Benefits and Risks of Bisphosphonate Therapy for Osteoporosis

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Context: There has been considerable concern recently in the scientific and lay media regarding the benefits *vs.* the risks of bisphosphonates for the treatment of osteoporosis. Risks include possible associations with osteonecrosis of the jaw (ONJ) and atypical femur fractures. In this perspective, we review the use of bisphosphonates for the treatment of osteoporosis, including an objective assessment of the risks *vs.* the benefits of these drugs.

Evidence Acquisition: Authors' knowledge of the field and results of focused literature searches are presented.

Evidence Synthesis: Bisphosphonates have proven efficacy in the prevention of bone loss and in the reduction of fractures in postmenopausal women and men with established osteoporosis. Although bisphosphonates, at doses used to treat osteoporosis, may be associated with an increased risk of ONJ and atypical femur fractures, many more fractures are prevented by the use of these drugs compared to the relatively low risk of these complications. Although oral bisphosphonates are associated with upper gastrointestinal side effects and iv bisphosphonates with acute phase reactions, the association of bisphosphonate use with esophageal cancer and atrial fibrillation is not well supported by current data.

Conclusions: Bisphosphonates have been proven to prevent fractures in patients with established osteoporosis or those who are at high risk of fracture. In contrast, the incidence of major complications associated with bisphosphonate use, such as ONJ and atypical femur fractures, is very low. (*J Clin Endocrinol Metab* 97: 2272–2282, 2012)

This position statement is intended to serve as a guide for clinical endocrinologists as well as other physicians regarding the use of bisphosphonates for the treatment of osteoporosis. It reflects the expert opinion of the authors (independent of The Endocrine Society or any other organization) and summarizes the benefits of bisphosphonates for patients at risk for osteoporotic fractures and also their potential for adverse effects. These include esophageal disease, atrial arrhythmias, osteonecrosis of the jaw (ONJ), and atypical femur fractures. A possible association of these adverse events with bisphosphonate use has led physicians and patients to question whether their potential risks outweigh the predictable antifracture benefits of this class of drugs. The most recent topic of concern is atypical femur fractures in patients taking bisphosphonates, as outlined in a recent report by a task

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Abbreviations: BMD, Bone mineral density; CTX, C-terminal telopeptide of type I collagen; eGFR, estimated glomerular filtration rate; ONJ, osteonecrosis of the jaw.

force of the American Society for Bone and Mineral Research (ASBMR) (1). The evidence associating bisphosphonate use with these events will be critically assessed. The thesis of the article is that the risk of serious complications associated with bisphosphonate use for osteoporosis is very low, particularly when viewed in the context of their proven benefits for fracture risk reduction in patients with osteoporosis or those who are at high risk for fracture.

Pharmacology and Mechanism of Action

Bisphosphonates are synthetic analogs of naturally occurring pyrophosphates in which the oxygen atom in the latter has been replaced by a carbon atom in the bisphosphonate molecule. Their general formula is shown in Fig. 1 with R_1 and R_2 representing side chains. The R_2 position is the site that has given rise to the different bisphosphonate molecules, whereas the R_1 position is invariably a hydroxyl group. Currently approved bisphosphonates for the treatment of osteoporosis act by inhibiting bone resorption with a consequent increase in bone mass largely due to refilling of the remodeling space and an increase in mineralization density. The compounds used are primarily nitrogen-containing compounds with nitrogen atoms in the side chain at R_2. The nitrogen is found in the straight alkyl chain (*e.g.* alendronate, ibandronate) or as part of a cyclized aromatic ring (risedronate, zoledronic acid). The nitrogen-containing bisphosphonates are administered orally (alendronate, risedronate, ibandronate) or iv (zoledronic acid, ibandronate). Absorption of oral bisphosphonates is low (0.6–1.5% of the administered dose). Bisphosphonates bind avidly to bone mineral with no substantial affinity for other tissues. About 40–60% of the dose distributes to bone, the remainder is excreted unchanged in the urine, and there is no substantial metabolism (2). This preferential uptake into bone affords bisphosphonates a high degree of target organ specificity.

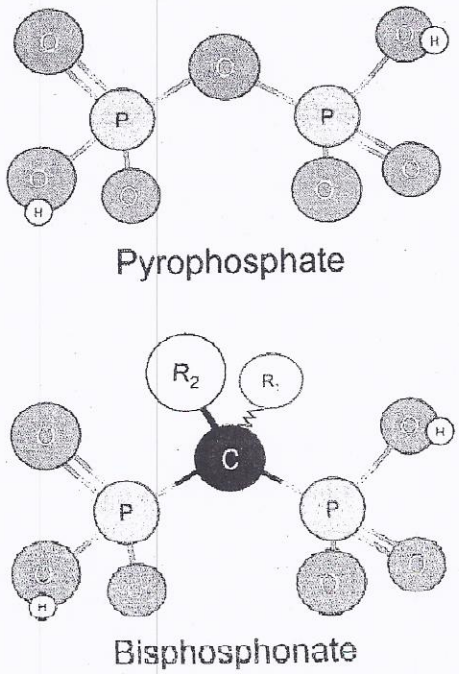


FIG. 1. Chemical structure of bisphosphonates compared with pyrophosphate.

Over the past 40 yr, much progress has been made in elucidating the mechanism of action and structure-function relationships of the bisphosphonates (3, 4). After adsorption to bone mineral, bisphosphonates are targets for uptake by osteoclasts where they inhibit a key enzyme in the mevalonic acid pathway, farnesyl pyrophosphate synthase. Inhibition of farnesyl pyrophosphate synthase blocks prenylation (posttranslational modification) of small GTPases, such as Ras, Rho, and Rac, which are signaling molecules in key osteoclastic functions such as maintenance of the cytoskeleton and ruffled border formation. Non-nitrogen-containing bisphosphonates (*e.g.* clodronate, etidronate) inhibit osteoclast function by a mechanism involving the accumulation of nonhydrolyzable ATP analogs, which disrupt cellular function and promote apoptosis.

Bone Histology after Therapy

Bisphosphonates lower fracture risk in large part by reducing the rate of bone remodeling and associated microarchitectural deterioration of bone as well as by increasing bone mass. Bone biopsy data from human subjects confirm this mechanism of action and document the absence of histological abnormalities (5), with the caveat that the available bone biopsy data are all from a non-weight-bearing site (iliac crest). Bone remodeling is the mechanism by which bone repairs microdamage caused by loading (targeted remodeling) and delivers calcium into the circulation (stochastic remodeling) (6, 7). Remodeling rates generally increase 2-fold within 12 months of menopause, triple by age 60, and remain elevated in untreated osteoporosis patients (8). Bone formation rates estimated by tetracycline labeling are reduced in patients on bisphosphonates. Most patients on bisphosphonates show reductions in remodeling to the range seen in healthy premenopausal women (9). Between 1 and 30% of bisphosphonate-treated patients show no tetracycline labels, even after extensive search of biopsy specimens (5, 9–11). However, whereas it is noteworthy that remodeling rates in premenopausal women are much lower than in postmenopausal women and both demonstrate tetracycline labels in bone biopsies

TABLE 1. The FDA registration among the bisphosphonates for fracture risk reduction efficacy according to the FDA registration trial data *vs.* the fracture efficacy among the bisphosphonates derived from nonregistration, pooled data, or observational data

	Evidence from FDA registration trials	Evidence from nonregistration, pooled, or observational data
Alendronate	Vertebral and hip	Vertebral, nonvertebral, and hip
Risedronate	Vertebral and nonvertebral	Vertebral, nonvertebral, and hip
Ibandronate	Vertebral	Vertebral, nonvertebral, and hip
Zoledronic acid	Vertebral, nonvertebral, and hip	Vertebral, nonvertebral, and hip

(10), about 5% of biopsies from untreated osteoporosis patients exhibit no tetracycline labels (10). Thus, it is possible that the subset of bisphosphonate-treated patients who exhibit markedly reduced remodeling may have had reduced remodeling before treatment. Long-term efficacy of bisphosphonates to maintain reductions in overall fracture risk is related to their reduction of bone turnover and the resultant effects on bone mechanical properties (12, 13).

Efficacy in Preventing Bone Loss and Fractures

The primary end-point required for Food and Drug Administration (FDA) approval of therapies for the treatment of postmenopausal osteoporosis is significant reduction in incident morphometric vertebral fractures over 3 yr compared with placebo (14). On the basis of this requirement, all daily oral and one iv bisphosphonate formulation (annual iv zoledronic acid) (15–19) obtained approval for the treatment of postmenopausal osteoporosis. Bisphosphonates also reduce the incidence of nonvertebral fractures, although nonvertebral fracture risk reduction did not reach a level of significance in the pivotal registration trials for either alendronate (15) or ibandronate (20), but did in the risedronate registration trial (18). Hip fracture risk reduction did not reach a level of significance in either the risedronate or ibandronate registration trials (17, 18, 20), but did in the registration trial for alendronate (15). For zoledronic acid, significant reductions in nonvertebral and hip fractures were seen. In non-registration trials, pooled/observational data sets, or *post hoc* analyses, all amino-containing bisphosphonates show evidence of fracture risk reduction at hip and other nonvertebral sites (21–24) (Table 1). Figure 2 shows the relative risk reduction for vertebral and hip fractures in postmenopausal women with known osteoporosis after 3 yr of therapy with the currently approved bisphosphonates, alendronate (15), risedronate (18, 21), ibandronate (20), and zoledronic acid (19). Point estimates of relative vertebral fracture risk reduction range from 40–70%, and relative hip fracture reduction ranges from 40–50% with these drugs. However, because there has never been a head-to-head fracture study comparing bisphosphonates, there is no basis for concluding that one bisphosphonate is superior to another (25). Overall, the data clearly demonstrate that bisphosphonates reduce the incidence of osteoporotic fractures in appropriately selected individuals.

The approvals for most non-daily bisphosphonate dosing regimens (weekly oral, monthly oral, and quarterly iv ibandronate) were not obtained on the basis of data showing fracture risk reduction, but rather according to "bridging studies." These studies have used bone mineral density (BMD) as a primary end-point and bone turnover markers as a secondary end-point. Approval of these non-daily dosing regimens is based on the expectation that an equivalent increase in BMD and/or reduction in bone turnover mediated by identical molecular structures conveys equivalent fracture reduction (14, 26).

There is a nonlinear relationship between the effect of bisphosphonate treatment on BMD and the magnitude of fracture risk reduction (27–30). As such, there are other mechanisms, not related to a change in BMD, whereby bisphosphonates increase bone strength (31–33). Thus, no change in BMD after initiation of bisphosphonate therapy is an acceptable outcome, assuming that secondary conditions that could mitigate a therapeutic response are not present (34). The reduction of

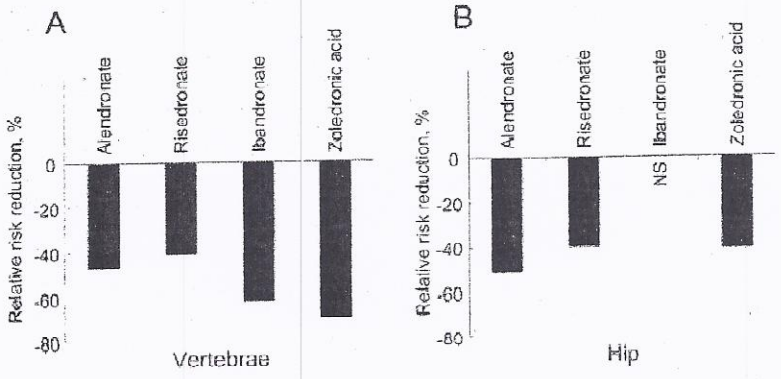
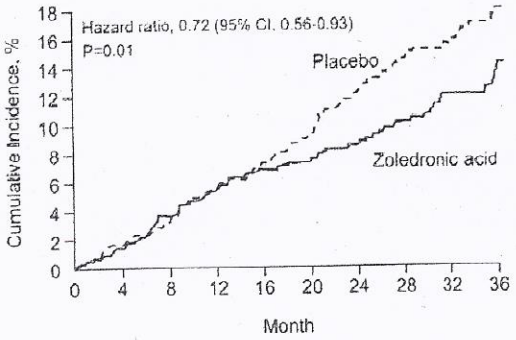


FIG. 2. Relative risk reduction for vertebral (A) and hip (B) fractures in postmenopausal women with known osteoporosis after 3 yr of bisphosphonate treatment. Data for alendronate are from Black *et al.* (15); for risedronate, from Harris *et al.* (18) and McClung *et al.* (21); for ibandronate, from Chesnut *et al.* (20); and for zoledronic acid, from Black *et al.* (19). NS, Not significant.

bone turnover to expected levels, although BMD may not have increased, is further evidence for a therapeutic response (29, 35, 36).

Although the evidence for efficacy of bisphosphonates in reducing fracture risk is established, fracture risk is not eliminated. Osteoporotic fractures may occur in patients taking a bisphosphonate. Like other pharmacological interventions for chronic diseases, no drug completely abolishes the end-point of the disease for which the drug is administered—in this case, bisphosphonate use for fracture risk reduction. This reality does not diminish the value of bisphosphonates in those patients who meet criteria for treatment. Although the bisphosphonate registration trials for postmenopausal osteoporosis included randomized placebo and treated groups through 3 yr, there are longer term bisphosphonate efficacy data: the 5- and 10-yr alendronate data (12, 13); the 10-yr data from the Fracture Intervention Trial (FLEX) (13); 7-yr risedronate data (37); the long-term ibandronate extension data (38); and the 6-yr zoledronic acid data (39). In some (37, 39), a placebo group was maintained. In none of the extension studies was the total initial randomized population included, so there is selection bias in the extension data. Only in the first 5 yr of the risedronate study (37) was the original placebo-randomized population continued. In addition, the long-term extension of the ibandronate trial included no prespecified fracture end-points. Nevertheless, the long-term bisphosphonate data we have suggest that maintenance of fracture benefit (incident rates) through 5 yr is comparable to the risk reduction seen during the first 3 yr of the randomized trial. Hence, despite the limitation of trial design with extension studies, where maintenance of a placebo group may be an ethical issue in higher risk patients, the data would suggest that antifracture benefit is maintained with 5 yr of bisphosphonates (or 6 yr from the zoledronic acid extension data).

Osteoporotic fractures at many sites are associated with increased mortality (40). The reduction in fractures by bisphosphonates might be expected, therefore, to be associated with reductions in the mortality as well as morbidity associated with hip fractures. Data from studies with zoledronic acid in the post-hip fracture population (Fig. 3) and other bisphosphonates have shown that overall mortality is reduced, although whether this is due to the reduction in hip fractures or an independent effect of bisphosphonates on mortality is unclear (41, 42). Nevertheless, the data that these drugs may be associated with a reduction in overall mortality in the post-fracture setting show another potential therapeutic benefit.



No. at Risk

Zoledronic acid	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

FIG. 3. Reduction in all-cause mortality over 3 yr after therapy with iv zolendronic acid in the HORIZON trial. [Reproduced from K. W. Lyles *et al.*: Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357:1799–1809, 2007 (41), with permission. © Massachusetts Medical Society.]

Complications

Renal, esophageal, and acute phase reactions

Approximately 50 to 60% of administered bisphosphonate is excreted unchanged by the kidneys, with the remainder taken up by bone. Renal toxicity due to iv bisphosphonates is related to the maximum drug level achieved and not the area under the curve of drug exposure (43, 44). Use of other agents that have nephrotoxic potential such as nonsteroidal antiinflammatory drugs or diuretics or the presence of preexisting renal impairment and dehydration at the time of bisphosphonate infusion increase the risk for renal toxicity with iv bisphosphonates. To avoid compromise of renal function, bisphosphonates should not be given to patients with an estimated glomerular filtration rate (eGFR) of 30 ml/min or less. For zoledronic acid, the threshold is less than 35 ml/min, and eGFR should be assessed before each infusion (45). Drug should be administered using the recommended dose and infusion time. In the phase 3 (HORIZON-Pivotal Fracture Trial) study, postmenopausal women treated with zoledronic acid demonstrated mild increases in serum creatinine in a renal safety subset measured 9–11 d after infusion, but there was no difference in eGFR in drug- *vs.* placebo-treated patients over the course of the registration trial (46) or in the 6-yr extension data (13, 39, 48). Intravenous ibandronate, dosed for osteoporosis (3 mg every 3 months), has shown no significant renal toxicity when treated patients have eGFR above 30 ml/min and no baseline renal comorbidities (49). However, there are no head-to-head data to compare renal effects between zoledronic acid and ibandronate.

Oral daily bisphosphonates have been associated with esophageal ulcers, esophagitis, and bleeding; however, these side effects lessened with the advent of weekly (alen-

dronate, risedronate) or monthly (ibandronate, risedronate) preparations (50). Recently, concern has emerged about an association between oral bisphosphonate use and an increased risk of esophageal cancer (51, 52). However, other analyses of population-based cohorts have failed to support that association (53–55). Thus, a link between oral bisphosphonate use and esophageal cancer is not established.

Approximately 18% of patients receiving first doses of iv bisphosphonate experience an acute phase reaction (fever, headache, myalgia, arthralgia, malaise) occurring within 24–36 h and lasting up to 3 d. The incidence is reduced approximately 50% by acetaminophen (500–1000 mg before and for 24–48 h after infusion) and decreases with subsequent infusions (56).

Atrial fibrillation

In the 3-yr HORIZON-Pivotal Fracture Trial (19), subjects treated with zoledronic acid were found to have an increased incidence of atrial fibrillation as a serious adverse event (*i.e.* requiring hospitalization, 1.3% with zoledronic acid *vs.* 0.5% with placebo; $P < 0.001$); the overall incidence of atrial fibrillation, however, was similar between the two groups. There were no significant differences in the rates of stroke, myocardial infarction, or deaths due to cardiovascular events, nor was there any relation to the timing of drug infusion, acute phase reactions, calcium levels, or electrolyte abnormalities. This report prompted additional investigation of the risk of atrial fibrillation in *post hoc* analyses of other trials and reviews of healthcare databases. Only one of these studies (57), a population-based case-control study with alendronate, found any association between the use of bisphosphonates and atrial fibrillation. Zoledronic acid was not associated with an increased risk of atrial fibrillation in the HORIZON Recurrent Fracture Trial (41) (subjects were older and presumably at higher risk for the arrhythmia) or in any of the oncology trials where subjects received zoledronic acid in doses that were approximately 10 times the dose for osteoporosis (*i.e.* 4 mg monthly instead of the dose for osteoporosis, which is 5 mg yearly) (58–60). *Post hoc* analyses of studies with other bisphosphonates, including alendronate (61), risedronate (62), and ibandronate (63), did not show a statistically significant increase in the risk of atrial fibrillation. Although a population-based case-control study in U.S. women suggested an increase in the risk of atrial fibrillation in women with past, but not current, use of alendronate (57), another study in the United States (64), two studies in Denmark (65, 66), and a study in the United Kingdom (67) did not show an increased risk of atrial fibrillation with long-term bisphosphonate use. In their most recent review of these data, the FDA recommends that patients should not stop taking their bisphosphonate medication because of this theoretical concern, stating that "across all studies, no clear association between overall bisphosphonate exposure and the rate of serious or nonserious atrial fibrillation was observed" (68). Thus, the possible association of atrial fibrillation with bisphosphonate use is not well supported by current data.

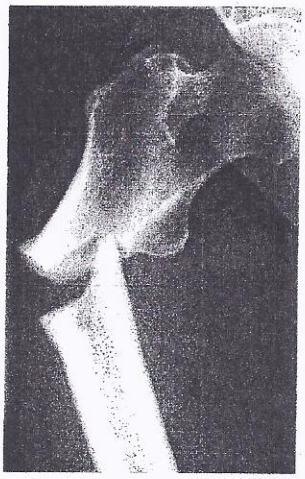
Osteonecrosis of the jaw

ONJ associated with bisphosphonate therapy in cancer patients was reported in 2003 (69) and is now generally recognized as a very rare complication of long-term bisphosphonate therapy at doses used to treat osteoporosis (70). The ASBMR task force on ONJ defined a confirmed case of bisphosphonate-associated ONJ as an area of exposed bone in the maxillofacial region that did not heal within 8 wk after identification by a health care provider in a patient who was receiving or had been exposed to bisphosphonates and had not had radiation therapy to the craniofacial region (Fig. 4) (70). Clinical symptoms and signs of ONJ include pain, swelling, paresthesias, suppuration, along with soft tissue ulceration and intra- or extraoral sinus tracts. Radiographic abnormalities range from none to varying radiolucencies or radiopacities.

The incidence of bisphosphonate-associated ONJ is highest in patients with underlying malignancies who receive high doses of iv bisphosphonates (*e.g.* zoledronic acid, 4 mg iv every 3–4 wk) to decrease the risk of skeletal complications of malignancy: between 1 and 10% of these patients may go on to develop ONJ (70). By contrast, the risk of developing ONJ in patients treated with bisphosphonates (oral or iv) for osteoporosis is much lower, although the precise estimates of risk vary considerably; this problem is further compounded by the absence of robust

FIG. 4. Photograph showing an area of bone exposure (*asterisk*) in a patient with bisphosphonate-associated ONJ. [Reproduced from Y. Morag *et al.*: Bisphosphonate-related osteonecrosis of the jaw: a pictorial review. RadioGraphics 29:1971–1984, 2009 (47), with permission. © Radiological Society of North America.]

TYPICAL Subtrochanteric Fracture
- Spiral pattern
- Substantial comminution
- Thin cortices



ATYPICAL Subtrochanteric Fracture
- Transverse or short oblique orientation
- No comminution
- Thick cortices – focal or generalized

FIG. 5. Radiographic appearance and characteristics of a typical *vs.* atypical subtrochanteric fracture (courtesy of Dr. Melvin Rosenwasser, Columbia University, New York, NY).

population-based data on the risk of ONJ in the absence of bisphosphonate use. The most rigorous epidemiological data come from a population-based study from Germany, which used a central national registry (71). Of the 300 cases of ONJ identified, 97.6% were in patients with underlying malignancy. Based on three identified patients in the registry treated with oral alendronate for osteoporosis and a denominator of 780,000 people in Germany on a bisphosphonate for osteoporosis, the estimated prevalence of bisphosphonate-associated ONJ was approximately 1 in 250,000 (0.0004%) (71). In contrast, several surveys of oral and maxillofacial surgeons have generated higher prevalence estimates (0.001–0.10%) (72–74), perhaps due to selection bias in the survey approach. Overall, however, even using the higher prevalence estimates, the risk of bisphosphonate-associated ONJ appears to be extremely low in patients treated for osteoporosis. In addition to high-dose iv bisphosphonate use, however, certain additional risk factors have been identified that may increase risk even with lower dose bisphosphonate therapy (oral or iv): dental extraction, oral bone-manipulating surgery, poor-fitting dental appliances, intraoral trauma, glucocorticoid use, diabetes, and alcohol abuse (70). Although it has been suggested that low serum C-terminal telopeptide of type I collagen (CTX; a bone resorption marker) levels may identify patients at risk for ONJ (75), the clinical utility of this approach is questionable given that virtually all patients on a bisphosphonate will have reduced serum CTX levels. In addition, some experts suggest stopping the bisphosphonate for a period of time (generally several months) before and after invasive dental procedures, but there are no data to suggest that this approach will improve dental outcomes (70).

Management of ONJ is generally conservative, including pain control and oral antimicrobial rinses to minimize the risk of infection (70). Recent case reports have suggested that stimulating bone turnover with teriparatide may aid resolution of symptoms and healing of the osteonecrosis (76, 77), although this approach needs to be evaluated rigorously using randomized, controlled trials.

Subtrochanteric fractures

Recently, bisphosphonates have been associated with unusual femur fractures (for review, see Ref. 1). In contrast to common femoral neck and spiral intertrochanteric hip fractures, "atypical" femur fractures are located in the subtrochanteric region and shaft regions of the femur and also have radiographic characteristics of stress or fatigue fractures. Incomplete atypical femur fractures have a lucent linear fracture line that originates at the periosteal surface of the lateral cortex, often with localized cortical thickening at the fracture site, termed "beaking," that represents periosteal callus formation. Additionally, a completed atypical femur fracture has a transverse or short oblique (30%) orientation without comminution and a medial spike. There is often generalized cortical thickening of the femoral shaft. Associated hyperemia and marrow edema can be detected by technetium scanning and magnetic resonance imaging. There is a history of prodromal pain in approximately 75%, bilateral fractures in 25–50%, and delayed healing in at least 25% of atypical fractures. These radiographic and clinical features suggest that the pathogenesis is distinct from osteoporotic fractures. Figure 5 provides radiographic examples of typical *vs.* atypical subtrochanteric fractures. Atypical fractures are most commonly reported in patients receiving alendronate, most likely because it is the most widely used bisphosphonate and has been available for the longest period of time. These fractures also have been reported in patients receiving other bisphosphonates. The mean duration of bisphosphonate exposure ranges from 5 to 7 yr, depending on the series. In patients with atypical fractures, there are often comorbid conditions and concomitant drug exposures, including agents other than bisphosphonates such as glucocorticoids or proton pump inhibitors.

Fractures of the subtrochanteric region and femoral shaft comprise 5 to 10% of all hip and femur fractures in the elderly (78, 79), but only 3 to 29% of fractures in these locations have specific radiographic features of atypical

femur fractures (80–82). Thus, atypical femur fractures constitute less than 1% of all hip and femur fractures and are rare compared with the more common classical osteoporotic fractures of the femoral neck and intertrochanteric regions. There were no cases of atypical femur fractures in the registration studies for oral bisphosphonates involving more than 17,000 patients (1). A secondary analysis of all hip and femur fractures that occurred in three large randomized clinical trials of alendronate and zoledronate did not find an increased risk of subtrochanteric or femoral shaft fractures, but given that fractures in this location account for only 5 to 10% of all proximal femur fractures, the study was underpowered (83).

Most registry studies that relied on diagnostic coding, without radiographic review to ascertain specific features of atypical fractures, have not found associations between subtrochanteric and femoral shaft fractures and bisphosphonate use (84–86). A Danish national cohort study found that rates of subtrochanteric and femoral shaft fractures were higher in patients on bisphosphonates than in age-matched controls, with no difference between short-term and long-term users (87). Although two studies found a declining incidence of femoral neck and intertrochanteric fractures (78, 79), one reported a stable incidence (78) and the other a rising incidence of subtrochanteric and femoral shaft fractures, temporally coincident with an increase in prescriptions for bisphosphonates (79). In contrast, Park-Wyllie *et al.* (88) found a significant 2.74-fold (95% confidence interval, 1.25–6.02) increased relative risk of subtrochanteric and femoral shaft fractures in women with more than 5 yr of bisphosphonate use.

Studies that include radiographic review to ascertain atypical features consistently demonstrate associations between atypical femur fractures and bisphosphonates, with very high odds ratios, ranging from 15.33 (81) to 38.5 (89), but have demonstrated that atypical femur fractures also occur in bisphosphonate-naive patients. Although odds ratios describing relative risk are high in a number of studies, absolute risk is uniformly very low. In this regard, Schilcher *et al.* (89) reported an absolute risk of five cases per 10,000 patient-years (95% confidence interval, 4–7), attributable to bisphosphonate use, that decreased 70% per year after stopping bisphosphonates. Park-Wyllie *et al.* (88) reported that in 52,595 women with at least 5 yr of bisphosphonate therapy, a subtrochanteric or femoral shaft fracture occurred in 71 (0.13%) during the subsequent year and 117 (0.22%) within 2 yr. A few case reports and anecdotal findings suggest that teriparatide therapy can improve or hasten healing of these fractures (90, 91).

To summarize, the collective evidence does indicate an association between long-term bisphosphonate use and atypical femur fractures, although the absolute risk of these fractures in patients treated with bisphosphonates appears to be extremely low. A number of possible mechanisms have been proposed whereby bisphosphonates may lead to these fractures (for reviews, see Refs. 1 and 92), but the underlying pathogenesis of these fractures is currently unclear. Of note, bisphosphonate therapy itself does not lead to generalized cortical thickening, raising the possibility that a particular subset of patients who have pretreatment cortical thickening may be predisposed to this complication.

The "Drug Holiday"

Concern about ONJ and atypical femur fractures has led to discussions about the consequences of long-term use of bisphosphonates without an interruption in therapy and the safest duration of therapy in general (93, 94). The concept of a drug holiday has arisen with the goal of providing a hiatus during which reduced bone turnover caused by the bisphosphonate may partially recover (or increase). If the duration and degree of suppression of bone turnover are contributing to, or associated with, the increased risk of complications such as ONJ and atypical femur fractures, then perhaps this drug-free time may reduce risk of these adverse events. However, available data do not clearly point to this pathogenetic sequence. Nevertheless, patients whose fracture risk has clearly been reduced by bisphosphonate therapy (BMD has improved and no fractures have occurred) might be candidates for the drug holiday. On the other hand, in individuals who after 5 yr of continuous bisphosphonate therapy are still regarded to be at high risk for fracture (BMD still very low and/or an intervening fragility fracture has occurred), the drug holiday would not be an attractive option (13, 39, 48). In this situation, the risks of stopping therapy may exceed the risks of continuing therapy. Thus, each case must be individually considered. The optimal length of the drug holiday is also not known. Evidence from several studies has shown that global fracture protection afforded by the bisphosphonate (*e.g.* alendronate or zoledronic acid) is attenuated 3–5 yr after bisphosphonate therapy is discontinued, although there is some residual fracture protection (13, 39, 48). In a typical, albeit empirical, approach, the bisphosphonate is stopped for 1–3 yr until the return of bone resorption markers (*e.g.* CTX) into the mid-range of young adults, when therapy may then be reinitiated. This approach, however, is not validated by evidence, and further data are needed to inform practitioners on this important issue. At an FDA advisory committee meeting held on September 9, 2011, considerable diversity of opinion was expressed on the safety of long-

term bisphosphonate use; although no formal report was issued, the advisory panel voted to recommend that bisphosphonate labels should further clarify the duration of use, without stating what that clarification should be.

Weighing the Benefits and Risks of Bisphosphonate Therapy

In this report, we have considered the risks of bisphosphonate therapy in the context of their proven benefits to prevent disabling osteoporotic fractures. The main focus of discussion with regard to recently reported adverse events of bisphosphonates is ONJ and atypical femur fractures. The evidence for the association of bisphosphonates with esophageal cancer in published data is weak, and there is no clear association between bisphosphonates and atrial fibrillation. Some patients who are at significant risk of osteoporotic fractures and their physicians decide against bisphosphonate treatment because of the potential risks of ONJ or atypical femur fractures. The impression held by some patients and health care professionals is that the risks of ONJ or atypical femur fracture outweigh the demonstrated benefits of bisphosphonates to reduce fractures and their associated complications.

Over 2 million osteoporotic fractures occur annually in the United States. Approximately 300,000 of these fractures are hip fractures. Hip fracture is associated with increases in mortality that exceed 20%, as well as major increases in morbidity (95). During the period 1996–2006, which coincides with the introduction of three bisphosphonates, the reported incidence of hip fractures declined substantially in the United States (78). More recent estimates confirm this impression (http://www.abstracts2view.com/asbmr/view.php?nuASBMR11L). Although one cannot be certain that the downturn in the reported incidence of hip fractures is due to the availability of bisphosphonate therapy for osteoporosis, it is likely that these agents are, at least in part, responsible. With the reduction in hip fractures come substantial benefits in terms of lives saved, morbidity reduced, and reductions in health care costs (96). Thus, because osteoporotic fractures are a major public health problem, the proven benefits of bisphosphonates should also be emphasized.

We recognize, and have identified where appropriate, particular areas of uncertainty and directions for future research. Chief among these are the optimal duration of therapy with a bisphosphonate and the possible efficacy of a drug holiday in mitigating the potential risks of long-term bisphosphonate therapy, including ONJ and subtrochanteric fractures. Additional studies are also needed to examine the possible link between oral bisphosphonate use and esophageal cancer, as well as the possible mechanisms by which bisphosphonates may lead to ONJ and subtrochanteric fractures.

These uncertainties notwithstanding, deciding not to treat a patient with osteoporosis with a bisphosphonate because of the concern for rare associated events such as ONJ and atypical femur fractures places that individual at risk for a fracture with its own dire consequences, including morbidity, loss of independence, and mortality. Given the very low incidence of ONJ and atypical femur fractures in patients treated with a bisphosphonate for osteoporosis *vs.* the marked reduction in risk of fracture associated with these drugs, the risk:benefit ratio clearly favors treating patients at high risk of fracture, such as those with osteoporosis by virtue of a previous hip or spine fracture or BMD T-score below −2.5. The National Osteoporosis Foundation also recommends treatment based on meeting FRAX guidelines (10-yr fracture risk of 3% for hip or 20% for any osteoporotic fracture) (97), although the risk:benefit ratio of this approach needs to be further assessed.

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