Jury's Out on Weekly vs. Monthly Bisphosphonates

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WASHINGTON — With billions of dollars at stake and the number of osteoporosis patients expected to grow, the battle for market share among osteoporosis drugs is heated. New data are emerging all the time, including results from several studies presented at an international symposium sponsored by the National Osteoporosis Foundation.

For the oral bisphosphonates, the question is whether women are more likely to stick with weekly formulations, like alendronate (Fosamax) and risedronate (Actonel), or monthly formulations, like ibandronate (Boniva). And the answer depends on whom you ask, judging from four poster presentations.

Two studies involving researchers from Roche Laboratories Inc. (codeveloper of Boniva, along with GlaxoSmithKline) suggested that not only did women prefer once-monthly ibandronate but they were also more likely to persist with the drug than were those on once-weekly alendronate or risedronate.

In the first study, Dr. John A. Sunyecz of Laurel Highlands Ob.Gyn. in Hopwood, Pa., and his colleagues assessed data from the HealthCare Integrated Research database, which contains claims data for roughly 17.5 million patients. Persistence was estimated as the proportion of patients who remained on therapy with no refill gaps based on a grace period, determined by the dosing window for weekly bisphosphonates (30-day gap) and monthly ibandronate (45-day gap).

Data collection began in April 2005 and is ongoing. Researchers identified women at least 45 years old with at least one claim for a monthly (ibandronate) or weekly (alendronate or risedronate) bisphosphonate. A total of 4,335 women were identified on alendronate or risedronate and 213 on ibandronate.

The unadjusted 9-month persistence rates were 41% for patients receiving monthly ibandronate and 33% for those on weekly bisphosphonates. The median time to discontinuation was 145 days for those on ibandronate and 115 days for those on weekly therapy.

Monthly ibandronate users were 31% more likely to be persistent with therapy, compared with those on weekly alendronate or risedronate, after controlling for age, copay, comorbidities, and prescriptions greater than a 30-day supply. "After accounting for potential confounding factors, the increased likelihood of persistence reflects the independent effect of dosing frequency on patient persistence," the researchers wrote.

In the second study, postmenopausal women were enrolled in a prospective, open-label study if they had been receiving once-weekly alendronate or risedronate for the prevention or treatment of osteoporosis or osteopenia for a minimum of 3 months. The women were given once-monthly ibandronate (150 mg) for a period of 6 months, wrote Dr. Neil C. Binkley, associate director of the University of Wisconsin, Madison, Institute on Aging, and his colleagues.

A total of 1,678 women completed the Osteoporosis Patient Satisfaction Questionnaire (OPSAT-Q) at baseline and at the end of the study or upon withdrawal. This questionnaire included four domains: convenience, quality of life, overall satisfaction, and side effects. Greater scores represented greater satisfaction or less bother/lower frequency of side effects. The summary score was the average of the four domain scores converted to a 100-point scale. Patients also completed a four-item preference questionnaire after the OPSAT-Q at 6 months.

After 6 months, 74% of the women preferred once-monthly ibandronate, whereas 8% preferred once-weekly therapy and 5% did not cite a preference. The remainder of patient responses were not evaluable. Overall, 70% of patients (1,087 out of 1,543) in the intention-to-treat population showed improvement in satisfaction with monthly ibandronate, compared with previous weekly therapy, after 6 months. The summary score and convenience, quality-of-life, and overall satisfaction domain scores improved.

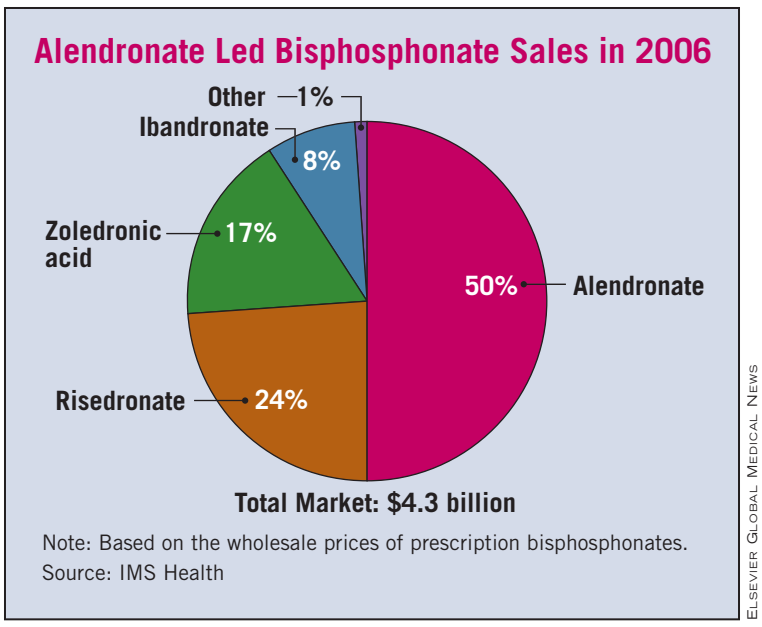
Compliance with ibandronate was 96%, with 94% taking at least 80% of their monthly ibandronate doses. Experience of stomach upset within 48 hours of dosing or missing three doses over 3 months with previous weekly therapy was associated with improved treatment satisfaction after 6 months of monthly ibandronate therapy.

However, in two studies involving researchers from Merck & Co. Inc. (maker of Fosamax), once-monthly ibandronate seemed to offer no advantage in persistence over once-weekly alendronate.

In the first study, Thomas W. Weiss, Dr.P.H., of U.S. Outcomes Research, Merck & Co. Inc., and his colleagues assessed data from the Longitudinal Prescription database, which contains prescription drug information for more than 150 million unique patients. Data were collected for the period of September 2004 to November 2006.

Women at least 50 years old were included if they filled a new (index) prescription for weekly alendronate, weekly risedronate, or monthly ibandronate. They were excluded if they had a prescription for any bisphosphonate during the 12 months before the index date, in order to focus only on newly treated patients. All of the women were followed for 1 year. They were considered persistent users if they did not have a therapy break of more than 30 days between the end of one prescription's supply and the beginning of the next.

The results included 84,399 women on alendronate, 51,588 on risedronate, and 29,998 on ibandronate. In all, 46%, 48%, and 54% of the women on alendronate, risedronate, and ibandronate, respectively, had no refills after the initial prescription. Patients with an index prescription for once-monthly ibandronate were 39% more likely to discontinue after filling their first prescription, compared with those on weekly alendronate.



Note: Based on the wholesale prices of prescription bisphosphonates.
Source: IMS Health

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"The results of this analysis suggest that persistency rates are not improved by monthly dosing of oral bisphosphonates versus weekly dosing," the authors wrote.

In a second study, Dr. Weiss and colleagues assessed the differences in women who persisted on weekly vs. monthly bisphosphonate therapy. The data come from the Drivers of Adherence to Bisphosphonate Therapy (DASH) study. For this study, the researchers contracted with a large pharmacy with more than 3,000 stores in 28 states.

Potential participants were identified by their retail pharmacy dispensing records. Patients were initially defined as persisters if they filled their bisphosphonate prescriptions at least five times in a 17-month period. Persistence was confirmed using the interview process. The researchers used a 57-item survey to assess reasons for persistence with bisphosphonate therapy. The final sample included 377 patients who persisted on weekly alendronate and 190 who persisted on monthly ibandronate.

Belief in the efficacy of osteoporosis drugs and the absence of side effects and drug interactions were strong determinants of persistence with bisphosphonate therapy. In all, 93% of weekly persisters reported belief in the drug's effectiveness, compared with 88% of monthly persisters. In both groups, 83% reported an absence of side effects.

However, weekly persisters reported fewer side effects, more positive beliefs about drug safety and efficacy, and fewer osteoporosis concerns than monthly persisters did. Weekly and monthly persisters were equally likely to report out-of-pocket costs and remembering to take the bisphosphonates as their biggest problems. Altogether, 45% of weekly persisters and 52% of monthly persisters reported out-of-pocket costs being a problem. And 37% of weekly persisters and 35% of monthly persisters reported that remembering to take the drugs was a problem.

Dosing frequency was not cited as a problem by many in either group—13% of weekly persisters and 7% of monthly persisters. "The DASH study suggests that the major drivers of persistency with bisphosphonates are belief in the effectiveness of the therapy and the lack of side effects and drug interactions, not dosing frequency," the researchers wrote.

Compliance is key to successful treatment with these drugs because bioavailability is notoriously poor.

Under optimal conditions—when patients follow dosing instructions perfectly—bioavailability of oral bisphosphonates is minuscule. Relative to a reference intravenous dose, the mean oral bioavailability of alendronate in women is 0.64% for doses ranging from 5 to 70 mg when administered after an overnight fast and 2 hours before breakfast. Mean oral bioavailability is 0.63% for 30 mg of risedronate and 0.6% for 2.5 mg of ibandronate.

But optimal conditions are demanding for a patient. Patients on alendronate and risedronate should take the drugs with plain water first thing in the morning and at least 30 minutes before food, beverages, or other medications, and they should not lie down for 30 minutes after taking either of these drugs.

Patients on ibandronate are advised to take the drug at least 60 minutes before the first food or drink in the morning and before taking any oral medications or supplements, including calcium, antacids, and vitamins. These patients should not to lie down for 60 minutes after taking the drug.

However, even when those instructions are followed, patients don't completely maximize bioavailability, which improves greatly the longer patients wait before eating. For 10 mg alendronate, bioavailability is reduced by about 40% when taken either 30 minutes or 1 hour before breakfast, when compared with dosing 2 hours before eating. The package labeling for alendronate also notes that "bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast." Drinking coffee or orange juice when alendronate is taken reduces bioavailability by about 60% as well.

For risedronate, the extent of absorption of a 30-mg dose when administered 30 minutes before breakfast is reduced by 55%, compared with dosing in the fasting state. Dosing 1 hour before breakfast reduces the extent of absorption by 30%, compared with dosing in the fasting state. Dosing either half an hour before breakfast or 2 hours after dinner results in a similar extent of absorption.

For ibandronate, the oral bioavailability is reduced by about 90% when taken with breakfast, in comparison with that observed in fasted patients. Both bioavailability and the effect on bone mineral density are reduced when food or beverages are taken less than 60 minutes after an ibandronate dose. ■