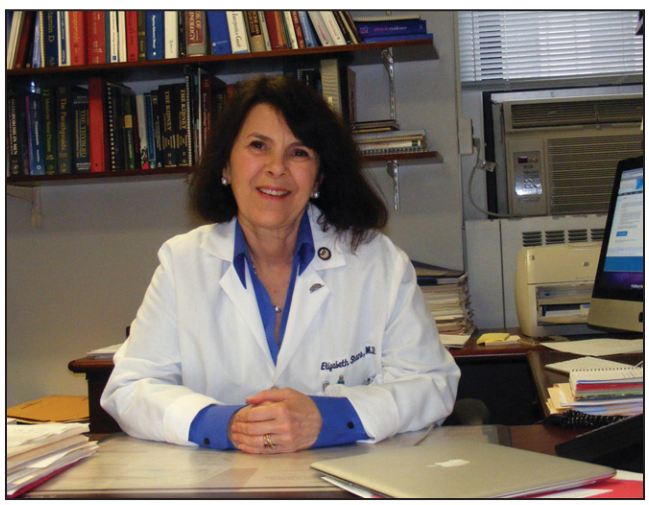
FDA Stands Pat on Long-Term Bisphosphonates

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.

Brian Gladnick, and colleagues from the Hospital for Special Surgery in New York, 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; 9 had never been treated with bisphosphonates.



COURTESY COLUMBIA UNIVERSITY MEDICAL CENTER

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

The researchers performed bone core biopsies for each patient and analyzed both the micro-architecture and material properties of the bone. No difference in the bone micro-architecture was observed, but among the patients who had been treated with bisphosphonates, the investigators found reduced bone tissue heterogeneity. Specifically, those who had received bisphosphonates had reduced mineral content and crystal size, compared with the control group.

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 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.

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.

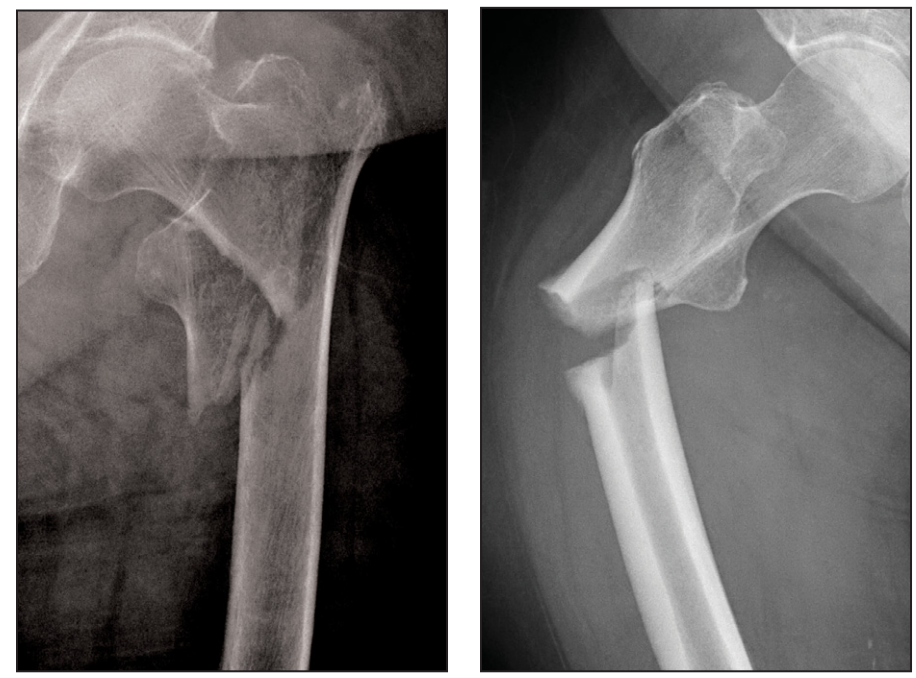
The FDA has been following the issue since 2008, when case reports showed that atypical subtrochanteric femur fractures were occurring in osteoporotic women using bisphosphonates. In June 2008, the FDA requested information from all bisphosphonate manufacturers about this potential safety issue. The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

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

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 less 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, she said.

And indeed, a study published a week after the FDA's statement suggested that the risk of subtrochanteric femur fractures is not significantly increased in women taking bisphosphonates, even among those treated for up to 10 years.

That study included a review of 283 hip or femur fractures in 14,195 women with 51,287 patient-years of follow-up and showed that only 12 subtrochanteric or diaphyseal femur fractures occurred in 10 women, for a rate of 2.3 per 10,000 patient years, Dennis M. Black, Ph.D., of the University of California at San Francisco and his colleagues wrote.



IMAGES COURTESY DR. MELVIN ROSENWASSER, COLUMBIA UNIVERSITY

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

The analysis included data from the phase III Fracture Intervention Trial (FIT), the FIT Long-Term Extension (FLEX) trial, and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT); the relative hazard ratios for subtrochanteric and diaphyseal femur fractures were 1.03 for alendronate vs. placebo in the FIT trial, 1.50 for zoledronic acid vs. placebo in the HORIZON-PFT trial, and 1.33 for continued alendronate use vs. placebo in the FLEX trial (N. Engl. J. Med. 2010 March 24[doi10.1056/NEJMoa1001086]).

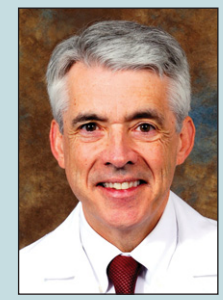
Dr. Shane noted in an interview that "[i]t may well be that this type of fracture is associated with bisphosphonates, but we don't yet know who is vulnerable and we need more information and more research in order to determine that."

The Hospital for Special Surgery study was supported by a grant from the National Institutes of Health. The Columbia researchers received no compensation for their study. Dr. Shane receives research support from Eli Lilly, Merck, and Novartis. The three-study analysis was supported by Merck and Novartis. The investigators reported financial relationships with Merck and Novartis.. ■

MY TAKE

Smoke Signals May Be False Alarm

It's against the law to shout "fire" in a crowded theater (unless there really is a fire).



Recent misleading reports in the lay press of cases of "atypical" femur fractures in patients taking Fosamax, and recent (non–peer reviewed) reports of orthopedic research suggesting a strong link between bisphosphonates and subtrochanteric femur fractures appear to be in that vein.

In a statement, the FDA said, "At this point, the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures." We have reviewed the data (J. Clin. Endocrinol. Metab. 2010 Feb. 19 [doi:10.1210/jc.2009-1947]).

Because of the small number of cases reported, it is unlikely that a sufficiently large series of such fractures could be assembled to begin to tease out risk factors for the fractures.

Lost in the "smoke" is the serious problem caused by osteoporosis, the deaths and disability associated with fractures and the benefits of alendronate and similar drugs in reducing the risk of fractures. Life is about balancing benefits with risks. For the vast majority of patients with osteoporosis, the benefits of alendronate and other approved treatments for osteoporosis far outweigh the risks.

NELSON B. WATTS, M.D., *is an endocrinologist and director of the University of Cincinnati's bone health and osteoporosis center. He disclosed that he has relationships with several pharmaceutical companies, including Amgen Inc., Procter & Gamble, Sanofi-Aventis, and Novartis Pharmaceuticals Corp., which manufactures the bisphosphonate Reclast (zoledronic acid).*

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