New Mexico Bone Club 2019: Lessons Learned from Discussion of Case Presentations

Akshaya Kambhatla, MD; Rachana Thapa, MD; Jaren Trost, MD

About New Mexico Bone Club

E. Michael Lewiecki, MD
President, Osteoporosis Foundation of New Mexico

The New Mexico Bone Club is an ongoing series of educational meetings for healthcare professionals sponsored by the Osteoporosis Foundation of New Mexico (OFNM). Bone Club meetings have been held in Albuquerque, NM, about 3 times per year for the past 22 years. Each meeting consists of a presentation by an expert in the bone field or discussion of case presentations. Continuing medical education (CME) credits are provided. The reach of the meetings has recently been extended through the use of live videoconferencing, allowing participation anywhere there is an Internet connection.

The tradition in recent years is for one bone club meeting each year to consist of case presentations by fellows from University of New Mexico (UNM) Health Sciences Center. This is a summary of the bone club meeting of May 23, 2019, with presentations by the fellows under the direction of Patricia Kapsner, MD, Director of Endocrinology Fellowship Program at UNM.

OFNM is dedicated to promoting osteoporosis awareness and high quality care of skeletal diseases. In addition to bone club meetings, OFNM sponsors the annual Santa Fe Bone Symposium [1], Bone Health TeleECHO [2], and the Albuquerque Osteoporosis Support Group. For more information about upcoming educational events and archived past programs, visit the OFNM website at www.ofnm.org.

Managing skeletal health in a patient on aromatase inhibitor therapy

Akshaya Kambhatla, MD
UNM Endocrinology Fellow

Case presentation. A 62-year old woman has right breast cancer treated with lumpectomy (06/27/2018) and radiation therapy (08/20/2018 to 09/24/2018). She was started on anastrazole, an aromatase inhibitor (AI), on 10/01/2018. She has type 2 diabetes mellitus and a multinodular goiter, for which she was seen in endocrinology clinic. She does not smoke, has normal body mass index (BMI), and no family history of osteoporosis. She has no known fracture. Laboratory studies were unremarkable except for slightly low serum 25-OH-D of 28 ng/mL and slightly elevated HbA1c of 6.3%. Dual-energy X-ray absorptiometry (DXA) 07/2018 showed normal bone mineral density (BMD), with L1-L4 T-score = 1.1 and left total hip T-score = 0.1.

Background. AI therapy is associated with an increase in bone resorption, loss of BMD, and increase in fracture risk. Antiresorptive therapy can prevent bone loss, reduce fracture risk [3], and prolong disease-free survival [3] in women receiving AI therapy.

Clinical question. Should this patient receive antiresorptive therapy to prevent adverse skeletal consequences of AI therapy?

Guidelines. Recent consensus guidelines from 7 international organizations [4] recommend that fracture risk be evaluated in all women who are beginning AI therapy and that advice be given regarding exercise and vitamin D/calcium supplementation. Bone-directed therapy should be provided for women at high risk of fracture, such as those with T-score < -2.0, or T-score < -1.5 and one clinical risk factor for fracture (e.g., age > 65 years, family history of hip fracture, smoking), or at least two clinical risk factures for fracture regardless of BMD. The fracture risk assessment tool, FRAX [5], may be helpful for estimating fracture risk, although it may underestimate fracture risk in patients on AI therapy. A FRAX adjustment that may account for the increase in fracture risk with AI therapy is ticking the "rheumatoid arthritis" box, since this disease accounts for about the same increase in fracture risk. A reasonable cut point for therapeutic intervention that may be cost effective in some settings is 10-year probability of hip fracture ≥ 3.0% or major osteoporotic fracture ≥ 20%. These are the same cut points used to identify women without a history of breast cancer for osteoporosis treatment according to guidelines of the National Osteoporosis Foundation [6]. These cut points have not specifically been assessed in women taking AIs.

When treatment is indicated, consider bisphosphonates or denosumab. The evidence for skeletal benefit is strongest for denosumab 60 subcutaneously (SC) every 6 months (Q6M0 or zoledronic acid 4 mg intravenously (IV) Q6M. Although oral bisphosphonates are an option, long-term compliance and antiresorptive effects are likely to be better with injectable therapy.

Case discussion. This patient is at risk for rapid bone loss and increasing fracture risk. However, in consideration of current low fracture risk estimation according to normal T-scores and adjusted FRAX calculation, non-pharmacological management (healthy lifestyle, good nutrition, fall prevention) was recommended. It was also suggested that she be monitored with periodic measurement of BMD every 1-2 years and regular reassessment of clinical risk factors for fracture. If fracture risk rises to levels above the thresholds suggested by the guidelines, pharmacological therapy with denosumab or zoledronic acid will be considered. There is uncertainly regarding continuation of antiresorptive therapy after an AI is discontinued, especially for patients treated with denosumab (see next case). The decision to treat with an antiresorptive agent after stopping AI therapy should consider the level of fracture risk at that time and the class of antiresorptive therapy used.

Clinical use of bone turnover markers after stopping denosumab

Rachana Thapa, MD
UNM Endocrinology Fellow

Case presentation. This is a 71-year-old postmenopausal woman with osteoporosis treated with denosumab. She has a past medical history of ovarian cancer in 2014, treated with total hysterectomy and bilateral salpingo-oophorectomy plus chemotherapy (2014). Other medical concerns include mild intermittent asthma, monoclonal gammopathy of undetermined significance (MGUS), and alcoholism, now in remission. She initially presented to UNM Hospital after a motor vehicle accident in 5/2017 with left pubic rami and left 5-7th rib fractures. DXA in 7/2017 showed T-scores of -1.8 at L1-L2, -1.7 at the left femoral neck, -1.4 at the left total hip, and -0.6 at the left 33% radius. There was no previous DXA available for review. A

magnetic resonance imaging (MRI) study in 7/2018 was done as part of surveillance for her MGUS; this revealed a recent right sacrum insufficiency fracture "probably due to altered weight bearing mechanics from left pelvic fracture." She was referred to the endocrinology clinic for management of her osteoporosis.

The patient had moved to New Mexico from out of state in 2017. Review of old records showed a history of "traumatic fracture of pelvis 2010 after hard fall from bicycle" as well as an old fracture deformity right, inferior pubic ramus seen on a radiographic bone survey in 2015. There was mention of a DXA done in 2012 with a report of T-score -2.8 at the L1-L2. Her osteoporosis treatment included alendronate 70 mg weekly, followed by 3 annual doses of zoledronic acid IV 5 mg, and then denosumab 60 mg SC Q6M beginning in 8/2014. Laboratory studies have been unremarkable, including normal serum calcium, 25-OH-D, parathyroid hormone (PTH), and renal function tests.

Clinical question. Given prolonged treatment with bisphosphonates (total of 13 years) followed by denosumab and T-scores now > -2.5, should denosumab be stopped and can measuring bone turnover markers (BTMs) provide helpful information in monitoring the offset of antiresorptive effect?

Bone turnover markers. BTMs are biochemical byproducts of bone remodeling that can be measured in blood and urine. Bone resorption markers include C- and N-terminal telopeptides of type 1 collagen (CTX and NTX, respectively). Bone formation markers include procollagen type 1 amino-terminal propeptide (P1NP) and osteocalcin. Bone specific alkaline phosphatase (BSAP) is a bone formation marker that is particularly useful in patients with chronic kidney disease (CKD), as this is not excreted by the kidneys. The International Osteoporosis Foundation/International Federation of Clinical Chemistry (IOF/IFCC) has recommended using CTX for bone resorption and P1NP as bone formation marker in clinical studies. Bone resorption markers are subject to diurnal variation and can be affected by food intake, and therefore should be measured in the morning after an overnight fasting state. Also, because manual and automated assays give different results for the same analysis, changes in BTMs can be compared only if the laboratory continues to use the same assay.

Clinical trials have shown that treatment of osteoporosis with antiresorptive therapy leads to an initial drop in bone resorption markers followed by drop in bone formation markers. On the other hand, treatment with the anabolic agents teriparatide and abaloparatide leads to an initial rise in bone formation markers and a later rise in bone resorption markers. In untreated patients, both P1NP and CTX were associated with increased fracture risk when adjusted for BMD and clinical risk factors [7]. The magnitude of the BTM response has been shown to be associated with the level of compliance with treatment. The least significant change (LSC) estimates are about 56% for serum CTX and 38% for serum P1NP [8]. The Endocrine Society and American Association of Clinical Endocrinologists (AACE) practice guidelines recommend considering the use of BTMs to monitor response to osteoporosis therapy and to identify non-compliance [9, 10].

Case discussion. Although discontinuation of denosumab without follow-up therapy is generally not recommended due to evidence of rapid bone loss and increase in fracture risk [11], we must keep in mind that this patient had more than a decade of previous bisphosphonate treatment. This may continue to exert an antiresorptive effect that might mitigate the expected rise and overshoot

of bone turnover that might occur after stopping denosumab. If denosumab is stopped in this patient, it might be reasonable to monitor a BTM, such as CTX, and resume an antiresorptive agent if the level rises above baseline. An alternative would be to continue patient on denosumab until we have more studies that will help guide next steps.

Anabolic therapy beyond 24 months of lifetime use

Jaren Trost, MD
UNM Rheumatology Fellow

Case presentation. Ms. M is a 71-year-old Caucasian woman with systemic lupus erythematosus (SLE) diagnosed at age 14 years, with complications that have included nephritis, pericarditis, myocarditis. She is currently taking prednisone 5 mg and hydroxychloroquine 200 mg daily, and has a left ventricular assist device (LVAD) in place due to severe congestive heart failure. She is frail and ambulates with the aid of a walker. The patient has severe osteoporosis, first diagnosed 20 years ago, with very low T-scores and a history of low-trauma fractures. These fractures include sacral insufficiency fractures and multiple vertebral fractures. She has recent vertebral fractures at T10 and T12 with approximately 25-30% vertebral height loss. Initial treatment with alendronate and then risedronate was discontinued due to gastrointestinal (GI) intolerance. She was then treated with teriparatide (about 15 years ago) for 2 years, followed by IV zoledronic acid, last administered 7/2015. Because of worsening chronic kidney disease, she was switched to denosumab, but missed scheduled dose in 2018 due to out-of-state care for an exacerbation of heart failure. Denosumab was resumed in 1/2019. The most recent DXA study 2/2018 showed a T-score of -4.2 at the left femoral neck and -3.1 at the left total hip.

Clinical question. Considering her complex clinical circumstances, what is now the best treatment strategy to reduce fracture risk, and should anabolic therapy be given again?

Case discussion. Despite having received a full 24-months of treatment with teriparatide (the lifetime limit for teriparatide and/or abaloparatide according to recommendations of the US Food and Drug Administration [FDA]), her very high risk of fracture suggests that another course of anabolic therapy with teriparatide or abaloparatide be considered. Because of her severe cardiac disease, it would be prudent to avoid romosozumab [12], the latest anabolic agent to be approved for the treatment of women with postmenopausal osteoporosis at high risk for fracture. Since there is some evidence that switching from denosumab to teriparatide may be followed by bone loss [13], a combination of denosumab and anabolic therapy may be appropriate. Continuing efforts should be made to minimize exposure to glucocorticoids, as well as maintaining an adequate intake of calcium and vitamin D, and avoiding falls.

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