Parathyroid Hormone Prevents First Fractures

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SAN ANTONIO — Intact human recombinant parathyroid hormone prevented both recurrent and first fractures in a multinational, randomized, placebo-controlled study of postmenopausal women with osteoporosis, Mark P. Ettinger, M.D., said at the annual meeting of the American College of Rheumatology.

Previous studies have shown that the parathyroid hormone (PTH) analog teriperatide can prevent fractures in patients with advanced disease who already have had a fracture. The Treatment of Osteoporosis With PTH (TOP) study was the first to demonstrate the prevention of first fractures in patients with earlier disease, Dr. Ettinger said.

"This is extremely important, because the presence of any existing fracture greatly increases the risk of subsequent fractures," he said in a late-breaking abstract session.

The TOP study included 2,532 women whose mean age was 64.4 years and whose mean spine, total hip, and femoral neck bone mineral density (BMD) T-scores were –3.0, –1.9, and –2.2, respectively.

The study population was very different from other osteoporosis treatment cohorts, in that the patients were younger, and only 19% already had fractures. In previous PTH phase II and teriperatide phase III trials, fracture prevalence ranged from 37% to 100%, he said.

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Patients were randomized to 100 mcg subcutaneous PTH daily or placebo. All patients also took 700 mg calcium and 400 U vitamin D each day.

A total of 1,737 patients—72% and 65% of the placebo and PTH groups, respectively—completed the 18-month study.

At study completion, the vertebral fracture incidence was 3.33% in the placebo group and 1.14% in the PTH group, which represented a relative fracture risk reduction of 66%, said Dr. Ettinger, medical director emeritus of Radiant Research, Stuart, Fla.

In a per-protocol analysis, patients who had a fracture before entering the study had a 69% relative fracture risk reduction; those without a previous fracture had a risk reduction of 63%.

At month 18 the mean spine, total hip, and femoral neck BMD had increased by 7.2%, 2.2%, and 2.5%, respectively, in the PTH group relative to the placebo group, he said. This included patients allowed to take PTH on a less-than-daily schedule.

About 9% of the PTH group withdrew because of headache, dizziness, nausea, or vomiting, or elevated serum or urine calcium levels. Overall, 16% of PTH patients and 12% of placebo patients withdrew during the course of the study. There were two deaths in the placebo group and one in the PTH group; this was judged to be unrelated to treatment.

"The results of the TOP study may change our treatment paradigm somewhat and shift our target population to younger patients or those with less severe disease someday," Dr. Ettinger told this newspaper. The recommended use for anabolic agents such as PTH and its analogs is to give them for 18-24 months, after which an antiresorptive agent, such as a bisphosphonate, is given to preserve the gains, continue improvement of bone density and quality, and continue mineralization.

Bisphosphonates are not given concurrently with PTH because they tend to blunt the response to PTH, at least for the first 6 months, he said. More information is needed as to how much blunting might occur with less potent antiresorptives, such as estrogen or raloxifene.

PTH (1-84) is a recombinant molecule with 84 amino acids in its peptide chain; teriperatide is a structural analog with the first 34 amino acids in its peptide chain.

Dr. Ettinger disclosed that he received research grants and consulting fees from many pharmaceutical companies including NPS Pharmaceuticals, the Salt Lake City–based manufacturer of PTH. An expanded new drug application package for the company's proprietary formulation, Preos, is planned for February 2005, according to the NPS Web site. ■