



Time-Course Changes in Bone Metabolism Markers and Density in Patients with Osteoporosis Treated with Romosozumab: A Multicenter Retrospective Study

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Purpose: In this multicenter retrospective observational study, we examined the early effects of romosozumab in patients with severe osteoporosis in terms of time-course changes in bone metabolism marker, improvement in bone density, and adverse effects.

Materials and Methods: Patients with severe osteoporosis were included. We investigated the progress of TRACP 5b and PINP before and 1–2 months after the administration of romosozumab. We also investigated the bone density of lumbar spine, femoral neck, and the entire femur, measured by the DXA method, before and 5–7 months after the administration of romosozumab.

Results: A total of 70 patients (7 males and 63 females, age 75.0±3.6 years) participated in this study. Significant improvements in TRACP 5b and PINP levels were observed before and 1–2 months after romosozumab administration. The average bone density of lumbar spine, femoral neck, and the entire femur were measured before and 5–7 months after romosozumab administration; and a significant increase only observed in the lumbar spine.

Conclusion: Consistent with the findings of previous clinical studies, romosozumab has both bone formation-enhancing and bone resorption effects (dual effect). In addition, romosozumab also demonstrated improvement in bone density from the early phase after the administration, though the result was only seen in the lumbar spine.

Key Words: Bone and bones, bone density, bone resorption, metabolism, osteogenesis, osteoporosis

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INTRODUCTION

Osteoporosis is one of the major causes of locomotive syndrome. In Japan, the number of patients with osteoporosis has been increasing every year, mainly in elderly female. It is estimated that the number of patients with osteoporosis, including asymptomatic undiagnosed cases, would reach 13 million. Among patients aged over 50 years, 14.5% of male and 51.3% of female have osteoporosis.¹ In recent years, various drugs have been used for the treatment of osteoporosis, with a certain ef-

fect on the improvement in bone density. However, since there could be a large difference in the time-consuming effect onset for bone density depending on the patient background, drugs with short-run effect or secured effect are still not available at present.²

Romosozumab, which was recently approved for use in Japan, has a strong dual effect on both the enhancement of bone formation and the inhibition of bone resorption, along with a fast improvement effect on abnormal bone metabolism, in patients with osteoporosis. Moreover, the dual effect of this drug results in an early stage improvement in bone density.³⁻⁵ Romosozumab is a humanized immunoglobulin monoclonal antibody that binds to sclerostin, a suppressor of bone formation, and inhibits its action. Sclerostin is an extracellular inhibitor of the classical Wnt signaling pathway secreted by osteocytes.³⁻⁵ Romosozumab specifically binds to sclerostin and prevents it from binding to LRP5 and LRP6, thereby inhibiting the suppression of classical Wnt signaling in osteoblast lineage cells. The resulting activation of classical Wnt signaling increases bone formation, decreases bone resorption, and increases bone mass and strength in cortical and trabecular bone.

In the FRAME study, the mean improvement in CTX (bone resorption marker) at 1 month after treatment with romosozumab was approximately 35% (statistically significant improvement compared to that in the pre-treatment period), and the mean increase in TRACP 5b (bone formation marker) was approximately 95% (statistically significant improvement compared to that at pre-treatment).³ However, there are only a few reports available on the therapeutic efficacy of romosozumab, as the drug has been recently approved in Japan.

In this multicenter retrospective observational study, we examined the early effects of romosozumab in patients with severe osteoporosis patients, with respect to time-course changes in bone metabolism marker, improvement in bone density, and adverse effects.

MATERIALS AND METHODS

The present multicenter retrospective observational study was conducted in seven institutions located in Japan, following approval by the Institutional Ethics Committee [Approval code: 2888 (School of Medicine, Chiba University)]. The opt-out method was used for patient's consent. Patients who received romosozumab during the period from March 2019 to September 2020, after the launch of romosozumab, were included. In addition, the following five criteria were used for enrollment.

Inclusion and exclusion criteria

The definition of severe osteoporosis followed the diagnostic criteria of the Japanese Society of Bone Metabolism and the Japanese Osteoporosis Society as follows: 1) bone mineral density value of -2.5 SD or less with one or more fragility fractures;

2) lumbar vertebral bone mineral density of less than -3.3 SD; 3) number of existing vertebral fractures of two or more; and 4) semi-quantitative evaluation method results indicating existing vertebral fractures of grade 3. In all cases, X-rays were taken on the spine and hip joints, and an orthopedic specialist confirmed the presence of fractures. In addition, the indication criteria for this study were as follows: 1) TRACP 5b and P1NP were measured before and 1–2 months after treatment; 2) bone mineral density of lumbar spine, femoral neck, and total femur were measured by three DXA methods before and 5–7 months after treatment; 3) side effects were checked (including the occurrence of new fragility fracture, osteonecrosis of the jaw, and atypical fracture) at each dose; and 4) concomitant use of active vitamin D (Edirol, 0.75 $\mu\text{g}/\text{day}$). Exclusion criteria were as follows: 1) patients with secondary osteoporosis; 2) inability to walk on their own; 3) history of fracture within 1 year (any site); 4) history of surgery within 1 year (any site); and 5) patients with carcinoma (any carcinoma).

Survey of all target cases

We investigated the progress of TRACP 5b and P1NP before and 1–2 months after the administration of romosozumab, with respect to time-course changes in bone metabolism marker. To exclude diurnal variation and variability due to renal function decline and dietary effects, TRACP 5b and P1NP, which have been reported to be less sensitive to these effects, were used for evaluation. Blood samples were collected in the morning after fasting before breakfast. In addition, to determine the improvement in bone density, we investigated the bone density of lumbar spine, femoral neck, and the entire femur, measured by the DXA method, before and 5–7 months after the administration of romosozumab. We also investigated the occurrence of new fragility fractures and adverse effects (e.g. jaw osteonecrosis and atypical fracture).

Effects of romosozumab in drug-naïve patients vs. patients who switched to romosozumab from another bone resorption inhibitor

We compared the following effects in patients who were drug-naïve and those who switched to romosozumab from another bone resorption inhibitor: the average change rate for TRACP 5b, P1NP, bone density of lumbar spine, bone density of femoral neck, and bone density of the entire femur in each group.

Statistical analysis

JMP[®] 15 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. For comparisons among all subjects and between those with and without premedication, the pre- and post-treatment values of each parameter were compared and analyzed using a paired t-test, with $p < 0.05$ being considered significantly different. For the comparison between drug-naïve patients and those who switched from bone resorption inhibitors, the mean rate of change of each parameter [(measured

value after administration–measured value before administration)/measured value before administration] was calculated and analyzed using an unpaired t-test, and $p < 0.05$ was considered a statistically significant difference.

RESULTS

Survey of all target cases

A total of 70 patients (7 males and 63 females) participated in this study. The average age of the patients was 75.0 ± 3.6 years. Improvements in both bone metabolism markers were observed when the levels before and 1–2 months after romosozumab administration were compared, with statistically significant changes in the average TRACP 5b level from 505.5 ± 316.7 mU/dL to 297.0 ± 214.1 mU/dL ($p < 0.05$) (average improvement rate: $33.1 \pm 27.0\%$) and in the average P1NP level from 48.5 ± 33.3 $\mu\text{g/L}$ to 102.0 ± 71.0 $\mu\text{g/L}$ ($p < 0.05$) (average increase rate: $140.1 \pm 138.3\%$) (Figs. 1 and 2).

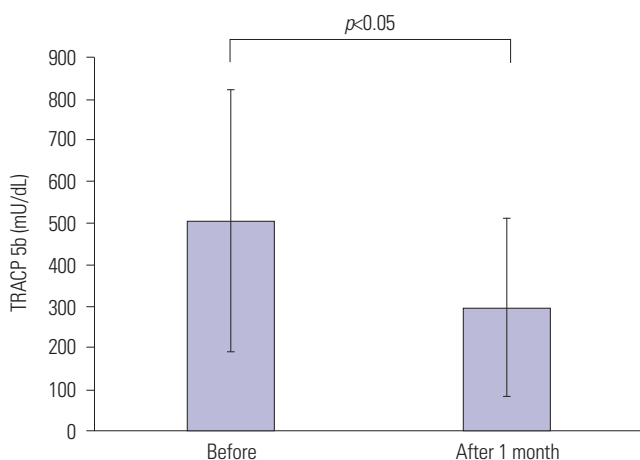


Fig. 1. Progress of TRACP 5b before and 1–2 months after the administration of romosozumab.

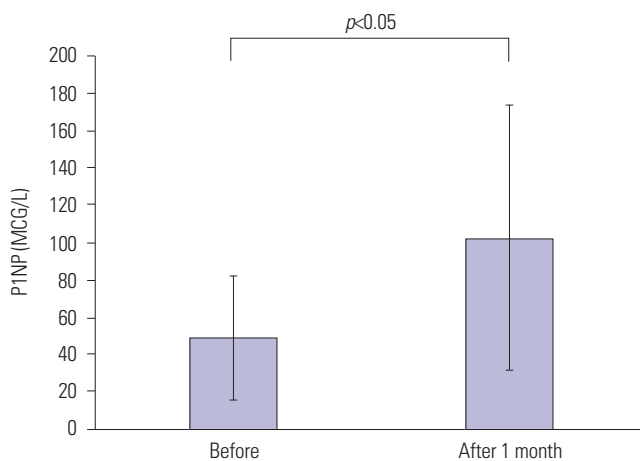


Fig. 2. Progress of P1NP before and 1–2 months after the administration of romosozumab.

Measurement of the average bone density [young adult mean (YAM)] of lumbar spine, femoral neck, and the entire femur before and 5–7 months after romosozumab administration indicated a significant increase only in the lumbar spine; lumbar spine $63.3 \pm 12.4\%$ to $67.8 \pm 12.7\%$ ($p < 0.05$) (the average increase rate: $7.6 \pm 4.3\%$), femoral neck $60.4 \pm 10.0\%$ to $61.3 \pm 9.4\%$ ($p > 0.05$) (the average increase rate: $1.8 \pm 6.5\%$), and the entire femur $67.9 \pm 8.2\%$ to $68.7 \pm 8.6\%$ ($p > 0.05$) (the average increase rate: $1.4 \pm 5.5\%$) (Fig. 3).

There was only one case of vertebral fracture as an occurrence of a new fragility fracture (the patient was injured in a fall 1 month after romosozumab administration; occurrence rate 1.4%). Apart from this case, there was no apparent adverse event observed in any patient during the study, including the cases for jaw osteonecrosis and atypical fracture.

Effects of romosozumab in drug-naïve patients vs. patients who switched to romosozumab from another bone resorption inhibitor

Among the patients included in the study, 35 were drug-naïve (1 male and 34 females). The average age of the patients in this group was 75.6 ± 3.7 years. Table 1 shows the results of the drug-naïve group.

Improvements in both bone metabolism markers were observed when the levels before and 1–2 months after romosozumab administration were compared, with statistically significant changes in the average TRACP 5b level from 714.7 ± 275.8 mU/dL to 385.7 ± 255.6 mU/dL ($p < 0.05$) (average improvement rate: $45.9 \pm 23.1\%$) and in the average P1NP level from 70.6 ± 28.3 $\mu\text{g/L}$ to 138.0 ± 74.1 $\mu\text{g/L}$ ($p < 0.05$) (average increase rate: $103.4 \pm 103.4\%$).

The average bone density (YAM) of lumbar spine, femoral neck, and the entire femur before and 5–7 months after the romosozumab administration indicated a significant increase only in lumbar spine; lumbar spine: $60.0 \pm 10.9\%$ to $65.8 \pm 10.8\%$ ($p < 0.05$) (the average increase rate: $9.9 \pm 4.0\%$), femoral neck: $55.3 \pm 4.9\%$ to $56.4 \pm 4.9\%$ ($p > 0.05$) (the average increase rate: $2.4 \pm 8.4\%$), and the entire femur: $63.0 \pm 5.1\%$ to $63.6 \pm 5.2\%$ ($p > 0.05$) (the average increase rate: $1.2 \pm 7.2\%$).

Total 35 patients (6 males/29 females) switched from a previous bone resorption inhibitor (alendronate, $n=18$; risedronate, $n=6$; minodronate, $n=8$; and ibandronate, $n=3$) to romosozumab. The average age of the patients in this group was 74.1 ± 3.4 years. The average administration period of previous bone resorption inhibitor was 22.6 ± 14.9 months. Table 2 shows the results of the patients who switched to romosozumab.

Improvements in both the bone metabolism markers were observed when the levels before and 1–2 months after romosozumab administration were compared, with statistical significance change in average TRACP 5b level from 249.8 ± 101.2 mU/dL to 188.6 ± 42.6 mU/dL ($p < 0.05$) (average improvement rate: $17.6 \pm 22.6\%$) and change in average P1NP level from 21.5 ± 12.3 $\mu\text{g/L}$ to 58.0 ± 32.5 $\mu\text{g/L}$ ($p < 0.05$) (the average increase rate:

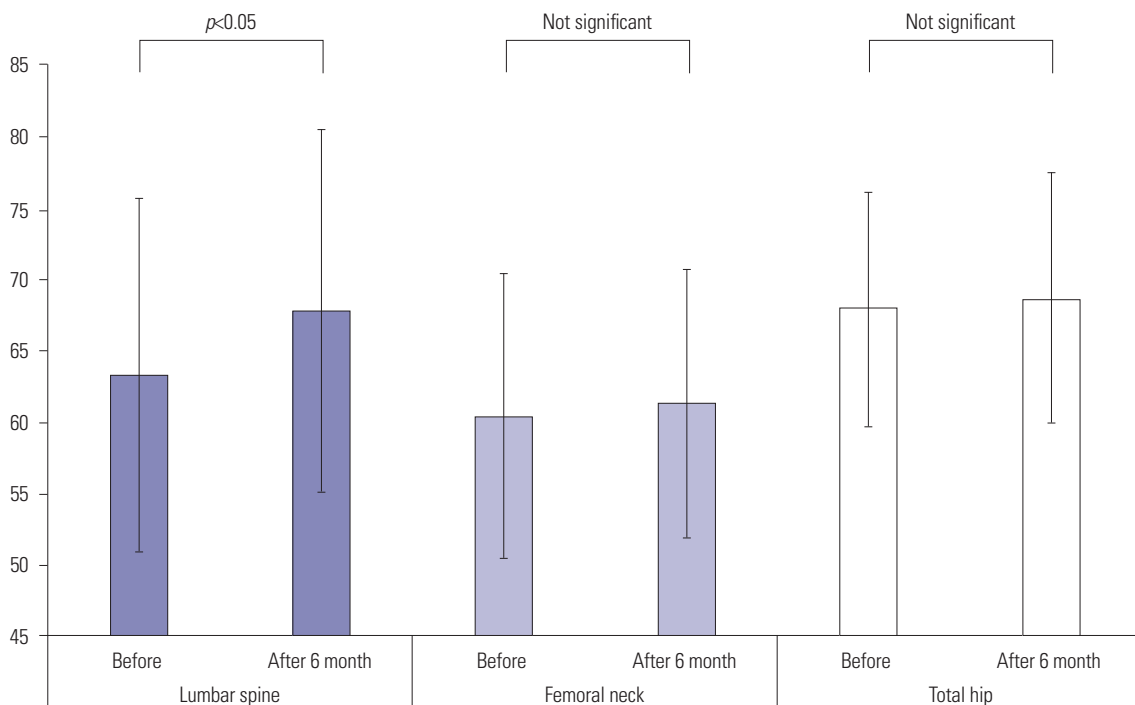


Fig. 3. Measurement of the average bone density (young adult mean) of lumbar spine, femoral neck, and the entire femur before and 5–7 months after romosozumab administration.

Table 1. List of Results for N Group (Naïve Cases)

Bone metabolism markers	Before	After 1 month	p value (paired t-test)
TRACP 5b (mU/dL)	714.7±275.8	385.7±255.6	<0.01
P1NP (MCG/L)	70.6±28.3	138.0±74.1	<0.01
Young adult mean	Before	After 6 months	p value (paired t-test)
Lumbar spine (%)	60.0±10.9	65.8±10.8	0.04
Femoral neck (%)	55.3±4.9	56.4±4.9	0.35
Total hip (%)	63.0±5.1	63.6±5.2	0.62

Table 2. List of Results for C Group (Those Who Switched to Romosozumab from a Previous Bone Resorption Inhibitor)

Bone metabolism markers	Before	After 1 month	p value (paired t-test)
TRACP 5b (mU/dL)	249.8±101.2	188.6±42.6	<0.01
P1NP (MCG/L)	21.5±12.3	58.0±32.5	<0.01
Young adult mean	Before	After 6 months	p value (paired t-test)
Lumbar spine (%)	67.7±15.5	70.5±15.0	0.34
Femoral neck (%)	67.3±11.1	67.8±10.1	0.64
Total hip (%)	74.3±7.0	75.5±7.7	0.62

186.0±163.3%).

The average bone density (YAM) of lumbar spine, femoral neck, and the entire femur before and 5–7 months after romosozumab administration showed a slight increase (statistically insignificant) in all domains; lumbar spine: 67.7±15.5% to 70.5±

Table 3. Comparison between N Group (Naïve Cases) and C Group (Those who Switched to Romosozumab from a Previous Bone Resorption Inhibitor)

	Mean change rate (%)		p value (unpaired t-test)
	N group	C group	
TRACP 5b	45.9±23.1	17.6±22.6	<0.01
P1NP	103.4±103.4	186.0±163.3	<0.01
Lumbar spine	9.9±4.0	4.5±2.6	<0.01
Femoral neck	2.4±8.4	1.0±2.7	0.32
Total hip	1.2±7.2	1.5±1.8	0.81

15.0% ($p > 0.05$) (the average increase rate: 4.5±2.6%), femoral neck: 67.3±11.1% to 67.8±10.1% ($p > 0.05$) (the average increase rate: 1.0±2.7%), and the entire femur: 74.3±7.0% to 75.5±7.7% ($p > 0.05$) (the average increase rate: 1.5±1.8%).

Group comparison

The average change in TRACP 5b was 45.9±23.1% for the N group (naïve cases) and 17.6±22.6% for the C group (those who switched to romosozumab from a previous bone resorption inhibitor) (Table 3). Therefore, patients in the N group showed a significantly better improvement rate in the levels of bone resorption marker. The average change in P1NP was 103.4±103.4% for the N group and 186.0±163.3% for the C group, thereby suggesting that the patients in the C group had a significantly better increase rate ($p < 0.05$). The average change rate of YAM in N group vs. C group were as follows: 9.9±4.0% vs. 4.5±2.6% ($p < 0.01$) for lumbar spine, 2.4±8.4% vs. 1.0±2.7% ($p > 0.05$)

for femoral neck, and $1.2 \pm 7.2\%$ vs. 1.5 ± 1.8 ($p > 0.05$) for the entire femur. Therefore, the results indicated that the patients in the N group had a significantly favorable result only for lumbar spine, but there was no significant difference between groups in terms of femoral neck and the entire femur.

DISCUSSION

The results from the present study showed that the levels of both bone markers, TRACP 5b and P1NP, improved significantly 1 month after romosozumab administration. These results were in line with the results of previous clinical studies, and proved the dual effect of romosozumab in actual clinical practice.³⁻⁵ However, unlike the previous studies, which reported that the average bone density (YAM value) of lumbar spine, femoral neck, and the entire femur, measured using the DXA method, before and 5-7 months after romosozumab administration significantly increased at all sites, this study showed improvement in YAM only in the lumbar spine.^{3,4} This could be attributed to the difference in sample sizes of different studies. For example, compared to the 70 cases in the present study, there were significantly larger number of patients in the FRAME study (3589 cases) and STRUCTURE study (218 cases). In addition, the increase in bone density was 7.6% for lumbar spine, 1.8% for femoral neck, and 1.4% for the entire femur in the present study. However, the results in FRAME study and STRUCTURE study were similar: 9.7% and 4.5% for lumbar spine, 2.3% and 1.0% for femoral neck, and 4.7% and 1.5% for the entire femur, respectively.^{3,4} Based on these findings, it was suggested that a difference in sample size may have resulted in no significant difference between femoral neck and total bone density in the present study.

According to the previous reports on new fragility fracture, romosozumab administration for 12 months resulted in a significant reduction in new morphological vertebral fracture (73%), non-vertebral fracture (25%), and clinical fracture (36%) in all patients compared to placebo.⁵ In the present study, there was only one new fragility fracture case (occurrence rate of 1.4%, with a fracture upon falling one month after romosozumab administration), thus demonstrating the high rate of fracture prevention. Besides this case, there was no serious adverse effect observed in the current study. Nonetheless, considering the fact that one case of atypical femur fracture and two cases for jaw osteonecrosis were reported in the romosozumab group in the FRAME study, the accumulation of cases and long-term follow-up would be required in the future.⁴

Table 1 shows the results of the present study and the results of bone metabolism marker/bone density at each site in drug-naïve patients in the FRAME study.⁴

In the FRAME study, the average improvement rate in the bone resorption marker (CTX:C-terminal cross-linked telopeptide of type I collagen) within 1 month after romosozumab

administration was approximately 35% (a statistically-significant improvement), which was similar to that in the present study (46%). In addition, the average increase rate in the bone resorption marker (TRACP 5b) was approximately 95% (a statistically significant improvement), which was similar to that in the present study (103%). Additionally, the results related to the improvement rate of bone density in the FRAME study (9.7% for lumbar spine, 2.3% for femoral neck, and 4.7% for the entire femur) were similar to those observed in the present study (9.9% for lumbar spine, 2.4% for femoral neck, and 1.2% for the entire femur). However, although there was a statistically significant improvement for all the three sites in the FRAME study, in our study, statistically significant improvement in bone density was observed only in the lumbar spine. This finding may also be attributed the remarkably small number of cases in this study.

Table 2 shows the results of the present study, bone metabolism marker of STRUCTURE study for cases switching from bone resorption inhibitor (alendronate), and bone density at each site.⁵ Our results regarding the levels of bone metabolism marker (TRACP 5b) 1 month after romosozumab administration (approximately 18%) were in line with those observed in the STRUCTURE study (18%, a statistically significant improvement). Also, the average increase in the rate of bone resorption marker (TRACP 5b) was approximately 150% (a statistically significant improvement) in the STRUCTURE study was similar to the result obtained in the present study (approximately 186%). The improvement rate in bone density in the STRUCTURE study was 7.2% for lumbar spine, 2.1% for femoral neck, and 2.3% for the entire femur, which were similar to the results obtained in the present study (4.5% for lumbar spine, 1.0% for femoral neck, and 1.5% for the entire femur). However, while a statistically significant improvement was observed at all the three sites in the STRUCTURE study, significant increase was not observed in any of the three sites in the present study. In this respect, as mentioned previously, the remarkably small number of cases may have been a potential reason for this observation.

In the present study, a comparison between the drug-naïve cases and cases who switched to romosozumab from bone resorption inhibitor showed a significant improvement in the average change of TRACP 5b/P1NP levels in the drug-naïve group and the switching group, respectively. It can be said that the result is self-evident, when we consider the baseline of bone metabolism marker in each group before romosozumab administration. This implies that the turnover of bone metabolism was high in the drug-naïve group (high levels of both TRACP 5b and P1NP) and low in the switching group (low levels of both TRACP 5b and P1NP) due to the effect of bone resorption inhibitor. This suggests a favorable improvement rate for TRACP 5b level in the drug-naïve group (higher level) and for P1NP in the switching group with a lower P1NP level when the dual-effect romosozumab is administered.

The improvement rate of bone density can be confirmed as

significantly favorable only for the lumbar spine in both drug-naive and switching groups. However, the anabolic window could be possibly related to the difference when we consider such result. The anabolic window is a concept proposed by Bilezikian, et al.^{6,7} as integrating the difference between bone formation marker and bone resorption marker. Therefore, the increase in bone density can become more favorable when the area becomes larger. According to the concept of anabolic window, it was presumed that the area of anabolic window was naturally larger in the drug-naive group. Thus, we hypothesize that patients in the drug-naive group may experience more benefits from romosozumab administration compared to those who were previously administered other bone resorption inhibitors.

This study has a few limitations that should be considered while interpreting the results. Since romosozumab was recently launched in Japan, the number of cases was small and the follow-up period was short in this study. Another limitation is that bone metabolic markers were not evaluated before and 1 month after the treatment due to the insurance coverage in Japan (TRACP 5b can be tested only once when it is performed as a diagnostic aid for metabolic bone disease and bone metastasis and once when it is performed as an adjunctive indicator for follow-up treatment within 6 months). Other limitations include the use of a wide variety (for example, the evaluation of fractures was performed only by x-ray and not by MRI) of diagnostic criteria for severe osteoporosis due to a multicenter retrospective observational design of the study, no randomized classification of the drug-naive group and the switching group, and the use of various premedications in the switching group. In order to address these limitations, we are planning to further conduct a multicenter retrospective study in the future using strict criteria, randomized grouping, and unified premedication in the switching group.

In conclusion, the present study retrospectively examined the changes over time in bone metabolism markers and improvement in bone density with romosozumab administration in patients with severe osteoporosis. A statistically significant improvement in the levels of the two bone metabolism markers, TRACP 5b and P1NP, was observed 1 month after romosozumab administration. In addition, the average bone density of lumbar spine, femoral neck, and the entire femur (YAM) before and 5–7 months after romosozumab administration showed a statistically significant improvement. In conclusion, consistent with the findings of previous clinical studies, romosozumab has both bone formation-enhancing and bone resorption effects (dual effect). In addition, romosozumab also showed improvement in bone density from the early phase after the administration, though the result was only seen in the lumbar spine.

AUTHOR CONTRIBUTIONS

Conceptualization: Kazuhide Inage, Sumihisa Orita, Yawara Eguchi, Yasuhiro Shiga, and Seiji Ohtori. **Data curation:** Kazuhide Inage, Sumihisa Orita, Yawara Eguchi, Yasuhiro Shiga, and Seiji Ohtori. **Formal analysis:** Kazuhide Inage, Sumihisa Orita, Yawara Eguchi, Yasuhiro Shiga, and Seiji Ohtori. **Funding acquisition:** Kazuhide Inage, Sumihisa Orita, Yawara Eguchi, Yasuhiro Shiga, and Seiji Ohtori. **Investigation:** all authors. **Methodology:** Kazuhide Inage, Sumihisa Orita, Yawara Eguchi, and Yasuhiro Shiga. **Project administration:** Kazuhide Inage and Seiji Ohtori. **Resources:** Kazuhide Inage, Sumihisa Orita, Yawara Eguchi, Yasuhiro Shiga, and Seiji Ohtori. **Software:** Kazuhide Inage, Sumihisa Orita, Yawara Eguchi, Yasuhiro Shiga, and Seiji Ohtori. **Supervision:** Seiji Ohtori. **Validation:** Masao Koda, Yasuchika Aoki, Toshiaki Kotani, Tsutomu Akazawa, Hiroshi Takahashi, and Miyako Suzuki-Narita. **Visualization:** Kazuhide Inage. **Writing—original draft:** Kazuhide Inage. **Writing—review & editing:** all authors. **Approval of final manuscript:** all authors.

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