Panel Okays Drug to Cut Breast Cancer Risk in Postmenopause

BY LORINDA BULLOCK
Associate Editor

A Food and Drug Administration advisory panel has recommended that raloxifene be approved to reduce the risk of invasive breast cancer in postmenopausal women who have osteoporosis or who are at high risk of breast cancer.

The Oncologic Drugs Advisory Committee on July 24 recommended approval of raloxifene, a selective estrogen receptor modulator. The drug was originally approved by the FDA in 1997 to prevent and treat osteoporosis in postmenopausal women.

More than 52 million prescriptions for raloxifene have been filled since its approval, according to a statement from Eli Lilly and Company, which markets the drug as Evista.

Using data gathered from 37,000 postmenopausal women over a 10-year period, Eli Lilly submitted a new drug application to the FDA in 2006 to extend the drug's use to reducing breast cancer risk in this same group of patients.

If approved, Evista would be the "first and only therapy available to address two leading health issues for postmenopausal women—osteoporosis and breast cancer," Gwen Krivi, Ph.D., vice president of Lilly Research Laboratories, said in a written statement.

Although the committee voted to approve the indication for breast cancer risk reduction in postmenopausal women with osteoporosis (8 to 6) and in postmenopausal women at high risk for breast cancer (10 to 4), the agency is not obligated to approve these new indications.

The advisory committee reviewed four large studies also submitted in the application: The Study of Tamoxifen and Raloxifene (STAR) trial; Raloxifene Use for the Heart (RUTH) trial; Multiple Outcomes of Raloxifene Evaluation (MORE); and the Continuing Outcomes Relevant to Evista (CORE) trials.

Dr. Wulf Utian, executive director of the North American Menopause Society, said in an interview that the advisory committee's decision was a positive step that "increases the [number] of products available as potential reducers of breast cancer."

Currently, tamoxifen is the only other drug that is indicated for the reduction of breast cancer incidence in women at high risk for the disease.

Dr. Utian said the recommendation to approve raloxifene for the two new indications comes at a good time, because tamoxifen sales and use have been "disappointing" because of various side effects and particularly because of the drug's association with an increased risk of uterine cancer.

Both doctors and patients may be more accepting of raloxifene, because it is already a well-known product for osteoporosis in postmenopausal patients, and its added benefit of reducing breast cancer would make it a viable alternative to tamoxifen for these women, he said.

When the RUTH study was published, it raised some concerns about risk of death from stroke and the incidence of blood clots associated with raloxifene use (N. Engl. J. Med. 2006;355:125-37).

Marcia Stefanick, Ph.D., from Stanford (Calif.) University, wrote in an accompanying editorial: "What level of breast cancer risk would justify the use of raloxifene for the prevention of breast cancer for a given person, if one takes into account the competing risks and patient preferences? Complicating the answer is our inability to predict these risks with high accuracy on an individual basis" (N. Engl. J. Med. 2006;355:190-2).

Dr. Utian said the prevalence of both stroke and venous thromboembolism increases with age, but most of the women who would start taking tamoxifen or raloxifene for prevention would do so at a younger age, when both the prevalence and absolute risk for these adverse events would be lower. Dr. Utian disclosed that he serves as a consultant to various pharmaceutical companies, including Eli Lilly and some of its competitors. ■

Sleep Apnea Tied to Risk Of Gestational Diabetes

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Pregnant women with obstructive sleep apnea have a 2.3-fold increased risk of gestational diabetes and a 4.2-fold increased risk of pregnancy-induced hypertension, compared with women without the sleep disorder, according to a poster presentation at the International Conference of the American Thoracic Society.

Previous data have suggested that obstructive sleep apnea (OSA) may induce systemic hypertension and diabetes mellitus in the general population, but the connection was much less clear in pregnant women, Dr. Michael S. Nolledo of the Robert Wood Johnson Medical School, Princeton, N.J., said in a press briefing.

Physicians dealing with women with gestational diabetes or pregnancy-induced hypertension (PIH) should inquire about sleep-disordered breathing, especially because it is easy to treat OSA with continuous positive airway pressure (CPAP), he said.

But he acknowledged that his study contains no direct evidence that treating sleep apnea will improve PIH or gestational diabetes.

The study relied on data from the 2003 National Inpatient Sample, sponsored by the Agency for Healthcare Research and Quality. The database includes all inpatient records from a sample of about 20% of U.S. community short-stay hospitals and provides weights to calculate national estimates.

Using this database, the investigators calculated that there were 3,979,840 deliveries in the United States in 2003, of which 167,227 were complicated by gestational diabetes and 300,902 were complicated by PIH. The overall rate of sleep apnea for these women was 1.14/10,000—but that rate was 4.01/10,000 among women with gestational diabetes and 5.52/10,000 among women with PIH.

When controlled for age and race, women with sleep apnea were 3.5 times more likely to develop gestational diabetes; when controlled for obesity, the odds ratio was still 2.3. Similarly, the odds ratio for PIH in women with sleep apnea was 6.6 when controlling for age and race, and 4.2 after also controlling for obesity.

In an interview, Dr. Nolledo acknowledged that the overall rate of OSA recorded in the database—just over 1/10,000, or 0.01%—is much lower than the 2%-4% rate of OSA estimated for the general population.

He attributed this in part to the fact that physicians don't inquire about sleep-disordered breathing. Another explanation could be that physicians may be more inclined to ask about sleep-disordered breathing when faced with patients with gestational diabetes or PIH, he said, and that alone can account for the apparent increases in risk. ■

Oral Contraceptives May Worsen Low Androgen in Anorexics

BY MARY ELLEN SCHNEIDER
New York Bureau

TORONTO — Although physicians commonly prescribe oral contraceptives for women with anorexia nervosa, new research presented at the annual meeting of the Endocrine Society suggests that the androgen levels are already low in these women and that they are further reduced by the use of oral contraceptives.

But the jury is still out on the long-term consequences for skeletal health and body composition in women with the disease, said Dr. Karen K. Miller of Massachusetts General Hospital, Boston.

Dr. Miller and her colleagues analyzed androgen levels in 217 community-dwelling women to determine the physiologic consequences of prescribing oral contraceptives to women with anorexia nervosa.

The investigation included four arms comprised of 137 women with anorexia nervosa who were not receiving oral contraceptives; 32 women with anorexia nervosa who were receiving oral contraceptives; 21 women of normal weight with hypothalamic amenorrhea; and 27 healthy eumenorrheic controls.

All of the women with anorexia nervosa met the DSM-IV criteria for anorexia nervosa, were less than 85% of ideal body weight, and had an intense fear of gaining weight or strong denial of low weight. Anorexic women not receiving oral contraceptives had been amenorrheic for at least 3 consecutive months and had not received hormonal contraceptives within the previous 3 months. Those receiving oral contraceptives had to have been receiving them for at least 3 months.

All of those with hypothalamic amenorrhea were 90%-110% of ideal body weight; had been amenorrheic for at least 3 months; had normal FSH, prolactin, testosterone, and free testosterone levels; an LH-to-FSH ratio of less than 2.5; absence of hirsutism; and no history of an eating disorder.

Healthy controls were 90%-110% of ideal body weight and eumenorrheic. Controls were excluded from the study if they had a history of amenorrhea or an eating disorder, had a history of any major medical illness, or if they had used oral contraceptives within the previous 3 months.

The investigators found that lowest free testosterone levels occurred in women with anorexia nervosa who were receiving oral contraceptives.

The mean body mass index (BMI), percent ideal body weight, percent fat, total fat mass, and fat-free mass were lower in the anorexia nervosa groups, compared with women who had hypothalamic amenorrhea and the healthy controls. Analysis of the androgen levels in the four groups showed that total testosterone levels were lower in women with anorexia nervosa than they were in healthy controls.

Levels of total testosterone were similar in anorexic women who received oral contraceptives and those who did not receive them. The total testosterone levels were normal in women with hypothalamic amenorrhea, said Dr. Miller.

The levels of free testosterone were lower in women with anorexia nervosa than they were in healthy controls, and the lowest levels occurred in women with anorexia nervosa and who were receiving oral contraceptives. The levels were normal in women with hypothalamic amenorrhea.

The investigators also found that the levels of dehydroepiandrosterone (DHEAS) were lower only in women with anorexia nervosa who were receiving oral contraceptives, compared with healthy controls. DHEAS levels were normal in women with anorexia nervosa not receiving contraceptives and in women with hypothalamic amenorrhea.

Free testosterone levels were predictive of bone mineral density and body composition in women with anorexia nervosa, hypothalamic amenorrhea, and healthy controls. DHEAS levels also predicted bone density, but were weaker predictors than free testosterone and did not predict fat-free mass, Dr. Miller said.

Intervention studies are needed to determine the relationship between androgens and bone density and body composition in women with anorexia nervosa, she added. Studies are also needed to determine whether oral contraceptive use is harmful to their skeletal health. ■