# Severe Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: 9 Clinical Cases Report

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**Context:** Denosumab inhibits bone resorption, increases bone mineral density, and reduces fracture risk. Denosumab was approved for the treatment of osteoporosis and the prevention of bone loss in some oncological situations. Denosumab discontinuation is associated with a severe bone turnover rebound (BTR) and a rapid loss of bone mineral density. The clinical consequences of the BTR observed after denosumab discontinuation are not known.

**Cases Description:** We report 9 women who presented 50 rebound-associated vertebral fractures (RAVFs) after denosumab discontinuation. A broad biological and radiological assessment excluded other causes than osteoporosis. These 9 cases are unusual and disturbing for several reasons. First, all vertebral fractures (VFs) were spontaneous, and most patients had a high number of VFs (mean = 5.5) in a short period of time. Second, the fracture risk was low for most of these women. Third, their VFs occurred rapidly after last denosumab injection (9–16 months). Fourth, vertebroplasty was associated with a high number of new VFs. All the observed VFs seem to be related to denosumab discontinuation and unlikely to the underlying osteoporosis or osteopenia. We hypothesize that the severe BTR is involved in microdamage accumulation in trabecular bone and thus promotes VFs.

**Conclusion:** Studies are urgently needed to determine 1) the pathophysiological processes involved, 2) the clinical profile of patients at risk for RAVFs, and 3) the management and/or treatment regimens after denosumab discontinuation. Health authorities, physicians, and patients must be aware of this RAVF risk. Denosumab injections must be scrupulously done every 6 months but not indefinitely. (***J Clin Endocrinol Metab*** **102: 354–358, 2017)**



Denosumab is a fully human monoclonal antibody that inactivates receptor activator of nuclear factor κB ligand. It inhibits bone resorption, increases bone mineral density (BMD), and reduces fracture risk (1–3). Denosumab 60 mg twice per year has been approved in several countries since 2010 for 1) reducing fracture risk in both postmenopausal women and men with osteoporosis and 2) increasing bone mass in patients at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer or androgen deprivation therapy for prostate cancer. The benefit-to-risk ratio guides osteoporosis treatment duration. Antiresorptive treatments with denosumab or bisphosphonates are associated with the occurrence of osteonecrosis of the jaw and atypical femoral fracture. These side effects are related to the dose and the duration of the treatment. In many guidelines, bisphosphonates are recommended for 3 to 5 years (4). No optimal duration is defined for denosumab. However, it seems reasonable to apply the same recommendations as for bisphosphonates in clinical practice. After bisphosphonate discontinuation, no rebound effect is observed and the antifracturary benefit persists. Discontinuation of denosumab is associated with a severe bone turnover rebound (BTR) and a rapid loss of BMD. Denosumab cessation after 4 60-mg injections induced a severe BTR for 2 years, and the BMD

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Abbreviations: BMD, bone mineral density; BTR, bone turnover rebound; DXA, dual-energy X-ray absorptiometry; FRAX, fracture risk assessment tool; RAVF, rebound-associated vertebral fracture; VF, vertebral fracture.

gain in the lumbar spine and total hip was completely lost after 1 year (5). Patients who discontinued the pivotal trial after 2 to 5 denosumab doses seem to not present an excess of fracture risk during the off-treatment period (6). However, the median off-treatment interval was 8 months, and 1/3 of the patients had begun other osteoporosis treatments during the off-treatment period. Therefore, the clinical consequences of the BTR observed after denosumab discontinuation have not been prospectively studied.

## Cases description

We reported 3 cases of rebound-associated vertebral fractures (RAVFs) after discontinuation of denosumab (7). These cases could be anecdotal, but within this publication, 6 additional women with spontaneous clinical RAVFs were evaluated at our center. Thus, we report the cases of 9 women who presented between 1 and 9 spontaneous vertebral fractures after denosumab discontinuation. Patients' characteristics are described in Table 1. The mean ± SD age was 62.4 ± 10.1 years. The mean ± SD 10-year fracture risk for major osteoporotic fractures (FRAX tool for Switzerland, https://www.shef.ac.uk/FRAX/tool.aspx?country=15) was 17.4% ± 8.1%. Among the clinical risk factors for osteoporosis, 3 women had already had an osteoporotic fracture, and 2 were taking an adjuvant aromatase inhibitor (cases 5 and 8). None had received glucocorticoids. Eight women were naive of osteoporotic treatment before denosumab initiation. One woman (case 7) received bisphosphonates for 3 years, 11 years before denosumab initiation. Dual-energy X-ray absorptiometry (DXA) was performed before the denosumab initiation (Table 2). One woman (case 4) had osteopenia. Denosumab was initiated for osteoporosis in 7 women and for bone preservation due to aromatase inhibitor treatment in 2 women (cases 5 and 8). These 9 women received 2 to 8 denosumab doses every 6 months. The reasons for denosumab discontinuation (Table 1) were the patient's wish (distrust medication, 3 cases), the treatment duration (4 years, 2 cases), the disappearance of osteoporosis in DXA control (2 cases), the end of the aromatase inhibitor treatment (1 case), and the omission of the denosumab dose (1 case). All women except 1 (case 4, denosumab treatment omission) had a DXA about 6 months after the last denosumab injection (Table 2). The mean ± SD BMD gain was 11.3% ± 4.2% (minimum, +6.7%; maximum, +20.7%) at the lumbar spine and 3.2% ± 4.4% (minimum, −5.0%; maximum, +13.5%) at the total hip. These 9 women each had between 1 and 8 clinical spontaneous vertebral fractures 9 to 16 months after the last denosumab injection (Table 1; Fig. 1). Considering a 6-month period of effectiveness for denosumab treatment, the interval between that time and the incidence of fractures varies between 3 and 10 months (Fig. 1). All the vertebral fractures (VFs) were painful. Percutaneous vertebroplasty were performed in 3 women (cases 2, 8, and 9) due to severe back pain. Ten new symptomatic and spontaneous VFs occurred in these 3 women in the month following vertebroplasty. In total, 50 spontaneous VFs were diagnosed in these 9 women. All VFs were documented by magnetic resonance imaging and assessed by a radiologist. A broad biological assessment excluded renal failure, hypercalcemia, hyperthyroidism, primary hyperparathyroidism, multiple myeloma, mastocytosis, and malabsorption. Two women (cases 2 and 9) had a vertebral biopsy that confirmed the absence of pathology other than osteoporosis (case 9, Fig. 2). Both women had a DXA after the occurrence of VFs, respectively 10 and 16 months after the last denosumab injection. In comparison with the DXA performed after the last denosumab injection, BMD decreased by

**Table 1. Patients' Characteristics**

| Case No. | Age[a] | BMI[a] | FRAX MOF,[a] % | Prevalent OP Fx, Vertebral/ Nonvertebral, No. | Dmab Doses, No. | Time since Last Dmab, No. | Incidence of Vertebral Fx, No. | Reason for Dmab Discontinuation |
|---|---|---|---|---|---|---|---|---|
| 1 | 52 | 21.5 | 11 | 0/0 | 5 | 9 | 5 | No more OP |
| 2 | 52 | 23.6 | 11 | 0/0 | 8 | 10 | 7 (+2[b]) | Tx duration |
| 3 | 55 | 22.1 | 11 | 0/0 | 7 | 10 | 2 | No more OP |
| 4 | 56 | 23.0 | 12 | 2/0 | 2 | 11 | 8 | Patient's wish |
| 5 | 61 | 20.0 | 15 | 0/0 | 2 | 12 | 1 | Tx omission |
| 6 | 61 | 23.1 | 16 | 1/0 | 8 | 10 | 6 | Tx duration |
| 7 | 71 | 22.7 | 27 | 1/1 | 2 | 11 | 5 | Patient's wish |
| 8 | 77 | 20.7 | 20 | 0/0 | 6 | 15 | 3 (+2[b]) | End of AI |
| 9 | 77 | 18.8 | 34 | 0/0 | 5 | 16 | 3 (+6[b]) | Patient's wish |

Abbreviations: AI, aromatase inhibitors; BMI, body mass index; Dmab, denosumab; Fx, fracture; MOF, major osteoporotic fracture; OP, osteoporosis; Tx, treatment.

[a]At the beginning of the denosumab treatment.

[b]One month after vertebroplasty.

**Table 2. Bone Mineral Density Expressed in Standard Deviations Before Denosumab Initiation and 6 Months After Denosumab Discontinuation**

| Case No. | Denosumab Doses, No. | Lumbar Spine Before, SD | Lumbar Spine After, SD | Total Hip Before, SD | Total Hip After, SD | Femoral Neck Before, SD | Femoral Neck After, SD |
|---|---|---|---|---|---|---|---|
| 1 | 5 | −3.1 | −2.3 | −2.5 | −2.1 | −2.7 | −2.0 |
| 2 | 8 | −2.8 | −2.2 | −2.5 | −2.7 | −2.9 | −2.7 |
| 3 | 7 | −3.1 | −2.4 | −2.0 | −1.2 | −2.3 | −2.1 |
| 4 | 2 | −1.7 | NR | −1.0 | NR | −2.4 | NR |
| 5 | 2 | −3.9 | −3.5 | −1.9 | −1.6 | −2.1 | −2.2 |
| 6 | 8 | −3.0 | −2.3 | −1.9 | −1.7 | −1.8 | −1.8 |
| 7 | 2 | −4.5 | −3.1 | NA | NA | NA | NA |
| 8 | 6 | −3.9 | −3.1 | −1.1 | −1.2 | −1.8 | −1.4 |
| 9 | 5 | −4.1 | −3.7 | −3.4 | −3.6 | −4.1 | −3.9 |

Abbreviations: NA, not available (bilateral hip replacement); NR, not realized; SD, standard deviation.

8% and 11% at the lumbar spine and by 8% and 6% at the total hip, respectively, in cases 2 and 9. β-crosslaps (fasting blood samples in early morning; normal ranges for premenopausal women: 25–573 ng/L) were measured after the occurrence of VFs in 4 women (cases 2, 5, 6, and 8) 10 to 16 mo after the last denosumab injection. All the values (median, 1147 ng/L; minimum, 840 ng/L; maximum, 1352 ng/L) were higher than the upper limit of normal value for the premenopausal women (573 ng/L). All women were taking adequate calcium and vitamin D supplementation during and after denosumab treatment.

## Discussion

These 9 cases are unusual and disturbing for several reasons. First, all VFs were spontaneous, and most patients presented with a high number of VFs in a very short period of time: 50 VFs were diagnosed in 9 women (mean, 5.5). Second, the associated fracture risk was low for most of these women: 6 were relatively young (<65 years old), 6 had never had an osteoporotic fracture, and none had had treatment by glucocorticoids. At the beginning of denosumab treatment, their 10-year FRAX probability for major osteoporotic fractures was <20% for 6 women. Third, their VFs occurred rapidly after the last denosumab injection (9–16 months), and no other treatment of osteoporosis was introduced during this period. The described features imply that the observed VFs seem to be related to denosumab discontinuation and unlikely to the underlying osteoporosis or osteopenia. Shortly after the occurrence of VFs, the β-crosslaps measured in 4 of 9 women were high, and the DXA measured in 2 of 9 women showed a rapid decrease of BMD. Moreover, 2 cases of multiple vertebral fractures after denosumab discontinuation were published recently by 2 different groups (8, 9). We hypothesize that the severe BTR is involved in microdamage accumulation in trabecular bone and thus promotes VFs.

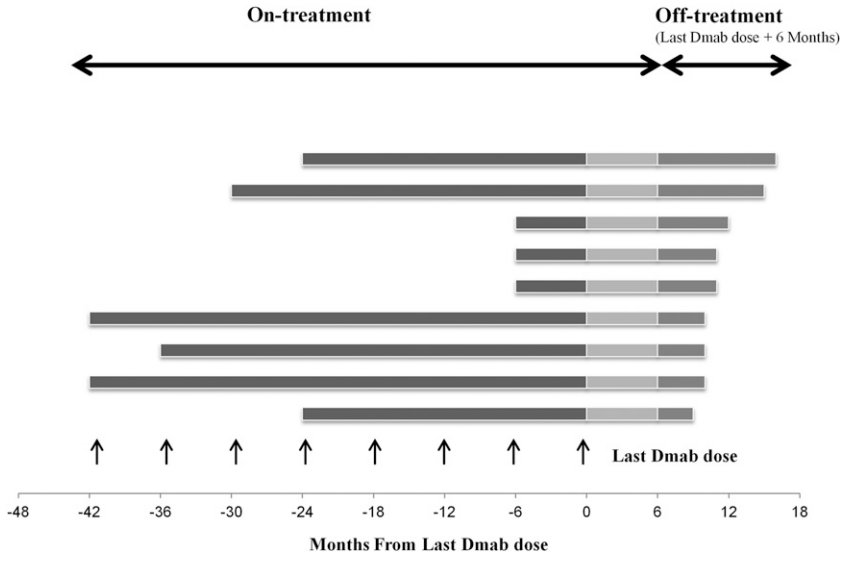


**Figure 1.** Vertebral fractures occurrence according to the on- and off-treatment duration. Each horizontal bar represents the length of on- and off-treatment for 1 patient. The patients are arranged by decreasing time since denosumab discontinuation and the occurrence of vertebral fractures. The arrows represent the denosumab injections. Dmab, denosumab.

The documentation of these 9 cases is not complete for several reasons. First, all these women were followed by their general practitioners. So, the bone densitometry monitoring is not standardized, and the dosage of β-crosslaps is rarely or never performed. Second, these RAVFs after denosumab discontinuation were initially not suspected. We suspected this side effect only after seeing 3 cases. Third, all these women were referred to our center with a variable delay after the occurrence of VFs (from 1–54 months).

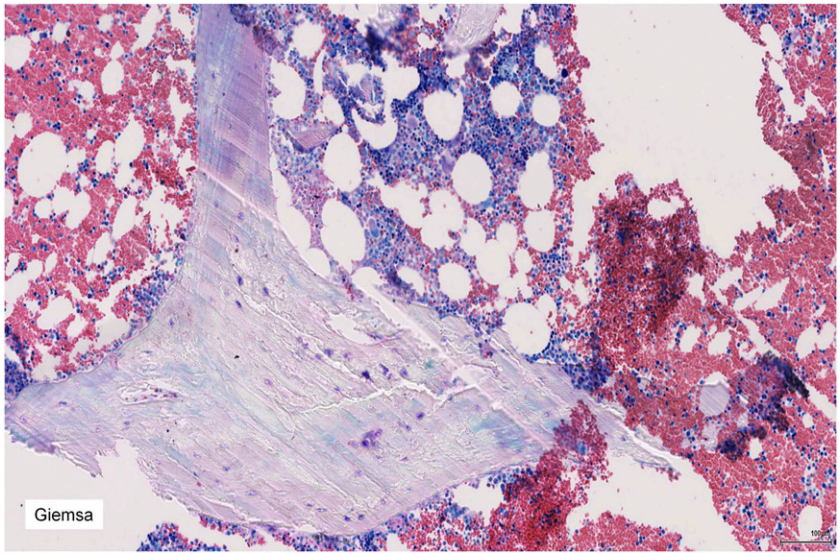


**Figure 2.** Giemsa coloration of aspiration biopsy vertebra L5 at the time of the vertebroplasty (case 9). Biopsy specimen shows no focal lesions or abnormal architecture. The hematopoietic marrow is trilinear and histologically normal. The immunohistological examination of the κ/λ ratio was 1. Analysis of the bone tissue does not show any malignant disease.

As there is no recommendation on the management of denosumab discontinuation, we sought to review some aspects. How should the BTR be reduced after denosumab discontinuation? The Lausanne University Bone Unit treats around 200 patients per year with denosumab. We identified 32 women (mean ± SD age of 65.1 ± 10.7 years) followed at our clinic for osteoporosis and who have discontinued denosumab. None reported fracture after denosumab discontinuation. Twenty-six women were treated with bisphosphonates before denosumab initiation (n = 8), after denosumab discontinuation (n = 12), or at both times (n = 6). Six women have not received any bisphosphonates. β-crosslaps were measured around 1 year after the last denosumab injection. The median values (minimum to maximum) were as follows: 577 ng/L (320–1278) for the women exposed to bisphosphonates before, 130 ng/L(100–659) for those exposed to bisphosphonates after, 202 ng/L (144–762) for the women exposed to bisphosphonates before and after, and 1190 ng/L (521–1399) for the women never exposed to bisphosphonates. This suggests that the administration of bisphosphonates prior to initiating denosumab or after discontinuation of denosumab (about 6 months after the last injection) reduces or prevents the BTR.

What is the treatment if VFs occur rapidly after denosumab discontinuation? Due to the severity of the situation, a combined teriparatide-denosumab treatment may be the best option (10). However, teriparatide should not replace denosumab because of the increased BTR and the risk of bone loss. An antiresorptive treatment with denosumab or a potent bisphosphonate is another option, because it is necessary to rapidly reduce the severe BTR. Vertebroplasty seems to increase the risk of new vertebral fractures. Percutaneous vertebroplasty or kyphoplasty is associated with an increased risk of new vertebral fractures in patients with particular fragility (11). The 3 women treated with vertebroplasty sustained 10 new vertebral fractures in the following month.

The severity of these cases reported raises the question of denosumab's place in the treatment of osteoporosis. On one extreme, one could conclude that denosumab is an unsafe drug and should never be used. However, this treatment is very effective in decreasing vertebral and nonvertebral fracture risk (1). On the other extreme, one could conclude that denosumab should be given for life and never discontinued. This appreciation is dangerous since denosumab treatment duration is associated with increased occurrence of osteonecrosis of the jaw and atypical femoral fracture. Moreover, increasing treatment duration increases the risk of nonplanned denosumab discontinuation. The expected compliance of the patient and the resources to guarantee medical examination at regular intervals should be considered before starting denosumab treatment. However, once denosumab is started, it should be scrupulously given every 6 months. The current difficulty is how to manage the denosumab discontinuation. Perhaps more consideration should be granted to the bisphosphonates to decrease or prevent the BTR and the RAFVs after denosumab discontinuation. Two types of randomized controlled trials are urgently needed to define the best management. First, is a pretreatment with bisphosphonates (which one and how long?) effective to decrease these risks? Second, is a posttreatment with bisphosphonates (which one, at which time, and how long?) effective to decrease these risks?

## Conclusion

In conclusion, studies are urgently needed to determine 1) the pathophysiological processes involved, 2) the clinical profile of patients at risk for RAVFs, and 3) the management and/or treatment regimens in case of denosumab discontinuation. In the meantime, health authorities, physicians, and patients must be aware of this RAVF risk, and denosumab injections must be scrupulously done every 6 months but not indefinitely.

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