Denosumab Reduced Fracture Risk in Trials

BY SHERRY BOSCHERT

Results of two separate pivotal trials of the investigational drug denosumab show significant decreases in the risk of fractures during 36 months of twice-yearly injections in 7,868 postmenopausal women with osteoporosis and in 1,468 men receiving androgen deprivation therapy for prostate cancer, compared with placebo injections.

The two randomized, double-blind, multicenter trials were published in the New England Journal of Medicine (2009 [doi:10.1056/NEJM0a0809493]; 2009 [doi;10.1056/NEJM0a0809003]).

The FDA's Reproductive Health Drugs Advisory Committee has recommended approval of the drug for treating osteoporosis in postmenopausal women but not for preventing it. (See story, p. 8.)

The benefits of denosumab therapy have the potential to extend beyond osteoporosis to the management of rheumatoid arthritis.

Rheumatologist Robin Dore noted in an interview with RHEUMATOLOGY NEWS that patients with rheumatoid arthritis are at increased risk of fracture even if they have never received glucocorticoid therapy due to the chronic inflammatory state seen in these patients. If a phase III trial in RA patients "confirms the findings of our smaller phase II study [Arthritis Rheum 2008;58;1299-309], in my opinion denosumab could be used as a therapy to treat both the [RA] and low bone mass seen in this population of patients," she said.

"Our phase II study was too small to evaluate the efficacy of denosumab to reduce fractures in patients [with RA] but it was found to increase bone mineral density in patients [with RA] both with and without glucocorticoid treatment

and with and without bisphosphonate treatment."

Although a phase III study in RA patients (if performed) would be larger, "it still would not have the power to demonstrate fracture reduction in this population," said Dr. Dore of the University of California, Los Angeles.

In osteoporotic postmenopausal women aged 60-90 years with a baseline bone mineral density T score of less than –2.5 but not less than –4.0 at the lumbar spine or total hip, the cumulative incidence of new vertebral fractures was 2.3% on denosumab and 7.2% on placebo, a relative decrease of 68%.

Reduction in new vertebral fracture was the primary end point of the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial. The primary outcomes of HALT (Hormone Ablation Bone Loss Trial) showed significantly improved lumbar density at 24 months in the denosumab group (an increase of 5.6%), compared with the placebo group, which had a bone density loss of 1%, in men receiving androgen deprivation therapy for prostate cancer. The age range of the denosumab group was 48-92 years and the age range of the placebo group was 50-97 years. The original 2-year study protocol was extended to 3 years for further evaluation. One of the secondary end points showed significantly decreased risk for new vertebral fractures at 36 months on denosumab (1.5%), compared with placebo (3.9%), a relative improvement of 62%.

Amgen, the company that is developing the drug for the United States, has applied for FDA approval for denosumab (to be marketed as Prolia) to treat postmenopausal osteoporosis and to prevent bone loss in patients undergoing hormone ablation for prostate or breast cancer. A previous study found that denosumab was associated with increased bone mineral density in women receiving aromatase-inhibitor therapy for breast cancer (J. Clin. Oncol. 2008;26:4875-82).

Dr. Steven R. Cummings of the University of California, San Francisco, and his associates in the FREEDOM trial noted that rare adverse effects associated with other osteoporosis therapies—necrosis of the jaw and fractures of the femoral shaft—were not seen with denosumab. However, theoretical concerns have been raised previously about a possible increase in the risk of cancer or infection with denosumab because of the drug's potential effects on the immune system.

Dr. Cummings reported no significant increase in the rate of serious infections, but did find significant increases

Denosumab use was not associated with jaw osteonecrosis or femoral shaft fractures seen with other agents.

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in risks for eczema (3% vs. 1.7% on placebo), cellulitis (0.3% vs. less than 0.1%), and flatulence (2.2% vs. 1.4%).

Dr. Matthew R. Smith of Massachusetts General Hospital, Boston, and his associates in HALT reported that rates of adverse events were similar between groups. However, rates were higher in the denosumab group, compared with placebo, for serious adverse events (34.6% vs. 30.6%), serious adverse events related to infection (5.9% vs. 4.6%), and cataracts (4.7% vs. 1.2%), although none of the cataracts was considered to be related to the drug treatment.

In an accompanying editorial, Dr. Sundeep Khosla of the Mayo Clinic, Rochester, Minn., noted that a previous study of 314 women with low bone mineral density found that neoplasms developed in six patients randomized to denosumab therapy and in none on placebo, and serious infections developed in three patients on the drug and none on placebo (N. Engl. J. Med. 2006;354:821-31). "Although not statistically significant, such findings support ongoing surveillance of patients receiving denosumab," Dr. Khosla suggested (N. Engl. J. Med. 2009 [doi:10.1056NEJMe0905480]).

The studies were funded by Amgen. Dr. Cummings has received fees and/or grant support from Amgen, Eli Lilly, GlaxoSmithKline, Organon, Pfizer, and Novartis. Dr. Smith has received fees from Amgen, Novartis, and GTx. Their study associates work for, are invested in, and/or receive support from Amgen and other companies. Dr. Khosla reported having no potential conflicts of interest related to these topics. Dr. Dore reported receiving funding from Amgen for clinical trials, is a consultant to Amgen, and participates on their speakers bureau. ■