



ILLUMINATE and CETP inhibition – Where now?

- Interview with Professor Philip Barter, Director of the Heart Research Institute, Sydney, Australia

Final results of the ILLUMINATE trial were reported at the AHA 2007 Scientific Sessions and published simultaneously on-line in the *New England Journal of Medicine*. **CETPi Forum** spoke to the lead author of ILLUMINATE, Professor Philip Barter.

These new data suggest that the excess of cardiovascular events and death seen in ILLUMINATE may have been due to 'off-target' effects of torcetrapib. What is meant by 'off-target' effects?

Answer: The pharmacologic target of torcetrapib was CETP inhibition for which it was extremely effective. The evidence from both animal and human studies, including the large trials, is that torcetrapib had additional pharmacological effects beyond inhibiting CETP. One of these was to stimulate the adrenal gland to secrete aldosterone, a hormone that retains sodium in the body, reduces serum potassium, increases serum bicarbonate and raises blood pressure. The increase in blood pressure is relatively small and was known before the ILLUMINATE trial commenced. But it is only after seeing changes in sodium, potassium and bicarbonate in the ILLUMINATE trial that we got clues that one explanation for the increase in blood pressure was an excess of aldosterone. This off-target effect of torcetrapib has now been confirmed in animals and cell culture studies.

How are these effects suspected of being responsible for the increase in cardiovascular events and death seen in ILLUMINATE?

Answer: The increase in aldosterone and blood pressure will almost certainly have contributed to the harm caused by torcetrapib in ILLUMINATE. However, at this time, we cannot say with certainty that they explain everything. It is likely that torcetrapib also had other harmful effects on the walls of arteries. The blood pressure changes and increase in aldosterone have provided clues regarding possible mechanisms of these harmful effects. Ongoing basic research is investigating several possibilities.

Why are 'off-target' effects more likely to be the cause than CETP inhibition itself?

Answer: The available evidence indicates that CETP deficiency of genetic origin is not associated with harm so long as it is associated with an HDL cholesterol level greater than 60 mg/dL (1.5 mmol/L). About 80% of the people taking torcetrapib in the ILLUMINATE trial had HDL cholesterol levels greater than 60 mg/dL. Furthermore, a new analysis from the ILLUSTRATE trial using intravascular ultrasound to measure coronary atheroma showed that those patients whose HDL cholesterol was increased most by

torcetrapib had regression of atheroma. In addition, torcetrapib has been shown to dramatically reduce atherosclerosis in rabbits. So, it appears to be most unlikely that CETP inhibition was the problem but rather that the harm was caused by an off-target effect of the drug, possibly related to aldosterone and an associated toxicity in the artery wall.

How do you explain the increase in non-cardiovascular effects with torcetrapib in ILLUMINATE?

Answer: At present we cannot explain the increase in non-cardiovascular deaths. It is possible, however, that people with cancer or with infections were frail and more susceptible to the cardiovascular problems that were clearly apparent in the overall population. It should be noted that while there was an apparent excess of deaths from cancer and infection, there was no evidence of an increase in the number of non-fatal cancers or infections in the people treated with torcetrapib. It is also worth noting that the difference in cancer deaths between the two groups was not statistically significant and may well have reflected the play of chance.

We have seen that torcetrapib effectively raises HDL cholesterol in ILLUMINATE, and in the imaging trials such as ILLUSTRATE. Why then was there no reduction in atherosclerosis progression, as might be expected?

Answer: The precise answer to this is not known. One possibility is that the HDL was not effective, although there is no evidence to support that. Another possibility is that the HDL was highly effective (as it is in rabbits treated with torcetrapib) but that the harmful off-target effects counteracted the beneficial effects of the HDL.

Are there any data to suggest that torcetrapib influences HDL function?

Answer: There are published studies showing that HDL from people treated with torcetrapib has normal (or possibly increased) functionality in terms of extracting cholesterol from macrophages.

Based on the ILLUMINATE data, is the HDL hypothesis still valid?

Answer: The ILLUMINATE trial was designed to test the effects of raising HDL by inhibiting CETP. In no way does it invalidate the HDL hypothesis. Given that a substantial proportion of the residual cardiovascular risk in people treated with statins relates to a low level of HDL, the need to develop effective HDL-raising therapies remains a very high priority. In the meantime, we should continue to use niacin (nicotinic acid) as a front-line HDL raising drug.

Are CETP inhibitors that do not share the same 'off-target' effects as torcetrapib therefore still a viable proposition for development?

Answer: On the basis of all we currently know, there is a compelling case for continuing development of CETP inhibitors that do not share the off-target effects of torcetrapib. But as with any new class of drug, such products must be tested in large-scale trials to ensure not only that they are effective but also that they are safe.