# Watch for Adverse Effects of Bisphosphonates in Paget's

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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. This information is expected to be included in the 2006 updated etidronate package insert.

► **Acute phase response.** This transient flu-like syndrome consisting of fever, myalgia, and leukopenia has been reported within 24-96 hours after first treatment with a bisphosphonate in 5%-40% of patients. It is seen more often with the intravenous 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.

► **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 of 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.

Dr. Lyles has financial ties to Proctor & 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. ■

# *Cathepsin K Predicts Response in Paget's*

FORT LAUDERDALE, FLA. — Serum cathepsin K levels could be used to measure treatment response in patients with Paget's disease of bone, Dr. Daniela Merlotti said at a meeting sponsored by the Paget Foundation for Paget's Disease of Bone and Related Disorders.

Cathepsin K, a cysteine protease enzyme, is the most abundantly synthesized protein of the resorbing osteoclast and plays a role in the degradation of organic matrix in the bone, noted Dr. Merlotti of the University of Siena, Italy.

**Cathepsin K levels at 3 months predicted 6-month response to IV bisphosphonate treatment.**

**DR. MERLOTTI**

At baseline, serum cathepsin K levels were significantly higher in 60 Paget's disease patients, compared with 50 age-matched controls, and were higher in patients with polyostotic disease than in those with monostotic disease.

Baseline cathepsin K correlated positively with cross-linked telopeptide of type I collagen (sCTX) and urinary calcium, but not with total or bone-specific alkaline phosphatase (ALP).

Overall, intravenous bisphosphonate treatment reduced cathepsin K levels by 28% at 3 days, 34% at 30 days, 45% at 3 months, 29% at 6 months, and 32% at 1 year.

For the group as a whole, serum ALP decreased by 33% at 30 days and 24% at 90 days, and then increased slightly thereafter up to 1 year.

Cathepsin K levels at 3 months predicted treatment response: Patients whose cathepsin K was decreasing at 3 months had an 18% reduction in total serum ALP levels at 6 months. Those whose cathepsin K was rising at 3 months showed a 5% increase in total serum ALP at 6 months.

# *Vitamin D Deficiency Often Present in Paget's Disease*

FORT LAUDERDALE, FLA. — Screening for vitamin D deficiency should be part of the initial evaluation of patients with Paget's disease, Dr. Jennifer J. Kelly and Dr. Arnold M. Moses said in a poster presentation at a meeting sponsored by the Paget Foundation for Paget's Disease of Bone and Related Disorders.

Blood collected from 37 patients (mean age 72) at their initial visit to a metabolic bone clinic revealed that just three (8%) had levels of 25(OH)D considered to be optimal (greater than 32 ng/mL), while 21 (58%) were vitamin D deficient (below 20 ng/mL), said the investigators, of the State University of New York Upstate Medical University, Syracuse.

The median 25(OH)D level among the 24 men in the group was 20 ng/mL, compared with just 13 ng/mL among the 13 women. Women were more likely than men (5 vs. 2) to be grossly deficient (0-9 ng/mL), while men were in the majority in the intermediate range between 10 and 32 ng/mL (20 men vs. 7 women). Levels greater than 32 ng/mL were seen in only two men and one woman.

Season also influenced 25(OH)D levels, which were on average 9 ng/mL higher during the "light" months (May-September) than during the "dark" period of November-March. Of the 13 patients whose blood had been collected during the light months, 7 (54%) had 25(OH)D levels of 20 ng/mL or above, compared with just 3 (20%) of 15 sampled during the dark months. ■

# Pagetic Activity Tracked in Monostotic Disease

FORT LAUDERDALE, FLA. — The use of $^{18}$F-fluoride positron emission tomography may be useful in the follow-up of patients with monostotic forms of Paget's disease, Dr. Jean-Pierre Devogelaer said at a meeting sponsored by the Paget Foundation for Paget's Disease of Bone and Related Disorders.

In Paget's disease of bone, biochemical markers are used to monitor treatment response. However, in patients with limited bone involvement, these global indices often remain in the normal range, said Dr. Devogelaer, professor of rheumatology at Catholic University of Louvain and Saint-Luc University Hospital, Brussels.

Positron emission tomography (PET) using $^{18}$F-fluoride as an imaging agent appears to be of value in measuring regional skeletal metabolism, and therefore may be helpful in determining whether bisphosphonate therapy should be stopped or prolonged depending on the local level of pagetic activity, he said.

Twelve patients with monostotic Paget's disease of bone underwent 1-hour dynamic $^{18}$F-fluoride PET scans at baseline and at 1, 6, and 12 months after bisphosphonate treatment (intravenous pamidronate in nine, oral risedronate in two, and oral tiludronate in one). Biochemical markers were measured at the same time points.

The affected areas were pelvis in three patients, tibia in three, femur in two, and humerus, vertebral body, skull, and scapula in one patient each.

Changes in bone metabolism as measured by the PET scans were assessed in two ways: via dynamic plasma clearance of $^{18}$F-fluoride to bone mineral, which requires arterial blood sampling; and with a standardized uptake value, a semiquantitative index that averages the tracer uptake with respect to the injected dose and the body weight. Calculation of the standardized uptake value does not require arterial sampling and therefore is a far more convenient method for measuring pagetic activity in a clinical setting, Dr. Devogelaer noted.

The two values correlated with each other at all time points. Both showed huge activity prior to treatment and significant drops thereafter, by about 30% at 1 month, 40% at 6 months, and nearly 50% at 1 year.

In contrast, the biochemical markers correlated with the PET scan results at baseline but not after treatment: Total alkaline phosphatase dropped by about 25% at 1 year, but remained within the normal range throughout the study. Fasting levels of urinary N-terminal cross-linking telopeptide of type I collagen (NTX) decreased significantly up to 6 months, but not thereafter.

Bone-specific alkaline phosphatase dropped by about 30%-35% at 1 month, but remained significant only up to 6 months. Such changes in biochemical markers are not adequate for follow-up, he noted. ■