Anastrozole Most Likely to Spare Lipid Levels

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Anastrozole was the only third-generation aromatase inhibitor that didn't exert adverse effects upon serum lipid profiles in the Letrozole, Exemestane, and Anastrozole Pharmacodynamics trial, Dr. Eugene McCloskey reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

LEAP was a randomized, open-label, phase I study designed to assess the effects of the aromatase inhibitors on key safety parameters—lipids, bone metabolism, and adrenal function—for this drug class.

The LEAP trial had 90 healthy postmenopausal women taking randomly assigned aromatase inhibitors for 24 weeks, with 12 weeks' follow-up.

A clearer understanding of how the drugs stack up in terms of these safety issues has become imperative in light of their rapidly expanding use in clinical practice. International guidelines recommend the use of an aromatase inhibitor for up to 5 years as part of the routine treatment of hormone receptor–positive breast cancer in postmenopausal women.

The drugs are also in phase III trials for chemoprevention—again for up to 5 years of use—in healthy postmenopausal women at high risk for breast cancer. That's long enough for a drug with adverse effects on lipids to potentially have a considerable negative effect on cardiovascular risk, said Dr. McCloskey of the academic unit of bone metabolism at University of Sheffield (England).

LEAP involved 90 healthy postmenopausal women who took their randomly assigned aromatase inhibitor for 24 weeks, with a further 12 weeks of follow-up post treatment.

Exemestane (Aromasin) was associated with a significant 15% decrease in cardioprotective HDL cholesterol at 24 weeks, with a corresponding increase in the LDL:HDL ratio. The drug also conferred a significant increase in the apo B:apo A-I ratio, also strongly associated with accelerated atherosclerosis and increased cardiovascular risk. After patients were off the drug for 12 weeks, these adverse lipid effects were reversed.

Letrozole (Femara) was associated with a significant increase in triglycerides at 12 weeks and a lesser, nonsignificant increase at 24 weeks. However, serum triglycerides were highly variable over the course of this study, and it's possible that the observed increase in the letrozole group was a result of the play of chance, according to the physician.

Anastrozole (Arimidex) had no effect on any lipid parameters in this AstraZeneca Pharmaceuticals LP–sponsored study.

Each of the aromatase inhibitors was associated with modestly increased serum markers of bone turnover and modest reductions in bone mineral density by dual-energy x-ray absorptiometry at 24 weeks, with no significant difference among the drugs.

Exemestane was associated with a significant reduction in parathyroid hormone, which regulates serum calcium.

At 24 weeks, three subjects in each treatment arm had adrenal insufficiency as defined by abnormal responses to an adrenocorticotropic hormone stimulation test.

In light of the LEAP findings, it's appropriate to carry out large randomized trials with clinical cardiovascular end points—such as acute MI and the need for coronary revascularization—in order to better define the risk profiles of the various aromatase inhibitors, Dr. McCloskey said.

In a separate presentation, Dr. Shalini Singh presented reassuring 1-year lipid data on 242 healthy postmenopausal women randomized to anastrozole or placebo in the second International Breast Cancer Prevention Study (IBIS-II), a multicenter chemoprevention trial involving 6,000 healthy postmenopausal women at increased risk for breast cancer.

A year of anastrozole resulted in a marginally significant decrease in LDL cholesterol compared with placebo, and no significant differences in total cholesterol, HDL cholesterol, or triglycerides, according to Dr. Singh of the Wolfson Institute of Preventive Medicine at Queen Mary, University of London, which is the sponsor of IBIS-II. ■