Teriparatide Boosts Periodontal Surgery Recovery

Pilot study shows agent improves bone gain, probing depth, clinical attachment.

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 online (N. Engl. J. Med. 2010 Oct. 16 [doi:10.1056/NEJMoa1005361]).

The patients who were treated with teriparatide also demonstrated 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 study findings at the annual meeting of the American Society for Bone and Mineral Research in Toronto.

She and her coinvestigators used teriparatide, a recombinant agent that contains the first 34 amino acids of parathyroid hormone, because of its activity as an anabolic agent and evidence from prior studies 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," said Dr. Bashutski.

The 6-week regimen consists of daily teriparatide injections, which produce "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, according to Dr. McCauley. Teriparatide increased 1-year bone gain at a rate that was 10-fold higher than placebo.

Parathyroid hormone stimulates formation of preosteoblast cells and bone.

DR. BASHUTSKI

"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.

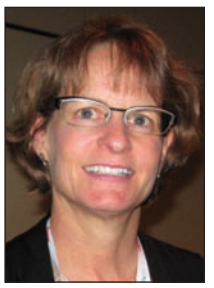
"We know that most connective tissue healing goes on during the first 6 weeks," according to Dr. McCauley. "The thought was to augment that healing with this agent."

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).

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 in the study 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 of teriparatide or placebo, administered daily by subcutaneous injection, for 6 weeks. All patients also received a daily supplement of calcium and vitamin D.



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

DR. McCAULEY

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 associated with a 2.42-mm (33%) average reduction in probing depth at the surgical site after a period of 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 an average of 1.58 mm (22%) at 1-year follow-up, compared with baseline, in the teriparatide patients, significantly better than the average value of 0.42 mm (7%) for 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.

At entry to the study, five patients in the teriparatide arm and nine in the placebo group had osteopenia on dual x-ray absorptiometry examinations. At the 12-month follow-up, patients in both of the study arms showed no significant changes in bone density scores or in quality of life scores.

Teriparatide treatment was not associated with any pattern of adverse events that differed from the placebo group.

Although teriparatide is available in the United States 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. Such a mode of delivery would preclude the necessity of administering daily injections. Teriparatide formulations of this type now exist, but they have not reached the clinical-testing stage. ■

VITALS

Major Finding: In patients undergoing periodontal surgery, daily 20-mcg injections of teriparatide for 6 weeks led to an average 29% bone gain at the surgery site after 1 year, compared with an average 3% gain in the placebo group.

Data Source: A randomized, single-center pilot study of 40 patients with severe periodontal disease.

Disclosures: The investigator-initiated study received partial funding from Eli Lilly & Co., the company that markets teriparatide (Forteo). Dr. McCauley has received research grants and transportation support from Lilly. She has also received research grants and has been a consultant to Amgen, but 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.

Ten Years Between Osteoporosis Screenings Okay for Some

BY MITCHEL L. ZOLER

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR BONE AND MINERAL RESEARCH

TORONTO – Women aged 67 years or older with a bone mineral density T score higher than –1.50 on dual-energy x-ray absorptiometry can have their next DXA examination deferred for at least 10 years with a low risk that they'll progress to osteoporosis in the interim, according to an analysis of data from more than 5,000 U.S. women.

"Fewer than 10% of women with a BMD [bone mineral density] T score of more than –1.50 were estimated to transition to osteoporosis if followed for 15 years," Dr. Margaret L. Gourlay said.

For these women, "repeat testing before 10 years is unlikely to show osteoporosis," she said, and for women with a T score of –1.50 to –1.99, "a 5-year interval could be considered."

The results provide the first evidence-based guidance available on the appropriate interval for osteoporosis screening in elderly women.

"The value of these results is that we can be less concerned about women with good BMD," Dr. Gourlay said in an interview. "We don't need to go on autopilot and screen [all women] every 2 years."

Medicare reimburses for screening women aged 65 years or older with dual-energy x-ray absorptiometry (DXA) every 2 years, she noted, and hence U.S. physicians often recommend this screening interval.

Earlier this year, however, an updated review of osteoporosis screening by the U.S. Preventive Services

Continued on following page

Continued from previous page

Task Force (USPSTF) noted that no evidence existed to support any screening interval (Ann. Intern. Med. 2010;153:99-111).

The results "were a surprise in a good way," said Dr. Gourlay, a family physician at the University of North Carolina in Chapel Hill. "This is good news for women with good BMD. For women with higher bone density, we're probably doing some unnecessary testing."

The new results also showed that the T score exerted the strongest influence on the osteoporosis screening interval, more so than clinical risk factors for fracture. Adjustment for "risk factors did not make too much of a difference, so physicians do not need to make a FRAX calculation" to decide a screening interval, she said. "They can just go by the BMD."

"With FRAX [the World Health Organization's Fracture Risk Assessment Tool] you don't just look at BMD, but primary care physicians can't stop [in the middle of a patient consultation] to calculate a FRAX score," Dr. Gourlay said.

"When a patient has a BMD result in the good range, the main value of the new results is that we can be less concerned about these women" and the need for rescreening in the near future, she noted.

"The importance [of the new findings] is not the absolute time estimates we found; it's the magnitude of the difference.

'When a patient has a BMD result in the good range, the main value of the new results is that we can be less concerned about these women' and the need for rescreening in the near future.

A 16-year interval [for 10% of women to develop osteoporosis] for women in the top two T score groups, and a 5-year interval [for women with a baseline T score of –1.50 to –1.99] is quite different" from the way most physicians practice today, she said.

She cautioned that the finding needs confirmation from similar analyses using different data sets, and that it remains up to health policy-setting groups, such as the USPSTF, to consider the findings and use them to formulate updated screening recommendations. But, she added, the findings have already influenced her own approach to handling screening intervals.

"If I have a patient who missed a test and her prior T score was more than –1.50, I'm not nearly as worried now," said Dr. Gourlay.

The analysis used data collected in the Study of Osteoporotic Fractures (SOF), which enrolled women aged 65 years or older in four U.S. cities starting in 1986 and has followed them since then.

Dr. Gourlay and her associates focused on 5,036 women in the study who underwent at least two serial BMD measures over a total of 15 years. Patients were excluded from analysis if they had osteoporosis at any hip site at baseline, had an incident hip fracture, or were treated with a bisphosphonate or calcitonin. Patients also were excluded if they died or dropped out of the study.

The analysis included 1,275 women who had at least one normal baseline BMD value (a T score of –1.00 or greater) and 4,279 women with at least one T score that identified them as having osteopenia (–1.01 to –2.49).

Some women fell into both categories if they underwent at least three DXA examinations starting with at least one normal T score followed by at least one osteopenic score.

At baseline, the rate of estrogen use ran 25% in women with a normal T score at baseline and 16% in women with osteopenia – relatively high rates by today's standards but typical for practice in the 1980s.

During follow-up, full transition to osteoporosis occurred in fewer than 1% of the participants with a T score of at least –1.00 at baseline, fewer than 5% of those with a T score of –1.01 to –1.49 at baseline, and 22% of women with a score of –1.50 to –1.99 at baseline. Transition to osteoporosis took place in 65% of women who had a T score of –2.00 to –2.49 at baseline.

After Dr. Gourlay and her associates adjusted for the covariates of age and continuous bone mineral density, they found that it took an estimated 16 years for 10% of women with a T score of –1.00 or higher at baseline to transition to osteoporosis.

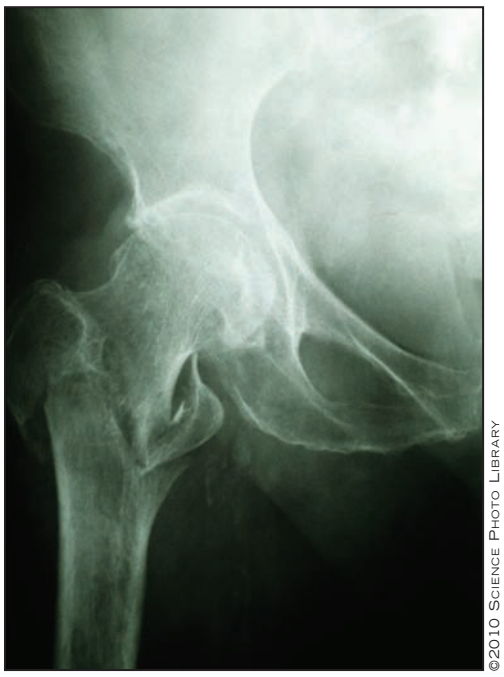
The other three T score subgroups that were analyzed underwent covariate adjustment for age, body mass index, current estrogen use, any fracture after age 50, current smoking, and oral glucocorticoid use.

After adjustment, the average time for 10% of women to transition to osteoporosis was found to be 15.5 years in women following a T score measure of –1.01 to –1.49, 4.5 years in women with a T score of –1.50 to –1.99, and 1.2 years in women with a T score of –2.00 to –2.49.

The investigators performed an additional analysis that stratified women by their age at the baseline DXA examination.

Even among women who were 85 years old, it took an average of nearly 11 years for 10% to develop osteoporosis following a baseline T score of –1.01 to –1.49.

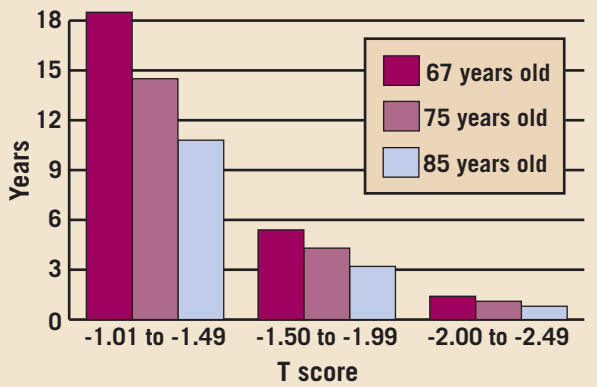
Dr. Gourlay said that she had no disclosures relevant to this study. ■



©2010 Science Photo Library

X-ray of the hip shows a fracture due to osteoporosis in an elderly woman. Less frequent screening may be indicated.

Impact of Baseline Age and T Score on Time to Develop Osteoporosis



Notes: Based on data for 5,036 women. Time for 10% of women studied to transition to osteoporosis after adjustment.
Source: Dr. Gourlay

Elsevier Global Medical News

UK Agency Recommends Denosumab for Osteoporosis

BY JENNIE SMITH

FROM THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

The U.K. National Institute for Health and Clinical Excellence said in September that it would recommend the osteoporosis drug denosumab for older women at risk of fractures who cannot take oral bisphosphonates.

NICE's standard treatment recommendation for this patient group is alendronate and either risedronate or etidronate.

All of these agents are oral medications associated with adverse upper-GI effects if not taken according to instructions. Patients must take the medicines before meals and should not lie down for at least half an hour afterward. Denosumab, by contrast, is an injection administered twice annually.

Denosumab (Prolia, Amgen) is a monoclonal antibody that reduces osteoclast activity, limiting bone breakdown.

The NICE reviewers, in deciding to recommend denosumab, considered results from a manufacturer-sponsored phase III randomized controlled trial of denosumab 60 mg subcutaneously every 6 months in 7,868 osteoporotic women aged 60-90 years.

After 3 years, 7.2% of the placebo patients sustained a new vertebral fracture, compared with 2.3% of those who were taking denosumab, a 68% reduction. Nonvertebral fractures were 6.5% with denosumab versus 8% with placebo, and hip fractures were reduced by 40% to 2.3% in the treatment arm.

The drug was also shown to increase bone mineral density at the lumbar spine by 9% over the 3 years compared with placebo, and by 6% at the hip.

The NICE reviewers, while acknowledging denosumab's effectiveness, nonetheless noted that it was not being considered as a replacement for the cheap and widely available oral bisphosphonates, but as an alternative only where these were unsuitable.

Denosumab is not being considered as a replacement for the cheap and widely available oral bisphosphonates, but as an alternative only where these agents are unsuitable.

Denosumab costs approximately $290.00 for a 1-mL prefilled syringe (60 mg per mL solution), and about $580.00 for 1 year of treatment.

Women eligible for treatment with denosumab must be intolerant of, have contraindications to, or be unable to comply with manufacturer instructions for taking alendronate and risedronate or etidronate.

They must also have bone density scores indicative of fracture risk. Other clinical risk factors for fracture that may be considered are alcohol consumption of more than 4 units per day, parental history of hip fracture, and rheumatoid arthritis.

NICE's guidance on denosumab, which is in final appraisal stage, mirrors its guidance on strontium ranelate, another treatment option for postmenopausal women at risk of fracture who cannot take bisphosphonates. ■