Editorial

»Robert L. Barbieri, MD Editor in Chief

Consider denosumab for postmenopausal osteoporosis

Easy to use and effective, this recently approved agent appears well suited to ObGyn office practice

CASE Bone loss and fracture in a cancer survivor

"Ms. Clark" is a 61-year-old breast cancer and thyroid cancer survivor who has osteoporosis.

As part of her breast cancer care, she completed 5 years of hormone therapy, including 3 years of tamoxifen and 2 years of an aromatase inhibitor. The care she received for thyroid cancer included suppressive therapy with thyroxine, which has yielded a thyroid-stimulating hormone (TSH) level of 0.03 mIU/L (normal range, 0.5–5.7 mIU/L).

Before starting treatment with an aromatase inhibitor, Ms. Clark's bone density T-score at the hip was –2.6. She was given a diagnosis of osteoporosis and started on alendronate, 70 mg weekly.

Follow-up bone density study, 1 year after she completed aromatase inhibitor therapy, revealed a T-score at the hip of –2.8. Evaluation for a secondary cause of osteoporosis was unremarkable. Ms. Clark reported that she was adherent with the alendronate, vitamin D, and calcium regimens for osteoporosis.

Given the bone loss, a thyroid specialist recommended annual intravenous zoledronic acid (Reclast). Alternatively, her ObGyn recommended subcutaneous injection of denosumab (Prolia) every 6 months.

While Ms. Clark awaited her health insurer's authorization of either of these two agents, she suffered a low-impact wrist fracture that necessitated reparative wrist surgery.

At this point, which one of these two alternative therapies would you recommend for Ms. Clark?

Osteoporosis manifests as low bone mass and microarchitectural disruption and fragility, with an associated increased risk of low-impact fracture. The World Health Organization defines osteoporosis as a bone mineral density (BMD) T-score ≤–2.5 (2.5 or more standard deviations below the young-adult, gender-matched reference mean).

Most authorities recommend an ounce of prevention for postmenopausal women who have osteoporosis: namely, that they be offered treatment to reduce their risk of fracture.

In Ms. Clark's case, she was at risk of this skeletal disorder because she had been treated with an aromatase inhibitor for breast cancer and was taking a suppressive dose of thyroxine to treat thyroid cancer. In addition to exercise, calcium, and vitamin D, her initial treatment for osteoporosis was an oral bisphosphonate—an appropriate first-line agent.

Unfortunately, Ms. Clark experienced a slight decline in her BMD with this regimen. Two physicians proposed that she consider an alternative agent for the osteoporosis. One of them recommended IV zoledronic acid; the other, denosumab (**TABLE**, page 12).

Searching for secondary causes of osteoporosis

In most women who have established osteoporosis and who have not responded adequately to an oral bisphosphonate, evaluation for secondary causes of osteoporosis is warranted. The workup includes:

History identifies problems such as smoking, excessive alcohol consumption, use of a glucocorticoid, eating disorders, and bowel dysfunction that impairs vitamin D and calcium absorption, such as celiac or inflammatory bowel disease.

Physical exam focuses on assessing for low body mass index and endocrine disorders.

Laboratory evaluation includes measurement of serum chemical constituents, including calcium, phosphorus, albumin, alkaline phosphatase, and endocrine analytes, including parathyroid hormone (PTH), 25-hydroxyvitamin D, and TSH.

If a secondary cause of osteoporosis is identified, it can be treated. For example, if hyperparathyroidism is identified, removal of a parathyroid adenoma (or more than one) would likely improve bone health.

CONTINUED ON PAGE 12

Side by side: Denosumab and zoledronic acid for osteoporosis

Agent	By what route is the drug given?	Are there precautions to take when administering the drug?	Have acute reactions been reported?	Does the drug increase the rate of infection?	Does it present a risk of osteonecrosis?	What is the drug's approximate annual cost?*
Denosumab	Subcutaneous	No	No	Yes	Yes	$1,600
Zoledronic acid	Intravenous	Yes: The medication must be infused no faster than over 15 min. The patient needs to be properly hydrated before infusion begins	Yes: Approximately 40% of patients experience an acute reaction that may include arthralgias, fever, flu-like symptoms, and myalgias	No	Yes	$1,200

*To the patient, before any reimbursement by health insurance.

CASE CONTINUED **Evaluation comes up empty**

Except for TSH, which has been suppressed as part of Ms. Clark's thyroid cancer treatment, no abnormal findings were noted that might point to a secondary cause of osteoporosis.

Alternatives when first-line therapy is unsuccessful

When first-line treatment for osteoporosis is unsuccessful, alternative FDA-approved options include:

- daily subcutaneous injection of PTH
- twice annual subcutaneous injection of denosumab
- annual slow IV infusion of zoledronic acid
- every-3-month IV infusion of ibandronate.

CASE CONTINUED **Guided by patient preference**

Ms. Clark did not want daily subcutaneous injections. If an IV medication was warranted, she preferred annual over every-3-month infusion. On her physicians' recommendations, therefore, she focused on the pros and cons of denosumab and IV zoledronic acid.

Denosumab

Osteoclasts are the major cell type that dissolve bone mineral and resorb bone matrix. Nuclear factor kappaβ ligand (RANKL) is a circulating stimulator of osteoclast formation and, thus, osteoclast activity and bone resorption.

Denosumab, approved by the FDA in 2010 for the treatment of osteoporosis, is a human monoclonal antibody against RANKL. The drug:

- blocks the action of RANKL
- reduces osteoclast formation and activity
- reduces bone resorption.

Denosumab is administered as a 60-mg subcutaneous injection every 6 months.

Randomized trial #1. Denosumab led to greater increases in bone density than oral alendronate. In a comparison of denosumab and alendronate, 1,189 postmenopausal women who had osteoporosis were randomized to treatment with subcutaneous denosumab, 60 mg every 6 months, or oral alendronate 70 mg a week for 1 year.

After 1 year of treatment, denosumab produced a significantly greater increase in bone density than alendronate did (at the lumbar spine, 5.3% compared to 4.2%, respectively; at the hip, 3.5% and 2.6%).[1]

Randomized trial #2. Directly relevant to the case of Ms. Clark, denosumab has been demonstrated to be effective for treating postmenopausal women treated previously with alendronate. Five hundred postmenopausal women taking alendronate, 70 mg weekly, were randomized to **1)** stop alendronate and start denosumab or **2)** continue alendronate therapy.

After 12 months of treatment, BMD increases were significantly greater in the women receiving denosumab than in those receiving alendronate at the hip (1.9% compared to 1.0%, respectively) and lumbar spine (3.0% and 1.8%).[2]

Last, in addition to improving BMD, denosumab, in comparison to placebo, has been demonstrated to reduce the rate of fractures of the hip (by 40%) and lumbar spine (by 68%) and of nonvertebral fractures (by 20%), such as the wrist.[3]

Potential for adverse effects

Compared with placebo, more than 5% of subjects receiving denosumab in trials reported back pain, pain in an extremity, musculoskeletal pain, or cystitis. More than 5% developed hypercholesterolemia.

In addition:

- Denosumab reduces osteoclast activity, thereby reducing resorption of calcium from bone. For women who are hypocalcemic, acutely reduced calcium release from bone stores may precipitate symptomatic hypocalcemia, including perioral paresthesia, muscle twitching, and carpopedal spasm.
- RANKL is an activator of immune function. Denosumab blocks RANKL activity and may therefore be associated with an increased risk of skin infection, such as cellulitis. Denosumab may be associated with an increased risk of dermatitis, rash, and eczema.
- All agents that strongly suppress osteoclast activity reduce bone turnover and may be associated with osteonecrosis. Most cases of osteonecrosis have been reported in patients with cancer or known metastatic cancer, including myeloma and breast cancer. In a study of more than 2,000 women who had breast cancer metastatic to bone, denosumab and IV zoledronic acid were associated with a risk of osteonecrosis of 2% and 1.4%, respectively.[4] An invasive dental procedure is a risk factor for osteonecrosis of the jaw in patients who are taking an agent that suppresses osteoclast activity. Many oral surgeons recommend discontinuing osteoporosis treatment prior to a major dental operation.

Zoledronic acid

At a dosage of 5 mg annually by IV infusion, zoledronic acid improves BMD and decreases the risk of fracture.

Randomized trial. 7,765 postmenopausal women who had osteoporosis were randomized to annual IV infusion of 5 mg of zoledronic acid or placebo for 3 years. Over 3 years of treatment, zoledronic acid, compared with placebo, was associated with a reduced rate of vertebral (3.3% compared with 10%, respectively) and hip fractures (2.5% and 1.4%).[5]

Practical matters

Zoledronic acid must be administered as an IV infusion over at least 15 minutes; rapid administration can damage renal glomeruli and result in renal dysfunction. Renal damage can be avoided by **1)** infusing zoledronic acid slowly and **2)** ensuring that the patient is hydrated before beginning.

ObGyn practices do not routinely administer "prolonged" IV infusion of medications, however. Committing resources to develop an infusion service may therefore not be an optimal use of limited resources in an ObGyn practice.

An alternative to IV infusion of zoledronic acid is subcutaneous administration of denosumab. Given that drug's ease of use, it appears singly suited for use in an ObGyn generalist's practice.

CASE Plan put in action

Ms. Clark underwent reconstructive wrist surgery. She also started denosumab treatment as an every-6-month subcutaneous injection. Her physicians await the results of the next bone density test.

OBG@QHC.COM

References

1. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass. A randomized blinded phase 3 trial. J Bone Miner Res. 2009;24(1):153–161.
2. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res 2010;25(1):72–81.
3. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756–765.
4. Stopeck AT, Lipton A, Body JJ, et al. Densoumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer. A randomized, double-blind study. J Clin Oncol. 2010;28(35):5132–5139.
5. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809–1822.