The Caveats of Paget's Bisphosphonate Prescribing

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FORT LAUDERDALE, FLA. — Bisphosphonate therapy has dramatically improved the lives of patients with Paget's disease, but it's important to keep in mind the caveats when prescribing them, Dr. Kenneth W. Lyles said at a meeting sponsored by the Paget Foundation for Paget's Disease of Bone and Related Disorders.

Clinical trials have demonstrated that all bisphosphonates are capable of improving bone remodeling and reducing pain. Efficacy at normalizing serum alkaline phosphatase levels varies from 15% with etidronate to 53% with pamidronate to 73% with risedronate to 89% with zoledronic acid.

"We are developing drugs that really help control this disease and improve pain. . . . They're very good drugs, but they come with a set of considerations," said Dr. Lyles, professor of medicine at Duke University, Durham, N.C.

Potential adverse events are uncommon but have been reported with one or more of the various bisphosphonates:

► **Osteomalacia.** There have been some recent reports of patients developing osteomalacia after receiving etidronate at doses of 5 mg/kg for longer than 6 months, which exceeds the label recommendations.

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► **Iritis.** Rarely, iritis occurs with aminobisphosphonate therapy. If further treatment is necessary, patients can be switched to a nonaminobisphosphonate such as etidronate or tiludronate.

► **Acute phase response.** This transient flu-like syndrome consisting of fever, myalgia, and leukopenia has been reported 24-96 hours after first treatment with a bisphosphonate in 5%-40% of patients. It is seen more often with the intravenously agents than the oral ones. Its mechanism isn't completely understood, although it appears to be associated with an excessive release of tumor necrosis factor and interleukin-6 in treatment-naive patients. Patients should be warned of the possibility, and treated with aspirin, ibuprofen, or acetaminophen if it occurs, he advised.

► **Osteonecrosis of the jaw.** A series of papers since 2003 have reported this complication with alendronate, pamidronate, and zoledronate therapy. Most cases have occurred in patients who undergo tooth extraction or other dental procedures while on bisphosphonates, although malignancy and renal impairment have also been identified as risk factors. In patients who must undergo dental procedures, it may be best to give higher doses of bisphosphonate and shorten the course.

► **Hypocalcemia.** Because aminobisphosphonates rapidly block bone resorption, they can lead to hypocalcemia followed by a secondary hyperparathyroid response to restore normocalcemia. Although hypocalcemia has been reported in less than 1% overall among treated patients, severe cases have occurred in patients with malignancy, hypoparathyroidism, and unrecognized vitamin D deficiency. Patients should always be screened for vitamin D and parathyroid hormone prior to initiation of bisphosphonate therapy, and should be on calcium supplementation afterward. "If you miss this, you can have substantial problems," Dr. Lyles noted.

► **Vitamin D deficiency.** Vitamin D insufficiency and frank deficiency are being observed increasingly among the elderly in general, and among patients with Paget's disease in particular. Indeed, one study of 104 subjects over age 98 years revealed that 95% had undetectable levels of serum 25-hydroxyvitamin D, and that 38 of them had sustained a total of 55 fractures (J. Clin. Endocrinol. Metab. 2003;88:5109-15). Vitamin D supplementation is advised for patients with Paget's disease of bone before, during, and after bisphosphonate treatment, he advised.

Dr. Lyles has financial ties to Procter & Gamble, Aventis, Amgen, Roche/GlaxoSmithKline, Merck & Co., and Novartis Pharmaceuticals.

He holds a patent for the use of zoledronate in patients who have sustained hip fractures. ■