Let Patient Preferences Guide Bisphosphonates Use

BY KERRI WACHTER
Senior Writer

WASHINGTON — Physicians and patients need to work together to decide for or against long-term bisphosphonate treatment for osteoporosis. The body of evidence is still evolving and there's no one-size-fits-all answer, said Dr. Sundeep Khosla, research chair of the division of endocrinology at the Mayo Clinic in Rochester, Minn.

"I think ultimately the patient has to decide with her physician. … Patient values factor into this," said Dr. Khosla at an international symposium sponsored by the National Osteoporosis Foundation. A physician can inform a patient about the best information that is currently available in terms of fracture risk and the risk of complications. However, the patient has to decide what risk she is willing to take with regard to fracture.

Dr. Khosla discussed the pros and cons of long-term bisphosphonate use in the context of a hypothetical patient familiar to many physicians. A 60-year-old woman started on vitamin D/calcium supplements and 70 mg/week alendronate 5 years ago when her dual-energy x-ray absorptiometry (DXA) scan revealed a spine T score of –2.6 and a total hip T score of –2.0. She also has a family history of hip fracture. Her bone mineral density (BMD) has increased about 5% at the spine and 3% at the hip. She has not had any clinical fractures. She asks if she should continue with alendronate and if so, for how long.

So should a patient who has been on alendronate for 5 years continue with therapy? In favor of continuing, it does appear that continuation will reduce the risk of clinical vertebral fractures.

Alendronate is the longest-available bisphosphonate, with 10 years of follow-up data. In one analysis of 10 years of data for postmenopausal women on varying regimens of alendronate, those on 10 mg daily of alendronate had increased BMD for the spine and hip (N. Engl. J. Med. 2004;350:1189-99). Spine BMD increased by 13.7% from baseline over that period, and total hip BMD increased by 6.7%. Smaller gains in BMD were noted for women on 5 mg daily of alendronate: 9.3% and 2.9% for the spine and total hip, respectively. For women in the discontinuation group, spinal BMD leveled off (an increase of 0.3% from years 6-10) and total hip BMD declined slightly (a decrease of 1% from years 6-10).

There was an initial reduction in vertebral fractures for women on alendronate, but there was no difference in vertebral fractures during years 6-10. However, the study was not adequately powered to assess fractures.

This study "told us that alendronate did in fact have sustained effects over 10 years on bone density and bone turnover markers," said Dr. Khosla. However, the fracture data were inconclusive: "At best, there was no clear evidence for an increase in vertebral or nonvertebral fractures following long-term alendronate therapy."

Other data suggest that stopping treatment for 5 years will increase the risk of nonvertebral fractures and minor vertebral deformities.

In the FLEX (Fracture Intervention Trial [FIT] Long-Term Extension) study, published late last year, researchers assessed the effects of continuing or stopping alendronate after 5 years of treatment (JAMA 2006;296:2927-38). In this study, women who had received 5 years of alendronate therapy were randomized to continue on 5 mg/day or 10 mg/day alendronate, or to stop therapy.

For women on placebo for years 5-10, total hip BMD returned to baseline levels. Women on both doses of alendronate gained and maintained a 4% increase in hip BMD over baseline during the same period. In terms of spine BMD, women on placebo during years 5-10 had a slight increase and women on alendronate had a steeper increase.

Women who continued on alendronate for 10 years had an almost 50% reduction in clinical vertebral fractures, compared with those who stopped treatment after 5 years. There was no difference between the groups in terms of nonvertebral or morphometric vertebral fractures.

"So if you look at clinical vertebral fractures, what you see is that if the BMD was greater than –2.0, there doesn't appear to be any real benefit [to continued alendronate]. But if you have a BMD less than –2.0 or less than –2.5 … it appears that both of these subgroups benefitted from continuing alendronate for 10 years as opposed to stopping it after 5 years."

The study provides some useful clinical answers. "It says that continuation of alendronate for 10 years does maintain bone mass and reduces bone remodeling, compared with discontinuation after 5 years," said Dr. Khosla. Discontinuation did not increase the risk of nonvertebral fractures or x-ray–detected vertebral fractures, but the risk of clinically detected vertebral fractures was significantly increased in those who discontinued therapy after 5 years.

"For many women, stopping alendronate after 5 years for up to 5 more years does not significantly increase fracture risk, but women at high risk of vertebral fractures—such as those who already have a vertebral fracture or those [who might have] very low bone density—may benefit by continuing beyond 5 years."

Fewer data are available for risedronate. Over 5 years, women on risedronate had continued modest increases in spine bone density, and relative stabilization of femoral-neck bone density, judging from findings from the Vertebral Efficacy With Risedronate Therapy–Multinational (VERT-MN) trial (Bone 2003;32:120-6). Women on placebo had a reduction in femoral-neck bone density and a relative stabilization of spine bone density during the 2-year extension of the trial that originally was designed to run 3 years. During the 2 years of the extension, women on risedronate had more than a 50% reduction in vertebral fractures, compared with women who stopped therapy.

Even fewer data are available for ibandronate. In a 3-year study of almost 3,000 women, the incidence of new vertebral fractures in women on oral daily ibandronate (2.5 mg) was 11%, compared with 6% for women in the placebo group (Bone 2005;37:651-4).

"There are potential concerns with long-term bisphosphonate therapy," said Dr. Khosla. One important question is whether the continued and potent inhibition of bone turnover could be harmful because of the increased mineralization of bone that has been observed in animal models.

There is also concern about the accumulation of microdamage. "Here, the thought is that because bone constantly needs to repair microcracks and microfractures, if you [inhibit] resorption for long periods of time, these microcracks will accumulate, and you can start to see a paradoxical increase in fractures in various sites because you haven't repaired the skeleton normally," said Dr. Khosla.

Animal and human studies do show that bisphosphonate-induced inhibition of bone resorption is associated with increased bone mineralization. Increased bone mineralization does increase bone strength, but only up to a point because bone also becomes too stiff.

However, despite the results of animal studies with high doses of bisphosphonates, there is no evidence in humans for increased accumulation of microdamage. "This is a theoretical concern," said Dr. Khosla. ■

Lanreotide Approved for Long-Term Acromegaly Treatment

BY ELIZABETH MECHCATIE
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A sustained-release formulation of the somatostatin analogue lanreotide has been approved by the Food and Drug Administration for the long-term treatment of acromegaly patients who have had an inadequate response to or cannot be treated with surgery or radiotherapy.

Lanreotide is administered via a deep subcutaneous injection every 4 weeks for 3 months, after which time the dosage is adjusted based on the patient's response, which is determined by a reduction in serum growth hormone or insulin growth factor-1 (IGF-1) levels, as well as changes in symptoms of acromegaly, according to the labeling.

In the United States, the prolonged-release formulation of lanreotide, which the label says is a synthetic octapeptide with a biological activity similar to naturally occurring somatostatin, is being marketed as Somatuline Depot.

The label cites two long-term, randomized multicenter studies of different doses of Somatuline Depot in patients with acromegaly. In a 1-year study, 108 patients with active acromegaly were randomized to receive a 60-mg, 90-mg, or 120-mg injection of lanreotide or placebo, after which all patients received a fixed dose every 4 weeks for 4 months (4 injections), followed by a dose-titration phase of 8 injections for a total of 13 injections over 12 months. At the end of the first month, 63% of the patients treated with lanreotide had more than a 50% drop in mean growth hormone (GH) levels from baseline, compared with none of the 25 patients on placebo. At week 16, the end of the fixed dose phase, 72% of the lanreotide-treated patients had more than a 50% reduction in mean GH level, which was maintained for the rest of the study.

The second study described in the label was a 48-week, open-label, uncontrolled study of 63 patients with an IGF-1 level that was at least 1.3 times the upper limit of the age-adjusted normal range. During a 4-month fixed-dose phase, patients received four injections of 90 mg of Somatuline Depot every 4 weeks. This was followed by a dose-titration phase, during which the dose was adjusted based on GH and IGF-1 levels at the beginning of this phase, and again, if needed, after patients received another four injections. After 48 weeks, 43% of the patients achieved a normal age-adjusted IGF-1 concentration. The mean IGF-1 concentration after treatment was 1.3 ± 0.7 times the upper limit of normal, compared with 2.5 ± the upper limit of normal at baseline. The drop in IGF-1 levels "over time correlated with a corresponding marked decrease in GH concentrations," according to the label, which cited the most common adverse reactions associated with treatment as diarrhea, cholelithiasis, abdominal pain, nausea, and injection site reactions.

It is a longer-acting version of octreotide, making its administration easier and helping with patient compliance.

DR. COBIN

Somatuline Depot, which has been available in Europe for a while, will be "a useful addition to our formularies," Dr. Rhoda H. Cobin of Mount Sinai School of Medicine, New York, said in an interview. It is a longer-acting version of octreotide, used in the United States, which makes administration easier and will help with patient compliance, said Dr. Cobin, the immediate past president of the American College of Endocrinology and past president of the American Association of Clinical Endocrinologists.

Somatuline Depot is manufactured by Ipsen. Tercica, has the U.S. distribution rights and expects to launch the drug in the fourth quarter of 2007, according to Ipsen. ■