Vit D, Testosterone Improve Joint Pain Scores

BY BRUCE JANCIN

SAN ANTONIO — Testosterone undecanoate and high-dose vitamin D show promise for the treatment of aromatase inhibitor–associated musculoskeletal pain in breast cancer patients, according to two double-blind, placebo-controlled, randomized trials presented at the San Antonio Breast Cancer Symposium.

There's a caveat regarding the high-dose vitamin D regimen: Although it improved pain scores and bone mineral density at the femoral neck, it also caused hypercalciuria to such an extent that nearly one in five treated patients had to be dropped from the study at the 2-month mark, according to Dr. Antonella Rastelli of the Siteman Cancer Center at Washington University in St. Louis.

If we don't monitor patients on high–vitamin D regimens for urinary calcium, they may develop kidney stones.

DR. RASTELLI

"I think that's actually a point of caution. I'm seeing and hearing that everybody is using vitamin D already. There could be a considerable number of patients who are receiving it for a long time, perhaps 4 or 5 years, while we give an aromatase inhibitor. Down the line, if we don't monitor their urinary calcium excretion, we may see kidney stones," she warned.

Dr. Rastelli reported on 60 postmenopausal women with hormone receptor–positive breast cancer and low to marginal serum vitamin D levels of 10-29 ng/mL. All had developed significant musculoskeletal pain since going on adjuvant anastrozole at least 8 weeks prior to enrollment. All were placed on oral calcium at 1,000 mg/day and vitamin D_3 at 400 IU/day.

In addition, patients randomized to the active treatment group received vitamin D_2 (ergocalciferol) at 50,000 IU/week for 8 weeks if their baseline serum vitamin D level was 20-29 ng/mL, and for 16 weeks if it was 10-19 ng/mL. Thereafter, they got 50,000 IU once monthly for the balance of the 6-month trial. The control group received placebo on the same schedule.

At 2 months of follow-up, women in the high-dose vitamin D arm had significantly lower pain scores than did controls on both the Brief Pain Inventory and the Fibromyalgia Impact Questionnaire. They also scored significantly better than controls on the Health Assessment Questionnaire–Disability Index domains that specifically assessed ability to climb steps and walk on flat ground.

These benefits were no longer significant at the 4- and 6-month follow-ups, probably because by then the high-dose vitamin D had been switched from weekly to monthly therapy, Dr. Rastelli said.

In future studies, she plans to continue high-dose vitamin D for a longer period in an effort to achieve more lasting benefits. In addition, she is considering using daily cholecalciferol to maintain more stable serum vitamin D levels than is possible with weekly ergocalciferol. She is also interested in broadening the study population to include patients with vitamin D levels that are currently considered normal.

Separately, Dr. Steve N. Birrell reported on 90 postmenopausal women with breast cancer who had been on adjuvant anastrozole for a median of 16 months and were experiencing significant joint pain. They were randomized in a double-blind manner to 3 months of oral testosterone undecanoate at 40 or 80 mg/day, or to placebo.

Eligibility for the trial required that patients have baseline visual analog scale scores in excess of 50 out of a possible 100 for both pain and stiffness. At follow-up assessments at 1 and 3 months, a strong placebo effect was evident, with roughly 40% of controls reporting their pain and stiffness scores had dropped below 50.

However, a significant treatment benefit was seen with high-dose testosterone, with three-quarters of patients on 80 mg/day reporting scores below 50 for both pain and stiffness at 3 months, according to Dr. Birrell, head of the breast cancer unit at Flinders Medical Centre, Adelaide, South Australia.

The safety data were reassuring, with good tolerability of testosterone therapy at both doses. Two testosterone-treated patients developed mild acne, and one experienced mild hirsutism. There was no hint of an increase in serum estradiol levels in connection with testosterone therapy, which is unsurprising in light of the fact that aromatase inhibitors are widely used to block conversion of testosterone to estradiol in athletes who illicitly use anabolic steroids to enhance performance, he noted.

Dr. Birrell's own preclinical studies suggest that testosterone therapy does not impinge upon the anticancer effects of aromatase inhibitor therapy. In fact, there was evidence of a synergistic antiproliferative effect that warrants further study, the surgeon continued.

The biological rationale for testosterone therapy in aromatase inhibitor–associated joint morbidity lies in the premise that affected patients have a reduced ability to convert endogenous testosterone to 5-alpha-dihydrotestosterone. This potent testosterone metabolite appears to be important in reducing the proinflammatory interleukins present in the synovium of patients with inflammatory joint disease, Dr. Birrell explained.

"It's really quite interesting that women on aromatase inhibitors have a significant increase in Sjögren's syndrome, where it has been demonstrated that there is a perturbation in the ability to convert testosterone into activated dihydrotestosterone," he observed.

Session chair Dr. Charles L. Loprinzi of the Mayo Clinic in Rochester, Minn., commented that he considers both the testosterone and high-dose vitamin D trials to be pilot studies which, although encouraging, don't rise to the level of being practice changing.

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DR. BIRRELL

Dr. Birrell said that crossover studies of testosterone therapy for aromatase inhibitor–associated joint pain will be difficult to conduct.

"Women on testosterone in this trial were very keen to stay on it," he noted.

Dr. Birrell's study was also supported by a research grant from AstraZeneca. Dr. Birrell disclosed that he is a stockholder in Chavah Pty Ltd., which is developing novel cancer therapies. ■

VITALS

Major Finding: High-dose vitamin D improved pain scores and bone mineral density at the femoral neck in postmenopausal women with hormone receptor–positive breast cancer, but also caused hypercalciuria that required nearly one in five treated patients to be dropped from the study.

Data Source: Placebo-controlled study of 60 patients.

Disclosures: The study was supported by a research grant from AstraZeneca.

Chronic PPI Use Did Not Lower BMD in Children in Pilot Study

BY MIRIAM E. TUCKER

NATIONAL HARBOR, MD. — Bone mineralization was not significantly altered among 17 children receiving chronic proton pump inhibitor therapy, including 12 who were also using inhaled steroids.

Proton pump inhibitors (PPIs) are commonly prescribed for acid suppression in children with gastroesophageal reflux, sometimes for long periods.

A significantly increased risk of bone fracture has been reported in adult patients receiving long-term PPI therapy (JAMA 2006;296:2947-53), and chronic acid suppression has also been shown to impair calcium absorption, thereby promoting bone resorption (Am. J. Med. 2005;118:778-81).

However, this pilot study is believed to be the first to look at bone mineralization or fractures in children on PPIs, Dr. Stephanie Willot said in a poster presentation at the annual meeting of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

The 17 patients (12 boys) had a mean age of 7.8 years (range 0.8-16.7 years). All had severe gastroesophageal reflux secondary to esophageal atresia and had received PPI therapy at a mean dosage of 2.0 mg/kg daily (1.0-3.2 mg/kg) for a mean of 2.6 years (0.6-11.3 years). Twelve of the children were also receiving chronic inhaled steroid therapy for pulmonary disease.

Lumbar spine areal bone mineral density (BMD) was assessed by using dual x-ray absorptiometry and was compared with normative data. Volumetric BMD, a parameter that more accurately assesses BMD in patients with short stature, was also calculated in order to account for differences in bone size, said Dr. Willot of the division of pediatric gastroenterology at Sainte-Justine Hospital, University of Montreal, who conducted the study with colleagues from the division of pediatric endocrinology.

No patient had a history of traumatic fracture. Five patients (29%) had a statural growth delay of less than –2 standard deviations for age. Among the 14 children older than 2 years, 5 (35%) had a body mass index less than the 10th percentile.

No patient had a significantly low BMD, defined in the study as a *z* score less than –2 standard deviations for age. Although six patients (35%) had a *z* score BMD of less than –1 standard deviation for age, they all had normal volumetric BMD (ranging from –0.8 to 0.6 standard deviation), as did the other seven children who were older than 4 years of age, Dr. Willot and her associates reported.

In a follow-up interview, Dr. Willot said that, given the small sample size of the study and its cross-sectional nature, its implications are limited to the finding that BMD is not low in children on chronic PPI therapy. "We cannot conclude about the association between PPI and fracture risk. In the future, we would like to follow our cohort to assess BMD in a longitudinal way to establish if *z* score could decrease during the course of PPI treatment."

Dr. Willot stated that she had no personal financial disclosures. ■