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COMMENTARIES

Long-Term Bisphosphonates for Osteoporosis: An Introduction

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Since the introduction of alendronate in the mid 1990s, bisphosphonates have revolutionized the treatment of osteoporosis. Bisphosphonate treatment has convincingly been shown to be effective in the treatment of postmenopausal osteoporosis (1). Many millions of women are under treatment worldwide. Postmarketing surveillance has yet to show evidence of any prevalent side effect of bisphosphonates that was not observed early in their use. This is all good. Yet, as the first patients given bisphosphonates approach the 10-year anniversary of bisphosphonate treatment, we find ourselves asking how long our patients should be treated. Long-term bisphosphonate therapy has been the subject of reviews (2;3), editorials (4), and a workshop at the 2004 Annual Meeting of the American Society for Bone and Mineral Research. Issues regarding mechanisms of fracture protection and possible risks of long-term bisphosphonate therapy are presented in this commentary. We asked Ian Reid to summarize recent data on long-term effects of alendronate (5) and Socrates Papapoulos to discuss the basis for long-term treatment (6). Both authors suggest approaches to rethinking therapy after the five- to 10-year mark, as has Paul Miller in a recent review (2).

Fracture prevention by bisphosphonates and other antiresorptive agents is correlated much better with reduction in markers of bone turnover (7;8) than with gain in BMD (9;10). Explaining this requires a model. What is it about lowering the rate of bone turnover that accounts for protection against fragility fracture? It is believed that microarchitectural effects of antiresorptive agents may prevent the occurrence of "stress risers" (*e.g.*, resorption pits or plate perforations that weaken bone locally); antiresorptive agents could thereby strengthen bone out of proportion to their net effect on BMD (11-13). It remains to be proven that bisphosphonates prevent the occurrence of stress risers in humans or that their microarchitectural effects account for fracture protection. Nonetheless, in a model based on microarchitectural effects, a sustained reduction in bone remodeling might be predicted to produce sustained protection against fracture.

As discussed by Reid (5) and Papapoulos (6), a series of long-term studies now show clearly that treatment of postmenopausal women with risedronate for up to seven years (14) or alendronate for up to 10 years (15-17) leads to a sustained and nonprogressive reduction in the level of bone turnover markers to the level in premenopausal women. Why are the effects of bisphosphonates nonprogressive? Orally active bisphosphonates are deposited on the mineralizing bone surface, and osteoclasts are exposed only to bisphosphonate that was recently administered or released from matrix as the result of bone turnover (6). If inhibition of bone resorption is proportional to the amount of newly administered bisphosphonate, rather than to the cumulative dose, it follows that inhibition of bone resorption by alendronate and risedronate will be sustained and nonprogressive, as presented in detail by Reszka and Rodan (3). Consistent with the biochemical data, histomorphometric analysis of a small number of bone biopsies

discloses that bone turnover rates and architectural features in women treated with alendronate for five to 10 years are similar to those of premenopausal women (18).

Fracture data from the Fracture Intervention Trial (FIT) extension (FLEX) study were recently presented in abstract form (16). FLEX was a five-year study in which 1099 women, who were previously treated with alendronate in FIT, were rerandomized to alendronate (either 5 or 10 mg/day) or placebo. Although absolute reductions in long-term fracture rates cannot be determined because there was no continuous placebo group, these data are reassuring to patients and their physicians, suggesting that continuation of bisphosphonates for up to 10 years is safe and effective. Thus, long-term bisphosphonate therapy creates a new steady state in which bone turnover is reduced and no deleterious effects on bone are evident, with fracture protection for at least five years and encouraging fracture data to 10 years of treatment. So, why not simply leave patients on bisphosphonates indefinitely? Concerns about indefinite treatment arise because, even though inhibition of bone resorption may be nonprogressive for 10 years of treatment, bisphosphonates do accumulate in bone.

Bisphosphonates have a long residence time in bone. The terminal half-life of alendronate is approximately 10 years (3), and alendronate will therefore accumulate in bone for up to three half-lives, or 30 years. Inhibition of bone resorption is sustained for at least five years after cessation of alendronate therapy (16;17), illustrating that alendronate released from the matrix during bone remodeling effectively inhibits osteoclasts. If inhibition of bone resorption is proportional to the sum of the recently administered alendronate dose plus previously administered alendronate that is released from the matrix, as proposed (3), then over time, as alendronate release from saturating bone matrix stores continues to increase, bone resorption rates could slow eventually to dangerous levels. The release of alendronate from bone matrix after 10 years of 10 mg/day is estimated to be equivalent to 2.5 mg/day orally (3).

The mineralization of bone increases during bisphosphonate therapy (19;20). The primary phase of mineralization of newly formed bone takes weeks, but the secondary phase occurs over years. As bone remodeling slows, the net age of existing bone increases, allowing more time for secondary mineralization to take place. Increased tissue mineral content (rather than a remodeling transient or a true increase in the ratio of bone volume to total volume) is largely responsible for the sustained increases in BMD during bisphosphonate therapy (20). As tissue mineral content increases, bone becomes tougher and is protected from fracture, but bisphosphonates at high doses produce highly mineralized and homogeneous bone that is brittle and subject to microfracture damage (21). Preliminary reports indicate that after five years of risedronate (22) or 10 years of alendronate treatment (18), tissue mineral content, on average, is in the normal premenopausal range – about where one might want it. The effects of longer term accumulation are unknown, however.

High-dose intravenous bisphosphonate therapy of cancer-induced bone disease has recently been associated with osteonecrosis of the jaw (23;24). Most patients were also receiving chemotherapy or corticosteroids, and without good case-control data, the role of bisphosphonates in this complication is impossible to establish. We are aware of a number of unreported cases, however, suggesting that the complication is not rare in cancer patients treated with bisphosphonates. In one study, six of 63 patients with osteonecrosis of the jaw were receiving oral bisphosphonates for treatment of osteoporosis (24). It seems likely to us that jaw osteonecrosis is a dose-related side effect of bisphosphonate therapy that is rare in the oral dose range and more common with intravenous bisphosphonate use. Good case control studies are necessary to confirm or refute this interpretation and define risk factors for osteonecrosis; duration of oral bisphosphonate therapy and cumulative dose will be an important consideration.

As patients pass the five- and 10-year anniversaries of bisphosphonate therapy, a

number of strategies are available to reduce bisphosphonate dose or provide drug holidays, as outlined in the accompanying papers (5;6) and other reviews (2;3). These strategies would continue bisphosphonate therapy at a lower net dose, and thereby avoid further accumulation of bisphosphonates in bone after the five- to 10-year window in which their safety and efficacy have been demonstrated or can be inferred. We believe that such strategies deserve consideration, because we are unlikely ever to have data to determine whether chronic bisphosphonate therapy is too much of a good thing.

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