Raloxifene Has Breast Ca Benefits but Stroke Risks

BY DEEANNA FRANKLIN
Associate Editor

Raloxifene did not significantly increase the risk of coronary events in women with coronary heart disease or those at high risk for the disease in a randomized study of more than 10,000 postmenopausal women.

In addition, treatment with raloxifene for a median of 5 years decreased the risk of invasive breast cancer and vertebral fractures but increased the risks of venous thromboembolic events and fatal stroke, study investigators reported.

Dr. Elizabeth Barrett-Connor of the University of California, San Diego, and her colleagues concluded that when considering the use of raloxifene in a postmenopausal woman, clinicians should "weigh the benefits and risks against the availability of alternative interventions" (N. Engl. J. Med. 2006;355:125-37).

In an accompanying editorial, Marcia L. Stefanick, Ph.D., agreed with that conclusion, but noted that, for postmenopausal women similar to those in the study who have or are at increased risk of coronary heart disease (CHD), the modest benefits offered by raloxifene as a breast cancer prophylaxis "do not seem to justify the risks."

"For now, there is no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns," said Dr. Stefanick of Stanford (Calif.) University (N. Engl. J. Med. 2006;355:190-2).

The Raloxifene Use for the Heart study, an international, multicenter, randomized, double-blind, placebo-controlled trial, was conducted to determine of the effect of the drug on clinical coronary events. The study was supported by Eli Lilly, maker of raloxifene (marketed as Evista).

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A total of 10,101 postmenopausal women were enrolled from June 1998 through August 2000. The participants were at least 1 year post menopause and had established CHD or were at increased risk for CHD.

A total of 5,057 participants were randomized to receive 60 mg of oral raloxifene daily, and 5,044 were randomized to placebo.

The median duration of follow-up was 5.6 years; 80% of those in the raloxifene group and 79% in the placebo group completed the study.

Both groups had similar baseline characteristics, "except that the raloxifene group had a slightly higher cardiovascular risk score and a higher proportion of women reporting coronary artery bypass grafting," the researchers said.

In both groups, the mean age was 68 years.

There was no significant difference between the raloxifene and placebo groups in the study's combined coronary end point of death from coronary causes, nonfatal myocardial infarction, or hospitalization for an acute coronary syndrome other than myocardial infarction (533 events vs. 553 events, hazard ratio of 0.95).

Raloxifene, a nonsteroidal selective estrogen-receptor modulator, reduced the incidence of invasive breast cancer (hazard ratio, 0.56), another primary outcome in the study.

The researchers attributed this finding "to a reduction in estrogen-receptor–positive invasive breast cancer.

The absolute risk reduction per 1,000 women treated with raloxifene for 1 year was 1.2 cases of invasive breast cancer and 1.2 cases of estrogen-receptor–positive invasive breast cancer."

There was no significant difference between the two groups in the incidence of estrogen-receptor–negative invasive breast cancer.

The overall stroke rate, a secondary outcome, did not differ between groups, but the incidence of fatal stroke was 49% higher in the raloxifene group, compared with the placebo group (59 events vs. 39 events); the absolute risk increase was 0.7 per 1,000 woman-years.

The incidence of venous thromboembolic events was 44% higher in the raloxifene group, compared with placebo (103 events vs. 71 events); the absolute risk increase was 1.2 per 1,000 woman-years.

However, the raloxifene group also showed a 33% lower incidence of all breast cancers, with an absolute risk reduction of 0.9 per 1,000 woman-years.

Raloxifene users also had a 35% lower incidence of clinical vertebral fractures; their absolute risk reduction was 1.3 per 1,000 woman-years.

The raloxifene group also had a lower rate of death from noncardiovascular causes (188 events vs. 231 events in the placebo group), but there was no significant difference between groups in death from any cause or overall death from cardiovascular causes.

In addition, participants in the placebo group showed an increase of 3.6% in low-density lipoprotein (LDL) cholesterol and a 0.9% increase in high-density lipoprotein (HDL) cholesterol, compared with a 4.4% decrease in LDL cholesterol and a 2.3% increase in HDL cholesterol for raloxifene users. ■

Growth Hormone Tx Often Needed Into Mid-20s, Study Finds

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

BOSTON — To maintain skeletal health and reach optimal bone development, patients with childhood-onset growth hormone deficiency should continue therapy as they approach young adulthood, according to new treatment guidelines issued by The Endocrine Society.

"The mind set in the past has been that you treat these children until they stop growing," Dr. Mark Molitch said at the society's annual meeting. "But the bones don't mature until the mid-20s, so they may still need the hormone as they transition into adulthood."

In addition, he said, skeletal maturity may occur more slowly in patients with delayed onset of puberty or decreased gonadotropin secretion, so continuation of treatment is even more important for this population. Bone mineral density testing may provide additional valuable information for the decisions about continuing therapy.

The new guidelines, presented for the first time at the meeting, recommend retesting all children with idiopathic growth hormone deficiency as soon as possible after discontinuing the medication. Although many will have normal values, therapy should be quickly reinstituted for those who remain deficient.

The guidelines are based on 166 published studies examining the prevalence and diagnosis of growth hormone deficiency in adults, as well as treatment strategies and their long-term risks and benefits, said Dr. Molitch, chairman of the guidelines committee and professor of endocrinology at Northwestern University, Chicago.

Bone mineral density testing may facilitate decisions about whether to continue therapy.

DR. MOLITCH

The recommendations are aimed only at adults with clinically proven deficiency.

In the past, the insulin tolerance test was the favored diagnostic tool. However, this test carries an increased risk in patients with seizure disorders and cardiovascular disease, and requires close monitoring of even healthy patients. Recently, Dr. Molitch said, stimulation testing with growth hormone releasing hormone-arginine (GRHR-arginine) has gained favor. The test is less affected by age or obesity.

In a recent study of five different tests, including stimulation with GHRH-arginine and insulin tolerance, the stimulation test had 95% sensitivity and 91% specificity at the growth hormone cutoff level of 4.1 mcg/L; insulin testing was 96% sensitive and 92% specific at the cutoff level of 5.1 mcg/L.

Testing is indicated for adults with pituitary disease; surgery, trauma, or radiation in the pituitary area; or other pituitary deficiencies. Although children with idiopathic growth hormone deficiency should be retested as they approach adulthood, testing may be unnecessary for those with low insulinlike growth factor–1 and known defects, lesions, surgery or radiation of the hypothalamic-pituitary region, or a proven genetic defect of their capacity to secrete growth hormone. "This [combination] generally suffices to document continuing growth hormone deficiency," the guidelines state. The evidence strongly supports individualized growth hormone dosing regimens. Generally, treatment should start low and be titrated upward based on clinical response, side effects, and IGF-1 levels.

Younger patients are likely to need higher doses, as are women, especially those on oral contraceptives, Dr. Molitch said. Patients aged 30-60 years can usually start at 300 mcg/day; dosing should be increased by 100-200 mcg/day every 1-2 months, with a therapeutic target of an IGF-1 level in the upper half of the normal range.

Older patients should be started on 100-200 mcg/day, while those younger than 30 years may benefit from initially higher doses (400-500 mcg/day).

Although no studies have linked growth hormone therapy with malignancies, the guidelines recommend against using the hormone in anyone with an active cancer. There is no evidence that treatment affects the recurrence of pituitary tumors. Patients with diabetes may need adjustments to their diabetes medications when on growth hormone. The side effects of growth hormone therapy are usually dose-related and can be alleviated by adjusting the medication. The most common are related to fluid retention. These effects occur in up to 18% of patients and include paresthesias, joint stiffness, peripheral edema, arthralgia, and myalgia. Increased blood pressure is sometimes seen, but can be avoided with appropriate dosing.

Therapy offers significant benefits, including a decrease in fat mass and its attendant risk reductions of improved lipid levels and decreased insulin resistance. The modest increases in muscle mass improve exercise tolerance, which in turn has beneficial effects on blood pressure and cardiac function. Patients with childhood-onset growth hormone deficiency also may experience improvements in left ventricular muscle mass and end diastolic volume, as well as stroke volume. Therapy also benefits bone health with both anabolic and antiresorptive effects.

While no studies have confirmed a mortality benefit with growth hormone therapy, some do suggest that mortality is increased in those with hypopituitarism. It is not proved that growth hormone decreases it. ■