COMMENTARY

Bisphosphonate Drug Holiday? Celebrate?

**Commentary on article by Jordan C. Villa, MD, Arianna Gianakos, BS, Joseph M. Lane, MD
Bisphosphonate Treatment in Osteoporosis: Optimal Duration
of Therapy and the Incorporation of a Drug Holiday**

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Bisphosphonates are the mainstay of treatment of osteoporosis, a condition characterized by low bone density and/or poor bone quality leading to an increased risk of fracture. Using either oral or intravenous formulations of this class of drug has led to successful treatment of this chronic metabolic disease with fracture risk reduction ranging from 47 to 70% for vertebral fractures, 28–50% for hip fractures, and 19–38% for other non-vertebral fractures. This is unique when you consider the polypharmacy necessary to manage other chronic illnesses such as diabetes or hypertension. Unique also to this class of drug is their accumulation in the target tissue, with binding in bone hydroxyapatite that can inhibit osteoclast function long after the drug has been discontinued. A third but more troublesome outcome of bisphosphonate use is the rare but seemingly, at least to patients, paradoxical increase of a rare type of femur fracture known as atypical femur fracture.

The latter two features are the key driving forces behind the concept of the “drug holiday”—a cessation or pause in bisphosphonate treatment. The goal is to attenuate the small risks of prolonged treatment without losing the large benefit of decreased fracture risk. At October’s ASBMR conference, a presenter commented that the drug holiday is “an evidence-free zone.” This article by Villa et al. presents the

available evidence along with expert opinion, guiding the practitioner based on risk stratification that did not exist in the binary yes/no treatment decisions that characterized early bisphosphonate use. Alternative treatments that have not been implicated in atypical fractures, such as estrogen, raloxifene, and teriparatide, are discussed in the article as is denosumab which, as with all potent anti-resorptives, does carry the risk of atypical fractures but whose suppression of bone turnover wanes quickly upon discontinuation of the drug.

Bisphosphonates initiated in patients with low bone density that did not at initiation of treatment meet current FRAX guidelines for therapy can safely be discontinued. In patients with T-scores between –2.0 and –2.5, a temporary pause in treatment is reasonable after 3–5 years depending on the bisphosphonate used. The holiday can be continued as long as bone mineral density does not significantly decline, the bone turnover markers stay in a therapeutic range, and there are no new fractures.

The message should come through loud and clear that treatment should not be stopped in those with osteoporosis as defined by T-scores of –2.5 or less, vertebral fractures, or ongoing high-dose glucocorticoid treatment and possibly elevated bone turnover markers though this is controversial. The authors do advise monitoring for over-suppression of bone turnover markers that may indicate a need to pause, decrease the dose of the bisphosphonate given, or switch to another agent. Switching should also be considered if bone density declines, bone turnover remains high (NTX>35 or CTX>450), the patient is poorly adherent or intolerant to bisphosphonate therapy, or if a new fracture occurs while on treatment.

Just as we monitor the efficacy of our treatments, so, we must continue to research and review the evolving science surrounding the bisphosphonate holiday. Too many patients and physicians consider the “5 years of Fosamax” as a hard stop or even cure of the disease without the acknowledgment

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of continued risk of fracture and changes in bone metabolism over time.

Compliance with Ethical Standards

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