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EDITORIAL

Bisphosphonate therapy: how long is long enough?

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The unique pharmacological properties of bisphosphonates (tight binding to bone mineral, long retention in the skeleton) provide both opportunities and challenges for clinicians [1]. Unlike all the other drugs used to treat osteoporosis, the effects of bisphosphonates on bone remodeling persist after stopping therapy. Knowledge of these properties prompted studies to evaluate the duration of effects on bone remodeling, bone mineral density, and fracture risk upon stopping treatment, beginning with the early phase 2 and phase 3 studies with alendronate and risedronate and continuing until the extension of the most recent phase 3 bisphosphonate fracture study, the HORIZON trial with annual intravenous dosing of zoledronic acid [2–11]. The initial studies with alendronate demonstrated gradual decreases in BMD and increases in biochemical markers of bone turnover toward baseline values over several years [2–8]. In contrast, resolution of the effects of risedronate on bone mineral density and bone turnover within 1 year was reported [9, 10]. At the other end of the spectrum, minimal changes in both BMD and turnover markers were observed in the first 3 years upon stopping annual intravenous zoledronic acid therapy after three doses [11]. The more limited information about the effects of discontinuing therapy on fracture risk suggests that, after 3–5 years of treatment, protection from fracture persists for 1–2 years and then gradually wanes [8, 9, 11, 12].

These studies have evaluated the off effects of therapy after exposure of 2 to 5 years in clinical trial settings. Although interesting, this information is of limited relevance to the majority of patients in daily practice since most patients discontinue oral bisphosphonate therapy within the first few months of treatment, the average duration treatment being only a few months [13]. Appreciation of these facts led Ström and colleagues to address two questions in their recent paper: (a) how long must oral bisphosphonates be taken before fracture protection can be observed after stopping treatment and (b) what is the duration of fracture risk reduction after short-term treatment? [14] Taking advantage of the robust Swedish database, they were able to follow more than 17,000 mostly treatment-naïve patients who were begun on oral bisphosphonate therapy. They monitored fracture rates in subgroups stratified by treatment duration and by time off therapy. These rates were then compared to those observed in patients who took their prescribed drug for less than 1 month. The authors observed that the patients taking oral alendronate and risedronate for at least 1 year had lower rates of fracture after stopping therapy that did the control group. However, this fracture protection was only evident during the first 6 months after treatment was stopped. During that interval, a reduction of 60 % in the adjusted risk of fractures requiring hospitalization was noted. Patients treated for 1–6 months or 6–12 months had more modest reductions in fracture risk during the first 6 months after stopping treatment (21 and 37 %, respectively). While there were trends toward better fracture protection beyond 6 months after stopping in patients who received treatment for more than 1 year, those effects were not statistically significant. These analyses are limited, of course, by a relatively small sample size and limited statistical power. No differences in the effects of alendronate or risedronate on the magnitude or duration of fracture protection were noted.

There are several clinical messages in these interesting data. The observations confirm the suspicion that taking an oral bisphosphonate for less than 6 months has little effect on

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fracture risk, and that treatment for less than 1 year is suboptimal compared to longer-term treatment. These results conform to clinical trial data that consistently demonstrate a reduction in vertebral fracture risk within the first 12 months of bisphosphonate therapy whereas the more modest effects on non-vertebral and hip fracture incidences are generally not observed until exposure of more than 1 year [15–18]. Secondly, the Ström data demonstrate that therapy for at least 1 year does provide at least short-term residual clinical benefit. It would be helpful to know both the median duration and the ranges of bisphosphonate exposure in this group in the study.

Based on previous clinical trial data, there appears to be no greater effect on fracture risk with long-term bisphosphonate treatment (more than 3 years) compared to shorter-term treatment (1–3 years) [11, 19]. However, it is possible that the duration of therapeutic response upon stopping treatment might be longer with longer exposure to the bisphosphonate. The only evidence I am aware of that pertains to this question is an unpublished comparison of urinary N-telopeptide (NTX) values over 6 years in early postmenopausal women treated with placebo or with alendronate 5 mg daily for 2, 4, or 6 years in the EPIC study [6]. NTX values approached the value in the placebo comparison group perhaps slightly more slowly after 4 years of treatment than that occurred when treatment was stopped after only 2 years (Fig. 1). Indirect comparisons of the persistent reduction in markers a bone turnover over 3 years after three annual doses of intravenous zoledronic acid appear to be different than the gradual offset observed over several years after only a single dose [11, 20]. Unfortunately, the question of whether the duration of fracture protection beyond 1 year is correlated with the duration of response after stopping was not able to be addressed in the Ström study. Their study could also not address the question of whether there were differences in the duration of effects after short-term exposure to alendronate or risedronate. Due to the aforementioned rates of the off effects of alendronate and risedronate, follow-up for much longer than 1 year would be necessary to determine whether treatment effects persisted longer after stopping alendronate.

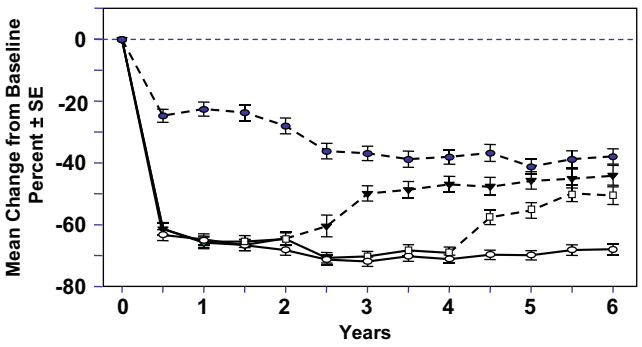

Fig. 1 Urinary N-telopeptide/creatinine values in young postmenopausal women receiving placebo for 6 years, alendronate 5 mg daily for 2 years followed by placebo for 4 years, 4 years followed by placebo for 2 years or for 6 years. *Solid lines* denote intervals on alendronate while *dashed lines* denote intervals on placebo. These previously unpublished data are from the study by Wasnich et al. [6]

These new data by Ström provide information about the minimal treatment interval to provide at least a short-term effect after discontinuing treatment, but they do not tell us about the optimal duration of treatment. However, there probably is no "optimal" bisphosphonate treatment regimen. It is highly likely that the appropriate duration of therapy is different for individual patients depending on bone turnover, age, renal function, absolute fracture risk, and other clinical factors. The information provided in the Ström paper makes it clear that we should not be content if a patient takes an oral bisphosphonate for only 1 year. Like other drugs such as estrogen, raloxifene, or denosumab which do not have skeletal retention, there appears to be no long-term benefit from short-term oral bisphosphonate treatment. Clearly, therapy for 1 year or less is not long enough.

Based on extant information, patients should be encouraged to remain on bisphosphonate therapy for an interval of 3–5 years in the absence of intolerance or side effects. As described above, patients can be reassured that fracture protection will be realized within the first few months after starting treatment and will persist throughout the treatment interval. In contrast, the risk of atypical femoral fracture, the most probable serious complication of long-term bisphosphonate therapy, is very low during the first 5 years of treatment [21]. After that interval of 3–5 years, the decision about whether to continue or to temporarily discontinue bisphosphonates can be addressed as has been suggested by several authors [22–24]. Upon deciding that oral bisphosphonate therapy is appropriate for a patient, adherence to therapy must then be encouraged by explaining the objectives of treatment (strengthening the skeleton and reducing fracture risk), the very favorable benefit to risk ratio during the first years of treatment and the risk of fracture associated with no or short-term treatment.

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