Jury's Out on Weekly vs. Monthly Bisphosphonates

BY KERRI WACHTER
Senior Writer

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

For 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). The answer depends on whom you ask, judging from four poster presentations.

Two studies with researchers from Roche Laboratories Inc. (codeveloper of Boniva, with GlaxoSmithKline) suggested women prefer once-monthly ibandronate and are more likely to persist with it.

In the first study, Dr. John A. Sunyecz of Laurel Highlands Ob.Gyn. in Hopwood, Pa., and 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. Persistence was assessed for a 9-month follow-up period.

The unadjusted 9-month persistence rates were 41% for patients on 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 versus those on weekly drugs after controlling for age, copay, comorbidities, and prescriptions for more than a 30-day supply.

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

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. The survey covered domains of convenience, quality of life, overall satisfaction, and side effects. Greater scores represented greater satisfaction. 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.

For both weekly and monthly users, belief in bisphosphonates' efficacy and the absence of side effects were determinants of persistence with therapy.

After 6 months, 74% of women preferred once-monthly ibandronate, while 8% preferred once-weekly therapy and 5% did not cite a preference. Overall, 70% in the intention-to-treat population showed improvement in satisfaction with monthly ibandronate, versus 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 doses. Stomach upset within 48 hours of dosing or missing three doses over 3 months with previous weekly therapy were associated with improved treatment satisfaction after 6 months of monthly ibandronate therapy.

However, in two studies with researchers from Merck & Co. (maker of Fosamax), ibandronate offered no advantage in persistence over alendronate.

In the first study, Thomas W. Weiss, Dr.P.H., of U.S. Outcomes Research for Merck and his colleagues assessed data from the Longitudinal Prescription database, which contains prescription information for over 150 million 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 prescription for weekly alendronate, weekly risedronate, or monthly ibandronate. Women were excluded if they had a prescription for any bisphosphonate during the 12 months prior to the index date. All were followed for 1 year. They were considered persistent users if they did not have a therapy break of over 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, versus those on alendronate.

In a second study, Dr. Weiss and colleagues assessed the differences in women who persisted on weekly vs. monthly bisphosphonates. The data came from the Drivers of Adherence to Bisphosphonate Therapy (DASH) study. In this study, the researchers worked with a large pharmacy (over 3,000 stores in 28 states).

Participants were identified by dispensing records. Patients were defined as persisters if they filled their prescriptions at least five times in 17 months. 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 drugs' efficacy and the absence of side effects were strong determinants of persistence with bisphosphonates. In all, 93% of weekly persisters reported belief in the drug's effectiveness, versus 88% of monthly persisters. In both groups, 83% reported no 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. Altogether, 45% of weekly persisters and 52% of monthly persisters reported cost to be a problem, and 37% of weekly persisters and 35% of monthly persisters reported that remembering to take the drugs was a problem.

Just 13% of weekly persisters and 7% of monthly persisters cited dosing frequency as a problem. Compliance is key because bioavailability is poor even under optimal conditions, when instructions are followed perfectly. 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 prior to 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. Patients are instructed to take the drugs with plain water first thing in the morning and at least 30 minutes before food, beverages, or other medications. In addition, they are instructed not to lie down for 30 minutes after dosing. 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 are instructed not to lie down for 60 minutes after dosing.

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

For risedronate, the extent of absorption of a 30-mg dose when administered 30 minutes before breakfast is reduced by 55%, versus dosing while fasting. For ibandronate, the oral bioavailability is reduced by about 90% when taken with breakfast, versus when taken in fasting patients. Both bioavailability and the effect on bone mineral density are reduced when food or beverages are consumed less than 60 minutes after an ibandronate dose. ■

Stock Up on Tongue Depressors for Bisphosphonate Patients

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — When you're seeing patients who are taking bisphosphonate drugs for osteoporosis, don't forget to look in their mouths, Dr. Steven T. Harris said at a meeting on diabetes and endocrinology sponsored by the University of California, San Francisco.

Osteonecrosis of the jaw recently was added to the precautions section of the prescribing information for all intravenous and oral bisphosphonates, so it is incumbent upon clinicians to look for this very rare complication.

"One of the things I've changed in my clinical practice in the past couple of years is that I laid in a supply of tongue depressors and I've started to look in people's mouths, which I was not routinely doing before," said Dr. Harris of the university.

Media reports about this side effect of bisphosphonates have caught the attention of patients, some of whom raise concerns about it during visits, he added.

Though no universally accepted definition exists for osteonecrosis of the jaw, a growing consensus characterizes it as an oral cavity lesion with one or more bare bone spots, in the absence of local malignancy or radiation therapy to the head and neck. This is not the same as a patient on bisphosphonate therapy complaining of tooth pain.

"This is a look in the mouth, and there is bone where there should be normal pink mucosa," Dr. Harris said.

Osteonecrosis of the jaw primarily has been seen in cancer patients receiving high-dose intravenous bisphosphonates therapy, usually monthly. In that population, approximately 0.5%-10% of patients may develop osteonecrosis of the jaw, a range affected by the underlying malignancy.

In patients on oral bisphosphonates, however, rough estimates suggest perhaps 1 patient per 100,000 may develop osteonecrosis of the jaw per year, he said.

The pathophysiology of this disorder is not understood.

Known risk factors for osteonecrosis of the jaw include cancer; concomitant therapies like chemotherapy, radiation, or corticosteroids; poor oral hygiene; and comorbid disorders such as preexisting dental disease, anemia, coagulopathy, or infection.

Be vigilant in patients with poor dental hygiene or procedures such as tooth pulling or teeth implants, Dr. Harris said. ■