Disappointing results with major studies with torcetrapib

Results from ILLUSTRATE and RADIANCE failed to demonstrate any benefit on progression of atherosclerosis with torcetrapib administered in combination with atorvastatin, despite substantial increases in HDL cholesterol.[1,2] Both studies were simultaneously reported in the New England Journal of Medicine.[3,4]

Torcetrapib development was terminated on 2 December, 2006 after the Data Safety Monitoring Board overseeing the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) trial reported an adverse imbalance of mortality and cardiovascular events in the torcetrapib arm.[3]

ILLUSTRATE

ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) was a prospective, randomised, multicentre double-blind study in patients with clinical evidence of coronary disease, as confirmed by cardiac catheterisation and a baseline intravascular ultrasound (IVUS). Patients completed a run-in period of 4 to 10 weeks with lifestyle intervention and atorvastatin 10-80 mg adjusted at 2-weekly intervals until LDL cholesterol levels had achieved guideline targets (100 mg/dl or 2.59 mmol/L). Patients who met this goal were then randomised to receive either torcetrapib 60 mg daily or a matching placebo, in addition to atorvastatin, for 2 years. At the end of the treatment period, a second IVUS was performed, examining the same coronary arteries. Researchers measured the change in percent atheroma volume (the primary variable) in the artery, comparing the baseline to the follow-up ultrasound.

A total of 1,188 patients were enrolled and 910 underwent repeat IVUS (77%). Treatment with the combination of torcetrapib/atorvastatin increased HDL cholesterol by 61% and decreased LDL cholesterol by 20%, relative to levels observed in the atorvastatin-only group. Despite these findings, there was no significant difference between the two groups with respect to the change in percent atheroma volume (increases of 0.19% with atorvastatin alone vs. 0.12% with the combination, $p = 0.72$). There was a small beneficial effect on normalised atheroma volume with the combination ($p=0.02$), although no significant difference between the groups with respect to the change in atheroma volume in the most diseased vessel segment. Torcetrapib was also associated with an increase in systolic blood pressure, averaging 4.6 mmHg. A significant increase in blood pressure was also reported in the ILLUMINATE trial (see ILLUMINATE terminated on HDL Forum).

Commenting on these results, Dr Steven Nissen, Chairman of Cardiovascular Medicine at Cleveland Clinic and lead investigator said: "While we found that the torcetrapib/atorvastatin combination markedly increased HDL cholesterol levels and lowered LDL cholesterol in patients, this drug also substantially raised blood pressure and failed to slow the build-up of plaque. It is yet to be determined if this failure represents a problem unique to torcetrapib or predicts a lack of efficacy for the entire class of similar drugs.'

RADIANCE 1 AND 2

The RADIANCE 1 and 2 studies (Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor), were reported by Dr John Kastelein, Academic Medical Center, University of Amsterdam, The Netherlands. These trials were designed to test the efficacy of torcetrapib on progression of coronary atherosclerosis, as measured by carotid intima media thickness (CIMT) in a total of 1,656 patients.

RADIANCE 1 included patients with heterozygous familial hypercholesterolemia (diagnosed by genotyping or World Health Organization criteria). Patients completed a 6-14 week run-in period, during which they were treated with atorvastatin 20 mg, 40 mg or 80 mg, titrated at 4-weekly intervals to achieve LDL targets, in addition to therapeutic lifestyle intervention. RADIANCE 2 consisted of patients with mixed hyperlipidemia (fasting triglycerides >150 mg/dL and <500 mg/dL, eligible for statin treatment in accordance with NCEP ATP III, no HDL criteria). In both studies, patients were randomised to torcetrapib 60 mg daily or placebo, in addition to atorvastatin, for 2 years. B-mode carotid ultrasonography was performed at baseline, and at 6, 12, 18 months and the end of the study. The primary endpoint was the raw annualised progression in CIMT, defined as change in maximal CIMT during a particular time interval divided by time expressed in years. Secondary endpoints included mean CIMT of the common carotid artery.

In RADIANCE 1, 850 patients were evaluable for the primary endpoint. Treatment with the combination of torcetrapib and atorvastatin raised HDL cholesterol by 52% (from 52.9 mg/dL to 81.5 mg/dL) compared with about 8% with atorvastatin alone (from 51.8 mg/dL to 52.4 mg/dL), and decreased LDL cholesterol by 21%. Despite this, there was no significant difference between the treatment groups with respect to the increase in maximum CIMT (0.0047 mm/year with the combination vs. 0.0053 with atorvastatin alone, p=0.87). Notably, mean systolic blood pressure increased by 2.8 mmHg with the combination treatment compared with atorvastatin alone. There was also a 2-fold increase in serious cardiovascular adverse events in the torcetrapib arm (5.2% vs. 2.4%).

In RADIANCE 2, there was no difference in maximal CIMT at any time point in either study group (1.36 mm^3 with torcetrapib combination vs. 1.37 mm^3 with atorvastatin alone at study close, p=0.46). The incidence of serious cardiovascular adverse endpoints was nearly double in the torcetrapib combination group (9.5% vs. 5.6%). A similar increase in systolic blood pressure as in RADIANCE 1 was also reported.

Dr. Kastelein suggested that the lack of efficacy with torcetrapib might be due to a number of factors including:

- CETP inhibition may not be an anti-atherogenic therapeutic strategy
- HDL particles carrying CETP/torcetrapib may be vasculotoxic
- The combination of torcetrapib/atorvastatin may have broader effects on the vasculature that are not yet understood.

Explanation for these disappointing findings highlights the need for greater understanding of the functions of HDL.[5] [See also commentary from the Editors appearing shortly in Forum].

References

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