THE BISPHOSPHONATE DRUG HOLIDAY: WHAT IT IS AND WHO COULD BENEFIT

Postmenopausal women and other people with osteoporosis have benefitted greatly from the array of effective antiresorptive drugs on the market. Since their introduction over a decade ago these drugs, most in a class called bisphosphonates, have prevented millions of fractures and the excess morbidity and mortality that accompany them.

While the safety and efficacy of these drugs in short-term use are well established, their long-term impacts are less certain. Findings from extension trials are conflicting, but may suggest the absence of long-term benefits beyond five years of use. This, coupled with the emergence of evidence associating bisphosphonates with rare but serious side effects, has lead to the concept of the “drug holiday,” a period in which the drug is stopped, followed by monitoring and resumption of treatment when or if indicated.

This issue of “Osteoporosis: Clinical Updates” takes a look at the current thinking on bisphosphonate treatment duration and drug holidays. How long should treatment continue? Forever? For every patient? How can providers identify patients who would benefit from taking a drug holiday or discontinuing treatment altogether? How can providers identify patients who would benefit from staying the course without a drug holiday?

To help practitioners frame long-term management decisions, we will take a look at existing data and outline expert opinion in the field. We will then apply this data and opinion to the discussion of three patient cases.

Editor-in-Chief, Angelo Licata, MD, PhD

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Osteoporosis: Clinical Updates

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Statement of Educational Purpose
Osteoporosis Clinical Updates is published to improve osteoporosis patient care by providing clinicians with state-of-the-art information and pragmatic strategies on prevention, diagnosis, and treatment that they may apply in clinical practice.

Overall Objectives
Despite the availability of effective preventive, diagnostic, and treatment protocols for osteoporosis, research indicates that it is significantly underdiagnosed and undertreated in the general population. Through this publication, NOF encourages participants to incorporate current evidence and expert recommendations into clinical practice to improve the bone health of their patients.

Upon completion of each issue of Osteoporosis Clinical Updates, participants should be able to:
- Recognize concepts in osteoporosis research and clinical practice
- Identify implications of these concepts for osteoporosis patient care
- Adopt evidence-based strategies to study, prevent, and/or treat osteoporosis
- Improve patient care practices by integrating new data and/or techniques

Intended Audience
This continuing education activity is intended for health professionals who care for patients at risk for or suffering from osteoporosis practicing in primary care, endocrinology, geriatrics, gynecology, internal medicine, obstetrics, orthopedics, pediatrics, physiology, radiology, rheumatology, and/or physical therapy. This includes physicians, nurse practitioners, registered nurses, pharmacists, physician assistants, technologists, researchers, public health professionals and health educators with an interest in osteoporosis and bone health.

Activity Objectives
Upon completion of this CE material, the participant should be able to:
- Summarize expert opinion and recommendations related to bisphosphonate treatment duration and drug holidays.
- Recognize when it would be appropriate to consider a bisphosphonate drug holiday in osteoporosis patient care.
- Help patients appreciate the risk of rare adverse effects of bisphosphonate therapy as compared to the risk for osteoporosis-related fractures.
- Draft treatment plans for patients who would likely benefit from taking a bisphosphonate drug holiday.
- Identify patients who would probably benefit from staying on bisphosphonate therapy.

Osteoporosis: How Long to Treat, When to Take a Holiday, and When to Stay the Course

On a daily basis, the skeleton sustains microscopic damage. Healthy bone repairs itself (and maintains calcium-phosphorus homeostasis) through a tightly coupled process of programmed bone destruction and creation termed remodeling. It is a slow, continuous process in which old bone is removed (resorption) and replaced with new (formation). This repair process relies on the balanced action of osteoclasts, which remove old damaged bone, and osteoblasts, which replace the bone removed.

Osteoporosis results when this normal repair process is unbalanced: more old bone is resorbed than new bone formed. An array of conditions, medications, and genetic factors can lead to uncoupled bone remodeling. The most common of these is hormonal: the loss of estrogen at menopause or of testosterone with aging or prostate cancer treatment.

The goal of osteoporosis therapy is to restore the balance of resorption and formation closer to healthy levels. It can be done by inhibiting excessive resorption through use of antiresorptive agents or by promoting levels. It can be done by inhibiting excessive resorption through use of antiresorptive agents or by promoting levels. It can be done by inhibiting excessive resorption through use of antiresorptive agents or by promoting levels. It can be done by inhibiting excessive resorption through use of antiresorptive agents or by promoting levels.

The most widely used drugs for treating osteoporosis are not the same. All osteoporosis medications work through use of anabolic agents. Through use of antiresorptive agents or by promoting levels. It can be done by inhibiting excessive resorption through use of antiresorptive agents or by promoting levels. It can be done by inhibiting excessive resorption through use of antiresorptive agents or by promoting levels.

Antiresorptive medications include bisphosphonates, estrogen agonist/antagonists, hormone therapy (HT), the RANKL inhibitor denosumab, and calcitonin, which is no longer FDA recommended for treatment of osteoporosis.

Millions of prescriptions are written for osteoporosis medications each year. Studies have shown these drugs to exert differing influence on fragility fracture, both the likelihood and the location of fractures, as summarized in the table on page 3.

Bisphosphonates are incorporated into bone in the remodeling process. As a result, they persist in the body after discontinuance—some drugs longer (alendronate, risedronate) than others (risedronate, ibandronate). Their protective effects have been shown to persist as well. Clinical research has been done to assess residual effects of bisphosphonates in the time after treatment is stopped.

The large Fracture Interventional Trial Long-term Extension (FLEX) study compared ten years versus five years of alendronate treatment in over 1,000 postmenopausal female patients. The overall summary of findings suggested that, while ten years of treatment better maintained BMD and bone turnover, it did not translate into significant fracture-prevention benefits for most women. For women with moderate or low fracture risk, continuing alendronate for ten years resulted in no significant reduction in nonvertebral and morphometric (“silent”/asymptomatic) vertebral fractures. Significant reduction was seen only in rates of clinical (symptomatic) fracture, regardless of BMD or previous vertebral fracture.

In high-risk women, those with hip T-scores at osteoporotic levels (-2.5 or below) after five years on alendronate, subgroup analysis showed 50% fewer nonvertebral fractures in those that continued alendronate therapy compared to those that discontinued at five years. (Note in this analysis, women with T-scores lower than -3.5 were excluded. Individuals with hip T-scores at or below -3.5 are at very high fracture risk.) Five years after discontinuing alendronate treatment, BMD had decreased and markers of bone turnover had increased. Nevertheless, both measures were slightly better than baseline in all groups.

In summary, women in the FLEX trial who were at high risk of fracture after being treated with alendronate for five years clearly benefited from continuing treatment for ten years rather than discontinuing at five.

Similar results have been seen in studies of risedronate and zoledronic acid with a few differences. The loss of effect appears more rapid with risedronate: After three years of risedronate treatment it took one year to return to near-baseline BMD and markers of bone turnover (as opposed to 5 years with alendronate).
Ventral fractures remained reduced in the year after treatment was discontinued.1 Zoledronic acid showed persistent effects on BMD and bone turnover for longer (three years).

Although the numbers were small and the confidence interval wide, no significant difference was seen in clinically evident vertebral fractures or nonvertebral fractures.4 However, a 49% lower risk for morphometric vertebral fractures was observed in the zoledronic acid continuous treatment group.

Evaluating Risk/Benefit
(Putting Risk Into Perspective)

Serious side effects of bisphosphonate treatment are rare. The most common adverse effect, esophageal irritation and heartburn, is associated only with oral bisphosphonates. For patients unable to sit up or stand after taking a pill or patients with severe gastroesophageal reflux disease (GERD) or other gastroesophageal issues, parental therapy may be preferable.

The IV bisphosphonates are generally well tolerated, usually resolve in a few days and can be improved with analgesic pretreatment and tend to taper off with each subsequent infusion.

**Figure 2.** Study results showing impact of discontinuation on BMD, biochemical bone turnover markers, and fractures.

<table>
<thead>
<tr>
<th>Drug With Duration On &amp; Off</th>
<th>Spine BMD</th>
<th>Hip BMD</th>
<th>Bone Turnover Markers</th>
<th>Morphometric Vertebral Fracture</th>
<th>Clinical Vertebral Fracture</th>
<th>Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (5 years &amp; 5 years off versus 10 years on)1</td>
<td>↓ but above baseline</td>
<td>↓ but above baseline</td>
<td>↑ but below baseline</td>
<td>No significant difference from continuous treatment</td>
<td>↑ compared to continuous treatment group</td>
<td>No significant difference from continuous treatment</td>
</tr>
<tr>
<td>Risedronate (3 years on &amp; 1 year off)</td>
<td>↓ but above baseline</td>
<td>↓ but above baseline</td>
<td>No significant difference from placebo</td>
<td>↑ but below baseline</td>
<td>No significant difference from placebo*</td>
<td>No significant difference from placebo*</td>
</tr>
<tr>
<td>Zoledronic Acid (3 years on &amp; 3 years off versus 6 years on)2</td>
<td>↓ but above baseline</td>
<td>↓ but above baseline</td>
<td>↑ but below baseline</td>
<td>↑ compared to continuous treatment group</td>
<td>No significant difference from continuous treatment</td>
<td>No significant difference from continuous treatment</td>
</tr>
</tbody>
</table>

These are not the side effects that tend to worry patients. The side effects that cause concern are the extremely rare events that have been splashed across newspapers and television nationwide over the past few years: atypical femur fractures, osteonecrosis of the jaw (ONJ), and esophageal cancer. It is hard to compete with the power of these messages, which may start with major media outlets but trickle all the way down to emails forwarded by friends and family.

Healthcare providers can educate their patients to counter distorted perceptions of the risks associated with these drugs in relation to their established benefits. One method is to compare the patient’s 10-year risk for each outcome: atypical fracture vs. vertebral fracture, ONJ vs. hip fracture, etc. The graphic below illustrates relationships between familiar health threats and adverse effects of bisphosphonate therapies in a typical postmenopausal woman with an estimated 20% risk of major osteoporotic fracture based on verified risk factors. A 20% ten-year projected risk for osteoporosis-related fracture is the threshold for treatment under WHO guidelines (3% for hip fracture).

Data from a large Swedish population study found the increased risk of atypical fractures attributable to bisphosphonate use is very low: 0.0005 per year of use.2 This risk is more than offset by the number of fractures prevented: 10 typical osteoporotic hip fractures prevented for each excess atypical fracture incurred.3 Or, to include all osteoporosis-related fractures and not just those at the hip, alendronate treatment prevents 200 clinical fractures for each atypical hip fracture it causes.

In response to these data, the U.S. Food and Drug Administration issued a Drug Safety Alert in 2010 that recommended periodic review of patients treated with bisphosphonates, especially those treated more than five years. The Safety Alert recommended discontinuance of bisphosphonate treatment in patients who suffer atypical fractures.4

The incidence of ONJ is even lower: an estimated 1 case in every 10,000-100,000 patients taking bisphosphonates.5 However, when it occurs, ONJ is a very problematic condition: an exposed jawbone that has not healed for more than 8 weeks that is not due to radiation therapy. Possible co-factors that increase the risk of ONJ include:

- Older age, cancer, anemia, coagulopathy, diabetes
- Corticosteroids, chemotherapy, radiation, smoking
- Poor oral hygiene, dentures
- Pre-existing dental disease, infection, or invasive bone procedures

Data suggest that ONJ is more common in people using intravenous bisphosphonates at doses higher than those prescribed for osteoporosis and in patients on therapy for more than two years. Experts have suggested doing any invasive dental procedures before starting treatment or suspending therapy for three or more months before and after such procedures, although there is no evidence to support these recommendations.4

Studies investigating risk of esophageal cancer in patients on oral bisphosphonates have produced conflicting findings—either no increased risk or a very small increase, accounting for 1 to 2 incidents per 1000 users over 5 years as compared to untreated populations.6,7 The FDA currently considers the evidence to be insufficient to necessitate labeling changes and continues to review the issue.8

There are no randomized clinical trial data quantifying the impact of drug holiday on the incidence of serious rare side effects. However, data from the Swedish study discussed earlier suggest that risk of atypical fractures decreases with discontinuation.9

**Figure 3.** Incidence of atypical fracture in women who never or ever took bisphosphonates in Swedish study.9

<table>
<thead>
<tr>
<th>Bisphosphonate Use History</th>
<th>Number of Women</th>
<th>Atypical Fractures</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Age-Adjusted Absolute Risk/Year of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1,437,820</td>
<td>13</td>
<td>1.0</td>
<td>NA</td>
</tr>
<tr>
<td>Ever</td>
<td>83,311</td>
<td>46</td>
<td>47.3 (25.6-87.3)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Drug Holiday Recommendations:
Summary of Expert Opinion

Unlike most drugs, bisphosphonates persist in the skeleton and continue to be released long after administration. The drug holiday takes advantage of this residual effect. Although data are limited, enough is known for experts in the field of bone health to make recommendations regarding how and when patients can confidently be removed from therapy with yearly follow up. A bisphosphonate holiday does not mean no therapy and should not be
taken as a suspension of all treatment. People diagnosed with osteoporosis are at continuing risk for bone loss and fracture. It is essential that patients understand the need for ongoing surveillance and bone-healthy measures to protect against fracture.

Treatment duration guidelines published by the American Association of Clinical Endocrinologists (AACE) recommend that patients should be evaluated after initial periods of treatment (3-5 years depending on age). If BMD is stable or increased and the patient has had no fractures, AACE guidelines suggest that a drug holiday of at least one year may be offered with annual follow up.

Many clinical experts recommend using biochemical markers of bone turnover to monitor patients during drug holiday intervals. Increased bone turnover activity during a drug holiday is generally thought to indicate loss of residual drug effect and possible accelerated bone loss, deterioration of bone, and increased fracture risk. However, specifics of this connection remain unstudied and poorly quantified.

Despite the uncertainty, it may be helpful to monitor biomarkers in patients who have stopped bisphosphonate therapy. If after one year, markers are elevated, the drug’s beneficial effect has likely begun to wane. It may be worth considering resumption, change, or augmentation of the patient’s therapy.

It may also make sense to resume or change medications if, after one year, the patient’s BMD has declined more than the least significant change of the measuring device or if the patient has experienced a fracture. If the fracture is atypical, the FDA would recommend against resuming bisphosphonate therapy. Other treatment options can then be explored.

Based on existing data, it appears that longer drug holidays (2-3 years) are possible for zoledronic acid and alendronate and shorter drug holidays for risendronate and ibandronate (1 year). Patients with high fracture risk, BMD below -2.5 at the hip, or other risk factors for fracture (prevalent fractures, smoking, glucocorticoid use, etc.) may well benefit from continued therapy without a drug holiday.

All patients with low bone mass or osteoporosis can benefit from the following fracture prevention measures.

Nutritional support of bone health:
• Adequate intake of calcium, through diet first, supplement as needed to reach 1000-1200 mg daily depending on age.
• Adequate vitamin D (test serum levels and supplement as needed)
• Adequate protein intake
• Low alcohol consumption

Interventions to reduce fall risk:
• Avoidance of sedating medications during daytime hours
• Improvement of balance, muscle strength, and coordination
• Treatment of vision, neurologic, or rheumatic disorders that affect movement and proprioception
• Modification of domestic environment to increase safety (remove tripping hazards, add hand bars, optimize lighting, etc.)

Billions of women are currently treated for osteoporosis with bisphosphonate drugs. Emerging data suggest that many could benefit from a bisphosphonate holiday, a change to non-bisphosphonate treatment, or some combination of the two. As a result, clinicians managing these patients are increasingly called upon to tailor osteoporosis therapy to individual patients over many years of treatment.

**Patient Cases: Bisphosphonate Drug Holiday**

In the following case studies, we will discuss the clinical considerations and potential applications for bisphosphonate drug holidays in typical patients.

**Case 1: 66-Year-Old Postmenopausal Caucasian Woman on Ibandronate**

The first patient we will discuss is a 66-year-old recently retired teacher. When diagnosed with osteoporosis six years ago, the patient was prescribed ibandronate 150 mg once monthly. She has had no problems taking the ibandronate and remembers to take it each month.

The patient presents to her primary care provider for her bi-annual DXA follow-up. She expresses concern regarding her bisphosphonate therapy. She is worried about possible side effects and is not sure she is benefiting from treatment. She is also trying to reduce prescription costs.

Baseline BMD
• Hip: 0.74 g/cm² and 0.73 g/cm²; T-scores -2.6/-2.7 (left/right femoral neck)
• Lumbar spine: 0.72 g/cm²; T-score -2.8

Current BMD (6 Years from Baseline)
• Hip: 0.75 g/cm² and 0.74 g/cm²; T-scores -2.5/-2.6 (left/right femoral neck)
• Lumbar spine: 0.73 g/cm²; T-score -2.7

These scores indicate no change or a small improvement from the baseline measurements done on the same machine. They are stable, but still in the range of osteoporosis (below -2.5).

**Has the patient benefitted from bisphosphonate treatment?**

It seems clear that she has. In the six years since her baseline DXA, the patient’s bone density has remained stable.

The clinician takes a medical history focusing on known risk factors for osteoporosis-related fracture: family history, prior fracture, current smoking, alcohol abuse, sedentary lifestyle, low-calcium diet, vitamin D deficiency, glucocorticoid use, and secondary causes of bone loss.

The patient’s medical history is remarkable for COPD, hypertension, hyperthyroidism, and menopause at age 50 years.

The patient has no known family history for osteoporosis. She has no personal history of bone fractures as an adult, does not drink alcohol. The patient is a current smoker, averaging 30 packs per year. Despite her COPD, the patient walks about 1 mile daily.

The patient takes daily Advair and albuterol as needed to control her COPD. In addition, she takes daily lisinopril-hydrochlorothiazide for hypertension and manages hypothyroidism with daily levothyroxine.

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The patient takes daily Advair and albuterol as needed to control her COPD. In addition, she takes daily lisinopril-hydrochlorothiazide for hypertension and manages hypothyroidism with daily levothyroxine.

The patient is not lactose intolerant and supplements her balanced diet with 600 mg calcium (carbonate) with lunch, and 1000 IU vitamin D daily.

The patient’s current height is 5’2”, and weight is 140 lbs. This is compared to her height and weight 6 years ago, which were 5’4” and 130 lbs, respectively.

Other pertinent labs include 25-OH Vitamin D level, sufficient at 32 ng/mL, and TSH, within normal limits.
Suggested Duration of Holiday

<table>
<thead>
<tr>
<th>Low Risk (e.g., prevention)</th>
<th>Don’t treat</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mildly ↑ Risk (e.g., younger + T-score just below -2.5 + no additional risk factors or osteopenia with risk factors)</td>
<td>Treat for 4-5 years (alendronate/risedronate) or 3 years (zoledronic acid)</td>
<td>If BMD is stable, stop until significant ↓ in BMD, ↓ bone markers, or fracture</td>
</tr>
<tr>
<td>Moderately ↑ Risk (e.g., older, T-score below -2.5, no fractures, some risk factors)</td>
<td>Treat 5-10 years (alendronate/risedronate) or 3 years (zoledronic acid)</td>
<td>If BMD is stable, stop for 2-3 years (alendronate/zoledronic acid) or 1 year (risedronate) or until significant ↓ in BMD, ↓ bone markers, or fracture</td>
</tr>
<tr>
<td>High Risk (e.g., older, very low BMD, multiple risks or fractures)</td>
<td>Treat 10 years</td>
<td>If BMD is stable, stop for 1-2 years or until significant ↓ in BMD, ↓ bone markers, or fracture; possibly use alternate medication during holiday, such as raloxifene or teriparatide.</td>
</tr>
</tbody>
</table>

Figure 5. Summary of expert opinion on duration of treatment, duration of drug holiday, and monitoring.4,6,11 ,13,15

at 2.2 mU/L. Should this patient be offered a bisphosphonate drug holiday? Good arguments can be made on both sides of this question.

What is the argument in favor of a drug holiday? There are several factors in favor of discontinuation and monitoring:

• The patient has responded to ibandronate with stable BMD for six years.
• The patient prefers to stop taking the medication.
• The patient engages in a bone healthy diet, no drinking, and some exercise.

Do expert opinions provide support for a drug holiday in this case? While data specifically for ibandronate do not exist, AACE guidelines suggest that a drug holiday of up to one year can be offered without significant loss of antifracture efficacy for patients on risedronate – which ibandronate most closely resembles.13

If a drug holiday is recommended, what is the treatment plan? First, modifiable risk factors for fracture should be addressed. The clinician explores options for alternatives to Advair (which contains an inhaled corticosteroid) for treating the patient’s COPD, such as tiotropium. Consultation with the patient’s pulmonologist may be required. Obviously, smoking cessation is essential. This will require powerful motivation on the part of the patient. Predicating her drug holiday on quitting may improve motivation. Clinicians can aid in smoking cessation through pharmacologic and nonpharmacologic methods.

The patient would be taken off ibandronate for one year. After one year, the patient would be measured for BMD, markers of bone turnover, and serum 25-OH vitamin D. At that time, she would be assessed for any medication changes or new diagnoses, and evaluated on physical for any changes in balance or gait disturbance. This would be followed by annual physical, workup of calcium, vitamin D, and bone markers and biannual DXA in subsequent years. Ibandronate or some other approved osteoporosis treatment would be reintitated if/when any of the following occur:

• BMD decreases more than the least significant change (LSC) for the DXA device used.
• Bone markers return to pre-treatment levels (el- evated above normal).
• Patient experiences a fracture.

Do insurance plans cover measurement of biochemical markers of bone turnover? Many do. The patient’s insurance company may require documented medical indication for approval.

Clinicians should confirm the patient’s insurance coverage for the test and any specific submission requirements.

What is the argument against a drug holiday for this patient? It could be argued that the benefits of treatment currently outweigh real and potential harm.

Medication has stabilized the patient’s BMD. She is, however, still at high risk of fracture, particularly vertebral fracture. (Spine BMD -2.7) Vertebral fractures lead to back pain, reduced lung volume, restricted mobility, and ~20% increased mortality. They are particularly problematic for patients with COPD, who already have reduced lung volume.

This patient has probably already experienced vertebral fracture (height loss of two inches). Her risk is only going to get worse as she ages and as her COPD progresses. Data for alendronate suggest that clinical vertebral fractures significantly increased in patients who discontinued treatment after 4-5 years over those who continued.16,17

The risk of rare adverse effects, such as ONJ and atypical fracture, are extremely low for this patient. She has had no adverse effects to date. She has had no problem taking the medication. Its cost is relatively low. Most important, the patient is still at high risk of fracture.

Do FDA recommendations offer any guidance? About ibandronate? No. However, the FDA subanalysis of alendronate and zoledronic acid suggested that patients with a history of fracture and a BMD below -2.5 may benefit further from continued treatment.18

What factors should go into this patient’s treatment plan? Data with alendronate exist out to 10 years. Some experts recommend continuing for 10 years then re-evaluating. As data become available, the plan would be to monitor the patient’s BMD and markers of bone turnover, and continue to weigh risk vs. benefit yearly based on new data.

To establish the extent and nature of the patient’s spinal deterioration, she will be referred for evaluation by vertebral fracture assessment (VFA) or radiograph. In addition, she will be counseled on maintaining a bone healthy lifestyle – especially smoking cessation. She will be encouraged to continue her daily walks. The patient will be supplemented to minimally maintain adequate intakes of calcium and vitamin D. Serum 25(OH) vitamin D concentration will be measured yearly with aggressive replenishment when needed.

Case 2: 57-Year-Old Caucasian Postmenopausal Woman on Alendronate

The second patient we will discuss is a younger postmenopausal woman currently taking alendronate. She has been on a weekly 70 mg dose for five years. The patient was diagnosed with osteoporosis at age 52 after natural menopause at age 50. Her BMD is stable; the...
CME Program Eligibility
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The patient’s risk of adverse effects such as ONJ or atypical fracture, very low to begin with, may decline further with discontinuation of the drug. Because of her age, she is likely to need some form of treatment for osteoporosis over the next 20+ years. Mitigating potential cumulative harms of medication is probably a good idea.

How would the patient’s drug holiday be managed clinically?

The provider explains to the patient that she has benefitted from taking alendronate and that this benefit will be slowly lost over time with discontinuation. It is uncertain how long it would take for her to completely lose all gains made on the drug, but research has shown it to be maintained for at least 1–2 years. The plan will be to continue the patient’s bone-healthy diet, supplementation, and alcohol consumption/nonsmoking practices, increase her weight-bearing exercise, and follow her bone health by checking markers of bone turnover and DXA.

What else can be done to protect the patient’s bone health?

Steps to reduce bone-loss risk where possible can also be taken. For example, the patient’s use of PPIs and SSRIs can be reviewed. Both classes of drugs have been associated with increased bone loss and fracture risk. The clinician investigates non-PPI alternatives for treating her uncomplicated depression that use of non-SSRI medications, and nonpharmacologic options for treating her uncomplicated depression that...
adrenalone. She had stomach problems with adrenalone and discontinued it after three years in favor of once-yearly zolendronic acid. She has tolerated the infusions well.

Why does the patient want to suspend treatment? The patient is concerned about side effects of zolendronic acid, especially ONJ. She has recently had multiple dental extractions that were necessitated by advanced periodontal disease. She is anxious to proceed with dental implants as soon as possible, and her oral surgeon is concerned about healing.

Baseline BMD
- Hip: 0.67 g/cm² and 0.68 g/cm², T-score -3.3/-3.2 (left/right femoral neck)
- Lumbar spine: 0.78 g/cm², T-score -2.8

Current BMD
- Hip: 0.68 g/cm² and 0.70 g/cm², T-score -3.2/-3.0 (left/right femoral neck)
- Lumbar spine: 0.74 g/cm², T-score -2.6

Medical History
- Height by stadiometer at age 50: 5’7”
- Current Height by stadiometer: 5’7”
- Weight: 133 lbs (45 at age 50)
- CBC unremarkable. Specific labs for vitamin D, calcium within normal range.
- Does not smoke
- Does not drink
- Exercises regularly, swims and golfs
- Balanced diet includes dairy
- Daily calcium-vitamin D supplementation 800mg/400 IU

Can this patient reasonably take a break from bisphosphonates without unacceptable fracture risk? Perhaps. On the one hand, the patient’s fracture risk following treatment is still significant, despite the fact that her BMD has stabilized. Given her age and hip T-score below -2.5, her risk of hip fracture is significant. In addition, 2.5 inches in height loss could very well signify morphometric fractures in the patient’s spine, pointing to a high risk for subsequent vertebral fractures.

The dilemma here is that we don’t know what the fracture risk is for patients who have been treated. This is because T-score-based risk projections are premised on untreated patients. We assume the risk is high, but we don’t know. These drugs affect quality of bone as well as density, so subtle improvements beyond BMD may be present. This is the rationale for interpreting stable BMD as good sign.

On the other hand, the positive impact of zoledronic acid on bone density and bone turnover has been shown to persist for up to three years following discontinuation. Although there is no clear data translating these impacts into reduced fracture numbers, it can be assumed that the patient would not lose too much ground if she forgoes one annual infusion.

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The patient could then schedule her oral surgery for the year off of bisphosphonate treatment. Theoretically, this could give her the time to heal completely before resuming bisphosphonate therapy. Data on timing of bisphosphonate treatment and ONJ do not currently exist; however, what is known about the action of the medication on bone suggests that such an approach could be prudent.

The provider recommends a one-year holiday from bisphosphonate treatment.

During the patient’s bisphosphonate holiday, what can be done to control her fracture risk? Because the patient is at such high risk for fracture, the provider prescribes raloxifene 60 mg/day. The patient has no history of thromboembolic issues or coronary artery disease. She is counseled to increase her total daily intake of calcium to 1200 mg through diet and to increase her vitamin D supplementation to 800 IU/day.

At the end of one year, the patient’s markers of bone turnover and BMD will be measured. If either indicates significant bone loss, she will be returned to treatment on zoledronic acid. If she has no new fractures and measurements are stable or above baseline, she may be evaluated for a second year bisphosphonate holiday with continued raloxifene.

Another possible approach would be to prescribe teriparatide for two years, during which time the dental work could be completed. Then, after the dental work and healing are complete, resumption of zoledronic acid could be considered.

SUMMARY

There is clearly a need for more research, including head-to-head comparisons of different drugs, durations, and fracture outcomes over the decades during which people may be at heightened fracture risk due to osteoporosis. In the coming years, data are likely to accumulate regarding relative and absolute risk of the range of identified adverse side effects. As novel approaches are developed, we will need data on alternatives: combinations, anabolics, holiday cocktails, etc. In the meantime, clinical management decisions will require patient- and medication-specific solutions.

References
Osteoporosis International

Osteoporosis International is the leading scientific journal for clinical research in osteoporosis and related bone diseases. Published monthly, the journal is an international, multi-disciplinary joint initiative of NOF and the International Osteoporosis Foundation.

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