American Society for Bone and Mineral Research
Walter Alexander

From September 11 to 15, 2009, approximately 4,300 clinical practitioners and experimental scientists gathered in Denver, Colorado, to attend the 31st annual meeting of the American Society for Bone and Mineral Research (ASBMR). This article reviews four high-interest sessions on osteoporosis in postmenopausal women.

Bazedoxifene (Viviant) in Fracture Prevention
• Stuart L. Silverman, MD, Medical Director, Osteoporosis Medical Center, Beverly Hills, Calif.; and Clinical Professor, University of California, Los Angeles, and Cedars–Sinai Medical Center, Los Angeles, Calif.

A five-year follow-up of a clinical trial among patients receiving Wyeth’s bazedoxifene (Viviant, BZD) at a dose of 20 mg or 40/20 mg revealed sustained success in preventing fractures. In global phase 3 studies, BZD, a selective estrogen receptor modulator, demonstrated both efficacy and safety in preventing and treating postmenopausal osteoporosis. At three years, in a trial involving 7,492 women, new vertebral fractures were significantly reduced by both BZD 20 and 40 mg/day and raloxifene (Evista, Eli Lilly) at a dose of 60 mg/day, compared with placebo, but there was no overall treatment effect on nonvertebral fractures. A two-year extension of the three-year core study included 1,000 healthy postmenopausal women 55 to 85 years of age with confirmed osteoporosis in each of four groups: BZD 20 mg, BZD 40/20 mg, raloxifene 60 mg, and placebo.

In the BZD 40/20-mg group, women received the larger dose for four years and then 20 mg for the fifth year. All women received daily calcium, up to 1,200 mg, and vitamin D 400 to 800 International Units (IU). The primary endpoint was the incidence of radiographically confirmed new vertebral fractures (at T4-L4) from baseline to 60 months. At five years, the cumulative scores for the incidence of new vertebral fractures were significantly lower (P < 0.05) for both the 40-mg and 40/20-mg groups of patients (Table 1).

Again, rates of nonvertebral fractures were similar among groups. Among higher-risk women with risk factors used in the FRAX algorithm—for example, a femoral neck bone mineral density (BMD) T-score of −3 or lower (worse) or prevalent vertebral fracture status—fracture rates were significantly lower for the BZD groups combined (9.1% vs. 12.7% for placebo; P = 0.049). FRAX is the World Health Organization’s Fracture Risk Assessment Tool, which estimates the likelihood of fracture over 10 years. Breast and gynecological adverse events were significantly lower with BZD than with placebo.

Observing that BZD showed sustained efficacy over five years, Dr. Silverman concluded, “Overall findings at five years were consistent with those seen at three years and support a sustained anti-fracture effect for BZD in postmenopausal women with osteoporosis.”

Zoledronic Acid (Reclast) and Teriparatide (Forteo)
• Felicia Cosman, MD, Medical Director, Clinical Research Center, Helen Hayes Hospital, West Haverstraw, N.Y.; and Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, New York, N.Y.

Combination therapy with daily teriparatide (Forteo, Eli Lilly) and a once-yearly 5-mg zoledronic acid injection (Reclast, Novartis) provided the most rapid increases in BMD at both spine and hip and may be considered for patients at a high risk of fracture, according to new study results.

Bisphosphonates suppress bone remodeling, and parathyroid hormone (PTH) and teriparatide stimulate bone formation. While the combination is theoretically promising, experience has suggested that daily bisphosphonates may blunt PTH-induced bone formation. Dr. Cosman’s study tested whether a one-time infusion of zoledronic acid, combined with daily teriparatide, could overcome this effect. The primary objective was to determine whether this combination’s effect on lumbar spine BMD was noninferior to teriparatide alone.

The trial included 412 treatment-naïve women (mean age, 65 years) at 35 centers in four countries. All had T-scores of −2.5 or lower at the femoral neck, hip, or spine or T-scores of −2 or lower at any site, plus one or more documented osteoporosis-related fractures. Patients were randomly assigned to receive intravenous (IV) zoledronic acid 5 mg at baseline with or without subcutaneous (SQ) teriparatide 20 mcg/day or IV placebo at baseline plus teriparatide at a dose of 20 mcg/day. All women received 1,000 to 1,200 mg of calcium and 400 to 800 IU of vitamin D daily.

At one year, the combination produced increases in lumbar spine BMD that were similar to those of teriparatide alone and greater increases than with zoledronic acid alone (P = 0.0001). At one year, hip BMD increased with the combination, similar to that seen with zoledronic acid alone and greater than that with teriparatide alone (P < 0.05). Clinical fractures were reported in 2.9% of patients receiving the combination, in 5.8%

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of the teriparatide patients, and in 9.5% of the zoledronic acid patients. Increases in both hip and spine BMD were more rapid than with either drug alone.

Serious adverse events were noted at rates of 9.5% with the combination, at 10.9% with teriparatide monotherapy, and 14.6% with zoledronic acid alone. There were no adverse events related to atrial fibrillation, osteonecrosis of the jaw, or hypocalcemia. No long-term effects on renal function were observed.

Dr. Cosman concluded, “When we consider hip and spine BMD outcomes together, combination therapy provided the overall best BMD outcome.”

Denosumab (Prolia): A Subgroup Analysis
• Steven Boonen, MD, Professor of Geriatric Medicine, Leuven University, and Head, Gerontology and Geriatrics Section, Department of Experimental Medicine, Gasthuisberg Campus, Leuven, Belgium; Coordinator, Leuven University Hospital Center for Metabolic Bone Diseases; and Senior Clinical Investigator, National Fund for Scientific Research, Belgium

Prior presentations of results from the overall FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months) showed a significantly reduced fracture risk among 7,808 high-risk postmenopausal women with osteoporosis who were receiving denosumab (Prolia, Amgen). A fully human monoclonal antibody, denosumab inhibits osteoclast development, function, and survival.

The FREEDOM population, however, was at lower risk for fractures than populations in comparable trials of the bisphosphonates, zoledronic acid (Reclast) in the HORIZON trial (Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly), and alendronate (Fosamax, Merck) in the Fracture Intervention Trial (FIT-I). Fewer patients in FREE- DOM had baseline femoral neck T-scores of less than –2.5, and fewer had vertebral fractures at baseline (e.g., 24% vs. 63% in HORIZON and 100% in FIT-I). Three-year fracture rates in FREEDOM were 7.2% for new vertebral fractures, 8% for nonvertebral fractures, and 1.2% for hip fractures. Nonvertebral fractures are generally defined as those of the wrist, leg, humerus, pelvis, or clavicle.

Dr. Boonen’s analyses included a prespecified evaluation of nonvertebral fractures in women with a higher baseline risk. Patients had to meet two or more of these criteria: age 70 years or older, a BMD T-score of –3.0 or lower, or prevalent vertebral fractures. Also included was a post hoc analysis of women with two or more prevalent vertebral fractures and/or one or more prevalent vertebral fractures with moderate or severe deformity.

The incidence of fracture reduction in the prespecified high-risk group was a nonsignificant 12%. However, the post hoc analysis of nonvertebral fractures in patients with baseline femoral neck BMD T-score of –2.5 or lower (36% of the FREE- DOM population) found a 35% risk reduction, compared with placebo ($P = 0.0027$) in those with a femoral neck BMD T-score of –2.5 or lower and a 62% reduction ($P = 0.0065$) in patients 75 years of age or older.

Regarding the analysis among these women, he noted, “We wanted to take into account the traumatic effect of age, because the vast majority of hip fractures occur in women over 75 years.”

Dr. Boonen concluded, “The risk reductions in vertebral, nonvertebral, and hip fractures with denosumab in the higher-risk subgroups were consistent with the treatment observed for the overall study population.”

Denosumab (Prolia): A Cost-Effectiveness Model
• Oskar Ström, Doctoral Candidate, Karolinska Institute, Stockholm, Sweden
• David Macarios, MBA, BSC, Amgen, Thousand Oaks, Calif.

Based on the United Kingdom’s cost-effectiveness standard of £20,000 (approximately $31,870) per quality of life-year (QALY) saved, a U.K. analysis using the FRAX fracture risk calculator showed that denosumab was cost effective compared either with no treatment or treatment with risedronate (Actonel, Procter & Gamble/Sanoﬁ-Aventis). Whereas traditional cost-effectiveness modeling takes into account three risk factors for fracture (age, BMD, and previous fractures), FRAX includes hip fracture in a patient’s mother or father, previous fracture, alcohol use (3 or more units/day), body mass index, rheumatoid arthritis, secondary osteoporosis, current smoking, and glucocorticoid use. Investigators also took persistence with therapy into account.

Intervention costs in the model were calculated at £305 ($486) per year for the twice-yearly denosumab SQ injection and at £301 ($479.70) per year for risedronate. Relative risk ratios for fracture were based on denosumab data from FREE- DOM and risedronate data from the National Institute of Clinical Excellence (NICE). Persistence with denosumab, showing tolerability resembling that of placebo, was estimated at a rate 60% better than that demonstrated with oral bisphosphonates.1

For a 70-year-old woman with a T-score at the osteoporosis threshold of –2.5 without other risk factors, the median incremental cost-effectiveness ratio for denosumab was £15,157/QALY ($24,150), compared with placebo, and £11,267/QALY ($17,592), compared with risedronate. Both sums were well within the accepted range. The cost-effectiveness threshold most often recognized in the U.S. is $50,000 per QALY gained.

The U.K.’s willingness-to-pay standard of £20,000 deﬁnes an intervention threshold for denosumab versus placebo among individuals with a 10-year risk of major osteoporotic fracture between 10% and 20%. For denosumab versus risedronate, the intervention threshold falls at a 10-year risk of between 8% and 14% for a major fracture.

In an interview, Mr. Macarios concluded: “The basic finding is that denosumab is a cost-effective therapy compared with existing alternatives and against no treatment. So it’s worth it to treat women with this new agent.”

REFERENCE