Cancel the denosumab holiday

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Denosumab, a fully human IgG2 anti-RANK ligand antibody, quickly and substantially inhibits bone remodeling [1]. As expected by the pharmacology of denosumab, this inhibition of remodeling is completely reversible upon stopping treatment [2]. In clinical trials, discontinuing therapy after 2 years results in a rapid rebound in bone turnover markers, raising concern about whether that high remodeling rate and consequent rapid bone loss that occurs has clinical relevance beyond a simple waning of the treatment benefit [3, 4]. Despite these concerns, many patients stop denosumab therapy, sometimes upon the advice of their physicians, especially in preparation for invasive dental procedures [5–7]. Three recent reports have described five patients in whom denosumab treatment was stopped because substantial gains on bone mineral density (BMD) had been achieved and who then experienced vertebral fractures within the first several months after discontinuing therapy. These cases re-focus our attention on the concern about a rebound in fracture risk and make it clear that a “holiday” from denosumab therapy is not justified in patients with osteoporosis [8–10].

It is well established that denosumab treatment of postmenopausal women with osteoporosis and of men and women receiving hormone ablation therapy for the management of prostate and breast cancer is associated with substantial (about 70 %) reduction in the risk of vertebral fracture [11–13]. In women with osteoporosis, hip fracture risk is reduced by 40 % and non-vertebral fracture risk by 20 %, and efficacy may be sustained with long-term therapy [11, 14]. Progressive

increases in bone mineral density (BMD) are observed with long-term therapy with increments from baseline of 18 and 8 % observed in the lumbar spine and total hip region, respectively, after 8 years, and emerging evidence suggests that the proximal femur BMD achieved on therapy is a good indicator of an individual patient’s risk of non-vertebral fracture [14, 15].

There are few reasons to stop denosumab therapy. Refractoriness to therapy has not been demonstrated. Intolerance is uncommon. Although rare cases of atypical femoral fracture have been described in patients who have received denosumab (most often in patients with a history of previous bisphosphonate use), there is no clear signal of any risk associated with the duration of therapy [16]. However, despite the favorable benefit risk profile, many—perhaps most—patients will discontinue therapy. In observational studies, persistence of 83–95 % after one year of denosumab therapy (meaning the patient received a second dose six months after their initial dose) and 68 % at 24 months has been described [17–20]. Data regarding longer-term treatment or outside a clinical trial setting are not yet available. The usual reasons for discontinuing treatment exist (perceived intolerance or ineffectiveness, concerns about rare side effects, cost, etc.). In addition, physicians themselves may recommend that treatment be stopped after several years in patients whose BMD has increased sufficiently to move the patient above the threshold of osteoporosis and out of a high-risk category [15, 21].

The rebound in remodeling rates to values higher than pre-treatment levels with rapid bone loss upon stopping denosumab is well documented. In the phase 2 study of Miller et al., follow-up after discontinuing denosumab treatment was available in 50 patients [3]. After two years of treatment with 210 mg denosumab every 6 months or 30 mg every 3 months, serum CTX levels increased to twice the placebo

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value at 6–12 months after stopping therapy and fell back to baseline two years after treatment was discontinued. The mechanism of the overshoot in bone resorption is not understood but could be due to an expanded pool of osteoclast precursors that are simultaneously activated or to a high RANK ligand/OPG ratio after denosumab is cleared from the circulation. BMD in the lumbar spine and total hip had increased, on average, by about 8 and 5 %, respectively, but fell back to or near baseline within one year of stopping therapy. Similar responses to treatment withdrawal, including an overshoot in remodeling markers and loss of the 6 % gain in lumbar spine BMD within 1 year, were observed in the phase 3 prevention study in which women had received the clinical denosumab dose of 60 mg every 6 months for 2 years [4].

The important clinical question is whether this interval of high turnover and rapid bone loss results in an abnormally high fracture risk—a rebound to a level of risk higher than just a return to the pre-treatment fracture status. That concern is based on evidence that fracture risk is directly related to bone turnover in untreated postmenopausal women who are losing bone mass at a modest rate [22]. There is also evidence that the rapid bone loss in early menopause is associated with more rapid destruction of trabecular microarchitecture than occurs in older postmenopausal women who are losing bone less rapidly [23]. That BMD values in individual patients returned to their own baseline value upon stopping denosumab suggests that the magnitude of bone loss may be related to the amount of BMD gain during treatment [3]. There is little information about the effects of withdrawal after longer-term denosumab treatment when BMD gains on therapy would be larger than those in the studies by Miller et al. and Bone et al. Preliminary evidence suggests that the loss of lumbar spine and total hip BMD is about the same (6–7 % over 12 months) in women with low bone mass who had received denosumab for 8 years during which increases in the spine and hip BMD of 16.8 and 6.2 % had occurred at the time treatment was stopped [24]. Unfortunately, these patients were not followed longer to determine whether the rapid bone loss continued during the subsequent year.

In the small groups of patients followed in clinical trials after discontinuation of denosumab, we have no evidence of a rebound in fracture risk. In the study by Miller et al., it was reported that there was no increase in fracture incidence in the small subgroup that stopped therapy, but the fracture rates were not provided [3]. In the low-risk population studied by Bone et al., clinical fractures occurred in eight of 256 patients during the two-year post-treatment observation [4]. Those fractures were evenly divided between patients who had received denosumab or placebo during the previous two years of active treatment. Brown and colleagues reported fracture incidence in 797 patients who discontinued denosumab or placebo in the phase 3 FREEDOM trial [25]. The average duration on therapy before patients discontinued was about 3.4 doses,

or less than two years. Clinical fractures occurred after stopping therapy in 9 and 7 % of patients who had received placebo or denosumab, respectively. The rate of vertebral fractures was lower (5.6 per 100 patient-years) in those who had taken denosumab compared to a rate of 9.3 in the previous placebo group. However, the median off-treatment interval was only eight months, and the maximum off-treatment interval was 24 months. Additionally, 28–42 % of these patients had begun other osteoporosis treatments during their off-treatment follow-up.

Studies of the effects of discontinuing other osteoporosis drugs on fracture risk provide little insight. The unique skeletal retention of bisphosphonates results in a variable but slow rise in remodeling markers without rebound and without rapid bone loss as is observed when denosumab is withdrawn [26–29]. Upon stopping raloxifene, the very modest on-treatment effects of BMD and remodeling markers return to baseline within one year, and no fracture data were provided during the off-treatment interval [30].

The initial lumbar spine BMD response to teriparatide is at least as great as that seen with denosumab [31]. When teriparatide is stopped, bone loss occurs, but BMD does not, on average, return to baseline levels within 18 months of discontinuation, and a persistent effect on vertebral fracture risk was reported at the end of the 18-month post-treatment follow-up [32]. However, the relative risk reduction reported at that time point (41 %, CI 15–38) was clearly lower than the 65 % risk reduction reported on treatment with 20 µg teriparatide daily. This suggests that the protection from vertebral fracture had abated or had even reversed during the off-treatment interval. Unfortunately, since it is not possible to deduce the fracture incidence during the off-treatment interval from the study report, the question of whether a rebound in fracture risk occurred cannot be answered.

An exuberant increase in remodeling markers and rapid bone loss, reminiscent of the denosumab experience, was observed when odanacatib was discontinued after two years [33]. The increase in lumbar spine BMD (about 6 %) during two years of odanacatib therapy was similar to that reported by Miller et al. and by Bone et al. after two-year treatment with denosumab. The resolution of the high bone markers occurred more quickly after stopping odanacatib (normalized within 12 months) than denosumab (24 months). Thus, patients stopping odanacatib were exposed to a shorter interval of high bone turnover. The patients who discontinued odanacatib were followed for up to three years after stopping treatment, but the incidence of fracture in that small group of patients was not reported [34].

In contrast to the small studies evaluating responses to withdrawal of osteoporosis drugs, there are several, much larger studies evaluating the skeletal effects of stopping estrogen therapy in postmenopausal women. In such patients, estrogen use has been associated with preservation or

improvement in bone mineral density and a reduction in fracture risk in both observational and randomized control trials [26, 27, 35–38]. When treatment is stopped after 2–10 years, relatively rapid bone loss occurs with lumbar spine BMD returning to levels observed in untreated women within 1–2 years [26, 27, 39–42]. This rate and amount of bone loss is similar to that observed in the denosumab discontinuation studies. Markers of bone turnover also quickly return to baseline or untreated levels upon stopping estrogen [26, 27, 42, 43]. In older postmenopausal women with osteoporosis, urinary NTX returned to the levels in untreated patients within three months after withdrawal of conjugated estrogen 0.625 mg daily without evidence of rebound [26]. In contrast, when estrogen-progestin therapy was discontinued after four years in younger postmenopausal women without osteoporosis, urinary NTX increased to levels above that seen in untreated women, returning to the untreated levels two years after withdrawal, a pattern not unlike that observed upon stopping denosumab [27]. Unfortunately, fracture incidence after estrogen withdrawal was not reported in those studies.

In several observational studies, clinical fracture risk has been observed to increase as much as 50 % in women who stopped estrogen therapy compared to those who continued [44, 45]. Assuming that estrogen reduced fracture risk by about 1/3, this 50 % increase would put the risk back at pre-treatment levels. In both Women's Health Initiative (WHI) studies, fracture protection noted on estrogen therapy was lost within 3–5 years of stopping estrogen therapy [46–48]. There was no evidence of a rebound in clinical fracture risk. This was most clearly shown in Figure 1 of the study by Heiss and colleagues [46]. During the first three years after withdrawal of estrogen-progestin therapy, the cumulative incidence plots of hip fracture were the same in women who had taken estrogen-progestin or placebo.

There are precedents of physiologic or biochemical rebounds upon stopping antihypertensive and anticoagulant therapy, resulting in higher risks of untoward clinical events [49, 50]. We have too little evidence from clinical trials about discontinuing denosumab and other osteoporosis drugs to be confident that such a rebound in risk does not occur. Moreover, the lack of evidence of a rebound in fracture risk in the estrogen withdrawal studies should not be reassuring. The risk of vertebral fracture, the fracture observed in the five cases after stopping denosumab and the one most likely to occur in states of significant remodeling imbalance, was not assessed in the estrogen withdrawal studies. More importantly, none of the estrogen studies evaluated populations of women with osteoporosis who were at high risk for fracture before treatment. In such women, whose trabecular architecture may not be seriously impaired, rapid bone loss for 1–2 years would not significantly alter fracture risk, just as vertebral fracture risk does not increase substantially during the few years of relatively rapid spinal bone loss in early menopause. In

contrast, four of the five reported cases with vertebral fractures upon denosumab withdrawal did have osteoporosis with lumbar spine T-score values ranging from –2.5 to –4.1. In these women, whose vertebral microarchitecture was likely damaged prior to treatment, high turnover would increase the number and depth of stress risers on previously thinned trabeculae, leading to trabecular perforation and a sudden increase in fragility. That multiple vertebral fractures happened within 8–16 months after the last dose of denosumab makes this scenario very believable.

These five cases, of course, do not prove an association between stopping denosumab and a rebound in fracture risk, but they have put a clinical face on our concern, and they derail the concept of a “denosumab drug holiday.” Obviously, we need more research and experience. However, unless or until more evidence teaches us differently, it is appropriate to act as if rebound in fracture risk upon stopping therapy is a real possibility, especially in patients with osteoporosis prior to therapy.

Fortunately, we have a simple treatment strategy that would likely prevent this remodeling rebound. Bisphosphonate therapy has consistently been shown to prevent bone loss in clinical situations of recent estrogen deficiency (menopause or beginning aromatase inhibitor therapy) [51–53]. More pertinently, alendronate prevented the bone loss that occurred when estrogen or parathyroid hormone therapy was discontinued [54, 55]. Alendronate also prevented bone loss upon stopping denosumab [56]. While not yet studied after withdrawal from denosumab, a single dose of intravenous zoledronic acid, known to inhibit bone turnover for up to five years, would very likely be effective in this setting [57, 58]. For patients with osteoporosis who have received denosumab for 2 years or longer and who then stop therapy, whether it be in response to a perceived side effect or because they have reached their treatment “target,” administering one dose of zoledronic acid to prevent the rapid bone loss seems like a very reasonable treatment strategy. Reassessment 1–2 years later would direct further management. For patients about to undergo an invasive dental procedure, there is no evidence that stopping denosumab therapy reduces the very low risk of osteonecrosis of the jaw. Rather than withholding therapy prior to and for some time after the oral surgical procedure, planning for the surgery to be performed 3–4 months after a denosumab dose would be preferable, allowing time for the oral lesions to heal before the next scheduled dose.

Conclusion

It is very plausible, given the rapid increase in bone remodeling and bone loss upon stopping denosumab, that a rebound increase in fracture risk ensues. So, until further notice, cancel the denosumab holiday. Interrupting therapy, even for a short

time, runs the risk of not only discarding much or all of the benefit derived while on treatment but of exposing the patient to an unacceptable risk of vertebral fracture. Patients should be encouraged to continue denosumab therapy long term. If discontinuation does occur, appropriate steps must be taken to prevent the rapid bone loss and probable acute fracture risk.

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Compliance with ethical standards

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