Torcetrapib Failure May Not Doom Other Drugs in Class

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

The demise of torcetrapib may be a "bitter disappointment" to researchers, but it's too soon to give up on the entire class of HDL cholesterol–raising agents, several of which are still under development, experts say.

"While this is a huge setback for the field of lipid therapy, it would be a big mistake for patients and physicians to get the impression that this research is a lost cause," said Dr. Frederick Samaha of the University of Pennsylvania, Philadelphia. "There are several different drugs being looked at. We can't presume from the failure of one that all of them will have similar problems."

Torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, was furthest along that pipeline, however, and was the only one in a phase III trial (ILLUMINATE). The study randomized 15,000 patients with existing coronary heart disease to atorvastatin alone or to a combination of atorvastatin and torcetrapib.

But Pfizer Inc. abruptly halted it after an interim data analysis showed significantly more deaths in the combination arm than in the monotherapy arm (82 vs. 51). Although details haven't been released, the imbalance in mortality appears to have been driven by cardiovascular events, Dr. Samaha said in an interview.

"It's very disappointing. Of all the HDL-raising drugs, this class holds the most promise. [CETP inhibitors] increase HDL by 50%-100%, much more than even the second most effective drug, niacin. So we had a lot of really high hopes for torcetrapib."

The question facing researchers, he said, is whether the mortality risk associated with torcetrapib will extend to any of the other CETP inhibitors under development by Hoffmann-La Roche Inc., Merck & Co., AstraZeneca Pharmaceuticals LP, and Bayer Pharmaceuticals Corp. "We can't tell right now whether this is a class effect, or whether it's specific to this one drug alone," said Dr. Samaha, who is investigating the effect of niacin plus statins on cardiovascular events in the AIM-HIGH trial.

There are two possible culprits behind the increased mortality among torcetrapib patients, he said: the drug's hypertensive effects, which caused significant blood pressure hikes in a small number of patients in the phase II studies, and accelerated atherogenesis.

Blood pressure effects are likely to be drug specific, as other CETP inhibitors in development haven't thus far shown similar problems. But a finding that torcetrapib, a drug designed to prevent or decrease atherosclerotic plaque, actually increases it could have devastating implications for all CETP research. "That would most likely be a class effect that we would see with any of these drugs," said James McKenney, Pharm.D., a primary investigator for torcetrapib's 2006 safety and efficacy studies.

CETP inhibitors increase HDL cholesterol by limiting the amount of cholesterol that leaves the HDL particle, Dr. Samaha said. "What you end up with is larger HDL particles with more cholesterol associated with them. Whether those particles are still as cardioprotective [as normally occurring HDL] is something we don't know."

He's not alone in voicing this concern. Boosting HDL levels this way has always been a controversial idea, according to Dr. Michael Davidson, director of preventive cardiology at Rush University Medical Center, Chicago. But despite uncertainty about the cardioprotective effects of CETP-modulated HDL cholesterol, he said in an interview, "a lot of us were still optimistic, because the 50% increase in HDL that we saw in the earlier studies was so significant that it should have resulted in a significant mortality risk reduction."

That reduction should also have been large enough to offset the potential problem of hypertension, said Dr. Davidson, who worked with Dr. McKenney on the phase II studies (J. Am. Coll. Cardiol. 2006;48:1774-81; 1782-90).

In those studies, blood pressure increases were widely variable in both groups; however, significant jumps—systolic increases greater than 10 mm Hg from baseline or diastolic increases greater than 15 mm Hg from baseline—occurred in only about 3% of patients. "It was a concern," Dr. Davidson said, "but we thought raising the HDL that much would offset any potential risks. Obviously, this blood pressure issue may be much more serious than we first imagined."

While Pfizer has yet to release the causes of the deaths in its phase III study, Dr. Davidson thinks the drug's hypertensive effects may play into the picture. "Perhaps we didn't see a clear signal about this in the earlier trials because they included relatively healthy subjects, while the phase III trial involved sicker patients who had preexisting cardiovascular disease."

But because the other CETP inhibitors under development haven't shown any effect on blood pressure thus far, torcetrapib may be an outlier among them. "It may just be a specific issue to this drug. I believe this class of drugs still has a lot of potential." However, he cautioned, until the deaths in both arms of the ILLUMINATE trial have been adjudicated, it will be impossible to understand the drug's full risk picture.

Two upcoming imaging trials will provide valuable additional clues to torcetrapib's risks. One of these, the ILLUSTRATE trial, uses intravascular ultrasound to evaluate atherosclerotic plaque burden, said Dr. Steven Nissen, a principal investigator in that study.

ILLUSTRATE included 1,190 patients randomized to the combination of torcetrapib and atorvastatin or to atorvastatin alone. Data collection is complete; Dr. Nissen, medical director of the Cleveland Clinic Cardiovascular Coordinating Center, said he will present the results at the American College of Cardiology meeting in March. ■

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