Pros and Cons of Continued Bisphosphonate Use

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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 one analysis of 10 years of data for postmenopausal women on alendronate, those on 10 mg daily of the bisphosphonate had higher BMD for the spine and hip.

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.

Another major concern has been the association between bisphosphonate use and jaw osteonecrosis.

"This is a very feared complication of long-term biphosphonate therapy," said Dr. Khosla. "This is something that is just coming to [our] attention, and we haven't quite figured out how to deal with it."

The exposed bone that is the hallmark of jaw osteonecrosis occurs in other conditions, sometimes confounding diagnosis. The American Society for Bone and Mineral Research created a task force to examine the relationship between bisphosphonates and jaw osteonecrosis. One goal is to develop a case definition for bisphosphonate-associated jaw osteonecrosis.

Although data on jaw osteonecrosis associated with oral bisphosphonate use are limited, it's estimated that the risk is somewhere between 1 in 10,000 and less than 1 in 100,000 patient-treatment years. "This may be an underestimate because of underreporting," said Dr. Khosla. The estimate may also be low because the risk is associated with cumulative exposure, and perhaps this complication will become more common with more patients on oral bisphosphonates for longer periods.

"It's clear that the risk of jaw osteonecrosis in patients with cancer, treated with high doses of intravenous bisphosphonates, is higher," said Dr. Khosla. In these patients, the risk is estimated to be 1-10 per 100 patients.

"I think that all we can do as physicians is provide information and factor in the patient's values. I don't think as a physician you can completely leave the decision to the patient. They get bewildered." ■

Antiresorptives May Decrease Fracture Risk in Older Women

MONTREAL — Antiresorptive drugs help reduce the risk of low-trauma, nonvertebral fractures among women over 50 being treated in a real-world setting, according to a Canadian case-control study presented at the annual meeting of the International Bone and Mineral Society.

Women with a prevalent fracture or with frank osteoporosis appeared to have most to gain from these drugs in terms of fracture risk reduction.

Dr. Suzanne Morin of McGill University in Montreal, and her colleagues, obtained data from the Canadian Multicentre Osteoporosis Study (CaMos), in which more than 6,000 women over the age of 50 were randomly selected from nine regions across Canada for follow-up. The women in this study underwent a standardized interview that addressed demographics and medical history. They also underwent measurement of their bone mineral density (BMD).

The researchers conducted a case-control analysis of the CaMos data in which women with self-reported incident low-trauma fractures, excluding fractures of the head, hands, feet, or vertebrae, were matched with up to three controls with respect to time in study, age, prevalent osteoporosis, prevalent vertebral deformity, prior clinical low-trauma fracture, and availability of baseline BMD.

Overall, 477 cases and 1,377 matched controls were included in the analysis. Among matched cases, 37% were current users of antiresorptive agents, compared with 41% among matched controls. Antiresorptive agents used included estrogen, bisphosphonates, selective estrogen receptor modulators (SERMs), and calcitonin.

Current use of antiresorptive drugs was associated with an adjusted odds ratio of 0.68 for risk of having a low-trauma fracture. Among women with a prevalent fracture or a BMD indicative of osteoporosis, the OR was 0.58, compared with an OR of 0.88 for women with neither of these risk factors.

—Alison Palkhivala