Absorption Similar for Nasal, Injected Teriparatide

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — A nasal spray formulation of the osteoporosis drug, teriparatide, has cleared its first scientific hurdle.

Intranasal parathyroid hormone (PTH1-34) demonstrated a similar absorption profile as the approved injectable product, Forteo, in a phase I, pharmacokinetics study, Dr. Gordon Brandt and colleagues reported in a poster at the annual meeting of the American Association of Clinical Endocrinologists.

Twelve healthy men and women, ages 20-40 years, received a 20-mcg injection of teriparatide on day 1, followed by single doses of teriparatide nasal spray on 4 subsequent days. Two nasal formulations at two dose levels were evaluated: Formulation No. 1 was given at 200 mcg and 400 mcg and formulation No. 2 at 500 mcg and 1,000 mcg. Blood samples were collected up to 4 hours post treatment.

The times of maximal drug concentration for teriparatide nasal spray and Forteo were not statistically different, reported Dr. Brandt, executive vice president, clinical research and medical affairs, Nastech Pharmaceutical Co., Bothell, Wash., which sponsored the study.

While Forteo achieves a 50-pg/mL peak blood level after subcutaneous administration, the tested doses of nasal spray delivered up to a 400-pg/mL peak blood level, Dr. Brandt said in an interview. "In this first-in-man study, we administered higher doses than are required, so in subsequent studies we will adjust the doses," he said.

Still, while the bioavailability of Forteo was 95%, the bioavailability of the nasal formulation No. 1 was only about 5%-8% and 12%-15% for the second formulation.

Intersubject variability for the nasal sprays was similar to or lower than Forteo, suggesting that intranasal dosing may provide consistent dosing. "I think the take-home is that contrary to what you might think, the nasal spray in fact doesn't result in markedly greater variability than an injection," he said.

There was no nasal irritation with the nasal sprays. Interestingly, two patients developed hypercalcemia after the Forteo injection, whereas there were no reports of hypercalcemia following any nasal spray dosing.

Procter & Gamble has signed an agreement with Nastech to further develop the nasal spray formulation, Dr. Brandt said. The U.S. Food and Drug Administration has put the nasal formulation on a 505(b)(2) regulatory path, which requires only a single noninferiority study of the nasal sprays versus Forteo. The timing of this study has not been announced. In a separate poster at the same meeting, cost and side effects were identified as significant barriers for patients considering teriparatide.

In a retrospective study of 84 patients who had received a recommendation for teriparatide for severe osteoporosis since 2004, 28 patients (33%) refused the drug primarily because of cost, concerns about subcutaneous injections, or anxiety surrounding the incidence of osteosarcomas in rat studies, Dr. Pauline Camacho and Laurie Bachrach, of Loyola University Health System, Chicago, reported. A 28-day supply of teriparatide averaged $96.50.

Of the 56 patients who tried teriparatide, only 34 took the drug for 1 year. At 1 year, the mean change in bone mineral density of the lumbar spine was 6.9%.

Of the 52 patients who responded to a survey about side effects, 26 reported one or more. ■

Jaw Osteonecrosis Occurred in 1% of Cancer Patients on IV Bisphosphonate

BY SHARON WORCESTER
Southeast Bureau

ATLANTA — A retrospective analysis of data from nearly 4,000 patients treated with intravenous bisphosphonates suggests that osteonecrosis of the jaw in patients with metastatic cancer is an important but rare event in these patients, Dr. Ana O. Hoff reported in a poster at the annual meeting of the American Society of Clinical Oncology.

Reports of an association between bisphosphonate treatment and osteonecrosis of the jaw (ONJ) in patients with metastatic bone disease prompted this study examining the frequency of and risk factors for ONJ, explained Dr. Hoff of the University of Texas M.D. Anderson Cancer Center, Houston.

The cohort studied included patients treated from September 1996 to February 2004. The most common diagnoses were breast cancer and multiple myeloma, and the indications for intravenous bisphosphonate treatment included metastatic bone disease, hypercalcemia, and osteoporosis.

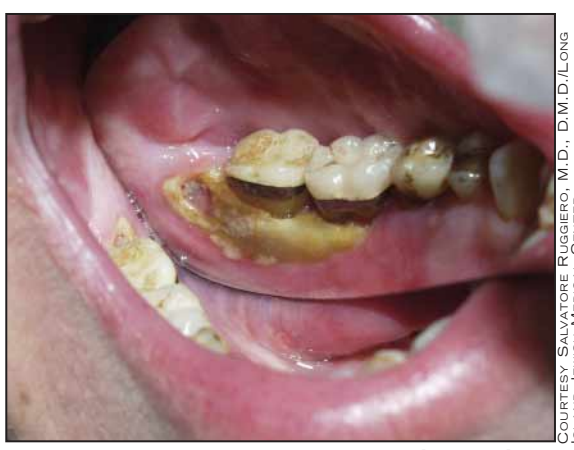
ONJ, which developed in 29 patients (0.73% overall, including about 1% of breast cancer patients and 2% of multiple myeloma patients), was defined as exposed nonhealing bone of at least 3 months' duration.

Mean cumulative doses of the bisphosphonates used (pamidronate and zoledronate) were significantly higher, and duration of disease and follow-up were significantly longer, in ONJ patients than in those who didn't develop ONJ.

Dental extractions, estrogen-receptor–positive tumors, and treatment with pamidronate and zoledronate were shown to be significant risk factors for ONJ in breast cancer patients. In multiple myeloma patients, significant risk factors were dental extractions, periodontal disease, and osteoporosis.

About 70% of ONJ patients reported no pain with bone exposure, Dr. Hoff noted.

Management of ONJ included aggressive oral hygiene, oral rinses, debridement of necrotic bone, and antibiotic therapy. Of 15 ONJ patients followed longer than 6 months, 1 healed, 1 improved, 1 remained stable, and 9 experienced disease progression. ■



COURTESY SALVATORE RUGGIERO, M.D., D.M.D./LONG ISLAND JEWISH MEDICAL CENTER

Rare occurrence of spontaneous ONJ in a patient undergoing bisphosphonate therapy is pictured.

Race May Be ONJ Risk

White cancer patients on intravenous bisphosphonate therapy for bone metastases may be at higher risk for osteonecrosis of the jaw, Dr. Tamer Aiti reported in a poster at the meeting.

A retrospective study by Dr. Aiti and colleagues at John H. Stroger Jr. Cook County Hospital, Chicago, found that 6 of 161 patients with metastatic breast cancer developed this rare complication in the mandible bone. Five of the six patients were white. Yet whites accounted for less than a third of the population reviewed. All but 29 patients were nonwhite.

The investigators calculated that white patients had significantly more bisphosphonate infusions, 21 on average, compared with a mean of 13.5 infusions in nonwhite patients.

The patients were treated with zoledronic acid and/or pamidronate between Jan. 1, 2001, and Oct. 30, 2005. None had prior glucocorticosteroid therapy.

Dr. Aiti of the department of surgical oncology at the University of Illinois at Chicago, called for larger studies to consider not only race, but also confounding variables such as type of bisphosphonate therapy and cumulative dose, as well as other possible risk factors.

—Jane Salodof MacNeil

Island Study to Research Genes, Osteoporosis Link

HARROGATE, ENGLAND — To better understand the genetic components of osteoporosis, a University of Edinburgh researcher is planning to study the relationship between the two in the isolated population of the Orkney Islands.

Dr. Stuart Ralston, professor of rheumatology and head of the school of molecular and clinical medicine at University of Edinburgh, said research has shown that bone mineral density (BMD) in osteoporosis patients is almost certainly regulated by genetic signals.

Genetic factors explain 60%-85% of the variance in BMD, including type I collagen affecting bone structure, vitamin D receptors affecting mineralization, estrogen receptors affecting hormone action, and interleukin-1 and interleukin -6 affecting inflammation. However, the effects of individual genes appear to be small and may be magnified only by the interactions of multiple genes.

Orkney—an archipelago of 70 or so islands about 10 miles off the northern tip of Scotland—is one of the more isolated regions of Europe, and it has good genealogical records, making it possible for researchers to get a clearer picture of the way genetics affects bone health, Dr. Ralston said.

Dr. Ralston said colleagues were already planning to test the Orkney Islands population for genetic factors related to cardiovascular disease, so he asked them to tack on the factors for osteoporosis as well.

"Linking studies conducted in general isolated populations are good," Dr. Ralston said June 26 during a workshop at the annual conference of the National Osteoporosis Society.

"If you're going to study osteoporosis or any other complex disease, I would study an isolated population because you're more likely to find something," Dr. Ralston said.

One study of the Icelandic population showed that a variation in the gene BMP2 in chromosome 20 was correlated to osteoporosis. That study found that variation was present in 5% of people with low BMD at spine or hip or a fracture, compared with 1% in the control population.

Dr Ralston said he confirmed that work with an isolated population in northeast Scotland, where 3% of fracture patients had that same variation, compared with 0.04% of the control population.

"It's still rare," Dr. Ralston explained. "One of the advantages of studying an isolated population is that you're more likely to discover a gene. One of the disadvantages of this is, is it applicable for the rest of the world?"

The study will go beyond the BMP2 gene to include the entire human genome for correlations to osteoporosis. But even with research into the genetic components of osteoporosis, identifying a single marker that will help physicians identify likely hip fracture patients may be impossible, he said.

—Jonathan Gardner