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ORIGINAL ARTICLE

The effect of romosozumab on bone mineral density depending on prior treatment: a prospective, multicentre cohort study in Switzerland

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Abstract

Summary This multicentre, prospective cohort study measured the effect of romosozumab for 12 months on bone mineral density, taking into account prior therapies. Prior antiresorptive therapy blunted the BMD response to romosozumab, and the duration was correlated with BMD changes at both the lumbar spine and total hip.

Introduction In Switzerland, romosozumab is administered to high-risk osteoporosis patients. Our study aimed to assess the effect of romosozumab on bone mineral density (BMD), taking into account prior therapies.

Methods This multicentre, prospective cohort study measured the effect of romosozumab for 12 months in patients in a nationwide Swiss osteoporosis registry. BMD and bone turnover marker (P1NP and CTX) changes were measured and compared between pre-treated and treatment naïve patients.

Results Ninety-nine patients (92 women and 7 men, median age 71 years [65, 76]) were enrolled from January 2021 to December 2023. Among them, 22 had no prior treatment before romosozumab, while 77 had previous therapy (including 23 with a history of prior teriparatide therapy), with a median duration of 6 years [4, 11] of cumulative antiresorptive treatment. Over 12 months, romosozumab led to BMD changes of 10.3% [7.5, 15.5] at the lumbar spine, 3.1% [1.1, 5.8] at the total hip and 3.1% [0.5, 5.3] at the femoral neck, indicating notable variability. Significantly lower BMD responses were observed in pre-treated patients, with the duration of prior antiresorptive therapy inversely associated with BMD increases at the lumbar spine and hip. Other predictors of BMD changes at the total hip included baseline T-scores at the hip, body mass index and baseline CTX level, while the BMD response at the lumbar spine was associated with the lumbar spine T-score at baseline, age and baseline CTX level.

Conclusion Prior antiresorptive therapy blunted the BMD response to romosozumab, and the duration was correlated with BMD changes at both the lumbar spine and total hip.

Keywords Bone mineral density · Fractures · Osteoporosis · Romosozumab

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Introduction

Romosozumab is a bone-forming agent that inhibits sclerostin, exerting a dual effect on bone by increasing bone formation and decreasing bone resorption [1, 2]. It leads to substantial gains in bone mineral density (BMD) at both the lumbar spine and hip [3–5], and reduces the incidence of fractures in postmenopausal women [4, 5]. Romosozumab has demonstrated significantly greater efficacy in reducing fracture risk compared to alendronate [5]. In Switzerland, romosozumab is approved for the treatment of postmenopausal women at high risk of fragility fractures, and may be authorized as an exception for men with a very high fracture risk [6]. Specifically, reimbursement is provided for the following patients: those who have experienced a major osteoporotic fracture within the last 24 months and who have a T-score ≤ -3.5 SD (lumbar spine or hip); those with two major osteoporotic fractures; and those without fractures but with a very high fracture risk. This very high fracture risk category is defined by FRAX® Switzerland as exceeding the intervention threshold by 20%, as per the recommendations of the Swiss Association against Osteoporosis [7]. While romosozumab may be used as a first-line therapy, most patients meeting the reimbursement criteria are likely to have been pre-treated with antiresorptive agents. Both clinical trials and real-world data have shown that prior antiresorptive therapy blunts the BMD gains under romosozumab [8–10]. In a randomised phase III trial, the effect of romosozumab on BMD and bone strength was assessed against teriparatide in patients previously treated with oral bisphosphonates for at least 3 years [11]. However, there is limited knowledge regarding the effects of romosozumab after treatment with parenteral bisphosphonates, denosumab or teriparatide. Our study aims to evaluate the impact of romosozumab on BMD in a real-world population, taking into account prior oral and parenteral therapies, and to identify the most relevant predictors of BMD gains at both the lumbar spine and total hip.

Methods

Setting and outcome

This ongoing, prospective, multicentre cohort study aims to analyse the efficacy and safety of romosozumab in patients with osteoporosis. The data are being systematically recorded by treating physicians in a national registry for osteoporosis maintained by the Swiss Osteoporosis Platform. This registry consecutively enrols subjects referred for a dual-energy X-ray absorptiometry (DXA) scan, and to date, three outpatient centres in Bern, Zurich, and Lucerne include patients undergoing romosozumab therapy. Previously described variables are assessed for each patient [12–14], and additional data are collected for patients receiving romosozumab, including cardiovascular risk factors and outcomes. The primary objective of this initial analysis was to identify predictive factors, in particular prior therapies, for changes in BMD after 12 months of therapy with romosozumab. The primary endpoints were the percentage changes in BMD (in g/cm2) under romosozumab at the lumbar spine, total hip and femoral neck. The secondary endpoints included the evolution of bone turnover markers (BTMs), as well as safety outcomes and the fracture rates before and during romosozumab therapy.

Study population

The patients reviewed in this study were treated with romosozumab for 11–12 months (210 µg monthly) and evaluated by DXA between January 1, 2021, and December 31, 2023. Postmenopausal women and men aged ≥ 50 years who received ≥ 11 romosozumab injections and who underwent DXA and vertebral fracture assessment (VFA) on the days of the first and last romosozumab injections were eligible for the study.

BMD at the lumbar spine (L1-L4), total hip and femoral neck was measured before starting romosozumab ("baseline", DXA1) and at the last romosozumab injection (DXA2). At both time points, VFA was performed with standardized screening for morphometric vertebral fractures [15]. Clinically or morphometrically diagnosed vertebral fractures were confirmed by MRI and/or lateral X-rays of the thoracolumbar spine. All measurements in each patient were performed using the same device. All patients were asked once a month about clinical fractures and side effects. Calcium (albumin corrected) and 25-OH vitamin D levels in the serum were measured before starting romosozumab, and calcium was also measured at least once 1–3 months after its initiation. If possible, C-terminal telopeptide of type I collagen (CTX) and/or N-terminal propeptide of type 1 procollagen (P1NP) concentrations were recorded at baseline, 1–3 months after starting romosozumab and at the last injection. The normal reference range for the CTX concentration in postmenopausal women was 0.06–0.50 ng/ml, while that for the P1NP concentration was 15–59 ng/ml.

The study protocol was reviewed and approved by the local ethical committee (swissethics, 2022–02189), and all patients provided written informed consent for further use of their health-related data.

Statistical analysis

The primary outcome was the difference in BMD (g/cm^2) after romosozumab treatment, expressed as the percentage of the BMD at the initial assessment. To investigate the association between prior antiresorptive therapy and the change in BMD after romosozumab treatment, we performed linear regression that first includes only romosozumab treatment as the covariate, and then also age, body mass index (BMI), prior anabolic therapy, and P1NP and CTX concentrations (both at baseline and after 1–3 months). Prior antiresorptive therapy was modelled as a binary value (yes/no) and also as the duration in years. As some blood tests results (P1NP and/or CTX) were missing in some patients, we applied multiple imputation including age, BMI, T-scores at the lumbar spine, total hip and femoral neck and P1NP and CTX-levels (at baseline and after 1–3 months) to construct 20 datasets based on chained equations. We carried out a sensitivity analysis to assess the impact of enrolment site, using linear mixed models with enrolment site as random factor. Continuous variables were summarised as median with interquartile range and compared using the Wilcoxon-Mann–Whitney test, while categorical variables were shown as number with percentage and were compared using Fisher's exact test. All analyses were conducted using Stata 16.0 (StataCorp LLT, 4905 Lakeway Drive, College Station, Texas).

Results

Study cohort

Between January 1, 2021 (the date of the first enrolment of a patient receiving Evenity® (romosozumab), which was approved in Switzerland in August, 2020), and December 31, 2023, 234 patients received ≥ 1 dose of romosozumab and were evaluated by DXA and VFA at one of the three outpatient centres (Fig. 1).

Of the 234 patients, 124 had ongoing treatment with romosozumab, while 110 discontinued romosozumab. Eleven of the 110 patients stopped taking romosozumab due to possible side effects, including one case each of myocardial infarction, stroke, and death (suspected septic shock after abdominal infection). A total of 99 patients each received 11–12 romosozumab injections and were switched to a subsequent antiresorptive therapy (denosumab $n=49$, zoledronate $n=41$, ibandronate $n=7$, alendronate $n=1$, unknown $n=1$). All patients received calcium and vitamin D supplementation during and after romosozumab therapy.

Age distribution, sex, BMI (kg/m^2), prevalent vertebral and non-vertebral fractures, prior treatment, baseline T-scores at different locations, baseline bone turnover markers and calcium and vitamin D levels are shown in Table 1,

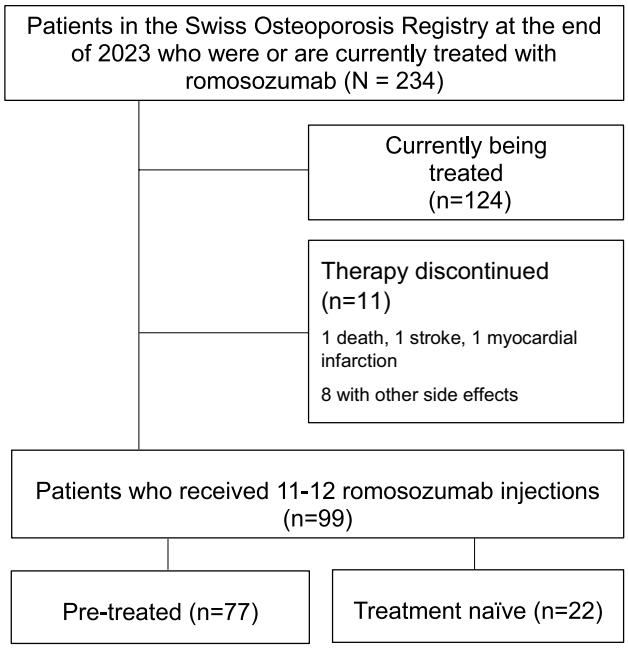

Fig. 1 Flowchart of study cohort

according to prior therapy or lack thereof. Patients who were treatment naïve before romosozumab was started exhibited lower baseline T-scores and higher CTX and P1NP levels, respectively, than patients who had received prior antiresorptive therapy. They also had a significant lower vitamin D level, although the mean level of 25 OH vitamin D (74 nmol/l) indicates sufficient repletion. Further, the P1NP level, measured 1–3 months after romosozumab was started, was significantly higher in treatment-naïve patients. In addition, a comparison of included ($n=99$) and excluded ($n=11$) patients revealed no significant differences, except that all excluded patients were treatment naïve before romosozumab was started (data not shown).

Description of prior treatment modalities before romosozumab

The majority of the 99 patients ($n=77$, 78%) received different prior therapies before the initiation of romosozumab. These prior treatment sequences included various bisphosphonates, as well as denosumab and teriparatide. Specifically, 74 patients received bisphosphonates (median cumulative duration of 5 years [3, 7]) and 29 received denosumab (median duration of 5 years [2, 7]). Twenty-three patients were treated with teriparatide at some point, although most of them received a long course of antiresorptive therapy (median 3 years [1, 7]) between teriparatide treatment and the start of romosozumab administration. Further, the cumulative duration of antiresorptive therapy (e.g., administered before teriparatide and after teriparatide/before

Table 1 Patient characteristics at baseline

	Total ($N=99$)	Naïve ($n=22$)	Pre-treated ($n=77$)	p-value
Age (years)	71 (65 to 76)	71 (63 to 75)	71 (65 to 77)	0.69
Sex				0.65
Female	92 (93%)	20 (91%)	72 (94%)	
Male	7 (7.1%)	2 (9.1%)	5 (6.5%)	
BMI (kg/m2)	22 (20 to 25)	23 (20 to 26)	22 (20 to 24)	0.46
Pre-treated with TPTD	23 (23%)	0 (0.00%)	23 (30%)	**0.002**
Duration of antiresorptive pre-treatment (years)	5.0 (0.00 to 9.0)	0.00 (0.00 to 0.00)	6.0 (4.0 to 11)	**< 0.001**
Prior non-vertebral Fx	58 (59%)	10 (45%)	48 (62%)	0.10
Prior vertebral Fx	61 (62%)	17 (77%)	44 (57%)	0.19
Number of prior Fx	2.0 (1.0 to 4.0)	2.0 (1.0 to 3.0)	2.0 (1.0 to 4.0)	0.69
T-score lumbar spine	-3.2 (-3.7 to -2.1)	-3.8 (-4.3 to -3.0)	-3.0 (-3.7 to -1.9)	**0.003**
T-Score total hip	-2.4 (-2.8 to -1.9)	-2.8 (-3.0 to -2.3)	-2.3 (-2.7 to -1.7)	**0.008**
T-score femoral neck	-2.4 (-2.9 to -1.9)	-2.8 (-3.0 to -2.1)	-2.3 (-2.7 to -1.9)	0.08
P1NP (ng/ml)	37 (28 to 49)	64 (35 to 71)	34 (27 to 44)	**0.007**
CTX (ng/ml)	0.31 (0.21 to 0.42)	0.43 (0.39 to 0.59)	0.29 (0.19 to 0.39)	**0.024**
Calcium (mg/l)	2.37 (2.26 to 2.43)	2.37 (2.29 to 2.44)	2.36 (2.25 to 2.44)	0.88
25 OH Vit. D (ng/ml)	84 (72 to 104)	74 (58 to 83)	88 (75 to 106)	**0.012**
P1NP after 1–2 months	77 (57 to 96)	93 (81 to 120)	76 (56 to 95)	**0.022**
CTX after 1–2 months	0.19 (0.12 to 0.29)	0.22 (0.16 to 0.41)	0.19 (0.11 to 0.29)	0.25
Calcium after 1–2 months	2.3 (2.3 to 2.4)	2.3 (2.2 to 2.4)	2.3 (2.3 to 2.4)	0.29

Abbreviations: BMI: Body mass index (kg/m^2), CTX: C-terminal telopeptide of type I collagen, Fx: fractures, P1NP: N-terminal propeptide of type 1 procollagen, TPTD: teriparatide

Continuous variables: Median ± interquartile range [IQR], Categorical variables: Percentage of total of each subgroup

romosozumab) was 6 years [3, 9], and this duration did not differ from that in patients who received prior antiresorptive treatment, but not teriparatide before romosozumab (median duration of 6 years, [5, 11], $p=0.15$).

Most patients ($n=49$) were switched directly from a parenteral bisphosphonate pre-treatment to romosozumab, while 27 underwent a drug holiday of approximately 1–2 years between their last treatment and the initiation of romosozumab.

Predictors of BMD changes under romosozumab

Over 12 months, romosozumab led to BMD changes of 10.3% [7.5, 15.5] at the lumbar spine, 3.1% [1.1, 5.8] at the total hip and 3.1% [0.5, 5.3] at the femoral neck, indicating notable variability at both the lumbar spine and hip. Significantly smaller BMD responses were observed in pre-treated patients, specifically 10.1% [5.8 to 14.4] at the lumbar spine, 2.9% [0.7, 4.7] at the total hip and 2.0% [0.1, 5] at the femoral neck ($p=0.05$, $p=0.02$ and $p<0.001$, respectively), as shown in Fig. 2. Treatment-naïve patients, on the other hand, experienced BMD changes of 14.6% [9.9, 17.9] at the lumbar spine, 5.0% [3.1, 7.4] at the total hip and 5.9% [3.0, 8.3] at the femoral neck (Table 2).

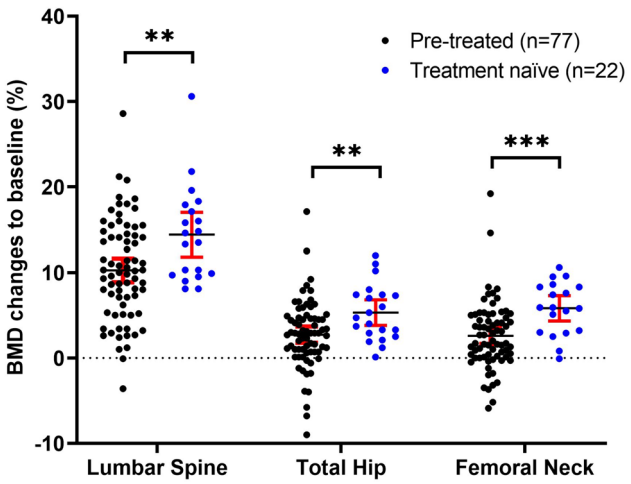

Fig. 2 Percentage BMD changes relative to baseline (mean ± 95% CI) in pre-treated ($n=77$, black) versus treatment-naïve patients ($n=22$, blue) after 12 months of romosozumab treatment. ** $p \leq 0.005$, *** $p \leq 0.001$

A linear regression model was used to analyse other predictors of BMD response, as summarised in Table 3. This analysis shows that higher age was associated with a lower BMD increase at the lumbar spine (-0.18% per year) but not

Table 2 Patient characteristics at the end of treatment with romosozumab

	Total ($N=99$)	Naïve ($N=22$)	Pre-treated ($N=77$)	p-value
CTX at 12 months	0.20 (0.13 to 0.30)	0.33 (0.22 to 1.1)	0.19 (0.13 to 0.29)	0.15
Calcium at 12 months	2.3 (2.3 to 2.4)	2.3 (2.3 to 2.4)	2.4 (2.3 to 2.4)	0.99
25 OH Vit. D at 12 months	83 (70 to 99)	89 (75 to 118)	80 (68 to 92)	0.38
BMD Δ lumbar spine (%)	10.3 (7.5 to 15.5)	14.6 (9.9 to 17.9)	10.1 (5.8 to 14.4)	**0.005**
BMD Δ total hip (%)	3.1 (1.1 to 5.8)	5.0 (3.1 to 7.4)	2.9 (0.70 to 4.7)	**0.002**
BMD Δ femoral neck (%)	3.1 (0.50 to 5.3)	5.9 (3.0 to 8.3)	2.0 (0.10 to 5.0)	**<0.001**
T-score DXA2 LS	-2.5 (-3.0 to -1.5)	-2.9 (-3.3 to -2.3)	-2.3 (-3.0 to -1.3)	**0.013**
T-score DXA2 TH	-2.2 (-2.6 to -1.7)	-2.4 (-2.7 to -1.9)	-2.1 (-2.4 to -1.6)	0.08
T-Score DXA2 FN	-2.3 (-2.7 to -1.7)	-2.4 (-2.7 to -1.9)	-2.2 (-2.6 to -1.7)	0.41
Side effects				0.51
None	65 (66%)	17 (77%)	48 (62%)	
Local skin reaction	20 (20%)	3 (14%)	17 (22%)	
Systemic reaction	13 (13%)	2 (9.1%)	11 (14%)	
Subsequent therapy				0.48
Denosumab	49 (49%)	14 (64%)	35 (45%)	
Zoledronate	41 (41%)	6 (27%)	35 (45%)	
Ibandronate	7 (7.1%)	2 (9.1%)	5 (6.5%)	
Alendronate	1 (1.0%)	0 (0.00%)	1 (1.3%)	
Unknown	1 (1.0%)	0 (0.00%)	1 (1.3%)	

Abbreviations: DXA2: DXA scan after terminating romosozumab, LS: lumbar spine, TH: total hip, FN: femoral neck

Continuous variables: Median ± interquartile range [IQR], Categorical variables: Percentage of total of each subgroup

at the total hip. Conversely, lower BMI was associated with a smaller BMD increase at the hip, but not at the lumbar spine. In addition, the duration of antiresorptive pre-treatment was associated with a smaller BMD increase at both the spine and hip, and this occurred even after adjusting for age and BMI (Fig. 3). Elevated CTX levels at baseline were correlated with a more favourable BMD response at both the lumbar spine and hip. Neither P1NP levels at baseline nor those after 1–3 months were associated with BMD responses at the lumbar spine or hip. P1NP and CTX levels at baseline and during follow-up are depicted in Fig. 4, showing higher levels of both over time in treatment-naïve patients. Additionally, associations were separately analysed for treatment-naïve and pre-treated patients (Suppl. Table 1). This analysis showed that the baseline T-score at the lumbar spine was associated with the BMD response at the lumbar spine, and the total hip and femoral neck T-scores were associated with the BMD response at the hip. Furthermore, the baseline CTX level was associated with the BMD response at the lumbar spine, even among treatment-naïve patients.

Out of all 77 patients with prior antiresorptive therapy, most patients received a parenteral bisphosphonate as their last treatment cycle, and only one was switched directly from denosumab to romosozumab. While the BMD response at the lumbar spine significantly correlated with the prior cumulative duration of bisphosphonate treatment ($r=$ -0.37, $p=0.004$), no correlation was found between the cumulative duration of denosumab therapy and the BMD increase at the lumbar spine ($r=$ -0.02, $p=0.83$). The BMD changes at the total hip weakly correlated with the cumulative durations of both denosumab ($r=$ -0.23, $p=0.027$) and bisphosphonates ($r=$ -0.26, $p=0.013$). Of note, the enrolment site had no impact on the results (data not shown).

Safety outcomes

Out of 99 patients, 33 (33%) reported experiencing adverse effects following romosozumab treatment. These encompassed both local skin reactions at the injection site ($n=20$) and systemic reactions, predominantly myalgia and arthralgia, occasionally accompanied by headaches. One patient with a documented history of psoriatic skin disease exhibited symptom exacerbation following the injections, necessitating treatment with topical corticosteroids to manage flares. Additionally, a patient with pre-existing vertebral fractures experienced a subsequent vertebral fracture within 1 month of initiating romosozumab therapy. This fracture was successfully managed with vertebroplasty, and romosozumab administration was continued without further fractures thereafter.

Table 3 Univariate regression model of BMD response under romosozumab

Localization	Covariate	Estimate (95% CI)	*p*-value
Lumbar spine			
	Age (years)	-0.18 (-0.31 to -0.05)	**0.007**
	BMI (kg/m2)	-0.08 (-0.41 to 0.24)	0.609
	Pre-treated (y/n)	-4.49 (-7.47 to -1.51)	**0.004**
	Duration of prior AR therapy	-0.41 (-0.66 to -0.17)	**0.001**
	Pre-treated with TPTD (y/n)	-1.21 (-4.29 to 1.87)	0.438
	T-score lumbar spine	-2.66 (-3.63 to -1.68)	**< 0.001**
	T-score total hip	-1.60 (-3.37 to 0.16)	0.074
	T-score femoral neck	-1.14 (-2.99 to 0.71)	0.225
	Baseline P1NP	0.05 (-0.00 to 0.11)	0.069
	Baseline CTX	10.15 (2.70 to 17.6)	**0.009**
	P1NP after 1–2 months	0.01 (-0.02 to 0.03)	0.567
	CTX after 1–2 months	1.85 (-5.19 to 8.88)	0.599
Total hip			
	Age (years)	-0.05 (-0.13 to 0.04)	0.271
	BMI (kg/m2)	0.22 (0.01 to 0.42)	**0.037**
	Pre-treated (y/n)	-2.84 (-4.78 to -0.90)	**0.005**
	Duration of prior AR therapy	-0.25 (-0.42 to -0.09)	**0.002**
	Pre-treated with TPTD (y/n)	-1.30 (-3.26 to 0.65)	0.189
	T-score lumbar spine	-0.71 (-1.42 to 0.00)	0.051
	T-score total hip	-1.69 (-2.76 to -0.63)	**0.002**
	T-score femoral neck	-1.62 (-2.74 to -0.49)	**0.005**
	Baseline P1NP	0.02 (-0.01 to 0.05)	0.254
	Baseline CTX	6.45 (1.96 to 10.93)	**0.006**
	P1NP after 1–2 months	0.01 (-0.01 to 0.02)	0.480
	CTX after 1–2 months	0.94 (-2.58 to 4.46)	0.593
Femoral neck			
	Age (years)	-0.08 (-0.17 to 0.01)	0.068
	BMI (kg/m2)	0.29 (0.08 to 0.49)	**0.006**
	Pre-treated (y/n)	-3.12 (-5.13 to -1.10)	**0.003**
	Duration of prior AR therapy	-0.25 (-0.42 to -0.09)	**0.003**
	Pre-treated with TPTD (y/n)	0.04 (-1.95 to 2.02)	0.969
	T-score lumbar spine	-0.48 (-1.22 to 0.25)	0.194
	T-score total hip	-0.92 (-2.04 to 0.20)	0.106
	T-score femoral neck	-1.34 (-2.47 to -0.22)	**0.020**
	Baseline P1NP	0.01 (-0.02 to 0.04)	0.539
	Baseline CTX	1.26 (-3.20 to 5.72)	0.572
	P1NP after 1–2 months	0.01 (-0.01 to 0.02)	0.292
	CTX after 1–2 months	-0.14 (-4.39 to 4.10)	0.946

Abbreviations: AR: antiresorptive, y/n: yes or no, TPTD: teriparatide

Continuous variables: Median ± interquartile range [IQR], Categorical variables: Percentage of total of each subgroup

Discussion

In this prospective, registry-based cohort study, treatment with romosozumab for 12 months led to BMD increases at both the lumbar spine and total hip. The BMD changes, however, were highly variable, particularly in pre-treated patients (78% of all patients who received romosozumab had received prior antiresorptive therapies for a median duration of 6 years). These pre-treated patients showed a significantly lower BMD response at both the lumbar spine and hip compared to treatment-naïve patients, and the duration of antiresorptive pre-treatment was associated with the BMD response at both locations. Previous studies in Japanese patients reported that the effect of romosozumab depended

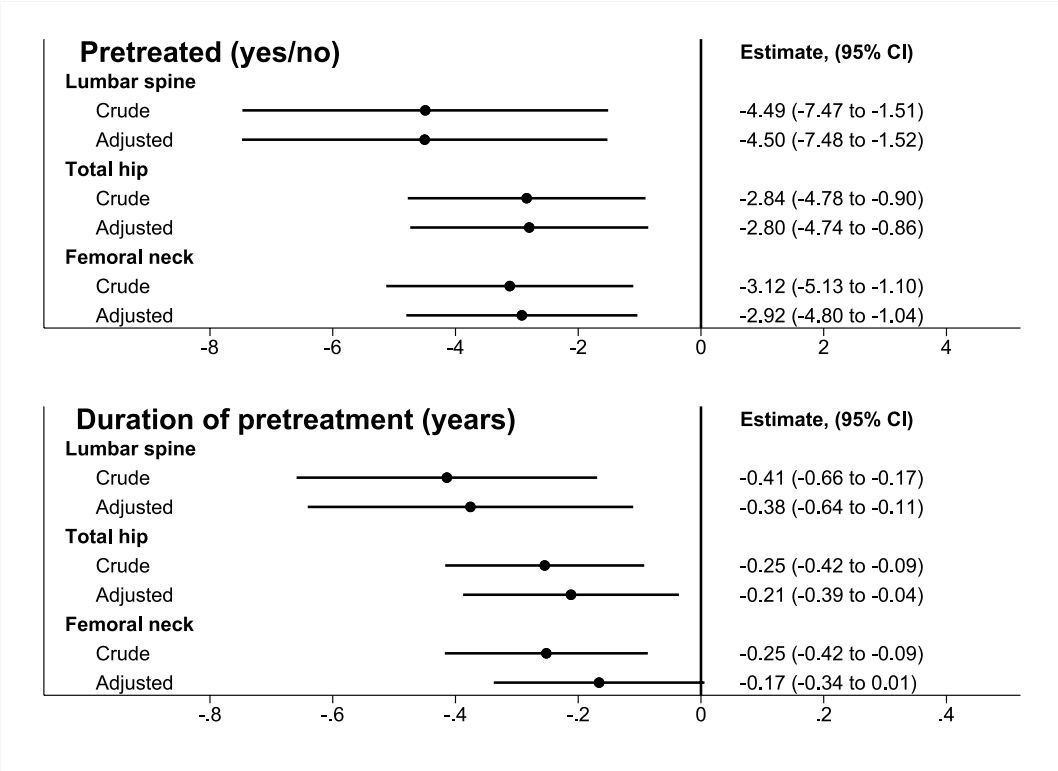

Fig. 3 BMD response under romosozumab depending on prior antiresorptive therapy (yes/no) and its duration (years) in a univariate regression analysis (crude) and after adjusting for age and BMI (adjusted)

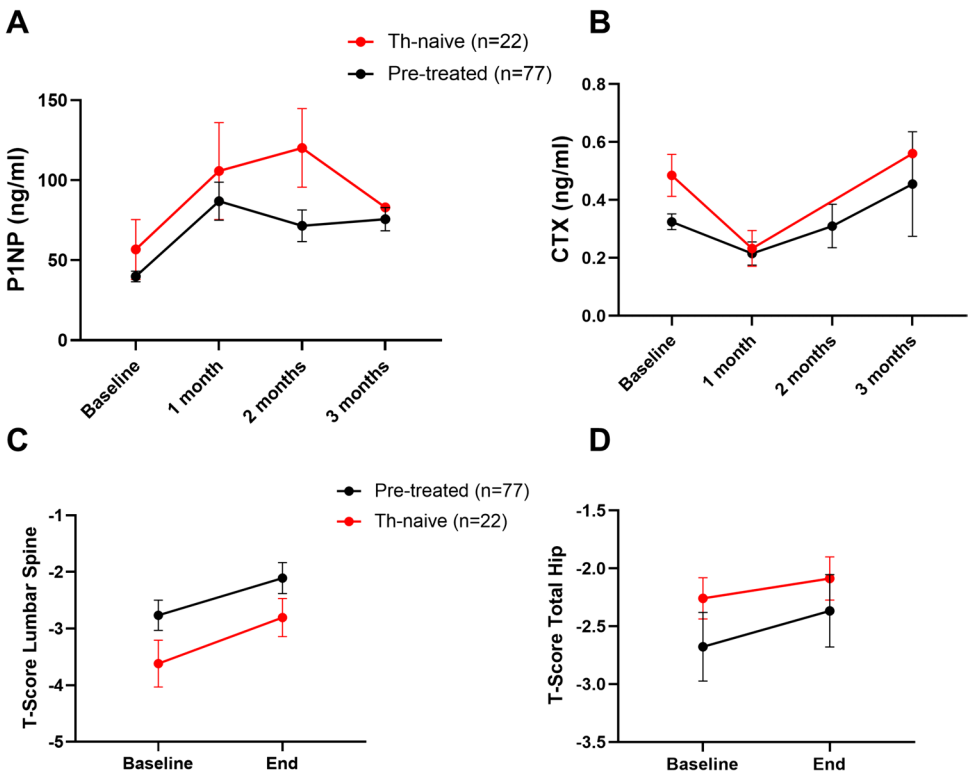

Fig. 4 Longitudinal changes in P1NP (**A**) and CTX (**B**) levels and T-scores at the lumbar spine (**C**) and total hip (**D**) during treatment with romosozumab in pre-treated (black) and treatment-naïve patients (red). Data are shown as mean ± 95% CI. Note that most patients had a P1NP and CTX measurement at baseline and at least one within the first 3 months, but not all patients had 3–4 measurements

on a history of prior treatment [9], as well as its duration [10]. However, the authors only differentiated between pre-treatment for 1 year versus more than 1 year. In clinical practice, it is probable that patients eligible for romosozumab therapy have undergone prior treatment with antiresorptive agents, and also potentially anabolic agents, for an extended period. Accordingly, our study population was treated with various, individualized regimens before the initiation of romosozumab. However, most received parenteral bisphosphonates as their last treatment cycle before starting romosozumab. Only one patient with long-term denosumab therapy (8 years) was switched directly to romosozumab, and this individual showed BMD loss at the total hip of -9%, while the BMD at the lumbar spine did not change significantly (+ 1.2%). Transitioning to romosozumab after 12 months of denosumab appears to improve lumbar spine BMD and maintain total hip BMD [8, 16], but less is known about the BMD changes after switching from long-term denosumab therapy to romosozumab. This sequence could be unfavourable due to the increased overshoot of bone resorption following long-term denosumab treatment [17]. Thus, almost all patients in our study who received prior denosumab therapy received at least 1 year of bisphosphonates (mainly zoledronate) before they were switched to romosozumab. In these patients ($n = 29$), the duration of prior denosumab therapy did not correlate with the BMD response at the lumbar spine, while the duration of prior bisphosphonate therapy was associated with a significantly lower BMD increase at both the lumbar spine and total hip under romosozumab. While bisphosphonates bind to the bone mineral and remain in the skeleton after treatment discontinuation [18], the monoclonal antibody denosumab exhibits transient treatment effects and may therefore have less of an impact on future responses to anabolic agents. Nevertheless, it remains unclear why prior antiresorptive therapies mitigate the BMD response to romosozumab. While it is understandable that previous antiresorptive therapy blunts the BMD response to teriparatide, given that the majority of bone formation is remodeling based [19], one might anticipate that prior antiresorptive therapies would have less of an impact on the BMD response to romosozumab, which primarily involves modeling-based bone formation. One theory, as discussed by Cosman et al. [8], posits that some of the initial BMD gain (i.e., the weak antiresorptive effect of romosozumab) might be attributed to overfilling of the remodeling cavities present at the time romosozumab is administered. The bone remodeling surface area is smaller in patients who have received prior antiresorptive agents compared with those who have not. Another potential explanation is that even modeling-based bone formation requires active bone surfaces, whose area may be reduced in patients who have received prior treatment. This hypothesis is supported by our observation that higher baseline CTX levels are associated with a better BMD response to romosozumab, even among treatment-naïve patients. Additionally, due to the coupling between osteoclasts and osteoblasts during antiresorptive treatments, there might be a reduction in bone-forming osteoblasts prior to romosozumab treatment in pre-treated patients.

Other predictors of BMD response in this study were age (only lumbar spine) and BMI (only total hip and femoral neck). Surprisingly, neither baseline nor follow-up P1NP levels after 1–3 months of romosozumab treatment were associated with BMD responses at the lumbar spine or hip, which is in contrast to prior reports [20]. However, we observed significantly higher P1NP levels at month 2 of romosozumab therapy in treatment-naïve compared to pre-treated patients. One possible explanation for this discrepancy could be variations in the timing of P1NP level measurements during follow-up, as this timing has not been standardised across all patients.

The BMD changes under romosozumab in pre-treated patients were comparable to those in the STRUCTURE trial, where patients were switched to either romosozumab or teriparatide after 3 or more years of oral bisphosphonates [11]. In that randomised controlled trial, areal BMD measurements were performed along with quantitative CT evaluations of integral, cortical and trabecular volumetric bone mineral density at the hip, as well as assessments of bone strength by infinitive analysis. In contrast to teriparatide, 1 year of romosozumab led to significant increases of volumetric cortical BMD and bone strength, whereas both treatments increased integral and trabecular BMD. Thus, prior antiresorptive therapies did not completely mitigate these improvements in the STRUCTURE trial, leaving it unclear how the fracture rate under romosozumab could differ in pre-treated versus treatment-naïve patients.

The findings of this study are limited by its observational nature, relatively small sample sizes and unequal subgroups. Since the treatment-naïve patients demonstrated lower T-scores than the pre-treated patients, the percentage BMD gains are presumably overestimated, and the true differences might be smaller. Further, even though the patients were prospectively enrolled and monitored, there was a partial lack of information on BTM parameters during romosozumab therapy, which could limit the reliability of the associated results. The strength of this study lies in the precise recording of therapies administered prior to romosozumab, including specific agents and treatment durations.

We conclude that prior antiresorptive therapy, particularly the long-term administration of bisphosphonates, blunted the BMD response to romosozumab, and the duration correlated with changes at both the lumbar spine and total hip. On the other hand, there was a variable BMD response in treatment-naive individuals, indicating that other factors may also play a role. It will be of considerable interest to analyse fracture data trends within a substantially expanded

cohort undergoing the transition from long-term antiresorptive therapy to treatment with romosozumab.

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Data sharing Data may be obtained from a third party and are not publicly available. Restrictions apply to the availability of these data. Data are owned by a third party, the Swiss Osteoporosis Registry Association. Data may be obtained after approval and permission from the Board.

Declarations

Disclosures JEG: Sandoz, Amgen, UCB Pharma. MW: UCB Pharma, Eli Lilly. SO: Amgen, Mylan. US: Janssen, Novartis, Pfizer, Sandoz, AbbVie, Amgen, Eli Lilly. CS: Abbvie. HRZ: Novartis, Jansen, Abbvie and Celgene, HJH: Amgen, Sandoz, Eli Lilly, Labatec. KR, GS, BG, SR and TL have nothing to declare.

Conpeting interests None.

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