



What do the torcetrapib imaging trials tell us?

The results of three trials investigating the effects of the CETP inhibitor, torcetrapib, on atherosclerosis progression were presented at the annual meeting of the American College of Cardiology held in New Orleans in March 2007.^{1,2} One of these trials, ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) used intravascular ultrasound (IVUS) to assess the effect of torcetrapib 60 mg daily (added to atorvastatin) on coronary atheroma burden. The other two trials - RADIANCE I and RADIANCE II (Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor) - used ultrasound to assess the effects of treatment with torcetrapib 60 mg/day in addition to atorvastatin on carotid intima-media thickness (CIMT). The results of ILLUSTRATE and RADIANCE I have now been published in the New England Journal of Medicine.^{3,4}

The findings of all three trials were consistent. Despite the fact that torcetrapib treatment increased HDL cholesterol substantially, by 61% in ILLUSTRATE³ and 52% in RADIANCE I⁴, there was no evidence that the addition of torcetrapib to atorvastatin had any benefit on atherosclerosis progression over and above that with atorvastatin alone. These results must be viewed in the light of the fact that the very large (15,000 patients) morbidity and mortality endpoint trial with torcetrapib (ILLUMINATE, Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) was terminated in December 2006 after a median follow up of only 18 months because of a statistically significant excess of deaths in the group treated with torcetrapib.

So, what do the imaging trials tell us?

They certainly tell us that torcetrapib does not promote regression of atherosclerosis in either coronary or carotid arteries. But they do not help us understand why there was an excess of deaths in the torcetrapib arm in the ILLUMINATE Trial. Moreover, while the imaging trials showed no evidence of benefit with torcetrapib, they also did not provide evidence of harm.

So, we are left with the question: were the excess deaths in the torcetrapib arm of ILLUMINATE due to CETP inhibition or were they due to an unknown serious adverse effect of torcetrapib unrelated to CETP inhibition?

This question is of major importance and must be answered before decisions can be made about the development of other CETP inhibitors.

It is possible that further analysis of the ILLUMINATE data and further basic research with torcetrapib may provide clues. If the problem with torcetrapib was an off-target adverse effect unrelated to CETP inhibition and if the mechanism can be elucidated, the way will be open to develop other members of the class that can be shown not to have this adverse effect.

References

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2. Kastelein JJ, Bots ML, Riley WA, et al. Carotid B-Mode Ultrasound Evaluation of the Antiatherosclerotic Efficacy of Toretapib/Atorvastatin Compared With Atorvastatin Alone in Subjects With Heterozygous Familial Hypercholesterolemia. Presented at American College of Cardiology 56th Annual Scientific Session, abstract 405-7.
3. Nissen SE et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007;356:1304-16.
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