Review: Clinical Trial Outcomes

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CLINICAL INVESTIGATION

Long-term extension trials to prove the efficacy and safety of bisphosphonates

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Paul D Miller
University of Colorado Medical School, Medical Director, Colorado Center for Bone Research, 3190 South Wadsworth Boulevard, Lakewood, CO 80227, USA
Tel.: +1 303 980 9985
Fax: +1 303 980 1367
E-mail: millerccbr@aol.com

Bisphosphonates are nonmetabolizable analogs of pyrophosphates. They have a high selectivity to bone remodeling sites, become retained and recycled, providing a long duration of continual effect after discontinuation. Bisphosphonates have been registered for postmenopausal osteoporosis for 20 years. Four bisphosphonates are currently registered for postmenopausal osteoporosis – alendronate, risedronate, ibandronate and zoledronic acid. They were all registered on the evidence of fracture-risk reduction over 3 years compared with placebo. Beyond 3 years, there are very few bisphosphonate data where a placebo group has been maintained and none where the original randomized sample size for registration has been continued. Hence, long-term fracture efficacy data depends on observing the fracture-risk reduction in the group continued on long-term bisphosphonates to the risk reduction observed during the first 3 years of the clinical trial, where the placebo group was maintained. In this regard, long-term bisphosphonate administration seems to maintain a reduction in fracture risk. In addition, with the exception of a low risk of acute renal failure with rapid administration of intravenous zoledronic acid, long-term bisphosphonates are exceptionally safe. The reports of osteonecrosis of the jaw and atypical subtrochanteric femur fractures are associations with long-term bisphosphonates without established causality. Bisphosphonates are highly effective and safe to reduce incident fractures in postmenopausal osteoporosis when used in the right population for the right duration.

Keywords: atypical femur fractures • bisphosphonate drug holidays • bisphosphonates • bone mineral density • bone turnover • fractures • osteonecrosis of the jaw • osteoporosis • renal effects of bisphosphonates

Bisphosphonate discovery spans four decades [1,2] and bisphosphonate registration and utilization in clinical medicine spans nearly two decades. Hence, no other pharmacological agent for the management of metabolic bone disease has the depth and breath of efficacy and safety of use in human beings for osteoporosis management as the bisphosphonates.

Bisphosphonates are biological analogs of naturally occurring compounds, the pyrophosphates. Pyrophosphates are by products of ATP metabolism but have no biological activity because they undergo rapid enzymatic degradation by ubiquitous pyrophosphatases (e.g., acid phosphatase and alkaline phosphatase). Pyrophosphates do accumulate in chronic kidney failure and may have a role in mineralization defects observed in many subjects with chronic kidney disease.

The bisphosphonate core chemical structure backbone is a P-C-P bond, making them nonbiodegradable by pyrophophatases. Bisphosphonates have a high and

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selective affinity for bone binding to the denuded calcium–phosphorus surface that has been exposed to the circulation during bone resorption. Bisphosphonates are not metabolized. They become detached from bone surfaces and reattach to resorptive surfaces continuing their biological activity. All bisphosphonates, as a class, have two similar mechanisms of action to inhibit bone resorption. One mechanism is physiochemical, by binding to the calcium–phosphorus surface in resorption cavity, stabilizing the resorption depth. The second mechanism of action is a cellular one, with the bisphosphonate being phagocytized by the osteoclast, which disrupts the cellular activity of the osteoclast. The differences among bisphosphonates are their affinity for the calcium–phosphorus surface (and rate of detachment) and their ability to inhibit one of the enzymatic pathways in the osteoclast, FPPS [2]. The bisphosphonate with the greatest affinity, lowest detachment and strongest effect on FPPS is zoledronic acid, which explains the ability to extend dosing intervals. Once entering the blood stream, bisphosphonates vanish from the circulation in a few minutes due to their rapid uptake by bone. Unbound or recycled bisphosphonates are excreted in the urine [3]. Renal excretion is accomplished by glomerular filtration and proximal tubular secretion [4,5].

Treatment of postmenopausal osteoporosis: outcome data

Registration for treatment of postmenopausal osteoporosis must first demonstrate fracture-risk reduction over a predetermined time period compared with a placebo group [6–11]. All daily formulations of bisphosphonates achieved this end point.

The intermittent dosing formulations of the oral (weekly or monthly alendronate, risedronate and ibandronate) and quarterly intravenous (iv.) ibandronate were subsequently approved, not on the basis of any fracture data, but on noninferiority end points; that intermittent dosing induced a noninferior increase in spinal bone mineral density as the fracture-proven daily dosing [12–14]. Because there are no head-to-head studies with fractures as a prespecified end point, clinical differences among bisphosphonates are unknown.

US FDA-approved indications differ among bisphosphonates, if they do not meet registration agencies predetermined end points. The minimal FDA prerequisite for registration, for any bisphosphonate, is evidence of fracture reduction over 3 years, compared with placebo, but the type of fracture is not prespecified. In addition, as clinical trials matured in their required primary or secondary end points, studies became powered for the desired end point. While alendronate is registered for reduction in vertebral and hip fractures; risedronate for vertebral and nonvertebral fractures; ibandronate for vertebral fractures, and zoledronic acid for all three (global) risk reduction, there is no plausible reason not to believe that all bisphosphonates may have global fracture risk reduction [15–18]. Several observational database analyses of bisphosphonate efficacy suggests reduction in all fracture types by all registered bisphosphonates [19–22]. As patients gain a better understanding of the large benefit of bisphosphonate therapy, better persistence and adherence to therapy may result in better outcomes [23–25].

While fracture-risk reduction is the best evidence for efficacy, clinicians use surrogate markers of bone strength that show earlier and faster changes with therapy to assess effectiveness of treatment. Surrogate markers of improvements in bone strength, such as increases in bone mineral density (BMD) and/or reduction in bone turnover markers are useful but imperfect indicators of changes in bone strength, since fracture-risk reduction may be seen in clinical trial subjects whose bone density remains stable when compared with the placebo group who lose BMD [26–28]. However, data from the extension of the zoledronate postmenopausal osteoporosis registration clinical trial suggest a nearly linear relationship between the increase in total hip BMD and reduction in fracture risk [29]. Furthermore, there was an independent robust contribution observed between the reduction in the resorption bone marker C-telopeptide and fracture-risk reduction; an observation suggested several years ago from two meta-analysis examining this relationship [30,31]. Certainly, while fracture-risk reduction remains the most important clinical outcome, surrogate markers (both changes in BMD and bone turnover markers) are important measurements used in clinical practice to monitor bisphosphonate efficacy [28,32].

Bisphosphonate clinical trials were originally powered for 3-year end points. What about effects on fracture-risk reduction beyond 3 years of use? The bisphosphonate clinical trials all have extension data beyond the initial preplanned 3-year registration trial, yet none has maintained the initial randomized population sample size for which the power calculations for fracture-risk reduction were performed [33–38]. Hence, evidence for continued efficacy beyond 3 years is limited by drop-outs and the selection bias that is fundamentally inherent in subset analysis. In addition, in the two extension trials that had a re-randomized population, the primary end point was changed to BMD rather than fracture-risk reduction, which is one of the reasons the FDA discounted all data from any of the extension studies [39].

The alendronate and zoledronate extension clinical trials are the two trials that used a re-randomized withdrawal study design, where the extension population was re-randomized in a blinded fashion that may be

more robust, hence, these two trials should be examined in detail since they form the efficacy basis for the analyses that make recommendations concerning the duration of bisphosphonate use [39,40].

In the FLEX trial, patients were given alendronate for 10 years, or for 5 years then off therapy for 5 years [33]. In addition, there was a placebo group that had 5 years of alendronate then no further therapy for 5 years. Fracture rates stayed down during the second 5 years of alendronate, comparable to the first 5 years of the initial randomized trial. In those subjects who were on 5 years then came off for 5 years, hip BMD declined a small but significant amount and the collagen crosslink, C-telopeptide, increased 30% from baseline within 1 year of discontinuation. The C-telopeptide then plateaued so that by the end of the 5-year 'off-therapy' it was still 32% higher than the continuation group and below the pretreatment baseline value. There were no differences in morphometric or nonvertebral fracture events at 10 years between the two groups in FLEX. There were fewer clinical vertebral fractures in the long-term treated group (55%) that met statistical difference from the placebo group (2 vs 5%) (Figure 1) [33]. These data suggest that there is an increase in clinical vertebral fracture risk after stopping 5 years of alendronate. This greater risk was seen in the FLEX population with and without prevalent vertebral compression fractures and whose T-score entering FLEX was -2.0 or lower. In a *post hoc* analysis of the FLEX data, nonvertebral fracture-risk reduction was also observed in the subset of patients without prior vertebral compression fractures, however, only in those with T-scores entering FLEX of -2.5 or lower at the femoral neck hip [34].

The zoledronate ('HORIZON') extension data did not have a placebo group that continued off therapy from the original 3-year pivotal trial [37]. This extension trial had two arms; the continuation arm, which received 6 years of zoledronate ('Z6') administration, and the discontinuation group, which received the initial 3 years of zoledronate then went to placebo ('Z3P3'). In the discontinuation group there was a significantly greater increased risk of morpho-metric vertebral fractures compared with the group that continued with 6 years of zoledronate. Since all of the subjects in the HORIZON registration trial had prevalent vertebral fractures, the continuation efficacy is confined to those higher-risk patients with vertebral compression fractures. The numbers of morphometric vertebral compression fractures were too small to assess a specific T-score level where efficacy was maintained or lost.

In a *post hoc* pooled analysis of 5-year fracture data from the ibandronate clinical trials, it was found that time-to-fracture for all clinical fractures, nonvertebral fractures and clinical vertebral fractures were significantly longer for women with postmenopausal osteoporosis treated with monthly oral or iv. ibandronate with a calculated annual cumulative exposure ≥10.8 mg compared with those receiving placebo [38], although the placebo rates were derived from a different clinical trial – the lower dose iv. ibandronate trials [41]. The doses of ibandronate regimens that showed this global fracture efficacy include the marketed monthly oral 150 mg and quarterly iv. 3 mg regimens. These pooled higher dose ibandronate data suggest that the initial ibandronate registration trial ('BONE') may have under dosed the level needed to see a hip fracture reduction [10].

Hence, the extension data are limited, not by the duration of exposure to bisphosphonates (up to 7 years for risedronate) [36], but by the lack of any long-term placebo group where the initial randomized population was maintained. Therefore, the FDA's critique of "lack of long-term efficacy data" for bisphosphonates is rather unfair since there will never be a long-term study where the placebo group is retained in subjects at high risk for fractures. The long-term maintenance of the reduction in fracture rates in FLEX subjects, without prevalent vertebral fractures to similar degrees as the initial placebo-controlled randomized population, is reassuring that a long-term benefit of bisphosphonates may be maintained after 5 years of use. In addition, the large observational studies provide reassurance with regards to the long-term benefit of bisphosphonates with continual exposure.

Bisphosphonate safety

Bisphosphonates are exceptionally safe medications [42,43]. Treatment in millions of patients worldwide has been associated with side effects but no clear toxicity as pharmacologically defined, with the exception of rare

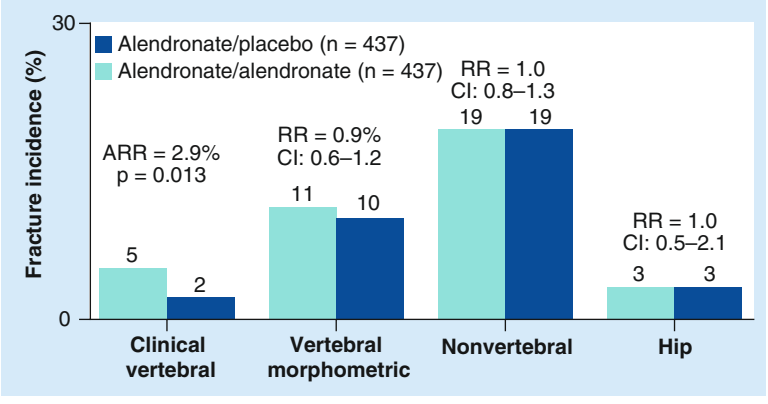

Figure 1. The risk for clinical vertebral fractures, morphometric vertebral fractures, nonvertebral fractures and hip fractures from the FLEX trial.
ARR: Absolute risk reduction; RR: Relative risk.
Reproduced with permission from [32].

effects on renal function with rapid infusion of the iv. bisphosphonate, zoledronic acid. The safety issues to be highlighted are gastrointestinal adverse effects, including esophageal cancer; musculoskeletal side effects; acute phase reaction; atrial fibrillation; renal safety; osteonecrosis of the jaw (ONJ) and atypical femur fractures.

■ Gastrointestinal adverse effects & esophageal cancer

Esophageal ulcers, esophagitis and bleeding have been associated with oral daily bisphosphonates; however, these potential side effects – anecdotal or epidemiological reports – have lessened with the advent of weekly (alendronate, risedronate) or monthly (ibandronate, risedronate) preparations [44]. Nevertheless, upper gastrointestinal side effects have been the major cause of discontinuation of oral bisphosphonates. Concern has emerged about an association between oral bisphosphonate use and an increased risk of esophageal cancer, a concern that remains invalidated. The bulk of evidence points away from an association between bisphosphonate and esophageal cancer. Further studies looking at the potential risk for carcinogenicity are clearly needed; nevertheless, the current data do not support a causal association between oral bisphosphonates and esophageal carcinoma.

■ Musculoskeletal side effects

Musculoskeletal pain has been reported with all bisphosphonates [45]. The pain is usually diffuse and can range from a spectrum of mild and transient pain to severe and prolonged pain. There is no evidence that bisphosphonates induce rhabdomyolysis or elevated CPK levels. While this may be a class effect, some patients may tolerate one bisphosphonate better than another. The musculoskeletal side effect usually disappears within days after stopping the bisphosphonate.

■ Acute-phase reaction

Approximately 10% of treatment-naive patients receiving their first doses of iv. bisphosphonate (or high-dose oral) experience an acute-phase reaction (fever, headache, myalgia, arthralgia and/or malaise) occurring within 24–36 h and lasting up to 3 days [46]. The incidence is reduced approximately 50% by acetaminophen (500–1000 mg before and for 24–48 h postinfusion) and decreases in incidence and severity with subsequent infusions.

■ Atrial fibrillation

In the 3-year HORIZON Pivotal Fracture Trial [11], subjects treated with zoledronic acid had an increased incidence of serious adverse events of atrial fibrillation (1.3% with zoledronic acid vs 0.5% with placebo; $p < 0.001$). 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 other electrolyte abnormalities. This report prompted additional investigations of the risk of atrial fibrillation in *post hoc* analyses of other bisphosphonate trials and reviews of healthcare databases. None of these studies found an 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 (subjects were older and presumably at a higher risk) [47]. Similarly, there was no increase in the rate of atrial fibrillation in an extension of the HORIZON pivotal trial [37], nor in any of the oncology trials where subjects received zoledronic acid in doses that were approximately ten-times the dose for osteoporosis (i.e., 4 mg monthly instead of the dose for osteoporosis, which is 5 mg yearly). *Post hoc* analyses of studies with other bisphosphonates, including alendronate, risedronate, and ibandronate, did not show a statistically significant increase in the risk of atrial fibrillation [10]. Population-based case-control studies are conflicting, some showing an increase in the risk of atrial fibrillation in women with past (but not current) use of alendronate, others showing no increased risk [48–53,101]. Besides a dearth of data associating bisphosphonates with atrial fibrillation, there is no clear biologically plausible mechanism by which this might occur. 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." Therefore, the issue of atrial fibrillation as being possibly associated with bisphosphonate use is not established.

■ Renal safety

Oral bisphosphonates are not nephrotoxic and, in fact, are effective at reducing fracture risk without any negative effects on renal function based on *post hoc* analyses in patients with an estimated glomerular filtration rate (eGFR) as low as 15 ml/min [54–56]. The FDA warning not to use bisphosphonates in patients with an eGFR <30 or 35 ml/min (for iv. zoledronic acid) is based on the lack of data in this population. Approximately 50–60% of administered bisphosphonate is excreted unchanged by the kidneys, with the remainder taken up by bone. Rapid infusion of iv. bisphosphonates may induce acute renal failure, especially in patients with reduced renal function or who are underhydrated. Use of other agents that have nephrotoxic potential, such as nonsteroidal anti-inflammatory drugs or diuretics, also increase the risk for renal dysfunction. To avoid

compromise of renal function, bisphosphonates should not be given to patients with reduced glomerular filtration rate (≤30 ml/min for risedronate and ibandronate, <35 ml/min for alendronate and zoledronate). Zoledronate should never be administered in <15 min and, if there are any concerns, a slower infusion time (30–60 min) seems to be an even safer approach. Though the FDA specifically states measuring creatinine clearance before each zoledronic acid infusion, eGFR calculation is also acceptable. In the Phase III HORIZON study, a small but significant number of postmenopausal women treated with zoledronic acid demonstrated increases in serum creatinine concentration 9–11 days after the second infusion; the serum creatinine concentration returned to normal before the next infusion and there were no difference in eGFRs in drug- versus placebo-treated patients over the course of the trial [57]. In the 3-year extension data (6 years of zoledronic acid therapy), there were no differences in eGFR between placebo and annual zoledronic acid (Figure 2) [58]. Ibandronate iv., dosed for osteoporosis (3 mg every 3 months), has shown no significant renal toxicity if treated patients have eGFRs >30 ml/min and no baseline renal comorbidities [59].

Despite the lack of evidence regarding the use of bisphosphonates in patients with severe renal impairment and end-stage renal disease (glomerular filtration rate <15 ml/min), treating patients suffering fragility fractures with bisphosphonates for up to 3 years should be considered, but only after the diagnosis of osteoporosis is confirmed by a bone biopsy, since such patients may have fractures due to other forms of metabolic bone disease (e.g., renal osteodystrophy) [60–62].

■ Osteonecrosis of the jaw

ONJ is defined as exposed necrotic bone in the maxillofacial region not healing after 8 weeks in patients with no history of craniofacial radiation [63]. It has been described in patients receiving chronic bisphosphonate therapy, as well as subjects not using bisphosphonates. The incidence is estimated to be 0.7 per 100,000 patient-years exposure, although it is difficult to get accurate estimates because not all cases of ONJ are reported and not all cases reported are truly ONJ. Risk factors for developing ONJ include invasive dental procedures and pre-existing dental disease, cancer and anticancer therapy, severe immunosuppression, iv. bisphosphonates, duration of exposure to bisphosphonate therapy, glucocorticoids and smoking. A causal link between bisphosphonate use and ONJ has not been established, although it appears to be likely. Despite a number of potential mechanisms, including over-suppression of bone turnover, the pathophysiology of ONJ remains poorly defined.

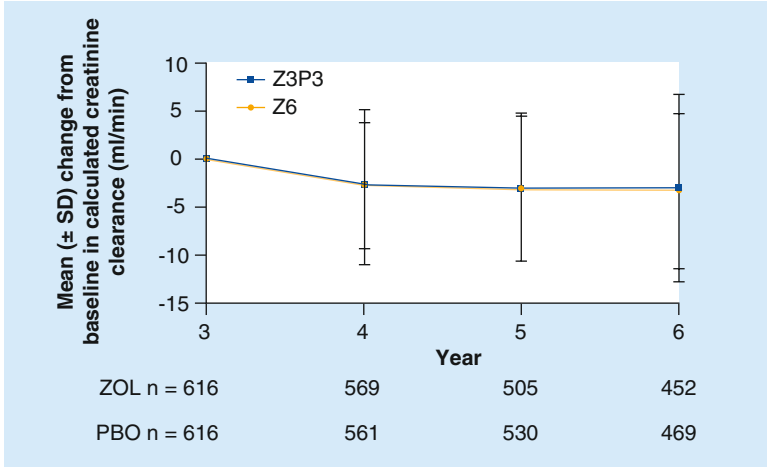

Figure 2. The changes in estimated glomerular filtration rate between the treated and PBO groups in the long-term ZOL extension trials.
PBO: Placebo; ZOL: Zoledronic acid.
Reproduced with permission from [57].

Although the guidelines published by the dental societies suggest to discontinue the oral bisphosphonate for 3 months prior to performing the dental surgery, if a patient has been treated for more than 3 years (aiming to restart the bisphosphonate when the bone has healed), there is no evidence to support that this would lower ONJ risk, especially since bisphosphonates stay in bone for years [64,65]. Patients considering dentoalveolar surgery while taking bisphosphonates should be advised of the risks and alternatives.

■ Atypical femur fractures

Atypical subtrochanteric femur fractures are unusual femoral fractures that are typically associated with minimal or no trauma, have been seen without bisphosphonate use, although the risk seems to be greater with longer duration of bisphosphonate use [66,67]. The risk rises from two/100,000 cases of patient-years exposure with 5 years of bisphosphonate use to 100/100,000 patient-years exposure with 10 or more years of bisphosphonate use. Despite these associations, no causality has been established between bisphosphonates and atypical subtrochanteric femur fractures. These fractures present with prodromal pain in the region of the fracture that is a persistent pain, not mitigated by any body position, and have characteristic radiographic findings including; cortical hypertrophy, a transverse fracture pattern and medial cortical spiking (Figure 3) [42]. The early radiological changes and 'beaking' of the cortex in patients with bisphosphonate-associated atypical femur fractures may also be seen by dual energy x-ray absorptiometry if the region of interest of the dual energy x-ray absorptiometry is lowered to the midshaft femur

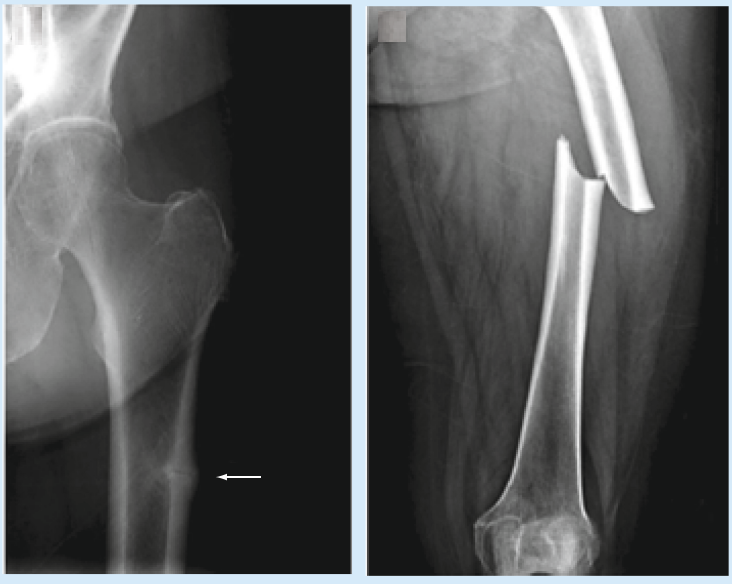

Figure 3. The radiological changes seen with bisphosphonate associated atypical subtrochanteric femur fractures.
Reproduced with permission from [41].

region [68]. The initial American Society for Bone and Mineral Research task force criteria for defining subtrochanteric femur fractures (Box 1) have been modified to include as a major criteria the periosteal lateral cortex reaction and allows for minimal comminution of the fracture pattern [66,69].

The risk for these fractures drops off greatly after bisphosphonate discontinuation, even though the bisphosphonate is being recycled in the circulation [67]. However, the risk does not completely go away so patients on or off bisphosphonates should still be advised of the prodromal symptoms that may predate the fracture. If such typical symptoms appear, x-rays or, if needed, femur MRI or computerized tomography should be done to identify early radiological changes. Identification of an early lateral cortical fracture should lead to discontinuation of the bisphosphonate, followed by methods of reducing impact on the affected limb and consultation with orthopedic surgeons concerning surgical support.

Finally, it should be kept in mind the benefit that bisphosphonate development has had on reducing the rates of typical hip fractures. It seems that for each bisphosphonate-associated atypical femur fracture that occurs, approximately 60 typical hip fractures are saved, compared with nonbisphosphonate-treated patients [70]. In addition, prior to bisphosphonate development the rate of typical hip fractures was approximately 463/100,000 patient-years and was even higher in the clinical trials where subjects had pre-existing morphometric vertebral fractures (800/100,000 patient-years) [67]. After bisphosphonate registration for postmenopausal osteoporosis, the typical hip fracture rate decreased to 384/100,000 patient-years but then has increased again to 544/100,000 patient-years with discontinuation of bisphosphonates in epidemiological data. This benefit–risk ratio for these hip fractures events can also be adjusted according to the patient's baseline fracture risk; higher risk patients receive a higher benefit–risk ratio than lower risk patients [71].

The recommended duration of use of bisphosphonates and/or the initiation of a 'bisphosphonate drug holiday' has been recommended by the FDA in part on the basis of the lack of efficacy beyond 5 years [39], although underlying the FDA's limit of use recommendations was the fear of rare atypical femur fractures with longer term (beyond 5 years) bisphosphonate use. Nevertheless, the benefit of bisphosphonate administration far outweighs any risk and these highly favorable aspects of bisphosphonate use, for the treatment of osteoporosis, have recently been reviewed by two authoritative groups [43,72].

Box 1. The American Society for Bone and Mineral Research task force on atypical femur fractures.

Major features

- Distal to the lesser trochanter to proximal to the supracondylar flare
- Minimal or no trauma
- Transverse or oblique
- Noncomminuted
- Complete fractures through both cortices and may have a medical spike, incomplete fractures involve only the lateral cortex

Minor features

- Localized periosteal reaction of the lateral cortex
- Generalized increase in cortical thickness
- Prodromal symptoms such as a dull aching pain in the groin or thigh;
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (vitamin D deficiency, retinoic acid and hypophosophatasia)
- Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids and proton pump inhibitors)

Reproduced with permission from [67].

All-cause mortality

A number of published observations suggest that bisphosphonates decrease the risk of all-cause mortality [73–76]. A great proportion of this reduction in all-cause mortality is related to a reduction in cardiovascular mortality. There is also increasing evidence that the use of bisphosphonates is associated with a decreased risk of breast and colorectal cancers [77–84]. These observations need to be validated by larger prospective studies.

Future perspective

Bisphosphonates have been registered for the treatment of postmenopausal osteoporosis for 20 years. They have robust effects on reducing the risk of all (global) fractures. They have a very unique pharmacology in that they are not metabolized and attach only to bone, where they exert their favorable effects on bone strength through multiple mechanisms, including increasing bone mineral density and bone microarchitecture. Their ability to retain their biological properties after detachment from bone and recycling is a favorable feature of bisphosphonates allowing a bisphosphonate 'break' ('drug-holiday') in lower risk patients. Their benefit–risk ration is very high and accordingly, they should be the dominant therapy for osteoporosis at this time.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

Background

- Bisphosphonates are nonmetabolizable inhibitors of bone resorption; have a strong affinity for bone tissue without uptake into any other tissue; are recycled retaining biological activity and are excreted by the kidney.

Postmenopausal osteoporosis

- Bisphosphonates reduce the risk for vertebral, nonvertebral and hip fractures and have a very robust benefit–risk ratio. This beneficial effect is seen in subjects with bone mineral density criteria for osteoporosis at the femoral neck or in patients with prevalent vertebral compression fractures.

Bisphosphonate safety

- Bisphosphonates are safe therapies for higher risk postmenopausal women. While upper gastrointestinal side effects are not uncommon, adverse effects on other tissues is not seen, other than rare reports of acute renal failure if zoledronic acid is administered too rapidly (faster than 15 min). Hence, zoledronic acid is contraindicated in patients with glomerular filtration rates less than 35 ml/min. Both osteonecrosis of the jaw, as well as atypical subtrochanteric femur fractures are rare events associated with bisphosphonate use and the US FDA has suggested limiting use of bisphosphonates to 3–5 years.

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