

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-

Table 1. Antidepressive Benefits of Bisphosphonates for the Treatment of Postmenopausal Osteoporosis

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

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

Table 1 provides an overview of the anti-fracture efficacy with bisphosphonates in pivotal, registrational 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.

ANTIFRACTURE AND CLINICAL EFFICACY OF BISPHOSPHONATES

- Based on current evidence, a "drug holiday" from amino-bisphosphonates is not justified in patients who remain at high risk for spine fracture.

The risk of osteonecrosis of the jaw and atypical subtrochanteric femoral fractures with long-term amino-bisphosphonates is very small compared with the antitac- tive benefits provided in individuals at moderate or high fracture risk.

Protection from important fractures persists with long-term amino-bisphos- phonates therapy in patients with osteoporosis.

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 resorbative, bandionate, alendronate, and zoledronic acid. Bisphosphonates with higher affinity are more rapidly taken up.

here were no differences between groups in total cases of group, 0.5% in the placebo group; $P < 0.01$.⁹ although annual intravenous zoledronic acid (1.3% in the treated adverse event was reported in the pivotal phase III trial of An increased incidence of atrial fibrillation as a serious

ATRIAL FIBRILLATION

prevented, in addition to prevention of other fractures.¹⁶ Associated with bisphosphonate use, 100 hip fractures were that for every subtrochanteric fracture (typical and atypical) hospital discharge records (1996–2007), which suggested treatment. Consistent with this was an analysis of 90 million fractures, compared with the beneficial effects of years is small for the individual osteoporosis patient at high fracture associated with bisphosphonate use even beyond 5 hospital discharges (1996–2007),¹⁷ which suggested These results suggest that the absolute risk of atypical fracture discontamination.

Risk diminished substantially and rapidly after bisphospho- 8.4/10,000 patients/year with use of more than 2 years. The 10,000 patients/year for up to 2 years of treatment and did not take bisphosphonates was 1.8 atypical fractures per in atypical femoral fracture risk between patients who did or patients with a history of bisphosphonate use.¹⁸ The difference did femoral fractures occurred, of which 78% were in pat- 11,000 hip fractures, 59 radiographically confirmed atypi- lation survey of >12,000 femur fractures (including about with treatment for 8–10 years. In a Swedish national popu- 2 years to 113.1 such fractures per 100,000 patients/years treated atypical femoral fractures per 100,000 patients/years treated for an average of 5.5 years.¹⁷ Risk increased from 1.78 also occur in bisphosphonate-naïve patients.^{19–21} Sparse in- formation is available about the incidence of atypical fem- oral fractures in an American population identified 142 also occurs in a medical age, impaired renal function, if not some, but not all,^{20,21} studies. Atypical femoral fractures have been identified as risk factors for atypical fractures in 38. Glucocorticoids and proton-pump inhibitor therapy femoral shaft fractures that is a complication of osteopor- osis, distinguishing these fractures from the more common "typical" possessing a medial spike, absence of comminution), dis- tortion, occurring shaft, transverse or short oblique orientation, occurring and femoral fracture (located in the subtrochanteric region, occurring shaft, transverse or short oblique orientation, occurring and femoral fracture (located in the major features of an A consensus document defined the major features of an

ATYPICAL FEMUR FRACTURES

by the American Dental Association. In patients with osteo- porosis, the benefit of bisphosphonates in reducing frac- ture risk far outweighs the remote potential risk of osteo- necrosis of the jaw.

of the paucity of evidence supporting this approach, the use of bisphosphonates has been recommended,²² but because serum C-telopeptide of Type I collagen in dental resorption, to assess the risk of jaw osteonecrosis in patients with the risk of osteonecrosis of the jaw.²³ The use of potential risk of osteonecrosis of the jaw,²⁴ the use of events (eg, fractures) secondary to low bone density, not the decision based primarily upon the risk for skeletally related surgery. The American Dental Association suggests that value of withholding bisphosphonates before invasive dental procedures (eg, fractures) there is uncertainty about the Due to lack of evidence, there is uncertainty about the bisphosphonate use has not been established.

bisphosphonates, and causality between this disorder and oral This problem also occurs in patients exposed to bispho- coticoid therapy, and chemotherapy may be risk factors. Risk with duration of therapy.^{25–28} Poor oral hygiene, glu- patients of oral bisphosphonate therapy for osteoporosis, esti- mated users of the healthy adult population is unknown. In chronic users bisphosphonates delivered frequently to an immuno- suppressed population.²⁸ The incidence of osteonecrosis of the jaw in patients receiving bisphosphonates for osteopo- dures during oncology therapy, with high doses of intrave- often observed (95% of cases) after invasive dental proce- dures 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 proce- dures within 8 weeks in the maxillofacial region, with no healing pose bone in the maxillofacial region, with no healing

BISPHOSPHONATE-ASSOCIATED OSTEOECCROSIS OF THE JAW

fracture, atrial fibrillation, and esophageal cancer. Curances include bisphosphonates to undesirable medical re- ports have linked bisphosphonates to osteonecrosis of the jaw, atypical femur fractures in clinical trials were low, highly publicized postmarketing re- rates of serious adverse events reported in bisphosphonate seen in healthier clinical trial subjects.²⁷ While the overall predispose them to undesirable medical occurrences not complications, advanced age, comorbidities, other medi- cally often have conditions (eg, comorbidities, other medi- world," clinical setting. Additionally, patients treated clinically often come to attention after many thousands, if not millions, of patients are exposed to a drug in the "real are relatively common. Rare treatment-related complica- terms) may be identified in placebo-controlled trials if they able (ie, causally related) to the therapy ("side effects") in lay Adverse events and serious adverse events that are attribut- able, or birth defect) did not differ between groups re- ceiving bisphosphonates or placebo in pivotal clinical trials. Adverse events associated with bisphosphonates or placebo in hospitalization, prolongation of hospitalization, resulting in death, hospital- ability, or birth defect) did not differ between significant dis- medicial 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, hospital-ization, or birth defect) did not differ between groups re- ceiving bisphosphonates or placebo in pivotal clinical trials. Adverse events and serious adverse events that are attribut- able, or birth defect) did not differ between groups re-

RISKS ASSOCIATED WITH BISPHOSPHONATE

THERAPY

It is unusual to contemplate a drug holiday in the treatment of most chronic diseases because with therapies, benefit usually diminishes rapidly over time as the drug is gradually removed from the skeleton.

BISPHOSPHONATE "DRUG HOLIDAY"

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

Inflammatory Eye Disorders

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

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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.

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}

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

Impairment of Renal Function

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.^{6-8,38-63} Isolated cases of serious esophageal complications or upper gastrointestinal hemorrhage have occurred.⁶⁴ Oral bisphosphonates are contraindicated in patients with esophageal cancer.

ESOPHAGEAL CANCER

arterial fibrillation or other cardiovascular events. While carotid artery fibrillation could be the result of a transient decrease in serum calcium, the serious adverse events were not clustered around calcitonin, the result of a transient decrease in serum calcium about the time of the therapy for osteoporosis.⁵¹

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Table 2 Recommendations for Dung Holiday from Bisphosphonates

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MONITORING A DRUG HOLIDAY

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 indefinite period of time.

are met.

These purchases should not be limited to take a drug holiday—decision should be an individual, informed choice with discussion of the potential benefits and risks.

regular intervals.

Consider drug holiday after 3-5 years of alendronate, risendronate, or zoledronic acid therapy.

No information about ibandronate and drug holidays.

Discontinue therapy

Drug holiday not justified.

Urid hot meet current treatment criteria at the time of treatment initiation.

now > -2.5 (1-score), and no prior hip or spine fracture.

of ongoing high-dose glucocorticoid therapy.

1-scale skull = -2:3 at the hip,
previous fracture of the hip or spine

High-risk

Table 2 - Recommendations for Drug Category

These data suggest that, after bisphosphonate exposure of 3-5 years in postmenopausal women with osteoporosis, fracture rates persist 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 a typical femoral fracture 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 often to monitor patients can only be "expert opinion."

isocommuniacal or oral dysphonia, where are no data

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 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 bisphosphonate use, there is little evidence of a relationship between bisphosphonate use and the risk of atypical femoral fractures.

adapt). 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 databases.^{80,81}

