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THERAPEUTICS AND MEDICAL MANAGEMENT (S JAN DE BEUR AND B CLARKE, SECTION EDITORS)

Stopping Denosumab

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Abstract

Purpose of Review Denosumab discontinuation is associated with a rebound effect manifesting by an increased risk of multiple spontaneous vertebral fractures. The purpose of this review is to (1) better characterize this risk and (2) find solutions to avoid it.

Recent Findings In the absence of a potent bisphosphonate prescription at denosumab discontinuation, the frequency of multiple vertebral fractures is common or frequent (≥ 1/100 and < 1/10). In five recent case series, the median number of vertebral fractures was 5 within 7 to 20 months (median 11) after the last denosumab injection. Prescribing bisphosphonate before starting denosumab and/or after stopping denosumab may reduce this risk. However, only small case series have evaluated these strategies.

Summary After the second denosumab dose, there is a rebound effect with an increased risk of multiple vertebral fractures. A potent bisphosphonate prescribed at denosumab discontinuation could reduce this risk. As denosumab discontinuation is characterized by many uncertainties, denosumab is a second-line treatment for osteoporosis. Studies are urgently needed to define the management of denosumab discontinuation.

Keywords Denosumab discontinuation · Osteoporosis · Rebound effect · Spontaneous multiple vertebral fractures

Introduction

Denosumab is a human monoclonal antibody against RANK-ligand (RANKL). It prevents RANKL from binding to its receptor on the surface of osteoclasts, thereby blocking their maturation, function, survival, and activity. Denosumab decreases bone resorption, increases bone mineral density (BMD), and reduces fracture risk [1]. After 3 years of treatment, the risk of radiological vertebral fractures (VFs) decreases by 68%, that of non-vertebral clinical fractures by 28%, and hip fracture risk decreases by 40% [1]. The BMD gain is continuous over 10 years, reaching 21.7% on the lumbar spine and 9.0% on the femoral neck [2]. During these 10 years, the annual fracture risk stays low, ranging between 0.70 and 1.47% for radiological VFs and between 0.84 and 2.59% for non-vertebral clinical fractures [2]. Denosumab also reduces the risk of clinical fractures by 50% in postmenopausal women with breast cancer receiving aromatase inhibitors (AIs) [3]. Denosumab 60 mg every 6 months has been proposed: (1) for postmenopausal women with osteoporosis; (2) for men with osteoporosis; (3) to protect from bone mass loss, in women with additional fracture risk factors receiving adjuvant AI therapy for breast cancer, and in men receiving androgen deprivation therapy for non-metastatic prostate cancer; and (4) for glucocorticoid-induced osteoporosis in men and women at high fracture risk. This review does not address oncologic clinical situations treated with higher denosumab dosage (multiple myeloma, bone metastases from solid tumors, hypercalcemia of malignancy refractory to bisphosphonates, or giant cell tumor).

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Table 1 Risk of vertebral fractures after denosumab discontinuation: observational studies

Study (ref)	Patients (*n*)	Age at DD	Follow-up after last D + 6 months (months)	Patients with OP Tx	Patients with ≥ 1 VF (%)	Patients with ≥ 2 VF (%)
[6]	82 (+ 2)	69	12.0	17.0%	8.5% (11.9%)	4.9% (7.1%)
[12••]	327	75	7.0	14.5%	7.1%*	4.3%*
[12••]	678	79	3.4			
[16]	38	81	12.0	0.0%	10.5%	2.6%

D, denosumab; *DD*, denosumab discontinuation; *n*, number; *OP*, osteoporosis; *ref*, reference; *Tx*, treatment; *VF*, vertebral fracture

*Per 100 participant-year

The Rebound Effect After Denosumab Discontinuation

In a phase 2 multiple dose study and in the phase 3 fracture prevention trial, denosumab discontinuation was associated with an increase of the bone turnover markers (BTMs), CTX and P1NP, and a decrease of BMD [4, 5••]. More precisely, stopping denosumab after four 60 mg injections induced an increase in BTMs values above baseline during 2 years, and after 1 year BMD had decreased to baseline levels [5••]. Later it was shown that loss of lumbar spine BMD gain on denosumab within 1 year after its discontinuation appears regardless of treatment length [5••, 6, 7]; at the same time, hip BMD loss is equal to or even greater than the gain achieved during treatment [5••, 6, 7]. The clinical consequences of what can be called a rebound effect manifesting by a severe BTMs increase and a rapid loss of BMD were not anticipated. They appeared to the medical community after the description of several case reports or cases series describing the occurrence of multiple spontaneous clinical vertebral fractures (MSCVFs) after denosumab withdrawal [8, 9, 10••, 11•]. These cases were reported in women with either postmenopausal osteoporosis or treated for BMD preservation when receiving concomitant AIs. A post hoc analysis of the FREEDOM and FREEDOM Extension trial concluded that VFs risk was similar after denosumab or placebo discontinuation [12••]. Surprisingly, the risk of VF increased sharply after placebo discontinuation too, although less highly than after denosumab discontinuation; the later also induced a stronger risk of MSCVFs (60.7% vs 34.5% of patients with VFs, respectively). However, different small and heterogeneous retrospective studies suggest that bisphosphonates given before or after denosumab may reduce BTMs rebound and BMD loss at denosumab discontinuation (see below).

Following these publications, several authors and medical societies advocate for, at denosumab discontinuation, a period of treatment with a bisphosphonate or another antiresorptive agent (estrogens or SERMs) to preserve BMD gain and avoid the risk of VF or MSCVFs [12••, 13–15].

Characterization of Vertebral Fracture Risk After Denosumab Discontinuation

The true incidence of VFs after denosumab discontinuation is not known, but can be approximated from observational studies (Table 1). In one of them, 82 patients were treated with denosumab for 4 to 8 years (mean age 69 years at the end of treatment); eight had been treated with a bisphosphonate before denosumab initiation, and 17 received an osteoporosis treatment after denosumab discontinuation [6]. One year later, seven women had had clinical VFs (8.5%), including four with MSCVFs. The authors mention two additional patients with MSCVFs who declined to participate in the observational phase. In another observational study, 38 patients treated with denosumab for 7 to 10 years (mean age 81 years at the end of

Table 2 Cases series: patients with at least one vertebral fracture after denosumab discontinuation

Study (ref)	Patients (*n*)	Age at DD (y) (mean ± SEM)	D doses (*n*) (mean ± SEM)	Months last D—FV median (min-max)	Number VF median (min-max)
[10••]	24	63.8 ± 7.3	6.2 ± 2.0	11(8–16)	5 (1–9)
[11•]	9	74.2 ± 5.3	4.9 ± 1.6	11 (7–18)	4 (1–9)
[18]	35	66.3 ± 9.6	6.7 ± 2.9	11 (7–20)	5 (1–11)
[19]	9	66.9 ± 8.0	6.0 ± 1.6	10 (8–18)	5 (2–8)
[20]	7	64.1 ± 6.4	7.4 ± 1.7	11 (8–20)	5 (2–7)
Total*	70*	67.3 ± 7.5	6.3 ± 2.0	11 (7–20)	5 (1–11)

D, denosumab; *DD*, denosumab discontinuation; *n*, number; *ref*, reference; *VF*, vertebral fracture; *y*, years

*Analysis at individual level. The 14 cases included in studies 1 and 3 were taken into account once

treatment) were followed for 17 months after the last injection, without receiving any other treatment for osteoporosis [16]. Four women (10.5%) had at least one clinical VF, including one with MSCVFs. The post hoc analysis of the FREEDOM and FREEDOM Extension trial evaluated 1001 women who stopped denosumab after seven or 10 years: 678 were followed for about 9 months after the last denosumab injection and 327 for about 12 months after the last injection. During this follow-up, 47.3% had X-ray control and 14.5% took osteoporosis treatment (including denosumab) [12••]. The annualized risk of VFs was 7.1%, of which 60.7% were MSCVFs. The risk of MSCVFs was higher in patients with previous VF. It is possible that these three observational studies underestimate VFs risk, particularly because of shorter follow-up than the biologic rebound, and because of the potential impact of the treatment received before and/or after denosumab [17].

The clinical features of women with VFs after denosumab discontinuation were analyzed in five case series (Table 2): two published in 2017 and 2018 and three presented at congresses in 2018 (World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases in Krakow; Annual European Congress of Rheumatology in Amsterdam) [10••, 11•, 18–20]. In the first cases series [10••], 24 Swiss and Greek postmenopausal women (64.1 years at the time of VFs) presented 112 spontaneous clinical VFs (median 5; min 1, max 9) within 8 to 16 months (median 11) after their last denosumab injection. They had received 2 to 10 denosumab injections inducing a lumbar spine BMD T-score increase from − 2.9 to − 2.1 SD. Most had low fracture risk: 16 (66%) had never had a fracture, and five received denosumab for the prevention of bone loss associated with AIs. In the second case series, nine Israeli elderly women (74.2 ± 5.3 years) presented 36 spontaneous clinical VFs (median 4; min 1, max 9) within 7 to 18 months (median 10) after their last denosumab injection [11•]. The number of denosumab injections prior to discontinuation was 4.9 ± 1.6. They were at high risk of fracture and had a prolonged prior exposure to bisphosphonate (7.4 ± 3.2 years). We conducted a single-center observational study in Lausanne, Switzerland, which currently includes 34 women and one man (66.3 ± 9.6 years at last denosumab injection) [18]; 14 of these cases were previously published [10]. They experienced 172 spontaneous clinical VFs (median 5; min 1, max 11) within 7 and 20 months (median 11) after their last denosumab injection [18]. The number of denosumab injections prior to discontinuation was 6.7 ± 2.3. Eight women received a bisphosphonate before denosumab, nine received denosumab for AIs bone loss prevention, and 24 (69%) had never had a fracture. Younger women seem at higher risk as the number of VFs is inversely associated with age (5.4 ± 2.0 vs 2.8 ± 1.3 for women ≤ vs > 65 years, respectively; $p < 0.001$), and the delay between denosumab discontinuation and the occurrence of VFs increases with age (10.4 ± 1.3 vs 12.7 ± 2.6 months, for women ≤ vs > 65 years, respectively; $p = 0.008$) [18]. Another case series in Madrid, Spain, included nine women, 66.9 ± 8.0 years, who experienced 47 MSCVFs (median 5; min 2, max 8) 8 to 18 months (median 11) after last denosumab injection [19]. The number of denosumab injections prior to discontinuation was 6.0 ± 1.6. In the fifth case series in Barcelona, Spain, seven women (median age 65 years) experienced 32 MSCVFs (median 5; min 2, max 7) 8 to 20 months (median 11) after their last denosumab injection [20]. The number of denosumab injections prior to discontinuation was 7.4 ± 1.7. In all series, a thoracolumbar MRI, and in some cases a vertebral biopsy, ruled out a pathological fracture. Finally, vertebroplasty has been found to increase the risk of new spontaneous clinical VFs in the month following the procedure [10••, 11•, 18, 19], an indirect index of vertebral fragility during this period.

In the cases series, CTX values at the time of VFs diagnosis were two to three times higher than the upper limit of the normal range for premenopausal women [9, 18–20], as described in the observational studies of denosumab discontinuation during the rebound phase [4, 5••]. In all of them, a broad biological assessment excluded an underlying disease explaining the high bone turnover. CTX values were not correlated with the number of VFs, but increased with the number of previously received denosumab doses ($R^2 = 0.28$) [18]. CTX values represent osteoclast activity, and osteoclastogenesis has already been evocated at the origin of the rebound effect [21]. We hypothesize that this severe high bone turnover is involved in microdamage accumulation in trabecular bone and thus promotes VFs. Due to the connection with the excess of osteoclast activity, some authors have proposed the term "rebound-associated vertebral fracture" for these MSCFVs [11•, 18–20, 22].

The published cases series only concern patients who have not received any anti-osteoporosis treatment between last denosumab injection and the occurrence of VFs, except for one case [19]. From them, it can be concluded that (1) VFs occur within 7 to 20 months (median 11) after the last denosumab injection; (2) the median number of MSCVFs is between four and five (min 1, max 11); (3) CTX values are extremely high at the time of MSCVFs; and (4) vertebroplasty performed at this time may increase the risk of new VFs. It should be noted that the median MSCVFs number might be overvalued. Indeed, in patients with less spontaneous (one or two) VFs, the diagnosis may have been missed, or patients may not have been referred to a specialized center.

Why Stop Denosumab?

Because of the excellent results over 10 years of treatment, and the uncertainty about the management of denosumab discontinuation, why stop denosumab? A retrospective study

evaluated the discontinuation of injectable osteoporosis treatment in 4756 patients; 617 had received denosumab [23]. At 12 and 24 months, 48.8% and 64.3% discontinued denosumab, respectively, highlighting the difficulty of continued treatment during a chronic illness, even with an injectable formulation. However, discontinuation at and beyond 1 year was lower with denosumab than with IV bisphosphonates. On the other hand, there may be clinical reasons to stop denosumab. When it is given for bone preservation in women receiving adjuvant AI therapy for breast cancer, it is supposed to be discontinued at the time of AI discontinuation. In men and women receiving denosumab for osteoporosis treatment, it is mostly discontinued when patients have reached a target T-score outside the osteoporosis zone. In addition, the risk, although low, of osteonecrosis of the jaw and atypical femoral fracture increases with denosumab treatment duration [2], and the risk-benefit ratio can favor the decision to stop the treatment. In the case series that reported the MSCVFs, the main reasons for denosumab discontinuation were end of AI treatment, no more osteoporosis, omission of one denosumab dose, patient's wish, atypical femoral fracture, dental intervention, or administrative [9, 10••, 11•, 18, 19].

For all these reasons, whether it is the willingness of the patient or the decision of the practitioner, it is necessary to consider that at some point denosumab may be discontinued.

How to Avoid the Rebound Effect?

The rebound effect at denosumab discontinuation should be controlled to avoid the risk of VF/MSCVFs and control the loss of the gained BMD. As far as it has been analyzed, the rebound does not appear after a single administration of denosumab, but after the second one [24, 25]. No randomized controlled trial has evaluated strategies to decrease the rebound effect after denosumab discontinuation. Some studies examined the effect of treatments given after or before denosumab; however, their design was not planned to specifically assess the benefit of these treatments on the prevention of the rebound effect.

Table 3 Proposals for follow-up after switching from denosumab to alendronate

1. T0. Initiate ALN 70 mg/week 5 to 6 months after the last denosumab and perform a DXA	
2. T2 – T4 – T6 – T9 – T12. Measure CTX	
	Goal < upper limit of the premenopausal normal range
2a.	if yes, continue with ALN
2b.	if no, switch to ZOL (see Table 4)
3. T12. Perform a DXA	
	Goal DXA T12- T0 ≤ LSN
3a.	if yes, continue with ALN
3b.	if no, switch to ZOL (see Table 4)
4. T12 – T18. Measure CTX	
	Goal < upper limit of the premenopausal normal range
4a.	if yes, continue with ALN
4b.	if no, switch to ZOL (see Table 4)
5. T24. Measure CTX and perform a DXA	

ALN, alendronate; *LSN*, least significant change; *T*, time in months; *ZOL*, zoledronate

Bisphosphonate After Denosumab Discontinuation

During the 1-year observational study of 82 patients who have received denosumab, bone loss was attenuated in those who took osteoporosis therapy at its discontinuation [6]. A single infusion of zoledronic acid 5 mg given 6 months after the last denosumab injection mitigated spine and total hip bone loss in two cases series [26, 27•]. In one, including six women, the loss of BMD gain was 50% on the spine and over 100% on the total hip [26]. In another cases series of 22 women, the loss of BMD gain was 40% and 45%, respectively [27•]. None of those 28 postmenopausal women experienced VF after denosumab discontinuation [26, 27•]. In another observational study, 11 women received zoledronic acid 15 to 165 days (median 65 days) after cessation of denosumab activity [28]. After less than a year, the loss of BMD gain was 27% on the spine and 13% on the total hip. In the particular context of this study (denosumab given for 2 years after 1 year of romosozumab; short follow-up), delaying the administration of IV zoledronic acid after denosumab discontinuation appears to better preserve BMD gain. However, the delay should not be too long, since FVSCMs could occur as early as 7 months after the last denosumab injection. In this same observational study, five women received once-weekly risedronate 35 mg at the end of the denosumab activity. After 1 year, the loss of BMD gain was 59% on the spine and 36% on the total hip. Fifty women who completed the DATA study (2 years of either teriparatide, denosumab, or a combination of both followed by 2 years of the alternate therapy) were evaluated 15 months after the end of the study [29]. BMD was maintained in women who received a prompt antiresorptive therapy (denosumab, zoledronic acid, oral alendronate, or oral ibandronate), and none of them experienced VF. These observations raise four questions. What bisphosphonate to give? How long after the denosumab stopped? At what dose and/or how often? For how long?

First, in order to limit/avoid the rebound effect after denosumab discontinuation, the prescription of a powerful antiresorptive treatment is mandatory (Tables 3 and 4). One way to quantify the antiresorptive effect of osteoporosis treatments is to measure the decrease in BTMs after its initiation. Raloxifene 60 mg daily decreases BTMs by 26.2% to 35.2%

Table 4 Proposals for follow-up after switching from denosumab to zoledronate

1. T0. 6 months after the last denosumab, perform a DXA and measure CTX	
	Goal: significant CTX activity
1a.	if yes, initiate ZOL
1b.	if no, measure CTX once a month until the goal
2. T3 – T6 – T9 – T12 after ZOL infusion. Measure CTX	
	Goal < upper limit of the premenopausal normal range
2a.	if yes, continue the follow-up
2b.	if no, give a new ZOL infusion
3. T12. Perform a DXA	
	Goal DXA T12- T0 ≤ LSN
3a.	if yes, continue the follow-up
3b.	if no, give a new ZOL infusion
4. T12 – T18. Measure CTX	
	Goal < upper limit of the premenopausal normal range
4a.	if yes, continue the follow-up
4b.	if no, give a new ZOL infusion
5. T24. Measure CTX and perform a DXA	

ALN, alendronate; *LSN*, least significant change; *T*, time in months; *ZOL*, zoledronate

[30]. Oral daily or quarterly intravenous injection of ibandronate decreases serum CTX by 53.4 to 59.9% [31]. In a 12-month head-to-head trial, once-weekly alendronate 70 mg was more efficacious than once-weekly risedronate 35 mg to decrease serum CTX (73.8% vs 54.7%) [32]. IV zoledronic acid 4 mg decreases serum CTX at 1 month by 83%, and at 1 year by 52% [33]. In order to minimize the high bone turnover at denosumab discontinuation, it seems therefore preferable to prescribe the more potent bisphosphonates.

Second, since bisphosphonates are deposited on bone resorption areas and denosumab very potently blocks bone resorption, they must probably be administered when the rebound effect has already begun. This consideration is of little importance for the repeated administration of an oral bisphosphonate [28], but is essential for a unique infusion of zoledronic acid. BMD gain is best preserved by delaying administration of zoledronate compared to administration 6 months after denosumab discontinuation [26, 27•, 28]. CTX levels change very quickly about 6 months after last denosumab injection, but with high variability between patients. CTX may thus be used as a marker of the rebound effect and their increase determines the timing of zoledronic acid infusion (Tables 3 and 4).

Third, the choice of a powerful bisphosphonate does not guarantee sufficient inhibition of the high BTMs increase and secondary bone loss. In one study, P1NP values doubled between 6th and 12th month after zoledronic acid infusion [28]. The durability of zoledronic acid effect in the context of this rebound is less than in studies of osteoporosis. For oral bisphosphonates, compliance and absorption are therefore essential, but it is also possible that the doses usually used in osteoporosis are not sufficient. The efficacy of oral bisphosphonates or zoledronic acid should be assessed every 2 to 3 months by measuring CTX, to ensure that they remain within the reference range of premenopausal women [34]. If the target is not reached, three strategies can be imagined: (1) to change the molecule, (2) to increase the doses, or (3) to decrease the intervals between two doses.

Fourth, the longevity of the BMD preservation with bisphosphonate was only evaluated after 1 year. The duration of bisphosphonate administration and CTX monitoring should be 24 months to cover the period of the rebound effect after denosumab discontinuation. This strategy requires a discussion with health insurances to provide off-label osteoporosis treatments, since, at this point, there is often no more densitometric osteoporosis. To verify the effectiveness of the proposed strategy, BMD should probably be measured once a year until 1 year after bisphosphonates are stopped (Tables 3 and 4) [34].

To date, no medical society or official conference at a congress has offered detailed recommendations on denosumab discontinuation. CTX-guided strategy to adapt antiresorptive therapies after denosumab discontinuation takes time and requires numerous controls. In the absence of dedicated studies, CTX control is currently not a guarantee of BMD gain preservation or the absence of VF/MSCVFs risk. Randomized studies are urgently needed to validate a simple therapeutic regimen. Two randomized, open-label, interventional studies investigating the effect on BMD of a single infusion of zoledronic acid (NCT03087851 and NCT02499237) are ongoing.

Bisphosphonate Before Denosumab Initiation

Prior treatment with bisphosphonates was postulated to decrease the risk of the rebound effect after denosumab discontinuation [25]. Bisphosphonates are stored for a long time in the bone matrix, especially since denosumab should slow down their release by decreasing osteoclastic activity. Unfortunately, this strategy does not always prevent MSCVFs [10••, 11•, 18, 19]. The small size of these studies does not allow determining if there is a difference according to the bisphosphonate used, its duration of use, and the time interval between the discontinuation of bisphosphonate and the introduction of denosumab. Therefore, the potential protective effect of prior treatment with bisphosphonate should be explored in studies specifically designed for this purpose. We can only hypothesize that administration of a potent bisphosphonate shortly before the introduction of denosumab should reduce the rebound effect after withdrawal.

How to Manage Vertebral Fractures Occurring After Denosumab Discontinuation (Table 5)

There is currently no recommendation for the management of VF / MSCVFs occurring after denosumab discontinuation. During this period of high bone turnover, the occurrence of VFs spreads over several weeks, and external (physical manipulation) or internal (vertebroplasty) spine manipulations increase their number [10••, 11•, 18, 19]. It is therefore necessary to emergently block the high remodeling and avoid vertebral manipulations during a few weeks. Denosumab is the only antiresorptive treatment that can inhibit bone resorption in a matter of days. Denosumab 60 mg decreases serum CTX by 83.6% after 3 days, and by 89.4% after 1 month [35]. In comparison, alendronate 70 mg decreases CTX by 20.9% after 3 days, and by 66.2% after 1 month [35]. Due to the severity of these VFs, we are prone to offer the most powerful anti-osteoporosis treatment. An anabolic agent like teriparatide seems to be the treatment of choice. However, switching from denosumab to teriparatide decreases BMD, and CTX increased more after switching from denosumab to teriparatide than in the same women treated with teriparatide de novo [36]. Indeed, concurrent denosumab and teriparatide administration increases spine and hip BMD more than either drug alone, although there is no fracture data due to the small size of the study [36]. For these reasons, teriparatide can be used in parallel with denosumab, but only after denosumab has controlled the rebound effect (few days), and in the absence of contraindications (active cancer). The usual length of teriparatide prescription is of 2 years. Since both drugs are associated with rapid bone loss when stopped, we propose, after stopping teriparatide, to continue denosumab alone for 1 year or until the desired BMD target. Then, the rebound effect must be prevented with a bisphosphonate as recommended above.

Table 5 What to do in case of vertebral fracture after denosumab discontinuation: proposals

1. Spine manipulation and vertebro-/kyphoplasty are contraindicated.
2. Perform a broad biological assessment (including serum CTX) and thoracolumbar MRI.
3. Resume denosumab quickly.
4. Add teriparatide about 1 week later (after checking that CTX are low) if no contraindication.
5. At teriparatide discontinuation, continue denosumab for one or more doses (depending of the BMD target).
6. After denosumab discontinuation, initiate a potent bisphosphonate (according to Tables 3 and 4).

Uncertainties About Denosumab Discontinuation

A recent review concluded: "denosumab discontinuation is characterized by more uncertainties than certainties" [37]. Uncertainties concern the risk of MSCVFs after denosumab discontinuation, the role of bisphosphonates as sequential therapy, and denosumab treatment duration.

According to the Swiss health authorities, the MSCVFs occurring after denosumab discontinuation are serious adverse events (as requiring hospitalization and/or resulting in persistent of significant disability or incapacity) and the link with denosumab discontinuation is certain [https://www.swissmedic.ch/swissmedic/fr/home/medicaments-a-usage-humain/surveillance-du-marche/health-professional-communication%2D%2Dhpc-/archive/dhpc-_-prolia%2D%2D-denosumab-.html]. The European Medicines Agency did not recognize this side effect [http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001120/WC500233877.pdf]. In the USA, an alert has been included in the treatment notice [https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/125320Orig1s180ltr.pdf], as in other countries. In the absence of a potent bisphosphonate prescription at denosumab discontinuation, the frequency of MSCVFs is common or frequent ($\geq 1/100$ and $< 1/10$) applying the classification of the Council of International Organizations of Medical Sciences.

The severity of the MSCVFs occurring after denosumab discontinuation raises the question of its place in the treatment of osteoporosis. At one extreme, one could conclude that denosumab is a dangerous drug and should never be used. However, it is very effective to reduce vertebral and non-vertebral fracture risk [1–3]. At the other extreme, one could conclude that denosumab should be given for life and never discontinued. However, denosumab treatment duration is associated with increased occurrence of osteonecrosis of the jaw and atypical femoral fracture [2]. In addition, the longer is the duration of treatment, the higher is the risk of unplanned discontinuation.

Although its effect on the MSCVFs risk reduction cannot be quantified, the prescription of a bisphosphonate at denosumab discontinuation is mandatory as all published data suggest a decrease in this risk. Thus, before starting denosumab, patients should be informed that bisphosphonate treatment would be necessary at some point, as well as close follow-up. However, the uncertainties regarding bisphosphonates prescription are multiple. First, is a pre-treatment with bisphosphonate (which one? For how long?) efficacious to attenuate bone loss, and eventually to avoid the MSCVFs risk, at denosumab discontinuation? Second, what is the optimal consolidation treatment with bisphosphonate (which one? how long? at what dose/frequency) after denosumab

discontinuation? Third, how to monitor the effectiveness of bisphosphonates (BTMs and/or BMD? how often? which values to target?).

The optimal duration of a denosumab treatment is not known, taking into account both the on-treatment benefits and the risk after treatment discontinuation. Is this benefit-risk ratio different depending on the osteoporosis severity, or the patient's clinical characteristics? Are there patients who do not have a rebound effect after denosumab discontinuation? How to identify them? Which parameters to follow and how often? What values should be targeted? Some patients may not receive bisphosphonates because of previous severe side effects. In these situations, denosumab cannot be stopped by spacing doses, since the risk of MSCVFs appears already 7 months after the last injection. One possibility would be to gradually reduce denosumab doses; however, to date, no experience has been reported. To limit this risk, it is currently recommended to prescribe a potent bisphosphonate when denosumab is stopped.

Conclusion

After the second denosumab dose, there is a significant rebound effect at the time of discontinuation, manifesting as a loss of BMD and a risk of MSCVFs. To limit this risk, it is currently recommended to prescribe a potent bisphosphonate when denosumab is stopped. Close and regular biological and clinical monitoring is required for approximately 2 years. However, no validated strategy exists. Pending these validation studies, and since the risk of MSCVFs is common and serious, denosumab should be a second-line treatment limited to specific indications, as is the case in some countries.

Compliance with Ethical Standards

Conflict of Interest Olivier Lamy, Delphine Stoll, Bérengère Aubry-Rozier, and Elena Gonzalez Rodriguez declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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References

Papers of particular interest, published recently, have been highlighted as:
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- •• Of major importance

1. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;8:756–65.
2. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017;5:513–23.
3. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015;38:433–43.
4. Miller PD, Bolognese MA, Lewiecki EM, et al ; Amg Bone Loss Study Group. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 2008;43:222–9.
5.•• Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turn-over markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab. 2011;96:972–80 **A well-detailed study on the biological and densitometric rebound effect at denosumab discontinuation.**
6. McClung MR, Wagman RB, Miller PD, Wang A, Lewiecki EM. Observations following discontinuation of long-term denosumab therapy. Osteoporos Int. 2017;28:1723–32.
7. Popp AW, Varathan N, Buffat H, Senn C, Perrelet R, Lippuner K. Bone mineral density changes after 1 year of denosumab discontinuation in postmenopausal women with long-term denosumab treatment for osteoporosis. Calcif Tissue Int. 2018;103:50–4.
8. Aubry-Rozier B, Stoll D, Gonzalez Rodriguez E, Lamy O. Severe spontaneous vertebral fractures after denosumab discontinuation: 3 cases reports. Osteoporos Int. 2016;27:1923–5.
9. Lamy O, Stoll D, Gonzalez-Rodriguez E, Hans D, Aubry-Rozier B. Severe rebound-associated vertebral fractures after denosumab discontinuation: nine clinical cases report. J Clin Endocrin Metab. 2017;102:354–8.
10.•• Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. J Bone Miner Res. 2017;32:1291–6 **The largest published observational study describing the characteristics of patients with multiple vertebral fractures after denosumab discontinuation.**
11.• Tripto-Shkolnik L, Rouach V, Marcus Y, Rotman-Pikielny P, Benbassat C, Vered I. Vertebral fractures following denosumab discontinuation in patients with prolonged exposure to bisphosphonates. Calcif Tissue Int. 2018;103:44–9 **An observational study that questioned the efficacy of bisphosphonates prescribed before denosumab to avoid the rebound effect upon discontinuation.**
12.•• Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res. 2018;33:190–8 **Post hoc analysis of a randomized trial that describes the high incidence of multiple vertebral fractures at denosumab discontinuation, despite very short follow-up.**
13. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guañabens N, et al. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. Bone. 2017;105:11–7.
14. Meier C, Uebelhart B, Aubry-Rozier B, et al. Osteoporosis drug treatment: duration and management after discontinuation. A position statement from the SVGO/ASCO. Swiss Med Wkly. 2017 Sep 5;147:w14484.
15. Chapurlat R. Effects and management of denosumab discontinuation. Joint Bone Spine. 2018. https://doi.org/10.1016/j.jbspin.2017.12.013.
16. Zanchetta MB, Boailchuk J, Massari F, Silveira F, Bogado C, Zanchetta JR. Significant bone loss after stopping long-term

denosumab treatment: a post FREEDOM study. Osteoporos Int. 2018;29:41–4.

17. Lamy O, Gonzalez-Rodriguez E. Underestimation of vertebral fractures after denosumab discontinuation. J Bone Miner Res. 2018;33:547.
18. Gonzalez-Rodriguez E, Aubry-Rozier B, Stoll D, Hans D, Lamy O. Clinical features of 35 patients with 172 spontaneous vertebral fractures after denosumab discontinuation: a single center observational study. Osteoporos Int. 2018;(suppl 1):P637.
19. Fernandez E, Benavent D, Bonilla G, Monjo I, Garcia S, Bernad M, et al. Rebound-associated multiple vertebral fractures after discontinuation of denosumab: nine cases report. Ann Rheum Dis. 2018;(suppl):A450.
20. Florez H, Ramirez J, Monegal A, Guanabens N, Peris P. Spontaneous vertebral fractures after denosumab discontinuation: a report of 7 cases. Ann Rheum Dis. 2018;(suppl):A447.
21. Anastasilakis AD, Yavropoulou MP, Makras P, Sakellariou GT, Papadopoulou F, Gerou S, et al. Increased osteoclastogenesis in patients with vertebral fractures following discontinuation of denosumab treatment. Eur J Endocrinol. 2017;176:677–83.
22. Popp AW, Zysset PK, Lippuner K. Rebound-associated vertebral fractures after discontinuation of denosumab-from clinic and biomechanics. Osteoporos Int. 2016;27:1917–21.
23. Modi A, Sajjan S, Insinga R, Weaver J, Lewiecki EM, Harris ST. Frequency of discontinuation of injectable osteoporosis therapies in US patients over 2 years. Osteoporos Int. 2017;28:1355–63.
24. Bekker PJ, Holloway DL, Rasmussen AS, Murphy R, Martin SW, Leese PT, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res. 2004;19:1059–66.
25. Uebelhart B, Rizzoli R, Ferrari SL. Retrospective evaluation of serum CTX levels after denosumab discontinuation in patients with or without prior exposure to bisphosphonates. Osteoporos Int. 2017;28:2701–5.
26. Reid IR, Horne AM, Mihov B, Gamble GD. Bone loss after denosumab: only partial protection with zoledronate. Calcif Tissue Int. 2017;101:371–4.
27.• Lehmann T, Aeberli D. Possible protective effect of switching from denosumab to zoledronic acid on vertebral fractures. Osteoporos Int. 2017;28:3067–8 **Switching from denosumab to zoledronic acid may have a protective effect on vertebral fractures.**
28. Horne AM, Mihov B, Reid IR. Bone loss after romosozumab/denosumab: effects of bisphosphonates. Calcif Tissue Int. 2018;103:55–61.
29. Leder BZ, Tsai JN, Jiang LA, Lee H. Importance of prompt antiresorptive therapy in postmenopausal women discontinuing teriparatide or denosumab: the Denosumab and Teriparatide Follow-up study (DATA-Follow-up). Bone. 2017;98:54–8.
30. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab. 2002;87:3609–17.
31. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol. 2008;35:488–97.
32. Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res. 2005;20:141–51.
33. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med. 2002;346:653–61.
34. Lamy O, Gonzalez-Rodrigez E, Stoll D, Aubry-Rozier B, Livio F. Multiple vertebral fractures after denosumab discontinuation: how to avoid them? Praxis. 2018;107:649–54.
35. McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, et al. AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006;354:821–31.
36. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386:1147–55.
37. Tsourdi E, Zillikens C. Certainties and uncertainties about denosumab discontinuation. Calcif Tissue Int. 2018;103:1–4.