Are Bisphosphonates, Heart Disorder Linked?

BY DENISE PETERSON
"The Pink Sheet"

The Food and Drug Administration will seek data for an "in-depth evaluation" of atrial fibrillation for the entire bisphosphonate class of drugs as well as continue to monitor any spontaneous postmarketing reports of the heart rhythm disorder, agency officials announced on Oct. 1.

FDA is not recommending at this point that physicians alter their prescribing choices or that patients change their medications.

The review encompasses products approved primarily to treat osteoporosis, slow bone turnover in Paget's disease, and treat bone metastases in cancer patients—specifically alendronate (Fosamax and Fosamax Plus D), risedronate (Actonel and Actonel with Calcium), ibandronate (Boniva), zoledronic acid (Reclast and Zometa), pamidronate (Aredia), and etidronate.

The evaluation follows publication of two studies describing increased rates of serious atrial fibrillation in older women treated with zoledronic acid or alendronate for osteoporosis (N. Engl. J. Med. 2007;356:1809-33 and N. Engl. J. Med. 2007;356:1895-6). In those studies, researchers found that more women who received one of the bisphosphonates developed serious atrial fibrillation versus those receiving placebo, according to the FDA announcement, which noted that overall rates of atrial fibrillation were not statistically different between the studies' active treatment and placebo arms.

Upon reviewing its postmarketing reports of atrial fibrillation in association with both oral and intravenous bisphosphonates, the agency did not find a "population of bisphosphonates users at increased risk" for the atrial fibrillation. And since atrial fibrillation is a common disorder in patients over age 65 years—the same population that was studied in the New England Journal of Medicine articles—the FDA cautioned that it is "unclear how these data … should be interpreted."

Further, the FDA's recent review and approval of zoledronic acid included data on possible associations with atrial fibrillation, the agency said.

Those reviews found that most incidents occurred more than a month after infusion of the drug, which is administered once yearly to treat postmenopausal osteoporosis.

The in-depth review may take up to 12 months, according to the FDA. This is the agency's second "early communication" of a drug safety review, part of FDA's efforts to be more transparent in oversight of postmarketing drug safety. The first communication, which was released in August, addressed the proton pump inhibitors omeprazole and esomeprazole. ■

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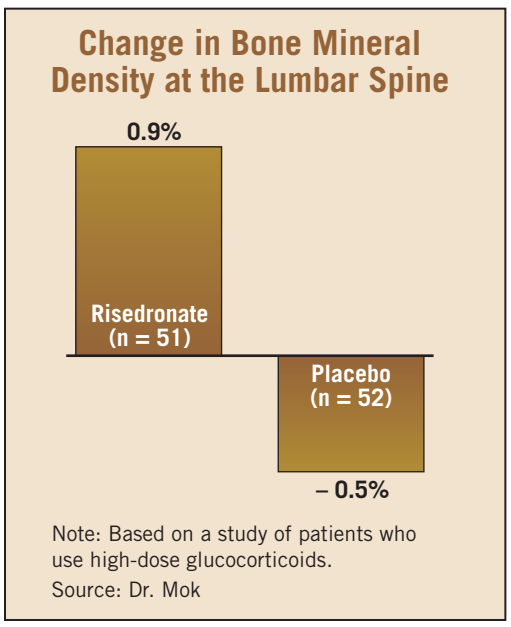
Risedronate Prophylaxis Halts Bone Loss During High-Dose Steroid Tx

BY JEFF EVANS
Senior Writer

Barcelona — Patients who use high-dose glucocorticoids can maintain or improve their bone mineral density with risedronate prophylaxis, Dr. Chi Chiu Mok reported at the annual European Congress of Rheumatology.

"The [American College of Rheumatology] recommends the first-line use of bisphosphonates in patients with T scores below –1 who are expected to use corticosteroids for more than 3 months," said Dr. Mok of the department of medicine at Tuen Mun Hospital, Hong Kong.

"Multiple clinical trials have confirmed the efficacy of bisphosphonates in the prevention and treatment of glucocorticoid-induced bone loss, and sometimes have demonstrated antifracture efficacy. But most [of these trials] recruited patients taking a relatively small dose of steroids," an equivalent of 7.5 mg/week of prednisolone or more.



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Dr. Mok and colleagues randomized 120 patients with conditions requiring 0.5 mg/kg per day prednisolone (or an equivalent glucocorticoid dose) for 6 weeks or more to 1,000 mg/day calcium plus 5 mg/day risedronate (Actonel) or placebo for 6 months. Mean age was 43 years, and 30% were postmenopausal.

At the end of the double-blind trial, risedronate patients had a significantly greater change in bone mineral density (BMD) at the lumbar spine (0.9%) than did placebo-treated patients (–0.5%). This was significant even after adjusting for baseline BMD, age, gender, body mass index, and cumulative steroid dosage. Risedronate patients maintained BMD in the hip and the whole body overall. Placebo patients lost BMD in both measurements.

Steroid-naive patients, who accounted for about 60% of all patients, had similar results. The maximum dosage of prednisolone given during the trial averaged 0.7 mg/kg per day.

Sanofi Aventis provided free daily-dosed risedronate, but did not otherwise fund the trial. Dr. Mok said that no investigators had conflicts of interest with Sanofi Aventis.

Overall, 51 risedronate- and 52 placebo-treated patients completed the trial. Withdrawals mainly occurred because of the daily drug protocol, but several patients died from their underlying medical condition; two withdrawals occurred in the risedronate group because of adverse events (one skin rash and one dyspepsia).

No patients had preexisting vertebral or hip fractures, although about 50% of the patients were osteopenic. The trial was not powered to test the antifracture efficacy of risedronate.

"Risedronate should be considered for primary prevention of bone mineral loss during periods of high-dose glucocorticoid therapy," Dr. Mok concluded. ■

Novel Osteoporosis Treatments Providing Hope for a Cure

BY ROBERT FINN
San Francisco Bureau

San Francisco — Several novel treatments for osteoporosis are under investigation, and one might even provide a cure, Dr. Steven R. Cummings said at a meeting sponsored by the University of California, San Francisco.

"Several of these treatments are based on fundamental biology, on biological mechanisms of bone formation and bone resorption," Dr. Cummings, director of the San Francisco coordinating center of the California Pacific Medical Center Research Institute, said. "[I expect] these to make a big difference in practice within the next 5 years."

Given by injection every 6 months, denosumab significantly increased spine and hip BMD.

DR. CUMMINGS

One treatment involves sclerostin, which is produced by osteocytes, the most common and longest-lived cellular component of bone. Residing in microscopic cavities within bones, osteocytes are 100 times more numerous than osteoblasts and osteoclasts combined. Their job appears to be to sense strain in the bone and to communicate the need for bone building to the osteoblasts.

Sclerostin is not found in any other cell. It powerfully inhibits bone formation by interacting with mesenchymal stem cells—the precursors of osteoblasts—and reducing osteoblast formation. Sclerostin is produced by a gene called SOST, and individuals with mutations in that gene have sclerosteosis, a congenital disease characterized by extremely high bone mass, often leading to intracranial pressure and death.

In one study, female rats that were ovariectomized lost 12% of bone mass. But when given a monoclonal antibody to SOST, their vertebral bone mineral density (BMD) rose by 26% and their leg BMD by 16% over 5 weeks.

"This is a promising treatment, extremely potent, very specific to bone that has, I think, the potential to be a cure for osteoporosis," Dr. Cummings said. "Human data might be available in the course of the next year."

Then there is denosumab, an antibody that binds to the RankL receptor on the surface of osteoclasts. Blocking those receptors inhibits the development and activity of osteoclasts and decreases bone resorption.

Given by injection every 6 months, denosumab significantly increased spine and hip BMD, compared with alendronate and placebo in human phase II trials. Phase III trials are underway.

A third potential treatment is to be found in β-blockers. Osteoblasts have been observed in close proximity to sympathetic nerves, and they also possess beta-2 receptors. β-Blockers increase osteoblast activity in vivo. Mice treated with propranolol show increased bone mass. In one study, women taking β-blockers experienced a 28% reduction in the risk of hip fracture.

"Observational data, especially in the case of β-blockers, is difficult to believe enthusiastically," Dr. Cummings said. "I don't think right now you should alter your clinical decisions about when you use β-blockers."

Finally, high levels of the amino acid homocysteine appear to result in cardiovascular disease, dementia, blindness, and osteoporosis. Homocysteine appears to bind to and alter cross-links between collagen fibers. Even high-normal levels have been associated with an increased risk of fracture. Treatment with folic acid and vitamin B_{12} reduces homocysteine levels.

At least one study has shown a large effect of the supplements in reducing fracture risk post stroke. In a randomized controlled trial, 628 patients were given daily doses of 5 mg folate and 1,500 mcg mecobalamin (a vitamin B_{12} analog) or placebo for 2 years. After adjustment, the patients taking supplements experienced an 80% reduction in the risk of hip fracture (JAMA 2005;293:1082-8).

"This is so dramatic that it's hard to believe," said Dr. Cummings. He added that he eagerly awaits further research.

Dr. Cummings receives research support and consulting fees from Eli Lilly & Co., Pfizer, and Novartis, and is a consultant to Merck. ■

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