COMMENTARY

# Warning of an increased risk of vertebral fracture after stopping denosumab

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Recent evidence has highlighted a serious risk of new vertebral compression fractures after discontinuation of the osteoporosis drug, denosumab.[1,2] Major societies of bone researchers and clinicians have called for physicians and patients to be made aware of the potential risk of multiple rebound fractures when denosumab is stopped and have urged patients to be warned upon starting the drug.[3] Patients already taking denosumab who are considering stopping treatment should discuss with their physicians the merits of either replacing the drug promptly with another antiresorptive osteoporosis medication or continuing treatment with denosumab until evidence emerges for safe "drug weaning."

Pharmacologic treatment of patients with osteoporosis who are at high risk for fracture may substantially reduce the future risk for fracture. Well-designed randomized placebo-controlled clinical trials have shown bisphosphonates, teriparatide and denosumab to reduce the relative risk of fragility fracture by 40%–60% in postmenopausal women.[4]

Use of denosumab became common in the last decade after publication of the results of the large Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial in 2009, which showed significant reductions in the incidence of vertebral fractures, as well as reduced nonvertebral and hip fractures, in postmenopausal women treated with denosumab compared with those who were treated with placebo.[5] Denosumab is a monoclonal antibody directed against the receptor activator of nuclear factor-κB ligand (RANKL), which normally stimulates osteoclastic bone loss. When this agent is injected subcutaneously at a dosage of 60 mg every six months, the action of RANKL is inhibited, leading to a rapid reduction in the activity of osteoclasts at the bone surface. In the FREEDOM trial, the drug was well-tolerated, with only a slightly higher incidence of eczema and cellulitis than in patients taking placebo.[5] In 2010, Health Canada approved the use of denosumab for women with osteoporosis, with variable reimbursement criteria among provinces.

In an open-label extension follow-up study involving participants in the FREEDOM trial who were given denosumab, a low vertebral fracture rate persisted, with a paucity of observed adverse effects. This led the study authors to conclude that patients with osteoporosis could be safely treated with denosumab for up to 10 years.[6] A study that used pharmacy claims data from Ontario reported a rapid uptake in the use of denosumab from 2012 to 2013.[7] However, studies have begun to report that adherence may be poor; a recent prospective observational study in the United States found that of 617 patients prescribed denosumab, 64.3% had stopped taking the drug after two years.[8]

Troubling reports of potential adverse effects upon stopping denosumab were first raised in 2011. Investigators from the FREEDOM trial showed that patients previously taking denosumab for two years who were then followed off medication had rapid drops in their bone density and a marked rise in their bone resorption markers that were well above baseline only 12 months after the last denosumab injection.[9] Case reports then appeared of new, often multiple, vertebral fractures that developed in patients within a few months of stopping denosumab — termed "rebound-associated" fractures. A systematic review of 24 cases of patients taking denosumab for 2.9 years, on average, reported a mean of 4.7 vertebral fractures per patient only 5.2 months from when the last injection of denosumab should have "worn off."[1] Attempts at vertebroplasty in 5 of the 24 patients were abandoned after all five patients had another fracture during the procedure.

By following participants who were originally randomly assigned in the FREEDOM trial, the association between discontinuation of denosumab and rapid development of vertebral fractures was strengthened. The investigators recently reported on the experience of all participants from that trial who had received

### KEY POINTS

- Denosumab, a well-tolerated, injectable inhibitor of osteoclast-mediated bone resorption, has been shown in randomized controlled trials to reduce significantly the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.
- Recent evidence shows that patients previously treated with denosumab who discontinue the drug have an increased risk for rebound vertebral fractures, which are often multiple and may occur as soon as eight months after the last injection of the drug.
- When prescribing denosumab, clinicians should consider the patient's ability to adhere to regular dosing and counsel the patient against discontinuation without medical consultation.

at least two doses of the study drug and who were followed for a minimum of seven months. Among the 1001 participants who previously took denosumab, the vertebral fracture rate quickly rose almost sixfold from 1.2 per 100 participant-years while on the drug to 7.1, similar to that of patients taking placebo. Furthermore, the patients who had stopped denosumab sustained multiple fractures at a rate of 4.2 per 100 participant-years compared to 0.4 while on denosumab and 3.2 in the 470 participants who took placebo. Of the 56 participants with new vertebral fractures, 60.7% had two or more and 23.2% had four or more fractures compared to multiple fractures in 38.7% of participants previously treated with placebo.[2] No evidence to date shows a rise in the nonvertebral fracture rate, and there is no indication whether the observed rise in vertebral fractures applies to patients treated with bisphosphonates before taking denosumab.

A recent commentary in the *Journal of Bone and Mineral Research* echoed the call made by specialist societies in suggesting that this information be widely disseminated and emphasizing that "drug holidays cannot be safely initiated in patients treated with denosumab."[10] Because patients treated with bisphosphonates may be aware of the evidence supporting some persistence of antifracture efficacy after discontinuation of these drugs, physicians should emphasize to patients taking denosumab that pausing treatment is unwise — even after only two doses (12 months) of therapy.

It is not clear why rebound fractures occur. Because denosumab does not induce osteoclast apoptosis but arrests the development and function of osteoclasts in a highly reversible manner, it is most likely that once the drug is cleared, there is a sudden reactivation of a dormant pool of osteoclast precursors and a high expression of RANKL occurs, increasing osteoclast-mediated bone resorption. Trabecular bone, the major subtype in vertebral bodies, may be somewhat more susceptible to this acute rebound than cortical bone.

In light of this emerging evidence, how should a physician proceed when considering denosumab? First, although there are reasonable 10-year safety data on the continuous use of denosumab in osteoporosis, there is no evidence about outcomes in patients with treatment expectancies beyond this period. Although continuing long-term therapy is an option, physicians should remember that reports of the association of uncommon adverse effects, such as atypical femoral fractures, with prolonged courses of bisphosphonates did not emerge until the drugs had been on the market for over 12 years.[11] Second, the use of autoreminders in electronic medical record systems may help physicians to ensure that denosumab prescriptions are available and filled on time. Finally, if a patient has either stopped or wants to discontinue denosumab, experts suggest that denosumab be replaced promptly with another antiresorptive osteoporosis drug.[3,10]

In the absence of clear evidence from clinical trials, the prescription of a once-weekly bisphosphonate administered orally for at least one year seems like a reasonable course of action. Replacement therapy should start no later than six to eight months after the last dose of denosumab. However, it is worth bearing in mind that Canadian data from a review of about 450 000 new prescriptions of bisphosphonates to older adults showed that less than half of these patients continued treatment for two years.[12] Physicians must review the risks and benefits of the use of denosumab with their patients before commencing therapy. Additional studies are needed to better guide safe "drug weaning" while maintaining antifracture efficacy.

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