



Discontinuing Denosumab: Can It Be Done Safely? A Review of the Literature

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Denosumab, which has been approved for the treatment of osteoporosis since 2010, is a fully humanised monoclonal antibody against a cytokine, receptor activator of nuclear factor kappa B ligand (RANKL), involved in bone resorption. Continued use of denosumab results in a potent and sustained decrease in bone turnover, an increase in bone mineral density (BMD), and a reduction in vertebral and hip fractures. The anti-resorptive effects of denosumab are reversible upon cessation, and this reversal is accompanied by a transient marked increase in bone turnover that is associated with bone loss, and of concern, an increased risk of multiple vertebral fractures. In this review, we outline the effects of denosumab withdrawal on bone turnover markers, BMD, histomorphometry, and fracture risk. We provide an update on recent clinical trials that sought to answer how clinicians can transition away from denosumab safely with follow-on therapy to mitigate bone loss and summarise the recommendations of various international guidelines.

Keywords: Denosumab; RANK ligand; Bone density; Spinal fractures; Bone remodelling; Bone resorption; Osteoporosis

INTRODUCTION

Denosumab is a fully humanised immunoglobulin G2 monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), which is a key mediator of osteoclast formation, function, and survival. It binds to and inactivates RANKL, preventing the maturation of precursor cells into mature osteoclasts, and also promotes the apoptosis of mature, activated osteoclasts, thereby inhibiting bone resorption. It circulates in the bloodstream, binding to RANKL in the extracellular fluid, and is cleared via the reticuloendothelial system with a half-life of approximately 26 days. Denosumab rapidly and significantly reduces bone turnover markers (BTMs). Serum C-telopeptide (CTX) is reduced by 86% as early as 1 month after denosumab administration, and this decrease is maintained at 72% at 36

months [1]. The pivotal Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) trial demonstrated that denosumab significantly reduced the risk of vertebral fractures by 68% and hip fractures by 40% during a 3-year period [1]. These effects were sustained at up to 10 years in the active extension study [2], and bone mineral density (BMD) of the spine and hip increased by 21.7% and 9.2%, respectively, over 10 years [2].

WHAT HAPPENS IF DENOSUMAB IS DISCONTINUED?

Bone turnover markers

The potent anti-resorptive effect of denosumab is reversible. Cessation of denosumab results in an increase in BTMs to lev-

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els higher than observed before treatment [3]. In postmenopausal women who were observed for 24 months off treatment, after completing six doses of denosumab, both CTX, a marker of bone resorption, and N-terminal propeptide of type 1 procollagen (P1NP), a bone formation marker, increased to the baseline level by 3 months after discontinuation. Subsequently, both BTMs rose above baseline levels, with a 63% increase in CTX and a 47% increase in P1NP at 30 and 36 months, respectively. These increases abated to baseline values by 24 months after stopping denosumab.

Bone mineral density

When denosumab is stopped, BMD decreases in all skeletal sites [3]. In fact, BMD gains at the lumbar spine, total hip, femoral neck and distal radius were all lost within 2 years of discontinuation [3]. Most of this decrease occurs rapidly, within 6 months of the last injection [2,3]. With longer-term denosumab usage, the bone loss after withdrawal of therapy preferentially affects the lumbar spine, a site with predominantly trabecular bone, and the entire hip, a site with an admixture of trabecular and cortical bone [4].

Bone histomorphometry

Trans-iliac bone biopsy findings of 15 postmenopausal women who received two doses of denosumab and were off treatment for about 2 years were compared to those of 15 subjects who were treated with placebo and underwent bone biopsy in the FREEDOM study, a denosumab phase 3 trial [5,6]. Static indices of bone formation and resorption, as well as dynamic indices of bone formation in those who had discontinued denosumab were similar to untreated post-menopausal women, showing histomorphometric evidence that the effect of denosumab on bone remodelling is reversed after discontinuation.

Fracture risk

Since changes in BTM, BMD, and bone histomorphometry with usage are reversed after discontinuing denosumab, we would expect the fracture risk to revert to its pre-treatment level. This possibility was investigated in several studies with relatively short duration of follow-up, where denosumab was stopped after a period of usage in postmenopausal osteoporosis patients, and the fracture rates seemed to be as high in patients who discontinued treatment as in those who received no treatment [3,7-9].

It has recently been suggested that the discontinuation of denosumab leads to an increased risk of multiple vertebral frac-

tures [10-12]. Most of these vertebral fractures occur within 1 year after stopping denosumab [11,13,14]. A *post hoc* analysis of the FREEDOM trial and its extension study examined this in detail by comparing the vertebral fracture rates of 1,001 subjects who discontinued denosumab after having at least two doses with the vertebral fracture rates of 470 participants who received placebo. After withdrawal of denosumab, the vertebral fracture rate increased from 1.2 per 100 participant-years (95% confidence interval [CI], 0.9 to 1.6 per 100 participant-years) to 7.1 per 100 participant-years (95% CI, 5.2 to 9.0 per 100 participant-years). The vertebral fracture rate after stopping denosumab was similar to the rates before and after stopping placebo, which were 7.0 per 100 participant-years (95% CI, 5.2 to 8.7 per 100 participant-years) and 8.5 per 100 participant-years (95% CI, 5.5 to 11.5 per 100 participant-years), respectively [15]. Among those who had vertebral fractures after denosumab was stopped, 34 out of 56 participants (61%) had multiple vertebral fractures as compared to 12 out of 31 participants (39%) in the placebo group, corresponding to a 3.4% and 2.2% risk of multiple vertebral fractures, respectively [15]. Nonetheless, the incidence of any vertebral fractures upon discontinuation of denosumab was still lower than the incidence reported in the placebo group. Smaller studies did not reveal an increase in fracture risk after stopping denosumab [3,7]. Real-world longitudinal evidence from a large database from Maccabi Healthcare Services, Israel showed that multiple vertebral fractures were observed in 0.8% of 1,500 individuals who discontinued denosumab compared to 0.1% of 1,610 persistent users of denosumab (incidence rate ratio, 14.63; 95% CI, 3.3 to 65.3) [9]. The estimated incidence of vertebral fractures from real-world data was found to be 1.1 per 100 person-years, as compared to 2.1 per 100 person years in clinical trials [9,15]. Lastly, while bone loss was evident from all skeletal sites, particularly at the spine and hip, on bone densitometry [4], denosumab withdrawal has not yet been shown to impose an excess risk of hip fracture or other major osteoporotic fractures. This discordance between observed vertebral fractures and the lack of evidence for non-vertebral fractures after denosumab discontinuation has yet to be elucidated.

Postulated mechanisms

The prevalent hypothesis is that microcracks in the bone may accumulate with prolonged suppression of bone resorption [16]. With discontinuation of denosumab, a reversal of its potent anti-resorptive effect ensues, which leads to a rebound in bone remodelling that transiently exceeds pre-treatment levels. This

“rebound phenomenon” may be accompanied by bone loss that is postulated to be related to an upregulation of osteoclast formation and activity [17]. The fact that most bone remodelling activity occurs on trabecular bone surfaces, not in cortical bone [18] could possibly explain why the spine, which is predominantly trabecular bone, is uniquely poised to be the bone most strongly affected by the “rebound phenomenon,” leading to vertebral fractures.

WHAT ARE THE RISK FACTORS FOR VERTEBRAL FRACTURES WHEN DENOSUMAB IS STOPPED?

Prior vertebral fractures [15], a longer duration of denosumab treatment [11,19], and a higher rate of bone loss after stopping [15] have been identified as risk factors for vertebral fractures after denosumab discontinuation. While longer treatment duration results in greater gains in BMD, it is associated with a higher rate of bone loss in terms of BMD post-discontinuation [19,20]. Higher CTX levels 6 months after discontinuation may reflect a greater rebound phenomenon and have also been associated with higher rate of bone loss after denosumab discontinuation [19].

SHOULD DENOSUMAB BE USED INDEFINITELY?

Based on denosumab’s unique mechanism of action in the extracellular environment, it does not reside in the skeleton, and has a biological effect that lasts as long as it is in systemic circulation. The complete reversibility of denosumab would argue for its continued use in osteoporosis, a chronic lifelong condition where the underlying pathophysiologic process persists. Furthermore, well-established data demonstrate its long-term efficacy [2]. It is also very well tolerated and safe, with adverse events being rare [1]. There were two cases of atypical femoral fracture in the 10-year FREEDOM extension trial, which derived a cumulative exposure-adjusted participant incidence of 0.8 per 10,000 participant-years [2]. Similarly, the incidence of osteonecrosis of the jaw is very low, with an estimated rate of 5.2 per 10,000 participant-years [2].

WHEN SHOULD DENOSUMAB BE DISCONTINUED?

While long-term treatment with denosumab may be offered in

individuals with high fracture risk, denosumab has been discontinued for various reasons such as the development of adverse events, administrative reasons, the patient’s own preference, or non-compliance. Notwithstanding the safety and efficacy of denosumab, it remains uncertain whether the favourable benefit-risk profile of denosumab remains if treatment is continued beyond 10 years. If long-term marked suppression of bone turnover is a risk factor for atypical femoral fractures and osteonecrosis of the jaw, then one may be cautious about using denosumab indefinitely in the absence of longer-term data, in view of the potentially higher risk of adverse events associated with prolonged suppression of bone turnover. Longer-term safety and efficacy data will help address these concerns. In other instances, denosumab has been stopped by the treating physician when the patient is no longer deemed to be at high fracture risk based on a treat-to-target strategy [21].

In recent years, a treat-to-target strategy has increasingly been discussed in the management of osteoporosis [21]. The proponents of such a strategy argue that goal-directed therapy is beneficial as it guides therapeutic management in improving clinical outcomes, similarly to how meeting a blood pressure threshold improves long-term cardiovascular outcomes. In osteoporosis, having a goal aids the patient and physician in the selection of the initial therapy based on the probability of reaching the target, provides information on whether the patient has been sufficiently responsive to chosen treatment, and supports treatment decision-making on whether to stop, continue, or switch treatment based on progress towards achievement of the treatment target.

It has also been suggested that the BMD T score is an appropriate goal [22]. Cessation of an anti-osteoporotic agent may be considered if the T-score is above a value in which there is an acceptably low risk of fractures. A T-score of >-2.5 has been a particularly useful goal for bisphosphonate therapy. However, this may be specific to the unique pharmacokinetic profile of bisphosphonates, which are retained in the skeleton, and evidence suggesting limited benefits continuing therapy above a T score of -2.5 [23]. With regard to denosumab, this threshold is less clear. In a *post hoc* analysis of the FREEDOM trial and its extension study, a higher total hip T-score obtained during treatment with denosumab was associated with a lower incidence of nonvertebral fractures. The risk of nonvertebral fractures plateaued at a total hip T-score of between -2.0 and -1.5 , which corresponds to a 1-year nonvertebral fracture incidence of about 2%. Approximately 25.9% of women achieved this target total hip T-score of -2.0 and 2.4% of women achieved a target of

-1.5 after 10 years of use of denosumab [24]. There has been no consensus in the recommendations for a target total hip T-score for denosumab discontinuation. Nonetheless, experts recommend that if denosumab is stopped for any reason, follow-on therapy such as a short-term course of bisphosphonate should be given to consolidate the gains in BMD made with denosumab.

HOW DO WE STOP DENOSUMAB SAFELY?

In order to transition from denosumab safely, clinicians can mitigate bone loss by not terminating denosumab use without follow-on therapy with an alternative agent. A number of studies have demonstrated that follow-on bisphosphonate therapy can potentially diminish the loss of BMD gains attained with denosumab. These are summarised in Table 1.

Alendronate

The effect of alendronate after denosumab discontinuation was first assessed in an exploratory analysis of the Denosumab Adherence Preference Satisfaction (DAPS) study. This was a randomised open-label crossover study that assigned 250 postmenopausal women to either alendronate for 1 year followed by denosumab for 1 year or *vice versa*. Individuals assigned to 1 year of alendronate after 1 year of denosumab maintained the BMD gained with denosumab, with a slight increase in BTMs with follow-on alendronate, as compared to the initial denosumab therapy [25].

Risedronate

The effect of risedronate after denosumab was assessed in a follow-up study of the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) study, where patients who received romosozumab or placebo for 1 year followed by denosumab for 2 years were transitioned to either zoledronic acid or risedronate [26]. Five participants received risedronate, which was started within 1 month of the end of the FRAME trial. They were compared to 11 patients who received zoledronic acid about 8 months from the last dose of denosumab. At 12 months after transition, participants who transitioned to risedronate had greater bone loss—59% of the BMD gained at the spine during the FRAME trial and 36% of the BMD gained at the hip—than those who transitioned to zoledronic acid, who lost 27% and 13% of the BMD gained in the spine and hip, respectively.

Zoledronic acid

In a small case series of 22 women with postmenopausal osteo-

porosis, a single infusion of zoledronic acid was administered 6 months after the last dose of denosumab [27]. These patients had received five doses of denosumab before discontinuation. At 2.5 years after the last dose of denosumab, a third of the BMD gained at the lumbar spine was lost. While this demonstrates that zoledronic acid did not sustain BMD gains, it was adequate to avoid complete bone loss.

In a retrospective observational study, 30 Japanese patients had denosumab discontinued after an average of three doses and received zoledronic acid about 9 months after the last dose of denosumab [28]. Eighteen patients had complete BMD data. BMD at the lumbar spine and femoral neck were maintained 12 months after zoledronic acid. Levels of serum tartrate-resistant acid phosphatase 5b, a bone resorption marker, remained suppressed 12 months post-zoledronic acid. None of the patients had any fractures. This seems to suggest that zoledronic acid could prevent the decline in BMD with denosumab cessation.

The first prospective randomised study evaluating the effect of zoledronic acid after denosumab discontinuation was the Zoledronic Acid to Maintain Bone Mass After Denosumab Discontinuation (AfterDmab) study [29]. Fifty-seven women with postmenopausal osteoporosis who were treated with denosumab for about 2 years and achieved osteopenia were randomised to zoledronic acid or two additional doses of denosumab. A single dose of zoledronic acid given 6 months after denosumab discontinuation maintained the BMD gains achieved with prior denosumab treatment at both the lumbar spine and femoral neck at 24 months post-randomisation. The control group that had an additional year of denosumab but did not receive follow-on zoledronic acid had a decrease in BMD at the spine and hip. Observations of the zoledronic acid arm were extended for another year, and there was no significant decline in BMD at the spine and hip at 3.5 years after denosumab cessation. These studies suggest that a single-dose regimen of zoledronic acid post discontinuation could largely maintain BMD gains [30]. In four of the 23 women in that study, the BMD values returned into the osteoporotic range. Thus, about one in five patients who receive a single-dose regimen of zoledronic acid post-denosumab may subsequently require additional osteoporosis treatment.

A recent randomised open-label study did not find the transition to zoledronic acid after denosumab discontinuation to be as effective in preventing bone loss as previous studies [19]. In this study, 61 participants with osteoporosis who were treated with denosumab for about 5 years and achieved osteopenia were randomised into three arms to evaluate the optimal timing of zoledronic acid. The first group was administered a single dose of

Table 1. Summary of the Results of Studies Evaluating Treatment after Discontinuation of Denosumab

Follow-on agent	Study	Type of study	No.	Characteristics of the patient population	Duration of DMB/onset of follow-on agent	Outcomes	
						BMD	Fracture
Alendronate	Freemantle et al. (2012) [25]	Randomized open-label crossover study	126	Exploratory analysis of 126 postmenopausal women assigned to 1 year of DMB followed by 1 year of ALN.	1 year/6 months after stopping DMB	BMD at 1 year of stopping DMB: • LS, 2.9% • TH, 1.5% • FN, 1.7%	1 Subject had a humerus fracture during ALN follow-on therapy.
Risedronate and zoledronic acid	Horne et al. (2018) [26]	Case series (subset of the phase III FRAME study)	19	Postmenopausal women who had received ROMO or placebo for 1 year followed by 2 years of DMB were treated with 1 year of RIS ($n=5$) vs. single-dose ZOL ($n=11$) vs. no treatment ($n=3$).	2 years/median 8 months (range, 6.4–11.8) from stopping DMB	BMD at 1 year of stopping DMB: • 59% and 36% loss of BMD gained (during the FRAME trial) at the LS and TH respectively with RIS. • 27% and 13% loss of BMD gained (during the FRAME trial) at the LS and TH for ZOL.	No clinical fractures occurred.
Zoledronic acid	Lehmann et al. (2017) [27]	Case series	22	Postmenopausal women who had 5 doses of DMB followed by single-dose of ZOL.	2.5 years/6 months after stopping DMB	BMD 2.5 years after stopping DMB: • LS, -3.8% • TH, -1.7% • FN, -0.6%	No new vertebral fractures, but 1 patient had a calcaneal fracture observed during ZOL follow-on therapy.
Zoledronic acid	Kondo et al. (2020) [28]	Retrospective observational study	30	29 Postmenopausal women and 1 male patient received an average of 3.1 doses of DMB followed by single-dose of ZOL.	Mean 1.5 years (range, 0.5–3)/mean 9 months after stopping DMB (range, 6–16.5)	BMD 1 year from ZOL therapy ($n=18$): • LS, 9.1% • FN, 6.1%	No new vertebral/nonvertebral fractures were observed during ZOL follow-on therapy.
Zoledronic acid	Anastasilakis et al. (2019) [29]	Open-label, multicentre, randomized, trial (AfterDmab)	57	Postmenopausal women treated with DMB and achieved BMD in the osteopenic range were randomized to single-dose ZOL ($n=27$) or continue DMB ($n=30$) for 1 year. No treatment was given subsequently and patients were followed until 2 years after randomization.	Mean 2.2 years/6 months from stopping DMB	BMD 2.5 years after stopping DMB with ZOL therapy: • LS, 0.1% • FN, data not given BMD 1 year after stopping DMB without ZOL therapy: • LS, -4.8% • FN, data not given The change in LS BMD was significantly different between groups ($P=0.021$)	3 Patients in the DMB group sustained vertebral fractures at 9, 12 & 12 months after last DMB dose whereas 1 patient in the ZOL group sustained clinical vertebral fractures at 12 months of single-dose ZOL.
Zoledronic acid	Makras et al. (2020) [30]	Single-arm observational extension of AfterDmab	23	In the third-year extension of the study, 23 of the 27 postmenopausal women who had single-dose ZOL in the ZOL arm of the AfterDmab study who did not require additional treatment were followed for another year.	Mean 2.4 years/6 months from stopping DMB	BMD 3.5 years after stopping DMB: • LS, -1.75% • FN, reported as no significant change	No new vertebral fractures were observed during the extension.

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Table 1. Continued

Follow-on agent	Study	Type of study	No.	Characteristics of the patient population	Duration of DMB/onset of follow-on agent	Outcomes	
						BMD	Fracture
Zoledronic acid	Anastasialakis et al. (2021) [31]	Single-arm observational extension of AfterDmab	15	To compare the 1-year effect of ZOL infusion given 6 vs. 18 months following the last DMB injection, 15 of the 30 postmenopausal women of the DMB arm received single-dose ZOL 18 months after last DMB dose (late-ZOL) and were compared to the 27 patients who had received ZOL 6 months after DMB (early-ZOL).	Mean 2.5 years/6 and 18 months from stopping DMB	BMD 1 year from ZOL therapy: <ul style="list-style-type: none"> Late-ZOL: LS, 1.8% Early-ZOL: LS, 1.7% (No between-group difference) Late-ZOL: FN, 3.4% Early-ZOL: FN, 0.1% (No between-group difference) The mean LS BMD was significantly higher in early-ZOL at end of study than in the late-ZOL group (0.976 ± 0.016 g/cm ² vs. 0.905 ± 0.015 g/cm ² respectively, $P=0.005$).	No new clinical or radiological fractures noted.
Zoledronic acid	Solling et al. (2020) [19]	Randomized, open-label, interventional study	61	Postmenopausal women and men above 50 years of age who received DMB for at least 2 years received single-dose ZOL 6 months ($n=20$) or 9 months ($n=20$) 9 months after the last DMB dose or when CTX had increased above 1.26 µg/L (OBS; $n=21$).	Mean 4.6 years/6 and 9 months from stopping DMB or when CTX >1.26 µg/L	BMD 1 year from ZOL therapy: <ul style="list-style-type: none"> 6 mo: LS, -4.8% 9 mo: LS, -4.1% OBS: LS, -4.7% (No between-group difference) 6 mo: TH, -2.6% 9 mo: TH, -3.2% OBS: TH, -3.6% (No between-group difference) 6 mo: FN, -3.0% 9 mo: FN, -3.5% OBS: FN, -4.6% (No between-group difference). 	Incidental vertebral fractures were observed in 2 women in the 9 mo group.
Zoledronic acid	Everts-Graber et al. (2020) [32]	Retrospective observational study	120	Postmenopausal women treated with DMB for 2–5 years received single-dose ZOL 6 months after last DMB injection.	Mean 3 years/6 months from stopping DMB	BMD median 2.5 years (range, 1–3.5) after stopping DMB: <ul style="list-style-type: none"> LS, -3.3% TH, -2.2% FN, -1.5% 	3 Patients developed vertebral fractures. 4 patients developed peripheral fractures: pubis, humerus, calcaneus, and distal radius.
Raloxifene	Ebina et al. (2021) [33]	Retrospective study	53	Postmenopausal women previously treated with oral BP ($n=26$) or TPTD ($n=27$) were switched to DMB (given 2.6 doses) then either switched to RAL ($n=13$), weekly/monthly BP (i.e., ALN, RIS, or IBN) (wmBP; $n=29$) or ZOL ($n=11$) at a mean of 7.2 months after denosumab.	Mean 2.6 doses/7.2 months after DMB	BMD 1.5 years after stopping DMB: <ul style="list-style-type: none"> RAL: LS, -2.7% wmBP: LS, 0.7% ZOL: LS, 1.9% (No between-group difference) RAL: FN, -3.8% wmBP: FN, -0.8% ZOL: FN, 1.8% FN BMD significantly decreased in the RAL group ($P=0.02$ between the RAL and ZOL groups; $P=0.048$ between the RAL and wmBP groups)	Clinical vertebral fractures were present in 23.1% (RAL) vs. 3.4% (wmBP) vs. 0% (ZOL) ($P=0.048$ for RAL vs. ZOL). Nonvertebral clinical fractures were present in 7.7% (RAL) vs. 3.4% (wmBP) vs. 0% (ZOL) ($P=0.71$ between groups)

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Table 1. Continued

Follow-on agent	Study	Type of study	No.	Characteristics of the patient population	Duration of DMB/onset of follow-on agent	Outcomes	
						BMD	Fracture
Teriparatide	Leder et al. (2015) [34]	Extension study of the randomized controlled trial DATA study- The DATA-Switch study	94	In DATA, postmenopausal women with osteoporosis were assigned to 24 months of TPTD, DMB, or both. In DATA-Switch, women assigned to TPTD received DMB ($n=27$), those who received DMB received TPTD ($n=27$) and those assigned to both received 24 months of DMB alone ($n=23$).	2 years	BMD 2 years after stopping DMB: • LS, 4.8% • TH, -0.7% • FN, 1.2% • DR, -5.0% (In the DMB-to-TPTD group)	No fracture data
Romoso-zumab	Kendler et al. (2019) [35]	Phase 2, dose-finding study, randomized controlled trial	167	Postmenopausal women with T score ≤ -2.0 and ≥ -3.5 received ROMO or placebo (month 0–24) followed by placebo ($n=19$) or DMB ($n=16$) from month 24–36, followed by 1 year of ROMO (month 36–48)	1 year	BMD 1 years after stopping DMB: • LS, 2.3% • TH, -0.0% • FN, 0.8% (in the DMB-to-ROMO group)	No fracture data

DMB, denosumab; ALN, alendronate; BMD, bone mineral density; LS, lumbar spine; TH, total hip; FN, femoral neck; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; ROMO, romosozumab; RIS, risedronate; ZOL, zoledronic acid; CTX, C-telopeptide; OBS, observation group; BP, bisphosphonate; TPTD, teriparatide; RAL, raloxifene; IBN, ibandronate; wmBP, weekly/monthly bisphosphonates; DATA, Denosumab and Teriparatide Administration Study.

zoledronic acid at 6 months after the last dose of denosumab. The second group received a single dose of zoledronic acid at 9 months after the last dose of denosumab, while a third group received a single dose of zoledronic acid when CTX was above 1.26 $\mu\text{g/L}$ (50% above the normal range for postmenopausal women and elderly men). The study was designed to evaluate if the timing of zoledronate influences its efficacy in inhibiting the reactivation of osteoclastic activity associated with denosumab withdrawal. This is because zoledronic acid needs active bone resorptive sites to bind to hydroxyapatite on bone surfaces for it to exert its effect. Suppressed bone remodelling from denosumab limits these bone resorptive sites, thus potentially reducing the ability of zoledronic acid to bind sufficiently and limiting its efficacy. In all three arms, BMD at 12 months after zoledronic acid showed a significant decline. Similarly, irrespective of the timing of zoledronic acid infusion, this regimen was insufficient to maintain suppression of bone turnover, as evidenced by the subsequent rise in CTX [19].

A very recent study published the results of another extension of the AfterDmab study, where patients in the original deno-

sumab arm (1 additional year of denosumab followed by 1 year of no treatment) with a decline in BMD were offered zoledronic acid or to resume denosumab. Fifteen of the 30 patients received zoledronic acid 18 months after the last denosumab dose and they were further observed for another year and compared with the original zoledronic acid arm, in which patients were given zoledronic acid 6 months after the last dose and observed for 1 year [31]. The aim was also to address the optimal timing of zoledronic acid in terms of its efficacy in preventing bone loss after denosumab withdrawal. Both spine and hip BMD were maintained, whether zoledronic acid was given earlier (6 months) or later (18 months).

Longer-term follow-up in a retrospective study of 120 women with postmenopausal osteoporosis treated with denosumab for about 3 years and then given zoledronic acid 6 months after the last denosumab injection demonstrated a partial loss of BMD between 1 and 4 years post-discontinuation. There remained 66% and 49% of BMD gained with denosumab at the lumbar spine and total hip, respectively, with all bone loss occurring in the first 18 months after zoledronic acid infusion [32]. This

again suggests that while zoledronic acid did not sustain all BMD gains, it was still adequate to avoid complete bone loss.

Data on the use of other therapeutic agents other than bisphosphonates after denosumab discontinuation are scarce. All other agents apart from bisphosphonates are reversible and their role as follow-on therapy after denosumab discontinuation needs more clarity.

Raloxifene

Raloxifene was evaluated in a retrospective multicentre study of 53 postmenopausal patients treated with denosumab who transitioned to either raloxifene or bisphosphonates (oral or intravenous) after the last dose of denosumab [33]. All had received prior treatment with either bisphosphonate or teriparatide. BMD was measured 1.5 years after the last dose of denosumab. The transition to raloxifene resulted in significant bone loss at the spine and hip compared to bisphosphonate therapy. The clinical vertebral fracture incidence was higher (23.1%) in the raloxifene group than in the oral bisphosphonate group (3.4%) and the zoledronic acid group (0%). Based on limited evidence, it appears that raloxifene is unable to attenuate the rebound increase in bone turnover after denosumab is discontinued.

Teriparatide

Transition from denosumab to teriparatide can lead to a decline in BMD. This decline in BMD was evident in the Denosumab and Teriparatide Transitions in Postmenopausal Osteoporosis (DATA-Switch) study, an extension of the Denosumab and Teriparatide Administration Study (DATA) in which 94 postmenopausal osteoporotic women were randomised to 24 months of teriparatide, denosumab, or a combination of both drugs. Patients assigned to teriparatide originally were assigned to 24 months of denosumab, while those who were originally randomised to 24 months of denosumab were given 24 months of teriparatide. Those who received a combination of both drugs subsequently received 24 months of denosumab only. Patients who were switched from denosumab to teriparatide saw a tran-

sient decrease in spine and hip BMD and a persistent decrease in forearm BMD [34]. With the decrease in BMD observed in this study, teriparatide as monotherapy after denosumab is not advised at present.

Romosozumab

The effect of transitioning to romosozumab after denosumab was evaluated in a phase two study of romosozumab [35]. When administered after denosumab in postmenopausal women with low BMD, romosozumab increased BMD in the lumbar spine by 2.3% and maintained BMD in the hip, although the increase was of a smaller magnitude than that observed in treatment-naïve patients [35]. While the results of this study suggest that romosozumab may offset the rebound increase in bone resorption observed after denosumab discontinuation, more data are needed to determine whether patients will benefit from transitioning from denosumab to romosozumab.

WHAT DO SOME OF THE GUIDELINES RECOMMEND?

In this section, we review the currently available guidelines and summarise the recommendations for the management of patients who discontinue denosumab. The key practice points are shown in Table 2.

The Endocrine Society 2019 osteoporosis guidelines state that denosumab administration should not be delayed or stopped without subsequent therapy [36]. The guidelines do provide some guidance regarding when denosumab may be stopped, stratified by fracture risk. High-risk individuals should continue or switch therapy after 5 to 10 years of use. Non-high-risk individuals may stop denosumab if they have no history of prior fractures, a T-score >-2.5 , and low Fracture Risk Assessment Tool (FRAX) scores. When stopping denosumab, the guidelines propose that zoledronic acid should be given 8 months after the last dose of denosumab. It is also suggested that bone turnover targets of CTX <280 ng/L or P1NP <35 μ g/L should be met to

Table 2. Summary of Recommendations Regarding the Discontinuation of Denosumab

If long-term denosumab is stopped, patients should be transitioned to a bisphosphonate, with either a single-dose of zoledronic acid 6 months from the last denosumab dose, or a short course (at least 1 year) of oral alendronate

Monitor serum CTX and BMD and redose if CTX is persistently elevated or if BMD shows a significant decline

CTX, C-telopeptide; BMD, bone mineral density.

mitigate the rebound in bone turnover, and that the dose can be repeated if needed [36,37].

The Swiss Association Against Osteoporosis issued guidelines in 2017 that do provide some guidance of when denosumab may be stopped stratified by fracture risk and recommends consolidating therapy with at least 1 year of a non-reversible antiresorptive (i.e., bisphosphonate therapy) after denosumab use [38]. Selective oestrogen receptor modulators may be used in place of bisphosphonates in patients with bisphosphonate intolerance. The guidelines recommend stopping denosumab after 3 to 5 years of use in individuals with low fracture risk and switching over to bisphosphonates for another 1 to 2 years. High-fracture-risk individuals should continue denosumab for up to 10 years or use denosumab in conjunction with 24 months of teriparatide and thereafter switch to bisphosphonates for another 1 to 2 years.

The European Calcified Tissue Society (ECTS) provided the most updated guidance on the issue. Guidance for denosumab discontinuation is stratified according to the duration of use and individual fracture risk [39]. Individuals with high fracture risk treated with denosumab for more than 2.5 years should continue denosumab for up to 10 years or alternatively switch to zoledronic acid starting 6 months after the last denosumab injection and monitor BTMs 3 and 6 months later, and a repeat dose should be considered if BTMs are persistently elevated. Alternatively, zoledronic acid should be given at 6 and 12 months after the last denosumab injection if BTMs are not available. Oral bisphosphonates for 12 to 24 months can be used in place of zoledronic acid. Conversely, individuals with low fracture risk treated with denosumab for less than 2.5 years may be switched to 1 to 2 years of oral bisphosphonates or zoledronic acid with close monitoring of BTMs and BMD. BTM targets of CTX <280 ng/L or P1NP <35 µg/L were specified as targets for an adequate response.

The American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE) 2020 recommends continuing denosumab for as long as clinically appropriate. The guidelines recommend transitioning to another antiresorptive if denosumab therapy is discontinued, but no further guidance is specified [40].

A recent position statement by the Health Insurance Committee of the Korean Endocrine Society provides guidance for denosumab discontinuation stratified according to fracture risk. High-fracture-risk individuals are recommended to continue denosumab or continue with an alternative therapy (e.g., romosozumab) if necessary [41]. All other patients should transition to

1 to 2 years of bisphosphonate use if denosumab is stopped. Selective oestrogen receptor modulator or hormone therapy can be used as an alternative if bisphosphonates are not appropriate.

HOW DO WE HANDLE INADVERTENT DISCONTINUATION OF DENOSUMAB DURING THE COVID-19 PANDEMIC?

With the implementation of social distancing strategies during the coronavirus disease 2019 (COVID-19) pandemic, treatment visits may be disrupted, which may affect the 6-monthly dosing of denosumab, which is usually administered by a healthcare professional. The The American Society for Bone and Mineral Research (ASBMR), AACE, Endocrine Society, ECTS, and National Osteoporosis Foundation (NOF) issued joint guidance [42] in which they recommend that patients who are unable to receive their scheduled denosumab injection within 7 months of the prior injection should transit to oral bisphosphonates such as weekly alendronate if possible. They have also advised that patients who cannot tolerate oral bisphosphonates due to an underlying gastrointestinal disorder should be temporarily switched to monthly ibandronate or weekly/monthly risedronate. Patients with renal impairment (estimated glomerular filtration rate of less than 30 to 35 mL/min) may consider an off-label use of a lower dose of oral bisphosphonate (e.g., alendronate at 35 mg weekly or 70 mg biweekly).

CONCLUSIONS

The discontinuation of denosumab may potentially be risky, as the rapid reversal following cessation leads to a rebound in bone turnover with subsequent bone loss and a possibility of multiple vertebral fractures. Patients should be informed of the importance of adhering to the dosing schedule and clinicians should be aware of this “rebound phenomenon.” The safest strategy when discontinuing denosumab would be one that is careful and deliberate. Present evidence, while limited, seems to support transitioning to a short course of bisphosphonate therapy with close monitoring of BMD and BTMs as a viable option to mitigate bone loss and the risk of multiple vertebral fractures.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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