Bisphosphonates are the cornerstone of treatment for osteoporosis. These agents are generally safe and well-tolerated, but concerns have emerged about adverse effects related to long-term use, namely osteonecrosis of the jaw and atypical femur fractures. For most patients at moderate or high risk of fracture, the benefits of treatment far outweigh these serious but rare risks. Bisphosphonates accumulate in bone with some persistent protective effect after therapy is stopped, making it is reasonable to consider a “drug holiday.” The duration of therapy and the length of the holiday should be based on clinical judgment.

Bisphosphonates are effective agents widely used in the treatment of osteoporosis. The nitrogen-containing bisphosphonates in clinical use today differ in their binding affinity to bone; the rank order is zoledronic acid > alendronate > ibandronate > risedronate. Bisphosphonates significantly decrease bone turnover markers in a dose- and compound-dependent manner, with a peak effect in 3-6 months. With continued treatment, this new steady state is maintained for at least 10 years. Prolonged use leads to the progressive accumulation of the drug in the skeleton, resulting in a bisphosphonate reservoir that continues to be slowly released for months or years after treatment is stopped. Because there might be some lingering anti-fracture effect after treatment is stopped, it is reasonable to consider a “drug holiday” from bisphosphonate therapy. In this Practice Pearl, we provide guidance regarding the use of such drug holidays in women using bisphosphonates for fracture risk reduction.

**Initiating treatment with bisphosphonates.** Based on the National Osteoporosis Foundation (NOF) guidelines, healthcare providers should consider treating postmenopausal women based on the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine (after appropriate evaluation to exclude secondary causes)
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) AND a 10-year probability of a hip fracture ≥ 3% OR a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm (ie, using the FRAX® web-based tool [http://www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/))
- Clinician’s judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities below these levels
**Long-term studies with bisphosphonates.** Although approval of bisphosphonates in the US was based on studies of 3 to 4 years duration, some studies have been extended, with zoledronic acid, risedronate, and alendronate suggesting efficacy for up to 6 years, 7 years, and 10 years, respectively. In the 3-year extension of the zoledronic acid HORIZON pivotal fracture trial, subjects who received 3 doses were randomized to one of two arms: a continuation group that received 3 more years of zoledronic acid and a discontinuation group that received placebo. There were small differences in bone density and bone turnover markers between the 2 groups, suggesting residual effects. However, there were significantly fewer morphometric vertebral fractures in the group that continued treatment compared with the placebo group (14 in those who were continued on treatment versus 30 in those who stopped).

The extension of the risedronate VERT-NA study was a 1-year follow-up of subjects who completed 3 years of risedronate therapy or placebo, then stopped their study medications. In the year off treatment, former risedronate users experienced a decrease in bone mineral density (BMD), but their BMD remained higher than baseline and higher than in the former placebo subjects. Furthermore, bone turnover markers increased and were similar to former placebo subjects. Despite the apparent resolution of treatment effect on these markers, former risedronate users had a 46% reduction in the risk of new vertebral fractures compared with the former placebo subjects. A recent study looking at the effect of discontinuing risedronate for 1 year after 2 or 7 years of treatment showed similar results in terms of BMD and bone turnover markers.

The extension of the alendronate Fracture Intervention Trial (FLEX) enrolled subjects who had approximately 5 years of alendronate treatment in the Fracture Intervention Trial into a second 5-year study where subjects were randomized to either continue alendronate or start placebo. Spine BMD increased more (+3.8%) in the long-term treated groups as opposed to the placebo group, with fewer clinical vertebral fractures in the long-term treated group compared to the placebo group (~2% vs. 5%, 55% RRR or relative risk reduction) at the end of the study. Non-vertebral fracture risk reduction was also observed in the subset of patients without prior vertebral compression fractures but only in those entering FLEX with T-scores of -2.5 or lower at the femoral neck hip.

**Adverse events associated with long-term bisphosphonate use.** Concerns about two uncommon but possible time-related adverse events have emerged: osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF). Although the above-mentioned studies did not identify any specific issues related to the prolonged use of these drugs, there is accumulating evidence of an association between prolonged bisphosphonate exposure and these two potentially serious conditions. In a retrospective review of the HORIZON trial with IV zoledronate for osteoporosis, one case of ONJ was reported in the treatment group and another in the placebo group. A total of 12 fractures in 10 women were classified as subtrochanteric in secondary analyses of the FIT, FLEX and HORIZON Pivotal Fracture Trials, indicating that the risk of such fractures with use of bisphosphonates was very low, even in women treated for up to 10 years. Furthermore, iliac crest biopsies after up to 10 years of treatment have not shown oversuppression of bone turnover. Importantly, no causal relationship has been established between prolonged bisphosphonate exposure and either of these outcomes. Even though the risks of ONJ and AFF may increase after 5 years of bisphosphonate therapy, the likelihood remains very low.
**Duration of treatment and follow-up assessment of BMD.** The above-mentioned safety concerns have generated extensive debate about how long to treat with bisphosphonates. Because bisphosphonates accumulate in bone and provide some residual anti-fracture benefit after therapy is stopped, it is reasonable to consider “drug holidays” – time off bisphosphonate therapy (but possibly on another agent) – and then resuming therapy. The FDA held a hearing in September 2011 to review the long term safety and efficacy of bisphosphonates and suggested reevaluation of the need for continuing bisphosphonate therapy beyond 3 to 5 years,14 with no clear recommendations on how patients discontinuing treatment should be managed. Subsequently, there has been considerable discussion about drug holidays, but it is difficult to find evidence to support the need for or the duration of a break in treatment or to establish the effectiveness of treatment after restarting therapy. Nevertheless, the data from the randomized clinical trials discussed above suggest that the risk of vertebral fractures is reduced beyond 5 years of therapy. In FLEX, the number needed to treat (NNT) for 5 years to prevent one clinical vertebral fracture was 17 in women with a prevalent vertebral fracture and a femoral neck T-score of -2.0 or below at the start of the extension trial, and 24 for women without vertebral fracture and a femoral neck T-score of -2.5 or below.15 Therefore, continuing treatment for 10 years seems to be beneficial for high-risk patients. Even though the risks of bisphosphonate therapy for osteoporosis are small, the risk/benefit ratio may be to the disadvantage of low-risk patients. For patients who have met criteria for treatment, therapy may be stopped for a drug holiday after a course of some years, with the intention to restart after some time off. We believe the following clinical scenarios are a reasonable guide for clinicians to follow16,17:

- **Low risk of fracture:** treatment is not needed. Bisphosphonate therapy should be discontinued if it has been prescribed. Example: 52-year-old woman, menopause at age 50, lowest T-score -1.4, no risk factors, bisphosphonate therapy for 2 years. Treatment was not indicated in the first place and can be discontinued.

- **Mild risk of fracture:** treat with bisphosphonate for 3-5 years, then offer a drug holiday. Example: 68-year old woman, menopause at age 48, lowest T-score -2.3, parent with a hip fracture, bisphosphonate therapy for 5 years and BMD stable over that time. Treatment was indicated, but a drug holiday might be considered after 5 years of treatment.

- **Moderate risk of fracture:** treat with bisphosphonate for 5-10 years, then offer a drug holiday of 3-5 years. Example: 70-year-old woman, menopause at age 47, initial lowest T-score -2.8, no risk factors, bisphosphonate therapy for 8 years and BMD increased over that time with current lowest T-score -2.4. Treatment was indicated but after 8 years of treatment, a drug holiday might be considered.

- **High risk of fracture:** treat with bisphosphonate for 10 years, then offer a drug holiday of 1-2 years. A non-bisphosphonate treatment (eg, raloxifene or teriparatide) may be offered during the “holiday” from the bisphosphonate. Example: 70-year-old woman, menopause at age 45, lowest initial T-score -3.5, requiring ongoing corticosteroid therapy for rheumatoid arthritis, history of a vertebral fracture, bisphosphonate therapy for 10 years. Treatment was indicated and she remains at high risk of fracture after 10 years. If a holiday from the bisphosphonate is considered, interval treatment with teriparatide or raloxifene would be prudent.
After a drug holiday is initiated, reassessment of risk should occur after 1 year for risedronate (which has the lowest skeletal affinity), 1-2 years for alendronate, and 2-3 years for zoledronic acid (which has highest skeletal affinity). A decrease in BMD or an increase in bone turnover markers have been used as an indication to restart therapy despite the lack of evidence on risk for fracture when these surrogate markers begin to change off bisphosphonates. We suggest that the holiday can be continued until there is significant loss of BMD or the patient has a fracture, whichever comes first. Ultimately, the duration of the holiday should be based on individual assessments of risk and benefit.

Summary:

- Bisphosphonates are generally safe agents with robust evidence for fracture risk reduction.
- With long-term use, a reservoir of bisphosphonates accumulates and is gradually released over months or years, resulting in a lingering anti-fracture benefit after therapy is stopped. This makes it possible to consider “drug holidays.”
- The duration of treatment and the length of the holiday should be individualized based on risk/benefit assessments.

References

5. HTTP://WWW.NOF.ORG/FILES/NOF/PUBLIC/CONTENT/FILE/344/UPLOAD/159.PDF.


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