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ORIGINAL RESEARCH

Bone Mineral Density Changes After 1 Year of Denosumab Discontinuation in Postmenopausal Women with Long-Term Denosumab Treatment for Osteoporosis

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Abstract

The aim of the present study was to document the changes in bone mineral density (BMD) 1 year after denosumab loss-of-effect following long-term treatment with subcutaneous denosumab 60 mg Q6M during 7 or 10 years and in the absence of any treatment with a bone active substance. All postmenopausal women with osteoporosis who participated to the randomized placebo-controlled FREEDOM core trial and its open-label extension at the University Hospital of Bern, Switzerland, and who accepted to undergo off-treatment follow-up during 1 year after discontinuation, were included ($N=12$). After 10 years of denosumab, mean lumbar spine (LS) BMD had increased by 21.2% vs. baseline. One year after discontinuation LS BMD had decreased by −9.1% vs. Year 10, resulting in a net gain of 10.2% vs. baseline. At total hip (TH) and femoral neck (FN), BMD had increased by 8.3 and 8.1% in Year 10 vs. baseline, respectively. 1 Year after discontinuation, BMD had decreased by − 12.7 and − 11.0% vs. Year 10, respectively, corresponding to net BMD losses of −5.5 and −3.8% vs. baseline, respectively. Similar albeit less pronounced changes were observed in those treated with denosumab during 7 years. Stopping denosumab after long-term exposure resulted in BMD losses of large order of magnitude at all measured sites, suggesting that treatment duration may predict the rate and amount of bone lost.

Keywords Osteoporosis · Denosumab · Bone mineral density · Long-term therapy · Rebound-associated bone loss

Introduction

The effects of denosumab withdrawal on bone have been studied in postmenopausal women with low bone mass exposed to a short-term 2-year treatment with subcutaneous denosumab [1, 2]. After denosumab loss-of-effect (i.e., 6 months after the last injection), bone turnover markers (BTM) increased above baseline within 3 months, reached a peak at 6 months, and returned to baseline value at 24 months [2]. Gains in bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) achieved at the lumbar spine (LS) and the total hip (TH) were offset within 12 months after denosumab discontinuation [1, 2] and remained at or below baseline values thereafter [2]. While results from an earlier post hoc analysis were reassuring with regard to fracture risk during the rebound phase [3], recent case reports [4–6] and a post hoc analysis of the FREEDOM trial and its extension [7] have triggered concerns of rebound-associated fractures after denosumab discontinuation.

Little is known about BMD changes following denosumab discontinuation after long-term treatment. The aim of the present study was to document the natural history of denosumab withdrawal, 1 year after loss-of-effect, in women treated with denosumab during either 7 or 10 years included in the FREEDOM trial and its extension.

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Materials and Methods

Included were all postmenopausal women who participated to the randomized placebo-controlled Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) core trial (3 years) [8–10] and continued in its open-label extension (7 years) [11–13] and accepted to undergo off-treatment follow-up during 1 year at the University Hospital of Bern, Switzerland.

Women included in FREEDOM were treated with either subcutaneous denosumab 60 mg Q6M or matching placebo during 3 years (Y0–3) with detailed study design published elsewhere [14]. All women included in the FREEDOM open-label extension had completed their 3-year visit, not discontinued the investigational drug and not missed more than one dose and were treated with subcutaneous denosumab 60 mg Q6M for up to seven additional years (Y4–10) [11–13]. Thereafter, as all participants had a *t* score above −2.5 and in accordance with the Swiss regulations reimbursing osteoporosis drugs only below that threshold, denosumab was not renewed and no treatment with a bone active substance was initiated, with adequate daily calcium and vitamin D being pursued. All women were proposed to attend follow-up visits, scheduled yearly after the denosumab discontinuation date (Year 11). The core study, its extension, and the follow-up were approved by the cantonal ethical review committee of Bern, Switzerland. All participants provided written informed consent.

Areal BMD was assessed by DXA at lumbar spine (LS), total hip (TH), and femoral neck (FN) at baseline, year 1, 2, 3, 4, 5, 6, 8, 10, and 11 using a Hologic bone densitometer (Hologic Inc., Bedford, MA, USA). Results were expressed in g/cm^2 according to protocol [10]. Lumbar and thoracic spine plain X-rays were performed at baseline and Year 10. Vertebral fracture assessment (VFA) by DXA was performed at Year 11. The FRAX-score was calculated by using the country-specific FRAX algorithm calibrated for Switzerland available under https://www.shef.ac.uk/FRAX [15].

Two groups were analyzed separately, although not formally compared. One group was treated with denosumab during 10 years before discontinuation (D10 + 1off), the other with placebo during 3 years followed by denosumab during 7 years preceding discontinuation (P3D7 + 1off). Descriptive statistics were used to calculate mean values and standard errors (SEM).

Results

Twelve women (nine in D10 + 1off and three in P3D7 + 1off) were included. Baseline characteristics at Year 0 and Year 10 are shown in Table 1. Mean time since last denosumab dose was 18.0 months, corresponding to a mean off-treatment duration after loss-of-effect of 12.0 months.

BMD Changes at the Lumbar Spine

As shown in Fig. 1 panel A, mean LS BMD (SEM) increased by 21.2% (1.2) in the D10 group and by 14.8% (2.1) in the P3D7 group between baseline and Year 10. 1

Table 1 Selected patient characteristics at Year 0 and 10

	D10 + 1off (*N* = 9)		P3D7 + 1off (*N* = 3)	
	Baseline (Y0)	Year 10 (Y10)	Baseline (Y0)	Year 10 (Y10)
Age (years)	68.8 ± 1.9 (62.5 to 80.4)	78.9 ± 1.9 (72.6 to 90.6)	65.5 ± 4.1 (63.0 to 73.5)	75.6 ± 4.1 (73.2 to 83.6)
Lumbar spine BMD *t* score	−3.0 ± 0.2 (−3.9 to −2.0)		−2.4 ± 0.3 (−3.0 to −2.0)	
Femoral neck BMD *t* score	−1.7 ± 0.3 (−3.2 to −0.5)		−1.6 ± 0.2 (−2.0 to −1.3)	
Prevalent vertebral fractures (%)	2/9 (22.2%)	4/9 (44.4%)	0/3	0/3
FRAX score, major osteoporotic fractures	18.1 ± 3.9 (6.5 to 38.0)	–	11.4 ± 2.2 (7.3 to 15.0)	–
FRAX score, hip fractures	4.5 ± 1.5 (0.4 to 12.0)	–	2.1 ± 0.7 (0.7 to 3.2)	–
Body height (cm)	158.1 ± 1.4 (149.3 to 164.0)	156.3 ± 1.6 (146.5 to 162.5)	157.7 ± 1.5 (155.0 to 165.0)	157.4 ± 1.4 (154.8 to 159.4)
Body weight (kg)	66.0 ± 3.1 (53.0 to 81.0)	64.6 ± 3.4 (54.0 to 79.5)	57.3 ± 2.6 (53.0 to 62.0)	60.1 ± 1.8 (57.7 to 63.5)
Serum creatinine (μmol/L)	65.0 ± 3.0 (44.0 to 71.0)	74.4 ± 4.9 (53.0 to 94.0)	65.0 ± 2.6 (53.0 to 71.0)	73.7 ± 9.3 (57.0 to 89.0)
Serum 25OH vitamin D (nmol/L)	54.8 ± 4.5 (35.3 to 73.3)		70.6 ± 13.3 (44.0 to 85.8)	
Serum alkaline phosphatase (IU/L)	85.1 ± 11.2 (54.0 to 167.0)	59.3 ± 2.8 (48.0 to 74.0)	70.3 ± 14.5 (47.0 to 97.0)	61.0 ± 7.8 (48.0 to 75.0)

All values are means ± SEM (minimum–maximum)

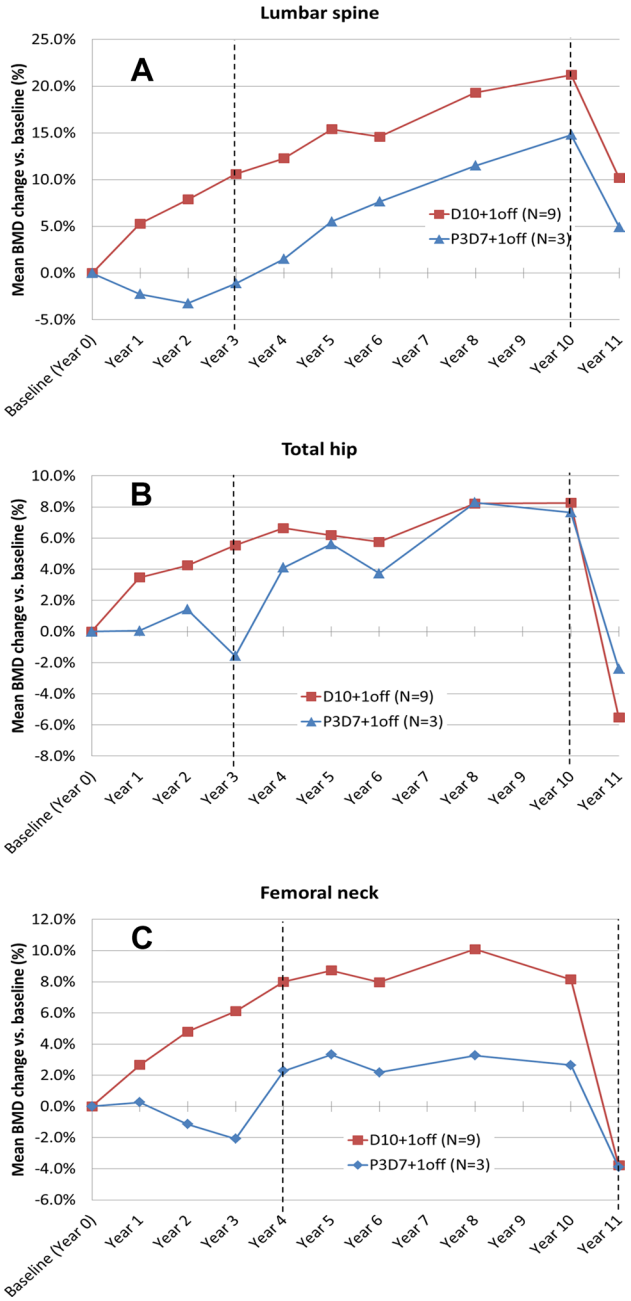

Fig. 1 Lumbar spine (Panel A), total hip (Panel B), and femoral neck (Panel C) BMD changes vs. baseline during 10 years on denosumab (D10, $N=9$, *squares*) or 7 years on denosumab after 3 years of placebo (P3D7, $N=3$, *triangles*) plus 1 year after loss-of-effect (+1off)

Year after discontinuation of denosumab and compared to Year 10, mean BMD had decreased by −9.1% (D10+1off) and by −8.6% (P3D7+1off). Stopping denosumab during 1 year after long-term continuous application during 10 or 7 years resulted in a residual mean net gain in LS BMD of +10.2 and +4.9% vs. baseline, respectively.

BMD Changes at the Total Hip

As shown in Fig. 1 panel B, mean TH BMD increased by 8.3% (1.7) in the D10 group and by 7.6% (2.1) in the P3D7 group between baseline and Year 10. 1 Year after discontinuation of denosumab and compared to Year 10, mean BMD had decreased by −12.7% (D10+1off) and by −9.3% (P3D7+1off). Overall, mean net loss in TH BMD at Year 11 vs. baseline was −5.5 and −2.4%, respectively.

BMD Changes at the Femoral Neck

As shown in Fig. 1 panel C, mean FN BMD increased by 8.1% (1.3) in the D10 group and by 2.6% (1.3) in the P3D7 group between baseline and Year 10. Corresponding median values were 3.7 and −3.9%, respectively. 1 Year after discontinuation of denosumab and compared to Year 10, mean BMD at FN had decreased by −11.0% (D10+1off) and −6.4% (P3D7+1off). Corresponding median values were −7.9 and −0.9%, respectively. Overall, mean net loss in TH BMD at Year 11 vs. baseline was −3.8 and −3.9%, respectively.

Patient Level BMD Changes

Importantly, all 12 patients included in this analysis experienced BMD losses after discontinuation of denosumab. In the nine patients treated during 10 years with denosumab these individual losses in Year 11 compared to Year 10 ranged from −5.2 to −17.1% at the lumbar spine, from −6.0 to −17.4% at the total hip, and from −2.4 to −19.1% at the femoral neck. While all patients had BMD residual gains post discontinuation of denosumab (i.e., compared to baseline) at the lumbar spine (ranging from +2.8 to +21.7%), all but one experienced net losses at the total hip (ranging from +1.3 to −13.7%) and all but three had net losses at the femoral neck (ranging from +5.3 to −9.4%).

One incident morphometric (moderate) vertebral fracture assessed by VFA was reported in the D10+1off group during the year following denosumab discontinuation (Year 11). No clinical fractures occurred after denosumab discontinuation.

Discussion

In postmenopausal women with osteoporosis treated with denosumab during 7 or 10 years, the unopposed discontinuation of denosumab resulted in rapid BMD decreases (over 1 year) at LS, TH, and FN of large magnitude (prior BMD gains more than offset at TH and FN). These changes occurred in a context consistent with a previously reported rebound-related high bone turnover state [16] with BMD

loss [17, 18] and increased fracture risk [4–7] after denosumab withdrawal.

The present findings suggest that in postmenopausal women with osteoporosis the duration of treatment with denosumab may be a predictor of the magnitude of bone loss to be expected after withdrawal. Earlier studies were performed in women with osteopenia [1, 2], or in a mixed population of patients treated with a bone active substance or not [17] and generally of much shorter duration [1, 2, 18] such that the present findings cannot be compared with the results of these larger studies. In this context, larger cohorts of the FREEDOM extension need to be stratified according to their duration of treatment with denosumab in order either to confirm or infirm the present findings.

Women who stopped treatment with denosumab in this study generally decided to do so because of reimbursement restrictions for antiresorptive treatments. In Switzerland, these treatments are reimbursed only in patients with a *t* score at or below −2.5. After 7 or 10 years of denosumab not a single woman qualified for reimbursed follow-up drug therapy. Recent research findings indicate that immediate intravenous zoledronate treatment at the time of loss-of-effect, 6 months after the last denosumab injection may offer only partial protection against bone loss [19]. Questions remaining to be answered include whether the evidence-based dose used to decrease fracture risk in postmenopausal osteoporosis is still adequate after denosumab withdrawal, whether this dose is the same or not independently of the duration of treatment with denosumab, whether delaying the administration of the dose by a few months after loss-of-effect increases efficacy based on a larger remodeling transient, and whether bone turnover marker guided initiation of bisphosphonate therapy may be a better option. Answers to these questions may contribute improving not only patient outcomes but also the reimbursement situation in Switzerland and possibly other countries.

Conclusions

One year after discontinuation of therapy following long-term denosumab treatment during 7–10 years, important BMD losses of unprecedented order of magnitude have been observed at all clinically important fracture sites (lumbar spine, total hip, and femoral neck). The consequences in terms of fracture risk are unknown and deserve further investigations. An urgent and unaddressed medical need remains for an evidence-based follow-up treatment after denosumab withdrawal aimed at preserving bone mass gains and related fracture risk reduction.

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Author Contributions Study design: AP and KL. Study conduct: AP and CS. Data collection: NV, RP, AP. Data analysis: AP and RP. Data interpretation: AP and KL. Drafting manuscript: AP. Revising manuscript content: AP, NV, HB, CS, RP, KL. Approving final version of manuscript: AP, NV, HB, CS, RP, KL. KL takes responsibility for the integrity of the data analysis.

Compliance with Ethical Standards

Conflict of interest Kurt Lippuner is a primary investigator in clinical development programs in the field of osteoporosis from Amgen. Albrecht Popp and Christoph Senn are Sub-Investigators in clinical development programs in the field of osteoporosis from Amgen, Albrecht Popp has received personal fees for participation in advisory board meetings from Amgen Switzerland and Labatech Pharma. Nadshathra Varathan and Romain Perrelet declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This study was approved by the cantonal ethical review committee of Bern, Switzerland. All participants have provided their written informed consent. The study was carried out in accordance with the principles enunciated in the current version of the Declaration of Helsinki (DoH), the Essentials of Good Epidemiological Practice issued by Public Health Schweiz (EGEP), the Swiss Law and Swiss regulatory authority's requirements as applicable.

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