Bisphosphonates and Nonhealing Femoral Fractures: Analysis of the FDA Adverse Event Reporting System (FAERS) and International Safety Efforts

A Systematic Review from the Research on Adverse Drug Events And Reports (RADAR) Project

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Background: In the United States, hip fracture rates have declined by 30% coincident with bisphosphonate use. However, bisphosphonates are associated with sporadic cases of atypical femoral fracture. Atypical femoral fractures are usually atraumatic, may be bilateral, are occasionally preceded by prodromal thigh pain, and may have delayed fracture-healing. This study assessed the occurrence of bisphosphonate-associated nonhealing femoral fractures through a review of data from the U.S. FDA (Food and Drug Administration) Adverse Event Reporting System (FAERS) (1996 to 2011), published case reports, and international safety efforts.

Methods: We analyzed the FAERS database with use of the proportional reporting ratio (PRR) and empiric Bayesian geometric mean (EBGM) techniques to assess whether a safety signal existed. Additionally, we conducted a systematic literature review (1990 to February 2012).

Results: The analysis of the FAERS database indicated a PRR of 4.51 (95% confidence interval [CI], 3.44 to 5.92) for bisphosphonate use and nonhealing femoral fractures. Most cases (n = 317) were attributed to use of alendronate (PRR = 3.32; 95% CI, 2.71 to 4.17). In 2008, international safety agencies issued warnings and required label changes. In 2010, the FDA issued a safety notification, and the American Society for Bone and Mineral Research (ASBMR) issued recommendations about bisphosphonate-associated atypical femoral fractures.

Conclusions: Nonhealing femoral fractures are unusual adverse drug reactions associated with bisphosphonate use, as up to 26% of published cases of atypical femoral fractures exhibited delayed healing or nonhealing.

Although hip fracture rates among older adults have declined coincident with use of bisphosphonates[1-5], concern exists regarding the sporadic occurrence of atypical femoral fractures and prolonged suppression of bone remodeling by bisphosphonates[6]. Atypical femoral fractures are usually atraumatic, are occasionally preceded by prodromal thigh pain, and have been reported in individuals on bisphosphonate therapy[7]. These fractures are transverse and

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A commentary by Michael J. Klein, MD, is linked to the online version of this article at jbjs.org.

TABLE I Major and Minor Criteria for Atypical Femoral Fractures[39]

Major features*
Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
Associated with no or minimal trauma, as in a fall from a standing height or less
Transverse or short oblique configuration
Noncomminuted
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
Minor features
Localized periosteal reaction of the lateral cortex†
Generalized increase in cortical thickness of the diaphysis
Prodromal symptoms such as dull or aching pain in the groin or thigh
Bilateral fractures and symptoms
Delayed healing
Comorbid conditions (e.g., vitamin-D deficiency, rheumatoid arthritis, hypophosphatasia)
Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors)

*Fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathological fractures associated with primary or metastatic bone tumors, and periprosthetic fractures are specifically excluded. All major features are required in order to satisfy the case definition of atypical femoral fracture. None of the minor features are required, but these have been associated with some such fractures. †Often referred to in the literature as ''beaking'' or ''flaring.''

may be bilateral; up to 26% of published cases exhibited delayed healing or nonhealing (Table I). Radiographs show thickened cortices and a "beaked" appearance to the transverse fracture (Fig. 1). Considerable concern has been raised by such fractures and has resulted in a decline in bisphosphonate use[8].

Bisphosphonates are synthetic analogues of pyrophosphate (O_3P-O-PO_3)[9], inhibit the formation and aggregation of calcium phosphate crystals, and are potent inhibitors of bone resorption. Their use is typically accompanied by an increase in bone mineral content[10]. After a certain duration of exposure, bone formation also decreases, which has been attributed to the

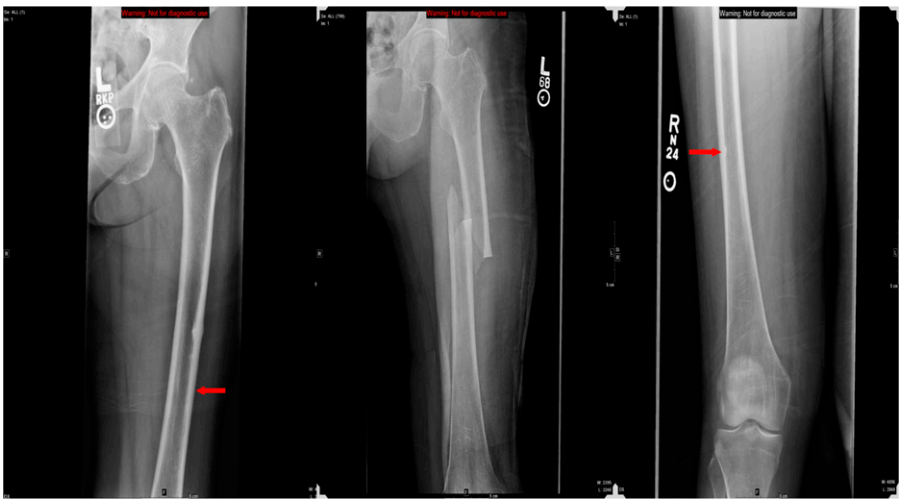

Fig. 1

Radiographic appearance of an atypical femoral fracture in a sixty-three-year-old woman who had been on bisphosphonate therapy for seven years prior to developing left thigh pain. The left panel is an initial anteroposterior radiograph of the left femur showing focal cortical thickening along the lateral proximal femoral diaphysis that represents an incomplete fracture (arrow). The central panel is an anteroposterior radiograph of the femur taken two days later showing a displaced fracture centered at the prior site of cortical thickening even though the patient had been placed on protected weight-bearing and did not sustain a trauma during the intervening time. The right panel is an anteroposterior radiograph of the right femur of the same patient, made after she had begun experiencing milder right thigh pain, demonstrating subtle cortical thickening along the lateral proximal aspect of the right femur that also represents a developing insufficiency fracture (arrow).

"uncoupling" that occurs between bone formation and resorption[11]. Atypical femoral fractures were not observed in clinical trials of bisphosphonate use in osteoporosis[12,13]. However, a growing number of cases have been reported internationally since 2004. Our objectives were to analyze the presence of nonhealing femoral fractures and atypical femoral fractures by a multifaceted approach: through a systematic review of atypical femoral fractures in the literature, an analysis of atypical femoral fractures and nonhealing femoral fractures in the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) (1996 to 2011) that addressed the identification of a safety signal, and a review of notifications and warnings established by international safety agencies.

Materials and Methods

A literature search was conducted with use of PubMed and Embase to identify English-language articles dated January 1990 to February 2012. Literature search terms included atypical femoral fracture, subtrochanteric fracture, nonhealing femoral fracture, nonunion diaphyseal fracture, malunion shaft fracture, bilateral femoral fractures, transverse fracture, and the names of individual bisphosphonates, among others (Fig. 2). Meeting abstracts were reviewed by one author (B.J.E.); if there were questions, three additional members of the RADAR (Research on Adverse Drug events And Reports) group (D.P.W., J.M.M., and P.S.) reviewed the data. The extracted data items were the subjects in each study, type of bisphosphonate(s), dose and duration of bisphosphonate exposure, clinical presentation, prodromal symptoms, characteristics of the fracture(s), level of trauma, and radiographic changes. Cases were reviewed for the presence of diseases and drugs affecting bone metabolism, the presence of vitamin-D deficiency, bone histology, management, and outcome. Case reports, case series, analyses of randomized clinical trials, and epidemiologic studies were eligible. Data were abstracted into a standardized case report form, and any discrepancies were discussed with the original authors.

The FAERS database from January 1996 through September 2011 was searched. Search terms included atypical femoral fractures, nonunion, or nonhealing femoral or subtrochanteric fractures, among others, in the absence of the terms malignancy or metabolic bone, combined with bisphosphonate drug names[14-18]. Reports that did not include the terms "atypical," "non healing," "nonhealing," or "fracture nonunion" were excluded as they could be related to the underlying osteoporosis.

We then conducted a disproportionality analysis within the FAERS data with use of proportional reporting ratio (PRR) and empiric Bayesian geometric mean (EBGM) values with accompanying 95% confidence intervals (CIs) to determine whether the number of atypical femoral fractures associated with bisphosphonates was greater than that for other drugs[19-21]. The PRR is a statistical aid to identify safety signals on the basis of the proportions of specified adverse reactions for drugs of interest, where the comparator is all other drugs in the database. The PRR and EBGM methods utilize a proportionate approach that utilizes the stability of a large database[19]. The EBGM method is a quantitative method for signal detection that stratifies by age, sex, and time, and it is less prone to false positive signals than the PRR method[19]. Judgments about the existence of a safety signal and signal strength are made on the basis of three pieces of information: the PRR (or EBGM), the chi-square value or 95% CI of the PRR, and the number of cases. A signal is defined as a PRR of ≥2, a chi-square of ≥4, and three or more cases (see Appendix).

Causality assessment for the published cases (n = 422) was conducted with use of the Naranjo and Bradford-Hill criteria[22,23]. The 10-point Naranjo probability scale assigns a weighted value to each possible answer to ten questions. The probability that the data indicates an adverse drug reaction is classified as definite if the total score is 9 or 10, probable if it is 5 to 8, possible if it is 1 to 4, and doubtful if it is 0[22]. To avoid inclusion of duplicate cases, the original authors were contacted when multiple publications involved the same case series. The Bradford-Hill criteria, which evaluate the likelihood of causality in a chronic disease, rely on multiple factors including temporal association, dose response, related experimental data, consistency of the findings, alternative explanations, coherence of the findings, and plausibility[22].

In addition, we searched for safety notifications disseminated by the FDA, the European Medicines Agency (EMA), Health Canada, and Australia's Adverse Drug Reactions Advisory Committee (ADRAC).

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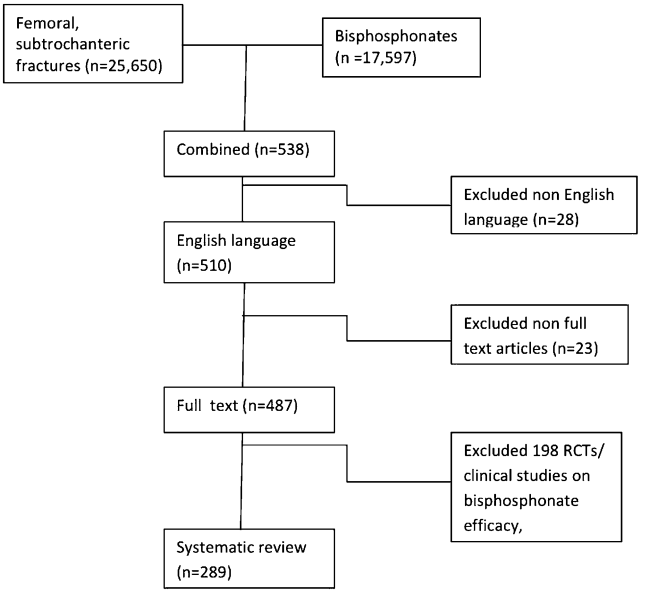

Fig. 2

Results of the literature search strategy. RCT = randomized controlled trial.

Results

The literature search involving atypical femoral fractures and bisphosphonates identified 538 manuscripts. Twenty-eight of these were excluded because they were not in the English language, twenty-three because the full text was not available, and 198 because they were randomized clinical trials focusing on bisphosphonate efficacy. The remaining 289 manuscripts were used for the systematic review (Fig. 2).

We identified an association between bisphosphonate therapy and nonhealing femoral fractures. The FAERS database contained 362 cases of nonhealing femoral fractures associated with bisphosphonates. The PRR for these fractures and bisphosphonate use was 4.51 (95% CI, 3.44 to 5.92), with most cases (n = 317) being attributed to alendronate (PRR, 3.32; 95% CI, 2.71 to 4.17) (Table II). Comorbidities were rare and included rheumatoid arthritis (n = 26, 7%) and breast cancer (n = 6, 2%). Concomitant medications included glucocorticoids (n = 35, 10%), etanercept (n = 36, 10%), estrogen (n = 12, 3%), and aromatase inhibitors (n = 3, <1%). The time line of safety reporting is depicted in Figure 3. No cases specifically diagnosed as atypical femoral fractures were identified in the FAERS database.

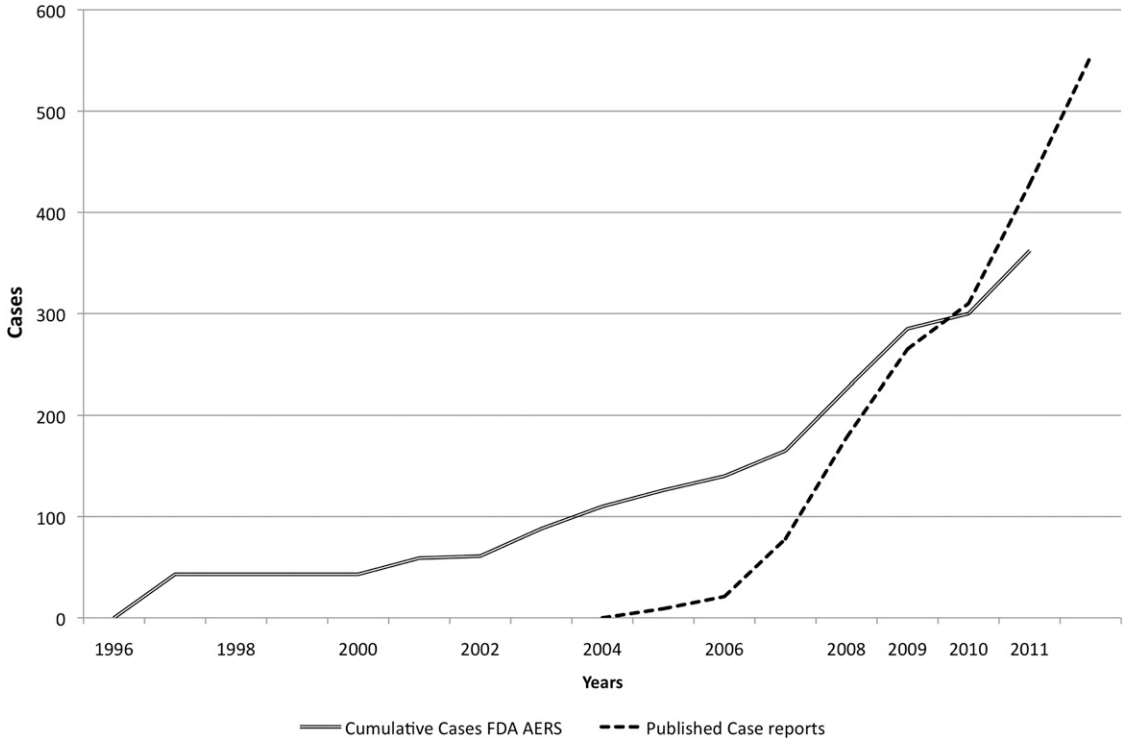

Fig. 3

Case reports in the literature and reports in the FAERS database of bisphosphonate-associated atypical femoral fractures from January 1996 to September 2011.

Case Series

From 2005 to February 2012, investigators published reports of 422 cases of atypical femoral fracture in patients on bisphosphonates. In 2005, Odvina et al. reported five cases of alendronate-associated femoral fracture with delayed fracture-healing, evidence of severe suppression of bone turnover, and reduced or absent osteoblastic surfaces[7]. Another report presented nine cases of atypical femoral fracture in 2005 and 2006 in Singapore[24]. Severe suppression of bone remodeling, resembling adynamic bone disease, was reported in 2006 in one patient in Hong Kong after ten years of alendronate use[25]. Twenty-five of seventy patients with atypical femoral fractures in New York had used alendronate for a median duration of 6.2 years[26]. The odds ratio (OR) for atypical femoral fracture in the alendronate users was 139.33 (95% CI, 19.0 to 939.4; $p < 0.001$)[26]. The fracture pattern was described as transverse or oblique, showing thickened cortices, with a unicortical-beak "chalk stick fracture" (Fig. 1). Femoral cortical stress reactions may herald the onset of an atypical femoral neck fracture[27] (see Appendix).

Epidemiologic Studies

Population-Based Studies

Abrahamsen et al. conducted an age-matched case control study of alendronate users who had sustained a prior non-hip fracture and found that the hazard ratio (HR) for femoral diaphyseal fracture with alendronate use was 1.46 (95% CI, 0.91 to 2.35; $p = 0.12$) compared with 1.45 (95% CI, 1.21 to 1.74; $p \leq 0.001$) for proximal femoral fracture. High compliance with alendronate use reduced the risk of fracture; however, the subgroup of prolonged compliant users (six years or longer) was limited to 178 patients who sustained thirty-nine hip fractures and five atypical femoral fractures[28]. Moreover, fractures were assessed with use of ICD (International Classification of Diseases)-9 codes, which are subject to ascertainment errors. Schilcher and Aspenberg identified five cases of femoral "insufficiency" fractures in bisphosphonate users (duration of use, 3.5 to 8.5 years). The incidence of atypical femoral fractures per 1000 person-years was 1 (95% CI, 0.3 to 2) among women on continuous bisphosphonate treatment compared with 0.02 (95% CI, 0.004 to 0.1) among nontreated women. Thus, the risk of atypical femoral fracture was increased by a factor of 46 (95% CI, 11 to 200) with bisphosphonate use[29]. A population-based study in Sweden ($n = 12,777$ femoral fractures) identified fifty-nine atypical femoral fractures (95% CI, 25.6 to 87.3). The increase in absolute risk of atypical femoral fractures with bisphosphonate use was five cases (95% CI, four to seven cases) per 10,000 person-years. The OR for atypical femoral fracture with bisphosphonate use was 33.3 (95% CI, 14.3 to 77.8), and the duration of bisphosphonate use influenced the risk, with an OR of 1.3 (95% CI, 1.1 to 1.6) per 100 daily doses of alendronate. The risk diminished by 70% per year after bisphosphonate use was discontinued; the OR was 0.28 (95% CI, 0.21 to 0.38) per year[30]. Kim et al. analyzed health-care utilization data and reported that a total of 104 subtrochanteric or diaphyseal femoral

TABLE II Proportional Reporting Ratio (PRR), Empiric Bayesian Geometric Mean (EBGM), and Odds Ratio for Nonhealing Femoral Fractures in the FAERS database

Drug	No. of Reports	Parameter	Value (95% CI)
Any bisphosphonate	362	PRR	4.51 (3.44, 5.92)
		Odds ratio	4.99 (3.76, 6.62)
		EBGM	1.46 (1.32, 1.62)
Alendronate	317	PRR	3.32 (2.71, 4.17)
		Odds ratio	3.71 (2.95, 4.67)
		EBGM	1.55 (1.39, 1.73)
Ibandronic acid	36	PRR	1.38 (1.01, 1.90)
		Odds ratio	1.43 (0.95, 2.05)
		EBGM	1.19 (0.90, 1.54)
Pamidronate	14	PRR	2.78 (1.74, 4.46)
		Odds ratio	3.29 (1.81, 6.01)
		EBGM	2.37 (1.37, 3.86)
Risedronate	38	PRR	1.84 (1.35, 2.51)
		Odds ratio	1.98 (1.38, 2.83)
		EBGM	1.71 (1.23, 2.32)
Zoledronic acid	26	PRR	1.43 (0.98, 2.08)
		Odds ratio	1.49 (0.98, 2.26)
		EBGM	1.18 (0.87, 1.58)

fractures were observed among 33,815 patients[31]. The incidence of subtrochanteric or diaphyseal femoral fractures per 1000 person-years was 1.46 (95% CI, 1.11 to 1.88) among the bisphosphonate users and 1.43 (95% CI, 1.06 to 1.89) among raloxifene and calcitonin users. The resulting HR for bisphosphonate use compared with raloxifene and calcitonin use was 1.03 (95% CI, 0.70 to 0.52). A retrospective study of the Kaiser Permanente database, which included 1,271,575 person-years of observations, indicated that the cumulative incidence of non-atypical femoral fractures was 18.2 (95% CI, 16.0 to 20.7) per 100,000 person-years compared with 5.9 (95% CI, 4.6 to 7.4) per 100,000 person-years for atypical femoral fractures. These rates were stable over time[32]. Age-adjusted rates of typical hip fractures in two national databases decreased by 31.6% among women and 20.5% among men from 1996 to 2007. In contrast, age-adjusted rates of subtrochanteric fragility fractures per 100,000 individuals remained unchanged among men ($p = 0.34$) but increased 20.4% among women, from 28.4 (95% CI, 27.7 to 29.1) in 1999 to 34.2 (95% CI, 33.4 to 34.9) in 2007. On the basis of the age-adjusted rates, there was an increase of one subtrochanteric fragility fracture for every decrease of approximately 100 typical femoral neck or intertrochanteric fractures[33].

Cohort Studies

Black et al. analyzed clinical trials and identified 284 recorded hip or femoral fractures among 14,195 participants. Ten of the participants had twelve femoral fractures, a rate of 2.3 per 10,000 patient-years. The relative hazard of atypical femoral fracture was 1.03 (95% CI, 0.06 to 16.46) for alendronate use in the FIT trial, 1.50 (95% CI, 0.25 to 9.00) for zoledronic acid use in the HORIZON trial, and 1.33 (95% CI, 0.12 to 14.67) for alendronate use in the FLEX trial. However, the study by Black et al. was underpowered[34]. Another study indicated that bisphosphonates were associated with an increased risk of femoral fracture (OR, >1000; $p = 0.0001$)[35]. Other authors estimated risks of 1 per 250,000 person-years and 1 per 1,000,000 person-years for alendronate and risedronate, respectively, although there may have been substantial underreporting and miscoding[36-38]. More recently, Dell et al. analyzed the records of a large health maintenance organization and identified 102 patients with atypical femoral fractures who had been on oral bisphosphonates for a mean of 5.5 years. The risk of atypical femoral fracture increased with increasing duration of treatment in patients in the Kaiser Permanente Healthy Bones Program, which included 188,814 patients who had used bisphosphonates. The age-adjusted incidence rate in those patients was 1.78 (95% CI, 1.5 to 2.0) per 100,000 person-years for an exposure of 0.1 to 0.9 year but increased to 113.1 (95% CI, 69.3 to 156.8) per 100,000 person-years for an exposure of 8.0 to 9.9 years[39]. We conclude that the incidence of atypical fracture of the femur increases with increasing duration of bisphosphonate use, but the rate remains much lower than the expected rate of devastating hip fractures in elderly osteoporotic patients. Lenart et al. reported that bisphosphonate use was more common in individuals with subtrochanteric and/or femoral shaft fractures compared with controls with intertrochanteric and/or femoral neck fractures (OR, 4.44; 95% CI, 1.77 to 11.35; $p = 0.002$). A typical radiographic pattern was identified in ten of the fifteen bisphosphonate users with subtrochanteric and/or shaft fractures. This radiographic pattern was strongly associated with bisphosphonate use (OR, 15.33; 95% CI, 3.06 to 76.90; $p < 0.001$). The duration of bisphosphonate use was longer in patients with subtrochanteric and/or shaft fractures compared with both hip fracture control groups ($p = 0.001$)[40]. A recent population-based study indicated a higher risk of atypical femoral fracture in alendronate users (OR, 1.74; 95% CI, 1.8 to 7.3); however, this risk was also elevated prior to initiation of therapy, pointing to an effect of the underlying disease being treated[41].

Causality Assessment

Causality was assessed with use of the Naranjo and Bradford-Hill criteria[22,42]. For the Naranjo criteria, the median value for the published case reports was five (indicating a probable adverse drug reaction) and ranged from two (possible) to seven (probable) in the individual reports; the quality of the reports was variable. For the Bradford-Hill criteria, a temporal relationship was evident as bisphosphonate use preceded the occurrence of atypical femoral fractures, although some cases occurred in bisphosphonate-naive patients[43]. There was consistency in the findings as results were replicated in studies in different settings such as North America, Europe, Australia, and Asia. The condition of plausibility was satisfied by known

preclinical findings[44-47] and findings of bisphosphonate-induced osteopetrosis in pediatric cases and of atypical femoral fractures associated with severe suppression of bone turnover[7,48,49]. Alternative explanations are conceivable as a prior unidentified metabolic abnormality could potentially predispose individuals to femoral fracture. Supporting experimental evidence is exemplified by the prevention of femoral fractures by limited weight-bearing after the identification of cortical stress reaction[27]. A dose-response relationship was noted in a study by Dell et al. in which a higher incidence of atypical femoral fractures was associated with longer bisphosphonate use[39]. Coherence of the findings is detailed below.

Basic Science Indicating Coherence of Data on Atypical Femoral Fractures According to the Bradford-Hill Criteria

In 2007, Yang et al. found that pamidronate administration for six months in a murine model resulted in elevated osseous levels of pamidronate (61.8 ± 15.7 ng/mg of bone) and that these levels were associated with a decrease in the time to failure during biomechanical testing[50]. Thus, there is concern that prolonged bisphosphonate residence in bone may result in skeletal damage[51]. This damage may result from the nonmetabolized nature of bisphosphonates and the ability of bisphosphonates to induce osteoclast failure and associated apoptosis[51]. Prevailing theories about possible mechanisms by which bisphosphonates induce atypical femoral fractures include cellular abnormalities with severe suppression of bone turnover, collagen abnormalities with increased cross-linking, mineral abnormalities with changes in crystal structure, and preexisting osteomalacia demonstrating a "hypophosphatasia-like appearance."

Bisphosphonates may produce severe suppression of bone turnover, histomorphometric findings of excess microcracks, decreased anisotropy, and increased secondary mineralization[51,52]. Bisphosphonates may "uncouple" bone formation from resorption in the context of suppressed remodeling, as reported by Somford et al.[53]. Iatrogenic osteopetrosis has been ascribed to aggressive bisphosphonate therapy leading to suppression of bone resorption[48,49]. Furthermore, bisphosphonates at micromolar concentrations can induce apoptosis of both osteoclasts[54] and osteoblasts[55].

Bisphosphonates exert effects on collagen cross-linking and collagen isomerization in cancellous and cortical bone, and such changes are determined by the degree of turnover suppression in bone[56,57]. Bone matrix is a two-phase system in which the mineral phase provides the stiffness and the collagen fibers provide the ductility and the ability to absorb energy (i.e., the toughness)[58]. The modulus of toughness is defined as the area under the stress-strain curve (the energy required to cause failure of the material, expressed in units that are independent of its size or geometry)[59], and nonenzymatic cross-linking contributes to bone toughness[60,61]. However, high levels of cross-linking of collagen decrease energy absorption via microdamage formation, which in turn accelerates brittle fracture[62-64]. Additionally, aging is associated with an increase in advanced glycosylated end products, which contribute to bone brittleness[65]. The mechanical integrity of collagen fibers from human cortical bones, assessed after demineralization, deteriorates with increasing subject age, and this deterioration is associated with a 30% to 50% decrease in the work to fracture, particularly its post-yield portion.

Bisphosphonates increase mean tissue age and mineralization, resulting in an increased propensity for microcracks and reduced bone resilience that collectively increase the fracture risk[52,66]. Furthermore, the mineral content (mineral/matrix ratio) of cortical bone but not cancellous bone has been shown to be increased by bisphosphonate treatment[52,57,67]. These consistent observations suggest that although alendronate treatment increases bone mass, it also decreases tissue heterogeneity and thus affects the mechanical properties of the tissue[67]. Healthy trabecular bone has broadly heterogeneous crystals, and crystal homogeneity in trabecular regions adversely affects the mechanical properties of bone[57]. Bisphosphonate therapy reduces the heterogeneity of crystals and contributes to increased brittleness of treated bone. Fourier-transform infrared spectrometry (FTIR) imaging of bone tissue revealed a more uniform composition in bisphosphonate-treated patients than in bisphosphonate-naive patients. The observed reductions in mineral and matrix heterogeneity may diminish tissue-level toughening mechanisms[68-71]. In a sheep model of rapid bone turnover, the use of zolendronate reduced the mineralization gradient from surface to core regions. Zolendronate restored mineralization levels, stiffness, and hardness but did not restore the gradients present in healthy tissue, and mineral crystal properties were altered[72].

Hypophosphatasia is a rare genetic disorder characterized by low serum alkaline phosphatase activity secondary to mutation(s) within the gene that encodes the isoenzyme of alkaline phosphatase[73,74]. As a consequence, inorganic pyrophosphate accumulates extracellularly and blocks skeletal mineralization, resulting in osteomalacia[73,74]. It has been proposed that bisphosphonates may cause a hypophosphatasia-like syndrome, at least focally where the fractures are occurring. Patients with hypophosphatasia develop Looser lines (milkman's fractures, pseudofractures) that closely resemble what is occurring in subjects receiving bisphosphonates. The symptoms, radiographic appearance, failure to heal, and requirement for intramedullary rodding associated with atypical femoral fractures are reminiscent of hypophosphatasia and X-linked hypophosphatemia[75].

Bisphosphonates have been shown to affect fracture-healing (in murine models). Alendronate's effects are dose-dependent, and supranormal doses adversely affect osteoclastic and osteoblastic function[76]. Fracture repair resulted in large calluses but was more delayed with alendronate treatment (because of delayed remodeling of woven bone into lamellar bone) compared with estrogen and raloxifene treatment[77,78]. Similar findings were noted with high-dose risedronate and zoledronic acid[79,80]. Through its direct effects on preosteoclasts, alendronate appears to regulate expression of ephrin-B1, which acts through the EphB1 and EphB3 receptors on osteoblasts to suppress their differentiation[81]. In a canine model, alendronate

did not cause adverse effects on union, strength, or mineralization of bone[82]. In humans, bisphosphonate use was associated with longer times to radiographic union of distal radial fractures[83,84]. However, use of alendronate resulted in improved spinal fusion after laminectomy, despite alendronate's usually detrimental biological effect on the healing process[85]. In one study, femoral insufficiency fractures after prolonged bisphosphonate therapy seldom healed spontaneously and most patients required surgery[86]. Treatment of atypical femoral fractures has an elevated failure rate, and revision surgery involving intramedullary nailing may be required[87]. Thus, the orthopaedic procedures required to treat atypical femoral fractures may be more complex, with the need for bone-stimulating agents such as a bone morphogenetic protein (BMP) or nailing. When nailing of fractures is performed in patients who have been on bisphosphonate therapy, healing is fair and occurs through endochondral union with development of a large callus[88]. However, the use of plates tends to be unsuccessful as healing occurs through intramembranous remodeling, which is typically delayed in patients who have been on bisphosphonate therapy. Consequently, the cost of such complex surgical care is estimated to be higher[88].

Safety Agency Reporting on Atypical Femoral Fracture and Bisphosphonates

Australia's ADRAC identified forty-four cases of femoral fractures associated with bisphosphonate use[89]. The Pharmacovigilance Working Party of the EMA's Committee for Medicinal Products for Human Use (CHMP) initiated a class review on bisphosphonates and atypical femoral fractures in July 2008 following published reports and a label change requested by the Australian authorities. The CHMP recommended that the risk of atypical femoral fractures be added to the product information for alendronate as an association was evident. In 2008, Australia's Therapeutic Goods Administration (TGA) mandated a label change for alendronate to include a warning about atypical femoral fractures[47]. The FDA issued a safety notification on March 10, 2010, and it deferred recommendations to the American Society for Bone and Mineral Research (ASBMR)[90], whose recommendations were published in September 2010[38]. The FDA subsequently announced label changes for bisphosphonates on October 13, 2010[91]. Health Canada issued a warning on October 14, 2010[92]. The time line for reporting of bisphosphonate-associated atypical femoral fractures is shown in Figure 3. The European Society of Clinical and Economic Aspects of Osteoporosis and the International Osteoporosis Foundation estimate the incidence at 1 per 1000 person-years[93].

Discussion

To our knowledge, our study is the first to identify a safety signal between bisphosphonates and nonhealing femoral fractures within the FAERS database. In March 2010, the FDA had stated that it was not able to identify a safety signal involving bisphosphonates and atypical femoral fractures within this database[90]. In the published case series, 26% of atypical femoral fractures were reported to have delayed fracture-healing[27,53,94-96]. Some of the nonhealing femoral fractures in the FAERS database could well be atypical femoral fractures. Analyses of adverse events with use of the Naranjo criteria identified atypical femoral fractures as a possible or probable adverse reaction to bisphosphonate therapy. Although atypical femoral fractures were not evident in premarketing clinical trials[12,97], such trials have limited subject numbers because they focus on efficacy, and they can thus identify only the most common adverse drug reactions. A median of seven years elapses between the time of drug approval and the time that notifications of serious adverse drug reactions are disseminated by pharmaceutical companies or the FDA[98]. Furthermore, Ioannidis and Lau showed that safety reporting in pharmaceutical clinical trials is largely inadequate[99].

There are several policy implications related to our findings, including an expected negative impact on the bisphosphonate prescribing patterns of health-care providers, concerns about long-term safety of patients who use bisphosphonates, the need for evidence-based clinical protocols for long-term use of bisphosphonates, and increased medical liability. Negative reporting in the media about bisphosphonates resulted in a decrease in bisphosphonate use by 29,633 individuals in Australia, and this was projected to result in an estimated seventy hip fractures, sixty other fractures, and fourteen deaths[8]. It is feared that concerns about bisphosphonate safety and the attendant decrease in prescriptions and reimbursement for bisphosphonate use might erase the 30% reduction in hip fracture incidence in the U.S. that has been attributed to bisphosphonates[5]; these concerns are especially important given the aging of the population[4].

Bisphosphonates are highly effective medications that increase bone mass and prevent fractures in individuals with osteoporosis. They prevent functional decline associated with fractures, prevent hospitalizations, and reduce disability, need for long-term care, and mortality[5,100-104]. Bisphosphonates are important in the treatment of cancer patients as they delay the onset of metastasis and reduce the risk of skeletal-related events, and they also palliate or control bone pain in multiple cancer types, thus preserving quality of life[105]. Preclinical studies suggest that bisphosphonates may have antitumor activity[106,107]. Zoledronic acid improves disease-free survival and overall survival, reduces the persistence of circulating and disseminated tumor cells, and decreases residual invasive tumor size in patients with early breast cancer and myeloma[108]. These data suggest that, in addition to providing benefits related to prevention of skeletal fractures, zolendronate may also potentially provide clinically meaningful benefits through anticancer activity[109].

We highlight the timeline of safety notifications by the EMA and ADRAC in 2008 and Health Canada and the FDA in 2010[90]. The ASBMR task force produced a case definition that will assist in future identification of cases (Table I)[38]. Following the occurrence of bisphosphonate-associated osteonecrosis of the jaw and atypical femoral fractures, clinicians appear to have begun using intermittent bisphosphonate therapy, in which

treatment with a bisphosphonate for five years is followed by a "drug holiday" to minimize long-term drug exposure[110]. It is noteworthy that no specific clinical guidelines for drug holidays have been published.

Class-related toxicities of bisphosphonates are anticipated, as is the case with osteonecrosis of the jaw111. Therefore, greater pharmacovigilance involving bisphosphonates is required. Collaborative research partnerships among orthopaedic surgeons, bone and mineral metabolism clinicians and scientists, and pharmacovigilance teams are essential. Although the FAERS received reports of bisphosphonate toxicity as early as 1996, there is generally a substantial delay before information of this nature becomes publicly available. In contrast, investigators rapidly reported bisphosphonate-related case series in peer-reviewed specialty publications. This highlights the critical importance of the observant clinician in pharmacovigilance. Comprehensive reporting on a small number of cases can identify a safety signal[14,113]. Initiatives by the RADAR group have identified safety signals in a number of severe adverse drug reactions (pure red cell aplasia[15,114], clopidogrel-associated thrombotic thrombocytopenic purpura[115], and osteonecrosis of the jaw[112]) on the basis of less than 100 cases; conversely, pharmacovigilance by the FDA and pharmaceutical manufacturers focuses on mining large data sets.

The association of atypical femoral fractures with bisphosphonate use is evident on the basis of a number of criteria and is strengthening by the likelihood of causality[116,117]. The existence of this rare adverse drug reaction is also supported by the entire preclinical science regarding bisphosphonate in bone. Most of the reported cases have been attributed to alendronate, the most commonly prescribed and longest-marketed bisphosphonate. It is unlikely that this is due to greater exposure as the proportional reporting ratio takes into account the number of nonhealing femoral fractures reported and total number of reports associated with the drug compared with the number of such fractures reported and total number of reports associated with all other drugs. Therefore, the longer a drug is marketed and the greater its use, the larger the number of reports becomes in all boxes of the cross-tabulation analysis simultaneously.

Limitations of this study include the risk of reporting bias in the original case reports[118] and case series, incomplete retrieval of identified research, the limited quality of the FAERS reports, and publication bias. Selective reporting within studies is also a limitation; for instance, we were not able to review radiographs, identify the duration of or compliance with bisphosphonates therapy, or have access to clinical data. Additionally, patient identifiers in these reports have been removed, which further limits the ability to eliminate redundancy. There may be reporting bias in reports from academic centers; however, there is little evidence of duplication in published cases from these sources. Limitations of the PRR and EBGM techniques stem from the voluntary nature of adverse drug reaction reporting to the FDA. It is estimated that <10% of adverse drug reactions are reported to MedWatch. The PRR or EBGM methodology represents an estimate of the comparative reporting rates for specific reactions to individual drugs, and these rates may be affected by external factors. Therefore, the PRR or EBGM results are not used as definitive evidence of the reaction, but rather as findings that must be combined with supporting information to serve as a signal that a direct relationship between the drug and reaction exists[115].

In conclusion, nonhealing femoral fractures are associated with bisphosphonate use. These fractures may be related to atypical femoral fractures, a rare adverse reaction to prolonged bisphosphonate therapy. Hip fracture rates and consequent morbidity and mortality among older adults in the U.S. have declined by 30% coincident with the use of bisphosphonates[1-5]. The benefits of bisphosphonates are 100-fold greater than the risk of atypical femoral fractures. Further research in this area is needed, such as further evaluation of the incidence of this adverse drug reaction, the creation of an international registry for bisphosphonate-related atypical femoral fractures, the development of novel imaging technologies to identify impending fractures, the development of predictive clinical models for the development of atypical femoral fractures, and genetic studies to identify genetic variants associated with atypical femoral fractures. In the final analysis, a better understanding of the mechanisms leading to these atypical femoral fractures may enable us to develop prediction rules for this uncommon adverse drug reaction and to stratify and target our care accordingly.

Appendix

eA A table summarizing case reports of atypical femoral fractures and a more detailed description of pharmacovigilance analysis tools are available with the online version of this article as a data supplement at jbjs.org. ■

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