



PIC QUESTION OF THE WEEK: 10/22/07

Q: Can patients take a *drug holiday* when using bisphosphonates for osteoporosis?

A. The bisphosphonates (alendronate, risedronate, and ibandronate) play an important role in the treatment and prevention of osteoporosis. Intravenous bisphosphonates (pamidronate and zoledronic acid) are also commonly used in the management of hypercalcemia associated with malignancy and in multiple myeloma. Although generally well tolerated, the long-term effect of these drugs on bone turnover has come into question. There is evidence that extended use of orally administered bisphosphonates can result in alteration of bone turnover, micro fractures, and, in rare cases, bone necrosis. Bisphosphonate-associated osteonecrosis of the jaw (BONJ) is a recently identified complication of these drugs, but primarily seen with intravenous products.

Bisphosphonates have extremely long elimination half-lives (some have proposed ≥ 10 years) and the potential to decrease bone repair with long-term use. Some authors have recommended that oral agents be discontinued after several years of continuous administration in order to maintain bone integrity and reduce the frequency of BONJ. One frequently cited study (FLEX Trial) examined the benefits and risks of continuous use of alendronate (5 or 10 mg) for ten years vs. five years of active treatment followed by an additional five years of placebo. Patients were evaluated for bone mineral density (BMD), markers of bone turnover, and the frequency of vertebral, hip, forearm, and other fractures. Although there was a moderate decline in BMD in those receiving placebo, the values at ten years still exceeded those at baseline. Patients given placebo also had an increase in biochemical markers of bone turnover and frequency of *vertebral fractures*, but no increase in non-vertebral fracture rates. The authors concluded that with the exception of women at high risk of vertebral fractures, a five-year course of alendronate might be sufficient. An earlier study of ten years duration utilizing various doses of alendronate and placebo indicated that BMD was greater in those treated continuously with alendronate than those receiving treatment for five years and subsequently administered placebo. In relation to the lumbar spine, BMD values at ten years were still above baseline in the placebo treated group. Details of these two trials can be obtained from the references listed below. Although standard guidelines have not been established, it appears that women with low risk of vertebral fracture may cautiously discontinue bisphosphonate therapy after treatment periods of approximately five years. They must be periodically monitored for changes in BMD and re-institute treatment if values significantly decline.

References:

- Length of bisphosphonate therapy. Pharmacist's Letter/Prescriber's Letter 2007;23(2):230203.
- Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after five years of treatment. The Fracture Intervention Trial Long-Term Extension (FLEX): A randomized trial. JAMA 2006;296:2927-38.
- Bone HG, Hosking D, Devogelaer JP. Ten years experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189-99.

Massouma Mohamedraza and Gabriel F. Smith, Pharmacy Clerkship Students

The PIC Question of the Week is a publication of the Pharmaceutical Information Center, Mylan School of Pharmacy, Duquesne University, Pittsburgh, PA 15282 (412.396.4600).