

Lipid Effects of Aromatase Inhibitors Detailed

In this class of breast cancer drugs, only anastrozole was found to have no effect on lipid parameters.

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Anastrozole was the only third-generation aromatase inhibitor that didn't exert adverse effects on 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.

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 a randomly assigned aromatase inhibitor for 24 weeks, with 12 weeks of follow-up.

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 Dr. McCloskey.

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 ACTH 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. ■

Obesity Drugs' Benefits May Not Outweigh Their Risks

BY ROBERT FINN
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Clinical testing on current weight-loss drugs has been inadequate to determine whether their benefits outweigh the risks of long-term use, according to a literature review by Canadian researchers.

The review, by Dr. Raj S. Padwal and Dr. Sumit R. Majumdar of the University of Alberta, Edmonton, took a close look at the two drugs currently approved by the Food and Drug Administration for the treatment of obesity—orlistat (Xenical) and sibutramine (Meridia)—and at another drug, rimonabant (Acomplia), that has not yet received FDA approval (*Lancet* 2007;369:71-7).

Although the three drugs all work by different mechanisms, clinical trials show that they tend to result in about the same modest degree of weight loss: an average of 5 kg (11 lbs), or roughly 5% of body weight. They all have side effects, but in general the side effects have been judged to be tolerable.

None of the drugs has been subjected to long-term testing. It's unknown, for example, whether the weight loss induced by these drugs translates to decreases in obesity-related morbidity and mortality. Dr. Padwal and Dr. Majumdar describe this as "a major gap in knowledge."

It's also unknown whether use of the drugs results in improvements in other consequences of obesity, such as osteoarthritis, gastroesophageal reflux disease, and reduced quality of life.

Furthermore, the existing clinical trials for orlistat, sibutramine, and rimonabant were all marred by high levels of attrition. In general, 40%-50% of all the patients enrolled in those trials dropped out before the trials were concluded. This

makes it difficult to assess the drugs' true levels of efficacy and safety in the general population.

"We think that antiobesity drug trials powered to show clinically important reductions in major obesity-related morbidity and mortality should be required either before these drugs are approved for widespread use or as a condition of ongoing approval," the authors wrote.

They advanced three justifications for this conclusion. First, drugs that improve secondary end points, such as weight loss, may not in the long run improve more clinically relevant end points, such as cardiovascular morbidity and mortality.

Second, a drug's toxicity may not be apparent on initial release. Rimonabant, for example, appears to decrease hunger by blocking endocannabinoid receptors in the brain. Preliminary data suggest that endocannabinoids may work to prevent stroke, limit the size of myocardial infarctions, and inhibit cancer-cell proliferation. Blocking endocannabinoid receptors on a long-term basis may therefore have unintended negative consequences.

Third, new drugs are expensive, and the enormous potential market for obesity drugs amplifies their cost to society. The lack of proof that these drugs improve overall outcomes makes it difficult to justify those costs.

Bariatric surgery is the only treatment proven to produce consistent and effective long-term weight loss, but Dr. Padwal and Dr. Majumdar described bariatric surgery as "neither a feasible nor desirable population-based treatment for obesity." They wrote that although it's important to address all aspects of the environment that encourage obesity, the search for novel drug treatments is both legitimate and necessary. ■

