Torcetrapib fails to slow atherosclerosis progression

28 March 2007

The cholesteryl ester transfer protein (CETP) inhibitor torcetrapib, which substantially raises high-density lipoprotein (HDL) cholesterol levels, does not halt the progression of atherosclerosis, the results of two studies presented at the American College of Cardiology Annual Scientific Session in New Orleans, Louisiana, USA, reveal.

These findings, from the Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE) 1 and 2 trials, follow on from the ILLUSTRATE trial results previously reported by *MedWire News*, and also presented at the conference. All ongoing torcetrapib trials were halted in December 2006 due to safety concerns.

RADIANCE 1, led by John Kastelein, from the Academic Medical Center in Amsterdam, The Netherlands, involved 850 patients with heterozygous familial hypercholesterolemia. The participants underwent B-mode ultrasonographic screening before commencing an atorvastatin run-in period, in which low-density lipoprotein (LDL) cholesterol levels were titrated to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines.

The participants were subsequently randomly assigned to receive once-daily torcetrapib 60 mg plus the titrated atorvastatin, or atorvastatin alone, with B-mode ultrasonography performed every 6 months for 24 months. In RADIANCE 2, which was led by Michiel Bots, from University Medical Center in Utrecht, The Netherlands, 758 patients with mixed hyperlipidemia underwent the same regimen.

Patients with torcetrapib experienced significant increases in HDL cholesterol levels in comparison with atorvastatin-only therapy, as well as substantial decreases in LDL cholesterol concentrations.

Despite this, the trials did not meet their primary endpoint with torcetrapib not reducing atherosclerosis progression. This result confirms the results of the ILUSTRATE study, which used intravascular ultrasound to look at torcetrapib's effects in the coronary arteries.

There was even evidence that some patients taking torcetapib had disease progression, none of which could be explained by the observed increases in blood pressure among patients taking the drug.

For example, patients in RADIANCE 1 taking only atorvastatin had an average yearly increase in maximum carotid intima–media thickness (CIMT) of 0.0053 mm, compared with an average annual increase of 0.0047 mm among patients taking both torcetrapib and atorvastatin.

However, the average CIMT for the common carotid artery decreased by 0.0014 mm per year among atorvastatin-only patients, but increased by 0.0038 mm per year in patients taking both atorvastatin and torcetrapib.

Kastelein concluded: "The addition of torcetrapib to statin therapy has no benefit at all on atherosclerosis progression, but it remains to be investigated whether this is a consequence of the molecule torcetrapib or whether the concept of CETP inhibition is a flawed hypothesis.

"Additional data from the ILLUMINATE study later this year will hopefully shed more light on this issue."

American College of Cardiology Annual Scientific Session: New Orleans, Louisiana, USA; 24–27 March 2007