**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. Susan Cobin, a clinical associate professor of medicine at the Icahn School of Medicine at Mount Sinai in New York, at the 11th International Symposium on Osteoporosis 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 her values are, she said. 

Dr. Cobin 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/day alendronate 5 years ago when she was diagnosed with osteoporosis at age 55. She had no personal history of fracture. Her bone mineral density (BMD) was low but 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;350:1189-90). 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 3 mg daily of alendronate: a 2.9% gain in spine and total hip BMD, 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). 

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 reduce bone loss 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 Tri- als [FIT]: Long-Term Extension) study, published last year, researchers found that 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 revealed a 50% reduction in clinical vertebral fractures, compared with those who stopped treatment after 5 years. There was no difference between 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 continuing 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 will increase that 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 mineral 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 for 5 years. During the 2 years of the extension, women on risedronate had more than a 50% reduction in vertebral fractures, compared with women on placebo. 

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% in women in the placebo group (Bone 2003;57:651-4). “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 microdamiage. “Here, the thought is that 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. 

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