

**Chad L. Deal, MD**

Department of Rheumatic and Immunologic Disease,  
Center for Osteoporosis and Metabolic Bone Diseases,  
Orthopedic and Rheumatologic Institute,  
Cleveland Clinic

# Denosumab cessation

**P**HYSICIANS AND PATIENTS have become accustomed to a drug holiday with osteoporosis therapy. The American Society for Bone and Mineral Research has published recommendations for long-term bisphosphonate treatment,<sup>1</sup> in which they suggested that after 5 years of oral or 3 years of intravenous bisphosphonate treatment, one should consider reassessing fracture risk.

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In women who have no factors that place them at high risk for fracture (hip T score less than -2.5, FRAX score indicating high fracture risk, previous fracture, or fracture on therapy), a holiday should be considered. For patients at high risk, continuing for up to 10 years of oral and 6 years of intravenous bisphosphonate should be considered. But a holiday is not forever. Therapy often needs to be restarted, especially if bone density declines or a fracture occurs.

A holiday is suggested since long-term use of bisphosphonates has been associated with atypical femoral fractures, and higher doses and longer duration of use have been associated with osteonecrosis of the jaw.

However, in the case of bisphosphonates, a holiday is “administrative.” Although administration of the drug is stopped, these drugs have a long half-life in bone, and their pharmacologic effects continue for years after discontinuation, depending on the drug and duration of treatment.<sup>2</sup> This prolonged effect after discontinuation is not the case with other therapies for osteoporosis, including the parathyroid hormone analogues abaloparatide and teriparatide, estrogens, estrogen agonists-antagonists (eg, raloxifene), romosozumab, and denosumab.

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## ■ RAPID BONE LOSS AFTER DENOSUMAB IS STOPPED

Romosozumab is a humanized monoclonal antibody against sclerostin, a cytokine in the Wnt signaling pathway that inhibits bone formation, and denosumab is a fully human monoclonal antibody against RANK-ligand, a cytokine necessary for osteoclast formation and function. Unlike bisphosphonates, which bind avidly to hydroxyapatite and have a long half-life in bone, the effect of these 2 monoclonal antibodies is transient.

In phase 2 trials of denosumab, the gain in bone mass with 2 years of treatment was completely lost after 1 year off therapy.<sup>3</sup> Markers of bone resorption increased after denosumab discontinuation to levels higher than baseline, suggesting a hyperresorptive state. McClung et al<sup>4</sup> found that bone mineral density in the lumbar spine had increased 16.8% after 8 years of denosumab therapy but declined 6.7% in the first year after stopping.

Some have described the dramatic decline in bone mass as if bone were a “spring”—ie, when pressure is released, the material wants to rebound to the pretreatment state. Finite element analysis, a measure of bone strength, was shown to increase with denosumab treatment in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial.<sup>5</sup>

## ■ MULTIPLE VERTEBRAL FRACTURES

In this issue, Dupont et al<sup>6</sup> report on a patient who experienced “rebound-associated” vertebral fractures after denosumab cessation.

Brown et al<sup>7</sup> analyzed 327 patients from the FREEDOM trial who discontinued denosumab after 2 to 5 doses and were followed for up to 24 months (median 0.8 years). Com-

**A bisphosphonate holiday is not forever: therapy often needs to be restarted**

pared with 470 patients who discontinued placebo, there was no difference in overall fracture rate, 13.5 per 100 patient-years for placebo vs 9.7 for denosumab-treated patients; for vertebral fractures, the rate was 9.3 per 100 patient-years for placebo vs 5.6 for denosumab patients.<sup>7</sup> Limitations of this analysis were the short follow-up period and initiation of other therapies in 42% of placebo and 28% of denosumab recipients.

Case reports of patients experiencing multiple vertebral fractures after denosumab discontinuation have subsequently been published.<sup>8</sup> However, these reports could not assess the change in vertebral fracture risk with discontinuation without a matched placebo control.

Cummings et al<sup>9</sup> analyzed the risk of new or worsening vertebral fractures after denosumab discontinuation in FREEDOM (3 years) and the FREEDOM extension trial (up to 7 additional years). In the 1,001 patients who discontinued denosumab, the vertebral fracture rate increased from 1.2 to 7.1 per 100 patient-years in the year after discontinuation. This fracture rate was similar to that in patients in the placebo group of the trial, suggesting a rapid return to a fracture rate as if on no therapy ( $n = 470$ , 8.5 per 100 patient-years). Although the overall fracture rate was not different, the proportion with 2 or more fractures (ie, multiple vertebral fractures) was 60.7% in patients who discontinued denosumab vs 38.7% in patients who discontinued placebo ( $P = .049$ ). The odds ratio for developing multiple vertebral fractures was 3.9 (95% confidence interval [CI] 2.1–7.2) in those with prior vertebral fractures (either before or during the trial), 1.6 (CI 1.3–1.1) with each additional year off treatment, and 1.2 (CI 1.1–1.3) per 1% decline in annual total hip bone mineral density. There were no differences in nonvertebral fractures with discontinuation.<sup>9</sup>

Multiple vertebral fractures were not reported with discontinuation of alendronate in the FLEX (Fraction Intervention Trial Long-term Extension) study (5 years of alendronate, then 5 years of placebo), or with discontinuation of zoledronate in the HORIZON-PFT (Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal

Fracture Trial) (3 years of zoledronate, then 3 years of placebo).<sup>10</sup> Discontinuation of bisphosphonates was not associated with rapid bone loss or with rapid increases in markers of bone resorption.

## ■ IF DENOSUMAB MUST BE STOPPED

Since fracture risk increases rapidly after denosumab discontinuation and multiple vertebral fractures occur with greater frequency, it is important to track patients who miss their scheduled injections. Further, if patients must discontinue denosumab (eg, because of adverse effects), another osteoporosis medication should be initiated to prevent bone loss and prevent fracture.

In the DAPS study (Denosumab Adherence Preference Satisfaction), 115 of 126 patients randomized to denosumab for 12 months were transitioned to alendronate for 12 months; 15.9%, 7.6%, and 21.7% lost bone mineral density in the lumbar spine, total hip, and femoral neck, respectively.<sup>11</sup>

In 6 patients who discontinued denosumab after 7 years and received 1 dose of zoledronate, bone mineral density declined in both the lumbar spine and hip at 18 to 23 months after infusion.<sup>12</sup> Bone mineral density remained significantly higher than baseline in the lumbar spine but declined to pretreatment levels in the hip. The authors suggested that more than 1 dose of zoledronate might be more effective for preventing bone loss.

The timing of administration of zoledronate may be important. Data suggest that if bone turnover is very low, bisphosphonate binding to bone may be reduced, and this lessens its efficacy in preventing bone loss. The ZOLARMAB trial (Treatment With Zoledronic Acid Subsequent to Denosumab in Osteoporosis, clinicaltrials.gov identifier NCT03087851) has enrolled 60 patients in 3 arms, ie, receiving a dose of zoledronate at either 6 or 9 months after denosumab discontinuation, or when a marker of bone resorption rises above a prespecified level. A second dose of zoledronate is given in patients who have a decline in bone mineral density or an increase in a marker of bone resorption. Results are expected in 2020 or 2021.

Given the risks associated with discontin-

**Fracture risk increases rapidly after stopping denosumab; we must track patients who miss scheduled injections**

uation, should we continue to prescribe denosumab? The answer is that denosumab clearly has a place in therapy for patients at high risk of fracture. Bisphosphonates are not recommended if the glomerular filtration rate is less than 35 mL/min/1.73 m<sup>2</sup>. Since denosumab is excreted by the reticuloendothelial system and not the kidney, it is preferred in patients with chronic kidney disease.

Many patients do not tolerate oral bisphosphonates because of gastrointestinal adverse effects or bone pain. With bisphosphonate therapy, increases in bone mass occur in the first 3 years of therapy, after which no further increases occur. Denosumab is unique in that increases in bone mass continue through 10 years of treatment. Analysis of the FREEDOM extension showed that the incidence of nonvertebral fractures was lower with higher total hip T scores achieved with treatment.<sup>13</sup> For these reasons denosumab will continue to have an important place in the treatment of patients with low bone mass. For those who must discontinue denosumab, a bisphosphonate is recommended. More information is needed on oral or intravenous bisphospho-

nate therapy and the appropriate timing of therapy after denosumab discontinuation.

## ■ CONSIDERATIONS DURING THE COVID-19 PANDEMIC

As a result of the current COVID-19 pandemic, there is a higher likelihood that patients will miss scheduled denosumab treatments. Many patients are appropriately wary about coming for an appointment, so it is incumbent on providers to make patients understand the risks of discontinuation.

Many assisted-living facilities and nursing homes do not want residents to go to “routine” healthcare visits. Whenever possible, we should encourage these facilities to administer denosumab to their residents and make financial considerations secondary. If a family member is a healthcare provider, an attempt should be made to have the drug administered at home, if possible.

We should go the extra mile to make sure our patients get appropriate treatment. If all else fails, an oral bisphosphonate should be started, and denosumab can be resumed at a later date.

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**Address:** Chad L. Deal, MD, Department of Rheumatic and Immunologic Disease, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; dealc@ccf.org