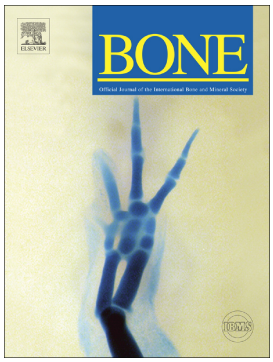

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Effects of Zoledronate on Bone Mineral Density and Bone Turnover after Long-term Denosumab Therapy: Observations in a Real-World Setting

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Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Background: The rebound effect after denosumab discontinuation is lessened with subsequent zoledronate therapy. However, it is unclear whether this mitigation is sufficient after long-term denosumab treatment.

Objective: This retrospective observational study analysed bone mineral density (BMD) and bone turnover marker (BTM) changes after denosumab therapy according to treatment duration and subsequent zoledronate regimen.

Methods: We measured the outcomes of 282 women with postmenopausal osteoporosis who discontinued denosumab and received zoledronate 6 months later. In patients with longer denosumab therapy (≥5 years), BTMs were measured every 3 months and a second zoledronate infusion was administered if BTM levels increased by ≥2-fold. The BMD of all women was measured before denosumab therapy, at the last injection and 1 to 2 years after the first zoledronate.

Results: Bone loss after switching from denosumab to zoledronate was higher in patients with 10±2 denosumab injections (n=84) compared to 5±2 injections (n=144, p<0.001 for lumbar spine and femoral neck), but there was no further increase with treatment durations of ≥15±2 injections (n=54, p=0.35 and p=0.20, respectively). BTMs in patients with ≥10 denosumab injections were elevated 6 months after zoledronate in some patients, but not all. Twenty-four women received a second zoledronate dose 6 months after the first one. BTMs in these patients were subsequently lower, but bone loss at both the lumbar spine and hip was comparable to that in patients with only one zoledronate dose (p=0.37 for lumbar spine and p=0.97 for femoral neck).

Conclusions: Rebound-associated bone loss reached a plateau after denosumab treatment durations of 4-6 years, irrespective of the frequency of subsequent zoledronate therapy.

1. Introduction

After discontinuation of denosumab, bone turnover markers (BTMs) increase to above pre-treatment values, a response described as the 'rebound effect'[1]. If no subsequent therapy is administered, bone mineral density (BMD) gained during treatment is rapidly lost, and reaches baseline values within 12 to 24 months after the last denosumab injection [1,2]. Furthermore, multiple spontaneous vertebral fractures during this period have been reported [3], particularly in patients with prevalent vertebral fractures and without bisphosphonate (BP) therapy after denosumab discontinuation [4–6]. Hence, to prevent bone loss and fractures after denosumab discontinuation, subsequent therapy with BPs has been recommended, with zoledronate as the most widely studied agent in randomized control trials [7–9]. However, the efficacy of zoledronate in preventing rebound-associated bone loss seems to depend on the duration of denosumab therapy [7]. It was reported that one zoledronate infusion 6 months after the last denosumab injection maintained BMD gains after denosumab treatment for 2-3 years, but not for 5 years [5,10]. Less is known about the benefit of subsequent zoledronate after longer denosumab therapy of >7 years, and closely related to this, about rebound-associated bone loss in the context of bone mass gains under denosumab therapy. Two observational studies reported pronounced bone loss after long-term denosumab therapy, but most patients did not receive subsequent BP treatment [11,12], which is meanwhile strongly recommended [13]. Thus, the optimal timing and frequency of zoledronate administration after denosumab discontinuation are issues that need to be addressed.

We therefore aimed to describe BMD changes in patients who were treated with denosumab for 2 to 9 years and who received subsequent treatment with zoledronate. We evaluated bone mass gains under therapy, bone mass changes

after switching to zoledronate and the evolution of BMD and BTMs in relation to the number of zoledronate infusions given (one versus 2 within 12 months).

2. Methods

2.1. Setting and Outcome

'ProOff' (Prolia Off-treatment) is a monocentric, observational study of prospectively enrolled patients at OsteoRheuma Bern, Switzerland [5,14]. The primary endpoint is the vertebral and non-vertebral fracture rate after denosumab discontinuation, and the secondary endpoints are the evolution of BMD and BTMs and the identification of risk factors for vertebral fractures and/or bone loss after denosumab discontinuation. The aim of the current analysis, performed 2 years after the first one, was to describe the BMD and BTM changes after denosumab discontinuation according to the denosumab treatment duration and subsequent zoledronate regimen. The fracture rate was not the primary endpoint in this subsequent analysis, which focused only on patients with subsequent zoledronate therapy.

2.2. Study Population

The patients reviewed in this retrospective study, which included data from August 2010 to March 2022, were treated with denosumab and at least one subsequent zoledronate infusion 6 months after denosumab discontinuation. Women who received ≥3 denosumab injections, who underwent dual-energy X-ray absorptiometry (DXA) and vertebral fracture assessment (VFA) on the days of the first and last denosumab injections and who had at least one follow-up visit with DXA and VFA evaluation 12-24 months after the first zoledronate infusion were eligible for the study.

Patients underwent DXA and VFA every 2 to 3 years after initiating denosumab therapy, according to Swiss national guidelines regarding pharmacological therapy for osteoporosis [15]. Denosumab was usually discontinued if there was sufficient BMD gain (T-score at lumbar spine and/or total hip ≥ -2.0 SD) and low fracture risk.

BMD at the lumbar spine (L1-L4), total hip and femoral neck was measured before starting denosumab (DXA1), at the last denosumab injection (DXA2) and at 18-30 months after the last denosumab injection (DXA3), always with a VFA as standardized screening for morphometric vertebral fractures [16]. Hologic Delphi S/N 70197 C or GE Lunar Prodigy Pro “Full” JBO/557-C devices were used for DXA and VFA. In most cases, the measurements of each patient were performed using the same device. If possible, C-terminal telopeptide of type I collagen (CTX) and/or N-terminal propeptide of type 1 procollagen (P1NP) concentrations were recorded before denosumab therapy and after discontinuation. The normal reference range of the CTX concentration in postmenopausal women was 0.06-1.00 ng/ml, while that of the P1NP concentration was 15-59 ng/ml.

The study protocol was reviewed and approved by the local ethical committee (swissethics, 2019-02286), and all patients provided written informed consent for further use of their health-related data.

2.3. Statistical analysis

Continuous variables are summarised as mean ± SD if normally distributed (tested with Shapiro Wilk) or as median with interquartile range otherwise. Categorical variables are shown as number with percentage. To explore differences between groups, we used ANOVA or the Kruskal-Wallis test for continuous variables and Fisher's exact test for categories. Comparison of patients with one versus two zoledronate infusions was performed with the Mann-Whitney test. The few missing values were replaced with the group mean. Analyses were carried out using Stata 16.1 (College Station, Texas), and figures were constructed with GraphPad Prism Version 9.3.1 (San Diego, California).

3. Results

Between August 2010 (the date of Prolia® (denosumab) approval in Switzerland) and March 2022, 440 women received ≥3 doses of denosumab and were evaluated by DXA and VFA in our rheumatology department (**Figure 1**). Of these 440 patients, 76 had a subsequent treatment regimen other than zoledronate (e.g., other BPs). A total of 34 women were excluded due to missing or invalid data, and 48 were excluded because follow-up with DXA after denosumab discontinuation was still pending. Of the 282 women who discontinued denosumab and were included in this study, 144 received 5±2 denosumab injections ("short duration" of treatment), 84 received 10±2 denosumab injections ("medium duration) and 54 received 15±2 denosumab injections ("long duration"). All patients received calcium and vitamin D supplementation.

3.1. Baseline characteristics

Age distribution, body mass index (BMI, kg/m^2), prevalent vertebral and non-vertebral fractures, prior treatment with antiresorptive agents, additional therapy with glucocorticoids or aromatase inhibitors, duration of denosumab treatment and baseline T-scores are shown in **Table 1**. All women were Caucasian. In addition, a comparison of included (n=282) and excluded (n=34) patients revealed no significant differences (data not shown).

3.2. BMD changes after denosumab discontinuation

All women in this study received a subsequent zoledronate infusion 6 months after the last denosumab injection. The mean BMD changes during denosumab therapy as well after discontinuation (measured 12 to 24 months (median: 16 [12 to 23]) after the first zoledronate infusion) are shown according to denosumab treatment duration in **Table 2**. This table also indicates T-scores at the last denosumab injection

("DXA2") and 18-30 months later ("DXA3"). The changes after denosumab discontinuation and subsequent zoledronate were significantly different between short (5±2 injections, n=144) and medium (10±2 injections, n=84) denosumab durations (p<0.001 each for lumbar spine, total hip and femoral neck), but not between medium and long (15±2 injections, n=54) durations (p=0.35 for lumbar spine, p=0.54 for total hip and p=0.20 for femoral neck) (**Figure 2**). The BMD changes after denosumab discontinuation and subsequent zoledronate therapy were also analysed in the context of BMD gains under therapy **(Figure 3).** The net BMD changes compared to baseline were significantly different between the long and short denosumab durations at the lumbar spine (p<0.001), total hip (p=0.020) and femoral neck (p=0.003). The BMD changes from baseline showed no significant differences between the short and medium durations at the lumbar spine (p=0.69), total hip (p=0.49) or femoral neck (p=0.12). Comparing the BMD changes to baseline between patients with medium and long denosumab durations demonstrated significant increases in the long-term group at the lumbar spine and the femoral neck (p<0.001), but not at the total hip (p=0.2).

3.3. Subsequent therapy with zoledronate

In contrast to patients with short-term denosumab treatment of <5 years, most of those with longer durations from 5 to 9 years received ongoing subsequent therapy with zoledronate (≥2 infusions). In 76 women with medium- or long-term denosumab therapy, CTX and/or P1NP was measured every 3 months after the first zoledronate infusion. In 24 women, the second zoledronate infusion was administered 6 months after the first one, due to a ≥2-fold increase of CTX and/or P1NP in the 3 monthly measurements after the first zoledronate infusion (**Figure 4**). A comparison of the women with one versus 2 zoledronate infusions within 12 months after denosumab

discontinuation revealed no significant differences in BMD at the lumbar spine (p=0.37), total hip (p=0.97) or femoral neck (p=0.46).

3.4. Vertebral and non-vertebral fractures after denosumab discontinuation

Within 24 months after denosumab discontinuation, 10 patients sustained non-vertebral fractures and 9 suffered vertebral fractures. Of the 9 patients with vertebral fractures, 4 had multiple vertebral fractures: one with medium-duration denosumab treatment (5 years) and 3 with long-term denosumab (7.5 8 and 8.5 years of denosumab therapy, respectively).

4. Discussion

4.1. BMD changes after switching from denosumab to zoledronate

This observational study examined the BMD changes of postmenopausal women who received different durations of denosumab treatment, and all were treated with subsequent zoledronate. Although zoledronate effectively preserved most of the BMD gains of women with a short denosumab duration (2.5 years), this was not the case in women with a medium denosumab duration of 5 years. Interestingly, we did not observe a further BMD decrease after denosumab discontinuation in patients with a long denosumab duration of 7 to 8 years. Thus, rebound-associated bone loss seems to reach a plateau after 6 years of denosumab therapy. One possible bias explaining these observations could be more intensive management of patients with longer denosumab treatment durations (≥5 years). In these patients, BTMs were assessed every 3 months after the first zoledronate infusion (which was always administered 6 months after the last denosumab injection), and zoledronate was reinitiated if there was a 2-fold increase in a BTM. Thus, about 20% of women with treatment durations of ≥5 years received a second zoledronate infusion 6 months after the first one. However, their BMD loss did not differ from women with only one zoledronate infusion. This may be attributed to the high BTM threshold for zoledronate re-administration. It can be assumed that BMD gains have already been lost by the time a BTM value has doubled. Therefore, mechanisms other than the frequency of zoledronate administration might explain the plateau in bone loss after long-term denosumab discontinuation. In a bone biopsy study of osteoporotic women who received denosumab for 10 years, bone matrix mineralisation was greater in patients who received denosumab for 2 to 3 years than in those administered placebo. With continued therapy, matrix mineralisation increased further from year 2

or 3 to year 5, but not thereafter [17]. Another study demonstrated maturation of matrix minerals, including steady-state microhardness, after long-term denosumab use (>5 years) [18]. Thus, while one subsequent zoledronate infusion was able to prevent the loss of added minerals in women with short-duration denosumab treatment, it might not be sufficient following medium-duration therapy [10]. It could be speculated that due to steady changes of mineralisation and maturation of matrix minerals during long-term denosumab use, no further bone loss occurs when zoledronate is administered beyond medium-duration denosumab treatment (i.e., during long-term use). Another explanation for the levelling off of bone loss after 6 years of denosumab therapy may be a limited pooling of osteoclast precursors which enter differentiation upon withdrawal of RANKL inhibition simultaneously (often described as a 'recycling' of immature osteoclasts) [19,20]. Also, some mechanisms of BMD gain during long-term denosumab therapy and the impact of subsequent zoledronate treatment may not be affected by rebound osteoclast activity after denosumab discontinuation; these could include mechanically driven modeling effects and improvement of muscle function during RANKL inhibition by denosumab [21–23]. Further, our observations argue against the 'mechanostatic' theory which implies that the skeleton of each individual tends to return to its pretreatment status [24]. The women with long-term denosumab therapy demonstrated lower baseline T-scores, but the net gains in BMD after discontinuation were significantly higher than in patients who received medium- or short-duration denosumab treatment. This may indicate that denosumab should ideally be administered on a long-term basis (>7 years) to maximise BMD gains without risking a linear increase in bone loss after switching to zoledronate.

Notably, our patients with longer durations of denosumab treatment had more severe osteoporosis (lower BMI, lower baseline T-scores) and therefore probably

numerically more fractures after denosumab discontinuation; indeed, some even experienced multiple vertebral fractures despite subsequent zoledronate therapy. However, no association was found between denosumab duration and (multiple) vertebral fractures after denosumab discontinuation in a large, retrospective, observational study [6].

4.2. Management of subsequent zoledronate administration

Sølling and colleagues performed a randomised, open-label clinical trial which investigated BMD changes in relation to the timing of the first zoledronate infusion after discontinuation of 4.6 years (mean, ± 1.6) of denosumab therapy [7]. There were no significant differences in BMD retention between patients who received zoledronate at 6 or 9 months after the last denosumab injection and a third group in which the precise time of administration depended on BTM levels, but the total hip BMD at 6 months after the first zoledronate dose was lower when infusions were administered later than 6 months [7]. Of the 61 patients in the trial, 19 (33%) received a second zoledronate infusion due to relevant BTM increase (CTX >1.26 µg/L) or BMD loss (>5% at the lumbar spine or total hip), and one patient received 2 additional zoledronate infusions within 12 months after the first. However, irrespective of its timing, zoledronate treatment did not fully prevent BMD loss in patients who discontinued denosumab. One reason may be that the threshold of (re-) initiation of zoledronate therapy was relatively high, with >50% up the normal range for postmenopausal women, and it cannot be ruled out that BMD changes would have been different with a lower cut-off. In the 2-year extension of this same trial, another 9 patients were re-treated with zoledronate due to BMD loss of >5%. Overall, however, CTX remained in the reference range and BMD was maintained during the second year [9]. In contrast to the randomised trial of Sølling and colleagues, the first

zoledronate infusion in our observational study was administered 6 months after the last denosumab injection in all patients. However, the 2 studies used similar approaches to subsequent management, with repeated testing of BTMs every 3 months and a comparable threshold for re-initiation of zoledronate therapy, and the results were consistent as well: Despite regular measurement of BTMs, bone loss occurred in most patients who switched from long-term denosumab to zoledronate, irrespective of the timing and frequency of subsequent zoledronate therapy.

An official statement of the European Society of Calcified Tissue recommends treating all patients with zoledronate 6 months after the last denosumab injection, measuring the BTM every 3 months in those with a denosumab treatment duration of ≥ 3 years, and considering repetitive zoledronate infusions in patients with persistently increased BTMs [13]. We would add that in order to prevent bone loss, these additional zoledronate infusions might be given even after a moderate increase of BTMs or at 3 months after the first zoledronate infusion regardless of BTMs. This approach, however, would have to be tested in prospective trials.

4.3. Limitations

Our retrospective observational study has several limitations, including possible confounding factors and selection bias. The decision to discontinue denosumab and switch to zoledronate was an individualized treatment decision made in collaboration between the treating physician and the patient. Usually, however, we discontinued denosumab due to T-scores above -2.0 SD at the total hip and a low fracture risk. Additionally, the study subgroups were numerically unequal, with fewer patients with a medium or long denosumab treatment duration than those with a short duration. Still, we found significant differences between the medium- and long-term groups in

terms of BMD changes during, but not after, denosumab therapy. Further, BTMs were not measured in all patients, which may have biased the comparison of bone mass changes after denosumab discontinuation in patients with one versus 2 zoledronate infusions. One important strength is the assessment of bone mass gains under denosumab therapy in addition to bone changes after discontinuation, which allowed for a description of 'net' BMD changes compared to baseline.

4.4. Conclusions

Our observations suggest that regarding BMD gains, denosumab treatment durations are ideally short (up to 3 years) or long (>7 years), but not medium (4-6 years). Our patients with medium-duration treatment did not achieve the best possible BMD gains under denosumab, and experienced the maximal rebound-associated bone loss after its discontinuation. Because this is the first time that BMD changes after long-term denosumab treatment have been compared to medium- and short-duration therapy, this observation needs to be confirmed. In addition, the frequency and timing of (repeated) zoledronate infusions should be further investigated to optimise sequential therapy with denosumab and zoledronate and thereby maximise the preservation of BMD gains achieved under denosumab therapy.

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Author contributions

All authors were involved in data acquisition or analysis and data interpretation and in drafting the article or revising it critically for important intellectual content. All authors approved the final version to be submitted for publication. Study conception and design: JE, SR, TL, HJH. Acquisition of data: TL, JE, US, HRZ. Analysis and interpretation of data: JE, TL and BG. BG and JE take responsibility for the integrity of the data analysis. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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6. Tables

Table 1 Patient characteristics at baseline

	Short Dmab 5±2 injections (n = 144)	**Medium Dmab** 10±2 injections (n = 84)	**Long Dmab** 15±2 injections (n = 54)	P-value
Age at inclusion	66 ± 8.0	65 ± 7.0	65 ± 7.3	0.52
BMI (kg/m^2)	23 [22 to 26]	22 [20 to 25]	22 [20 to 25]	**0.021**
Dmab injections	5.0 [5.0 to 5.0]	10 [10 to 11]	15 [14 to 15]	**<0.001**
Prior BP therapy				0.79
- no	91 (63%)	59 (70%)	37 (69%)	
- within 2 years*	21 (15%)	9 (11%)	8 (15%)	
- beyond 2 years*	32 (22%)	16 (19%)	9 (17%)	
Glucocorticoids	12 (8.3%)	8 (10%)	4 (7.4%)	0.92
Prior fractures				0.59
None	63 (44%)	29 (35%)	19 (35%)	
Non-vertebral	37 (26%)	26 (31%)	18 (33%)	
Vertebral	44 (31%)	29 (35%)	16 (30%)	
Aromatase Inhibitors	10 (6.9%)	13 (15%)	8 (15%)	0.08
Baseline T-score LS	-2.4 ± 0.75	-2.5 ± 0.84	-3.1 ± 0.99	**<0.001**
Baseline T-score TH	-1.7 ± 0.70	-1.8 ± 0.75	-1.9 ± 0.63	0.06
Baseline T-Score FN	-2.0 ± 0.64	-2.2 ± 0.73	-2.3 ± 0.69	**0.037**

* Before starting Dmab

Abbreviations: BP: Bisphosphonate, Dmab: denosumab, LS: lumbar spine, TH: total hip, FN: femoral neck

Table 2 BMD changes during and after denosumab therapy

	Short Dmab 5±2 Dmab (n = 144)	**Medium Dmab** 10±2 Dmab (n = 84)	**Long Dmab** 15±2 Dmab (n = 54)	P-value
% LS Gain	9.1 ± 3.8	12 ± 4.5	16 ± 5.7	**<0.001**
% TH Gain	4.4 ± 2.7	6.4 ± 3.9	7.1 ± 3.8	**<0.001**
% FN Gain	3.7 ± 4.0	4.6 ± 3.5	7.2 ± 3.9	**<0.001**
T-Score LS DXA2	-1.9 ± 0.71	-1.8 ± 0.86	-2.1 ± 0.97	0.07
T-Score TH DXA2	-1.4 ± 0.72	-1.4 ± 0.68	-1.6 ± 0.57	0.08
T-Score FN DXA2	-1.9 ± 0.64	-2.0 ± 0.63	-2.0 ± 0.61	0.55
% LS Loss	-3.1 ± 3.7	-5.6 ± 3.8	-5.0 ± 3.3	**<0.001**
% TH Loss	-2.0 ± 2.7	-3.5 ± 3.2	-3.2 ± 2.8	**<0.001**
% FN Loss	-1.4 ± 4.4	-3.4 ± 3.8	-2.6 ± 2.7	**<0.001**
LS % to Baseline	6.0 ± 5.0	6.3 ± 5.8	11 ± 5.7	**<0.001**
TH % to Baseline	2.5 ± 3.4	2.9 ± 4.7	3.9 ± 4.3	0.10
FN% to Baseline	2.3 ± 4.8	1.2 ± 5.3	4.6 ± 4.8	**<0.001**
T-Score LS DXA3	-2.1 ± 0.80	-2.2 ± 0.95	-2.6 ± 0.99	**0.005**
T-Score TH DXA3	-1.5 ± 0.74	-1.7 ± 0.74	-1.9 ± 0.62	**0.008**
T-Score FN DXA3	-2.0 ± 0.67	-2.1 ± 0.66	-2.1 ± 0.62	0.10
Fractures after Dmab discontinuation				0.14
None	136 (94%)	77 (92%)	49 (91%)	
Non-vertebral	5 (3.5%)	5 (6.0%)	0 (0.00%)	
Vertebral*	3 (2.1%)	2 (2.4%)	4 (7.4%)	

*4 patients had multiple vertebral fractures, one with a medium-duration denosumab (5 years) and 3 with long-duration denosumab (7.5, 8 and 8.5 years of denosumab therapy, respectively).

Abbreviations: Dmab: denosumab, LS: lumbar spine, TH: total hip, FN: femoral neck. DXA2: DXA scan at the last denosumab injection, DXA3: DXA scan 18 months after the last denosumab injection

7. Legends

Figure 1 Flow chart of the observational study

Flow chart of the inclusion of women who discontinued denosumab treatment and received subsequent zoledronate therapy. Dmab: denosumab, BPs: bisphosphonates, SERM: selective estrogen receptor modulator.

Figure 2 BMD changes after denosumab discontinuation according to denosumab treatment duration

BMD changes (mean ± 95%CI) between the last denosumab injection with subsequent zoledronate and follow-Up DXA 18-30 months later, according to denosumab duration. Abbreviations: Dmab: denosumab.

Figure 3 BMD changes compared to baseline during and after denosumab therapy

BMD gains under denosumab therapy ("Gains under therapy", left side) and net BMD gains 18-30 months after the last denosumab injection and subsequent zoledronate ("Follow-up 1-2 y later", indicating BMD changes (mean ± 95%CI) compared to baseline, right side) according to denosumab duration. Abbreviations: Dmab: denosumab.

Figure 4 BTM evolution after denosumab discontinuation

Changes (mean ± 95%CI) in CTX (A, B) and P1NP (C, D) levels in patients with one versus 2 zoledronate infusions between after last denosumab injection and 1 year later. The first zoledronate infusion was administered in all patients 6 months after the last denosumab injection. Abbreviations: Dmab: denosumab, ZOL: zoledronate.

Highlights

Ms. Ref. No.: BONE-D-22-00352

Title: Effects of Zoledronate on Bone Mineral Density and Bone Turnover after Long-term Denosumab Therapy: Observations in a Real-World Setting Bone

- Switching denosumab to zoledronate is associated with bone loss
- This bone loss is increased after 5 years of denosumab compared to 2.5 years
- But no further bone loss occurs in patients with denosumab treatment of >6 years
- This observation is irrespective of the frequency of subsequent zoledronate infusions

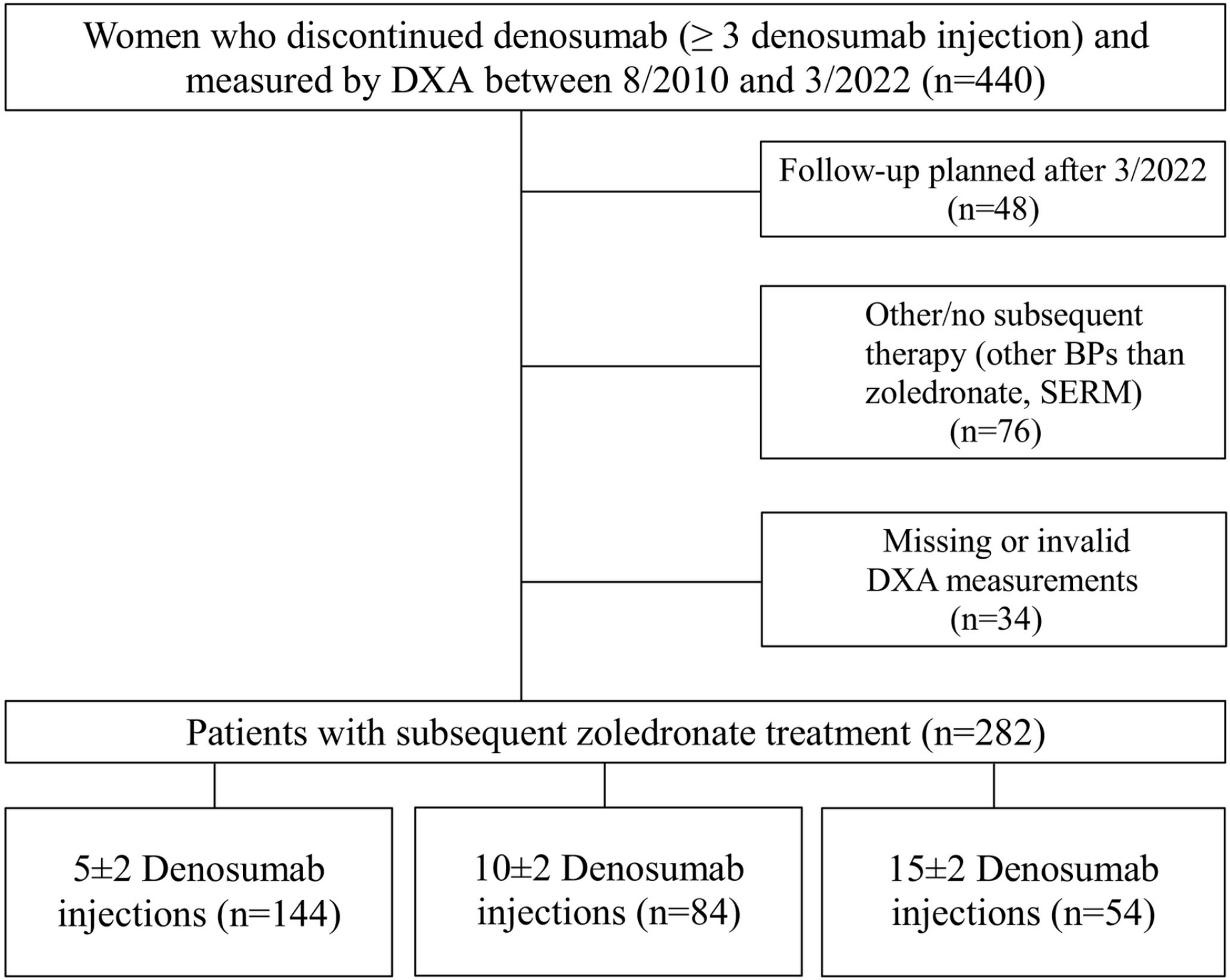
Women who discontinued denosumab (≥ 3 denosumab injection) and measured by DXA between 8/2010 and 3/2022 (n=440)
Follow-up planned after 3/2022 (n=48)
Other/no subsequent therapy (other BPs than zoledronate, SERM) (n=76)
Missing or invalid DXA measurements (n=34)
Patients with subsequent zoledronate treatment (n=282)
5±2 Denosumab injections (n=144)
10±2 Denosumab injections (n=84)
15±2 Denosumab injections (n=54)

Figure 1

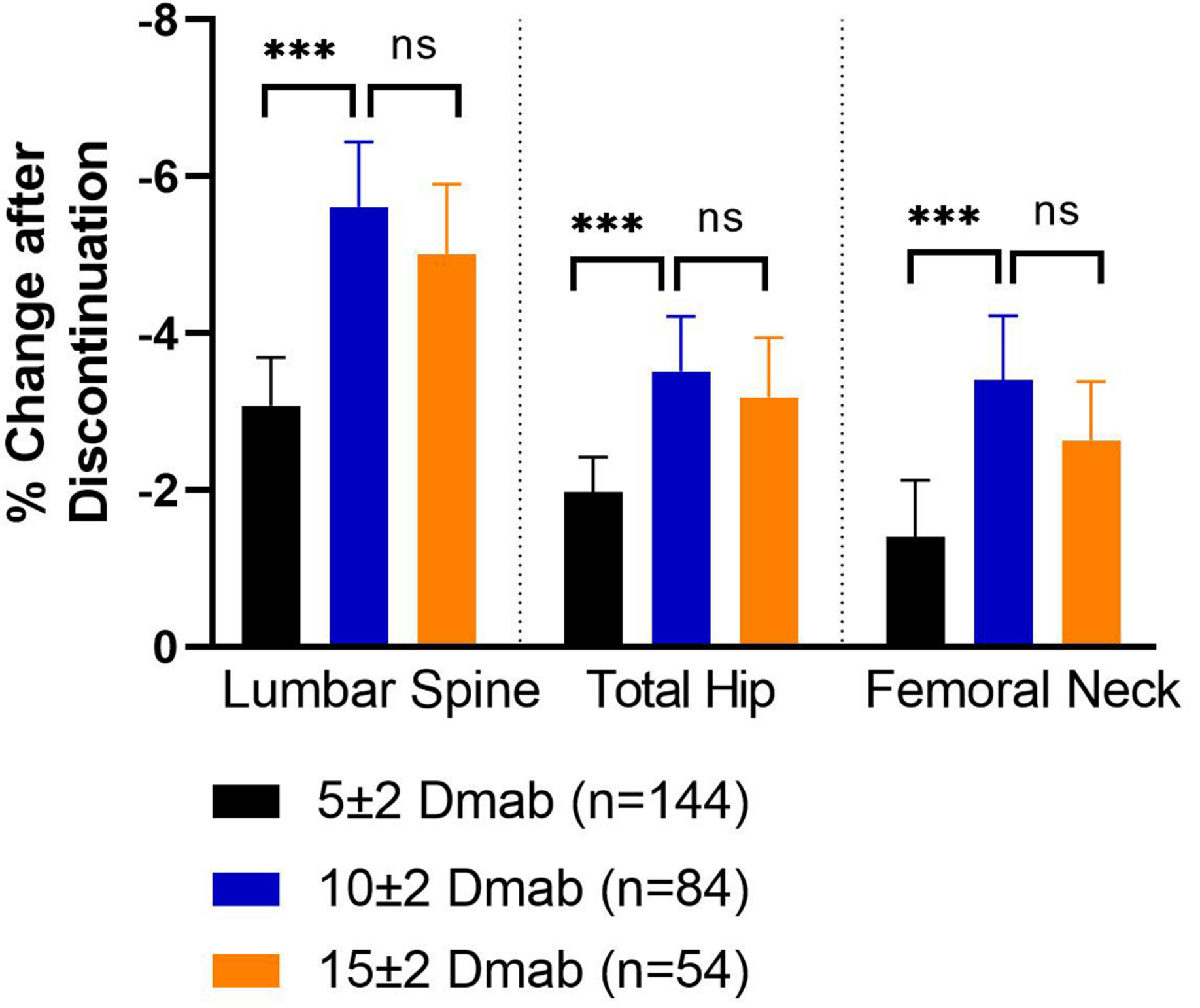
-8
-6
-4
-2
0
% Change after Discontinuation
***
ns
***
ns
***
ns
Lumbar Spine
Total Hip
Femoral Neck
5±2 Dmab (n=144)
10±2 Dmab (n=84)
15±2 Dmab (n=54)

Figure 2

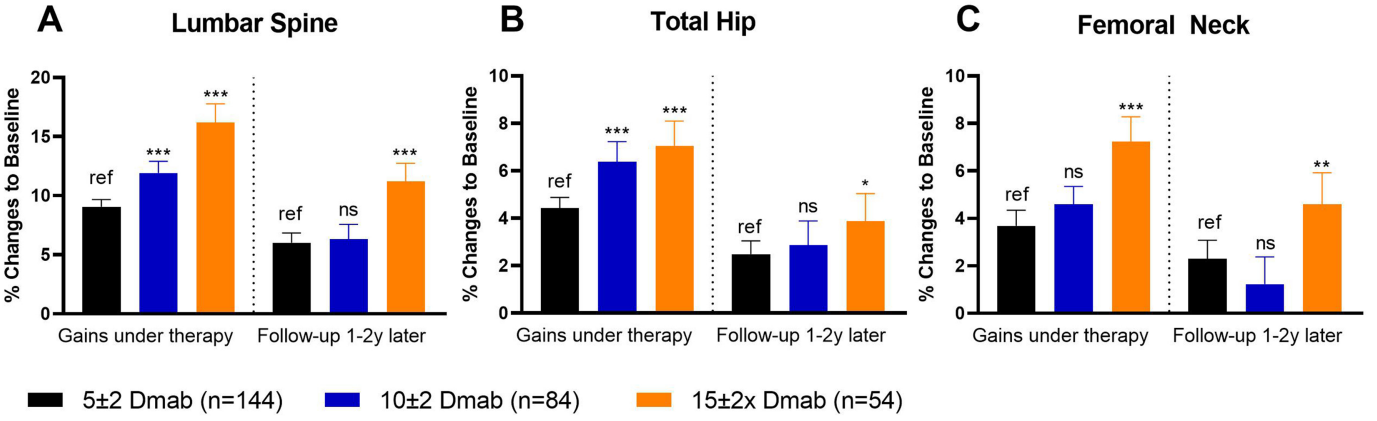
A
Lumbar Spine
B
Total Hip
C
Femoral Neck
% Changes to Baseline
ref
***
ns
*
**
Gains under therapy
Follow-up 1-2y later
5±2 Dmab (n=144)
10±2 Dmab (n=84)
15±2x Dmab (n=54)

Figure 3

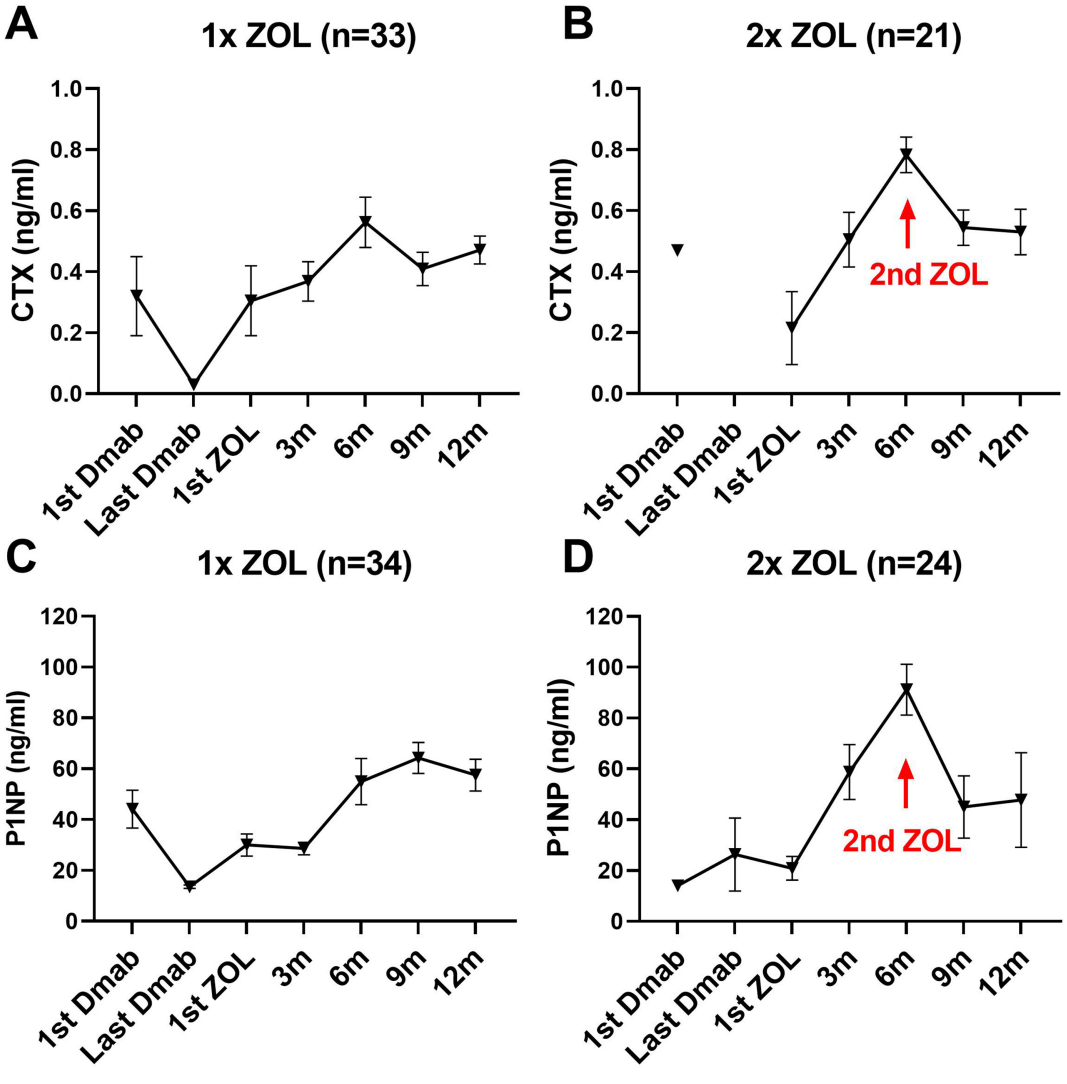
A
1x ZOL (n=33)
CTX (ng/ml)
1.0
0.8
0.6
0.4
0.2
0.0
1st Dmab
Last Dmab
1st ZOL
3m
6m
9m
12m
B
2x ZOL (n=21)
CTX (ng/ml)
2nd ZOL
C
1x ZOL (n=34)
P1NP (ng/ml)
120
100
80
60
40
20
0
D
2x ZOL (n=24)
P1NP (ng/ml)
2nd ZOL

Figure 4