Tibolone Cuts Fractures, Cancer, but Ups Stroke

BY MARY ANN MOON
Contributing Writer

Tibolone reduced the risk of vertebral and nonvertebral fractures as well as breast cancer in a large international clinical trial involving older women with osteoporosis, but it also raised the risk of stroke, researchers said.

The drug also appeared to reduce the risk of colon cancer in this study, but tripled the rate of vaginal bleeding and endometrial thickening that required biopsy, reported Dr. Steven R. Cummings and his associates in the Long-Term Intervention on Fractures with Tibolone (LIFT) study.

Tibolone is approved for treating menopausal symptoms in 90 countries and for treating osteoporosis in 45, but is not approved for either indication in the United States.

It's not clear why the drug was found to prevent breast cancer when it was found to raise the risk in previous studies.

DR. CUMMINGS

The LIFT study, sponsored by Organon, compared daily tibolone with placebo in 4,538 osteoporotic women aged 60-85 years who were treated at 80 medical centers in 22 countries. About 26% of these subjects had already had a vertebral fracture.

The trial was halted early, after a median of 34 months of treatment, when an interim analysis showed that the drug doubled the risk of stroke, particularly during the first year of use and in women aged older than 70 years. That analysis also showed that tibolone met the criteria for efficacy in preventing fractures.

At the time the study was stopped, more than 90% of the subjects had received at least 80% of their scheduled doses of tibolone or placebo.

The data showed that tibolone decreased the relative risk of vertebral fracture by 45% and the relative risk of nonvertebral fractures by 26%, said Dr. Cummings of the California Pacific Medical Center Research Institute and the University of California, San Francisco, and his associates.

The drug appeared to be particularly effective at preventing fractures in women who had already had a vertebral fracture, reducing the relative risk of further vertebral fracture by 61% and the relative risk of nonvertebral fracture by 47%, the investigators said (N. Engl. J. Med. 2008;359:697-708).

The magnitude of these bone effects was similar to that reported for estrogen, bisphosphonate, and raloxifene therapy.

Tibolone also cut the relative risk of breast cancer by 68%, a reduction similar to that reported for tamoxifen or raloxifene.

It is not clear why the drug was found to prevent breast cancer in this study when it was found to raise the risk of the disease in previous observational studies, Dr. Cummings and his colleagues noted.

Compared with placebo, tibolone appeared to decrease the rate of colon cancer. It showed no significant effect on other cancers.

Tibolone more than doubled the risk of stroke. "Among patients 70 years of age or older, the risk of stroke was 6.6 per 1,000 person-years in the tibolone group and 3.4 per 1,000 person-years in the placebo group," the researchers said.

The drug therefore is contraindicated in women older than 70 and "in women who have strong risk factors for stroke, such as hypertension, smoking, diabetes, and atrial fibrillation."

Nearly 10% of women receiving tibolone reported abnormal vaginal bleeding, and 499 of them required endometrial biopsy, compared with only 136 women taking placebo.

Four women in the tibolone group developed endometrial cancer, compared with none in the placebo group.

Other adverse effects of tibolone included weight gain, breast pain, vaginal discharge and infection, pelvic pain, and elevations in liver enzymes.

Nineteen percent of the tibolone group discontinued treatment because of adverse events, compared with 13% of the placebo group.

Tibolone did not appear to have a deleterious effect on venous thromboembolism or coronary heart disease events. However, this study was not adequately powered to assess the drug's effects on these cardiovascular outcomes.

Dr. Cummings reported that he has received consulting fees from, or has served on a paid advisory board for, Pfizer, Amgen, Eli Lilly & Co., GlaxoSmithKline, Procter & Gamble, and Organon. ■

Clinical Guidelines For Family Physicians

Prevention and Treatment of Osteoporosis

BY NEIL S. SKOLNIK, M.D., AND TINA H. DEGNAN, M.D.

Osteoporosis screening and treatment are effective but are underused by primary care physicians. The National Osteoporosis Foundation (NOF) has released an updated clinical guideline for the prevention and treatment of osteoporosis, using the World Health Organization fracture risk algorithm to provide an evidence-based approach to screening and treating the disease in postmenopausal women and in men aged 50 years and older (www.nof.org/professionals/Clinicians_Guide.htm).

Guidelines are most useful when they are available at the point of care. A concise yet complete handheld computer version of this guideline is available for download, compliments of Family Practice News, *at www.redi-reference.com.*

Bone Mass

Bone mass steadily declines after age 30 years. Bone mineral density (BMD) is measured by dual-energy x-ray absorptiometry (DXA) at the hip and spine, and then is noted as a T score (a comparison with mean BMD of the "young normal" reference population) and a *z* score (a comparison with age- and sex-matched controls).

Osteoporosis is defined as a T score of –2.5 or less, and patients with that score and a previous fragility fracture have severe or established osteoporosis. (A score greater than –1 is normal.) Fracture risk increases exponentially as BMD decreases. A T score between –1 and –2.5 denotes osteopenia, or low bone mass. More than 10 million Americans have osteoporosis, and another 34 million have osteopenia, says the NOF. Most fractures occur in those with osteopenia.

Universal Recommendations

Advise the general population to reduce fracture risk with sufficient calcium and vitamin D intake, regular weight-bearing and muscle-strengthening exercise, adoption of fall-prevention strategies, and avoidance of tobacco and excessive alcohol intake. Daily calcium intake should be 1,200-1,500 mg. More than 1,500 mg daily does not confer additional benefit and is not recommended. Daily intake of 800-1,000 IU of vitamin D_3 is recommended for adults older than age 50, with a goal serum 25(OH)D concentration of 30 ng/mL or greater. Levels should be measured in all patients who are at risk for vitamin D deficiency, and supplemented accordingly.

Assessment

The U.S. Preventive Services Task Force recommends that all women aged 65 and older, regardless of risk factors, be screened for osteoporosis with DXA, and that screening begin at age 60 for those with additional risk factors. BMD testing is also recommended for all men aged 70 or older, regardless of risk factors. Postmenopausal women younger than 65 and men aged 50-70 should be clinically evaluated for fracture risk, and BMD testing should be ordered based on increased risk.

After BMD has been tested, the 10-year fracture risk algorithm (FRAX) should be used to calculate 10-year probability of hip or other major osteoporotic fracture, based on femoral neck BMD and the following major risk factors: current age; sex; personal history of fragility fracture; low body mass index; glucocorticoid use (5 mg or more daily for 3 or more months); rheumatoid arthritis; secondary osteoporosis; parental history of hip fracture; current smoking; and alcohol intake of three or more drinks per day. FRAX is particularly useful in identifying patients with osteopenia. The online tool based on U.S. data is available at www.shef.ac.uk/FRAX.

Treatment

Pharmacologic treatment is advised for postmenopausal women and men aged 50 and older with one of the following: hip or vertebral fracture; osteoporosis by BMD measurement (T score of –2.5 or less); or osteopenia by BMD measurement (T score between –1 and –2.5), plus a history of other fracture, major risk factor for fracture, or a 10-year probability of hip fracture (3% or more) or other major osteoporotic fracture (20% or more), based on the FRAX.

Patients should be evaluated for secondary causes of osteoporosis, such as fall risk, before starting treatment. Baseline DXA should be performed and repeated after 2 years to assess treatment efficacy, and every 2 years thereafter.

Food and Drug Administration–approved drug classes for preventing and treating postmenopausal osteoporosis include bisphosphonates, calcitonin, estrogens, raloxifene, and parathyroid hormone. Bisphosphonates are first-line agents; they reduce the risk of vertebral fracture by about 50%, and hip or other fractures by 25%-50% over 3 years.

The Bottom Line

► Counsel patients about calcium and vitamin D intake, exercise, tobacco and alcohol use.
► Recommend BMD testing to all women aged 65 or older and to all men older than 70, regardless of risk factors.
► Assess all postmenopausal women younger than 65 and men aged 50-70 for risk, and recommend BMD testing based on increased risk.
► Before starting treatment, evaluate for possible secondary causes and get a baseline BMD.
► Treat those with a hip or vertebral fracture; a BMD T score of –2.5 or less or between –1 and –2.5; or a 10-year probability of hip fracture (3% or more) or other fracture (20% or more).
► Repeat DXA after 2 years to assess treatment efficacy, then every 2 years thereafter.

Dr. Skolnik *is an associate director of the Family Medicine Residency Program at Abington (Pa.) Memorial Hospital and a coauthor of "Redi-Reference Clinical Guidelines."* Dr. Degnan *works at Buckingham (Pa.) Family Medicine. She is a graduate of Drexel University, Philadelphia, and of the Abington residency program.*