

Denosumab's Effect Greater on Femoral Neck

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.

VITALS

Major Finding: 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.

Data Source: Subgroup analysis in the original study of 7,808 postmenopausal women aged 60-80 years with osteoporosis who received every 6 months either a subcutaneous injection of denosumab (60 mg) or placebo along with daily calcium and vitamin D supplements.

Disclosures: Dr. Cummings has been a consultant to Amgen Pharmaceuticals, which markets denosumab; to Merck, which markets alendronate; and to Eli Lilly and Company.

The preplanned subgroup analysis of data from the FREEDOM 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 the conference, sponsored by the University of California, San Francisco.

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 and epidemiology and biostatistics at the university.

The original FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) 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 subjects had bone mineral density T scores 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.

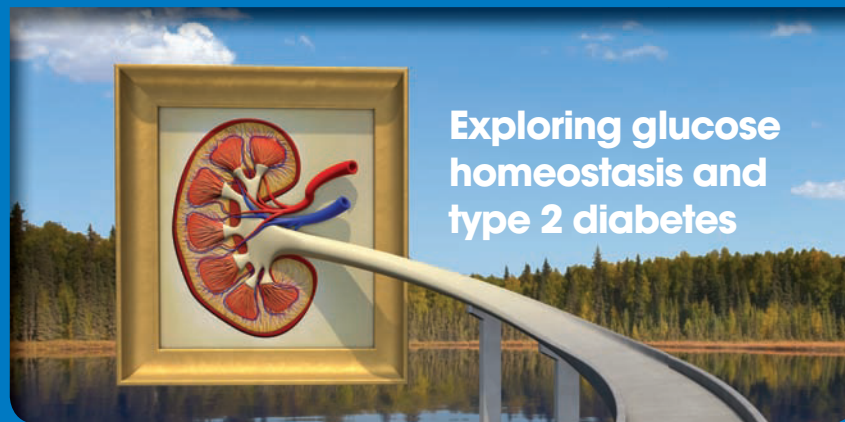
Data for 2,343 patients who continued denosumab for another 2 years and 2,207 patients who switched from placebo to denosumab in an ongoing extension of the trial suggest that the incidence of nonvertebral fractures continues to decline in the first 5 years of denosumab

use. The 5-year results have been submitted for publication, he said (“Denosumab’s Bone Benefits Persist at 5 Years of Therapy,” CLINICAL ENDOCRINOLOGY NEWS, May 2011, p. 26).

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. ■



Exploring glucose homeostasis and type 2 diabetes

Many organs play a role in glucose homeostasis

Fasting glucose levels are controlled by the body within a range of 70-110 mg/dL.¹ Lifestyle choices, including diet and exercise, are essential to help manage glucose levels.^{2,4} Maintaining glucose homeostasis is a multiorgan process involving the muscle, adipose tissue, liver, gastrointestinal (GI) tract, pancreas, brain, and kidney.^{5,6}

The body handles glucose through both insulin-dependent and insulin-independent pathways⁵

Insulin-dependent pathways located in the liver, muscle, and adipose tissue, and insulin-independent pathways, found mostly in the brain, kidney, GI tract, and liver, help create a complex interplay of processes essential for glucose management.^{5,6}

Type 2 diabetes mellitus (T2DM) is characterized by core defects of impaired insulin secretion from the pancreas and increased insulin resistance in the muscle, liver, and adipose tissue.^{5,7} These defects contribute to chronically elevated glucose levels.⁷

Because type 2 diabetes is the leading cause of kidney failure, the kidney is often viewed as a victim of the disease.⁸ But emerging understanding of renal-glucose transporters helps illustrate the ways in which the kidney is an active contributor to the disease as well.^{9,10}

- Sodium-glucose cotransporters (SGLTs) 1 and 2 are expressed in the kidneys, along with facilitative glucose transporters (GLUTs) 1 and 2, where they promote reabsorption of filtered glucose from the renal tubules back into the bloodstream in an insulin-independent process.^{9,10}
- In type 2 diabetes, the renal glucose transport system continues to reabsorb glucose even in the presence of high blood glucose, further worsening hyperglycemia.^{9,11}

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