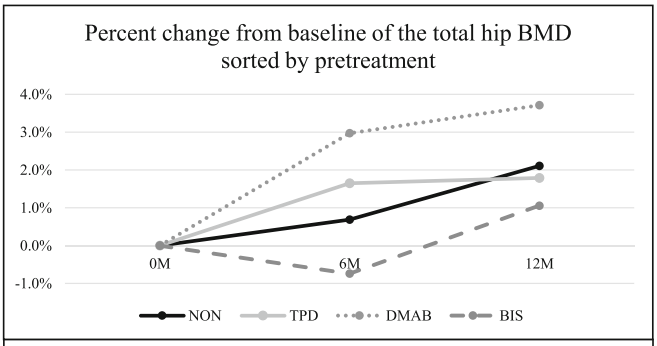
In this study, we found that 12 months of romosozumab treatment was relatively safe and it improved the spine BMD. Furthermore, the effect of romosozumab was better in cases who had severe osteoporosis with low spine BMD, high TRACP-5b, and high iP1NP at the start of romosozumab treatment. In addition, the effect was greater in patients who had not been treated previously for osteoporosis with other drugs and in the group who had started treatment with romosozumab early after the fracture.

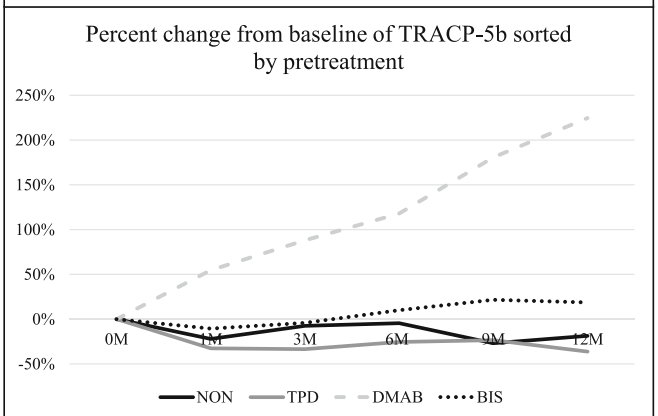
Incidence of new fractures: Safety and adverse events

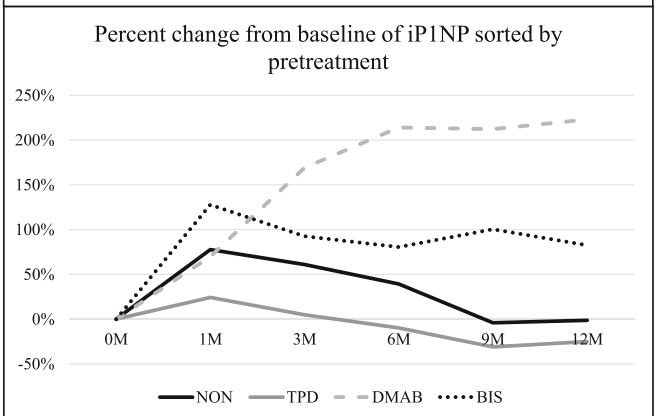
Previous studies indicated that the incidence of new VFs during treatment with romosozumab was 4% [11] or 0.5% [19]. Although simple comparison was impossible due to different patient backgrounds and selection criteria, the incidence of new VFs was 1.15% in our study, which is comparable to these reports. Since this was a retrospective study and did not include a placebo group or other comparison group, future studies with comparison groups are warranted.

Similar to previous reports [4], no fatal complications from romosozumab were observed during the treatment course. There was one death, but the Naranjo algorithm [12] results suggested that it was probably not related to romosozumab. The ARCH study reported a high incidence of CVD and CeVD events with romosozumab and called for attention [11, 19]. However, there were no cases in which such symptoms were suspected during our study. Although strict follow-up may be required when treating high-risk patients with CVD and CeVD, romosozumab was found to be a relatively safe drug to use. Like in previous reports [20], we found that the









TRACP-5b	1M	3M	6M	9M	12M
NON	-22.08%	-7.60%	-4.46%	-27.00%	-18.59%
TPD	-32.52%	-33.56%	-25.53%	-23.44%	-36.30%
DMAB	54.66%	88.03%	117.90%	180.83%	224.58%
BIS	-10.66%	-4.16%	9.91%	21.56%	18.64%

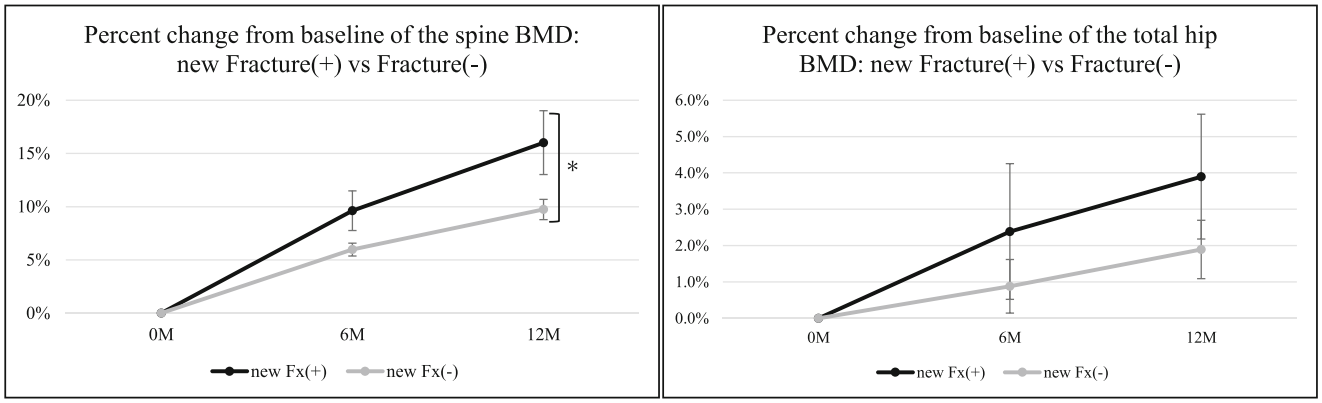
iP1NP	1M	3M	6M	9M	12M
NON	77.62%	61.05%	39.39%	-4.01%	-1.32%
TPD	24.27%	4.90%	-9.68%	-30.97%	-25.02%
DMAB	69.77%	169.02%	214.06%	212.32%	222.92%
BIS	127.82%	92.73%	80.61%	100.38%	82.53%

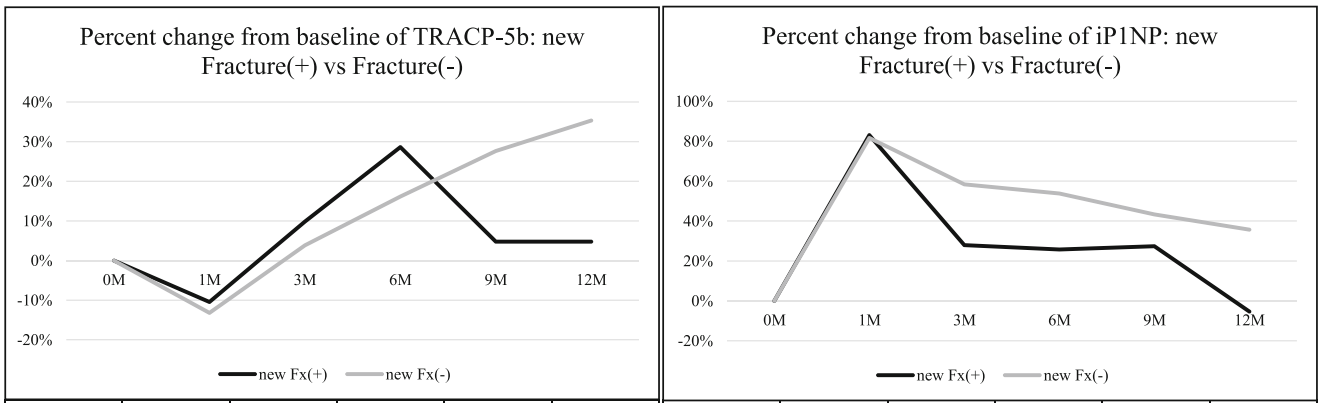
Fig. 3 **a** There was a significant difference between the NON and DMAB groups in percent change in the spine BMD at the sixth month of therapy (one-way ANOVA and Tukey test, p=0.0274). Also, there was a significant difference between the NON and BIS groups in percent change in the spine BMD at the twelfth month (one-way ANOVA and Tukey test, p=0.0358). **b** There were no significant inter-group differences in percent change in the total hip BMD. * significant difference (between NON and DMAB groups). ** significant difference (between NON and BIS groups). **c** TRACP-5b decreased in the NON, TPD, and BIS groups 1 month after starting romosozumab treatment, whereas in the DMAB group it increased immediately after starting the treatment. **d** iP1NP increased in the NON, TPD, and BIS groups at the first month of romosozumab treatment, and then decreased. However, DMAB group showed a continuous upward trend from 1 to 12 months

frequent side effect of romosozumab was post-injection pain. However, there were only two cases (0.76%) in which treatment was discontinued due to post-injection pain. In this study, the treatment discontinuation rate was high, and 59 cases (22.52%) were discontinued. The most common cause was discontinuation of the visits due to COVID-19. Namely, romosozumab is an injectable preparation that is always given in hospital, once every 4 weeks, and cannot be handled by online medical treatment. Therefore, there is a high risk of treatment interruption during such an unprecedented period. It is better to start treatment when continuous injections can be ensured during a 12-month period. In addition, there were two cases of prolonged PT-INR among patients taking warfarin. According to the Naranjo algorithm, this was possibly related to romosozumab. The detailed causal relationship is unknown, but it is a potentially serious side effect. Therefore, it is desirable to check coagulation status in patients using romosozumab while being on warfarin therapy.

Percent change from baseline in the spine and total hip BMD

Considering LSC as a reference standard, it was found that percent change in the spine BMD was higher than that of LSC after 6 months of romosozumab treatment, and it was significantly improved even at the 12th month. However, percent change in the total hip was below LSC even after 12 months of treatment with romosozumab, indicating that romosozumab had little effect on the total hip BMD. Romosozumab treatment may be desirable for use in patients with osteoporosis of the spine. In the phase III study [19], the therapeutic effect of 12-month romosozumab treatment was reported to be 12.1% in percent change in the spine BMD. In this study, the entire sample has a percent change of 10.67%, which was slightly lower than the literature data. This may be related to the fact that many patients in our study were previously treated with other drugs for osteoporosis before being treated with





TRACP-5b	1M	3M	6M	9M	12M
New Fx(+)	-10.45%	9.82%	28.61%	4.78%	4.78%
New Fx(-)	-13.22%	3.81%	16.14%	27.63%	35.34%

iP1NP	1M	3M	6M	9M	12M
New Fx(+)	83.09%	27.92%	25.71%	27.37%	-5.39%
New Fx(-)	81.64%	58.34%	53.77%	43.33%	35.69%

Fig. 4 **a** There was a significant difference between new fracture (+) and new fracture (-) groups in percent change in the spine BMD at the twelfth month (p=0.0155). **b** There was no significant difference in percent change in the total hip BMD between new fracture (+) and new fracture (-) patients. **c**, **d** Neither percent change in TRACP-5b nor iP1NP showed significant differences between patients with new fractures within 3 months before starting romosozumab group and other patients. New fracture (+): cases with new fractures within 3 months before starting romosozumab treatment. New fracture (-): cases with no new fractures within 3 months before starting romosozumab treatment. * significant difference (between new Fx(+) and new Fx(-) groups)

romosozumab. Examining only cases of postmenopausal osteoporosis not previously treated for osteoporosis, percent change in the spine BMD at the 12th month was 14.61% in this study, which was comparable to the previous study [19].

Percent change of corrected Ca

It is recommended to be aware of hypocalcemia during treatment with romosozumab. According to this study, the highest corrected Ca reduction rate was at the third month after starting romosozumab treatment. In cases where corrected Ca value at the start of romosozumab treatment was as low as 9.0 mg/dL, Ca value should be checked by the third month.

Percent change of bone resorption markers and bone formation markers

In this study, we investigated sNTX and TRACP-5b as bone resorption markers as in previous reports [4]. sNTX did not show any changes beyond MSC throughout romosozumab treatment, and was considered unsuitable for evaluation of romosozumab treatment. TRACP-5b was shown to change beyond MSC in the early phase of romosozumab treatment and was considered to be suitable for evaluation of this treatment. We also found that percent change in TRACP-5b at the first month correlated with percent change in the spine BMD at 12 months in both the entire sample and the NON group. Therefore, early percent change in TRACP-5b rate may be used for rough prediction of the therapeutic effect in the future. In this study, iP1NP and BAP were examined as bone formation markers as in previous reports [4]. iP1NP showed changed above MSC during the treatment phase from the first to twelfth month, and BAP from the first to the ninth month, suggesting that they are suitable as evaluation indices of romosozumab treatment.

Percent change in iPTH

In our study, iPTH dynamics showed a peak increase up to the third month after the start of romosozumab treatment, and then

decreased gradually. As reported previously, this might be related to a decrease in the level of calcium in the blood due to treatment with romosozumab [21, 22]. Indeed, the results of the current study showed that the greatest decrease in corrected Ca levels occurred at the third month, and the greatest increase in percent change in iPTH also occurred at the third month.

Factors affecting romosozumab treatment

Factors affecting the effects of romosozumab treatment

We examined the baseline predictors of good effect of romosozumab. First, we examined the predictors of changes in the spine BMD above LSC in the entire group treated with romosozumab. We found that these factors included BMD value, TRACP-5b value, and iP1NP value before starting romosozumab treatment. In particular, the spine BMD before starting romosozumab ≤0.682 g/cm^2, TRACP-5b before starting romosozumab ≥297 mU/dL, and iP1NP before starting romosozumab ≥29.50 mg/mL were good predictors of better results of romosozumab treatment.

When we analyzed only cases with postmenopausal osteoporosis without pretreatment, percent change in the spine BMD before starting romosozumab treatment and the pretreatment iP1NP value affected the percent change in the spine BMD at 12 months. In particular, the spine BMD before starting romosozumab ≤0.656 g/cm^2 and iP1NP before starting romosozumab ≥62.90 mg/mL were good predictors of better effects of romosozumab treatment in patients with postmenopausal osteoporosis with no pretreatment. The difference in iP1NP cut-off values between the entire group and postmenopausal osteoporosis with no pretreatment group might be due to the inclusion of patients previously treated with bone resorption inhibitors in the entire group.

Effects of pretreatment

Focusing on the treatment received just before starting romosozumab treatment, we examined the NON, TPD, DMAB, and BIS groups. The NON group showed the highest percent change in the spine BMD, while percent changes in the total hip did not differ significantly between the groups. Previous the structure study (a study of romosozumab in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy) showed that switch of bisphosphonates to romosozumab treatment led to an increase in percent change in the spine BMD by 9.8% at 12 months of romosozumab treatment [23]. Similar to our study, the transition group from bisphosphonates was reported to have a lower rate of increase in percent change in BMD [23].

In terms of bone metabolism markers, the DMAB group showed the most characteristic dynamics in both bone resorption and formation markers. However, percent change in BMD in the DMAB group at 12 months was not significantly different from other pretreatment groups. With romosozumab treatment after denosumab, the increase in BMD at 6 months was poor, but at 12 months, it showed the same rate of increase as other pretreatment groups. Therefore, there is no need to be concerned about the BMD value at 6 months of romosozumab treatment in patients pre-treated with denosumab.

Our results suggested that it is more effective to start using romosozumab before using other anti-osteoporosis drugs. However, a certain increase in percent change in the spine BMD can be expected regardless of the pretreatment.

Impact of fracture

The percent change in the spine BMD was high in patients with fractures that occurred shortly before starting romosozumab treatment. Fractures are known to affect bone turnover, and existing reports have shown that bone resorption first increases and then bone formation increases [24]. Romosozumab may have a greater impact by supplementing those changes. In cases with a new fracture, it may be advisable to actively consider starting treatment with romosozumab.

However, the sample size of this study was small, and there was an imbalance in the sex ratio and a variety of secondary osteoporosis diseases. It is necessary to increase the sample size in the future. Also, a comparison group such as placebo would be useful for more in-depth comparisons. The effects of previous treatment and concomitant medication should also be studied.

Conclusions

We showed that romosozumab significantly increased percent change in the spine BMD at 12 months. It was also relatively safe to use. For the evaluation of romosozumab therapy, we believe that TRACP-5b, iP1NP, and BAP are useful. We also examined the baseline predictors of good effect of romosozumab. Specifically, the effect of romosozumab was better in cases of severe osteoporosis with low spine BMD, high TRACP-5b, and high iP1NP at the start of romosozumab treatment. After starting romoszumab treatment, percent change in TRACP-5b level at the first month might be an indicator for the percent change in the spine BMD at 12 months. Also, the percent change in the spine BMD was more likely to be increased in patients who had not been previously treated with other anti-osteoporosis medications, indicating that anti-osteoporosis treatment should be started with romosozumab, if possible. In addition, romosozumab treatment is indicated in newly fractured patients. Continued

research on romosozumab treatment is needed to examine the efficacy and impact of the drug in the future, as well as the concomitant use of other drugs.

Abbreviations BMD, Bone mineral density; CVD, Cardiovascular disease; CeVD, Cerebrovascular disease; VF, Vertebral fracture; tALP, Total alkaline phosphatase; sNTX, Serum cross-linked N-telopeptide of type 1 collagen; TRACP-5b, Tartrate-resistant acid phosphatase 5b; iP1NP, Intact type I procollagen N-terminal propeptide; BAP, Bone alkaline phosphatase; iPTH, Intact parathyroid hormone; NON, No pretreatment group; TPD, Teriparatide; DMAB, Denosumab; BIS, Bisphosphonate; LSC, Least significant change; MSC, Minimum significant change; COPD, Chronic obstructive pulmonary disease; PT-INR, Prothrombin time-international normalized ratio; Fx, Fracture

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Availability of data and material The data are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate All procedures performed in this study 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. The study was approved by the Tokyo Women's Medical University Ethics Committee, number 5596.

Informed consent was obtained from all participants included in the study.

Consent for publication Not applicable.

Conflicts of interest Ayako Tominaga, Yoshiharu Kato, Hideharu Nishi, Yasushi Terayama, and Ken Okazaki declare that they have no conflicts of interest. Keiji Wada received a speaking fee from Amgen Inc.

References

1. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T (2010) Cohort profile: research on osteoarthritis/osteoporosis against disability study. Int J Epidemiol 39:988–995. https://doi.org/10.1093/ije/dyp276
2. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-Yo Y, Yoshida M, Saika A, Yoshida H, Suzuki T, Yamamoto S, Ishibashi H, Kawaguchi H, Nakamura K, Akune T (2009) Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 27:620–628. https://doi.org/10.1007/s00774-009-0080-8
3. Ebina K, Hirao M, Tsuboi H, Nagayama Y, Kashii M, Kaneshiro S, Miyama A, Nakaya H, Kunugiza Y, Okamura G, Etani Y, Takami K, Goshima A, Nakata K (2020) Effects of prior osteoporosis treatment on early treatment response of romosozumab in patients with postmenopausal osteoporosis. Bone 140:115574. https://doi.org/10.1016/j.bone.2020.115574
4. Tominaga A, Wada K, Kato Y, Nishi H, Terayama Y, Okazaki K (2020) Early clinical effects, safety, and appropriate selection of bone markers in romosozumab treatment for osteoporosis patients: a 6-month study. Osteoporos Int. https://doi.org/10.1007/s00198-020-05639-y
5. Baron R, Rawadi G (2007) Targeting the Wnt/beta-catenin pathway to regulate bone formation in the adult skeleton. Endocrinology 148:2635–2643. https://doi.org/10.1210/en.2007-0270
6. McClung MR, Grauer A, Boonen S et al (2014) Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 370:412–420. https://doi.org/10.1056/NEJMoa1305224
7. Ominsky MS, Vlasseros F, Jolette J, Smith SY, Stouch B, Doellgast G, Gong J, Gao Y, Cao J, Graham K, Tipton B, Cai J, Deshpande R, Zhou L, Hale MD, Lightwood DJ, Henry AJ, Popplewell AG, Moore AR, Robinson MK, Lacey DL, Simonet WS, Paszty C (2010) Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength. J Bone Miner Res 25:948–959. https://doi.org/10.1002/jbmr.14
8. Li X, Warmington KS, Niu QT, Asuncion FJ, Barrero M, Grisanti M, Dwyer D, Stouch B, Thway TM, Stolina M, Ominsky MS, Kostenuik PJ, Simonet WS, Paszty C, Ke HZ (2011) Inhibition of sclerostin by monoclonal antibody increases bone formation, bone mass, and bone strength in aged male rats. J Bone Miner Res 25:2647–2656. https://doi.org/10.1002/jbmr.182
9. Bandeira L, Lewiecki EM, Bilezikian JP (2017) Romosozumab for the treatment of osteoporosis. Expert Opin Biol Ther 17:255–263. https://doi.org/10.1080/14712598.2017.1280455
10. Miyauchi A, Dinavahi RV, Crittenden DB et al (2019) Increased bone mineral density for 1 year of romosozumab vs placebo, followed by 2 years of denosumab in the Japanese subgroup of the pivotal FRAME trial and extension. Arch Osteoporos 14:59. https://doi.org/10.1007/s11657-019-0608-z
11. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A (2017) Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med 377:1417–1427. https://doi.org/10.1056/NEJMoa1708322
12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239–245. https://doi.org/10.1038/clpt.1981.154
13. Gertz BJ, Clemens JD, Holland SD, Yuan W, Greenspan S (1998) Application of a new serum assay for type I collagen cross-linked N-telopeptides: assessment of diurnal changes in bone turnover with and without alendronate treatment. Calcif Tissue Int 63:102–106. https://doi.org/10.1007/s002239900497
14. Igarashi Y, Lee MY, Matsuzaki S et al (2002) Acid phosphatase as markers of bone metabolism. J Chromatogr B 781:345–358. https://doi.org/10.1016/s1570-0232(02)00431-2
15. Cavalier E, Souberlielle JC, Grandisseur R et al (2014) Inter-method variability in bone alkaline phosphatase measurement: clinical impact on the management of dialysis patients. Clin Biochem 47:1227–1230. https://doi.org/10.1016/j.clinbiochem.2014.04.007
16. Eastell R, Krege JH, Chen P, Glass EV, Reginster JY (2006) Development of analgorism for using P1NP to monitor treatment of patients with teriparatide. Curr Med Res Opin 22:61–66. https://doi.org/10.1185/030079905X75096
17. Fogelman I, Blake GM (2000) Different approaches to bone densitometry. J Nucl Med 41:2015–2025
18. Nishizawa Y, Miura M, Ichimura S, Inaba M, Imanishi Y, Shiraki M, Takada J, Chaki O, Hagino H, Fukunaga M, Fujiwara S, Miki T, Yoshimura N, Ohta H (2019) Executive summary of the Japan osteoporosis society guide for the use of bone turnover markers in the diagnosis and treatment of osteoporosis (2018 edition). Clin Chim Acta 498:101–107. https://doi.org/10.1016/j.cca.2019.08.012
19. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CAF, Milmont CE, Chen L, Maddox J, Meisner PD, Libanati C,

Grauer A (2016) Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 375:1532–1543. https://doi.org/10.1056/NEJMoa1607948

20. Mariscal G, Munez JH, Bhatia S et al (2020) Safety of romosozumab in osteoporotic men and postmenopausal women: a meta-analysis and systematic review. Monoclon Antib Immunodiagn Immunother 39:29–36. https://doi.org/10.1089/mab.2019.0049
21. Dempster DW, Zhou H, Recker RR, Brown JP, Recknor CP, Lewiecki EM, Miller PD, Rao SD, Kendler DL, Lindsay R, Krege JH, Alam J, Taylor KA, Janos B, Ruff VA (2016) Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: AVA osteoporosis study. J Clin Endocrinol Metab. 101(4):1353–1363. https://doi.org/10.1210/jc.2015-4181
22. Polyzos SA, Anastasilakis AD, Terpos E (2009) Transient secondary hyperparathyroidism following intravenous infusion of zoledronic acid. Support Care Canser 17:1329–1330
23. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK, Goemaere S, Hyldstrup L, Jodar-Gimeno E, Keaveny TM, Kendler D, Lakatos P, Maddox J, Malouf J, Massari FE, Molina JF, Ulla MR, Grauer A (2017) Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomized, open-label, phase 3 trial. Lancet 390:1585–1594. https://doi.org/10.1016/S0140-6736(17)31613-6
24. Veich SW, Findlay SC, Hamer AJ et al (2006) Changes in bone mass and bone turnover following tibial shaft fracture. Osteoporos Int 17:364–372. https://doi.org/10.1007/s00198-005-2025-y