Torcetrapib Fails to Halt Atherosclerosis

BY MARY ANN MOON
Contributing Writer
AND BETSY BATES
Los Angeles Bureau

NEW ORLEANS — Torcetrapib profoundly raised HDL cholesterol values and decreased LDL cholesterol levels, yet failed to halt the progress of atherosclerosis in two separate international trials, Dr. Steven Nissen said at the annual meeting of the American College of Cardiology.

The combined conclusions of the studies led Dr. Nissen, one of the trial investigators and president of the ACC, to conclude, "At this point, obviously, this molecule is dead."

Investigators remain puzzled why the investigational cholesterol ester transfer protein inhibitor, which led to unparalleled increases in HDL cholesterol, failed to reduce atheroma volume on carotid ultrasounds.

Although torcetrapib led to unparalleled increases in HDL cholesterol, it failed to reduce atheroma volume.

DR. NISSEN

In a late-breaking clinical trial session at the meeting, Dr. Nissen cited three possible explanations for the findings: An increase in blood pressure may have "counterbalanced" beneficial lipid effects, blood pressure may be a marker for an unknown toxicity associated with the drug, or cholesterol ester transfer protein (CETP) inhibition "may not generate HDL particles that function normally in facilitating reverse cholesterol transport," Dr. Nissen said.

Whatever the mechanism, the resulting antiatherogenic outcomes with torcetrapib reminded Dr. John J.P. Kastelein of "Dutch pancake—you can't get it any flatter. There was no difference whatsoever."

Dr. Nissen held out hope that other agents in the CETP class might prove beneficial. "My view is, you can't slam the door on the whole class when the only data we have are for a drug that had this unusual toxicity," he said at a press briefing.

The trials presented by Dr. Nissen and Dr. Kastelein were part of a huge development program of the first CETP inhibitor by Pfizer, manufacturer of torcetrapib. In December 2006, a third clinical trial was terminated early because of an excess of deaths and cardiovascular events among subjects who received torcetrapib. Pfizer immediately suspended the entire program.

Serious cardiovascular events also were higher with torcetrapib in the trials presented at the meeting; however, these were relatively small trials and not statistically powered to show a significant increase in adverse clinical events.

In the ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) trial, investigators at 137 medical centers throughout North America and Europe used intravascular ultrasound to assess coronary atheroma volume in 910 patients with known coronary atherosclerosis. The subjects were randomly assigned to receive either atorvastatin plus torcetrapib (464 subjects) or atorvastatin plus placebo (446 subjects) for 2 years, said Dr. Nissen of the Cleveland Clinic.

Adding torcetrapib to the statin induced an unparalleled 60% rise in HDL cholesterol and a 20% decline in LDL cholesterol, relative to atorvastatin alone.

"Thus, at the end of 24 months, treatment with torcetrapib resulted in an average HDL level that was actually higher than the LDL level, with an LDL to HDL ratio of 0.93: a ratio never before achieved in any major clinical trial," Dr. Nissen said in his presentation. However, it also induced a "substantial" increase in systolic blood pressure of 4.6 mm Hg, he said.

Further, percent atheroma volume, the primary efficacy measure, was not affected. Neither was progression of atherosclerosis in the most diseased segment of the target artery, a secondary measure. Another secondary measure—progression in total atheroma volume—improved with torcetrapib, but "the treatment difference was relatively small, particularly considering the long duration of the trial," wrote Dr. Nissen and his associates in an article published simultaneously with the presentation (N. Engl. J. Med. 2007; 356:1304-16).

In the RADIANCE 1 trial (Rating Atherosclerotic Disease Change by Imaging with a New DETP Inhibitor), investigators used ultrasound to assess the progression of carotid intima-media thickness over 2 years in 850 patients with familial hypercholesterolemia who were treated at 37 medical centers in North America, Europe, and South Africa. A total of 423 subjects were randomly assigned to receive torcetrapib and atorvastatin, while 427 received atorvastatin plus placebo.

"The net effect of torcetrapib was a 51.9% relative increase in HDL cholesterol and a 20.6% relative decrease in LDL cholesterol," wrote Dr. John J. P. Kastelein of the University of Amsterdam and his associates in an article published at the time of the meeting (N. Engl. J. Med. 2007 March 29 [Epub doi:10.1056/NEJMoa071359]).

Yet the drug failed to halt progression of carotid intima-media thickness and actually appeared to accelerate the atherosclerotic process in one segment of the artery. As in the study by Dr. Nissen and colleagues, torcetrapib significantly raised systolic blood pressure. It also induced more adverse cardiovascular events, particularly those related to increased blood pressure, than did placebo, Dr. Kastelein and his associates said.

The RADIANCE 2 study, which studied torcetrapib in 752 patients with mixed hyperlipidemia, showed "strikingly similar results," Dr. Kastelein said at the meeting. ■

Rosuvastatin Slowed Progress Of Carotid Atherosclerosis

BY MARY ANN MOON
Contributing Writer
AND BETSY BATES
Los Angeles Bureau

NEW ORLEANS — Rosuvastatin slowed the progression of carotid intima-media thickness in asymptomatic subjects at low risk of cardiovascular events but who nonetheless had subclinical atherosclerosis, Dr. John R. Crouse III reported at a conference sponsored by the American College of Cardiology.

The agent "basically halted progression" of intima-media thickness, Dr. Crouse said during a late-breaking clinical trials session at the meeting.

Unlike previous clinical trials of the drug involving high-risk subjects or patients with known cardiovascular disease, the METEOR (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) trial assessed asymptomatic people aged 45-70 years who were at low cardiovascular risk and had only moderately elevated cholesterol, but were found to have a relatively high carotid wall thickness on ultrasound examination.

The low-risk population was intentionally chosen for the study so that a placebo arm could ethically be included, said Dr. Crouse, professor of medicine and public health sciences at Wake Forest University in Winston-Salem, N.C.

A total of 984 subjects were enrolled in the study in August 2002–March 2004 at 61 medical centers throughout the United States and Europe, and were followed with serial carotid imaging for 2 years. The study was funded by AstraZeneca Pharmaceuticals LP, maker of rosuvastatin (Crestor).

Ultrasound measurements of carotid intima-media thickness were performed at enrollment and at 6-month intervals for 2 years. Measurements were made at 12 carotid artery sites in each patient, including the near and far walls of the right and left common carotid artery, carotid bulb, and internal carotid artery.

Results were available for 252 subjects who had been randomly assigned to receive placebo and 624 who had been assigned to receive 40 mg of rosuvastatin daily. This is not the recommended starting dosage but was selected "to provide the maximum efficacy expected to slow or delay progression of atherosclerosis," Dr. Crouse wrote in a report that was published at the time of the presentation (JAMA 2007;297:1344-53).

Carotid intima-media thickness progressed in the placebo group and regressed in the rosuvastatin group. The difference from baseline did not reach significance except at the common carotid artery.

The significant difference in progression between the placebo and rosuvastatin groups persisted across all clinical subgroups, regardless of subject age, sex, geographical location, race, body mass index, risk factors, blood pressure levels, or lipid levels, Dr. Crouse said.

Rosuvastatin did not induce regression of carotid atherosclerosis, as it has been shown to do in previous studies involving patients with more advanced disease, they added.

"This was focused on low-risk participants without advanced atherosclerosis, and this may have limited the opportunity to achieve disease regression," Dr. Crouse said at the meeting, which was also sponsored by the Society for Cardiovascular Angiography and Intervention.

LDL cholesterol declined by 49% and HDL cholesterol increased by 8% among patients taking rosuvastatin.

The frequency of adverse events was similar between the two groups, and most effects were of mild or moderate severity.

In an editorial comment accompanying the published report, Dr. Michael S. Lauer of the Cleveland Clinic Heart Center said, "At first glance, the METEOR findings suggest that there may be a role for routine arterial imaging" in low-risk people, and that routine rosuvastatin therapy may be warranted for those found to have increased carotid intima-media thickness.

But this would be "a radically different approach to primary prevention than what is recommended by current guidelines," and the METEOR results clearly do not justify such a change, he noted (JAMA 2007;297:1376-8).

For one thing, carotid intima-media thickness is merely a surrogate end point for clinical events, and the medical literature is rife with "numerous bad experiences whereby agents that improved surrogate end points yielded no benefit or were even found to cause harm when tested for their ability to prevent clinical events," Dr. Lauer wrote.

Moreover, there is only limited evidence that statin-induced changes in carotid intima-media thickness actually correlate with a decrease in atherosclerotic events.

The METEOR study had two additional weaknesses. "A fair number of enrolled patients failed to complete the protocol and were lost to follow-up. … [A] higher rate of follow-up clearly would have increased the credibility of the findings," he noted.

And the study was not powered to evaluate the drug's effect on clinical events. Among nearly 1,000 subjects, only six ischemic events occurred—all of them, "curiously," in subjects taking the study drug. "Ambitious event-based randomized trials involving large numbers of patients and communities must be done," Dr. Lauer said.

On the other hand, panel discussant Dr. Paul Ridker, of Brigham and Women's Hospital, Boston, told Dr. Crouse that the cholesterol changes and slowing of atherosclerosis progression in low-risk patients taking rosuvastatin was "very exciting. … This is not a group we normally think about [in terms of risk reduction]."

Dr. Crouse replied that caution should be used in extrapolating study findings with regard to screening and early treatment implications. ■

Pages 34a—34b