ORIGINAL

Use of raloxifene as a sequential therapy after romosozumab : an observational study

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Abstract : Objective : There have been no studies on the effectiveness of raloxifene as an antiresorptive agent following discontinuation of romosozumab. The aim of this study was to investigate the potential effectiveness of raloxifene following a romosozumab therapy. Methods : This study had an observational pre-post design and included 23 patients. Romosozumab 210 mg was administered subcutaneously once every 4 weeks for 12 months, after which all patients received raloxifene 60 mg/day for 24 months. We investigated the incidence of new fractures, safety, and bone mineral density (BMD). Results : We found no new fractures or adverse events. After the treatment with romosozumab, percent changes from baseline in BMD at the spine and total hip in treatment-naïve patients with primary osteoporosis (the Naïve-P group) were 12.3% and 4.6%, respectively. After subsequent administration of raloxifene, spinal and total hip BMD in the Naïve-P group decreased to baseline levels at 36 months and 30 months, respectively. Six months after switching to raloxifene, the respective percent changes from baseline in spinal and total hip BMD were 12.0% and 5.8%. Conclusion : Romosozumab followed by raloxifene is acceptable for use for only 6 months in the Naïve-P group. However, more aggressive use of this agent is not recommended. J. Med. Invest. 72 : 124-133, February, 2025

Keywords **:** *romosozumab, raloxifene, selective estrogen receptor modulator, bone mineral density, osteoporosis*

INTRODUCTION

Osteoporosis is a chronic condition that requires long-term treatment. Increasing evidence supports treatment strategies designed to improve bone mineral density (BMD) until the desired goals have been achieved and maintained in order to reduce the risk of fracture (1, 2). In the long-term management of a patient with osteoporosis, it is difficult for only one treatment to achieve these goals ; therefore, switching among various agents may be clinically warranted.

Romosozumab is an anti-sclerostin antibody agent that first became available in March 2019 in Japan for the treatment of osteoporosis in patients who are at high-risk of fractures (3). Romosozumab has the dual effect of promoting bone formation and decreasing bone resorption by inhibiting suppression of Wnt signaling (4). Pivotal studies have demonstrated the efficacy and safety of romosozumab (5, 6). However, the effect of romosozumab on BMD has been found to be reversible upon discontinuation, with BMD returning toward pretreatment levels over 12 months without follow-on therapy (7). Therefore, administration of romosozumab should be followed by an antiresorptive agent to maintain or augment the BMD gains and the reduction in fracture risk achieved (8). Denosumab and bisphosphonates have demonstrated effectiveness as antiresorptive agents following romosozumab in both maintaining increases in BMD and reducing the fracture risk (5, 9-11). However, chronic use of a bisphosphonate or denosumab has been associated with osteonecrosis of the jaw and atypical femoral fracture (9). Furthermore, denosumab is associated with rebound bone turnover, rapid bone loss, and multiple vertebral fractures after discontinuation (12). Moreover, these drugs are difficult to administer to patients who require dental treatment in Japan.

There is also evidence suggesting that raloxifene, a selective estrogen receptor modulator, increases BMD at the lumbar spine and reduces the vertebral fracture risk in postmenopausal women (13). Raloxifene has antiresorptive activity (14) and has demonstrated long-term safety (15), so may be desirable following a course of romosozumab. However, there have not been any studies or case reports on the effectiveness of raloxifene as an antiresorptive agent following discontinuation of romosozumab.

The aim of this study was to investigate the potential effectiveness of raloxifene as a novel sequential therapy following a 12-month course of romosozumab.

MATERIALS AND METHODS

Study design and participants

This prospective observational study included 23 patients who were started on romosozumab at our hospital from March 2019 onward. Following a 12-month course of romosozumab, they received an additional 24 months of treatment with raloxifene. The treatment protocol was approved by the ethics committee of Tokushima Kensei Hospital (approval number 2304) and conducted in accordance with the principles of the Declaration of Helsinki. Verbal informed consent was obtained from all patients and documented in the medical records.

All patients received a subcutaneous injection of romosozumab 210 mg on enrolment in the study and monthly thereafter. After 12 months of treatment with romosozumab, all patients received raloxifene 60 mg/day for 24 months. All patients required dental therapy at the end of treatment with romosozumab, making it difficult to administer sequential treatment with a bisphosphonate or denosumab. Patients were included in the study if they had a high risk of fracture, defined by a BMD level ≤ -2.5

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standard deviations (SDs) with at least one fragility fracture, a lumbar spinal BMD < –3.3 SDs, 2 or more past vertebral fractures, or a semiquantitative assessment score for post-vertebral fracture of grade 3, as defined by the Japan Osteoporosis Society (16). Treatment-naïve patients at high risk of fracture at the time of diagnosis started treatment with romosozumab. Those with a prior treatment history were switched to romosozumab upon prescription renewal. Patients were ineligible for participation in the study if they had experienced a cardiovascular event within the previous year. During the study, patients deemed to have good renal function (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2) received a vitamin D3 supplement and those considered to have poor renal function (eGFR < 60 mL/min/1.73 m^2) received an active vitamin D3 analog.

Study outcomes

The study was designed to allow a pre-post comparison of the study endpoints. The primary endpoints were the incidence of new fractures and changes in BMD and the secondary endpoints were serum bone metabolism marker levels and adverse events.

We also investigated whether previous therapy affected the outcomes of treatment of romosozumab followed by raloxifene. The pretreatment groups were based on the most recent antiosteoporosis agents administered before starting romosozumab.

Changes in BMD were assessed by dual-energy X-ray absorptiometry using a PRODIGY Fuga-C densitometer (GE Healthcare, Tokyo, Japan). Areal BMD was assessed at the lumbar spine (L1–L4) and total hip at baseline and after 6, 12, 18, 24, 30, and 36 months of treatment with romosozumab. Sites of previous fracture and surgery were excluded from the BMD measurements. Patients were excluded from the BMD assessment if they had an area that was fractured or underwent surgery during the study period. For the purposes of this study, the least significant change (LSC) in BMD from baseline was defined as 2.4% for the spine and 3.5% for the total hip at our institution. Serum analysis was performed in the morning before and after 1, 6, 12, 18, 24, 30, and 36 months of treatment with romosozumab. Bone metabolism was evaluated by measuring bone turnover markers, namely, procollagen type 1 N-propeptide (P1NP) for assessment of bone formation and tartrate-resistant acid phosphatase 5b (TRACP-5b) for indirect assessment of bone resorption (17, 18). The minimum significant change (MSC) in the percent value from baseline was 12.1% for P1NP and 12.4% for TRACP-5b (19). For patients treated with teriparatide, all baseline data were measured for 3–5 days after the last dose (for daily dosing) or for 1 week (for once-weekly dosing). For patients treated with a bisphosphonate (minodronate), all baseline data were measured for 1 month after the last dose. For patients treated with denosumab, all baseline data were measured for 6 months after the last dose. We also evaluated serum albumin-adjusted calcium, eGFR, and 25-hydroxyvitamin D levels.

Statistical analysis

Patient background characteristics are expressed as the mean ± SD and P1NP and TRACP-5b levels as the median [interquartile range]. Fisher's exact test was used to compare differences in categorical variables. The paired *t*-test was used for pre-post comparisons of normally distributed data. Unpaired samples were analyzed using the Mann–Whitney *U* test. Statistical comparisons between three groups were performed using the Kruskal–Wallis test with the Steel-Dwass test for post hoc comparisons.

All statistical analyses were performed using EZR (20) (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. A P-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

All 23 patients completed 12 months of treatment with romosozumab followed by 24 months of treatment with raloxifene. Their baseline demographics and clinical characteristics are shown in Table 1. The mean patient age was 70.8 ± 9.3 years and all patients were female. The mean BMD was 0.81 ± 0.11 g/cm^2 for the lumbar spine and 0.65 ± 0.08 g/cm^2 for the total hip. Thirteen patients (56.5%) had a prevalent vertebral fracture and one (4.3%) had a history of hip fracture. Ten patients (43.5%) had a history of anti-osteoporosis treatment ; 6 (26.1%) had received teriparatide, 2 (8.7%) had received denosumab, and 2 (8.7%) had received a bisphosphonate (minodronate). None of the patients were heavy drinkers or past or current smokers. Five (21.7%) of the 23 patients had a diagnosis of secondary osteoporosis, which was defined as diminished bone mass secondary to rheumatoid arthritis (5 patients, 21.7%) and current treatment with glucocorticoids (5 patients, 21.7%). The number of patients with each factor was counted, with patients having multiple factors counted once for each factor. None of the postmenopausal patients

Table 1. Clinical characteristics of all 23 patients at baseline

Variable	Value
Age (years)	70.8 ± 9.3
Female sex	23 (100)
Body mass index (kg/m^2)*	21.5 ± 3.6
Bone mineral density (g/cm^2)	
Lumbar spine	0.81 ± 0.11
Total hip	0.65 ± 0.08
Prior vertebral fracture	13 (56.5)
Prior hip fracture	1 (4.3)
Prior osteoporosis treatment	
None	13 (56.5)
Teriparatide	6 (26.0)
Denosumab	2 (8.7)
Bisphosphonate	2 (8.7)
Primary osteoporosis	18 (78.3)
Secondary osteoporosis	5 (21.7)
Concomitant use of vitamin D supplement	17 (73.9)
Concomitant use of active vitamin D	6 (26.1)
Serum total P1NP (μg/L)	60.5 [11.2, 102]
Serum TRACP-5b, mU/dL	346 [119, 663]
Serum albumin (g/dL)	4.1 ± 0.32
Serum corrected calcium (mg/dL)	9.5 ± 0.44
eGFR (mL/min/1.73 m^2)	65.2 ± 10.1
25OHD (ng/mL)	16.2 ± 5.6

The data are shown as the mean ± standard deviation, number (percentage), or median [interquartile range] as appropriate. *Calculated as weight in kilograms divided by the square of height in meters. 25OHD : 25-hydroxyvitamin D, eGFR : estimated glomerular filtration, P1NP : procollagen type 1 N-propeptide, SD : standard deviation, TRACP-5b : tartrate-resistant acid phosphatase 5

received estrogen therapy. There were no coexisting conditions affecting bone metabolism, such as thyrotoxicosis or primary hyperparathyroidism.

Table 2 shows the baseline characteristics when the patients were categorized as pretreatment-naïve (the Naïve group, n = 13) or pretreatment-positive (teriparatide, bisphosphonate, or denosumab ; the TBD group, n = 10). The patients were further divided according to type of osteoporosis and treatment status into the following six groups : a Naïve-P group (with primary osteoporosis and treatment-naïve, n = 11) ; a Naïve-S group (with secondary osteoporosis and treatment-naïve, n = 2) ; a TPD-P group (with primary osteoporosis and previously treated with teriparatide, n = 5) ; a TPD-S group (with secondary osteoporosis and previously treated with teriparatide, n = 1) ; a BD-P group (with primary osteoporosis and previously treated with a bisphosphonate or denosumab (n = 2) ; and a BD-S group (with secondary osteoporosis and previously treated with a bisphosphonate or denosumab, n = 2). The average duration of teriparatide use was 24.0 months in the primary group and 4.0 months in the secondary group ; the average duration of bisphosphonate use was 60.0 months and 24.0 months, respectively, and the average duration of denosumab use was 12.0 months and 12.0 months. There was no significant between-group difference in any parameter at baseline.

The median P1NP level in patients with primary osteoporosis was not significantly different between the three pretreatment groups (P = 0.333) but tended to be highest in the TPD-P group ; comparisons for statistical significance and tendency were similar in patients with secondary osteoporosis in all pretreatment groups.

The median TRACP-5b level in patients with primary osteoporosis was not significantly different between the three pretreatment groups (P = 0.105) but tended to be lowest in the BD-P group ; comparisons for statistical significance and tendency were similar in patients with secondary osteoporosis in all pretreatment groups.

Effects of romosozumab followed by raloxifene on incidence of new fracture and changes in BMD at the spine and total hip

There were no new fractures during the 36-month study period.

In the study group overall, spinal BMD increased from baseline by 7.8% ± 5.1% after 6 months and by 10.5% ± 5.4% after 12 months of treatment with romosozumab. The LSC in spine BMD from baseline was defined as 2.4% ; however, we found that spine BMD showed significant changes beyond the LSC in patients who had been treated with romosozumab for 6 and 12 months. After switching to treatment with raloxifene at 12 months, the mean percent change in spinal BMD from baseline tended to decrease, with a poor result of 2.7% ± 6.4% near the LSC at 36 months (Figure 1a). However, the mean percent change in spinal BMD between baseline and 18 months was 9.5% ± 4.7%, which was only a slight decrease compared with that at 12 months. Moreover, when the 12-month time point was taken as baseline, the mean percent change in spinal BMD from baseline showed a decreasing tendency, with a poor result of –3.3% ± 4.7% above the LSC from 24 months onward (Figure 1b). Conversely, the mean percent change in spinal BMD between the 12-month time point and the 18-month time point was –0.86% ± 2.8%, indicating maintenance of the BMD gained by treatment with romosozumab.

In contrast, the average percent change from baseline in total hip BMD was 1.6% ± 2.2% and 3.4% ± 3.6%, respectively, after 6 and 12 months of treatment with romosozumab in the patient group overall. Considering that the LSC in BMD at the total hip was defined as 3.5%, neither treatment for 6 months nor for 12 months had an effect that was more favorable than the LSC. After switching to raloxifene after 12 months, there was a

Table 2. Clinical characteristics of the Naïve group and the TBD pretreatment group

Variable	Naïve		Teriparatide		Bisphosphonate or denosumab	
	Primary OP	Secondary OP	Primary OP	Secondary OP	Primary OP	Secondary OP
n	11	2	5	1	2	2
Age (years)	72.2 ± 8.8	69.0 ± 1.4	66.2 ± 12.7	78.0	65.0 ± 2.8	79.0 ± 9.9
Body mass index (kg/m^2)*	21.5 ± 2.6	20.8 ± 1.6	23.3 ± 6.3	18.1	20.5 ± 3.9	20.4 ± 1.1
BMD (g/cm^2)						
Lumbar spine	0.80 ± 0.12	0.79 ± 0.00	0.82 ± 0.12	0.95	0.82 ± 0.08	0.75 ± 0.20
Total hip	0.64 ± 0.07	0.64 ± 0.00	0.72 ± 0.10	0.64	0.60 ± 0.01	0.61 ± 0.08
Rheumatoid arthritis	0	2	0	1	0	2
Use of glucocorticoids	0	2	0	1	0	2
Total P1NP (μg/L)	62.7 [26.8, 102]	41.5 [37.3, 45.6]	78.4 [49.5, 98.]	73.9	41.6 [11.2, 72.0]	47.4 [12.9, 81.9]
TRACP-5b (mU/dL)	372.5 [215, 663]	306.5 [228, 385]	420.0 [230, 660]	750.9	70.3 [56.4, 84.1]	151.5 [119, 184]
Albumin (g/dL)	4.1 ± 0.3	3.8 ± 0.1	4.1 ± 0.4	4.1	4.4 ± 0.1	4.2 ± 0.8
Calcium (mg/dL)	9.4 ± 0.3	9.1 ± 0.1	9.6 ± 0.7	9.3	9.9 ± 0.4	9.7 ± 0.5
eGFR (mL/min/1.73 m^2)	66.2 ± 8.9	74.5 ± 2.1	65.8 ± 8.0	60.0	68.0 ± 11.3	56.0 ± 26.9
25OHD (ng/mL)	15.5 ± 4.7	10.5 ± 6.2	22.4 ± 5.1	11.9	12.0 ± 0.8	17.4 ± 1.6

The data are shown as the mean ± standard deviation, number, or median [interquartile range] as appropriate. *Calculated as weight in kilograms divided by the square of height in meters. 25OHD : 25-hydroxy vitamin D, BMD : bone mineral density, eGFR : estimated glomerular filtration, Naïve : treatment-naïve, OP : osteoporosis, P1NP : procollagen type 1 N-propeptide, TBD : teriparatide, bisphosphonate, or denosumab, TRACP-5b : tartrate-resistant acid phosphatase 5b

tendency for the percent change in total hip BMD from baseline to decrease without any evidence of therapeutic effectiveness higher than the LSC at any time point (Figure 1c). When the 12-month time point was taken as baseline, the mean percent change in total hip BMD showed a tendency to decrease, with a poor result of -3.7% ± 4.2% above the LSC at 36 months (Figure 1d).

Next, the percent changes in BMD at the lumbar spine were compared between the Naïve-P, Naïve-S, TPD-P, TPD-S, BD-P, and BD-S groups (Figure 2). The percent change in BMD at the lumbar spine in patients with primary osteoporosis was increased in all groups during romosozumab treatment (Figure 2a). The mean rate of increase was greater in the Naïve-P group (9.5% ± 6.5% at 6 months and 12.3% ± 7.3% at 12 months) than in the TPD-P group (6.6% ± 3.8% and 8.5% ± 2.7%, respectively) or in the BD-P group (4.9% ± 1.4% and 8.9% ± 0.6%, respectively) ; however, the between-group difference was not statistically significant. After switching to raloxifene, the mean percent changes in spinal BMD from baseline showed a tendency to decrease in each group, with poor results of 4.7% ± 6.9% in the Naïve-P group and 3.8% ± 5.9% in the BD-P group near the LSC at 36 months. The therapeutic effectiveness of romosozumab disappeared from 30 months in the TPD-P group (Figure 2a). However, the mean percent change in spinal BMD between baseline and 18 months was 12.0% ± 5.5% in the Naïve-P group and 7.7% ± 0.3% in the BD-P group, which was only a slight decrease compared with that at 12 months, and was 5.5% ± 1.0% in the TPD-P group, which was a greater decrease compared with that in the other groups. With the 12-month time point as baseline, the mean percent change in spinal BMD decreased in each group, with poor results of −4.7% ± 5.1% above the LSC from 30 months in the Naïve-P group, −2.6% ± 2.1% from 18 months in the TPD-P group, and −3.9% ± 4.1% from 24 months in the BD-P group (Figure 2b). In contrast, the mean percent change in spinal BMD between the 12-month and 18-month time points was −0.18% ± 3.5% in the Naïve-P group and −1.1% ± 0.2% in the BD-P group, with maintenance of the BMD gained on romosozumab treatment except in the TPD-P group. The percent change in BMD at the lumbar spine in patients with secondary osteoporosis was almost the same as that in those with primary osteoporosis. The mean percent change in spinal BMD between baseline and 12 months was smaller in the Naïve-S group than in the Naïve-P group (8.8% ± 1.2% vs 12.3% ± 7.3%). The therapeutic effectiveness of romosozumab disappeared from 24 months in the TPD-S group and at 36 months in the Naïve-S and BD-S groups (Figure 2c). With the 12-month time point as baseline, the mean percent change in spinal BMD was −3.8% ± 1.7% in the Naïve-S group and −6.5% in the TPD-P group at 24 months ; these decreases were greater than the decreases of −2.1% ± 5.3% in the Naïve-P group and −2.6% ± 2.1% in the TPD-P group (Figure 2d).

The average percent change in total hip BMD from baseline in patients with primary osteoporosis was 1.8% ± 1.8% at 6 months and 4.6% ± 2.8% at 12 months in the Naïve-P group, 1.3% ± 2.0% and 2.6% ± 3.8%, respectively, in the TPD-P group and 0.3% ± 6.2% and 3.4% ± 0.4% in the BD-P group (Figure 3a). After switching to raloxifene, the maximum percent change in total hip BMD from baseline was 5.8% ± 3.5% at 18 months in the Naïve-P group, which decreased thereafter. However, the percent change in total hip BMD from baseline in the TPD-P and

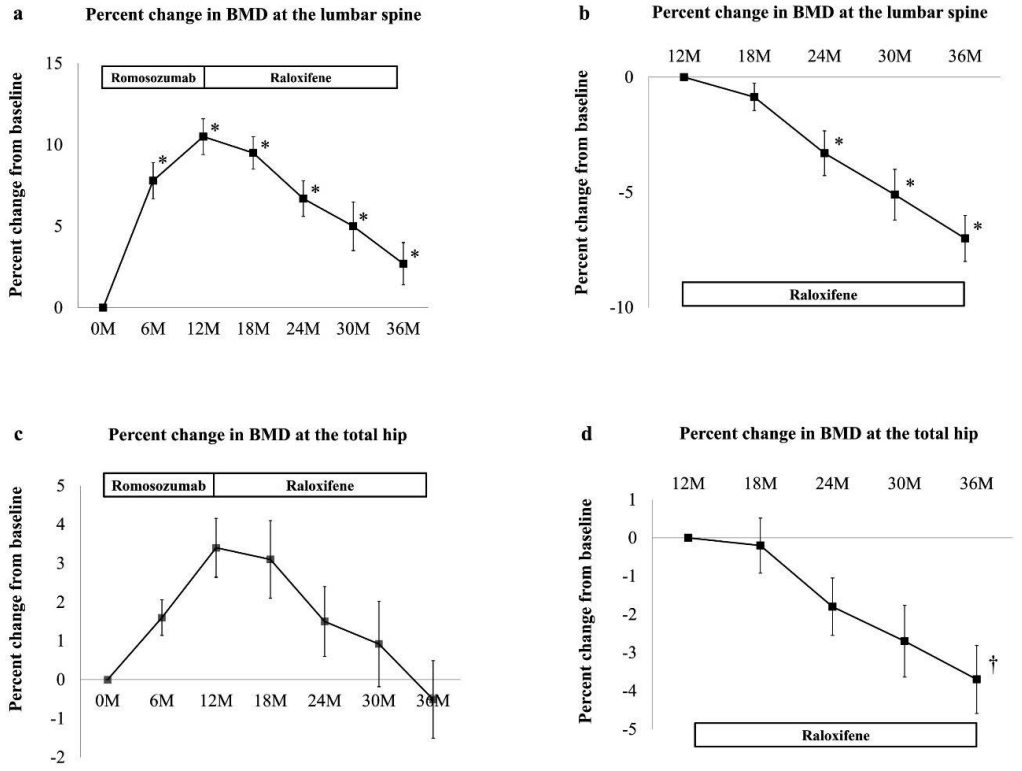

Figure 1. Percent change in BMD at the lumbar spine in all patients from baseline (a) and from 12 months (b) and at the total hip from baseline (c) and from 12 months (d). *Significant change beyond LSC (2.4%), †Significant change beyond LSC (3.5%). BMD : bone mineral density, LSC : least significant change

BD-P groups decreased continuously from 12 months onward, with a particularly poor result of –3.6% ± 7.7% above the LSC at 24 months in the BD-P group. With the 12-month time point as baseline, the percent change in total hip BMD in each group showed a tendency to decrease from 24 months, with poor results of –3.5% ± 3.9% at 36 months in the Naïve-P group, –4.7% ± 0.6% at 30 months in the TPD-P group, and –6.8% ± 7.8% at 24 months in the BD-P group (Figure 3b). The mean percent change in total hip BMD from baseline in patients with secondary osteoporosis was –7.7% at 12 months in the TPD-S group and continued to decrease in this group beyond 12 months after switching to raloxifene (Figure 3c). With the 12-month time point as baseline, the mean percent change in total hip BMD decreased in the Naïve-S group, with a poor result of –3.7% ± 3.2% at 18 months (Figure 3d).

Changes in calcium, 25-hydroxyvitamin D, and bone turnover markers during 3 years of treatment.

Serum albumin-adjusted calcium measurements after 1, 6, 12, 18, 24, 30, and 36 months of treatment did not indicate symptomatic hypocalcemia. All patients in the study received a vitamin D3 supplement or an active vitamin D3 analog depending on their renal function. The mean serum calcium level decreased from 9.40 ± 0.44 mg/dL at baseline to 9.27 ± 0.28 mg/dL after 1 month of treatment (P = 0.085). Thereafter, the serum calcium level returned to approximately the baseline value. The serum 25-hydroxyvitamin D increased significantly from 17.1 ± 5.8 ng/mL at baseline to 29.4 ± 8.3 ng/mL after 36 months (P < 0.001) in the 17 patients who received a vitamin D3 supplement (25 μg/day).

The percent change in serum P1NP from baseline in the patient group overall showed an increase above the MSC (12.1%) (19) at all time points through to 12 months with a peak at 1 month (Figure 4a). However, the percent change in P1NP from baseline did not show a significant change from 18 months onward after switching to raloxifene. With the 12-month time point as baseline, the percent change in P1NP showed a significant decrease beyond the MSC at each time point after switching to raloxifene (Figure 4b). The percent change in TRACP-5b from baseline in the patient group overall showed a significant decrease beyond the MSC (12.4%) (19) after 1 month and 12 months of treatment with romosozumab. In contrast, the percent change in TRACP-5b from baseline consistently showed a significant increase beyond the MSC after switching to raloxifene (Figure 4c). With the 12-month time point as baseline, the percent change in TRACP-5b showed a significant increase at all time points after switching to raloxifene therapy (Figure 4d).

The percent change in serum P1NP from baseline in the Naïve-P group showed an increase above the MSC at all time points through to 12 months, with a peak at 1 month, and showed a decrease above the MSC from 18 months onward after switching to raloxifene. The percent change in serum P1NP from baseline in the TPD-P group showed a decrease above the MSC from 6 months onward. The percent change in serum P1NP from baseline in the BD-P group showed an increase above the MSC at all time points through to 36 months, with a peak at 12 months (Figure 5a). Taking the 12-month time point as the baseline, the percent change in P1NP in each group showed a significant decrease beyond the MSC at each time point after switching to raloxifene (Figure 5b). The percent change in

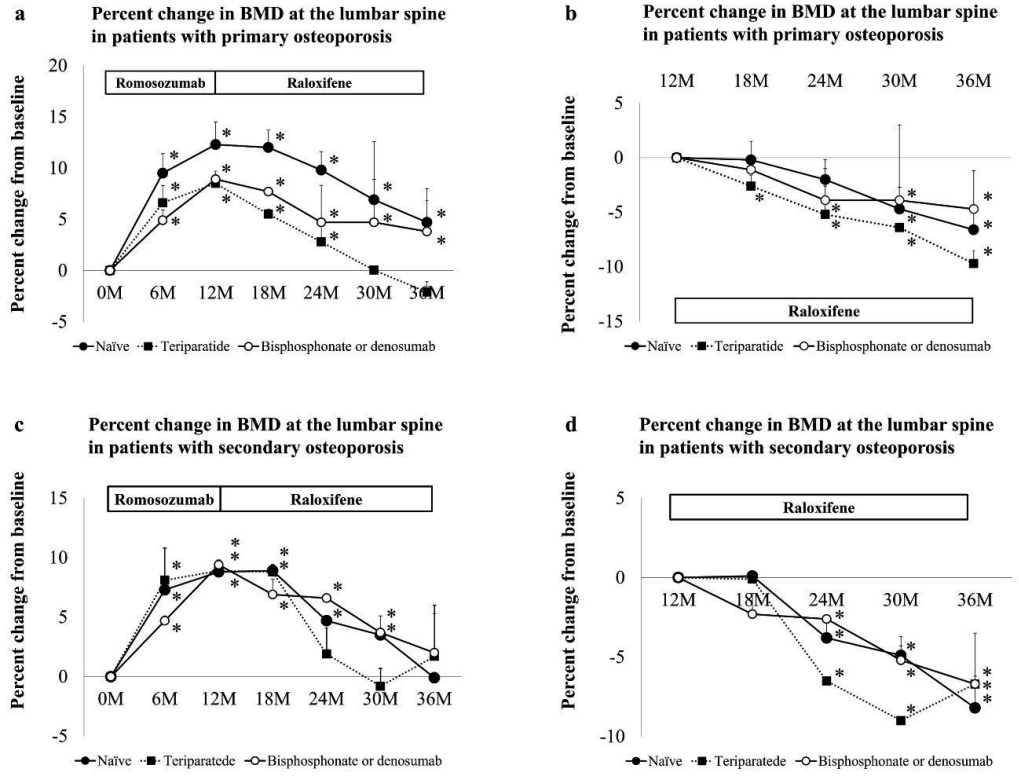

Figure 2. Percent change in BMD at the lumbar spine in the Naïve, TPD pretreatment, and BD pretreatment groups with primary osteoporosis from baseline (a) and from 12 months (b) and in the groups with secondary osteoporosis from baseline (c) and from 12 months (d). *Significant change beyond LSC (2.4%). BD, bisphosphonate or denosumab, BMD : bone mineral density, LSC : least significant change. Naïve : treatment-naïve, TPD : teriparatide

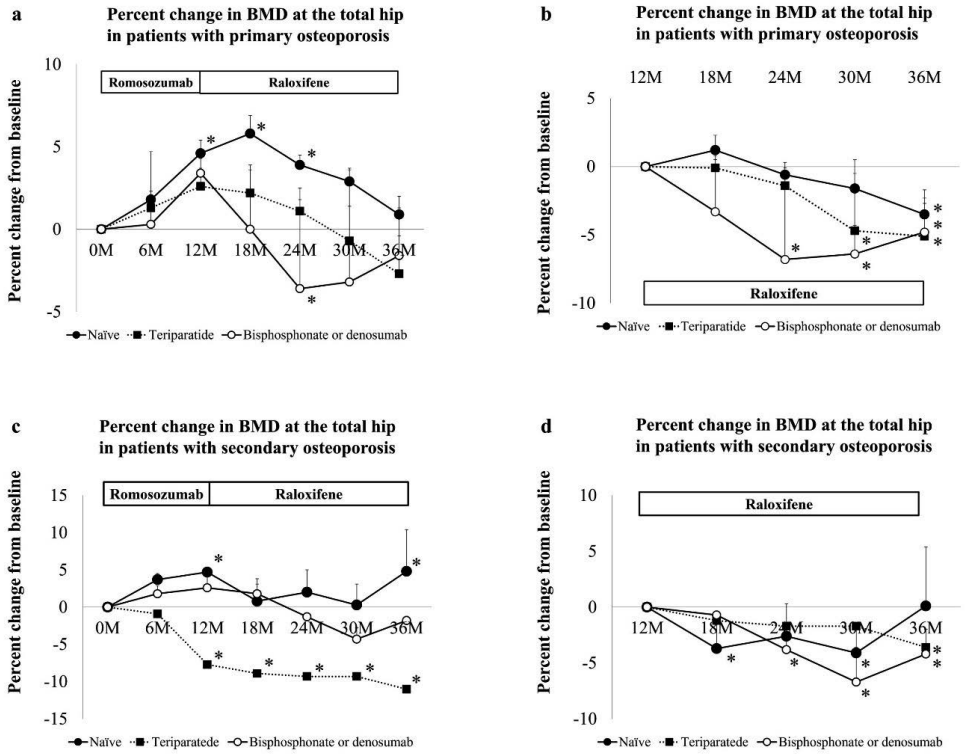

Figure 3. Percent change in BMD at the total hip in the Naïve, TPD pretreatment, and BD pretreatment groups with primary osteoporosis from baseline (a) and from 12 months (b) and in the groups with secondary osteoporosis from baseline (c) and from 12 months (d). *Significant change beyond LSC (3.5%). BD : bisphosphonate or denosumab, BMD : bone mineral density, LSC : least significant change, Naïve : treatment-naïve, TPD : teriparatide

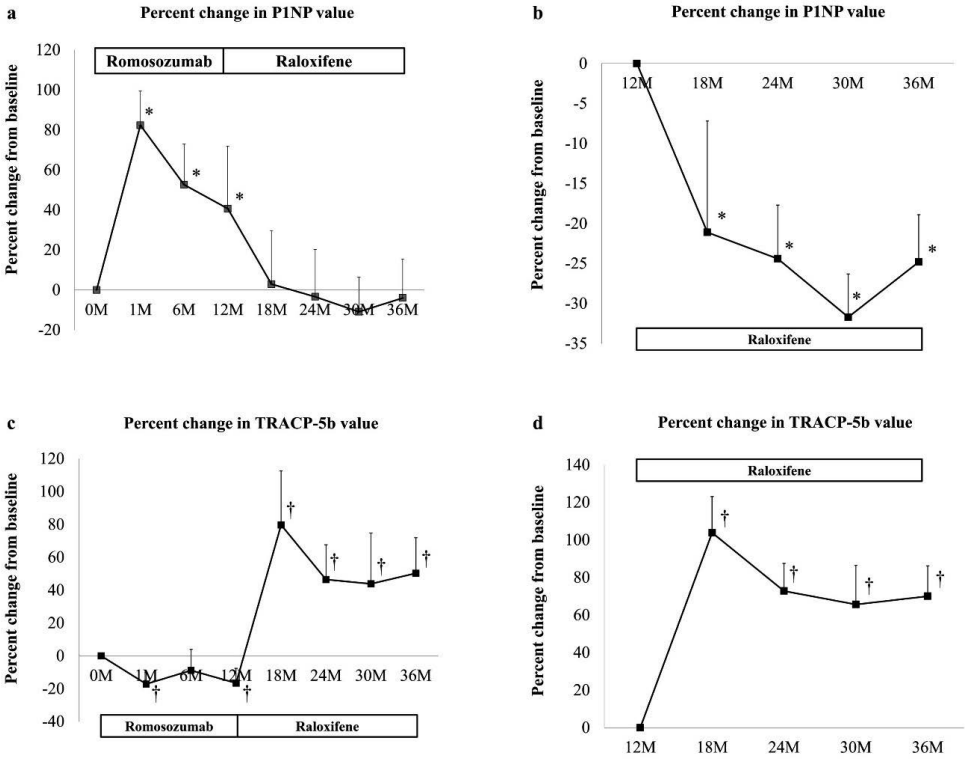

Figure 4. Percent change in P1NP in all patients from baseline (a) and from 12 months (b). Percent change in TRACP-5b in all patients from baseline (c) and from 12 months (d). *Significant change beyond MSC (12.1%). †Significant change beyond MSC (12.4%). MSC : minimum significant change, P1NP : procollagen type 1 N-propeptide, TRACP-5b : tartrate-resistant acid phosphatase 5b

TRACP-5b from baseline in the Naïve-P and TPD-P groups showed a significant decrease beyond the MSC after 1 month and 12 months of treatment with romosozumab. In contrast, the percent change in TRACP-5b from baseline in the Naïve-P and TPD-P groups consistently showed a significant increase beyond the MSC after switching to raloxifene except in the TPD-P group at 18 months. The percent change in TRACP-5b from baseline in the BD-P group consistently showed a significant increase beyond the MSC through to 36 months (Figure 5c). With the 12-month time point as baseline, the percent change in TRACP-5b in each group showed a significant increase at all time points after switching to raloxifene therapy (Figure 5d). The percent changes in P1NP and TRACP-5b from baseline in the patients with secondary osteoporosis showed almost the same tendency as those in patients with primary osteoporosis (Figure 6).

DISCUSSION

In this study, spinal BMD increased after 12 months of romosozumab and then decreased to the baseline level after 24 months of raloxifene, while BMD in patients with primary osteoporosis who were treatment-naïve before starting romosozumab was well maintained for up to 6 months after switching to raloxifene. The P1NP level decreased rapidly beyond the baseline value while the TRACP-5b level continued to increase after the switch to raloxifene.

Romosozumab, which has the dual effect of increasing bone formation and decreasing bone resorption, provides rapid gains in BMD during a 12-month course of treatment (21). However, the effect of romosozumab on BMD is reversible upon discontinuation, after which BMD returns toward pretreatment levels during 12 months without follow-on therapy (7). Therefore, romosozumab should be followed by an antiresorptive agent to maintain or augment the BMD gains and the reduction in fracture risk achieved (8). The pivotal studies confirmed the efficacy of denosumab and alendronate as antiresorptive treatments following romosozumab in terms of maintaining the increases in BMD and reducing the fracture risk (5, 9, 10). There is evidence suggesting that raloxifene increases BMD at the lumbar spine and reduces the vertebral fracture risk in postmenopausal women (13). Raloxifene also has antiresorptive activity (14), although its effect in terms of suppressing bone resorption is weaker than that of alendronate (22) and denosumab (23). However, the present study is the first to report on the effects of administration of raloxifene following treatment with romosozumab in the real-world setting.

We did not identify any romosozumab-related cardiovascular events (9), and there were no injection site reactions, which have been reported to be relatively frequent with romosozumab (24), or any venous thromboembolic events, which are reportedly an adverse event associated with raloxifene (25). Treatment with raloxifene for 24 months following 12 months of romosozumab was well tolerated in our study population, and all patients could receive their 36-month treatment course. The highest rate of reduction in corrected calcium was at 1 month after starting treatment with romosozumab. Hypocalcemia should be kept in mind during treatment with romosozumab. All patients in our study received a vitamin D3 supplement (25 μg/day) or an active vitamin D3 analog depending on their renal function when

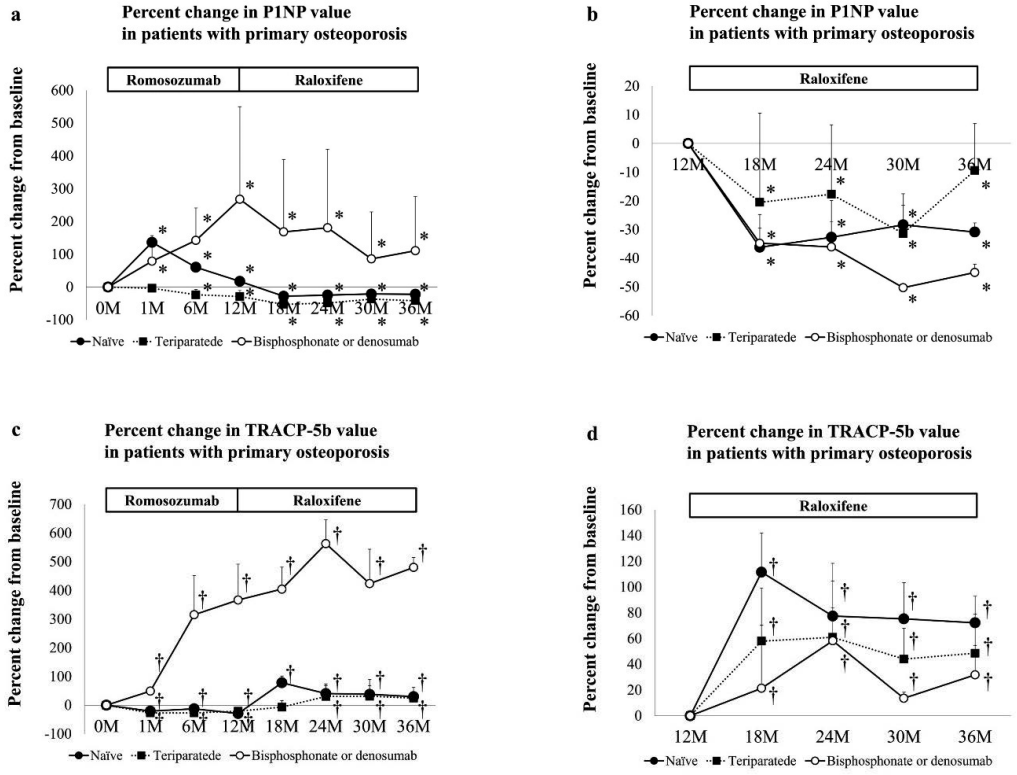

Figure 5. Percent change in P1NP in the Naïve, TPD pretreatment, and BD pretreatment groups with primary osteoporosis from baseline (a) and from 12 months (b). Percent change in TRACP-5b in each group with primary osteoporosis from baseline (c) and from 12 months (d). *Significant change beyond MSC (12.1%). †Significant change beyond MSC (12.4%). BD : bisphosphonate and denosumab, MSC : minimum significant change, Naïve : treatment-naïve, P1NP : procollagen type 1 N-propeptide, TPD : teriparatide, TRACP-5b : tartrate-resistant acid phosphatase 5b

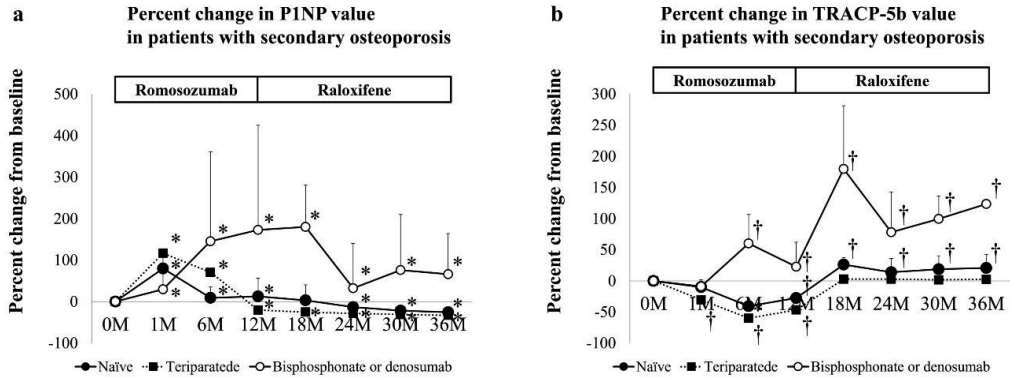

Figure 6. Percent change in P1NP in the Naïve, TPD pretreatment, and BD pretreatment groups with secondary osteoporosis from baseline (a). Percent change in TRACP-5b in each group with secondary osteoporosis from baseline (b). *Significant change beyond MSC (12.1%). †Significant change beyond MSC (12.4%). BD : bisphosphonate or denosumab, MSC : minimum significant change, Naïve : treatment-naïve, P1NP : procollagen type 1 N-propeptide, TPD : teriparatide, TRACP-5b : tartrate-resistant acid phosphatase 5b

starting treatment.

In this study, BMD in patients with primary osteoporosis who were treatment-naïve increased by a mean of 12.3% at the lumbar spine and by 4.6% at the total hip during a 12-month course of romosozumab and was maintained at 12.0% and 5.8%, respectively, during 6 months of sequential treatment with raloxifene. From then onward, BMD continued to decrease, so long-term use of raloxifene following romosozumab is not recommended. However, considering that if no treatment is given after romosozumab, the increase in BMD achieved by romosozumab is reduced to about half within 6 months (8), the efficacy of sequential treatment with raloxifene for 6 months following romosozumab is noteworthy. Of course, it is desirable to administer a bisphosphonate or denosumab as a sequential treatment after romosozumab. However, patients who require dental treatment after romosozumab may not be able to receive these drugs in the real-world setting. In this observational study, we administered raloxifene in some patients who were not candidates for bisphosphonate or denosumab as a result of needing dental treatment after completing romosozumab. Sequential raloxifene therapy for up to 6 months can allow such patients to safely undergo dental treatment while maintaining the gain in BMD achieved by romosozumab. The findings of this study suggest that sequential treatment with raloxifene for 6 months after romosozumab may be an option as a bridge to treatment with a bisphosphonate or denosumab. In previous studies (8, 26, 27), treatment with an anti-osteoporosis agent (teriparatide, bisphosphonate, or denosumab) before starting romosozumab markedly attenuated the changes in BMD, with a greater increase in BMD seen in treatment-naïve patients. The influence of pretreatment with raloxifene on the BMD-increasing effect of romosozumab is still unclear. If previous administration of raloxifene does not affect the BMD-increasing effect of romosozumab to a greater extent than a bisphosphonate or denosumab, in view of our present findings, a strategy of "first course of romosozumab, 6 months of sequential raloxifene, and a second course of romosozumab" might be established for severe treatment-naïve primary osteoporosis.

BMD at the spine decreased rapidly in the TPD-P and BD-S groups after switching to raloxifene, as did BMD at the total hip in the BD-P and Naïve-S groups. Therefore, raloxifene is not recommended, even as 6 months of sequential therapy following romosozumab, in patients with secondary osteoporosis who have been previously treated with teriparatide, a bisphosphonate, or denosumab.

The average duration of denosumab use was 12.0 months in our primary osteoporosis group and 12.0 months in our secondary osteoporosis group, and the respective average duration of oral bisphosphonate (minodronate) therapy was 60.0 months and 24.0 months. A previous study found that using an oral bisphosphonate or denosumab for more than 12 months attenuated the effect of romosozumab (28). The average duration of teriparatide use was 24.0 months in our primary osteoporosis group and 4.0 months in our secondary osteoporosis group. It has been reported that the duration of previous treatment with teriparatide does not have a clear impact on the effectiveness of 12 months of treatment with romosozumab (28). In the present study, previous use of teriparatide had a similar effect on the efficacy of romosozumab in both groups.

Our investigation of bone turnover markers showed that the percent change in the TRACP-5b level from baseline continued to decrease during treatment with romosozumab and increased rapidly after switching to raloxifene in both the treatment-naïve group and the group with a history of previous anti-osteoporosis treatment. Alendronate (9) and denosumab (10) have been reported to suppress any increase in bone resorption marker levels after discontinuation of romosozumab. As expected, when comparing the studies, the effect of suppression of bone resorption was weaker for raloxifene than for representative antiresorptive agents. However, in the treatment-naïve group, the percent change in the P1NP level from baseline decreased rapidly beyond the baseline value and continued to decrease after switching to raloxifene. A previous study demonstrated that the P1NP level increased slightly in a placebo group and returned to baseline in response to discontinuation of treatment in a romosozumab group (7). Therefore, raloxifene might have suppressed rebound bone resorption slightly in the treatment-naïve group in response to discontinuation of romosozumab. Another study demonstrated that raloxifene following denosumab could not suppress acceleration of bone resorption in response to discontinuation of denosumab, and both TRACP-5b and P1NP levels increased rapidly after switching to raloxifene (8). Based on these reports and our study findings, the rebound phenomenon associated with romosozumab might be weaker than that associated with denosumab.

We found no new fractures during 24 months of raloxifene follow-on treatment after discontinuation of romosozumab, even though the gains in bone mass after 12 months of romosozumab were lost after switching to raloxifene. Raloxifene reduces the vertebral fracture risk as effectively as alendronate despite having a weaker effect on spine BMD (29). The effect of raloxifene on the reduction of fracture risk might reflect an improvement in bone quality (30). A previous study (21) found that the new clinical vertebral fracture rate was 0.0% during 12 months of follow-on raloxifene after discontinuation of denosumab. However, another study of raloxifene after denosumab found a new clinical vertebral fracture rate of 22.3% after 18 months (vs 3.4% for a weekly or monthly bisphosphonate and 0.0% for zoledronate) (31). These studies concluded that raloxifene following denosumab had insufficient effectiveness because of loss of bone mass. There have been no reports on the ability of raloxifene to prevent vertebral fracture after discontinuation of romosozumab. However, loss of BMD as a result of relatively expensive treatment with romosozumab is a potential problem even if no new fragility fractures occur.

This study has some limitations. First, it had a small sample, which might have limited the statistical power. Second, the view that bisphosphonates and denosumab are difficult to use in patients who require dental treatment because of concerns about osteonecrosis of the jaw may be unique to Japan. However, the results of this study are useful for patients in whom it is not possible to administer a bisphosphonate or denosumab promptly after romosozumab.

CONCLUSIONS

In this study, raloxifene could not maintain the BMD gains made on romosozumab or suppress rebound bone resorption after discontinuation of romosozumab. Romosozumab followed by raloxifene is acceptable for use for 6 months in treatment-naïve patients with primary osteoporosis in whom a bisphosphonate or denosumab cannot be rapidly introduced for whatever reason. However, more aggressive use of raloxifene is not recommended.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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AUTHROTS' CONTRIBUTIONS

Kazuaki Mineta was responsible for conceptualization, methodology, visualization, formal analysis and writing - original draft. Toshihiko Nishisho was responsible for supervision, writing - review and editing. Masahiko Okada was responsible for investigation. Mitsuhiro Kamada was responsible for data curation. Sairyo Koichi was responsible for project administration.

DATA AVAILABILITY

The data used in this study are available from the corresponding author upon request.

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