

Bisphosphonate Therapy for Osteoporosis: Benefits, Risks, and Drug Holiday

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ABSTRACT

The amino-bisphosphonates are first-line therapy for the treatment of most patients with osteoporosis, with proven efficacy to reduce fracture risk at the spine, hip, and other nonvertebral skeletal sites. Further, bisphosphonates have been associated with a significant decrease in morbidity and increase in survival. Following the use of bisphosphonates in millions of patients in clinical practice, some unexpected possible adverse effects have been reported, including osteonecrosis of the jaw, atypical femur fractures, atrial fibrillation, and esophageal cancer. Because bisphosphonates are incorporated into the skeleton and continue to exert an antiresorptive effect for a period of time after dosing is discontinued, the concept of a drug holiday has emerged, whereby the risk of adverse effects might be decreased while the patient still benefits from antifracture efficacy. Patients receiving bisphosphonates who are not at high risk for fracture are potential candidates for a drug holiday, while for those with bone mineral density in the osteoporosis range or previous history of fragility fracture, the benefits of continuing therapy probably far outweigh the risk of harm.

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Amino-bisphosphonates decrease bone resorption by inhibiting osteoclast function¹ and have proven antifracture efficacy in patients with osteoporosis.² At least 4 million American women were prescribed bisphosphonates to treat osteoporosis in 2008.³ In addition, many men with osteoporosis and patients receiving glucocorticoids are receiving bisphosphonate therapy. With such a large number of patients receiving bisphosphonate therapy for ever-longer durations, there is an increasing chorus of questions about their long-term use.

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The majority of data about the fracture reduction efficacy and safety of bisphosphonates come from randomized, placebo-controlled phase III regulatory trials in postmenopausal women,⁴⁻¹⁰ mostly 3 years in duration, with fewer than 50,000 total subjects. Some trials were extended,¹¹⁻¹³ 2 with alendronate out to 10 years,^{12,14} but clinical trial data for long-term use of bisphosphonates are scarce, with no placebo-controlled data beyond 5 years.

This commentary weighs the known antifracture benefits of bisphosphonate therapy with their potential risks and provides guidance as to when a bisphosphonate drug holiday may be appropriate.

LONG-TERM RETENTION OF BISPHOSPHONATE IN THE SKELETON

The effects of most therapies resolve soon after discontinuation. Bisphosphonates are unique in that they bind to hydroxyapatite in bone and can remain there for years. During remodeling, which is significantly decreased by bis-

phosphonate therapy, some bound bisphosphonate is released from bone; a portion binds again to bone and is metabolically active. Skeletal binding affinity increases in rank order through risedronate, ibandronate, alendronate, and zoledronic acid.¹ Bisphosphonates with higher affinity are more quickly rebound, increasing skeletal retention.

The long residence time for bisphosphonates has potential benefits and risks. On the positive side, discontinuation of bisphosphonate therapy is associated with an anti-resorptive effect and antifracture protection that persists for an undefined period. However, if adverse effects are associated with skeletal persistence of these drugs, it might take a long time for these to resolve.

ANTIFRACTURE AND CLINICAL EFFICACY OF BIPHOSPHONATES

Table 1 provides an overview of the antifracture efficacy with bisphosphonates in pivotal, registration trials. Alendronate, risedronate, and zoledronic acid decreased fracture risk at the spine, nonvertebral sites, and the hip alone,² whereas ibandronate reduced vertebral but not nonvertebral fractures.¹⁵ In general, the efficacy of bisphosphonates changes with the patient’s primary risk profile—those with the highest fracture risk tend to have the greatest absolute reduction in

fracture risk. Hip fracture incidence decreased between 1996 and 2007 in the US when bisphosphonate use was widespread, supporting a possible benefit of bisphosphonate therapy in reducing the risk of hip fracture.¹⁶

Bisphosphonates also are approved for the treatment of men with osteoporosis and both men and women receiving glucocorticoids, based on studies demonstrating increases in bone mineral density. Only 2 sets of these studies, one in men and another in patients receiving glucocorticoids, have demonstrated reductions in vertebral fracture risk with 1 year of therapy.^{17,18}

The benefits of bisphosphonate therapy extend beyond fracture risk reduction and include a decrease in morbidity, reduced health care costs, and a significant increase in survival.¹⁹⁻²³ Oral and intravenous bisphosphonate use for up to 3 years was associated with a decrease in mortality of up to 28% in patients with recent low-trauma hip fractures.^{10,24} Older men and women treated with bisphosphonates over 5 years had an adjusted 27% reduction in risk of death compared with nonusers.²¹ In a recent meta-analysis, the use of osteoporosis therapies, including bisphosphonates, for more than 1 year was associated with a significant decrease in mortality in older patients at a high risk of fracture.²⁵

CLINICAL SIGNIFICANCE

- Protection from important fractures persists with long-term amino-bisphosphonate therapy in patients with osteoporosis.
- The risk of osteonecrosis of the jaw and atypical subtrochanteric femoral fractures with amino-bisphosphonates is very small compared with the antifracture benefits provided in individuals at moderate or high fracture risk.
- Based on current evidence, a “drug holiday” from amino-bisphosphonates is not justified in patients who remain at high risk for spine fracture.

Table 1 Antifracture Benefits of Bisphosphonates for the Treatment of Postmenopausal Osteoporosis*

Medication (Clinical Trial)	Y	Absolute Fracture Risk Reduction			Relative Fracture Risk Reduction			Number Needed to Treat to Prevent One Fracture		
		Vert fx	Non-vert fx	Hip fx	Vert fx	Non-vert fx	Hip fx	Vert fx	Non-vert fx	Hip fx
Alendronate (FIT I) ⁴	3	7.1%	2.8%	1.1%	47.1%	18.9%	50.8%	14	36	90
Alendronate (FIT II) ⁵	3	1.7%	1.5%	0.2%	44.3%	11.1%	20.7%	60	68	447
Risedronate (VERT NA) ^{6†}	3	5.0%	3.2%	0.4%	30.7%	38.1%	19.7%	20	31	276
Risedronate (VERT MN) ^{7†}	3	10.9%	5.1%	0.5%	37.6%	31.9%	18.2%	9	20	203
Risedronate (HIP) ⁸	3	NA	1.8%	1.1%	NA	16.1%	28.2%	NA	56	91
Zoledronic acid (HORIZON PFT) ⁹	3	7.6%	2.7%	1.1%	70.0%	25.2%	44.0%	13	37	91
Zoledronic acid (HORIZON RFT) ¹⁰	3	NA	3.1%	1.5%	NA	29.0%	42.9%	NA	32	67
Ibandronate (BONE) ^{15†}	3	4.9%	-0.9%	NA	62%	-11%	NA	20	NA	NA
Alendronate (Men) ¹⁷	2	5.0%	NA	NA	62%	NA	NA	9	NA	NA
Risedronate (GIO) ¹⁸	1	11.0%	NA	NA	70%	NA	NA	9	NA	NA

FIT = Fracture Intervention Trial; GIO = glucocorticoid induced osteoporosis; HIP = Hip Intervention Program; hip fx = hip fracture; NA = not assessed; nonvert fx = nonvertebral fracture; VERT = Vertebral Efficacy with Risedronate Therapy study; vert fx = vertebral fracture; Y = average years of follow-up.

*Widely ranging bone mineral density, age, and previous fracture status in the study populations make direct comparisons of therapies impossible. This table provides a broad overview of the general benefits of the therapies in the respective clinical trial population. For more information about the particular populations studied for each therapy, please refer to the referenced publication.

†Vertebral fracture incidence rate estimated from proportional hazards models.

RISKS ASSOCIATED WITH BIPHOSPHONATE THERAPY

The overall frequency of adverse events (any undesirable medical occurrence associated with the use of a medical product in a patient, irrespective of causality)²⁶ or serious adverse events (life-threatening, resulting in death, hospitalization, prolongation of hospitalization, significant disability, or birth defect) did not differ between groups receiving bisphosphonates or placebo in pivotal clinical trials. Adverse events and serious adverse events that are attributable (ie, causally related) to the therapy (“side effects” in lay terms) may be identified in placebo-controlled trials if they are relatively common. Rare treatment-related complications may only come to attention after many thousands, if not millions, of patients are exposed to a drug in the “real world” clinical setting. Additionally, patients treated clinically often have conditions (eg, comorbidities, other medications, advanced age, impaired renal function) that might predispose them to undesirable medical occurrences not seen in healthier clinical trial subjects.²⁷ While the overall rates of serious adverse events reported in bisphosphonate clinical trials were low, highly publicized postmarketing reports have linked bisphosphonates to undesirable medical occurrences including osteonecrosis of the jaw, atypical femur fracture, atrial fibrillation, and esophageal cancer.

OSTEONECROSIS OF THE JAW

Bisphosphonate-associated osteonecrosis of the jaw (exposed bone in the maxillofacial region, with no healing within 8 weeks in a patient with bisphosphonate exposure and no history of craniofacial radiation therapy) is most often observed (95% of cases) after invasive dental procedures during oncology therapy, with high doses of intravenous bisphosphonates delivered frequently to an immunosuppressed population.²⁸ The incidence of osteonecrosis of the jaw in patients receiving bisphosphonates for osteoporosis or the healthy adult population is unknown. In chronic users of oral bisphosphonate therapy for osteoporosis, estimates of that risk range between 1 in 1000 and 1 in 263,000 patient-years, with minimal evidence for an association of risk with duration of therapy.²⁸⁻³⁵ Poor oral hygiene, glucocorticoid therapy, and chemotherapy may be risk factors. This problem also occurs in patients unexposed to bisphosphonates, and causality between this disorder and oral bisphosphonate use has not been established.

Due to lack of evidence, there is uncertainty about the value of withholding bisphosphonates before invasive dental surgery. The American Dental Association suggests that “the decision to discontinue therapy should be a medical decision based primarily upon the risk for skeletally related events (eg, fractures) secondary to low bone density, not the potential risk of osteonecrosis of the jaw.”³⁶ The use of serum C-telopeptide of Type I collagen, a marker of bone resorption, to assess the risk of jaw osteonecrosis in patients on bisphosphonates has been recommended,³⁷ but because of the paucity of evidence supporting this approach, the use

of serum C-telopeptide of Type I collagen is not endorsed by the American Dental Association. In patients with osteoporosis, the benefit of bisphosphonates in reducing fracture risk far outweighs the remote potential risk of osteonecrosis of the jaw.

ATYPICAL FEMUR FRACTURES

A consensus document defined the major features of an atypical femoral fracture (located in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, occurring spontaneously or after minimal trauma, possessing a medial spike, absence of comminution), distinguishing these fractures from the more common “typical” femoral shaft fracture that is a complication of osteoporosis.³⁸ Glucocorticoids and proton-pump inhibitor therapy have been identified as risk factors for atypical fractures in some,³⁹ but not all,^{40,41} studies. Atypical femoral fractures also occur in bisphosphonate-naïve patients.⁴¹⁻⁴⁶ Sparse information is available about the incidence of atypical femoral fractures in patients with and without bisphosphonate treatment. Estimates of risk are inconsistent, but the risk appears to rise with increased duration of bisphosphonate exposure.^{40,46,47} A retrospective analysis of >15,000 femoral fractures in an American population identified 142 patients with radiographically confirmed fractures with atypical features, 128 of whom had taken a bisphosphonate for an average of 5.5 years.⁴⁷ Risk increased from 1.78 atypical femoral fractures per 100,000 patient-years treated for 2 years to 113.1 such fractures per 100,000 patient-years with treatment for 8-10 years. In a Swedish national population survey of >12,000 femur fractures (including about 11,000 hip fractures), 59 radiographically confirmed atypical femoral fractures occurred, of which 78% were in patients with a history of bisphosphonate use.⁴⁰ The difference in atypical femoral fracture risk between patients who did or did not take bisphosphonates was 1.8 atypical fractures per 10,000 patients/year for up to 2 years of treatment and 8.4/10,000 patients/year with use of more than 2 years. The risk diminished substantially and rapidly after bisphosphonate discontinuation.

These results suggest that the absolute risk of atypical fracture associated with bisphosphonate use even beyond 5 years is small for the individual osteoporosis patient at high risk of fractures, compared with the beneficial effects of treatment. Consistent with this was an analysis of 90 million hospital discharge records (1996-2007), which suggested that for every subtrochanteric fracture (typical and atypical) associated with bisphosphonate use, 100 hip fractures were prevented, in addition to prevention of other fractures.¹⁶

ATRIAL FIBRILLATION

An increased incidence of atrial fibrillation as a serious adverse event was reported in the pivotal phase III trial of annual intravenous zoledronic acid (1.3% in the treated group, 0.5% in the placebo group; $P < .001$),⁹ although there were no differences between groups in total cases of

atrial fibrillation or other cardiovascular events. While cardiac abnormalities could be the result of a transient decrease in serum calcium, the serious adverse events were not clustered at the beginning of the therapy or at the time of the annual doses. In analyses of other large clinical trials (mostly post hoc), there were no associations between atrial fibrillation and bisphosphonate treatment.^{10,48-50} After a review of these data, the US Food and Drug Administration concluded that concerns about atrial fibrillation need not be considered in decisions about therapy for osteoporosis.⁵¹

ESOPHAGEAL CANCER

Several cases of esophageal cancer occurring in patients with a history of oral bisphosphonate use have been reported.⁵² While one large case-control analysis reported a significant increase in the incidence of esophageal cancer with long-term oral bisphosphonate use,⁵³ other reports found no significant increases.⁵⁴⁻⁵⁶ The US Food and Drug Administration has determined that, at this time, there is not enough information to make definitive conclusions about a possible association between oral bisphosphonates and esophageal cancer.⁵⁷

OTHER RISKS AND CONCERNS

Gastrointestinal Intolerance

Although not observed in clinical trials, gastrointestinal intolerance, esophageal irritation, or erosion have been reported with oral bisphosphonate use, especially if taken incorrectly.^{6-8,58-63} Isolated cases of serious esophageal complications or upper gastrointestinal hemorrhage have occurred.⁶⁴ Oral bisphosphonates are contraindicated in patients with impaired swallowing.

Impairment of Renal Function

Bisphosphonates can be nephrotoxic when high doses are administered rapidly.^{65,66} Impaired renal function has not been observed in clinical trials when bisphosphonates are used according to prescribing instructions in well-hydrated patients, but postmarketing cases of renal failure after intravenous zoledronic acid have been reported. Bisphosphonate therapy is not recommended or is contraindicated in patients with significantly impaired renal function.⁶⁷

Flu-like Symptoms

Acute phase reactions with transient, mild to moderate influenza-like symptoms occur with monthly oral^{68,69} or intravenous bisphosphonate therapy.^{9,10,70,71}

Hypocalcemia

By inhibiting bone resorption, bisphosphonates reduce calcium efflux from bone, resulting in a small, transient decrease in serum calcium.^{72,73} Risk factors for symptomatic hypocalcemia include vitamin D deficiency, hypoparathyroidism, and impaired renal function.

Impaired Fracture Healing

To date, there is no clinical evidence that bisphosphonate therapy impairs fracture healing.

Inflammatory Eye Disorders

Very rare cases of inflammatory eye disorders have been described with oral and intravenous bisphosphonate use.^{74,75}

BISPHOSPHONATE “DRUG HOLIDAY”

It is unusual to contemplate a drug holiday in the treatment of most chronic diseases because with most therapies, beneficial drug effects rapidly diminish with discontinuation. However, the long skeletal residence time of bisphosphonates and concern about the risks of rare adverse events with long-term therapy raise the possibility that bisphosphonate therapy may be interrupted for a “drug holiday,” during which antifracture benefit might persist for a period of time while potential risks are minimized.⁷⁶ Intuitively, upon bisphosphonate discontinuation, both the potential benefit and risks of the residual bisphosphonate effect would decrease over time as the drug is gradually removed from the skeleton.

In assessing the potential utility of a drug holiday, it would be ideal to have clinical trial data comparing fracture risk between patients who continue or stop therapy; unfortunately, only 3 prospective studies have addressed this issue.^{12,77,78} In patients treated with annual zoledronic acid for 3 years, treatment for 3 additional years resulted in a 52% lower risk of morphometric vertebral fracture, compared with treatment for 3 years followed by placebo for the next 3 years (fracture rates 3.0% vs 6.2%, respectively).⁷⁷ The risks of other fractures—including clinical or symptomatic vertebral fractures—did not differ between groups. The Fracture Intervention Trial Long-term Extension trial randomized patients completing 5 years of alendronate therapy to 5 additional years of alendronate or placebo.¹² Although the subject number was small, those continuing alendronate for 10 years had fewer clinical vertebral fractures than the subjects receiving the drug for only 5 years (5.3% vs 2.4%, respectively). There was no difference between groups for morphometric vertebral or nonvertebral fractures. A post hoc analysis of the Fracture Intervention Trial Long-term Extension trial patients at high risk (T-score of < -2.5 , but without prevalent vertebral fracture) at the time of discontinuation demonstrated an increased risk for all clinical fractures associated with a discontinuation compared with remaining on alendronate therapy.⁷⁹ In a small study of patients given risedronate or placebo for 3 years who were then followed for an additional year after discontinuation, morphometric vertebral fracture incidence remained 46% lower in the former risedronate group, as compared with the former placebo group (6.5% vs 11.6%, respectively).⁷⁸ However, there was no group of patients continuing on risedronate, so it was not possible to compare fracture risk of discontinuing therapy with continuing ther-

Table 2 Recommendations for Drug Holiday from Bisphosphonates

Patient Category	Recommendation	Comment
High-risk: T-score still ≤ -2.5 at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.	Drug holiday not justified.	Re-assess the need for therapy at regular intervals.
Moderate risk: Hip bone mineral density value is now > -2.5 (T-score), and no prior hip or spine fracture.	Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy. No information about ibandronate and drug holidays.	These patients should not be forced to take a drug holiday—decision should be an individual, informed choice with discussion of the potential benefits and risks.
Low risk: Did not meet current treatment criteria at the time of treatment initiation.	Discontinue therapy	Re-start when indications for therapy are met.

apy. There is no information about fracture risk upon discontinuing ibandronate therapy. Increased risk of fracture upon discontinuing bisphosphonates compared with continuing therapy also has been observed in analyses of large health care databases.^{80,81}

It would be helpful to have clinical trials comparing rates of adverse and serious adverse experiences in subjects randomized to continuing or discontinuing bisphosphonate therapy. Logically, if rare undesirable medical occurrences are causally related to bisphosphonate use, the risk should diminish over time as the bisphosphonate is eliminated from bone. However, apart from the Swedish data suggesting that the risk of atypical femoral fractures decreases following discontinuation of oral bisphosphonate,⁴⁰ there are no data to answer this question.

These data suggest that, after bisphosphonate exposure of 3-5 years in postmenopausal women with osteoporosis, protection from fractures persists for an unknown interval of time when therapy is withdrawn, that this protection wanes within 3-5 years of discontinuation, and that the risk of atypical femoral fractures increases with duration of therapy, but may decrease upon withdrawal of treatment. There are currently no data about the effects of withdrawing therapy in men or patients receiving glucocorticoids. While there is little reason to think that the response to withdrawing treatment would differ between men and postmenopausal women, it is uncertain what the bone mineral density or fracture response to stopping therapy would be in glucocorticoid-induced osteoporosis.

There are limited data to guide decision-making about the initiation and termination of “drug holidays.” Treatment decisions should be individualized according to a consideration of all available clinical information. In the absence of clear evidence, any recommendations for initiating a drug holiday or how then to monitor patients can only be “expert opinion.”

Our recommendations for considering a drug holiday are presented in **Table 2**. The decision to stop or to continue

therapy must be individualized based upon an assessment of the patient’s current fracture risk. These recommendations are in accord with the proposals made by the US Food and Drug Administration about the duration of bisphosphonate therapy that became available after our paper was submitted for publication.⁸² A drug holiday should be viewed as a temporary, not permanent, suspension of active therapy. It should be remembered that discontinuing a bisphosphonate may not necessarily be a “holiday” from treatment, because persistence of the antiresorptive effect is expected for an undefined period of time.

MONITORING A DRUG HOLIDAY

There are no data providing information on how to monitor patients or when to restart therapy after a holiday. In trials with women who had previously been provided alendronate or zoledronic acid, women were followed for 5 and 3 years, respectively, after discontinuation of therapy, during which vertebral fracture risk increased in those who stopped the drug.^{12,77} In the absence of guidance from clinical trials, empiric approaches are necessary. Although the approach has not been studied, bone mineral density and biochemical markers of bone turnover measured 2-3 years after discontinuation may provide information about the persistence of the effect of the retained bisphosphonate. A significant decrease in bone density or a significant increase in bone turnover marker suggests that the benefits of bisphosphonate therapy may be diminishing and that it may be time to return to active therapy.⁸³ Another untested approach is to reevaluate the patient 2-3 years after discontinuation, making the decisions to restart therapy based on an updated assessment of fracture risk using algorithms initially developed for untreated individuals. For example, if the patient has a T-score ≤ -2.5 , or if the patient has a T-score between -1.0 and -2.5 and a World Health Organization’s Fracture Risk Assessment estimate of fracture risk that meets treatment guidelines, consider reinitiating therapy. If, at any

time during the drug holiday there is a fracture, restarting therapy (not necessarily a bisphosphonate) is advised. More research is needed about the role of serial bone density testing and bone turnover markers in monitoring fracture risk after therapy cessation, as well as the optimal therapies to use following a drug holiday.

WEIGHING THE BENEFITS AND THE RISKS

When all of the evidence is considered, the antifracture benefit provided by the amino-bisphosphonates far outweighs the potential risks of therapy in most patients at high risk of fracture. Depending on the severity of osteoporosis, between 9 and 60 patients need to be treated for 3 years to prevent one vertebral fracture (Table 1); between 20 and 68 patients need to be treated for 3 years to avoid one nonvertebral fracture. Even discounting the increased risk of fracture with advancing age, the number needed to treat for 8 years would be between 3 and 23 to prevent a vertebral fracture, and between 7 and 26 for nonvertebral fracture. Based on the range of risk estimates for osteonecrosis of the jaw, one case would occur for every 1000 to 100,000 patients treated. Using the data from California,⁴⁷ one atypical femoral fracture would occur in 1282 patients treated for 8 years. Based on the Swedish data,⁴⁰ 8 years of therapy would result in one atypical femoral fracture for every 149 patients treated (8.4 cases/10,000 patient-years).

These estimates of benefits and risks come from studies generally involving healthy older Caucasian postmenopausal women with osteoporosis and may not pertain to other patients including younger women, other races, patients at low fracture risk, and those with other medical problems or who take medications such as glucocorticoids or chemotherapy.

Careful attention must be taken to ensure that patients prescribed bisphosphonate therapy are likely to benefit. The World Health Organization's Fracture Risk Assessment tool⁸⁴ and similar Canadian Association of Radiology-Osteoporosis Canada Fracture Assessment tool⁸⁵ can help identify those patients at moderate-to-high risk for whom osteoporosis treatment is appropriate. In patients at low risk of fracture, the balance between benefit and risk makes treatment less attractive.

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