Panel Nixes Prevention Indication

Denosumab *from page 1*

ries of votes on the risks and benefits of denosumab.

The FDA generally follows the advice of its panels.

Amgen submitted safety and efficacy data from 30 trials involving more than 12,000 patients. For the indications for which it sought approval, denosumab would be given in a 60-mg dose twice a year subcutaneously.

Data on the placebo-controlled prevention indication were reported just days before the FDA committee meeting (N. Engl. J. Med. 2009;361:756-65). Reduction in new vertebral fracture was the primary end point of the Investigators for the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial. 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%.

At the meeting, the company presented a slice of the prevention data on 332 women with a lumbar spine T score between –1.0 and –2.5 who received either denosumab or placebo subcutaneously every 6 months out to 2 years. Amgen reported a statistically significant increase in bone mineral density at the lumbar spine and total hip.

The FDA reported a higher number of serious adverse events in women taking denosumab compared with placebo (19 vs. 9), with infections and neoplasms reported as the most common such events.

As a result, advisory committee members expressed concern about exposing otherwise healthy women to denosumab. Dr. Scott Emerson, a biostatistician from the University of Washington, Seattle, said he could not say that the benefits outweighed the risks "because there's a lot of uncertainty in this low-risk population."

For treatment of osteoporosis in postmenopausal women, Amgen presented data on 7,808 women assigned to denosumab subcutaneously every 6 months out to 3 years, or to placebo. They were required to have a T score greater than –4.0 and less than –2.5, and no previous severe vertebral fractures. The primary end point was new vertebral fracture. The mean age was 72 years.

For prevention, panelists were concern about exposing otherwise healthy women to a therapy shown to have a slightly higher risk of causing serious skin infections and neoplasms.

At 36 months, there was a 68% reduction in new vertebral fracture with denosumab (7.2% vs. 2.3% with placebo). The drug also reduced hip fracture and the risk of nonvertebral fracture, according to Amgen.

The FDA agreed that the drug was effective, but said its safety studies suggested that denosumab had a potential for oversuppression of bone remodeling, and also said that the higher rate of infections, malignancies, and dermatologic adverse events spoke to a potential for the drug also to have effects on immunogenicity.

The panel voted unanimously that denosumab's benefits outweighed its risks in postmenopausal women, but because of questions about its long-term impact on bone turnover and immunogenicity, suggested that the drug should be limited to those at high risk for fracture or with a history of fracture.

The advisory committee was much less convinced that denosumab was safe or effective for preventing or treating fracture in women receiving hormone ablation therapy for breast cancer.

Denosumab or placebo was given in a 4-year trial with a 2-years-on, 2-years-off dosing. Women were eligible if they were taking aromatase inhibitors and had T scores of –1.0 to –2.5. The primary end point was change in lumbar spine at 12 months. For placebo, there was a –0.7 decrease in bone mineral density; in the denosumab group, there was a 4.8 increase.

There were slightly more serious adverse events in the denosumab group. Of special concern were three new neoplasms, compared with one in the placebo group. The FDA also noted that Amgen had not conducted carcinogenicity studies because of the lack of an animal model.

Committee members also said that Amgen had not shown that denosumab did not affect the underlying disease or tumor progression when used in the breast cancer setting. Dr. Lawrence M. Nelson, a panel member and researcher at the National Institute of Child Health and Human Development, said he could not support use of the drug in breast cancer "because of concerns about the need for more data on how this affects the primary disease."

The company also studied the treatment and prevention of bone loss in men receiving androgen-deprivation therapy for prostate cancer. Data from the primary outcomes of the Denosumab Hormone Ablation Bone Loss Trial (HALT) were also reported shortly before the meeting (N. Engl. J. Med. 2009;361:745-55). Denosumab met the primary end point, which was a significant increase in lumbar spine bone mineral 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%). 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%.

The HALT trial reported that rates of adverse events were similar between groups. Rates were higher in the denosumab group, compared with placebo, however, 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%), though none of the cataracts were considered to be related to the drug treatment.

The FDA panel voted 9-4 that the benefits outweighed the risks of treatment in this group, but still had some concerns about long-term safety.

But the committee was more enthusiastic about denosumab in the prostate cancer setting, saying that Amgen had proved, at least in treating bone loss, that the drug reduced fracture risk.

Finally, the FDA advisers urged the agency to require Amgen to institute a risk evaluation and mitigation strategy (known as a "REMS") to help educate providers and patients about denosumab's risks.

Amgen has also applied for marketing approval in the European Union, Canada, Switzerland, and Australia. ■

Sherry Boschert contributed to this report.

Holiday From Bisphosphonates 'Reasonable' After 5 Years

BY BRUCE JANCIN

ESTES PARK, COLO. — Many bone disease experts are recommending a 1- to 2-year bisphosphonate holiday after 5 years of treatment in response to a recent spate of reports of atypical fractures of the femoral diaphysis.

There are now more than 70 reports of these atypical transverse fractures of the femoral shaft occurring in patients on bisphosphonates for longer than 5 years. Affected individuals have also had severely suppressed bone turnover markers, Dr. Michael T. McDermott said at a conference on internal medicine sponsored by the University of Colorado.

"This tells us that drugs that turn off a major process like bone remodeling may be very valuable for 3-5 years, but we have to ask, are they good for longer periods of time? We don't know the answer yet," observed Dr. McDermott, professor of medicine and director of diabetes practice at University of Colorado Hospital, Aurora.

These distinctive fractures have been bilateral in two-thirds of cases. There is no associated history of trauma, just spontaneous thigh pain. Radiographically they look like nonhealing stress fractures that have completed through the bone shaft.

Dr. McDermott has contacted many bone experts, who agree that a bisphosphonate holiday for 1-2 years is reasonable after 5 years of therapy in low-risk patients (those with a T-score greater than –2.5 and no history of fractures). "Treatment holidays are not advised for high-risk patients," he stressed.

For such patients—those who have a T-score less than –2.5 and/or previous fractures—options include a switch to an anabolic agent such as teriparatide (Forteo) or to a nonbisphosphonate antiresorptive agent such as raloxifene (Evista), estrogen, or calcitonin. Continuing the bisphosphonate in a high-risk patient is also a reasonable strategy.

Regardless, it's now doubly important to monitor bone mineral density and/or bone turnover biomarkers regularly in patients on long-term bisphosphonates, Dr. McDermott emphasized. ■

Bone Loss Linked to Benign Positional Vertigo

Benign positional vertigo appears to strongly correlate with osteopenia and osteoporosis in both men and women, researchers in a case-control study have concluded.

Compared to controls, patients with osteopenia were twice as likely to experience positional vertigo, and those with osteoporosis were three times as likely to experience the disorder, Dr. Ji Sook Kim and colleagues wrote.

"These findings suggest a deranged calcium metabolism in idiopathic benign positional vertigo," Dr. Kim of the Seoul National University College of Medicine, Korea, said in an interview. "Restoring normal calcium metabolism may prevent recurrences of BPPV."

The study compared bone mineral density in 209 patients with a diagnosis of idiopathic benign positional vertigo (BPV) and 202 controls. Most (142) were female; their mean age was 60 years.

Among female patients, only 28% had normal bone mineral density, while 47% had osteopenia and 25% had osteoporosis. Among female controls, normal bone mass was found in 57%; 33% had osteopenia and 9% had osteoporosis. (Percentages do not add up to 100% due to rounding.) The differences were significant at all points measured (Neurology 2009;72:1069-76).

In male patients, 48% had normal bone mass, while 40% had osteopenia and 12% had osteoporosis. In male controls, 67% had normal bone mass, 27% had osteopenia, and 6% had osteoporosis. The differences were significant at the femur and first lumbar vertebra, but not at the other lumbar measurements.

—Michele G. Sullivan