Raloxifene Found Effective in Invasive Breast Ca Prevention

BY ROBERT FINN
San Francisco Bureau

The osteoporosis drug raloxifene is as effective as tamoxifen in preventing invasive breast cancer in postmenopausal women, according to initial results of the Study of Tamoxifen and Raloxifene (STAR) trial. The large, randomized, double-blind trial also determined that women taking raloxifene experienced fewer side effects than did those taking tamoxifen.

Raloxifene is approved for treating and preventing osteoporosis in postmenopausal women. At present, tamoxifen is the only drug approved for reducing breast cancer risk in pre- and postmenopausal women.

"This is good news for women," said Dr. Leslie Ford, associate director for clinical research in the National Cancer Institute's Division of Cancer Prevention. "We think that this gives women a real choice for addressing two of the leading causes of morbidity and mortality as they age: breast cancer and fractures. ...We can't advocate for the off-label use of drugs, but we anticipate that the company that makes raloxifene will be requesting an approval from the [Food and Drug Administration] for breast-cancer risk reduction."

In the STAR trial, 167 of the 9,745 women in the raloxifene group and 163 of the 9,726 women in the tamoxifen group developed invasive breast cancers. There were no significant differences between the two groups in the risk of developing invasive breast cancer, which was the primary outcome of the trial.

For every 1,000 women similar to the high-risk women enrolled in the STAR trial, about 40 would be expected to develop breast cancer within 5 years if they did not take either drug. The risk would be decreased to about 20 cases of breast cancer for every 1,000 women within 5 years if they took either tamoxifen or raloxifene.

Women taking raloxifene had 36% fewer uterine cancers and 29% fewer blood clots than the women who took tamoxifen.

Dr. D. Lawrence Wickerham, associate chair of the National Surgical Adjuvant Breast and Bowel Project, characterized the results in unusually blunt terms. "We think raloxifene is the winner of this trial," he said at a joint press briefing held by the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project. The results have not yet been published. Additional data will be presented at the 42nd annual meeting of the American Society for Clinical Oncology (ASCO) to be held in Atlanta, Ga., in June.

The 19,471 women for whom complete information was available took tamoxifen or raloxifene daily for an average of 47 months. The average age of the women in the study was 58. There were no statistically significant differences in the number of fractures of the hip, wrist, and spine, with 100 for in the tamoxifen group and 96 in the raloxifene group.

Raloxifene proved inferior to tamoxifen in only one important measure. Tamoxifen has previously been shown to reduce by about half the incidence of lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS). Of the women taking tamoxifen, 57 developed LCIS or DCIS, compared with 81 of the women taking raloxifene.

The STAR study has been supported to date by $88 million from the National Cancer Institute and $30 million from Eli Lilly & Co., the maker of raloxifene. Both Eli Lilly and AstraZeneca Pharmaceuticals, the maker of tamoxifen, provided their drugs and matching placebos free of charge. ■

Pelvic Organ Prolapse May Be A Novel Fracture Risk Marker

BY KATE JOHNSON
Montreal Bureau

TORONTO — Women with pelvic organ prolapse may be at increased risk for fracture, according to a new analysis of data from the Women's Health Initiative trial.

"As a clinician, if I see a woman who is early postmenopausal with moderate to severe prolapse, it would behoove me to get her bone density assessed to quantify her risk for fracture, because now I believe this woman is more likely to have some form of fragility phenomenon happening," said principal investigator Dr. Lubna Pal of Albert Einstein College of Medicine, New York.

The study, which she presented as a poster at the annual meeting of the Society for Gynecologic Investigation, was based on the hypothesis that collagen deficiencies may be a unifying explanation for both pelvic organ prolapse (POP) and enhanced fracture risk in postmenopausal women, said Dr. Pal.

There is a high incidence of both prolapse and fractures in collagen-deficiency disorders such as Marfan syndrome and Ehlers-Danlos syndrome, she said. And the connection is biologically plausible, given that 90% of bone is collagen (thus making deficiency a risk factor for fracture) and that qualitative or quantitative deficiencies of tissue collagen may be more common in women with POP, than in women without.

The cross-sectional analysis included 11,096 postmenopausal women aged 60 years or older who were part of the entire WHI cohort. It found moderate to severe POP in 9% of the subjects and fragility fracture (fracture after age 55 years) in 19%.

After adjusting for confounders including age, body mass index, age at menopause, history of osteoporosis, late menarche, hormone replacement and oral contraceptive use, family history of fractures, smoking, nulliparity, and white race, the researchers found a statistically significant association between POP and fracture risk.

Women reporting moderate to severe POP were significantly more likely to have reported ever breaking a bone, compared with women with absent or mild POP (45% vs. 41%), and were also more likely to have reported a fragility fracture (21% vs. 19%), although this association was not statistically significant.

When bone mineral density (BMD) was analyzed in this context, women with moderate to severe prolapse had significantly lower total body and total hip BMD, compared with women who had absent or mild POP. They also had lower lumbar spine BMD—although this difference did not reach significance.

"Maybe as clinicians we should be recognizing this association and focusing on bone health in women who demonstrate genital prolapse," said Dr. Pal. "We would first of all tell them they are at risk for fracture; [second,] identify any bone problems [that] are treatable; and [third,] try to optimize their bone collagen or protein content with calcium, vitamin D, weight-bearing exercise, and protein intake." ■

Denosumab Increases Bone Density in Postmenopausal Women

BY MELINDA TANZOLA
Contributing Writer

The human monoclonal antibody denosumab has been found to increase bone mineral density in postmenopausal women, results of a recent randomized phase II study suggest.

Evaluation of the primary end point—the percentage change in lumbar spine bone mineral density from baseline to 12 months—indicated that denosumab was active and significantly superior to placebo (N. Engl. J. Med. 2006;354:821-31).

Dr. Michael R. McClung, of the Providence Portland (Ore.) Medical Center, and his fellow researchers evaluated 12 months of denosumab, compared with open-label oral alendronate (70 mg once weekly) or placebo in postmenopausal women with low bone mineral density, as defined by a "T score of –1.8 to –4.0 at the lumbar spine or –1.8 to –3.5 at either the femoral neck or total hip," the researchers reported.

Subjects randomized to the experimental arm received denosumab every 3 or 6 months.

Of the 412 study participants, 319 women were randomized to the seven denosumab groups, 47 to the alendronate group, and 46 to the placebo group; 369 women completed the 12-month treatment study.

At study end, women receiving denosumab had increases in bone mineral density at the lumbar spine of 3.0%-6.7%, compared with a 0.8% decrease with placebo, or a mean increase of 4.6% with alendronate. Bone mineral density was also found to be superior with denosumab, compared with placebo at the total hip (mean change, 1.9%-3.6% vs. –0.6%, respectively), the distal third of the radius (0.4%-1.3% vs. –2.0%), and the total body (0.6%-2.8% vs. –0.2%), the researchers reported.

They noted that "in exploratory comparisons, the observed mean changes in bone mineral density were at least as great with denosumab as with alendronate."

Denosumab targets the receptor activator of nuclear factor-β ligand (RANKL). By specifically binding to RANKL with a high affinity, denosumab inhibits RANKL activity.

In an accompanying editorial, Dr. Michael P. Whyte expressed concern that inhibiting RANKL, a member of the "tumor necrosis factor superfamily," might have unintended effects on the immune system (N. Engl. J. Med. 2006; 354:860-3). "Accordingly, larger and longer clinical trials of denosumab for the prevention of osteoporotic fracture must search for these potential complications," Dr. Whyte suggested.

The 'changes in bone mineral density were at least as great with denosumab as with alendronate.'

DR. McCLUNG

During the study, an investigation into bone turnover indicated a significant decrease in serum *C*-telopeptide with denosumab that had a dose-dependent duration; a similar pattern was noted for the urinary *N*-telopeptide to creatinine ratio. These markers of bone turnover were at least equivalent with denosumab, compared with alendronate.

Adverse events were calculated in 406 study participants who received at least one dose of denosumab, alendronate, or placebo. Dyspepsia, however, was found to be greater in the alendronate group.

In the denosumab-treated group, 5.7% of study participants reported a serious adverse event, compared with 4.3% in the placebo group, and 2.2% in the alendronate group. In both the denosumab and placebo arms, 2.2% of the women withdrew from the study due to adverse events, and 3.8% of the denosumab group reported clinical fractures, compared with 2.2% in both the placebo and alendronate groups.

Dr. McClung and his investigators noted that their study was not designed to test equivalency, and denosumab should be further investigated for the treatment and prevention of bone-loss diseases.

The study was developed and supported by Amgen Inc., the manufacturer of denosumab. Dr. McClung disclosed having served as a consultant for, and having received grant support from, Amgen. ■