Bisphosphonate Use Tied to Poor Bone Quality

BY MARY ELLEN SCHNEIDER

Early results from two small studies show that the long-term use of oral bisphosphonates could harm bone quality and potentially lead to an increased risk for femur fractures, but the Food and Drug Administration is advising patients to stay on their medication unless advised by their physicians to stop.

The studies showed an association between the use of bisphosphonate treatments for 4 or more years and decreasing bone quality, possibly because the bisphosphonates altered the material properties of the bone. The two studies were presented at the annual meeting of the American Academy of Orthopaedic Surgeons in New Orleans.

"Although bisphosphonates have demonstrated an improvement in bone quantity, little if anything is known about the effects of these drugs on bone quality," Brian Gladnick, one of the researchers from the Hospital for Special Surgery in New York, said in a statement.

Researchers at the Hospital for Special Surgery conducted a prospective pilot study in which they evaluated the bone composition of 21 postmenopausal women who presented to the emergency department with proximal femoral fractures. Of the patients enrolled in the study, 12 had a history of bisphosphonate use for an average of 8.5 years. Nine of the women had never been treated with bisphosphonates.

The researchers performed bone core biopsies for each patient and analyzed both the micro-architecture and material properties of the bone. No difference was seen in the bone micro-architecture, but the patients who had been treated with bisphosphonates had reduced bone tissue heterogeneity, with reduced mineral content and crystal size, compared with the control group. The study was supported by a grant from the National Institutes of Health.

In a second study, researchers at Columbia University in New York evaluated the bone structure of 111 postmenopausal women with primary osteoporosis. Of that group, 61 had been taking bisphosphonates for at least 4 years. The other 50 women had been taking calcium and vitamin D supplements.

The researchers at Columbia saw improved structural integrity early in the bisphosphonate treatment. However, the trends began to reverse after 4 years of treatment. After that point, continued treatment was associated with decreased axial strength and structural integrity. The researchers received no compensation for this study.

Both groups of investigators called for more research to gauge the effectiveness of long-term clinical use of bisphosphonates for osteoporosis treatment. However, they did not expect the findings to affect clinical practice anytime soon.

"The message here is bisphosphonates are not bad drugs, but perhaps we need to know more about the long-term effects," Dr. Melvin Rosenwasser, professor of orthopaedic surgery at Columbia University and one of the investigators on the Columbia study.

Further research could shed light on the best treatment approaches in women who have been taking bisphosphonates for more than 4 years. For example, it would be helpful for physicians to know the effects of a bisphosphonate drug holiday on bone quality, Dr. Rosenwasser said in an interview.

The FDA advised physicians to be aware of the possible risk of atypical subtrochanteric femur fractures in patients taking bisphosphonates, but said that at this point they saw no "clear connection" between bisphosphonate use and the risk of these fractures.

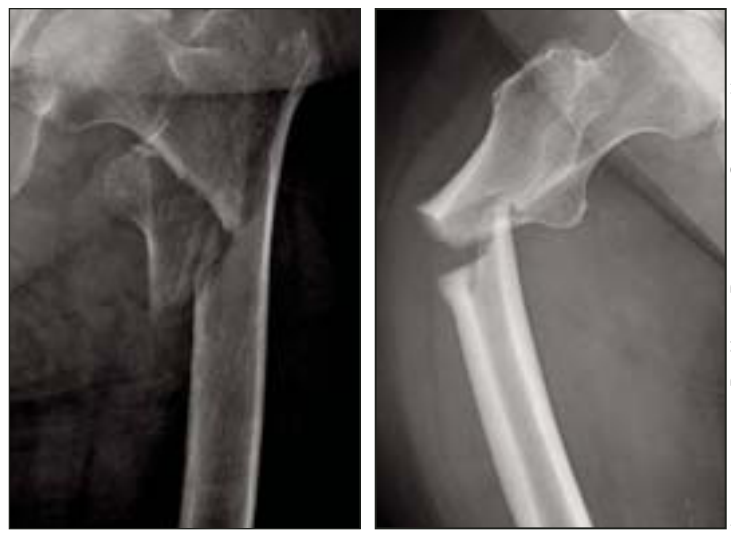
"FDA is working closely with outside experts, including members of the recently convened American Society of Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force, to gather additional information that may provide more insight into this issue," the agency said in a statement issued on March 10.

The agency has been following the issue since 2008, when case reports were published showing that atypical subtrochanteric femur fractures were occurring in women with osteoporosis who were using bisphosphonates. In June 2008, the FDA requested information from all bisphosphonate drug manufacturers about this potential safety issue. But the agency's review of the information did not show an increased risk for women using bisphosphonates.

Some manufacturers of bisphosphonate therapies (Fosamax, Actonel, Boniva, and Reclast) issued statements pledging to monitor reports of atypical fractures, but standing by the benefits of the therapies.

Courtesy Columbia University Medical Center

"We don't yet know who is vulnerable" to rare instances of atypical subtrochanteric fracture, Dr. Elizabeth Shane said.



Images courtesy Dr. Melvin Rosenwasser, Columbia University

A typical osteoporosis fracture (left), is contrasted with an atypical fracture in a patient after many years of bisphosphonate therapy.

The best information available to date indicates that atypical subtrochanteric fractures are rare, said Dr. Elizabeth Shane, an endocrinologist and professor of medicine at Columbia University who also co-chairs the American Society for Bone and Mineral Research Subtrochanteric Femoral Fracture Task Force. Preliminary estimates are that fewer than 1 in 10,000 patients taking bisphosphonates suffers from this type of fracture, she said. Contrast that with the fact that treating 1,000 women for 3 years with bisphosphonates can prevent 100 fractures, and the benefit of taking these drugs far outweighs the risks, said Dr. Shane, who receives research support from Eli Lilly, Merck, and Novartis.

"Every drug has side effects," Dr. Shane said in an interview. "It may well be that this type of fracture is associated with bisphosphonates, but we don't yet know who is vulnerable and we need more information and more research in order to determine that."

One goal of the task force convened by the American Society of Bone and Mineral Research will be to guide future research. The group, which began meeting last year, also is working to establish a case definition, review the literature, compare imaging techniques, and consider the best management of patients with these fractures.

The task force expects to wrap up its work in the next few months, Dr. Shane said. Once completed, a report will be submitted to the Journal of Bone and Mineral Research and to the FDA. The task force is likely to recommend establishment of an international registry, allowing researchers to better study the rare fractures, she said. ■

The FDA statement is at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm.

MY TAKE

Risk, Benefit Merit Discussion With Patients

Shortly after these two small case studies were presented at the American Academy of Orthopedic Surgeons meeting, ABC World News Tonight reported on the potential hazards of prolonged bisphosphonate therapy. Three days later, these studies appeared on the front page of USA Today. The reporting included some dramatic images of proximal femoral fractures, and newcaster Diane Sawyer highlighted the extensive prescribing of oral bisphosphonates by primary care physicians. She even wondered whether they (we) had any knowledge of these problems.

Although the findings were newsworthy, the two studies found nothing conclusive as to the effects of long-term use of antiresorptive therapy and these unique fractures. Moreover, the FDA has no plans to change its recommendations regarding drug labeling of oral bisphosphonates in light of these reports. It may be all noise with no signal, but there are plans to further investigate the issue.

To return to Ms. Sawyer's musings, as a primary care physician I have long questioned the use of oral bisphosphonates beyond the 5-year mark, and many of my colleagues are in the same camp. The data beyond 5 years do support continuing use, but are not as robust as for the first 5 years of therapy. We all know that bisphosphonates make for denser bones; the question raised once again is all about bone quality.

Physicians who prescribe oral bisphosphonates should talk about risk versus benefit with these patients. They should address these questions not only in the first year, but also in the 5th year and 10th year, should these drugs be used for that length of time.

ERIC G. TANGALOS, M.D., *is a professor of medicine at the Mayo Clinic in Rochester, Minn. He reported that he has been a consultant to Amgen and Novartis.*