Denosumab Effect Greater in Selected Patients

Patients with femoral neck osteoporosis had fewer fractures.

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS

SAN FRANCISCO – The pivotal clinical trial of denosumab showed a 20% decrease in nonvertebral fractures compared with placebo treatment, but a new subgroup analysis shows the protective effect is significantly higher in patients with femoral neck osteoporosis.

The preplanned subgroup analysis of data from the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial found that denosumab decreased nonvertebral fractures by 35% in patients with a femoral neck bone mineral density T score of –2.5 or lower and by only 3% in patients with higher femoral neck T scores, compared with patients in those subgroups who received placebo, Dr. Steven R. Cummings said.

The report of a 20% reduction in nonvertebral fractures in the overall trial for denosumab "underestimates its efficacy for those patients that we're most interested in treating with this drug – those with osteoporosis," he said at a conference on osteoporosis sponsored by the University of California, San Francisco.

The findings have been submitted for publication. The analysis is one of several preplanned subgroup analyses being conducted, though this one is "the most interesting result for clinical care," said Dr. Cummings, emeritus professor of medicine, epidemiology and biostatistics at the university.

The original FREEDOM study enrolled 7,808 postmenopausal women aged 60-80 years with osteoporosis to receive every 6 months either a subcutaneous injection of denosumab (60 mg) or placebo along with daily calcium and vitamin D supplements. All of the subjects had bone mineral density T scores that were less than –2.5 but not less than –4.0 at the lumbar spine or total hip. At 36 months, denosumab was associated with reductions of 68% in vertebral fracture and 40% in hip fracture (N. Engl. J. Med. 2009;361:756-65).

The FREEDOM results were the basis of the Food and Drug Administration's approval of denosumab in June 2010.

Data for 2,343 patients who continued denosumab for another 2 years and 2,207 patients who switched from placebo to denosumab in an ongoing extension of the trial suggest that the incidence of nonvertebral fractures continues to decline in the first 5 years of denosumab use. The 5-year results have been submitted for publication, he said.

For nonvertebral fractures, the incidence decreased from 2.6% in the denosumab group in the first year of the FREEDOM trial to 2.1% in year 2 and 2.2% in year 3. Nonvertebral fractures were seen in 1.4% of patients in year 4 and 1.1% of patients in year 5, extension study data show. Similar rates were seen for vertebral fractures.

The extension study did not include a placebo comparison, so "we did a pretty rigorous estimate of what the rates would be if the placebo group had continued out to 5 years," Dr. Cummings said. They estimated that nonvertebral or vertebral fracture rates would be 2.6% in the placebo group in years 4 and 5, more than twice that of patients on denosumab in the extension study.

A separate study highlighted another advantage of denosumab that it shares with zoledronic acid – greater adherence rates compared with oral therapies, he added. An open-label study of 250 women with untreated osteoporosis found an 87% adherence rate in the first year in patients randomized to get a denosumab injection every 6 months, compared with a 77% adherence rate for patients randomized to weekly oral alendronate therapy. Alendronate use was monitored by electronic bottle caps (Osteoporos. Int. 2011;22:1725-35).

The study's 2-year results, which have not yet been published, show that the difference in adherence rates between groups continues to widen, Dr. Cummings said.

Dr. Cummings has been a consultant to Amgen Pharmaceuticals, which markets denosumab; to Merck, which markets alendronate; and to Eli Lilly & Co. ■

Use IOM Guidelines on Calcium, Vitamin D Loosely

BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS SPONSORED BY THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

SAN FRANCISCO – Updated national guidelines on calcium and vitamin D intake should be followed loosely, cautioned Dr. Deborah E. Sellmeyer, director of the Metabolic Bone Center at Johns Hopkins University, Baltimore.

Controversy surrounds the Institute of Medicine's November 2010 report, "Dietary Reference Intakes for Calcium and Vitamin D," an update of 1997 guidelines. Dr. Sellmeyer uses the latest IOM report as a starting point and then tailors the recommendations to meet the needs of her patients. As a result, the amounts of vitamin D and calcium that her patients take usually vary from the guidelines, she said at a the meeting.

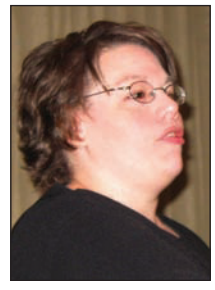
There is uncertainty about the cutoff level of serum vitamin D that's considered adequate and the potential side effects from ingesting too much calcium, she said.

The IOM recommends that adults take 600 IU vitamin D/day through age 50 and 800 IU/day for those aged 51 years and older, with a suggested upper tolerability limit of 4,000 IU/day. Those are the intake amounts that generally would be needed to reach a serum level of 20 ng/mL.

But many experts think that physiologic and fracture data suggest that a "sufficient" serum level should be in the 30-32-ng/mL range, she said. "It takes most people about 1,200 IU/day to reach that" serum level, said Dr. Sellmeyer, who advises her patients accordingly.

A 2010 study of high-dose vitamin D and fracture risk caused "a lot of consternation," she noted. The double-blind trial randomized 2,256 older women to a once-yearly oral dose of 500,000 IU cholecalciferol or placebo, and found higher rates of falls and fractures in the vitamin D group (JAMA 2010;303:1815-22).

"It's almost a moot point because you wouldn't give 500,000 IU once a year, but it did raise the idea that there may be some administration techniques, some regimens that would not be beneficial," Dr. Sellmeyer said.



Most people need about 1,200 IU/day of vitamin D to reach 'sufficient' serum levels in the 30-32-ng/mL range.

DR. SELLMEYER

The IOM committee that compiled the 2010 report expressed a great deal of concern about a potentially higher mortality risk with excessively high vitamin D serum levels. The concern was sparked by the committee's interpretation of an analysis of data from the Third National Health and Nutrition Examination Survey. Overall, that survey documented higher mortality rates in patients in the lowest quartile of serum vitamin D levels (Arch. Intern. Med. 2008;168:1629-37). However, the IOM committee noticed a statistically nonsignificant dip in mortality risk between the highest and second-highest quartiles of serum vitamin D before the mortality risk increased in each of the two lowest quartiles, constituting what some saw as a J-shaped curve of mortality risk.

Numerically, the lowest mortality was in patients with 24-32 ng/mL of serum vitamin D, but this was statistically not significantly different than in patients with a serum level greater than 32 ng/mL.

"I'm really not sure that there is a higher mortality," Dr. Sellmeyer said. "I think there is enough evidence to suggest that we probably ought to be a little more in the 30-40-ng/mL range."

The IOM recommends that adult males get 1,000 mg/day of calcium through age 70 years and 1,200 mg/day for those who are older. Adult women should get 1,000 mg/day through age 50 and 1,200 mg/day in older ages. The maximum tolerability limits were set at 2,500 mg/day for adults younger than 50 years or 2,000 mg/day for older adults.

It's important to remember that the recommended level includes both dietary and supplemental sources of calcium, she emphasized. "We see a lot of women who are taking 1,200-1,500 mg/day in supplements and also drinking two glasses of milk a day," she said. "Those [are the patients who] can get into trouble."

There are no data to suggest that ingesting more than 1,200 mg/day is better for skeletal health, and high doses of calcium increase the risk of developing kidney stones, studies show.

The most controversial aspect of calcium supplementation in recent years has been some preliminary evidence of a possible increased risk for vascular calcification with higher doses.

Initially, an analysis of data on 36,282 participants in the Women's Health Initiative (WHI) who were randomized to take 500 mg calcium carbonate with 200 IU vitamin D twice daily found no effect on risk of myocardial infarction (MI) or vascular calcification (Circulation 2007;115:846-54).

Then a randomized, controlled trial of 1,471 healthy women found that the group taking 1 g/day of calcium citrate showed a doubling in risk for MI and a trend toward higher risk of angina, compared with the placebo group (BMJ 2008;336:262-6). The investigators in that study reanalyzed the WHI data and found a 22% increase in risk for MI in women who at baseline had no personal calcium use (BMJ 2011;19:342:d2040).

There were significant differences in the comparison groups in the reanalysis, including differences in personal history of MI, Dr. Sellmeyer noted. "Whether this truly represents an increased risk or not is unclear," she said.

Another study by some of the same investigators "got a ton of press" even though it was a relatively small meta-analysis, she added. The attempted meta-analysis of 190 trials of calcium supplementation yielded 15 eligible trials, but most of the data came from 5 trials. The meta-analysis reported a 31% increase in risk for MI in calcium supplement users, with possibly a higher risk in those taking more than 1,600 mg/day (BMJ 2010;341:c3691). "It's really hard to know at this point" whether the risk of vascular calcification from supplementation is significant, Dr. Sellmeyer said. "I think it does behoove us to be judicious with our calcium and not let people consume more calcium than we think is really beneficial."

Dr. Sellmeyer said she has no relevant conflicts of interest. ■