Teriparatide Now a Preferred Drug for GIOP

BY BRUCE JANCIN

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

SAN DIEGO – Teriparatide has received a boost in status as a preferentially effective treatment for glucocorticoid-induced osteoporosis in the form of a second, confirmatory, randomized double-blind trial demonstrating the anabolic agent achieves substantially greater increases in bone mineral density compared to a bisphosphonate.

One of these studies also included fracture rates as a preplanned secondary end point; the trial showed a significant reduction in vertebral fractures with teriparatide (Forteo) as compared to alendronate (Fosamax).

These positive study findings are bolstered by a biologically plausible mechanism of benefit, observed Dr. Kenneth G. Saag. "Based upon the pathogenesis of glucocorticoid-induced osteoporosis [GIOP], we think that an anabolic agent makes some sense. It may be beneficial to stimulate osteoblasts to promote new bone formation," said Dr. Saag, professor of medicine and epidemiology at the University of Alabama at Birmingham.

Steroids are known to have apoptosis-mediated deleterious effects on both osteocytes and osteoblasts that lead to decline in bone function and an abrupt increase in fracture risk independent of bone mineral density (BMD). Osteoclasts are also unfavorably impacted because of cross talk and the indirect effects of sex steroids, insulin-like growth factor, and a modest effect of secondary hyperparathyroidism mediated through altered calcium absorption. In addition, higher-dose steroids have adverse effects upon muscle that can independently lead to a higher fracture rate, he explained.

The Food and Drug Administration has approved alendronate, zoledronic acid (Reclast), risedronate (Actonel), and teriparatide (Forteo) for treatment of GIOP. More recently, raloxifene (Evista) has joined the ranks of agents shown to increase BMD in patients on long-term steroids; this came in the form of a double-blind, placebo-controlled, 12-month study (Ann. Rheum. Dis. 2011;70:778-84).

Courtesy University of Alabama

Dr. Kenneth G. Saag noted that an anabolic agent such as teriparatide stimulates osteoblasts to promote new bone formation.

Subcutaneous daily teriparatide for up to 2 years also has the approval of the FDA for use in adults at high fracture risk because they are on sustained systemic steroid therapy.

There is no definitive study demonstrating that any of these agents actually prevents fractures in patients with GIOP.

However, data from a study in which Dr. Saag was lead investigator showed that teriparatide-treated patients had significantly fewer vertebral fractures than those assigned to alendronate. The study was a 36-month randomized, double-blind, clinical trial that assessed fracture rates as a preplanned secondary end point. The radiographic and clinical vertebral fracture rates in 169 alendronate-treated patients were 7.7% and 2.4%, respectively, compared with 1.7% and 0% in 173 teriparatide-treated patients ($P = .007$ and .037). No significant difference in nonvertebral fractures was found between the two treatment arms.

The primary study end point was the change in BMD from baseline. Here again teriparatide proved significantly more effective than the bisphosphonate, with a mean 11% increase at the lumbar spine, compared to 5.3% with alendronate.

Teriparatide-treated patients also had a 5.2% increase in BMD at the total hip and a 6.3% boost at the femoral neck, compared to 2.7% and 3.4%, respectively, with alendronate (Arthritis Rheum. 2009;60:3346-55).

Confirmation of teriparatide's superior BMD-building effect came from the EuroGIOPs trial presented by Dr. Claus C. Glüer at the ASBMR meeting.

EuroGIOPS was an 18-month, open-label, phase III clinical trial in which 92 men with GIOP were randomized to teriparatide or risedronate.

At 6 months the mean increase in lumbar spine BMD was 5.7% in the teriparatide group, compared with 3.3% in the risedronate arm.

At 18 months – the primary study end point – the teriparatide group averaged a 16.3% BMD increase over baseline, while the risedronate arm had a 3.8% rise.

Intriguingly, new clinical fractures occurred during 18 months of therapy in five patients on risedronate and none on teriparatide, a difference that came within a hair of statistical significance ($P = .056$).

Bone strength as formally measured in terms of anterior bending, axial compression, and axial torsion was also significantly greater in the teriparatide group, according to Dr. Glüer, who is professor of medical physics at the department of diagnostic radiology, University Hospital Schleswig-Holstein in Kiel, Germany.

The 2010 update of the American College of Rheumatology guidelines for the prevention and treatment of GIOP recommend bisphosphonates but not teriparatide for older adults at high risk of fracture who are taking less than 5 mg/day of prednisone for less than 1 month (Arthritis Care Res. 2010;62:1515-26).

The ACR guidelines recommend reserving use of teriparatide for high-risk patients – that is, those with a prevalent fracture or a World Health Organization Fracture Risk Assessment Tool (FRAX) score indicative of a greater than 20% 10-year risk of a major osteoporotic fracture – who are on at least 6 mg/day of prednisone for less than 1 month or on any dose of glucocorticoids for longer than 1 month.

Although Dr. Saag was a coauthor of the ACR guidelines, he was pleased to see a new commentary on the ACR guidelines published by the Professional Practice Committee of the ASBMR. The review recommends teriparatide or any of the bisphosphonates for high-risk patients, period.

Dr. Saag, who was not involved in the ASBMR review, recommended it as useful reading both for its areas of agreement with the ACR guidelines as well as for raising several patient scenarios in which the ASBMR committee believes the ACR recommendations either do not apply or might be improved upon (J. Bone Miner. Res. 2011;26:1989-96).

Dr. Glüer declared having no financial conflicts regarding the Eli Lilly–funded EuroGIOPs trial. Dr. Saag disclosed that he has received research grants from and serves as a paid consultant to Amgen, Eli Lilly, Merck, and Novartis. ■

Folic Acid, B Vitamins Fail to Cut Fracture Risk in Women

BY BRUCE JANCIN

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

SAN DIEGO – Combined daily supplementation with folic acid and vitamins B_6 and B_{12} proved to be a bust for reduction of nonvertebral fracture risk in a large, randomized, double-blind clinical trial conducted in women with known cardiovascular disease or multiple risk factors.

A secondary analysis of fracture outcomes in 5,442 female health professionals over age 42 years who participated in the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) showed an overall nonvertebral fracture incidence of 7.6% during an average 7.3 years of treatment and follow-up in the supplementation group and a similar 6.9% rate in placebo-treated controls, Dr. Douglas C. Bauer reported at the meeting.

Participants in WAFACS had known cardiovascular disease or at least three cardiovascular risk factors. The previously reported primary study end points were cardiovascular event rates and all-cause mortality, where supplements had no effect (JAMA 2008;299:2027-36).

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Major Finding: During an average 7.3 years of treatment and follow-up, the overall nonvertebral fracture incidence was 7.6% in the supplementation group, compared with 6.9% in placebo-treated controls.

Data Source: Secondary analysis of the 5,442-subject randomized, double-blind, placebo-controlled Women's Antioxidant and Folic Acid Cardiovascular Study.

Disclosures: WAFACS was funded by the National Heart, Lung, and Blood Institute. Dr. Bauer reported having no financial conflicts.

The new retrospective secondary analysis of WAFACS was undertaken because some prior observational studies had concluded that elevated homocysteine and low vitamin B_{12} levels are associated with increased fracture risk. The supplement regimen utilized in the trial was designed to lower homocysteine and boost vitamin B_{12} levels. It consisted of daily folic acid at 2.5 mg, vitamin B_6 at 50 mg, and vitamin B_{12} at 1 mg.

In all, 80% of participants reported greater than 66% compliance with therapy. Rates of hip, wrist, and total nonspine fractures were similar in both high-compliance subgroups, noted Dr. Bauer of the University of California, San Francisco. ■