Women Had 6-Year BMD Rise With Denosumab

ARTICLES BY KERRI WACHTER

DENVER — The investigational agent denosumab continued to increase bone mineral density in osteoporotic postmenopausal women during 6 years of continuous use, based on the results of an extension of a phase II study including 412 women.

"Over a period of 6 years, continuous treatment with denosumab resulted in progressive gains in [bone mineral density] in postmenopausal women," Dr. Paul Miller said at the annual meeting of the American Society for Bone and Mineral Research.

The 93 patients on denosumab 60 mg for 6 years had a continued increase in spine bone mineral density (BMD), with a mean cumulative increase from baseline in spine BMD of 13%. In addition, the reduction in resorption, as measured by serum C-telopeptide (CTX) levels, was sustained and plateaued over the course of continuous denosumab treatment.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.

The study was sponsored by Amgen Inc., which is developing the drug. Dr. Miller reported significant financial relationships with several pharmaceutical companies that make osteoporosis treatments, including Amgen.

In the parent trial, 412 women were randomized to receive denosumab, open-label oral alendronate (70 mg/wk), or placebo. Denosumab was given subcutaneously either every 3 months (at 6 mg, 14 mg, or 30 mg) or every 6 months (at 14 mg, 60 mg, 100 mg, or 210 mg). All participants took daily oral supplements containing elemental calcium (1 g) and vitamin D (400 IU).

Postmenopausal women up to 80 years of age were eligible if they had a bone mineral density T score from –1.8 to –4.0 at the lumbar spine or from –1.8 to –3.5 at either the femoral neck or total hip. An upper limit of –1.8 was selected to include subjects with both osteopenia and osteoporosis. The 2-year data were published in Bone in 2008 (43:222-9).

At the end of the first 2 years, patients were reallocated. Denosumab-treated patients who continued the study were reassigned based on their randomization group at enrollment. Patients originally randomized to denosumab 6 mg or 14 mg (every 3 months) or 14 mg, 60 mg, and 100 mg (every 6 months) received denosumab 60 mg every 6 months for the next 2 years. This is the dose selected for phase III trials.

Patients originally randomized to denosumab 210 mg every 6 months received placebo for the next 2 years. Patients randomized to denosumab 30 mg every 3 months first received placebo for 12 months and then were subsequently re-treated with denosumab 60 mg every 6 months for the next 12 months. Alendronate patients discontinued alendronate therapy at this time. The placebo group was maintained.

In the extension phase of the study, all patients received denosumab 60 mg every 6 months for 2 more years. Measurements of bone mineral density of the lumbar spine, total hip, and femoral neck were performed by dual-energy x-ray absorptiometry throughout the trial.

The 16 patients who had been on placebo for 4 years and were switched to denosumab 60 mg every 6 months for the last 2 years had gains in spine BMD that were comparable to those observed in the first 2 years of the trial for patients on denosumab 60 mg every 6 months. Similar results were obtained for hip BMD. Patients on denosumab for 6 years had an average cumulative hip BMD increase of 6%.

"The forearm data … are interesting because forearm BMD increased in the denosumab groups, unlike the other antiresorptive agents that have consistently shown a decrease," said Dr. Miller, whose group practice in Lakewood, Colo., specializes in the treatment of osteoporosis.

The adverse events seen during the extension were similar to those seen in the parent study. ■

Three Factors Found to Predict Bisphosphonate Prescriptions

DENVER — Significant predictors of receiving a bisphosphonate prescription within 90 days of a fracture for women are a low bone mineral density score after a fracture, being aged 65-74 years, and oral corticosteroid use, according to the results of a study of 2,000 women.

Factors Predicting Bisphosphonate Prescription

Risk Factor	Odds Ratio	*P* value
T-score ≤–2.5	4.90	<.001
Age 65-74 years	1.76	<.001
Oral corticosteroid use	1.67	<.05
Obesity	0.53	<.05

Note: Based on a study of 2,000 women, 188 of whom received a bisphosphonate.
Source: Dr. Asche

ELSEVIER GLOBAL MEDICAL NEWS

Women with a bone mineral density (BMD) T–score of –2.5 or less in the 90 days after a fracture were almost five times as likely to receive a bisphosphonate prescription than women with higher T–scores, according to a poster presented by Carl Asche, Ph.D., at the annual meeting of the American Society for Bone Mineral Research.

Women who were aged 65-74 years at the time of fracture were almost twice as likely to receive a prescription, compared with woman younger than 65. Similarly, women taking oral corticosteroids also were more likely to receive a bisphosphonate prescription, wrote Dr. Asche of the pharmacotherapy department at the University of Utah, Salt Lake City.

Using electronic health records from Geisinger Health System from Jan. 1, 2000, to June 30, 2007, women aged 50 years and older who had had a fracture were included. They also had to have continuous electronic health record activity for at least 365 days before and after the index date (the date of the fracture). Women were excluded if they had a diagnosis of osteoporosis, a bone mineral density score of –2.5 or less at the time of the fracture, a fracture in the 6 months prior to the index date, or a diagnosis of conditions known to impact bone density and quality.

The reseachers considered age, race, body mass index (BMI), BMD score 90 days after the fracture, smoking status, Charlson comorbidity index, oral corticosteroid use, and rheumatoid arthritis to be potential predictors of bisphosphonate prescription—alendronate (Fosamax), ibandronate (Boniva), or risedronate (Actonel).

A total of 2,000 women met the inclusion criteria, but less than 10% (188) received a prescription for a bisphosphonate within 90 days of fracture. "Very few women aged [over] 50 receive treatment with an oral bisphosphonate after having a fracture, leaving them potentially vulnerable to future fractures," Dr. Asche noted.

Obese patients (BMI 30-39.9 kg/m^2) were significantly less likely to receive a prescription than were normal weight or underweight patients (BMI less than 24.9 kg/m^2).

One limitation of the study is that it was not possible to determine if the fractures were fragility related or primarily due to an injury.

The study was supported by the Alliance for Better Bone Health—Procter & Gamble Pharmaceuticals and Sanofi-Aventis U.S., which copromote Actonel. Dr. Asche reported that he has a significant financial relationship with Sanofi-Aventis U.S. ■

Self-Scheduling Led to Increase in Bone Scans

DENVER — Women who are encouraged to self-schedule dual-energy x-ray absorptiometry scans via mailed brochures and letters undergo more scans than do those in usual practice, but it is still not a silver bullet strategy for identifying women with osteoporosis.

In study of 3,734 women, mailings of an educational osteoporosis brochure and a letter providing the opportunity to self-schedule increased the percentage of women receiving dual-energy x-ray absorptiometry (DXA) scans by 13% versus routine care, Dr. Amy Warriner and her coinvestigators reported in a poster presented at the annual meeting of the American Society for Bone Mineral Research.

The study involved 28 primary care physicians at the University of Alabama at Birmingham. The researchers identified women aged 65 years or older who had not had a DXA scan in the past 4 years, and were under the care of a university primary care provider.

The participating providers were randomized to provide an intervention or not. Intervention-group physicians mailed brochures containing information about osteoporosis and fracture risk. The brochures were created using patient feedback from focus groups. Each mailing included a letter providing patients with the opportunity to self-schedule a DXA scan. Two mailings were sent to each woman.

In all, 665 women were randomized into the intervention group and 3,069 into the control group. A total of 115 women in the intervention group were determined by their primary care provider not to be medically appropriate for DXA testing. Brochures and letters were mailed to the remaining 550 women.

In the intervention group, 19% of women received DXA scans. Half of these were self-scheduled and half were scheduled by the provider. In comparison, only 6% of women in the control group had DXA scans. DXA scan self-scheduling and receipt was 13% better with a mailing intervention when compared with normal practice. "However, more potent strategies will still be needed to further improve DXA screening rates," wrote Dr. Warriner, professor of medicine in the division of endocrinology and metabolism at the university.

The study was funded in part by Procter & Gamble, which comarkets the osteoporosis drug risedronate (Actonel). Dr. Warriner reported a significant financial relationship with Amgen Inc., which is developing the osteoporosis drug denosumab. Her coinvestigators reported significant financial relationships with a number of pharmaceutical companies that make osteoporosis drugs. ■