Bisphosphonates for the treatment of osteoporosis: insights for clinicians

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***Abstract*:** Osteoporosis is a common skeletal disease characterized by a reduction in bone strength and increased risk of fractures. Osteoporotic fractures are associated with substantial morbidity, mortality, and high healthcare costs. Treatments for osteoporosis have been shown to increase bone strength and reduce fracture risk. The drugs most commonly used to treat osteoporosis are bisphosphonates: stable analogs of naturally occurring inorganic pyrophosphate. The bisphosphonates share a common chemical structure with side chain variations that convey differences in their pharmacological properties, such as affinity for bone mineral and inhibitory effect on osteoclastic bone resorption. The clinical profiles of bisphosphonates, such as time of onset and offset of effect, may differ according to these pharmacological properties. Bisphosphonates can be administered orally or intravenously with a wide range of doses and dosing intervals. Randomized placebo-controlled clinical trials have shown that bisphosphonates reduce fracture risk in postmenopausal women with osteoporosis and have a generally excellent safety record. Clinical challenges in using bisphosphonates to treat osteoporosis include appropriate selection of patients for initiating therapy, choosing which bisphosphonate to use, monitoring therapy to assure that medication is taken correctly and the desired effect is achieved, determining when drug discontinuation should be considered, and managing side effects, possible side effects, and fear of side effects. Strategies for treating patients with bisphosphonates should consider each of these issues.

***Keywords*:** benefit, bisphosphonate, efficacy, osteoporosis, treatment, risk, safety

Introduction

Osteoporosis is a common systemic skeletal disease with serious clinical consequences due to fractures. It is characterized by low bone mineral density (BMD) and poor bone quality that reduces bone strength and increases fracture risk [Klibanski *et al.* 2001]. It has been estimated that more than 200 million people worldwide have osteoporosis [Cooper *et al.* 1992], including about 75 million in the United States (US), Europe, and Japan [European Foundation for Osteoporosis and Bone Disease, National Osteoporosis Foundation, 1997]. Osteoporotic fractures of the spine and hip are associated with increased morbidity and mortality [Center *et al.* 1999; Cooper, 1997]. Osteoporosis can be easily diagnosed before a fracture occurs by measuring BMD with dual-energy X-ray absorptiometry (DXA) using the diagnostic classification system of the World Health Organization (WHO) [World Health Organization, 1994] with standards for quality control and clinical application established by the International Society for Clinical Densitometry (ISCD) [Baim *et al.* 2008]. Fracture risk can be estimated using clinical risk factors for fracture and BMD results, when available, with electronic algorithms such as FRAX [World Health Organization, 2009; Kanis on behalf the World Health Organization Scientific Group, 2007], developed by the WHO in cooperation with other organizations, including the ISCD. Clinical practice guidelines based on cost–utility modeling have identified levels of fracture risk at which it is likely to be cost effective to treat with a pharmacological agent to reduce fracture risk, using numerous country-specific socio-economic assumptions and mortality data [Fujiwara *et al.* 2008; Kanis *et al.* 2008; National Osteoporosis Foundation, 2008; Siminoski *et al.* 2007]. Pharmacological agents that have been proven to reduce fracture risk with favorable benefit–risk

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ratios are now widely available [MacLean *et al.* 2008].

The drugs most often used in the treatment of osteoporosis are in the class of bisphosphonates (formerly called diphosphonates). These are analogs of naturally occurring inorganic pyrophosphate, an endogenous inhibitor of bone mineralization that has been found in body fluids that include plasma, urine, and synovial fluid [Russell *et al.* 1970]. Pyrophosphate is the simplest form of the polyphosphates, substances that inhibit the crystallization of calcium salts. Polyphosphates have been used as water softeners and have industrial applications as antiscaling additives in washing powders and oil brines [Fleisch, 2000]. Inorganic pyrophosphate, which may serve as an endogenous 'water softener' to inhibit calcification of soft tissue and regulate bone mineralization, consists of two phosphate groups linked by an oxygen atom (P–O–P structure), while bisphosphonates have a carbon atom connecting the two phosphate groups (P–C–P structure) [Russell *et al.* 2008]. The P–C–P configuration of bisphosphonates confers a resistance to chemical and enzymatic hydrolysis, resulting in a stable molecule that is absorbable when taken orally and not metabolized. Bisphosphonates were first synthesized by German chemists in 1865, with etidronate, a nonnitrogen-containing bisphosphonate, synthesized as early as 1897 [Fleisch, 2000]. This class of drugs is characterized by a strong affinity for hydroxyapatite in bone, a long skeletal half-life, and inhibition of bone resorption. Bisphosphonates have been used in clinical practice for the treatment of metabolic bone diseases that include heterotopic ossification, osteogenesis imperfecta, hypercalcemia of malignancy, Paget's disease of bone, metastatic bone disease, and multiple myeloma. The focus of this review is on the use of four nitrogen-containing bisphosphonates, alendronate, risedronate, ibandronate, and zoledronate (Table 1), for the treatment of postmenopausal osteoporosis (PMO). A thorough understanding of their pharmacological properties, efficacy, and safety is likely to enhance clinical outcomes in treating patients with osteoporosis.

Chemical structure, pharmacological properties, and mechanism of action

The affinity of bisphosphonates for hydroxyapatite and the magnitude of the antiresorptive effect are modulated by side chains designated R1 and R2 that are attached to the central carbon atom of the P–C–P core structure. An R1 substituent with a hydroxyl (–OH) or primary amino ($–NH_2$) group enhances attachment to hydroxyapatite, while variations in R2 are associated with substantial differences in antiresorptive potency and as well as differences in affinity for hydroxypapatite [Russell *et al.* 2008]. About 50% of bioavailable bisphosphonate, whether administered orally or intravenously, is rapidly incorporated into bone, with the remainder excreted unchanged by the kidneys through filtration and proximal tubular reabsorption [Lewiecki and Miller, 2007]. In kinetic studies using a constant composition method, the rank order of affinity for hydroxyapatite from highest to lowest was zoledronate > alendronate > ibandronate > risedronate [Nancollas *et al.* 2006]. Differences in binding affinity may result in differences in drug uptake and retention in the skeleton, diffusion within bone, and release and reuptake by bone. These factors, in turn, may be associated with differences in the rate of onset of antiresorptive effect when initiating bisphosphonate therapy and the rate of offset of effect when discontinuing therapy. This concept is supported by clinical data, such as a head-to-head clinical trial showing that treatment with alendronate resulted in a faster and greater reduction in bone turnover markers, as well as larger gains in BMD, compared with risedronate [Rosen *et al.* 2005]. The antiresorptive effect of a single intravenous (IV) dose of zoledronate persists for at least 1 year [Reid *et al.* 2002], while the antiresorptive effect of 3 years of oral risedronate therapy is no longer evident 1 year after stopping therapy [Watts *et al.* 2008]; some antiresorptive effect of 5 years of alendronate persists after 5 years off therapy [Black *et al.* 2006].

After attachment to the bone surface, bisphosphonates are internalized by osteoclasts, resulting in inhibition of osteoclast function and survival. Nonnitrogen-containing bisphosphonates (e.g. etidronate, clodronate, tiludronate) exert their antiresorptive effect by producing toxic analogs of adenosine triphosphate (ATP) that induce osteoclast apoptosis. Nitrogen-containing bisphosphonates inhibit osteoclastic bone resorption through a different mechanism of action. After entering the cytosol of the osteoclast, these drugs inhibit farnesyl pyrophosphate synthase (FPPS), an enzyme in the mevalonate pathway (the same pathway responsible for the synthesis of cholesterol), thereby reducing the prenylation (posttranslational modification) of

Table 1. Comparative features of four nitrogen-containing bisphosphonates commonly used for the treatment of osteoporosis.

	Alendronate	Risedronate	Ibandronate	Zoledronate
Brand name	Fosamax	Actonel	Boniva, Bonviva	Reclast, Aclasta
Approval date*	1995	2000	2003	2007
R1 side chain	OH	OH	OH	OH
R2 side chain	$(CH_2)_3NH_2$	CH_2-3-pyridine	$CH_2CH_2N(CH_3)$(pentyl)	CH_2-imidazole
Ranking of affinity for hydroxyapatite [Nancollas *et al.* 2006]	2	4	3	1
Ranking of antiresorptive potency [Dunford *et al.* 2001]	4	2	3	1
Administration	Oral	Oral	Oral, IV	IV
Dose	10 mg/day, 70 mg/week	5 mg/day, 35 mg/week, 150 mg/month, 75 mg/day for 2 consecutive days once monthly	Oral 150 mg/month, IV 3 mg every 3 months over 15–30 seconds	5 mg every 12 months over at least 15 minutes
Reduction of vertebral fracture risk	Yes [Cummings *et al.* 1998; Black *et al.* 1996]	Yes [Reginster *et al.* 2000; Harris *et al.* 1999a]	Yes [Chesnut *et al.* 2004]	Yes [Black *et al.* 2007]
Reduction of nonvertebral fracture risk	Yes [Black *et al.* 2000; Pols *et al.* 1999]	Yes [Harris *et al.* 1999b]	Not demonstrated except in *post hoc* subgroup analysis of high risk patients [Chesnut *et al.* 2004]	Yes [Black *et al.* 2007]
Reduction of hip fracture risk	Yes [Black *et al.* 1996]	Yes [McClung *et al.* 2001]	Not demonstrated	Yes [Black *et al.* 2007]
Comments	Available in inexpensive generic formulations	Added convenience of monthly oral dosing	Two dosing forms with long dosing intervals, IV dosing benefits patients unable to use oral bisphosphonates	IV dosing with longest dosing interval

Demonstration of fracture risk reduction considers only prospective randomized placebo-controlled clinical trials. IV, intravenous.
*Year of first approval by the United States Food and Drug Administration for the treatment of postmenopausal osteoporosis.

small guanosine triphosphate (GTP)ase signaling proteins. This decrease in prenylation has effects that include loss of the osteoclast ruffled border, the cell membrane that is adjacent to the bone surface and essential for bone resorption, and inhibition of release of lysosomal enzymes, impairment of acidification, and reduction of osteoclast survival, resulting in reduced function and survival of osteoclasts. *In vitro* and *in vivo* studies have shown that the rank order of potency for inhibition of FPPS and inhibition of bone resorption from highest to lowest is zoledronate > risedronate >> ibandronate > alendronate [Dunford *et al.* 2001], with agents having a heterocyclic moiety at R2 (zoledronate, risedronate) demonstrating greater potency than those with an alkyl-amino moiety (ibandronate, alendronate).

Orally administered bisphosphonates are poorly absorbed in the gastrointestinal (GI) tract, typically <1% even under ideal circumstances. It is therefore recommended that they be taken after an overnight fast with a glass of plain water followed by a postdose fast of 30 minutes (alendronate, risedronate) or 60 minutes (ibandronate). In order to minimize contact of the drug with the esophagus and reduce the risk of GI side effects, it is also advised that patients remain upright during the postdose fasting period.

Efficacy

Prospective randomized placebo-controlled clinical trials (RCTs) have demonstrated a reduction in vertebral fracture risk in women with PMO treated with daily oral alendronate [Cummings *et al.* 1998; Black *et al.* 1996], risedronate [Reginster *et al.* 2000; Harris *et al.* 1999a], and ibandronate [Chesnut *et al.* 2004], and with IV zoledronate every 12 months [Black *et al.* 2007]. 'Bridging studies' have shown an equivalent effect on BMD with intermittent dosing for weekly oral alendronate [Schnitzer *et al.* 2000], weekly oral risedronate [Brown *et al.* 2002], and monthly oral risedronate [Delmas *et al.* 2008a, 2008b]. Monthly oral ibandronate [Miller *et al.* 2005a] and IV ibandronate every 3 months [Delmas *et al.* 2006] are associated with a BMD response that is superior to daily oral dosing. RCTs have shown reduction of nonvertebral fracture risk with alendronate [Black *et al.* 2000; Pols *et al.* 1999], risedronate [Harris *et al.* 1999a], and zoledronate [Black *et al.* 2007]. Hip fracture risk reduction has been observed with alendronate [Black *et al.* 1996], risedronate [McClung *et al.* 2001], and zoledronate [Black *et al.* 2007]. In a post-hoc analysis, a significant reduction in the risk of nonvertebral fractures was reported with ibandronate in a subgroup of high-risk women with baseline femoral neck T-score <−3.0 [Chesnut *et al.* 2004]. A meta-analysis of data from four ibandronate clinical trials showed a reduction in the risk of nonvertebral fractures with doses currently used in clinical practice [Harris *et al.* 2008], which are higher than the 2.5 mg daily oral dose in the registration trial.

Despite the proven antifracture efficacy of bisphosphonates in RCTs, their effectiveness in clinical practice has been limited by poor compliance and persistence with therapy [Cramer *et al.* 2007], with some patients taking their oral bisphosphonate incorrectly and about 50% of patients started on an oral bisphosphonate no longer taking it 12 months later. Patients may not take an oral bisphosphonate correctly because they never received proper instructions, did not remember the instructions, or did not understand the rationale for such a complex dosing regimen. Patients may fail to continue to take medication because of side effects, perceived side effects, fear of side effects, cost, distrust of medications in general, or belief systems that differ from those of the prescribing physician. Poor compliance and persistence lead to a smaller BMD response [Yood *et al.* 2003], higher fracture risk [Caro *et al.* 2004], and greater healthcare costs [McCombs *et al.* 2004] compared with good compliance and persistence. Efforts to improve clinical outcomes with bisphosphonate therapy have included lengthening the dosing interval from daily to as long as once monthly with oral risedronate and ibandronate, once every 3 months with IV ibandronate, and once yearly with IV zoledronate. While some studies have shown modest improvement in persistence with longer dosing intervals [Cooper *et al.* 2006; Simon *et al.* 2002], persistence to therapy remains poor. In the subgroup of clinical practice patients who are persistent with therapy, there appears to be a reduction in fracture risk that is similar to what has been observed in RCTs [Wilkes *et al.* 2010].

Safety

The safety of osteoporosis therapy is a matter of major importance for physicians who prescribe the drugs and patients who take them. In RCTs, reported adverse events are generally mild and similar in subjects treated with bisphosphonates or placebo. However, with millions of

prescriptions written for these drugs in clinical practice, safety concerns, real or perceived, have arisen. Very rare adverse events may not be evident until many years after drug approval. Often potential side effects are initially presented as case reports in medical journals, sometimes with no clear causal relationship, no indication of the number of patients exposed to the drug in proportion to the number with the reported side effect, and no data on the risk of the same symptoms in patients not exposed to the drug. These reports may receive major coverage in the news media with little consideration of benefit *versus* potential harm. Since perception of harm weighs far more heavily in the minds of patients than actual probability of harm, potential risks with a wide range of probability are reviewed here.

Gastrointestinal intolerance

Oral bisphosphonates have been shown to cause upper GI injury in animals, especially after repeated daily exposure, with an acidic gastroesophageal milieu, and pre-existing esophageal irritation [Peter *et al.* 1998]. GI toxicity with bisphosphonates is likely a local effect rather than a systemic one, since these agents are rapidly bound to bone following absorption and normally only exist in high concentrations in the GI tract prior to absorption. In RCTs, there has been no reported difference in GI adverse events in bisphosphonate-treated subjects compared with controls [Cryer and Bauer, 2002]. However, observational studies of clinical practice patients suggest that about 20% may have GI intolerance to oral bisphosphonate therapy [Woo *et al.* 2010; Hamilton *et al.* 2003], perhaps in part due to improper drug administration, reporting bias, background GI disorders, or GI toxicity of the drug itself. Patients with preexisting upper GI disorders such as esophageal stricture, achalasia, or poorly controlled gastroesophageal reflux disease should not be treated with oral bisphosphonates.

Generic oral alendronate, now commonly used as first-line therapy for osteoporosis, may impart a greater risk of upper GI side effects and possibly a reduced therapeutic response compared with the brand name product. This is suggested by reports of a longer esophageal transit time [Perkins *et al.* 2008], greater esophageal adhesiveness [Shakweh *et al.* 2007], potentially unfavorable disintegration/dissolution profiles [Epstein *et al.* 2003], poorer persistence to therapy [Ringe and Moller, 2009], and reduced BMD response [Ringe and Moller, 2009] with some generic alendronate formulations compared with branded oral bisphosphonate, as well as more GI side effects [Adachi *et al.* 2009] compared with placebo. IV bisphosphonates have not been associated with an increase in GI side effects [Black *et al.* 2007; Delmas *et al.* 2006].

Esophageal cancer

In 2009, a letter to the editor of a medical journal reported that the FDA had received reports of 23 patients with esophageal cancer who had been exposed to alendronate [Wysowski, 2009]. An additional 31 cases of esophageal cancer in Europe and Japan were reported in patients treated with alendronate or other oral bisphosphonates. The reports did not provide data on the expected rate of esophageal cancer in similar patients not exposed to bisphosphonates and did not state the number of patients treated with bisphosphonates who were not diagnosed with esophageal cancer. National registry data from Europe [Abrahamsen *et al.* 2009] and Medicare claims data in the US [Solomon *et al.* 2009] later showed no link between bisphosphonate use and esophageal cancer. While more data are needed to fully assess the possibility of a link between bisphosphonate use and esophageal cancer, at this time there is no evidence to support a causal relationship.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ), first reported in association with bisphosphonates in 2003 [Marx, 2003], has been defined as exposed bone in the maxillofacial region with no healing within 8 weeks of identification by a healthcare provider, in a patient with exposure to a bisphosphonate and no history of radiation therapy to the craniofacial area [Khosla *et al.* 2007]. Most reported cases (about 95%) have been in cancer patients receiving high-dose IV bisphosphonates for the prevention or treatment of cancer-related bone disease [Woo *et al.* 2006; Marx *et al.* 2005]. In clinical trials of bisphosphonates for the treatment of osteoporosis involving more than 60,000 patient-years of exposure, no cases of ONJ have been prospectively identified. In a retrospective review of data in a large clinical trial with zoledronate, one potential case of ONJ was diagnosed in the treatment group and one in the placebo group [Black *et al.* 2007]. The risk of ONJ in patients receiving bisphosphonates for the treatment of osteoporosis is estimated to be

between 1 in 10,000 and 1 in 100,000 patient-treatment years [Khosla *et al.* 2007]. There is no evidence that IV bisphosphonates for the treatment of osteoporosis incur a greater risk than oral bisphosphonates. A causal relationship between bisphosphonate use and ONJ has not been clearly established, although it seems plausible, and the mechanism for such a relationship, if it exists, is unknown. In most patients, the benefit of reduction of fracture risk in patients treated for osteoporosis far outweighs the very remote potential risk of ONJ.

Hypocalcemia

Oral and IV bisphosphonates reduce calcium efflux from bone and commonly cause a small decrease in serum calcium and compensatory rise in serum parathyroid hormone (PTH) [Chesnut *et al.* 1995]. Hypocalcemia (defined as a serum calcium level less than 7.5 mg/dL) was reported in 0.2% of patients treated with IV zoledronic acid, all of whom were asymptomatic with spontaneous reversal of the laboratory abnormality [Black *et al.* 2007]. Symptomatic hypocalcemia occurs rarely but may be life threatening and require hospitalization [Maalouf *et al.* 2006]. Hypocalcemia is more common with IV dosing than with oral, and is more likely to occur in the presence of vitamin D deficiency, impaired parathyroid function, impaired renal function, and Paget's disease of bone. Patients with baseline hypocalcemia should not be treated with bisphosphonates until the underlying problem has been evaluated and the low serum calcium level is corrected.

Acute phase reaction

Transient flu-like symptoms, collectively called an acute phase reaction (APR), may occur after administration of bisphosphonates. This may be caused by the rapid release of pro-inflammatory cytokines from circulating T cells [Hewitt *et al.* 2005]. APR is seen rarely with oral therapy (more likely with monthly than weekly or daily dosing) and more commonly following IV bisphosphonates. Symptoms include low-grade fever, fatigue, bone pain, arthralgias, myalgia, and/or nausea, usually beginning within 24 hours of dosing and resolving over several days. It most often occurs in patients not previously treated with bisphosphonates and is less likely to occur on subsequent dosing. The likelihood of having an APR after an IV bisphosphonate may be reduced by administration of acetaminophen (paracetamol) prior to dosing [National Osteoporosis Foundation, 2008] and for several days thereafter.

Atrial fibrillation

The possibility that bisphosphonates might cause atrial fibrillation was raised in the pivotal trial of zoledronate for the treatment of PMO [Black *et al.* 2007]. An increased incidence of atrial fibrillation as a serious adverse event (often associated with hospitalization, whether or not the atrial fibrillation was the reason for hospitalization) was observed (1.3% versus 0.5% with placebo, $p < 0.001$). The overall incidence of atrial fibrillation was not significantly different between groups, and these events were not related to the timing of drug infusion, APR, or electrolyte imbalance. An increased risk of atrial fibrillation has not been observed in other studies with zoledronate. Post-hoc analyses of bisphosphonate clinical trials [Lewiecki *et al.* 2010; Cummings *et al.* 2007] and several large population-based studies [Heckbert *et al.* 2008; Sorensen *et al.* 2008] have been inconsistent in their findings, with no conclusive evidence that bisphosphonates increase the risk of atrial fibrillation. The FDA has reviewed the data and stated that 'healthcare professionals should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their bisphosphonate medication' due to concern with the risk of atrial fibrillation [US Food and Drug Administration, 2008b].

Atypical subtrochantic femur fractures

A report of nine patients on long-term alendronate with 'severely suppressed bone turnover' and low trauma nonvertebral fractures (including three patients with femoral shaft fractures) was published in 2005 [Odvina *et al.* 2005]. Since that time, other case reports of bisphosphonate-treated patients having atypical subtrochanteric femur fractures have emerged [Lenart *et al.* 2009; Neviaser *et al.* 2008; Lee *et al.* 2007; Goh *et al.* 2007; Schneider, 2006; Armamento-Villareal *et al.* 2006]. Some of these patients are described as having a prodrome of lateral thigh pain for weeks or months before sustaining a spontaneous or low trauma transverse femoral shaft fracture in bone that appears to have thickened cortices and unicortical 'beaking' at the fracture margin. Some but not all patients in these reports had severely suppressed bone turnover as assessed by absence of tetracycline labeling on transiliac bone biopsies. However, very low bone turnover and absence of tetracycline

labeling has been reported in some untreated patients with osteoporosis [Kimmel *et al.* 1990], and no causal relationship between bisphosphonate use and atypical fractures has been established. More data are needed to define the relationship, if there is one, between bisphosphonates and these types of fractures.

A secondary analysis of 3 large, randomized bisphosphonate trials with alendronate and zoledronate involving 14,195 women and 55,000 person-years of observation found that subtrochanteric and diaphyseal femur fractures were very rare, even in women treated with bisphosphonates as long as 10 years [Black *et al.* 2010]. The FDA recently stated that at this time there is no evidence of 'a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures' [US Food and Drug Administration, 2010].

Impaired fracture healing

The natural process of fracture healing is characterized by an initial osteoclast-independent inflammatory phase and subsequent formation of a woven bone callus, followed by remodeling of woven bone to lamellar bone that depends on osteoclast activity [Goldhahn *et al.* 2010]. The treatment of patients at high risk for fracture with antiresorptive drugs, particularly bisphosphonates, has raised concern over possible adverse effects on fracture healing due to changes in the function of osteoclasts [Fleisch, 2001]. Animal studies have shown that bisphosphonate treatment is associated with a callus that is either the same size or larger, with delayed remodeling to lamellar bone, and mechanical strength that is similar or greater than controls [Fleisch, 2001]. Large clinical trials with bisphosphonates for the treatment of PMO have not shown impairment of fracture healing. In a recent review of osteoporosis therapy in acute fracture settings, the International Society for Fracture Repair concluded that there is no evidence to support withholding antiresorptive therapy while a fracture heals, whether or not the patient was taking such therapy when the fracture occurred [Goldhahn *et al.* 2010].

Renal safety

The product labels for oral and IV bisphosphonates state that these agents should not be given to patients with severe renal impairment, defined as creatinine clearance <30 ml/min with ibandronate and risedronate or <35 ml/min with zoledronate and alendronate, principally due to lack of prospective data on efficacy and safety in such patients. However, a post-hoc analysis of clinical trial data in patients treated with risedronate showed that those with mild, moderate, and severe impairment of baseline renal function had preserved BMD, reduced incidence of vertebral fractures, and stable serum creatinine levels [Miller *et al.* 2005b]. Similar findings were reported in a post-hoc analysis of alendronate clinical trial data [Jamal *et al.* 2007]. Taken as a whole, the data suggest that oral bisphosphonates are effective and safe in patients with mild, moderate, and perhaps severe chronic kidney disease. There are no data on efficacy and safety in patients with kidney failure (end-stage renal disease), i.e. creatinine clearance <15 ml/ml or on dialysis.

Although nephrotoxicity has been described in cancer patients receiving rapid monthly IV infusions of zoledronate [Perazella and Markowitz, 2008], this appears to be a very rare occurrence in well-hydrated patients treated for osteoporosis with the recommended dose and infusion rate. In two large clinical trials of zoledronate 5 mg IV given over at least 15 minutes for the treatment of osteoporosis, no drug-related cases of acute renal failure were reported [Black *et al.* 2007; Lyles *et al.* 2007]. Similarly, there were no drug-related cases of acute renal failure in a large clinical trial with ibandronate IV 2 mg every 2 months and 3 mg every 3 months given over 15–30 seconds [Delmas *et al.* 2006].

Chronic bone and muscle pain

In 2008, the FDA released an alert covering all FDA-approved bisphosphonates stating that there was a 'possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates' [US Food and Drug Administration, 2008a]. The alert was largely based on a letter to the editor of a medical journal describing a small number of patients who had taken alendronate and developed severe and sometimes disabling bone, joint, and/or muscle pain [Wysowski and Chang, 2005]. A few additional patients taking risedronate were reported to have similar symptoms. However, an FDA review of clinical trial data leading to approval of alendronate and risedronate found no meaningful difference in reports of bone, joint, and/or muscle pain between treated and control patients. There is no evidence of a causal relationship between

bisphosphonates and these symptoms, and no rationale has been provided that might explain such a relationship. Nevertheless, continued awareness of this potential adverse effect of bisphosphonate therapy is appropriate.

Common clinical issues with bisphosphonates

The management of osteoporosis presents many challenges [Lewiecki, 2009], among which are decisions on starting, stopping, or changing bisphosphonate therapy. Often the medical evidence to guide these decisions is limited, nonexistent, or not applicable to the patient being treated. The application of evidence-based medicine and clinical practice guidelines to the care of individual patients requires consideration of all available information, including patient preferences, previous drug experiences, and affordability of treatment, tempered with the thoughtful judgment of a well-informed healthcare provider [Lewiecki and Binkley, 2009]. The following identifies a few of the many decision-making points involving bisphosphonate treatment, with suggestions for effective strategies in patient management. Other strategies may be equally valid depending on clinical circumstances.

Selection of a bisphosphonate

Once a decision to treat with a bisphosphonate has been made, a choice must be made to prescribe one of them. Which bisphosphonate is best? In the absence of head-to-head clinical trials with fractures as the primary endpoint, it is not possible to determine which one provides the greatest reduction in fracture risk [MacLean *et al.* 2008]. Cost considerations often mandate initiation of therapy with generic alendronate, provided no contraindications are present. Clinicians must be mindful of data suggesting that generic alendronate may be associated with greater risk of GI side effects and poorer persistence compared with the branded bisphosphonate product. In a patient with a questionable GI side effect from an oral bisphosphonate, discontinuation of the drug and rechallenge with the same or different oral bisphosphonate after symptoms have resolved may sometimes be effective [Adachi *et al.* 2001; Miller *et al.* 2000]. IV bisphosphonates are an alternative choice for primary treatment of osteoporosis, with particular clinical utility for patients with GI contraindications, GI adverse events, malabsorption, or poor response to therapy with oral bisphosphonates.

Compliance and persistence to therapy

Once a bisphosphonate is started, it is imperative that the patient take the drug regularly, correctly, and for a sufficient length of time to benefit from reduction in fracture risk. Before therapy is started, patients should be educated on the risk of fractures, the serious consequences of fractures, and the goal of therapy (i.e. to reduce fracture risk). They should be evaluated for factors that might result in poor tolerance to therapy, such as pre-existing upper GI conditions. Patients must fully understand the protocol for proper administration of oral bisphosphonate or the importance of returning as scheduled for the next dose of an IV bisphosphonate. One of the few methods with documented improvement in persistence is regular contact with a healthcare professional [Clowes *et al.* 2004]; a follow-up appointment or phone call a few months after starting oral bisphosphonate therapy may be helpful to ensure that the patient filled the prescription, is taking it as directed, and has a sufficient intake of calcium and vitamin D. Postfracture care may be improved by health systems approaches that include performance reviews to motivate changes in physician behavior [Harrington *et al.* 2005].

Assessing response to therapy

Patients may not respond to therapy as expected for reasons that include poor compliance and persistence, inadequate intake of calcium and vitamin D, malabsorption, or an unrecognized pre-existing or newly developed disease or disorder with adverse skeletal effects [Lewiecki, 2003]. BMD testing by DXA and measurement of a bone turnover marker (e.g. N-telopeptide, C-telopeptide) are clinical tools that can provide helpful information on response to therapy [Lewiecki and Watts, 2008]. A statistically significant decrease in BMD or failure to decrease the bone turnover marker as expected is of clinical concern and should trigger further evaluation for factors contributing to poor response and consideration of a change in the plan of treatment. A fracture while on therapy does not necessarily represent a poor response, since no drug can totally eliminate the risk of fracture, but may also be grounds for rethinking the treatment plan.

How long to treat

Bisphosphonate clinical trials extending as long as 10 years with alendronate [Black *et al.* 2006; Bone *et al.* 2004] and 7 years with risedronate [Mellstrom *et al.* 2004] suggest that these

agents are safe and effective for long-term use. The possibility that some patients may benefit from temporary withholding of treatment (drug holiday) after years of exposure has been raised because of the long skeletal half-life of bisphosphonates, evidence of continuing benefit of therapy for a period of time after discontinuation, and potential adverse effects of excessive suppression of bone turnover [Sebba, 2008]. Potential candidates for a drug holiday are patients who should not have been treated in the first place (e.g. changes in treatment guidelines may have altered the clinical perspective on the need to treat) and those who have received at least 5 years of bisphosphonate therapy and are no longer at high risk for fracture. For a patient started on a drug holiday, it is prudent to monitor BMD and/or a bone turnover marker periodically in order to determine when to end the holiday and resume therapy. Patients with 5 years or more of bisphosphonate therapy who at are high risk for fracture, as suggested by a T-score of −2.5 or less or a past history of fracture, may benefit from continued therapy [Schwartz *et al.* 2010].

Treating patients with chronic kidney disease

In patients with stage 1, 2, or 3 chronic kidney disease (glomerular filtration rate [GFR] >30 ml/min), there is little question that bisphosphonates have an excellent efficacy and safety profile [Recker *et al.* 2009]. While the product labels advise against the use of bisphosphonates in patients with GFR <30–35 ml/min, limited data suggest that oral bisphosphonate therapy in the usual doses is probably effective and safe [Miller, 2005]. When stage 4 chronic kidney disease patients (GFR 15–30 ml/min) require therapy and are unable to take oral bisphosphonates, IV bisphosphonates with a longer than usual infusion time may be considered [Lewiecki and Miller, 2007]. Whenever bisphosphonate therapy is contemplated in patients with GFR <30 or 35 ml/min, patients should be informed that this is unapproved 'off-label' drug use, and that efficacy and safety data are limited. In patients with stage 5 chronic kidney disease (GFR <15 ml/min) there is virtually no evidence for efficacy and safety of bisphosphonate therapy. When there is uncertainty in making the treatment decision in a patient with chronic kidney disease, referral to an osteoporosis specialist should be considered.

Treatment in the very old

In elderly (age ~70–80 years) and very elderly patients (age >80 years) frailty becomes an important predictor of falls, fractures, and mortality that is independent of BMD [Rizzoli *et al.* 2009]. While the evidence for antifracture efficacy of bisphosphonates in the very old is mostly limited to post-hoc subgroup analyses of small numbers of patients in clinical trials, it appears that these agents are effective and safe in this population [Aguirre and Lewiecki, 2009; Ettinger *et al.* 2005; Hochberg *et al.* 2005; Boonen *et al.* 2004]. Efforts to reduce fall risk in the elderly should address frailty by measures that include environmental safety, muscle strengthening, balance training, and eliminating or minimizing exposure to drugs that cause sedation, hypotension, dizziness, or impaired balance.

Conclusion

Oral and IV bisphosphonates reduce fracture risk in patients with osteoporosis. The effectiveness of these agents in clinical practice is limited by poor compliance and persistence with therapy. The safety profile is generally favorable. Side effects and possible side effects are rare in proportion to the benefit achieved.

Conflict of interest statement

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