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CLINICAL VIGNETTE

The Potential Dangers of Denosumab Cessation

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A 54-year-old female presented to discuss osteoporosis management. She underwent final menopause at age 50, which was typical for her family. She had osteoarthritis with left hip replacement at age 47 and sustained a femur fracture in the post-operative period. She was premenopausal at time of fracture with osteopenia on bone density testing. She was treated by an outside physician with teriparatide (Forteo) for 1-2 years followed by denosumab (Prolia) 60 mg SC q 6 months for 2 doses. Repeat bone density test showed improvement and she stopped denosumab injections. She remained off treatment, but restarted after she was scheduled for right hip replacement due to concerns about elevated risks for post-operative fracture. The patient underwent right hip replacement without problems and remained on densumab for an additional 3-4 doses, receiving her last dose six months prior to consultation regarding osteoporosis treatment options. After discussion about increased fracture risk following denosumab cessation, she was started on alendronate therapy for 3 months. One month after stopping denosumab, her bone turnover marker levels were initially low, but improved when rechecked two months later. The alendronate was restarted for an additional three months, and she has remained off osteoporosis medications with stable bone turnover markers and normal DXA.

	Ref. Range	10/2/2018 16:08	1/16/2019 12:13	3/5/2019 16:39	6/11/2019 11:21	9/4/2019 09:28	12/12/2019 14:45
Alkaline Phosphatase, Bone Spec	Latest Units: ug/L	5.0	5.7	6.7	6.0	5.7	8.0
Collagen Type I C-Telopeptide	Latest Units: pg/mL	104	116	350	106	384	173

Bone density scan data

T score	Spine	Femoral Neck	Total hip	Forearm
2006	0.6	-0.5	-1.3	
2008	0.4	-0.4	-1.5	
2011	-0.2	-0.8	-1.7	
2013	1.0	-0.8	-1.0	
2015	-0.7	-1.2	-1.6	
2017	0.0	-1.3	-1.3	-0.9
2019	0.1	Not measured	Not measured	-0.7

Indications for Starting Denosumab

Denosumab, a bone-modifying monoclonal antibody has been approved by the FDA to treat osteoporosis in postmenopausal females at high risk for osteoporotic fractures. Endocrine Society guidelines recommend using denosumab as an alternative agent for initial treatment.[1] In the 3-year double-blind, placebo-controlled phase of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial, denosumab had demonstrated benefit in comparison to placebo, in decreasing the relative risk of vertebral fractures by 68% (HR, 0.32; 95% CI, 0.26 to 0.40), hip fractures by 39% (HR, 0.61; 95% CI, 0.37 to 0.98), and non-vertebral fractures by 19% (HR, 0.81; 95% CI, 0.69 to 0.95).[2,3] In the FREEDOM Extension study, all patients received denosumab during the 7-year extension without a control group. Continuing low rates of new radiographic vertebral fractures (0.9% to 1.86% per year), non-vertebral fractures (0.84% to 2.55% per year), and hip fractures (0% to 0.61% per year) were noted in years 4 to 10. These rates were comparable to those in the initial phase 3 study in subjects taking denosumab, supporting a stable level of fracture reduction up to 10 years.[4]

Long-Term Management of Denosumab

At the doses used to treat osteoporosis the monoclonal antibody is not incorporated into bone, and this drug's actions reverse after 6 months. Injections should be given every 6 (±1) months and if longer intervals between doses occur, the drug's effect wears off and bone resorption rates rise promptly. Bone turnover increases to pretreatment levels or higher, and BMD declines 18 to 24 months after treatment discontinuation.[5,6] In the period after treatment discontinuation, patients are at higher risk of vertebral fractures, and this vulnerability may underlie the "rebound" vertebral fractures that have been reported with denosumab discontinuation or missed dosing.[6] Prior vertebral fractures before or during treatment were the strongest predictor of off-treatment new fractures.[7] Another cohort with a pre-treatment BMD T-score <= -2.5 was associated with rebound vertebral fractures after missed doses of denosumab.[8]

Based on available data, re-evaluation should be performed after 5 years of denosumab treatment. Denosumab should not be delayed or stopped without subsequent antiresorptive therapy (bisphosphonate, hormones therapy, or selective estrogen receptor modulator) to prevent a rebound in bone turnover, rapid BMD loss and increased risk of rebound vertebral fracture.[1]

- **Patients considered at high fracture risk** i.e. older, low BMD as defined by T-score <− 2.5 or with multiple vertebral fractures, especially on treatment or a high fracture risk score (FRAX) should either continue denosumab therapy for up to 10 years or be switched to an alternative treatment.
- **For patients at low risk i.e.** BMD has increased to T-score >− 2.5, a decision to discontinue denosumab could be made after 5 years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover.[7]

Current expert opinions recommend bisphosphonates (alendronate, risedronate and zoledronic acid) for bridging denosumab therapy cessation, and these medications should also be administered within 1-2 months of a missed dose of denosumab. The COVID-19 pandemic has resulted in cancelled visits and potentially missed or delayed denosumab treatment. Loss of insurance coverage also increases risk of abrupt treatment stoppage, due to the high expense of each injection. Alendronate reduces the relative risk of of spine and hip fractures by about 50% over 3 years in patient with a previous vertebral fracture or in patients with low T-score at the hip[9] and reduces the incidence of vertebral fractures by 48% over 3 years in people without a previous spinal fracture.[10] If a patient is not able to tolerate oral alendronate without aggravation of an underlying esophageal condition such as achalasia or Bartlett's esophagitis, the intravenous formulation (i.e. zoledronic acid) should be discussed.

For both cohorts of patients, it is important to encourage treatment of secondary risk factors. The National Osteoporosis Foundation recommends 1200 mg calcium daily for women 51 years of age and older (as well as men 71 years old or more) and 800 to 1000 international units of vitamin D daily in persons 50 years of age and older. It is preferable that the calcium and vitamin D intake comes from food sources but when not possible, supplements can be taken to attain the total recommended intake. The concurrent use of a proton pump inhibitor or H2 blocker can make absorption of calcium carbonate a challenge and calcium citrate can be advised in such patients. More calcium and vitamin D than usual may be required in those patients with malabsorption or short-bowel syndrome due to impaired absorption.[11,12] Regular weight-bearing and muscle strengthening exercise is important in reducing fall risk and improving bone mineralization.[13]

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