Ezetimibe Fails to Further Slow Atherosclerosis

BY MITCHEL L. ZOLER
Philadelphia Bureau

Results of a controversial study assessing ezetimibe's ability to slow atherosclerotic progression, when used in conjunction with a high-dose statin regimen, have cardiologists split on whether the findings signal a flawed study or a flawed drug.

The results were "disappointing, but not surprising because I had a lot of concern that this was not the right patient population and not the right methodology," said Dr. Michael Davidson, professor of medicine and director of preventive cardiology at the University of Chicago.

But other experts tied the study's negative result to limitations of ezetimibe itself.

"It appears that this method for lowering LDL cholesterol is not beneficial," said Dr. Steven Nissen, chairman of the department of cardiovascular medicine at the Cleveland Clinic. "Statins do many other things that ezetimibe does not do: Statins raise HDL cholesterol, lower triglycerides, and reduce inflammation."

One explanation why ezetimibe plus simvastatin failed to slow atherosclerotic progression better than simvastatin alone "is that there are differences in the drug effects that go beyond their reduction of LDL," commented Dr. Christie M. Ballantyne, professor of medicine at Baylor College of Medicine, Houston, and chief of the section of atherosclerosis and vascular medicine.

Amid a congressional investigation, results from the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial were released months before a formal meeting report, in a statement issued by Merck/Schering Plough Pharmaceuticals. The company, which markets ezetimibe as a solo agent (Zetia) and in combination with simvastatin (Vytorin), had been under pressure to release results from the trial, which ended in April 2006. A full report is expected at the annual meeting of the American College of Cardiology in late March. Merck also markets a formulation of simvastatin (Zocor).

ENHANCE was designed to test whether adding a 10-mg/day dosage of ezetimibe to an 80-mg/day dosage of simvastatin led to slower progression of atherosclerosis than use of the statin alone in patients with heterozygous familial hypercholesterolemia. The study randomized about 360 patients into two treatment arms; after washout, the mean baseline LDL cholesterol was about 319 mg/dL. Atherosclerotic burden was measured as intima-media thickness (IMT) using carotid ultrasound. The average baseline IMT in both groups was 0.69 mm.

Treatment with simvastatin alone over 2 years led to an average drop in LDL cholesterol of about 41% (a drop of about 130 mg/dL); the addition of ezetimibe led to a mean LDL decline of 58%, an additional 17% absolute drop that translated into an extra LDL fall of about 50 mg/dL.

Despite this LDL reduction, the average change in IMT was an increase of 0.0058 mm in the simvastatin-alone group, and an increase of 0.0111 mm in those also treated with ezetimibe. This difference in the primary end point was not statistically significant, and thus the findings failed to show a benefit from adding ezetimibe. There was a small increase in atherosclerotic progression with ezetimibe—the rate was almost twice as great as among patients on simvastatin only—but the difference was not statistically significant. The study was not designed to assess clinical events such as cardiovascular deaths or myocardial infarctions. Clinical and adverse events were similar and low in the two arms.

The undeniable fact, however, was that treatment with ezetimibe in this study failed to further slow atherosclerotic progression even though it cut LDL cholesterol levels by a whopping additional 50 mg/dL.

"It's a paradox," Dr. Nissen said. He cited a similarly designed 2001 study with 330 patients with heterozygous familial hypercholesterolemia that compared the impact of treatment with 80 mg/day of atorvastatin with 40 mg/day of simvastatin. In that study, simvastatin cut serum LDL levels by 41% and atorvastatin cut them by 51%. After 2 years, the simvastatin patients had a mean IMT progression of 0.036 mm, but the atorvastatin group had an average regression of 0.031 mm, a statistically significant difference (Lancet 2001;357:577-81).

Another possible explanation is that "80% of the participants had been on statins prior to the onset of the study. Hence, much of the atherosclerotic preventive effect of LDL lowering could have already happened," said Dr. Donald A. Smith, director of lipids and metabolism at Mount Sinai Medical Center, New York. Physicians will need to await further study results with ezetimibe "to confirm the 40-year experience that any method of lowering LDL cholesterol will provide preventive atherosclerotic effects," he said in an interview.

Some experts cited problems with the ENHANCE study's design. "Little imaging studies like this are virtually worthless," said Dr. Scott Grundy, professor of medicine and chairman of the Center for Human Nutrition at the University of Texas at Dallas. "I'm concerned that the hype generated about this small trial, without a clinical end point, may be enough to knock [ezetimibe] off the list of agents that can help get LDL to very low levels." Dr. Grundy has received research grants and honoraria from Merck and other pharmaceutical companies.

Design flaws in ENHANCE included its use of patients with heterozygous familial hypercholesterolemia who had already been on statin treatment, and its reliance on IMT measurements at three different sites in the carotid arteries, some of which are hard to measure reliably, Dr. Davidson said. He cited an effort by Merck/Schering Plough to refine the analysis by limiting the IMT measures used to only those from the common carotid as the main reason why release of the results had been delayed. Dr. Davidson is a consultant to and has received research support from Merck and Merck/Schering-Plough.

But relatively small, IMT studies have been fine in the past, contended Dr. Nissen, who disclosed that he has no conflicts of interest.

One thing experts agreed on was that ezetimibe's role remains unchanged: it's a second-line agent for patients who are already on a maximum statin dose but are still not at their LDL goal, and an alternative for those who can't tolerate statins.

But sales data suggest that not all physicians have been using it this way. According to analyst reports, combined U.S. sales of Zetia and Vytorin were more than $3 billion in 2006, and during the first half of 2007 alone combined sales topped $2 billion.

Using ezetimibe first "was never an evidence-based position," said Dr. Ballantyne, who is a consultant to and receives research support from Merck, Merck/Schering Plough, and other companies. ■

Calcium Supplementation Increases MI Risk in Older Women

BY DAMIAN McNAMARA
Miami Bureau

Calcium supplementation significantly increased the risk of a myocardial infarction among healthy, postmenopausal women, compared with those taking placebo, in a secondary analysis of an osteoporosis study.

Physicians should consider this increased cardiovascular risk against other clinical benefits of calcium supplementation in older women until confirmatory studies can be completed, the authors suggested.

"It is an important finding because so many women are prescribed calcium supplements," Dr. Rita F. Redberg said in an interview. "I would not recommend calcium supplementation based on this finding. This raises enough concern. With any supplement, you have to show evidence of benefit without risk," said Dr. Redberg, who was not involved in the study.

The HDL/LDL cholesterol ratios improved among the 732 women who took daily calcium supplementation, compared with the 739 participants who took placebo. This suggests that a different mechanism spurred the increase in myocardial infarction.

"This is an interesting point. It shows that just improving cholesterol does not reduce the risk of a heart attack," said Dr. Redberg, director of women's cardiovascular services and professor of medicine at the University of California, San Francisco. "It was the same finding with estrogen: It lowered LDL, increased HDL, but did not reduce the number of heart attacks in studies."

The current findings contrast with previous suggestions of cardiovascular benefit from calcium supplementation. One study found that calcium increases the HDL:LDL cholesterol ratio by almost 20% (Am. J. Med. 2002;112:343-7). In addition, a one-third decrease in deaths from cardiovascular events was observed among women who had the greatest intake of calcium from either diet or supplements in the Iowa Women's Health Study (Am. J. Epidemiol. 1999;149:151-61).

Following completion of a 5-year osteoporosis study (Am. J. Med. 2006;1119:777-85), Dr. Mark J. Bolland and his associates at the University of Auckland (New Zealand) reassessed their data to compare cardiovascular events. Women were randomized to 1 g/day of elemental calcium (Citracal) or placebo. All of the 1,471 participants were postmenopausal for at least 5 years and older than age 55 years at baseline, and 10% of those were older than age 80 at baseline.

Death, sudden death, myocardial infarction, angina, other chest pain, stroke, and transient ischemic attacks events were recorded every 6 months. In all, 336 women stopped taking the calcium and 296 stopped taking the placebo before the study end.

A total of 21 of the 732 women in the calcium group experienced 24 myocardial infarctions, a statistically significant difference compared with 10 of the 739 in the placebo group who had 10 such events. A composite end point of sudden death, myocardial infarction, angina, or chest pain was also higher in the calcium group (155 events among 87 women) compared with the placebo group (135 events among 93 women).

No significant differences were found in angina, chest pain, transient ischemic attack, stroke, or sudden death events between groups. There were 34 deaths in the calcium group and 29 in the placebo, a nonsignificant difference.

Dr. Redberg was not surprised by the elevated MI risk. She said research by Dr. Linda Demer, vice chair of medicine at the University of California, Los Angeles, has indicated increased cardiovascular risk associated with calcium. "It's called the calcium paradox. Women lose calcium from their bones as they get older and it ends up in their arteries and the lining of their vessel walls, leading to accelerated atherosclerosis. This study is a confirmation of that hypothesis."

The mean age was 74 years and all participants were white, a possible limitation for generalizing results to other ages or racial groups, the authors said. However, Dr. Redberg said that the inclusion of older women in the study is a strength because they are the most likely to be prescribed calcium supplements. It is very unusual for studies to include people older than age 80, she added.

"What is effective for women for preventing osteoporosis?" Dr. Redberg said. "First we had estrogen, then vitamin D and calcium, and the bisphosphonates, but all have been shown to have significant side effects or risk. It may be safest to prescribe diet and weight-bearing exercises to prevent osteoporosis." ■