How serious is the risk of atypical femur fracture for osteoporosis patients on bisphosphonates, and when is a “drug holiday” justified? There are no definitive studies or guidelines, but here are some strategies to consider.

1. **Bisphosphonates used to treat osteoporosis may increase the risk for atypical femur fractures,** but the absolute risk is low in the short term and can decline fairly quickly if the drug is withdrawn.

   The adjusted relative risk of atypical femur fractures (AFFs) associated with bisphosphonate use is 1.70 (95% CI, 1.22-2.37) but the absolute risk is very low, estimated between 3.2 and 50 cases /100,000 person years.\(^3\)\(^,\)\(^4\) Longer durations of bisphosphonate therapy, from five to nine years, have been shown to increase the absolute risk of AFFs to above 100 cases/100,000 person-years.\(^3\)\(^-\)\(^5\) The risk of AFFs declines after stopping therapy, even by as much as 70% in the following year if bisphosphonate therapy is stopped.\(^4\)

2. **Discontinuing bisphosphonates may be appropriate for some patients with osteoporosis.**

   In some subgroups of patients at higher risk for fracture, continuing bisphosphonate use beyond 3-5 years has achieved additional reductions in vertebral fracture risk.\(^5\)\(^,\)\(^7\) Even after they are discontinued, bisphosphonates affect bone resorption.\(^8\) In addition to AFFs, longer bisphosphonate use in non-cancer patients is also associated with a risk, although very low, of developing antiresorptive-related osteonecrosis of the jaw (ARONJ).\(^9\)\(^,\)\(^10\)

   It is important to discontinue bisphosphonate when appropriate, but there are limited data on the optimal duration of bisphosphonate therapy. The following approach has been suggested.\(^11\)\(^-\)\(^13\)
   - For patients whose **pretreatment fracture risk** was **low**: Discontinue bisphosphonate.
   - For those whose **pretreatment fracture risk** was **moderate or high**: Consider a “drug holiday” after 3 to 5 years of bisphosphonate therapy, if the patient does not have:
     - a history of hip or vertebral fracture, or
     - post-treatment hip bone mineral density (BMD) T-score below -2.5.
   - Continued treatment with a bisphosphonate or another FDA-approved therapy for osteoporosis is advised for patients whose **fracture risk** is estimated to remain high after 3-5 years of bisphosphonate therapy, including those with:
     - ongoing glucocorticoid use,
     - a history of hip or vertebral fracture, or
     - a hip BMD T-score ≤ -2.5 after treatment

   Therapy must be individualized, based on assessment of each patient’s current fracture risk and comorbidities. Discontinuation of a bisphosphonate may be considered if it does not seem to be reducing a patient’s fracture risk effectively or sufficiently. A decline in BMD or incident fragility fracture in any patient on bisphosphonate therapy should trigger investigation for potential issues with medication adherence, absorption, calcium and vitamin D intake, and for secondary causes of bone loss. A change in therapy should be considered.

3. **The optimal duration of a “drug holiday” from bisphosphonates has not been determined.**

   To date, there are no clinical trials to advise clinicians about the best approaches to restarting therapy after a “drug holiday.” The following recommendations are empirically based.\(^11\)\(^,\)\(^14\)
• Monitor bone density every 1-3 years.
• If the patient develops a hip or vertebral fracture, resume treatment with an FDA-approved therapy for osteoporosis.
• If bone density declines significantly, consider resuming bisphosphonate or initiating another therapy for osteoporosis.\textsuperscript{11}
• Although markers of bone turnover may increase after stopping bisphosphonates,\textsuperscript{11,15} it has not been established that these markers correlate with an increased risk for fracture after discontinuation of bisphosphonate therapy.\textsuperscript{11,12,15} Some practitioners monitor bone resorption markers and consider resuming treatment when these rise significantly or reach pre-treatment levels.\textsuperscript{16} However, without validated studies, there are few data to support using bone turnover markers to guide a decision to resume bisphosphonates.

4. Generally, routine dental treatment should not be deferred due to use of antiresorptive agents.

The incidence of ARONJ in osteoporotic patients has been estimated to range from 0.028 to 4.3%.\textsuperscript{17} In addition to increased risk after more than two years of bisphosphonate use, ARONJ has also been reported in patients receiving denosumab, another potent anti-resorptive medication (see below). Other risk factors for ARONJ include age over 65 years, periodontitis, smoking, denture use, and diabetes.\textsuperscript{7}

Invasive bone procedures have been associated with the highest risk of ARONJ, raising questions about the possible hazards of dental procedures in patients using anti-resorptive medications. However, no cases of ARONJ developed in a recent study of 1,480 tooth extractions in patients receiving oral bisphosphonates, comparing two different extraction protocols including antibiotic use.\textsuperscript{18}

Patients taking anti-resorptive agents should receive routine dental examinations and treatments, ideally beginning before or soon after initiating anti-resorptive therapy. The American Dental Association issued guidelines in 2011 that serve as a helpful resource for multidisciplinary teams.\textsuperscript{7}

5. Denosumab is another option to consider for some patients with osteoporosis.

Denosumab is a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine essential for osteoclast development, activation, and survival. Denosumab reduces bone resorption, increases bone mineral density, and reduces risks for vertebral, non-vertebral, and hip fractures. Unlike bisphosphonates, the elimination half life of denosumab is relatively short, at approximately 25 days\textsuperscript{[19]} making it an intriguing option for physicians and patients concerned about increased fracture risk with persistence and accumulation of bisphosphonates.

AFFs and ARONJ have been reported in patients treated with denosumab,\textsuperscript{19-21} perhaps related to the potency of this anti-resorptive agent, rather than a cumulative effect. Additional adverse events noted with denosumab include hypocalcemia, eczema, cellulitis, and urinary tract infection. Denosumab has been FDA-approved for the treatment of osteoporosis in postmenopausal women at high risk for fracture (2010), as well as for treatment of bone loss induced by aromatase inhibitors in women with breast cancer and by androgen deprivation in men with prostate cancer (2011), and then for men at high risk for fracture due to osteoporosis (2012).\textsuperscript{22} However, no trials have been published to date that compare fracture outcomes among patients taking denosumab with those among patients using other osteoporosis therapies.

Administered by subcutaneous injection every six months, denosumab may be beneficial for patients at high risk for fracture who cannot tolerate or do not respond to other therapy. As it is not cleared by the kidney, denosumab is also suitable for the treatment of osteoporosis in patients who have impaired renal function. Data are limited about use of denosumab in patients with a GFR below 30 ml/min. In patients with stage G4 or G5 chronic kidney disease, any associated metabolic bone disease should be excluded prior to its use.

The effects of denosumab in patients with rheumatoid arthritis have been assessed in only one placebo-controlled trial. All 218 patients in the trial were taking methotrexate; 90 of the patients in the trial received glucocorticoids at doses up to 15 mg of prednisone. Although fewer erosions were seen in patients treated with denusomab compared with the placebo group, denosumab did not control disease activity or prevent joint space narrowing.\textsuperscript{23} Hip and lumbar spine BMD increased in
the denosumab treated group compared to placebo in patients taking glucocorticoids, as well as in those not taking glucocorticoids. Concerns have been raised about using a drug that inhibits the immune modulator RANKL in patients who are using treatments for rheumatic disease that also modulate the immune system. Whether RANKL inhibition and concurrent use of other biologic agents, including anti-TNF therapies, will increase the risk for infections or result in other adverse events still needs to be determined.

References:


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