FDA Panel Rejects Denosumab in Prostate Ca

Toxicity concerns kept advisers from endorsing prophylactic use.

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. – A Food and Drug Administration advisory panel voted 12-1 that denosumab did not have a favorable risk-benefit profile as a treatment to reduce the risk of bone metastases in men who are at high risk for developing them with castrate-resistant prostate cancer.

Concern over the possibility of increased toxicity, especially osteonecrosis of the jaw, with longer drug exposure weighed heavily in the Oncologic Drugs Advisory Committee (ODAC) decision. The patient representative was the only panelist to vote in favor.

Denosumab (Xgeva) was approved in 2010 for the prevention of skeletal-related events in patients with bone metastases from solid tumors. The new indication, proposed by manufacturer Amgen, would start treatment earlier to avert bone metastases before they develop in men with castrate-resistant prostate cancer (CRPC).

Amgen said that denosumab "prolongs bone metastasis-free survival by reducing the risk of developing bone metastases."

The application is based on the results of a phase III international study of 1,432 men with CRPC at high risk of developing bone metastases. Bone scans were done every 4 months to evaluate for metastases and abnormal results were confirmed by subsequent x-ray, CT, or MRI.

The study found that survival free of bone metastases, the primary end point, was prolonged by a median of about 4 months in patients randomized to denosumab (120 mg subcutaneously every 4 weeks) compared with those on placebo – a statistically significant difference that represented a 15% reduction in risk.

But ODAC was nearly unanimous in finding that this difference in bone metastasis–free survival was modest and did not outweigh the risks of treatment, namely osteonecrosis of the jaw. In the study, almost 5% of those on denosumab developed osteonecrosis of the jaw, a known effect of treatment, compared with none of those on placebo. Panelists were concerned that this risk could increase with longer exposure to the drug.

"Again and again, this committee has dealt with the fact that when you're using a surrogate end point, the magnitude of benefit has to be looked at," said the panel chair, Dr. Wyndham Wilson, chief of the Lymphoma Therapeutics Section of the National Cancer Institute, Bethesda, Md. If the study had found a 1-year difference, the panel would not have been convened to address the risk-benefit question, he pointed out.

The panel was not asked specifically whether it recommended approval for this expanded indication. The FDA must make a decision by the Prescription Drug User Fee Act (PDUFA) action date of April 26, 2012.

Amgen issued the following statement after the ODAC vote: "We look forward to further discussions with the FDA as they continue to review our application," it said. "The development of bone metastases in men with castration-resistant prostate cancer is a clinically significant event, and delaying bone metastases in these men is a clear unmet need with no approved therapies."

In the study under consideration, bone metastasis–free survival was determined by time to first occurrence of bone metastasis or death, which was a median of 29.5 months among those on denosumab vs. 25.2 months among those on placebo.

There were no significant differences in overall survival, progression-free survival, or patient-reported outcomes between the two groups. In about two-thirds of cases, bone metastases were asymptomatic.

The question isn't whether or not this drug works, it's when the most effective time is to actually give it.

DR. WILSON

Denosumab, a monoclonal antibody that inhibits the RANK ligand (RANKL), is marketed as Xgeva at the same dose and schedule used in this study for prevention of skeletal events such as fractures from bone metastases. It is not indicated for the prevention of skeletal-related events in patients with multiple myeloma. During the meeting, Dr. Wilson observed that the question under consideration was not whether denosumab was effective, but whether it was better to administer the treatment when bone metastases are detected, as it is currently approved or in a prophylactic setting. "This isn't a question of whether or not this drug works, it is a question of when is the most effective time to actually give it."

Denosumab is also approved as Prolia, at a lower dose administered once a year, to treat postmenopausal women with osteoporosis who are at high risk of fracture; to increase bone mass in men who are at high risk of fracture while receiving androgen deprivation therapy for nonmetastatic prostate cancer; and to increase bone mass in women at high risk of fracture while receiving adjuvant aromatase inhibitor therapy for breast cancer.

The FDA usually follows the recommendations of its advisory panels. Panelists were cleared of potential conflicts before voting on denosumab. ■

Narcotics in Place of NSAIDs Mean More Falls, Fractures

BY BRUCE JANCIN

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

SNOWMASS, COLO. – The guideline-endorsed demotion of nonsteroidal anti-inflammatory drugs in favor of narcotic analgesics for chronic pain has led to a marked increase in falls, fractures, and other bad outcomes among elderly arthritis patients.

"The real take-home message here is that current guidelines for the treatment of pain should be revisited," Dr. Bruce N. Cronstein asserted at the conference.

Since the cyclo-oxygenase-2 (COX-2)-selective NSAID rofecoxib (Vioxx) was taken off the market in late 2004 because of a scandal related to cover-up of an increased risk of myocardial infarction, prescriptions for narcotic analgesics in elderly patients with arthritis have risen sharply. This trend accelerated following the 2007 publication of an American Heart Association scientific statement on the treatment of chronic pain in patients with or at increased risk for heart disease (Circulation 2007;115:1634-42). The AHA guidelines elevated short-term use of narcotic analgesics to first-tier status alongside aspirin, acetaminophen, and tramadol, while demoting both COX-2-selective and nonselective NSAIDs to second-tier status.

Data supporting the unintended consequences of such changes in treatment priorities come from a study by Dr. Cronstein, Dr. Paul R. Esserman professor of medicine at New York University, and his associates. They conducted a nested case-control study of 3,830 elderly patients with osteoarthritis (OA) in the Geisinger Health Plan in Danville, Pa., who had fractures and 11,490 others matched for age and Charlson Comorbidity Index without fractures. In a multivariate analysis, patients on narcotic analgesics had a threefold greater risk of falls or fractures than those on either COX-2-selective or nonselective NSAIDs.

Thus, the use of narcotic analgesics as the sole prescription medication for pain relief in elderly OA patients more than doubled after Vioxx was withdrawn from the market. The patients on narcotic analgesics with or without a COX-2-selective NSAID had a fourfold greater rate of falls or fractures than those on nonselective NSAIDs or COX-2-selective agents.

Dr. Cronstein noted that the AHA guidelines focus on the evidence of increased cardiovascular risk associated with nearly all NSAIDs without considering how the drugs stack up in terms of overall safety – noncardiovascular as well as cardiovascular – compared with the other major analgesic group: narcotic analgesics. And it turns out that the NSAIDs look pretty good in comparison, he added.

"You're trading off falls and fractures for MIs – and it turns out that in patients over age 65, the mortality from hip fracture is significantly greater than it is for MI," said Dr. Cronstein, who is also director of the Clinical and Translational Science Institute.

He cited a large Medicare study conducted that examined the comparative safety of analgesics in elderly arthritis patients and concluded that narcotic analgesics come up short.

The investigators, at Brigham and Women's Hospital, Boston, sifted through the population of Medicare beneficiaries in Pennsylvania and New Jersey to identify elderly patients with rheumatoid arthritis or osteoarthritis (OA) who were started on a nonselective NSAID, a COX-2-selective NSAID, or a narcotic analgesic during 1999-2005. They came up with 4,280 propensity score–matched patients in each of the three groups.

The composite incidence of fractures of the hip, pelvis, humerus, or radius was 26 per 1,000 person-years in patients on nonselective NSAIDs, 19 with COX-2-selective NSAIDs, and 101 with opioids.

While it's not really surprising that opiate analgesics should be linked with increased risk of falls and fractures, another finding in this study proved unexpected: The composite cardiovascular event rate was 77 per 1,000 person-years with nonselective NSAIDs, 88 per 1,000 with COX-2-selective NSAIDs, and 122 with narcotic analgesics.

'You're trading off falls and fractures for MIs,' while hip fracture is significantly deadlier than MI after age 65.

DR. CRONSTEIN

The patients taking opioids had a 77% greater risk of cardiovascular events and those taking COX-2-selective NSAIDs had a 28% greater risk than did patients on nonselective NSAIDs, according to findings from a multivariate Cox regression analysis. The fracture risk was 4.47-fold greater with narcotic analgesics than with NSAIDs. The GI bleeding risk was 40% lower in the COX-2-selective NSAID group than in the other groups. The all-cause mortality risk was 87% greater in the narcotic analgesic group than with nonselective NSAIDs, while COX-2-selective NSAIDs weren't tied to increased risk (Arch. Intern. Med. 2010;170:1968-78).

This work was funded by the National Institutes of Health, the Geisinger Clinic, and the Clinical and Translational Science Institute. Dr. Cronstein has served as a paid consultant to Allos, Bristol-Myers Squibb, Novartis, and several other pharmaceutical companies. ■