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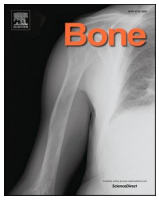

Rapid Communication

Bone mineral density response to romosozumab in post-menopausal women: A prospective observational real-world study

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ABSTRACT

Background: Romosozumab is approved in Europe for severe osteoporosis in postmenopausal women at high risk of fracture including older women, but whether bone mineral density (BMD) response varies with age remains unknown.
Purpose: To examine BMD changes in a real-world cohort of older women treated with romosozumab. We hypothesized that younger, treatment-naive patients and those with lower baseline BMD might experience greater BMD improvements.
Methods: Prospective observational study in one Italian and two Belgian centers. Multivariable linear and logistic regression models with imputation of missing data were used to determine the association between baseline variables and % BMD change or $\geq$ 3 % BMD increase after 12 months.
Results: We included 186 postmenopausal women with a median age of 76 years (range 52–96), lumbar spine T-score of −2.8 (interquartile range − 3.4;-1.8), mean total hip T-score of −2.4 (± standard deviation 0.95) and femoral neck T-score of −2.7 (−3.2;-2.2). After 12 months of romosozumab, BMD increased +9.16 % and + 3.00 % at the lumbar spine and total hip, respectively. A $\geq$ 3 % BMD increase was observed in 80.4 % at the spine, 51 % at the hip and 46 % at the femoral neck. Lower baseline BMD was independently associated with greater total hip BMD response. There was no significant association of BMD responses with age.
Conclusions: Baseline BMD was associated with total hip BMD response to romosozumab. Age itself was not associated with BMD differences. Our data support the effectiveness of romosozumab in older postmenopausal women in routine clinical practice.

1. Introduction

In postmenopausal women, the risk of osteoporotic fractures increases with advancing age and declining bone mineral density (BMD). Each standard deviation (SD) decline in total hip BMD more than doubles hip fracture risk, and increases vertebral fracture risk by more than 50 % [1]. By age 85 years, the average white woman has a BMD T-score of −2.5, the threshold to diagnose osteoporosis by dual-energy X-ray absorptiometry (DXA) [2]. The absolute fracture risk is highest in the oldest old (who also fall the most), but competing risk of mortality and long-term cost-effectiveness also need to be taken into consideration [3–5].

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The approach to treatment of older postmenopausal women with severe osteoporosis at high fracture risk varies between countries, due to different guidelines and reimbursement criteria [6]. In some European countries, most women in this category would qualify for anabolic therapies [7,8]. In other countries *e.g.* France, use of these therapies above age 75 years is restricted [9].

Few studies have examined whether the efficacy and safety of anabolic bone drugs vary according to age *per se*. Antiresorptive bone drugs (*e.g.* bisphosphonates or denosumab) are very effective in the oldest old [10,11]. Yet various mechanisms of cellular and molecular senescence are known to blunt osteoblast and osteocyte function, providing a rationale for anabolic drugs (such as teriparatide, abaloparatide or romosozumab) in this population [12].

Teriparatide increases BMD (mainly at the spine) by increasing bone turnover and remodeling-based bone formation. A subgroup analysis of a phase three randomized placebo-controlled trial with teriparatide showed no significant treatment-by-age interaction in women above *vs.* below 75 years [13]. In a real-world retrospective study of teriparatide users, we observed greater total hip BMD increases in younger postmenopausal women and those with lower baseline BMD [14]. Prior denosumab users switching to teriparatide experienced smaller lumbar spine BMD gains [14].

Romosozumab (a monoclonal antibody inhibiting sclerostin) stimulates both modelling-based bone formation and augments the positive bone balance within the remodeling unit, while inhibiting bone resorption, resulting in greater BMD gains compared to teriparatide [15–17]. Real-world cohort studies suggest that this translates into greater fracture prevention [18]. Further observational studies, mainly from Japan and one from Switzerland, have associated higher baseline BMD, duration of prior bisphosphonate or denosumab use (especially $\geq$3 years) and lower bone turnover with diminished BMD response to romosozumab [19–22]. However, it remains unclear whether age itself affects the BMD response to romosozumab (independent of lower BMD and prior therapy in older adults) [19].

Given this background, we aimed to test the hypothesis that in postmenopausal European women, older age, longer duration of prior therapy, and higher BMD at baseline would be associated with a diminished BMD response to romosozumab.

2. Methods

This study follows reporting recommendations for cohort studies [23].

2.1. Study design

We conducted a 12-month prospective (and partly retrospective) multicenter cohort study at the authors' institutions: the Center for Metabolic Bone Diseases, University Hospitals Leuven, the geriatrics department of Imelda Hospital Bonheiden (both in Belgium) and the rheumatology department of Verona University Hospital in Italy. Each institution's Ethics Committee approved the protocol, in line with national and European regulations. Retrospective data were obtained from electronic health records. Participants provided voluntary written informed consent for using their prospective data collected in routine clinical practice, in accordance with the Declaration of Helsinki. Consecutive patients were enrolled between December 1st, 2021 and December 31st, 2022, in Belgium, and between November 1st, 2022 and November 1st, 2023, in Verona. Sample size was not estimated *a priori*.

Postmenopausal women completing a 12-month romosozumab course (as part of routine clinical practice according to national osteoporosis guidelines and reimbursement criteria) were included. Participants with bone diseases other than osteoporosis (*e.g.* osteomalacia, monogenic bone diseases), uncontrolled endocrine diseases (*e.g.* active primary hyperparathyroidism) or those not completing a full 12-month course were excluded. Prior therapies were verified from medical records, referral letters or electronic reimbursement systems.

Reimbursement criteria in Belgium are based on a recent ($\leq$ 2 years) major osteoporotic fracture, in combination with either a T-score ≤ -2.5 at the lumbar spine or hip or a prevalent vertebral fracture of at least 25 % and at least 4 mm height loss [8]. Treatment is obtained in community pharmacies and self-administered or given by general practitioners, community nurses or directly by pharmacists according to patient preference. Italian patients required a T-score ≤ -2.5 at the lumbar spine or total hip (or ≤ -2.0 in the presence of $\geq$2 moderate/severe vertebral fractures or a hip fracture within the previous 2 years) and a documented fragility-fracture history ($\geq$ 1 moderate/severe vertebral fracture, or $\geq$ 2 mild vertebral fractures, or a hip fracture). Alternatively, women with a T-score ≤ -2.5 and $\geq$ 2 non-vertebral (non-hip) fragility fractures were also eligible. In all cases, a 10-year major osteoporotic fracture risk $\geq$20 % according to a validated calculator was required. Women with prior stroke or high cardiovascular risk (Italian 10-year cardiovascular risk score $\geq$ 20 %) were excluded. Romosozumab is generally self-administered in Italy.

2.2. Variables and outcomes

Demographic and clinical variables (age, height, body weight, fracture and medication history, laboratory and imaging results) were retrieved from electronic health records. BMD was measured by dual-energy X-ray absorptiometry (DXA) using a Hologic® Horizon A (Leuven), GE® Lunar Prodigy Primo (Bonheiden) or Lunar iDXA, GE HealthCare (Verona), by certified and experienced technicians in accordance with recommendations from the International Society of Clinical Densitometry [2]. The left total hip and femoral neck were used. In cases where left hip/femoral neck BMD values were unavailable, the corresponding right sided values were used.

2.3. Statistical analyses

The normality of data was evaluated *via* the Shapiro Wilk test. All continuous normally distributed variables were presented as mean $\pm$ SD, while continuous variables with skewed distributions were presented as median and interquartile range (IQR). Categorical data were presented as proportions and compared using the χ^2 statistic without Yates correction.

Univariable and multivariable linear regression models were used to determine the association between baseline predictor variables (*i.e.* age, center, body mass index [BMI], 25-hydroxyvitamin D, BMD, years of prior osteoporosis treatments used) and % change in BMD at the lumbar spine, total hip and femoral neck after 12 months of romosozumab treatment. Percentage change in BMD was calculated as ([BMD at follow-up - BMD at baseline]/BMD at baseline) *100. Model 1 was the unadjusted model, Model 2 was adjusted for center and Model 3 was adjusted for center, age, BMI, 25-hydroxyvitamin D, baseline BMD, years of prior osteoporosis treatments used. All predictor variables were transformed to facilitate comparison and interpretation. Results are expressed as standardized β-coefficients with 95 % confidence intervals (CI).

To identify characteristics of BMD responders *vs.* those without an anabolic response, a $\geq$ 3 % increase in BMD after 12 months of romosozumab treatment was defined as a cut-off *a priori*, in line with Tominiga et al. [24]. Of note, there is no universal agreement on responder criteria for osteoanabolic drugs [25]. Differences in patient characteristics were assessed using the unpaired *t*-test (normally distributed variables) or Mann–Whitney *U* test (variables with skewed distribution). Logistic regression analyses were performed to identify predictors of treatment response, with the same predictors as outlined above. Results are expressed as odds ratios (OR) with 95 % CI. BMD was rescaled from g/cm^2 to 0.1 g/cm^2 to make the interpretation of the logistic regression models more realistic and clinically relevant.

Missingness in predictor variables was handled under a Missing At

Random (MAR) assumption using multiple imputation by chained equations (MICE). Predictive mean matching (k = 5) was used for continuous variables. Outcomes (percent change in BMD and treatment response) were not imputed. The imputation model included all analysis variables and was conditioned on age and center. Forty imputed datasets after a 10-iteration burn-in with a fixed random seed were generated. Linear and logistic regression models were fit and estimates were pooled using Rubin's rule.

Analyses were considered as statistically significant if two-sided *p*-values were < 0.05. All statistical analyses were performed using Stata version 17.0 (Stata, College Station, TX, USA).

3. Results

3.1. Baseline and follow-up characteristics

One hundred eighty-six postmenopausal women between 52 and 96 years of age were included (Table 1), with $N = 66$ (35 %) over 80 years and $N = 30$ over 85 years (16 %). A minority was also diagnosed with glucocorticoid-induced osteoporosis (7.5 %) or secondary osteoporosis due to (treated or mild/well-controlled) primary hyperparathyroidism (4 %). Most patients had a recent (within the last two years) major osteoporotic fracture, in line with romosozumab reimbursement criteria in Belgium [8]. The population was not vitamin D deficient, with a median 25-hydroxyvitamin D concentration well above 20 ng/mL (or 50 nmol/L).

Table 2 shows the baseline and follow-up BMD, relative change and proportion of participants with a ≥ 3 % response at the lumbar spine, total hip and femoral neck, in all patients as well as subgroups of therapy-naïve *vs.* previously treated patients. The proportion of responders was significantly greater in therapy-naïve patients at the lumbar spine (χ^2 (1, $N = 143$) = 4.6732, $p = 0.030637$) and total hip (χ^2 (1, $N = 143$) = 4.5964, $p = 0.03204$), but not at the femoral neck (χ^2 (1, $N = 141$) = 0.7176, $p = 0.3969$).

Table 1
Baseline characteristics of the study population.

Variable ($N = 186$; full treatment)	Mean (SD)/median (IQR) or number (%)
Age (years) (N = 186)	76 (66; 83)
BMI (kg/m^2) ($N = 151$)	23.0 (21.0;26.7)
25-hydroxyvitamin D (ng/mL) ($N = 178$)	33.0 (26.4;42.2)
Type osteoporosis (N = 186)	
– Post-menopausal osteoporosis	164 (88.2 %)
– Glucocorticoid-induced	14 (7.5 %)
– Primary hyperparathyroidism	8 (4.0 %)
Center (N = 186)	
– Leuven	60 (32 %)
– Bonheiden	43 (23 %)
– Verona	83 (45 %)
T score lumbar spine ($N = 165$)	−2.8 (−3.4;-1.8)
T-score total hip ($N = 113$)	−2.4 (0.9)
T score femoral neck ($N = 140$)	−2.7 (−3.2;-2.2)
Previous treatment	
– Raloxifene (N = 186)	5 (3 %)
– Zoledronate ($N = 185$)	37 (20 %)
– Denosumab (N = 185)	25 (14 %)
– Teriparatide (N = 185)	12 (6.5 %)
– Oral bisphosphonates (N = 186)	64 (34 %)
Recent osteoporotic fracture	129 (69 %)
– Hip (N = 186)	37 (20 %)
– Vertebral (N = 186)	68 (37 %)
– Non-hip/non-vertebral (N = 186)	43 (23 %)
Total years of any prior treatment ($N = 184$)	1 (0;4)

Abbreviations: BMI = body mass index; IQR = interquartile range; SD = standard deviation.

3.2. Variables associated with BMD changes

Table 3 shows univariable and multivariable associations between baseline variables and BMD change at the lumbar spine, total hip or femoral neck. Lower baseline BMD at the hip was associated with greater BMD response to romosozumab at the hip, independently from other variables. More years of prior treatment or oral bisphosphonates was associated smaller BMD gains at the spine and total hip independent of center, but not in multivariable analysis. Age itself was not associated with BMD response to treatment. Femoral neck BMD gains were larger in Italian patients, independent of other variables. Due to the small number of cases, prior teriparatide or raloxifene use were not analyzed separately. Variance inflation factors varied from 1.11 to 1.52 in all analyses, indicating low concern for multicollinearity.

3.3. Predictors of BMD response

Characteristics of the responders *vs.* non-responder population at different sites are shown in Supplementary Tables S1-S3. Women with <3 % BMD increase at the lumbar spine had a significantly longer duration of prior treatments (median 3 years) or oral bisphosphonate exposure. Non-responders at the total hip had a significantly longer duration of prior treatments (median 3 years), oral bisphosphonates or zoledronate exposure. Non-responders at the femoral neck had significantly longer prior denosumab exposure. However, in logistic regression analyses, age or other baseline predictors were not significantly associated with the likelihood of a ≥ 3 % BMD response at the lumbar spine, total hip or femoral neck (Table S4).

4. Discussion

Bone anabolic drugs constitute a considerable advance in the treatment armamentarium of osteoporosis, especially for patients at very high or imminent fracture risk. However, the use of these drugs in geriatric populations raises several conundrums [6], including lack of evidence to inform clinical practice. Since older age is also associated with lower BMD and longer duration of prior antiresorptive therapies, it remains unclear whether age independently influences the response to romosozumab. In this real-world study of romosozumab users in routine clinical practice, we observed that, in line with our hypothesis and previous studies [19,21,24], higher baseline BMD and more years of prior bisphosphonate therapy were associated with a diminished BMD response. However, only higher baseline total hip BMD was independently associated with lower hip BMD responses in romosozumab users. Chronological age appeared not to have a major influence.

Our findings differ from previous studies. Tominaga et al. ($N = 92$ patients) found no effect of age, whereas early BMD and bone turnover marker changes predicted BMD response. In a multicenter Swiss cohort, Everts-Graber et al. ($N = 99$ patients) observed an inverse correlation of duration of prior therapy, lower baseline BMD and baseline bone turnover with BMD responses at the lumbar spine and hip. Age was inversely associated with BMD response at the lumbar spine, whereas BMI was associated with BMD gains at the total hip. Whether these differences between studies reflect the age ranges studied, biological or methodological differences requires further investigation.

Romosozumab was associated with large average BMD gains in both treatment-naïve and pretreated subgroups, independent of age. Empirical thresholds and treat-to-target goals for BMD gains associated with fracture prevention have been validated [26–28]. For example, according to validated surrogate threshold effects validated by Eastell et al., total hip BMD increases of 1.83 %, 1.42 %, 3.18 %, and 2.13 % reliably predict all, vertebral, hip, and nonvertebral fracture risk reduction [26]. Generally, in clinical practice, bone density changes for individual patients should also exceed the DXA machine's least significant change to be reliably interpreted as a meaningful difference. A recent study reported that 60 % of romosozumab treated women

Table 2
BMD at baseline and after 12 months of romosozumab.

	Baseline BMD (g/cm^2)	Follow-up BMD (g/cm^2)	Difference (%)	≥ 3 % BMD increase (%)
Total number of patients (N = 186)				
Lumbar spine (N = 143)	0.807 (0.742;0.938)	0.875 (0.800;1.022)	9.16 (4.83;14.6)	115 (80.4 %)
Total hip (N = 145)	0.682 (0.597;0.755)	0.711 (0.115)	3.00 (0.20;4.76)	91 (63 %)
Femoral neck (N = 141)	0.621 (0.109)	0.650 (0.563;0.729)	2.62 (−0.17;7.21)	65 (46 %)
Therapy-naïve patients (N = 88)				
Lumbar spine (N = 67)	0.810 (0.714;0.960)	0.915 (0.800;1.068)	10.6 (7.36;16.8)	59 (88 %)
Total hip (N = 65)	0.668 (0.112)	0.714 (0.118)	3.32 (1.38;5.93)	47 (72 %)
Femoral neck (N = 64)	0.619 (0.118)	0.658 (0.566;0.750)	3.00 (−0.458;9.96)	32 (50 %)
Patients with prior therapy (N = 98)				
Lumbar spine (N = 76)	0.804 (0.756;0.926)	0.874 (0.800;0.970)	8.20 (2.92;11.90)	56 (74 %)
Total hip (N = 80)	0.692 (0.606;0.749)	0.692 (0.632;0.775)	2.45 (0.000;4.34)	44 (55 %)
Femoral neck (N = 77)	0.623 (0.101)	0.639 (0.560;0.726)	2.56 (−0.654;5.47)	33 (43 %)

Data reported as mean (standard deviation, SD) or median (interquartile range, IQR) or number (%). BMD = bone mineral density.

Table 3
Univariable and multivariable associations between predictors and BMD change after 12 months of romosozumab.

	Variable	Model 1 (β-coefficient, 95 %CI)	Model 2 (β-coefficient, 95 %CI)	Model 3* (β-coefficient, 95 %CI)
Spine (N = 143)	Age	−0.28 (−3.68;4.24)		
	BMI	−2.22 (−10.83;6.38)		
	Baseline BMD	−2.16 (−6.16;1.84)		
	Center**			
	Bonheiden	2.10 (−8.70;12.91)		
	Verona	−2.61 (−11.72;6.50)		
	25-hydroxyvitamin D	0.21 (−3.51;3.92)		
	Years of oral bisphosphonates	**−5.37 (−9.33;-1.40)**	**−5.19 (−9.31;-1.06)**	−3.37 (−11.63;4.89)
	Years of zoledronate	−1.01 (−4.58;2.56)		
	Years of denosumab	0.85 (−2.87;4.57)		
	Years any treatment	**−4.32 (−8.12;-0.51)**	**−4.12 (−8.05;-0.17)**	−4.21 (−9.31;0.90)
	≥3 years denosumab treatment	2.64 (−13.25;18.54)		
Total hip (N = 110)	Age	9.35 (−1.65;20.34)		
	BMI	−0.47 (−9.37;8.43)		
	Baseline BMD	**−31.73 (−40.86;-22.60)**	**−31.42 (−40.58;-22.26)**	**−32.24 (−42.16;-22.31)**
	Center**	13.81 (−9.17;36.79)		
	Verona			
	25-hydroxyvitamin D	6.79 (−3.69;17.27)		
	Years of oral bisphosphonates	−3.26 (−13.82;7.30)		
	Years of zoledronate	6.47 (−3.30;16.24)		
	Years of denosumab	−0.20 (−9.64;9.23)		
	Years any treatment	−0.38 (−10.64;9.87)		
	≥3 years denosumab	−8.57 (−48.91;31.77)		
Femoral neck (N = 141)	Age	−1.09 (−2.77;0.59)		
	BMI	0.20 (−1.35;1.76)		
	Baseline BMD	−1.63 (−3.27;0.01)		
	Center**	−1.93 (−6.49;2.62)		**8.24 (3.97;12.50)**
	Bonheiden	**4.52 (0.75;8.29)**		
	Verona			
	25-hydroxyvitamin D	1.11 (−0.49;2.72)		
	Years of oral bisphosphonates	0.08 (−1.66;1.82)		
	Years of zoledronate	−0.16 (−1.76;1.44)		
	Years of denosumab	−1.18 (−2.66;0.31)		
	Years any treatment	−0.62 (−2.27;1.03)		
	≥3 years denosumab treatment	−3.17 (−9.35;3.01)		

Model 1: Unadjusted, Model 2: Adjusted for center, Model 3: Adjusted for center, age, BMI, baseline BMD, 25-hydroxyvitamin D, total years of any treatment (*i.e.* oral bisphosphonates, zoledronic acid, denosumab). *For each predictor variable in Model 3, adjustment was made for all listed covariates except the predictor itself. ** Center reference = Leuven. Bold = statistically significant. Abbreviations: BMD = bone mineral density; BMI = body mass index; IQR = interquartile range; SD = standard deviation.

reached the surrogate threshold BMD gain (≥ 3.18 %) associated with all fracture prevention [29]. Conversely, proposed criteria for treatment non-response in osteoporosis have included the occurrence of two or more fractures, ongoing BMD decline, or failure of modulation of bone turnover markers during treatment [30]. Yet there is no consensus on the classification of responders *vs.* non-responders to bone anabolic drugs [25]. To align with the previous study by Tominaga et al., we opted for a ≥ 3 % BMD increase to classify treatment responses as adequate [24]. However, placebo-controlled randomized trials with antiresorptives have also shown a ≈ 3 % BMD increase at the total hip and femoral neck and ≈ 5 % BMD increase at the lumbar spine after one year [31,32]. Since anabolics are currently more expensive than antiresorptives, anabolic responses could also be defined more stringently as exceeding those to be expected from (cheaper) antiresorptive therapies. For future studies, we propose to consider site-specific cut-offs as a potential benchmark to gauge treatment responses, potentially for both antiresorptive and anabolic drugs. In phase 3 randomized trials, romosozumab increased BMD 13 % at the lumbar spine and 6 % at the total hip compared to placebo or baseline in post-menopausal women naïve to bisphosphonates [17,31,33]. In prior bisphosphonate users, romosozumab was superior to teriparatide and increased BMD by 9.8 % at the lumbar spine and 3 % at the hip [16], which is also what we observed in routine clinical practice. Still, in bisphosphonate pretreated patients who continue to fracture or display very low T-scores, romosozumab may offer some benefits compared to switching to teriparatide or denosumab [34]. In any case, different cut-offs may be considered to define treatment response in naïve *vs.* pretreated patients [29].

Our study has several strengths compared to previous real-world studies, including its prospective design with multiple centers from different countries (increasing external validity) and moderate sample size. We also recognize several limitations. The confidence intervals for age were moderately broad, implying that we were only powered to exclude a large magnitude of effect of age. DXA scanners and laboratory methods differed between institutions, however our primary analysis focused on follow-up BMD changes within the same machine reducing bias associated with between-machines differences. Moreover, missing data and unmeasured confounders might have influenced the results. Heterogeneity in prior treatments with different sequences and drug holidays of various duration probably explain why a significant effect of prior therapies could not be observed in our study, in contrast to previous literature. Ebina et al. showed different BMD responses to romosozumab in different prior treatment groups (with similar ages and different baseline bone turnover markers) [21,22]. Variables such as bone turnover markers [35] or assessments of biological age, sarcopenia or frailty [36] were also not available in this multicenter investigator-driven study embedded in routine clinical practice. The finding that women from Italy had significantly greater femoral neck BMD improvements was unexpected and thus requires confirmation from further multinational studies. Whether any center differences could be related to population characteristics, genetic or environmental differences or *e.g.* better compliance from more intensive clinical follow-up (as was the case in Italy), remains unknown. Since we focused on BMD response in women who completed a 12-month romosozumab course, adherence, persistence or adverse effects (including fractures or cardiovascular events) were beyond the scope of this work. Larger multicenter cohort studies are clearly needed and currently ongoing. Finally, causality cannot be inferred from observational cohort studies. Subgroup analyses from randomized placebo-controlled trials with romosozumab (which have included participants up to 90 years of age) might be informative but remain lacking.

In conclusion, we showed that romosozumab is associated with a 9 % BMD increase at the lumbar spine and 3 % at the total hip, in a real-world clinical population of postmenopausal women who were mainly pretreated with other bone drugs (particularly bisphosphonates). Baseline total hip BMD was independently associated with subsequent BMD responses following romosozumab therapy, whereas there appeared to be no major independent association with age. Thus, our findings support the use of anabolic drugs like romosozumab in older adults, although further studies are needed to optimize the use in the oldest old.

CRediT authorship contribution statement

Evelien Gielen: Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Investigation, Formal analysis, Data curation. **Nadjia Amini:** Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Désirée Coppens:** Writing – review & editing, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Marian Dejaeger:** Writing – review & editing, Supervision, Data curation. **Jolan Dupont:** Writing – review & editing, Supervision, Investigation, Data curation. **Kurt De Vlam:** Writing – review & editing, Supervision, Investigation, Data curation. **Maurizio Rossini:** Writing – review & editing, Supervision, Data curation. **Ombretta Viapiana:** Writing – review & editing, Investigation, Data curation. **Michaël R. Laurent:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Giovanni Adami:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

Dr. Amini and dr. Coppens have nothing to declare. Prof. Gielen has received consultancy and lecture fees from Amgen, Takeda and UCB. Prof. Dejaeger has received research funding and expenses from UCB. Dr. Dupont has received consultancy fees and expenses from Daiichi Sankyo and UCB. Prof. De Vlam has received consultancy and conference fees from Abbvie, Amgen, Eli Lilly, Janssen-Cilag, Novartis Pharma, UCB and Pfizer. Prof. Rossini reports advisory board honoraria, consultancy fees and/or speaker fees from AbbVie, Eli-Lilly, ItalFarmaco, Neopharmed-Gentili, Theramex, and UCB. Prof. Ombretta has received advisory board honoraria and speaker fees from Gilead, Fresenius Kabi, Biogen, Eli-Lilly, UCB, Abbvie, MSD, BMS. Dr. Laurent has received consultancy and lecture fees from Alexion, A.M. Pharma, Amgen, AstraZeneca, Galapagos, Kyowa Kirin, Menarini, Orifarm, Pharmanovia, Sandoz, Takeda, Theramex, UCB and Will Pharma. Prof. Adami has received advisory board honoraria, consultancy fees and/or speaker fees from Theramex, UCB, Lilly, Galapagos, Fresenius Kabi, Amgen, BMS, Abiogen and Pfizer.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2025.117701.

Data availability

The dataset supporting the conclusions of this article are available upon reasonable request.

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