Teriparatide Prompted 29% Gain in Alveolar Bone

BY MITCHEL L. ZOLER

FROM THE NEW ENGLAND JOURNAL OF MEDICINE

Treatment for 6 weeks with teriparatide, a U.S.-approved drug that stimulates bone remodeling, led to significant, 1-year improvements in alveolar bone formation and clinical outcomes in a controlled, pilot study of 40 patients undergoing periodontal surgery.

Bone gain in the osseous defects of the 20 patients who were randomized to receive daily teriparatide injections became detectable early after treatment began and continued to improve during 12 months of follow-up, leading to a highly significant improvement in overall alveolar bone gain, compared with the 20 patients on placebo, Jill D. Bashutski, D.D.S., and her associates reported (N. Engl. J. Med. 2010 Oct. 16 [doi:10.1056/NEJMoa1005361]).

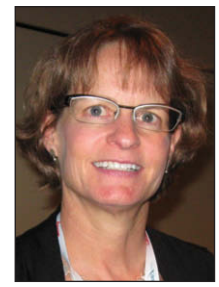
The teriparatide-treated patients also had significantly better 1-year improvements in periodontal probing depth and clinical attachment, reported Dr. Bashutski, a periodontist at the University of Michigan in Ann Arbor. The article's online publication was timed to coincide with Dr. Bashutski's presentation of the findings at the annual meeting of the American Society for Bone and Mineral Research in Toronto.

She and her associates used teriparatide, a recombinant agent that contains the first 34 amino acids of parathyroid hormone, because of its activity as an anabolic agent and prior evidence that it enhances bone remodeling and wound healing in areas of high bone turnover, such as fractures and surgical sites.

"We know that parathyroid hormone stimulates formation of preosteoblast cells, and these cells go on to eventually form bone." The 6-week regimen of daily teriparatide injections produces "an initial incentive for bone formation to occur" during subsequent months, said Dr. Laurie K. McCauley, the principal investigator of the study and professor and chair of periodontics and oral medicine at the University of Michigan, in an interview.

The positive effects that teriparatide treatment had on the study outcomes of bone gain, probing depth, and clinical attachment were also all clinically significant, Dr. McCauley added. Teriparatide increased 1-year bone gain at a rate that was 10-fold higher than placebo. "That's huge," she said.

The long-term sequence of events that teriparatide triggers likely explains how a 6-week course produced significant differences after 1 year, she said. "We know that most connective tissue healing goes on during the first 6 weeks. The thought was to augment that healing with this agent."



The outcome from "this small trial provides preliminary evidence that an agent that stimulates bone formation might confer additional benefit over that achieved with standard care in patients with periodontitis," commented Dr. Andrew Grey in an editorial that accompanied the article (N. Engl. J. Med. 2010 Oct. 16 [doi:10.1056/NEJMe1010459]). But many questions about this treatment remain, he said. "How durable is the effect of teriparatide? What is the optimal dosing regimen? Does teriparatide alter important [end points] such as tooth loss or the need for further operative intervention? Do antiresorptive agents, which cost considerably less than teriparatide, confer similar benefits?" asked Dr. Grey, an endocrinologist at the University of Auckland (New Zealand).

Improvements in periodontal probing depth and clinical attachment were significant.

DR. BASHUTSKI

The study enrolled patients (aged 30-65 years) with severe periodontal disease at the University of Michigan from January 2005 to June 2009. All patients had normal levels of calcium and parathyroid hormone, a minimum vitamin D level of 16 ng/mL, and no osteoporosis. All patients underwent conventional surgery on an osseous defect. Starting 3 days before surgery, patients began daily treatment with either 20 mcg teriparatide or placebo, administered daily by subcutaneous injection, for 6 weeks. All patients also received a daily supplement of calcium and vitamin D.

Patients who were treated with teriparatide had significantly better resolution of their periodontal bone defects at 6, 9, and 12 months following baseline, compared with the placebo patients. At 12 months, the teriparatide-treated patients averaged a bone gain of 1.86 mm (29%), compared with baseline, whereas the placebo patients averaged a 0.16-mm (3%) gain from baseline.

Teriparatide treatment was also linked with a 2.42-mm (33%) average reduction in probing depth at the surgical site after 12 months, compared with baseline. The placebo group averaged a 1.32-mm (20%) reduction in probing depth from baseline, a statistically significant difference. Clinical attachment improved by 1.58 mm (22%) at 1 year, compared with baseline, in the teriparatide patients, significantly better than the 0.42-mm (7%) average attachment improvement in the placebo group. No improvements in probing depth occurred in the teriparatide and placebo patients in areas of severe, chronic periodontitis that did not undergo surgery.

Teriparatide increased 1-year bone gain at a rate that was 10-fold higher than placebo. 'That's huge.'

DR. McCAULEY

At entry to the study, five patients in the teriparatide arm and nine in the placebo group had osteopenia on dual-energy x-ray absorptiometry examinations. At the 12-month follow-up, patients in both study arms showed no significant changes in bone density scores or in quality of life scores. Teriparatide treatment did not link with any pattern of adverse events that differed from the placebo group.

Although teriparatide is available for treating osteoporosis, its widespread use in patients who are undergoing periodontal surgery should await results from studies involving larger numbers of patients, Dr. McCauley said. She also cautioned against extrapolating the results to other types of bone surgery. Dr. McCauley said she would like to run studies on a delayed-release, topical formulation of teriparatide that would be implanted during surgery and would then release over the subsequent 6 weeks, precluding daily injections. Formulations of this type now exist, but have not reached the clinical-testing stage.

The study received partial funding from Eli Lilly & Co., the company that markets teriparatide (Forteo), but it was an investigator-initiated study. Dr. McCauley has received research grants and transportation support from Lilly. She has also received research grants and has been a consultant to Amgen Inc., but she has not received any honoraria or consulting fees. Dr. Bashutski said she has received travel expenses from the Colgate-Palmolive Co. Dr. Grey said that he has received travel expenses from Merck Sharp & Dohme (NZ) Ltd. ■

FDA Warns of Atypical Fractures Linked to Bisphosphonates

BY ELIZABETH MECHCATIE

FROM A BRIEFING BY THE FDA

The Food and Drug Administration on Oct. 13 issued a warning about the "possible" risk of the rare atypical femur fractures associated with bisphosphonate treatment in osteoporosis patients, after reviewing the final report on this association released Sept. 14 by the American Society for Bone and Mineral Research.

The FDA has requested that a warning about the association be added to the labels of all bisphosphonates approved for osteoporosis prevention and treatment, and that a medication guide explaining the risk and the symptoms of these fractures be provided to patients with each bisphosphonate prescription, said Dr. Sandra Kweder during the briefing.

The agency also is requiring a change to the "indications and usage" section of the bisphosphonate labels, which will note that the optimal duration of treatment with bisphosphonates is not clear when they are used to treat and/or prevent osteoporosis.

In March 2010, the FDA announced that it was reviewing reports of femur fractures associated with bisphosphonate use, and the report issued by an American Society for Bone and Mineral Research (ASBMR) task force concluded that long-term bisphosphonate treatment may be related to an increased risk of these fractures, described as atypical fractures of the subtrochanteric region of the hip and femoral shaft (http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/pdf).

The ASBMR report "helped us understand these fractures a little bit better and makes us confident that this is something that is potentially more closely related to these drugs, particularly [during] long-term use, than we previously had evidence for," said Dr. Kweder, deputy director of the Office of New Drugs in the FDA's Center for Drug Evaluation and Research.

These fractures affect the femoral shaft, are less likely to be associated with trauma than are typical osteoporotic fractures, are sometimes bilateral, and generally affect younger patients, she said. Affected patients have described dull aching thigh or groin pain weeks to months before complete fracture is identified, she noted. The data indicate that they are more common in patients who have been on treatment for more than 5 years.

Similar to the recommendations in the ASBMR report, the FDA's recommendations to health care professionals include evaluating any patient who presents with new thigh or groin pain for a femur fracture, stopping treatment in patients with evidence of a femoral shaft fracture, and periodically reevaluating the need for continued treatment, particularly in patients treated for more than 5 years.

The products affected are those approved for osteoporosis indications, such as alendronate (Fosamax), alendronate and cholecalciferol (Fosamax Plus D), risedronate sodium (Actonel), risedronate sodium with calcium carbonate (Actonel with Calcium), ibandronate sodium (Boniva), risedronate sodium (Atelvia), pamidronate injection (Aredia), and zoledronic acid injection (Reclast), as well as generic formulations of those drugs. ■

The FDA advisory is available at www.fda.gov/Drugs/DrugSafety/ucm229009.htm. Report serious adverse events linked with bisphosphonates to the FDA's MedWatch program at 800-332-1088 or www.fda.gov/medwatch/.