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# Bisphosphonates: New Dosing Regimens and Approaches to Treatment

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*New dosing regimens and other innovative approaches to bisphosphonate therapy appear promising, and will likely further enhance the already important role these agents play in the management of postmenopausal osteoporosis.*

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In an earlier issue of *Menopause Management* (Bilezikian JP. "PTH for Osteoporosis Treatment: An Update" 2002;11(1):22-3), advances in the treatment of postmenopausal osteoporosis were discussed in the context of anabolic agents. The discussion focused on the imminent approval of recombinant human parathyroid hormone (rhPTH 1-34) for the treatment of osteoporosis, viewed by this author as the most promising of the recent advances in osteoporosis treatment.

Since their FDA approval 6 years ago, bisphosphonates have played an increasingly important role in the prevention and treatment of postmenopausal osteoporosis. Many of the improvements in bisphosphonate therapy have less to do with the specific agent being used than with the new formulations of those agents and the innovative approaches to their use; specifically, formulations that enable more intermittent dosing, and the use of bisphosphonates in regimens involving combination therapy. Many questions remain with respect to the proper use of these drugs and the criteria for selecting appropriate candidates for bisphosphonate therapy.

Bisphosphonates are pyrophosphate analogues. Because of their affinity for bone mineral, bisphosphonates' effects are limited to the skeleton. Both alendronate and risedronate, the two bisphosphonates that are FDA approved for postmenopausal osteoporosis prevention and treatment, reduce skeletal turnover and improve bone mass. Increases in bone mineral density (BMD), especially in the spine and the hip, have been well documented with both agents.<sup>1,2</sup> Alendronate has been shown to reduce vertebral fracture risk,<sup>3</sup> and also nonvertebral and hip fracture risk in patients with osteoporosis.<sup>4</sup> In the longest prospective experience with bisphosphonates to date, Tonino and colleagues<sup>5</sup> have shown that gains in BMD obtained with alendronate are maintained over 7 years of treatment, without any "hidden" or unanticipated adverse events over time.

Risedronate has been shown to significantly reduce vertebral fractures during the first year of treatment.<sup>6,7</sup> In the only study in which hip fracture was the primary outcome, McClung and colleagues<sup>8</sup> reported a reduction in hip fracture risk of approximately 40% in older postmenopausal osteoporotic women with low

femoral neck BMD who were treated with risedronate; the drug had no significant effect on hip fracture risk in elderly women (over age 80) selected primarily on the basis of nonskeletal risk factors. Risedronate is approved for the prevention of glucocorticoid-induced osteoporosis; both alendronate and risedronate are approved for its treatment. Alendronate also is approved for the treatment of osteoporosis in men.

## Weekly Dosing

Dosing inconvenience and possible gastrointestinal (GI) intolerance provided the impetus for the development of formulations that would enable more intermittent dosing of bisphosphonates. Absorption of all bisphosphonates is poor; approximately 1% of the oral dose is absorbed.<sup>9</sup> Alendronate has been associated with an increased risk for upper GI irritation.<sup>10,11</sup> Clinical experience with risedronate has been more positive in terms of GI effects, but this has not been documented. To facilitate absorption and reduce the potential for esophageal irritation, patients taking bisphosphonates need to adhere to a strict administration regimen. Bisphosphonates must be taken at least 30 minutes

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before the first food, beverage or any other medication of the day, and must be taken only with plain water (6-8 ounces). Patients must not lie down for at least 30 minutes after taking the drug, and until after the first food of the day.

New formulations of bisphosphonates that enable weekly dosing are receiving a great deal of attention as a particularly effective approach to osteoporosis management. Two once-weekly formulations of alendronate were approved in October 2000: A 70-mg tablet was approved for osteoporosis treatment and a 35-mg tablet for osteoporosis prevention. A once-weekly formulation of risedronate is now under review by the FDA.

In their yearlong, multicenter, double-blind randomized trial, Schnitzer and colleagues evaluated and compared the safety and efficacy of three dosing regimens of oral alendronate in postmenopausal osteoporotic women.<sup>12</sup> The idea was that the once-weekly treatment with alendronate could provide similar efficacy to that achieved with standard daily dosing (10 mg) because of the agent's long duration of effect on bone. It was also hoped, as suggested in animal studies, that the potential for esophageal irritation might be reduced substantially with the more intermittent dosing.

The women in the study ranged in age from 42 to 95 years; all of the women had osteoporosis, defined as lumbar spine or femoral neck BMD  $\geq 2.5$  SD below peak premenopausal mean, or prior vertebral or hip fracture. The women were randomized to receive 10 mg once daily (the standard daily dose; n = 370), 35 mg twice weekly (n = 369) or 70 mg once weekly (7 times the daily oral treatment dose; n = 519). The primary efficacy endpoint was comparability of increases in lumbar spine BMD; secondary endpoints included hip and total-body BMD changes, and rate of bone turnover, as assessed by biochemical markers.

The investigators reported that reduction in bone markers (into the middle

of the premenopausal reference range), along with an increase in lumbar spine, total hip, trochanter and total-body BMD, were essentially indistinguishable across the three groups. At 12 months mean increases in lumbar spine BMD were 5.1% in the 70-mg once-weekly group, 5.2% in the 35-mg twice-weekly group and 5.4% in the 10-mg daily-treatment group. All three groups also demonstrated equivalent reductions in markers of bone turnover. Data on equivalency of the weekly and daily doses of alendronate in terms of fracture reduction were not reported in this study.

All of the treatment regimens were well tolerated, with patients experiencing a similar, low incidence (approximately 2%) of adverse upper GI events, such as esophageal irritation. The incidence of serious upper GI events, such as upper GI bleeding, was even lower (0.2% with the weekly regimen and 1.1% with the daily treatment). There was a trend toward a lower incidence of esophageal events in patients treated with the more intermittent dosing regimens, compared with those in the daily dosing group. The investigators concluded that the once-weekly 70-mg dosing regimen "will provide patients with a more convenient, therapeutically equivalent alternative to daily dosing, and may enhance compliance and long-term persistence with therapy." These same findings—with respect to BMD increases and bone turnover reduction—were again demonstrated after 2 years of treatment with weekly alendronate, with the same adverse event profiles as those seen at 1 year.<sup>13</sup>

Data on once-weekly risedronate, presented at the recent American College of Rheumatology meeting in San Francisco, demonstrated findings that were essentially the same as those already shown for alendronate.<sup>14</sup> Once-weekly risedronate (35 or 50 mg) was found to be as effective as the 5-mg daily regimen with regard to increasing bone mass and reducing bone turnover. It should be noted that the

authors reported equivalency with respect to BMD increases and bone turnover decreases between the study arms using the higher (50 mg) weekly dose and the 35-mg weekly dose. The adverse event profile was the same in all treatment groups.

### Clinical Significance of Once-Weekly Dosing

After its approval in October 2000, the once-weekly formulation of alendronate met with a dramatic, if not unprecedented, reaction; approximately 75-80% of the market for this agent switched to the weekly formulation within only 1-2 months. The rationale for the new formulation was clear, and the public clearly took to it. Despite this dramatic shift, it is likely that the 20-25% of patients who chose to remain on the daily alendronate regimen will continue to do so. Some individuals are simply uncomfortable with change; they are accustomed to the restrictions involved with taking alendronate and are doing well on their daily treatment regimens. For most patients, however, dosing convenience contributes significantly to the effective management of any chronic disease, including osteoporosis. Less-frequent dosing is likely to enhance compliance, especially when patients must follow strict administration regimens.

While compliance is an important aspect of any treatment regimen, it is especially critical when the duration of therapy is extended or chronic, as is the case with bisphosphonates. There is, however, some discussion about a possible worsening of compliance with these less-frequent dosing regimens. While, intuitively, it would seem that patients would find it easier to comply with a regimen that requires once-weekly, rather than once-daily, dosing, could the more intermittent dosing be more difficult to remember? The consequences of missing a dose of a once-weekly medication are far greater than those of missing a dose of medication taken on a daily basis; patients need to be

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made aware of this and encouraged to use whatever strategies they find helpful to remind them to take their weekly tablet.

There appear to be many fewer GI complaints with the weekly formulation of alendronate, and patients who have been unable to take the daily formulation because of GI distress might now be able to tolerate the once-weekly formulation.<sup>12</sup> As stated above, the adverse event profiles for risedronate were similar with the daily and weekly doses.<sup>14</sup> It is, however, important that patients understand that the administration instructions for weekly bisphosphonate therapy are the same as those for daily treatment.

### Future Approaches to Bisphosphonate Therapy

*Intravenous infusion.* Another approach to intermittent dosing of bisphosphonates might ultimately be enabled by IV infusion. IV bisphosphonate therapy could prove especially beneficial for older, more frail patients, and for those with a history of significant upper GI tract disease (e.g., esophageal strictures). Older patients, many of whom visit a clinician every 3 months for routine monitoring, would be able to receive their bisphosphonate therapy during their routine office visits, without concerns about handling the treatment regimen at home. This would be especially helpful for women who must already keep track of multiple drug regimens, as do many older patients.

In the late 1990s, investigators reported a significant increase in BMD with the use of IV ibandronate (1 or 2 mg) administered every 3 months<sup>15,16</sup>; a significant fracture reduction was not observed. More recently, ibandronate suffered a setback when the phase III trial failed to show a reduction in fracture incidence; it is believed that this might have been related to the dosing schedule.

In our practice, IV pamidronate (30 mg every 3 months for 1 year) has yielded an approximate 6% increase in lumbar spine BMD and a smaller, but still

impressive, increase in hip BMD.<sup>17</sup>

Another bisphosphonate, zoledronate, is now being studied in a regimen of once-yearly IV infusion; researchers have shown that the suppression of bone turnover achieved with this bisphosphonate is, indeed, maintained for a year after a single dose.<sup>18,19</sup> Furthermore, patients treated with this agent receive a small dose (1-2 mg) during an infusion that takes only 5-10 minutes (pamidronate infusion takes several hours). While this drug appears extremely promising, as does the concept of annual dosing, a great deal more research is needed. Potential downsides include the possible consequences when such a long-acting agent is given to a patient who is sensitive to the drug.

*Combination therapy.* A new treatment paradigm is represented by the possible use of bisphosphonates in combination therapy for osteoporosis treatment; investigators are studying combinations that include two antiresorptive agents or an antiresorptive with an anabolic, such as PTH. Concurrent treatment with alendronate and estrogen produced a somewhat greater (1-2%) BMD increase (more so in the lumbar spine than in the total hip) than did either agent alone in a placebo-controlled study conducted in hysterectomized women with low BMD.<sup>20</sup> At year 2, the women receiving placebo had a 0.6% mean loss in lumbar spine BMD, while those receiving alendronate alone or estrogen alone had a 6.0% mean increase; the mean increase in lumbar spine BMD was 8.3% in the women treated with combined alendronate and estrogen. Slightly greater decreases in biochemical markers of bone turnover were seen in the combined treatment group, but the mean absolute values remained within the normal postmenopausal range. In a yearlong, placebo-controlled trial conducted by Harris and colleagues, risedronate plus hormone replacement therapy (HRT) produced increases in BMD at all skeletal sites; BMD increases at the femoral neck and the

midshaft radius were modestly, but significantly, greater in the women treated with combined therapy than in those who received HRT alone.<sup>21</sup> The authors also report that the significant decreases in the biochemical markers of bone turnover observed in the study were somewhat greater in the patients receiving the combination therapy.

Sequential combination therapy, via HRT followed by alendronate, produced more impressive increases in BMD than did continuing HRT alone, in a study by Lindsay and colleagues.<sup>22</sup> Similar results have been reported when treatment with the selective estrogen receptor modulator (SERM) raloxifene is combined with alendronate.<sup>23-25</sup>

Even though there are no fracture data to support the view that combination therapy with two antiresorptives is better than single-agent therapy, the somewhat greater increase in bone density seen with the two agents is encouraging. On the other hand, there could be inherent disadvantages to combined antiresorptive therapy, in terms of oversuppression of bone turnover. In this regard animal studies conducted by Mashiba et al<sup>26</sup> have shown that prolonged suppression of bone turnover with very high doses of either alendronate or risedronate suppresses bone turnover by more than 90%, and is associated with the accumulation of microdamage, a term that refers to the appearance of bone in which breaks and other structural abnormalities can be detected at the microstructure level, but are not visible with clinical measurements.

There is no comparable evidence in human subjects that microdamage occurs with the recommended parameters of use for bisphosphonates; nevertheless, many experts recommend that suppression of bone turnover with combination antiresorptive therapy not exceed 70%.

A number of combined treatment regimens using an antiresorptive and an anabolic are currently being studied. These include studies of estrogen and PTH<sup>27-30</sup>

and an ongoing study of alendronate and PTH<sup>31</sup> that is being funded by the National Institutes of Health. Taking yet another approach, Watts and colleagues<sup>32</sup> have shown that adding androgens to HRT produces a greater change in bone density than that achieved with HRT alone.

Tibolone, a synthetic steroid with both antiresorptive and anabolic properties, shows promise as a more acceptable approach to “combination therapy” in women, since it is not an androgen. While not yet approved in the United States for osteoporosis treatment, tibolone has been shown to sequentially increase lumbar spine and total hip BMD, in a dose-related fashion.<sup>33</sup>

To date, there have been no studies showing improved fracture reduction with any of these combination regimens, as compared to single-agent therapy.

#### Longer-Term Bisphosphonate Findings

Data from longer-term use of bisphosphonates are now available; as discussed earlier in this article, the 7-year data on alendronate, reported by Tonino and colleagues,<sup>5</sup> are promising in what is the longest prospective experience with bisphosphonate therapy to date. A study by Cummings and colleagues<sup>34</sup> showed that women who lose BMD during the first year of treatment with alendronate (and raloxifene) are likely to experience BMD gains during their second year of therapy. In this study, analysis of data from the Fracture Intervention Trial showed that, among alendronate users who experienced the greatest first-year declines in BMD (1.4% had declines >4%), 92% had BMD gains averaging 4.8% during the second year of treatment.<sup>34,35</sup> In a study by Ravn and colleagues, involving 1,609 postmenopausal women, the investigators concluded that 4 years of treatment with alendronate (or HRT) was successful in preventing postmenopausal bone loss; alendronate recipients had overall BMD increases at the spine, hip and total body.<sup>36</sup>

When one group of women receiving alendronate was switched to placebo after 2 years of treatment, BMD declines were seen at all skeletal sites; the rates of decline were similar to those seen in the placebo group during years 1 and 2.

#### Conclusions

The advent of bisphosphonates for the prevention and treatment of osteoporosis has clearly been a pivotal event in the history of effective approaches to osteoporosis management. With new formulations, intermittent dosing schedules and approaches to combination therapy, the use of and adherence to this highly effective therapy for osteoporosis are likely to enjoy even further success.

Public awareness and education campaigns are stressing the importance of osteoporosis prevention. Women are learning that osteoporosis is not an inevitable consequence of aging and menopause but is, rather, a preventable disease; and the critical roles of diet, calcium and vitamin D supplementation, and exercise are being touted. There will, however, always be a role for pharmacologic intervention, in both the prevention and the treatment of this disease.

Bisphosphonates are just one component of a steadily growing arsenal of pharmacologic agents for the prevention and treatment of postmenopausal osteoporosis. New dosing formulations and innovative approaches to the use of these agents further enhance this “arsenal,” and provide women with a wider range of choices for osteoporosis prevention and treatment; this is especially important for women who cannot or will not take estrogen therapy. SERMS, such as raloxifene, along with anabolics and synthetic agents, such as tibolone, provide a still wider range of therapeutic options for midlife women.

Research on all of these agents continues, and longer-term data on bisphosphonates are now providing additional important information about the safety

and efficacy of these agents over time. Continuing research in related areas will likely shed new light on the causes of osteoporosis. Osteoporosis in men is an example of an area of research for which interest is growing steadily, as evidenced by an increase in the number of presentations and published reports on the topic over the past year. Men make up 20-25% of individuals with osteoporosis in the United States, but we are only now beginning to understand the causes of osteoporosis in men and how to treat it. Researchers are looking at the reasons men develop the disease, but at a much lower rate than that seen in women. What are the reasons for men's relative protection from developing osteoporosis? Do those reasons relate more to bone size (larger cross-sectional diameter) than to bone density? The answers to questions such as these will ultimately enable even more effective interventions in women at risk for, or already suffering from, osteoporosis. ■

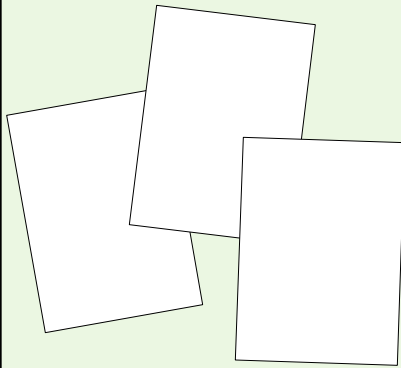
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