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 bisphosphonate association with cardiovascular, eye, and other adverse events. The agency also is looking at other possible signals that are not statistically significant.

**BY JEFF EVANS**
Senior Writer

Risedronate Prophylaxis Halts Bone Loss During High-Dose Steroid Tx

**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.”

**Novel Osteoporosis Treatments Providing Hope for a Cure**

**BY ROBERT FINN**
San Francisco — Several novel treatments for osteoporosis are under investigation, and one might even provide a cure, Dr. Steven R. Cummins 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.”

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 ovariec-tomized lost 12% of bone mass. 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 propafenone showed 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 bind to and alter cross-links between collagen fibers. Even high-normal levels have been associated with an increased risk of fracture. Treatment with folate and vitamin B12 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, 64 patients were given daily doses of 5 mg folate and 1,500 mcg mecobalamin (a vitamin B12 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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