Lipophilic Statins Lower ER-Negative Breast Ca Risk

No therapies were previously known to reduce the risk of estrogen receptor–negative breast cancer.

BY BRUCE JANCIN
Denver Bureau

San Antonio — Women on a lipophilic statin have a markedly reduced likelihood of developing estrogen receptor–negative breast cancer, Dr. Anjali Kumar reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

That's extremely welcome news. Although tamoxifen is of well-established benefit for the chemoprevention of estrogen receptor–positive breast cancer, there are no therapies known to reduce the risk of developing estrogen receptor–negative (ER-negative) breast cancer, explained Dr. Kumar, a surgeon at the University of California, San Francisco.

She presented a retrospective cohort study involving 2,141 breast cancer patients in the Kaiser Permanente Northern California Cancer Registry. In addition to large patient numbers, the Kaiser registry offers the advantages of electronic pharmacy records along with more reliable centralized estrogen receptor staining, with confirmation by a team of five pathologists.

In addition, the only statins on the Kaiser formulary—atorvastatin, simvastatin, and lovastatin—are lipophilic. Being lipid soluble, these drugs can more readily permeate cell and nuclear membranes, which in theory should enhance full expression of the statins' pleotropic benefits.

And that's not just theory: In earlier mouse studies that laid the groundwork for the Kaiser study, Dr. Kumar and her San Francisco colleagues showed that lipophilic statins conferred protection against ER-negative murine breast carcinoma. They also showed in vitro that ER-negative human breast cancer cell lines were more sensitive to lipophilic statins than ER-positive cells, and that lipophobic statins—namely, pravastatin and rosuvastatin—didn't inhibit growth of the malignant cells.

Of the Kaiser breast cancer patients, 17% had used a lipophilic statin for longer than 1 year prior to diagnosis of their malignancy. Their tumor was ER negative in only 2% of cases, compared with a 17% ER-negative rate among women who had taken a statin for less than a year or never. The age-adjusted relative risk of developing an ER-negative tumor was reduced by 36% among women who had used a statin for more than 1 year. A significant reduction in the probability of ER-negative cancer associated with lipophilic statin use was observed across all age groups, Dr. Kumar noted.

Eleven prior studies have looked at the statin/breast cancer relationship. Five found a protective effect against ER-negative cancers, including the only three studies restricted to lipophilic statins or featuring results stratified by statin type. All six studies that found no benefit for statin therapy looked at statins globally without distinguishing lipophilic from lipophobic agents, she continued.

Because the Kaiser study was confined to women already diagnosed with breast cancer, it couldn't address whether statin use reduces the overall incidence of breast cancer. However, two prior studies by others did show significant reductions.

Based upon the encouraging results of the Kaiser study along with the statins' remarkably good safety profile, Dr. Kumar and coworkers are continuing to explore the role of lipophilic statins in breast cancer prevention.

Now underway is a pilot biomarker study at the University of California, San Francisco, Dana-Farber Cancer Institute in Boston, Memorial Sloan-Kettering Cancer Center in New York, and the University of Chicago, where women with newly diagnosed ductal carcinoma in situ or stage I invasive breast cancer by core biopsy are being randomized to 3-6 weeks of fluvastatin at either 20 or 80 mg/day before undergoing definitive surgery. The goal is to learn whether statin therapy improves circulating and tumor biomarkers and brings favorable early changes in breast MRI images.

The investigators are also planning a study of long-term lipophilic statin therapy in *BRCA* mutation carriers that will be aimed at reducing their very high breast cancer risk. ■

Mifepristone Tied to Bleeding With Progesterone-Only IUS

BY KATE JOHNSON
Montreal Bureau

Montreal — Contrary to its effect with other progesterone-only contraceptives, mifepristone increases breakthrough bleeding in patients using the levonorgestrel intrauterine system, according to a new study.

"Mifespristone cannot be recommended as a therapy for breakthrough bleeding in new users of the LNG-IUS [levonorgestrel intrauterine system]," reported Dr. Megan Econimidis of the Keck School of Medicine at the University of Southern California in Los Angeles.

Over six cycles the median number of days of breakthrough bleeding was 57 in the mifepristone group, compared with 26 in the placebo group.

Mifepristone, an antiprogesterone, has been shown to decrease irregular bleeding in users of progesterone-only implants and injectables. It has been suggested that this effect may be due to mifepristone's functional inhibition of progesterone, which leads to the upregulation of endometrial estrogen receptors, she said at the joint annual meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society.

But Dr. Econimidis' study found that, when given to 20 regularly menstruating women who were new starters of the LNG-IUS, mifepristone actually had the opposite effect. "The local effect of the levonorgestrel on the endometrium may be triggering bleeding … [and] may not be allowing the mifepristone to act on the endometrium," she said in an interview. "In women who are on a progesterone-only implant or injectable, that mechanism, in terms of concentration of levonorgestrel on the endometrium, is less."

The women in the study, 18-45 years old, were randomized to mifepristone 50 mg or placebo every 2 weeks for six cycles. Treatment was started 2 weeks after LNG-IUS insertion. Subjects recorded their bleeding events in a diary and returned to the clinic for 14 visits during the study period. Endometrial biopsies were taken on day 21 of the menstrual cycle before LNG-IUS insertion, 14 days after insertion, and 7 days after the first dose of mifepristone or placebo.

Over the six cycles, the median number of days of breakthrough bleeding was 57 in the mifepristone group, compared with 26 in the placebo group; this difference was statistically significant. In addition, when all the subjects' cycles were combined, there were 22 (42%) mifepristone cycles with more than 8 days of breakthrough bleeding, compared with 16 (27%) placebo cycles. This difference was not statistically significant.

Endometrial biopsy results showed a decrease in endometrial estrogen receptors after mifepristone treatment, in contrast to other studies of progesterone implants and injectables, which have shown an increase in estrogen receptors after mifepristone, she said. ■

Continuous Oral Contraceptives More Likely to Suppress Ovulation

BY BOB BABINSKI
Contributing Writer

Montreal — Continuous oral contraceptive regimens suppress ovulation better than do conventional 21-day regimens, according to research presented at the conjoint annual meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society.

'The side effect of not bleeding is much more effective contraceptive control.'

DR. PIERSON

This effect of continuous oral contraceptives (COCs) has not been previously reported, said Roger Pierson, Ph.D., explaining that COCs have been promoted primarily for their ability to eliminate cyclic bleeding and premenstrual symptoms.

"The side effect of not bleeding is much more effective contraceptive control," said Dr. Pierson, professor of obstetrics, gynecology, and reproductive sciences at the University of Saskatchewan, Saskatoon.

In his single-center, randomized, open-label trial sponsored by the Canadian Institutes of Health Research, Dr. Pierson compared two different formulations of traditional 21-day oral contraceptive (OC) regimens with the same formulations given continuously for 28 days per cycle. Women took the pills for three cycles. Transvaginal ultrasonography was used to monitor follicular development once weekly for the first 3 weeks of the study and then every third day until the end of the third cycle.

The nine women on the 28-day regimen of 30-mcg ethinyl estradiol/150-mcg levonorgestrel and the 11 women on the 28-day regimen of 35-mcg ethinyl estradiol/250-mcg norgestimate showed less follicular development than did the women given the traditional 21-day regimens of both formulations (8 women in each group).

The women on the continuous regimen had no dominant follicles and no ovulations. Together, women on the standard regimens produced a total of eight dominant follicles, two of which ovulated.

The time to return of normal ovulation during the first cycle after contraceptive discontinuation was measured in both the conventional OC and COC groups, and this was compared with historical data for ovulation after discontinuation of other forms of contraception.

Follicles developing after discontinuation of COCs took about 5 days longer to ovulate than did follicles developing after discontinuation of conventional OCs. Time to ovulation for both OC groups was longer than in natural cycles. In addition, serum estradiol 17-β at a follicular diameter of 18 mm was significantly higher after discontinuation of OCs, compared with natural cycles. Dr. Pierson said the delayed return to normal ovulation was not significant, but noted the study's short length. ■

Kate Johnson of the Montreal Bureau contributed to this report.