BoneKEy-Osteovision. 2005 January;2(1):13-19
http://www.bonekey-ibms.org/cgi/content/full/ibmske;2/1/13
DOI: 10.1138/20050145

PERSPECTIVES

Long-Term Therapy of Osteoporosis with Bisphosphonates: Evidence and Implications for Daily Practice

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January 2005

Bisphosphonates are an efficacious treatment of osteoporosis. If administered daily for up to five years, bisphosphonates decrease the risk of osteoporotic fracture in at-risk postmenopausal women (1-12). Systematic reviews with metaanalyses have further demonstrated that the antifracture efficacy of alendronate and risedronate is consistent among trials and patient populations (13-15). To improve patient convenience and long-term adherence to treatment and decrease potential gastrointestinal complications that may be associated with daily use, once-weekly regimens (providing the sum of seven daily doses) have been developed for both alendronate and risedronate. Consistent with the pharmacological properties of bisphosphonates and the principles of bone cell biology, once-weekly bisphosphonate administration should be considered "continuous" treatment, distinct from administration at longer drug-free intervals, which are commonly referred to as "intermittent" or "cyclical" regimens. Following the demonstration of the efficacy and safety of bisphosphonate therapy for the treatment of osteoporosis, current studies address questions that are essential for their optimal clinical use. These studies can be classified into four broad areas: long-term efficacy and safety; mechanisms of antifracture efficacy; use at intervals longer than one week; and use in therapies along with other antiosteoporotic medications. The first of these issues, briefly reviewed here, is followed by a discussion of the implications in the management of patients with osteoporosis.

Long-Term Effect of Bisphosphonates on Bone Metabolism

Bisphosphonates have unique pharmacological properties: their intestinal absorption is poor, accounting for less than 1% of the administered dose; they have a short plasma half-life; and about one-half of the administered dose concentrates selectively in the skeleton at the bone surface. The capacity of the skeleton to retain bisphosphonate is large, and saturation of binding sites is impossible during treatment of osteoporosis, even if the drug is administered for decades. The remaining bisphosphonate is excreted (unaltered in urine), and up until now, no bisphosphonate metabolites have been identified *in vivo*. Bisphosphonates are then embedded in the skeleton, where they remain for a long time in a biologically inert form. Elimination from this compartment is very slow and can continue for years.

At the bone surface, bisphosphonates suppress bone resorption. In early studies in rats, daily injections of pamidronate suppressed bone resorption in a dose-dependent manner and significantly improved external calcium balance (16). More importantly, with all doses used, the rate of bone resorption decreased quickly and reached a plateau that was also dose-dependent and did not decrease further, despite the continuous administration of pamidronate. These results suggested, for the first time, that daily administration of bisphosphonate does not lead to progressive suppression of bone turnover, and hence, that the accumulation of

bisphosphonate in the skeleton is not associated with a cumulative effect on bone metabolism. This pattern of response has been shown repeatedly in human studies of daily oral bisphosphonate treatment administered for up to 10 years (9;17;18). In addition, a recent preliminary report of bone biopsies from patients treated with daily alendronate for five or 10 years showed the presence of double tetracycline labels in all specimens examined and values of activation frequency similar to those observed by the authors in premenopausal women (19). Double tetracycline labeling was also observed in all studied bone biopsies from women with osteoporosis treated with daily risedronate for five years (20). Thus, available data show sustained (not excessive) suppression of bone remodeling and provide no evidence of an unfavorable effect of long-term daily bisphosphonate therapy on bone metabolism in women with osteoporosis.

Long-Term Effect of Bisphosphonates on Skeletal Fragility

The long residence time of bisphosphonates in bone, and their ability to suppress bone turnover, have raised some concerns regarding their long-term safety on bone tissue. Such concerns can be addressed by evaluating the long-term effect of bisphosphonates on skeletal fragility.

Skeletal fragility has been examined in a series of extensions of three previously reported pivotal clinical trials: Vertebral Efficacy with Risedronate Therapy (VERT)-international, Alendronate Phase III, and Fracture Intervention Trial (FIT). It should be noted that none of these extension studies was specifically designed to assess antifracture efficacy, but rather safety and efficacy on surrogate endpoints, as well as consistency of the effect of bisphosphonates over longer time periods. The first study consisted of two 2-year extensions of VERT-international (21). During the first five years of the study, two groups of women with osteoporosis received either placebo or risedronate (5 mg/day); in the following two years, all patients received active treatment. During years six and seven, the rate of vertebral fracture was similar in patients who received placebo previously and those who continued on oral risedronate. In addition, the incidence of vertebral fracture in the risedronate group was similar to that observed in years zero to three and years four and five. Moreover, the number of women with nonvertebral fracture was not significantly different between the two groups during years six and seven (7.4% vs. 6.0%, respectively).

The second study (18) was an extension of the clinical trial originally reported by Liberman *et al*. (1). In this extension study, patients received alendronate (either 5 or 10 mg/day continuously for 10 years or 20 mg/day for two years, followed by alendronate 5 mg/day for three years, providing a total dose equivalent to 10 mg/day for five years, followed by placebo for five years). The rate of nonvertebral fracture during years six to 10 in patients treated with alendronate (10 mg/day) for 10 years was similar to that observed during the first three years of alendronate treatment, although patients were older and had a higher risk of fracture because of increased age (see also the commentary by Ian Reid [22]).

The recently reported results of the FIT extension (FLEX) study, which were in abstract form, support these conclusions (23). In FLEX, 1099 patients, who participated in FIT and received alendronate for five years (on average), were randomized to placebo, alendronate (5 mg/day), or alendronate (10 mg/day) and followed for an additional five years. At the end of the 10-year observation period, incidence of nonvertebral and hip fracture in the alendronate/placebo group was similar to that of the alendronate/alendronate group (20% vs. 19%, respectively, and 3% vs. 3%, respectively). In addition, incidence of clinical vertebral fracture was significantly lower in the alendronate/alendronate group than in the alendronate/placebo group (2% vs. 5%, respectively).

Taken together, these results are reassuring for clinicians, because they indicate that prolonged exposure of bone tissue to bisphosphonate is not associated with

adverse effects on bone fragility and bone metabolism. In addition, the favorable effect of bisphosphonates on skeletal integrity seems to be sustained. Concerns based on theoretical considerations are not therefore justified by the data reported thus far in patients with osteoporosis.

Clinical Implications of Bisphosphonate Therapy

In general, chronic diseases require chronic uninterrupted pharmacotherapy to maintain the desired clinical outcome. The nature of osteoporosis and the properties of available pharmacological interventions raise questions, however, about the general applicability of this approach to the management of the disease. For many years, research in osteoporosis focused on the development of effective and safe medications, and a systematic investigation of the issue of duration of treatment began only recently. In principle, the length of treatment with any antiosteoporotic medication is determined by pharmacological properties and the risk of the individual patient. In practice, pharmacodynamic responses following discontinuation of treatment in different groups of women can be decisive.

Pharmacodynamic responses following cessation of bisphosphonate therapy administered for prevention of bone loss were adequately investigated in the Early Postmenopausal Intervention Cohort (EPIC) study (24;25). Early postmenopausal women were treated with alendronate or placebo for two, four, or six years and were followed for six years. Cessation of treatment after two or four years was associated with progressive increases in biochemical indices of bone resorption toward the level seen in women treated with placebo and BMD decreases at a rate similar to those of placebo-treated women. Thus, there was neither a rapid increase in the rate of bone resorption, which could have consequences for trabecular architecture, nor "catch-up" bone loss, as observed in a parallel group that received hormone replacement therapy for four years. These observations suggest that alendronate administered for two to four years, followed by intervals without bisphosphonate therapy, may be adequate for the prevention of early postmenopausal bone loss. For a number of reasons, the discussion of which is beyond the scope of this short review, such an indication is not generally accepted in clinical practice. Moreover, these very interesting pharmacodynamic responses are specific for young postmenopausal women and should not be extrapolated to the treatment of women with osteoporosis who have a different metabolic and fracture risk profile. There are, however, available data that allow the formulation of certain practical conclusions and cautious recommendations for the treatment of postmenopausal osteoporosis.

About 10 years ago, exploratory studies of women and men with osteoporosis treated with daily oral pamidronate showed that cessation of long-term treatment (i.e., 6.5 years) was not associated with decreases in BMD of the spine and femoral neck and that the rate of vertebral fracture remained stable during two years of follow-up without bisphosphonate therapy (26). From these findings, we hypothesized that resumption of bone remodeling after cessation of treatment led to the release of the bisphosphonate previously embedded in bone. The concentration of released bisphosphonate was sufficient to correct the imbalance between bone resorption and bone formation and to protect skeletal integrity, but insufficient to maintain the level of suppression of bone resorption achieved during treatment and to further increase BMD. The long-term responses of women with osteoporosis treated with alendronate are in agreement with these early conclusions. For example, cessation of alendronate treatment after five years was followed by modest increases in biochemical markers of bone turnover to levels clearly lower than those before any treatment was administered (18). The lack of a control group receiving placebo during the entire period of observation precludes any conclusions about the magnitude of the response. BMD at the spine remained stable during the five years without bisphosphonate treatment, but increased further on continuing treatment. Finally, BMD of hip sites showed some decrease, but not back

to baseline. Similarly, in the FLEX study, patients who received placebo after five years of alendronate therapy showed a 25% increase in urinary N-telopeptide (NTx) excretion that remained stable during the following five years without bisphosphonate (23). Changes in BMD were similar to those of the extension of the Phase III study, with the exception of total hip BMD, which reached pretreatment values after 5 years without bisphosphonate treatment.

Although hard evidence is still lacking, results obtained thus far can help provisionally to formulate some treatment recommendations according to a patient's risk. For example, in patients with low fracture risk, alendronate treatment may be stopped after five years, an approach that could also have economic implications. Alternatively, treatment with alendronate could be continued at 5 mg/day or 70 mg every two weeks, as in the FLEX study, where 5 mg/day was sufficient to fully maintain the responses in biochemical indices of bone turnover and BMD. It should be noted, however, that this suggestion is based on theoretical considerations, because data supporting similar efficacy of 5 mg/day and 70 mg every two weeks are not available. Regardless of the course of action, patients should be followed regularly, because data reported both in the prevention and treatment studies are mean values, and therefore, some patients will respond differently for reasons we do not yet understand. In patients with a high risk of fracture (*e.g.*, those with prevalent vertebral fractures), I believe that treatment with alendronate should be continued beyond 5 years. It is safe, keeps bone turnover in the premenopausal range, and sustains (or even improves) BMD gain. A frequently asked question is whether patients should continue treatment beyond 10 years. In my view, this question of scientific importance has limited practical significance, because very few patients will fully comply with a treatment that is administered for 10 years. Similar to therapies of other chronic diseases, compliance and persistence with regard to antiosteoporotic treatment is poor, and with once-weekly bisphosphonate, only 44.2% of patients persisted with therapy after one year (27). Moreover, it should be also noted that for most other diseases, the equivalence of acute and chronic treatment is implicit; osteoporosis is a rare example of a chronic disease in which controlled studies have extended to 10 years.

An important practical issue is whether conclusions derived from pharmacodynamic responses following cessation of long-term therapy with pamidronate and alendronate can be extrapolated to treatment with other bisphosphonates, because differences may exist among them not only in terms of potency, but other pharmacological properties. At present, this issue cannot be adequately addressed because of the lack of long-term data with other bisphosphonates. In a short communication, Watts *et al*. (28) reported changes of bone turnover indices and BMD one year after cessation of three-year treatment with risedronate (5 mg/day) or placebo in patients with osteoporosis. Urinary NTx excretion increased by about 40% to values that were not significantly different from those of controls while serum bone-specific alkaline phosphatase returned to pre-treatment levels. Spine BMD decreased, but remained higher than baseline and that of controls. On the basis of these data it seems reasonable to conclude that treatment with risedronate should be continued beyond the third year, regardless of the patient's level of fracture risk. The exact period of risedronate therapy and potential differences in resolution of the effect between this bisphosphonate and alendronate remain to be determined from ongoing basic and clinical studies. Ideally, head-to-head studies, such as those reported for efficacy (29), should be performed, with the resolution of the effect of treatment as the endpoint. The situation with new regimens, where bisphosphonates are administered at intervals longer than two weeks (*e.g.*, ibandronate, orally once a month or intravenously every three months; zoledronate, intravenously once a year, etc.), is more complex, and it is too early to draw any conclusions, because none of these regimens has currently received regulatory approval.

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