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# How Long to Treat with Bisphosphonates?

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## Abstract

**Bisphosphonate class of drugs, the most commonly prescribed for the treatment of osteoporosis, is effective in preventing and treating bone loss and fractures. However, the treatment duration and the applicability of "drug holidays" for bisphosphonates need optimization in order to minimize long-term exposure. Drug holidays may prevent potential adverse events while still maintaining some degree of antifracture efficacy via residual antiresorptive activity by retained bisphosphonates. Patients receiving bisphosphonates, who are at low-moderate risk of fracture, are potential candidates for a drug holiday. However, for high-risk patients or patients with previous history of fragility fractures, the benefits of continuing bisphosphonate therapy considerably outweigh their potential harm. Evidence-based guidelines regarding starting and stopping a drug holiday are not available; therefore, it is appropriate to monitor patients on a drug holiday to assess a declining antiresorptive effect. In case of a significant rise in bone turnover markers or significant decrease in bone mineral density, it may be time to restart therapy.**

## Keywords

**Osteoporosis, Bisphosphonate, Drug Holiday, Fragility Fracture, Bone Mineral Density, Bone Turnover Markers**

## 1. Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1]. Osteoporosis and related fractures are well known to be associated with increased mortality [2]. Bisphosphonate class of drugs, the most commonly prescribed for the treatment of osteoporosis, is efficient in preventing and treating bone loss and fractures [3]-[5]. Structurally, bisphosphonates are stable derivatives of inorganic pyro-

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phosphate (PPi), a naturally occurring compound in which two phosphate groups are linked via ester bond. Bisphosphonates bind to hydroxyapatite crystals because of their high affinity towards bone mineral. They get incorporated into the active bone remodeling sites, causing loss of osteoclastic resorptive function as well as accelerating osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase, an enzyme in the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase pathway [6]. As a consequence of long-term use of bisphosphonates, rapid and substantial decrease in bone turnover markers (BTMs) occurs, which is dose- and compound-dependent [7]. They remain bound to the bone for many years. Following order shows the binding affinities of various drugs used in the treatment of osteoporosis: zoledronic acid > alendronate > ibandronate > risedronate > etidronate. Because of their high affinity toward bone mineral, even after bisphosphonate discontinuation, retained bisphosphonate provides residual pharmacologic action for many years. In contrast, some of the other antiresorptive therapies quickly lose their activity after discontinuation, including denosumab, estrogen, raloxifene, and calcitonin [8] [9]. It should be noted that bisphosphonates are very hydrophilic and are poorly absorbed from the gastrointestinal tract after oral administration (generally with absorption of <1%). Moreover, only about 50% of the absorbed drug is retained in the skeleton, whereas the remainder is eliminated in the urine without being metabolized. Furthermore, skeletal uptake and retention of bisphosphonates are primarily dependent upon various host factors (e.g., renal function, prevalent rate of bone turnover, and binding site availability) and bisphosphonate potency in bone matrix. In addition, the amount of bisphosphonate retained after either oral or intravenous (IV) administration varies widely both between patients and across clinical conditions and is primarily believed to reflect variations in bone turnover [8] [10].

At present, there are increased safety concerns surrounding the long term use of bisphosphonates, including atypical femoral fractures (AFFs), osteonecrosis of the jaw (ONJ), and esophageal cancer [11] [12], along with the possibility that fracture risk reduction may persist for years after stopping the treatment. Therefore, the possibility to introduce “drug holidays” and thereby to prevent potential adverse events during long-term bisphosphonate exposure while maintaining some degree of antifracture efficacy via residual antiresorptive activity by retained bisphosphonate is still unknown.

## 2. Are There Risks Associated with Bisphosphonate Drug Holidays?

It would be ideal to compare clinical trial data of bisphosphonate use in fracture risk between patients continuing therapy and those who stopped so that their potentiality for a drug holiday can be assessed; unfortunately, limited prospective studies have addressed this issue [13]-[15]. However, approval of bisphosphonates in the United States was based primarily on studies performed up to 3 to 4 years duration; however, some studies have been extended.

The Fracture Intervention Trial Long-term Extension (FLEX) trial randomized patients completing 5 years of alendronate therapy to additional 5 years of alendronate or placebo[13] therapy; 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. At the time of discontinuation, a post hoc analysis of the high-risk FLEX patients (T-score of <−2.5, but without prevalent vertebral fracture) demonstrated an increased risk of all clinical fractures associated with a discontinuation compared with patients continuing alendronate therapy [13] [16] (**Table 1**).

In Health Outcomes and Reduced Incidence with zoledronic acid Once Yearly (HORIZON) extension trial, patients were treated with annual zoledronic acid for 3 years. Treatment for additional 3 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) [14]. The risks of other fractures including clinical or symptomatic vertebral fractures did not differ between the groups (**Table 2**). In both FLEX and HORIZON trials, the groups that continued therapy showed maintenance or small increases in bone mineral density (BMD) and showed BTM suppression. However, there was decline in hip BMD and gradual increase in BTMs in the groups that discontinued therapy (total hip BMD in the FLEX trial returned to the pretreatment Fracture Intervention Trial baseline after 5 years of discontinuation).

The subjects in Vertebral Efficacy with Risedronate Therapy-North America (VERT-NA) study were extended for a 1-year follow-up after completing 3 years of risedronate or placebo therapy. They stopped their respective study medications after the follow-up period. In the follow-up year of treatment, former risedronate users experienced significant decrease in BMD at the lumber spine (−0.83%, 95% CI = −1.30 to −0.35) and fe-

**Table 1.** Effects of continuing or stopping alendronate after 5 years of treatment.

| Objective | Inclusion Criteria | Exclusion Criteria | Result | | | Author's Conclusion |
|---|---|---|---|---|---|---|
| | | | BMD | BTM | Fractures | |
| To compare the effects of discontinuing ALN treatment after 5 years vs. continuing for 10 years | Postmenopausal women<br>• Age 55 - 81 years old<br>• Low femoral neck BMD < −1.6) at FIT baseline<br>• Assigned to receive ALN during FIT and completed at least 3 years of blinded treatment during the trial and participated in the subsequent open-label period | FLEX baseline total hip BMD < −3.5)<br>• Total hip BMD at FLEX baseline ≤ FIT baseline<br>• Currently receiving and planning to continue medications that may affect bone metabolism<br>• Impaired renal function (SCr > 2 mg/dL) | Total hip BMD decline in ALN group was significantly lower than placebo group (−1.02% vs. −3.38%, respectively; mean difference = 2.36%, CI = 1.81% - 2.90%). Lumbar spine was the only BMD measurement that showed an increase in BMD for the duration of FLEX for both placebo and ALN users, but was significantly greater for the alendronate group (1.52% for placebo vs. 5.26% for alendronate; mean difference of 3.74%, CI = 3.03% - 4.45%). In all other sites, BMD decline was significantly slower in patients on ALN vs. placebo. | • ALN users had relatively stable BTM measurements vs. placebo<br>• BTM levels increased gradually in the placebo group, but remained below FIT baseline levels | No significant differences between groups for all clinical fractures (19.9% with ALN, 21.3% with PBO; RR = 0.93, 95% CI = 0.71 - 1.21);<br>No significant difference between groups for nonvertebral fractures (18.9% with ALN, 19.0% with PBO; RR = 1.0, 95% CI = 0.76 - 1.32);<br>No significant difference between groups for morphometric vertebral fractures (9.8% with ALN, 11.3% with PBO; RR = 0.86, 95% CI = 0.60 - 1.22);<br>Significant difference between groups for clinical vertebral fractures (2.4% with ALN, 5.3% with PBO; RR = 0.45, 95% CI = 0.24 - 0.85);<br>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 of all clinical fractures associated with a discontinuation compared with remaining on ALN therapy [16] | These results suggest that for many women, discontinuation of ALN for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years. |

The Fracture Intervention Trial Long-term Extension (FLEX) trial [13]. ALN—alendronate; BMD—bone mineral density; BTM—bone turnover marker; FN—femoral neck; HR—hazard ratio; LS—lumbar spine; NS—not statistically significant; OR—odds ratio; PBO—placebo, RR—relative risk; TH—total hip; FIT—Fracture Intervention Trial; CI—confidence interval; SCr—serum creatinine.

moral neck (−1.23%, 95% CI = −1.87 to −2.19) but remained above baseline and higher than in the former placebo subjects.

Furthermore, BTMs after 1 year returned to baseline levels were similar to former placebo subjects. Despite the apparent resolution of treatment effect on these markers, previous risedronate group (1-year holiday) had 46% lower risk of morphometric vertebral fracture (RR = 0.54, 95% CI = 0.34 to 0.86) compared with previous placebo [15] (**Table 3**). Similarly, a recent study reported decreased BMD in the total hip and trochanter regions as well as increasing BTMs in patients who were on risedronate treatment for 2 or 7 years and discontinued for 1 year [17].

Thus, these trials demonstrate that for some patients, there was an increased risk of vertebral fracture as early as 3 years after discontinuation. It bears noting that none of these extension studies were designed or powered to evaluate efficacy on vertebral or nonvertebral fractures; these trials were designed to evaluate safety and collected fracture events as safety parameters. Therefore, the importance of the fracture data collected in these studies needs to be viewed in light of this [18].

## 3. When and for Whom Should Bisphosphonate Holidays Be Considered?

There are only few data available to suggest the optimal bisphosphonate treatment duration or its optimal time for a drug holiday. As some studies have reported that the incidence of AFFs might increase after 5 years of bisphosphonate use [19], it seems reasonable to suggest that consideration of a drug holiday be made after this time point in low-risk patients. Based on FLEX and HORIZON extension trial [13] [14], high-risk patients with

**Table 2.** The health outcomes and reduced incidence with zoledronic acid once yearly (HORIZON) trial [14].

| Objective | Inclusion Criteria | Exclusion Criteria | Result | | | Author's Conclusion |
|---|---|---|---|---|---|---|
| | | | BMD | BTM | Fractures | |
| Patients who previously had 3 years of yearly ZOL infusions were then re-randomized to either continuing ZOL or receiving placebo infusions for 3 more years | • Men and women 50 years of age or older were eligible for inclusion within 90 days after surgical repair of a hip fracture sustained with minimal trauma (*i.e.*, a fall from standing height or a lower height)<br>• Ambulatory before the hip fracture and having both legs | • Previous hypersensitivity to a bisphosphonate,<br>• Potential for pregnancy,<br>• CrCl of <30 ml/min,<br>•Corrected serum calcium level of more than 11.0 mg/dl (2.8 mmol/L) or <8.0 mg/dl (2.0 mmol/L),<br>• Active cancer, metabolic bone disease other than osteoporosis, and a life expectancy of less than 6 months in the investigator's judgment | ZOL mean FN BMD change of 0.24% vs. −0.80% in PBO (mean difference 1.04%, $P < 0.001$);<br>ZOL mean LS BMD increased by 3.20 vs. 1.18% for PBO (mean difference 2.03%, $P < 0.01$);<br>At all sites, BMD after 6 y of ZOL therapy was significantly ($P < 0.05$) greater than for those given ZOL for 3 years and then PBO for 3 years (except distal radius) | S-PINP rose slightly in both the ZOL (19%) and PBO (33%) groups ($P < 0.001$), but remained substantially below pretreatment levels | Significant difference between groups for morphometric vertebral fractures (3.0% with ZOL, 6.2% with PBO; OR = 0.51, 95% CI = 0.26 - 0.95);<br>No significant differences between groups for all clinical fractures (HR = 1.04, 95% CI = 0.71 - 1.54);<br>No significant difference between groups for nonvertebral fractures (8.2% with ZOL, 7.6% with PBO; HR = 0.99, 95% CI = 0.26 - 0.95);<br>No significant difference between groups for clinical vertebral fractures (HR = 1.81, 95% CI = 0.53 - 6.2, NS) | The group that continued ZOL for a total of 6 years had a significantly lower incidence of radiographically adjudicated vertebral fracture |

BMD—bone mineral density; BTM—bone turnover markers; FN—femoral neck; HR—hazard ratio; LS—lumbar spine; NS—not statistically significant; OR—odds ratio; PBO—placebo; RR—relative risk; TH—total hip; ZOL—zoledronic acid; S-PINP—Serum N-terminal propeptide of type I collagen; CrCl—calculated creatinine clearance.

**Table 3.** Fracture risk remains reduced one year after discontinuation of risedronate [15].

| Objective | Inclusion Criteria | Exclusion Criteria | Result | | | Author's Conclusion |
|---|---|---|---|---|---|---|
| | | | BMD | BTM | Fractures | |
| To assess the resolution of effects of RIS therapy in postmenopausal women with osteoporosis who completed a 3-year, double-blind treatment period in which they received RIS 5 mg daily or placebo and were then followed for an additional year without RIS therapy | • Women at least 5 years post-menopausal enrolled in the original study.<br>• Age < 85 years<br>• Either ≥ 2 vertebral fractures or 1 vertebral fracture and low lumbar spine BMD (T-score ≤−2). | • Conditions that might interfere with evaluation of spinal bone loss<br>• Received drugs known to affect bone metabolism, including calcitriol or cholecalciferol within 1 month prior to study entry | In the previous RIS group, BMD significantly decreased at the LS (−0.83%, 95% CI = −1.30 to −0.35) and FN (−1.23%, 95% CI = −1.87 to −2.19), but remained above baseline. | BTM after 1 year returned to baseline levels | Previous RIS group (1-year drug holiday) had 46% lower risk of morphometric vertebral fracture (RR = 0.54, 95% CI = 0.34 - 0.86) compared with previous PBO<br>Nonvertebral fractures were 5.0% in previous PBO group and 4.8% in previous RIS group (NS) | Despite the apparent resolution of effect on BMD and BTM, the risk reduction of new vertebral fractures remained in the year after stopping treatment with the former RIS group. |

BMD—bone mineral density; BTM—bone turnover markers; FN—femoral neck; HR—hazard ratio; LS—lumbar spine; NS—not statistically significant; OR—odds ratio; PBO—placebo; RIS—risedronate; RR—relative risk; TH—total hip; CI—confidence interval.

osteoporotic BMD or history of fragility fracture (including prevalent vertebral fracture) should not be candidates for bisphosphonate holiday, as was also recommended by Black *et al.* [20]. Patients at low risk of fracture should usually discontinue bisphosphonate therapy [21], and many who are at moderate risk might also be candidates for drug holiday. **Table 4** summarizes some guidelines [22] and recommendations [23] to help determine which patients might be considered for drug holidays from bisphosphonate therapy.

## 4. How Would the Patient's Drug Holiday Be Managed Clinically?

Indeed, the provider needs to explain the patient that fracture risk reduction may persist for years after treatment is stopped. This benefit will be gradually lost over time with treatment discontinuation. Moreover, there are no data to recommend the appropriate time to restart therapy after a holiday (not necessarily bisphosphonate). Al

**Table 4.** Recommendations for bisphosphonates drug holiday.

| Fracture risk | Assessment | Recommendation/comment |
|---|---|---|
| High (> 20% 10-year risk of fracture), Previous fragility fracture and FN still T-score ≤ −2.5 | NA | Drug holiday not justified, Continue bisphosphonate therapy or switch to another proven drug such as teriparatide or denosumab |
| Moderate (1% - 20% 10-year risk of fracture), FN now (T-score > −2.5), and no previous history of fragility fracture | • Assess clinical risk factors for fracture<br>• Assess FN BMD<br>• Request lateral spine X-ray scan to investigate for any subclinical vertebral fractures | • May be candidate for drug holiday<br>• If vertebral fractures are found, stratify patient as high risk and continue bisphosphonate therapy<br>• If there is no previous history of fragility fracture, a drug holiday can be considered if FN BMD T-score is > −2.5 and there are no other important clinical risk factors<br>Restart when indications for therapy are met |
| Low (<10% 10-year risk of fracture), Did not meet current treatment criteria at the time of treatment initiation | • No important clinical risk factors for fracture | At low future fracture risk, should be withdrawn from therapy<br>• Monitor at extended intervals (3 - 5 years) |

BMD—bone mineral density; FN—femoral neck; NA–not applicable.

though this has not been studied, some experts recommend close monitoring of BMD and measurement of BTMs associated with BMD for the next 2 to 3 years following discontinuation. Stable or increasing BMD is associated with reduced fracture risk, and is considered an indication of good response to therapy. A significant increase in BTMs or decrease in BMD that meets or exceeds the least significant change indicates time to restart bisphosphonate therapy or to switch to another drug for treatment of osteoporosis [24]-[27]. Moreover, patients should be counseled to continue lifestyle management activities, such as performing weight-bearing activities, consuming adequate calcium and vitamin D, and avoiding cigarettes and alcohol for managing osteoporosis.

## 5. Conclusion

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. Furthermore, bisphosphonates have been associated with a significant decrease in morbidity and increase in survival. However, some rare but serious adverse events that have been associated with their use include ONJ and ATJs. For those who are at low-moderate risk of fracture with therapy, a drug holiday can be considered, whereas for patients at high risk of future fragility fractures, the antifracture benefits associated with bisphosphonates far outweigh their potential harm.

## Conflict of Interest

The authors have no conflict of interest.

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