

Femur Fractures May Be Tied to Bisphosphonates

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EXPERT ANALYSIS FROM A RHEUMATOLOGY SEMINAR SPONSORED BY UCLA

MARINA DEL REY, CALIF. — As the debate unfolds over both whether bisphosphonates cause femur fractures and the degree to which the benefits of drugs still outweigh the risks, a phenomenon has emerged.

Women who have taken bisphosphonates for years are being seen in doctors' offices with thigh pain that is easy to mistake for hip or knee arthritis. They have a unique constellation of radiologic findings on imaging, and they either have permanent titanium rods placed in their thigh bones or go on to full femur fractures—sometimes bilaterally—and permanent disability.

No one can yet say for sure whether they would have had those fractures regardless of bisphosphonate use, nor can anyone say if femur fractures are limited to alendronate (Fosamax) users or are a bisphosphonate class effect.

But a trend is emerging, and with it a treatment protocol.

"The thinking [among colleagues] is that this is novel and specific to bisphosphonate treatment, but only time will tell," Dr. Benjamin C. Bengs, an orthopedic surgeon at the University of California, Los Angeles, said in an interview.

The possibility must be added to the hip pain differential in women with long-standing use of the drugs, according to Dr. Bengs and others who were interviewed for this story.

Unusual Radiology Findings

For many of the doctors who were interviewed, the question isn't so much whether bisphosphonates cause femur fractures, but rather how to care for women with a long history of using the drugs, and how to recognize signs and symptoms of impending trouble.

Any woman with pain over the thigh and those x-ray findings is definitely a candidate for prophylactic rodding, said Dr. Bengs.

The unique findings on x-ray are cortical thickening that is most pronounced on the lateral side of the femur, accompanied by a beaking lesion, also on the lateral side of the femur. Intramedullary edema is often present.

The beaking lesion is the start of a horizontal or oblique stress fracture. In time, there generally develops a "little, lucent, dark line extending from the beak to the middle of the bone," Dr. Joseph Robinson, a radiology fellow at Cedars-Sinai Medical Center in Los Angeles, said in an interview.

"Lateral stress fractures are unusual. In our area, they are all related to bisphosphonates," Dr. Kambiz Motamedi, a diagnostic radiologist at UCLA Medical Center.

There is a strong belief "from our sports medicine folks and rheumatologists" that there is a relationship with bisphosphonates, he said.

Both Legs Must Be Examined

Standard hip x-rays don't go far enough down to detect the lesion, which is closer to the knee than the typical femur fracture would be, Dr. Robinson said. When they do a hip series, Cedars-Sinai radiologists are careful to image lower down so they don't miss it, he said, noting that they are also putting markers on skin to identify the source of pain.

If the lesion is found, it is imperative to image the other femur as well, said Dr. Stuart L. Silverman, a rheumatologist in private practice in Beverly Hills, Calif. The other femur can go on to fracture, often within 18 months, he said in an interview.

Dr. Bengs noted that in most cases, rodding is the usual treatment. It takes only a matter of weeks to recover from hip-to-knee rod placement, he said. It takes months to recover from a fracture, however, and older patients usually lose 10%-15% of their strength and ambulation during their convalescence, he added.

"The fractures are devastating," said UCLA and Cedars-Sinai rheumatologist



This femur fractured 2 days after the image revealed cortical thickening and a beaklike stress fracture, perhaps from bisphosphonates.

Dr. Solomon N. Forouzesh, who is the medical director of the rehabilitation department at Brotman Medical Center in Culver City, Calif. He said he's seen two cases in his practice.

Active, Osteopenic Women at Risk

Active women who have osteopenia—not osteoporosis—appear to be most at risk, Dr. Nancy Lane, a University of California, Davis, rheumatologist, said in an interview. "What I think is going on" is that bisphosphonates, by reducing bone turnover, lead to the overmineralization of cortical bone, she explained. "Over time, the bones become brittle [and] fail from too much mineralization. They cannot dissipate the load."



Women with thigh pain may have a bisphosphonate-induced fracture, said Dr. Benjamin C. Bengs.

It's "probably best not [to use bisphosphonates] in people with low risk of fractures who are very active," she said. In the past, she added, use of the drugs might have been "too aggressive."

A Drug Holiday Is Advised

As the story unfolds, doctors are using bisphosphonates for shorter lengths of time than in the past, followed by a drug holiday and ongoing bone-density monitoring.

The risk of fracture seems to "start at about 3 years and peaks between 5 and 6 years," Dr. Forouzesh said. To be ahead of the game, he advises not waiting until the risk peaks. "Back off ahead of time. I do a drug holiday in 3 or 4 years," he said.

It's not clear at this point if the phenomenon—if it is truly real—is limited to alendronate or is a bisphosphonate class effect.

Alendronate has been on the market the longest and has been the most widely used agent, Dr. Lane noted. "I am sure over time" it will emerge with other members of the class, as well, she said.

Meanwhile, there are efforts to raise awareness of the issue. The American College of Rheumatology issued a bulletin on the matter in March ("Atypical Femoral Fractures With Long-Term Bisphosphonate Use," which can be accessed online at www.rheumatology.org/publications/hotline/2010_03_22_bisphosphonate.asp).

At Cedars-Sinai, "we are trying to have [a conference] to make rheumatologists and others aware of how to deal with the problem," Dr. Robinson said.

A New Finding Unraveled, Slowly

Doctors first became aware of the issue a few years ago.

"First, there were a lot of reports in Singapore of unusual hip fractures before the lesser trochanter, [with] unusual x-ray changes," Dr. Silverman said.

Reports started to be seen in the United States, and physicians across the country began sharing their stories. Only by reexamining medical records did doctors realize that the patients shared a common history of bisphosphonate use, Dr. Bengs said.

At the present, it's "a slow-rolling

snowball that might turn out to be a very big deal given the number of women on bisphosphonates. Further vigilance and analysis are required," he said.

Many of the physicians who were interviewed for this story said they are concerned that women will go off the drugs because of press reports.

They point out that in a recent bisphosphonate manufacturer-sponsored study, investigators couldn't disprove a connection, but did conclude that the fractures are rare, and that the benefit of taking the drugs still outweighs the risks (N. Engl. J. Med. 2010;362:1761-71).

Another manufacturer-sponsored study showed that subtrochanteric femur fractures have occurred in people who have not used bisphosphonates (Osteoporos. Int. 2010;21[suppl. 1]:S7-24).

"We have a new radiologic finding, but no data that the incidence of the fractures has gone up," Dr. Silverman said.

The Food and Drug Administration said that it is staying on top of the issue. The agency continues "to evaluate the issue of the use of bisphosphonates and atypical femur fracture," a press person wrote in response to an e-mail inquiry.

The agency has no plans at present for an advisory committee meeting regarding the issue.

Concerned Women

As the issue continues to be examined, doctors are fielding questions from concerned women.

"My answer [to them] is that it's an unknown and unconfirmed [phenomenon], and that the data are not out there to answer the questions," said Dr. Eric M. Ruderman of the division of rheumatology at Northwestern University in Chicago.

At present, Dr. Ruderman doesn't stop bisphosphonate use because of fracture concerns, but he does have his patients take a drug holiday after 7 years because evidence is lacking for benefit after that point, he said. He continues monitoring bone density thereafter to assess the need for further treatment. ■

Disclosures: Dr. Motamedi, Dr. Robinson, and Dr. Forouzesh said that they had no conflicts to disclose. Dr. Bengs disclosed he is a paid consultant for Amgen Inc. Dr. Lane disclosed research grants, royalties, consulting fees from and positions of influence and ownership interests in Amgen, Eli Lilly & Co., and Pfizer Inc. Dr. Ruderman disclosed that he is a consultant for Amgen and Pfizer. Dr. Silverman disclosed he has served as a speaker, member of a speakers bureau, advisor for Eli Lilly, Novartis Pharmaceuticals Corp., Procter & Gamble, and Roche Inc., and that he has received research support from Eli Lilly, Procter & Gamble, Roche, and Novartis.