Medicine and the Current Correlation Between Fosamax and Fractures

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I. Introduction

Bisphosphonates (Fosamax, Boniva, Reclast, Actonel, etc.) are a class of drug administered to prevent bone fractures and bone loss. They have raised safety concerns in the past, most notably concerning the development of osteonecrosis of the jaw. In the past decade, however, reports surfaced concerning femur fractures sustained by women who had taken Fosamax or other bisphosphonates for five to ten years. For the most part, the women described in the reports fractured their femurs without taking part in strenuous activity. In fact, most were doing nothing more than standing or walking.

Based upon recent research, the fractures appear to be occurring because long-term administration of bisphosphonates interrupts the bone remodeling process. By altering this process, these drugs prevent small stress fractures from healing properly. When these stress fractures accumulate, they can cause a serious femur fracture. This paper discusses the most up-to-date medicine highlighting the correlation between bisphosphonates and these atypical femur fractures.

II. The Medicine

Given the mounting anecdotal evidence linking the drugs to the fractures, in June 2008, the FDA requested information from all bisphosphonate drug manufacturers related to subtrochanteric femur fractures. Following review of the information, the agency issued a Drug Safety Communication on March 10, 2010, and suggested that review of the available data failed to show an increased risk for women using the medications.1

Recent news reports have raised the question about whether there is an increased risk of this type of fracture in patients with osteoporosis using these medications. 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. 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.

Based on published case reports of atypical subtrochanteric femur fractures occurring in women with osteoporosis using bisphosphonates, FDA, in June 2008, requested information from all bisphosphonate drug manufacturers regarding this potential safety signal. All available case reports and clinical trial data were requested. FDA’s review of these data did not show an increase in this risk in women using these medications.2

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2 Id.
A. New England Journal of Medicine-5/13/10

Shortly following the FDA’s communication, the New England Journal of Medicine published an article entitled, “Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur.” The study, funded by Merck and Novartis (both are makers of bisphosphonates), purported to show that atypical femoral fractures in patients with osteoporosis were extremely rare and not significantly more common with bisphosphonates.3

The study included three trials and involved 51,287 patient-years of drug exposure. Of the 14,000+ patients involved in three trials, only 12 atypical fractures were recorded. The researchers calculated the overall rate of atypical fractures at 2.3 per 10,000 patient-years of observation, which they considered extremely low.4

However, they also stated that the study was “underpowered for definitive conclusions.” The apparent lack of relationship between bisphosphonate use and atypical femoral fractures suggested that duration of treatment may not be a factor in whatever risk bisphosphonates pose. However, in cautioning about the limits of their data, they noted that “atypical features could not be fully assessed, since radiographs were not generally available.” Further, the small number of events also precluded a definitive conclusion that the rate was not higher in patients treated with bisphosphonates. Finally, the trials did not involve long-term studies of bisphosphonate use.5

B. Journal of Bone and Mineral Research-9/14/10

On September 14, 2010, a task force from the American Society for Bone and Mineral Research issued a report on bisphosphonates and their relation to the fractures. This report caused the FDA to consider mandating label changes for bisphosphonates. The report was published in the Journal of Bone and Mineral Research and titled “Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research.”6 The task force reviewed over 300 hundred cases of atypical femur fractures and found that ninety-four percent of patients had taken bisphosphonates, most for more than five years.7

According to data cited in the report, a possible mechanism for the atypical femur fractures could be that the reduction in bone remodeling due to bisphosphonates was also associated with increased micro-damage accumulation because cracks were not efficiently removed.8 The research also suggested that decreased remodeling was not solely responsible for

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4 Id.
5 Id.
6 Shane E et al “Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American society for bone and mineral research” (Running Title: “A typical femoral fractures task force report”) J Bone Miner Res 2010; Published online Sept. 14, 2010.
7 Id.
8 Id.
reduced bone toughness, which implicated a specific effect of bisphosphonates that was independent of reduced turnover.\textsuperscript{9}

The task force also noted that more than half of the patients studied had reported groin or thigh pain for weeks or months before the fractures actually occurred, and more than a quarter of those who sustained atypical femur fractures in one leg suffered a fracture in the other leg as well.\textsuperscript{10}

Given their findings, the task force recommended changes to product labels alerting healthcare providers and patients to the possibility of sustaining atypical femur fractures with long term use of bisphosphonates.\textsuperscript{11}

In response to the task force’s report, the FDA issued a press release on September 14, 2010, and recommended that healthcare professionals be aware of the possible risk of atypical femur fractures in patients taking bisphosphonates. The FDA also indicated that it was considering label revisions following a review of all available long-term data.\textsuperscript{12}

\section*{C. Journal of Clinical Endocrinology \& Metabolism-9/15/10}

On September 15, 2010, the Journal of Clinical Endocrinology \& Metabolism published an article titled “Cumulative Alendronate Dose and the Long-Term Absolute Risk of Subtrochanteric and Diaphyseal Femur Fractures: A Register-Based National Cohort Analysis.” The report concluded that patients taking bisphosphonates were at a higher risk of atypical femur fractures than matched control subjects.\textsuperscript{13} However, large cumulative doses of bisphosphonates were not associated with a greater risk of the fractures than small cumulative doses, which the researchers suggested could be due to osteoporosis rather than to the administration of bisphosphonates.\textsuperscript{14}

\textbf{Context:}

Bisphosphonates are the mainstay of anti-osteoporotic treatment and are commonly used for a longer duration than in the placebo-controlled trials. A link to development of atypical subtrochanteric or diaphyseal fragility fractures of the femur has been proposed, and these fractures are currently the subject of a U.S. Food and Drug Administration review.

\[\text{\textsuperscript{9}Id.}\]
\[\text{\textsuperscript{10}Id.}\]
\[\text{\textsuperscript{11}Id.}\]
\[\text{\textsuperscript{12}FDA Statement on ASBMR report: Possible Increased Risk of Certain Types of Thigh Bone Fractures with Long-Term Bisphosphonate Use; September 14, 2010.}\]
\[\text{\textsuperscript{14}Id.}\]
**Objective:**

Our objective was to examine the risk of subtrochanteric/diaphyseal femur fractures in long term users of alendronate.

**Design:**

We conducted an age- and gender-matched cohort study using national healthcare data.

**Patients:**

Patients were alendronate users, without previous hip fracture, who began treatment between January 1, 1996, and December 31, 2005 (n = 39,567) and untreated controls, (n = 158,268).

**Main outcome measures:**

Subtrochanteric or diaphyseal femur fractures were evaluated.

**Results:**

Subtrochanteric and diaphyseal fractures occurred at a rate of 13 per 10,000 patient-years in untreated women and 31 per 10,000 patient-years in women receiving alendronate [adjusted hazard ratio (HR) = 1.88; 95% confidence interval (CI) = 1.62–2.17]. Rates for men were six and 31 per 10,000 patient-years, respectively (HR = 3.98; 95% CI = 2.62–6.05). The HR for hip fracture was 1.37 (95% CI = 1.30–1.46)) in women and 2.47 (95% CI = 2.07–2.95) in men. Risks of subtrochanteric/diaphyseal fracture were similar in patients who had received 9 yr of treatment (highest quartile) and patients who had stopped therapy after the equivalent of 3 months of treatment (lowest quartile).

**Conclusions:**

Alendronate-treated patients are at higher risk of hip and subtrochanteric/diaphyseal fracture than matched control subjects. However, large cumulative doses of alendronate were not associated with a greater absolute risk of subtrochanteric/diaphyseal fractures than small cumulative doses, suggesting that these fractures could be due to osteoporosis rather than to alendronate.\(^{15}\)

Given this accumulation of new data, on October 13, 2010, the FDA mandated bisphosphonate label changes and issued a Drug Safety Communication to the public regarding its concerns over the atypical fractures.

\(^{15}\) Id.
Atypical subtrochanteric femur fractures...are very uncommon and appear to account for less than 1% of all hip and femur fractures overall. Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.

These atypical fractures may be related to long-term bisphosphonate use. FDA will require a new Limitations of Use statement in the Indications and Usage section of the labels for these drugs. This statement will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis.

A medication guide will also be required to be given to patients when they pick up their bisphosphonate prescription.\textsuperscript{16}

\textbf{D. \textit{Journal of the American Medical Association-2/23/11}}

Several months after the FDA mandated a label change, the \textit{Journal of the American Medical Association} published a report which found that older women who used bisphosphonates had a significantly increased risk of sustaining femur fractures. In the study, entitled “Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women,” the authors conducted a 7-year longitudinal study in a group of women aged 68 years or older, and they found that long-term treatment with bisphosphonates increased the risk of these fractures in the thigh bone by 2.7 times.\textsuperscript{17} This was especially so for women who had taken bisphosphonates for over five years.\textsuperscript{18} A copy of the abstract follows:

\textbf{Context:}

Osteoporosis is associated with significant morbidity and mortality. Oral bisphosphonates have become a mainstay of treatment, but concerns have emerged that long-term use of these drugs may suppress bone remodeling, leading to unusual fractures.

\textbf{Objective:}

To determine whether prolonged bisphosphonate therapy is associated with an increased risk of subtrochanteric or femoral shaft fracture.

\textsuperscript{16} FDA Drug Safety Communication: Safety Update for Osteoporosis Drugs, Bisphosphonates, and Atypical Fractures; October 13, 2010.


\textsuperscript{18} Id.
**Design, Setting, and Patients:**

A population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of women aged 68 years or older from Ontario, Canada, who initiated therapy with an oral bisphosphonate between April 1, 2002, and March 31, 2008. Cases were those hospitalized with a subtrochanteric or femoral shaft fracture and were matched to up to 5 controls with no such fracture. Study participants were followed up until March 31, 2009.

**Main Outcome Measures:**

The primary analysis examined the association between hospitalization for a subtrochanteric or femoral shaft fracture and duration of bisphosphonate exposure. To test the specificity of the findings, the association between bisphosphonate use and fractures of the femoral neck or intertrochanteric region, which are characteristic of osteoporotic fractures, was also examined.

**Results:**

We identified 716 women who sustained a subtrochanteric or femoral shaft fracture following initiation of bisphosphonate therapy and 9723 women who sustained a typical osteoporotic fracture of the intertrochanteric region or femoral neck. Compared with transient bisphosphonate use, treatment for 5 years or longer was associated with an increased risk of subtrochanteric or femoral shaft fracture (adjusted odds ratio, 2.74; 95% confidence interval, 1.25-6.02). A reduced risk of typical osteoporotic fractures occurred among women with more than 5 years of bisphosphonate therapy (adjusted odds ratio, 0.76; 95% confidence interval, 0.63-0.93). Among 52,595 women with at least 5 years of bisphosphonate therapy, a subtrochanteric or femoral shaft fracture occurred in 71 (0.13%) during the subsequent year and 117 (0.22%) within 2 years.

**Conclusion:**

Among older women, treatment with a bisphosphonate for more than 5 years was associated with an increased risk of subtrochanteric or femoral shaft fractures; however, the absolute risk of these fractures is low.\(^{19}\)


The evidence establishing a relationship between the administration bisphosphonates and patients suffering atypical femur fractures became more apparent with the release of a May 4, 2011 report in the New England Journal of Medicine. The study, “Bisphosphonate Use and

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\(^{19}\) Id.
“Atypical Fractures of the Femoral Shaft,” was an overview of recent medical research that had linked bisphosphonates with spontaneous, non-traumatic femur fractures.\textsuperscript{20}

The study looked at 12,777 women aged 55 and older who suffered femur fractures in 2008. 59 of the women had an atypical femur fracture. The researches then compared those 59 patients with 263 others who had sustained more ordinary femur fractures. 78\% of the atypical fractures occurred on bisphosphonates; however, only 10\% of women with the ordinary fractures were taking the drugs.\textsuperscript{21}

In addition, the researchers looked at 1.5 million women in the National Swedish Patient Register who were 55 or older in 2008 and classified those who had taken bisphosphonates (over 83,000) into categories depending on length of use. They found that duration of use affected risk. For example, for every 100 days of bisphosphonate use, the risk of the atypical fracture rose by 30\%.\textsuperscript{22}

Risk of atypical fracture also declined after the drug was stopped. The risk was reduced by 70\% per year since the last use of the drug.\textsuperscript{23}

The researchers also found that for one unusual fracture to occur, 2,000 women had to take the bisphosphonate drugs for one year.\textsuperscript{24}

In sum, the findings in the study confirmed an increased risk of atypical femur fractures in patients taking bisphosphonates. Further, due to the long half-life of the medications (approximately 10 years), the elevated risk of sustaining such a fracture continued to exist when a patient stopped using the medicine.\textsuperscript{25}

A copy of the abstract follows:

**Background:**

Studies show conflicting results regarding the possible excess risk of atypical fractures of the femoral shaft associated with bisphosphonate use.

**Methods:**

In Sweden, 12,777 women 55 years of age or older sustained a fracture of the femur in 2008. We reviewed radiographs of 1234 of the 1271 women who had a subtrochanteric or shaft fracture and identified 59 patients with atypical fractures. Data on medications and coexisting conditions were obtained from national registries. The relative and absolute risk of atypical fractures associated with bisphosphonate use was estimated by means of a nationwide cohort analysis. The

\textsuperscript{21} Id.
\textsuperscript{22} Id.
\textsuperscript{23} Id.
\textsuperscript{24} Id.
\textsuperscript{25} Id.
59 case patients were also compared with 263 control patients who had ordinary subtrochanteric or shaft fractures.

Results:

The age-adjusted relative risk of atypical fracture was 47.3 (95% confidence interval [CI], 25.6 to 87.3) in the cohort analysis. The increase in absolute risk was 5 cases per 10,000 patient-years (95% CI, 4 to 7). A total of 78% of the case patients and 10% of the controls had received bisphosphonates, corresponding to a multivariable-adjusted odds ratio of 33.3 (95% CI, 14.3 to 77.8). The risk was independent of coexisting conditions and of concurrent use of other drugs with known effects on bone. The duration of use influenced the risk (odds ratio per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6). After drug withdrawal, the risk diminished by 70% per year since the last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38).

Conclusions:

These population-based nationwide analyses may be reassuring for patients who receive bisphosphonates. Although there was a high prevalence of current bisphosphonate use among patients with atypical fractures, the absolute risk was small.\textsuperscript{26}

III. Conclusion

Prior to the most recent study published in the New England Journal of Medicine, the available research showed a fairly weak association between the administration of bisphosphonates and development of atypical femur fractures. However, given the results of this study, there appears to be an extremely strong dose-response relationship between long-term bisphosphonate use and atypical femur fractures. This latest research strengthens the position of those claiming that the drug manufacturers failed to warn about the increased risk of sustaining an atypical femur fracture.

\textsuperscript{26} Id.