New data from ILLUMINATE: outcome trial with torcetrapib

New data from the ILLUMINATE trial, published on-line in the *New England Journal of Medicine*, November 5[1] do not disprove the hypothesis that CETP inhibition is cardioprotective. The ILLUMINATE trial was terminated on December 2, 2006 after a median follow up of only 18 months due to a statistically significant excess of deaths in the group treated with torcetrapib. The ILLUMINATE investigators conducted a series of exploratory, post-hoc analyses in an attempt to gain some insight into what may have occurred.

Background to the ILLUMINATE trial

The ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact on Atherosclerotic Events) trial was a double-blind randomised trial that included 15,067 patients at high cardiovascular risk (clinical evidence of cardiovascular disease or with type 2 diabetes). All patients were treated with atorvastatin at a dose necessary to reduce the level of low-density lipoprotein (LDL) cholesterol level to less than 100 mg/dL (2.6 mmol/L) before being allocated treatment with torcetrapib 60 mg daily or matching placebo. The follow-up was estimated to be 4.5 years in order to achieve enough events to test the hypothesis that treatment with torcetrapib was cardioprotective. The primary end point was the time to first occurrence of a major cardiovascular event, defined as coronary heart disease (CHD) death, nonfatal myocardial infarction, stroke or hospitalisation for unstable angina.

Analyses showed an excess of major cardiovascular events (464 vs. 373, hazard ratio 1.25; 95%CI 1.09 to 1.44, p=0.001) and deaths (93 vs. 59, hazard ratio 1.58; 95%CI 1.14 to 2.19, p=0.006) in the torcetrapib-treated group. The excess of deaths included both cardiovascular and non-cardiovascular causes.

At 12 months, torcetrapib increased HDL cholesterol by 72% and decreased LDL cholesterol by 25% over and above values achieved by treatment with atorvastatin alone. Torcetrapib also increased systolic blood pressure by 5.4 mmHg, decreased serum potassium and increased serum sodium, bicarbonate and aldosterone ($p<0.001$ for all comparisons). The effects of torcetrapib on blood pressure, aldosterone and electrolytes appear to be due to an off-target effect of the drug as other CETP inhibitors do not appear to raise blood pressure in species that express CETP, including humans.[2]

Follow up of patients for about 6 months after the trial was terminated provided no evidence of continuing clinical harm after the drug had been stopped.

New post-hoc analyses

The increased mortality and morbidity associated with the use of torcetrapib in the ILLUMINATE study may have been due to:

- an off-target effect of torcetrapib, unrelated to CETP inhibition and/or
- an adverse effect of CETP inhibition *per se*, with the possible generation of dysfunctional or even pro-atherogenic HDL.

Influence of electrolytes, HDL cholesterol and apolipoprotein A-I

Mortality rates were higher in torcetrapib-treated patients who had a decrease in potassium ≥1.0 mmol/L (the median change): 54 deaths (1.5%) vs. 35 deaths (1.0%) in patients with a decrease in potassium <1.0 mmol/L.

There were also more deaths in patients who had an increase in bicarbonate >0.7 mmol/L (median change): 54 deaths (1.47%) vs. 35 deaths (0.9%) in patients with increases in bicarbonate ≤ 0.7 mmo/L

Major cardiovascular event rates were lower in torcetrapib-treated patients who had increases in HDL cholesterol and apolipoprotein A-I greater than the median, as well as those who had smaller decreases in potassium and smaller increases in bicarbonate.

Influence of blood pressure

The relationship between events and changes in blood pressure was confusing. Paradoxically, there was an excess of both deaths and major cardiovascular events in the torcetrapib-treated patients who had a change in systolic blood pressure less than the median. However, further analysis showed that the patients who had the greatest increase in blood pressure also had the lowest level of blood pressure at baseline, making it difficult to interpret the relationship without further analysis.

Increases in blood pressure in torcetrapib-treated patients were also associated with a decrease in serum potassium and increases in serum sodium, bicarbonate and aldosterone. This suggests that torcetrapib may have activated the renin-angiotensin-aldosterone system (RAAS). Thus, the data suggest that off-target effects of torcetrapib contributed to the increased rate of major cardiovascular events and death.

These findings do not rule out the possibility of other unknown off-target effects of torcetrapib, or that CETP inhibition itself has adverse effects. In fact, it has been suggested that inhibiting CETP may generate HDL particles that are non-functional or even pro-atherogenic.[2] However, while the ILLUMINATE trial did not address the issue of how torcetrapib may have impacted on HDL function, major coronary event rates within the torcetrapib group were, if anything, lower in patients who had increases in HDL cholesterol or apolipoprotein A-I greater than the median. Additionally, preliminary analyses showed that major coronary event rates were lower in patients with higher levels of HDL cholesterol.

The ILLUMINATE trial investigators concluded that these analyses do not validate or invalidate the hypothesis that raising HDL cholesterol by inhibiting CETP is cardioprotective. Clearly, further testing in a large-scale clinical trial using a different CETP inhibitor that does not share the off-target pharmacologic effects of torcetrapib is needed.

References

1. Barter P, Caulfield M, Eriksson M et al. Effects of Torcetrapib on Morbidity and Mortality in Patients at High Risk for Coronary Events. New Eng J Med 2007;357:2109-22.
2. Rader DJ. Illuminating HDL – is it still a viable therapeutic target? N Engl J Med 2007;357:2180-3.