Major paper informs debate on use of good cholesterol raising drugs in reducing heart disease

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An international clinical trial to test whether a drug with the ability to enhance levels of good cholesterol is effective in reducing major cardiovascular disease events, which was terminated prematurely because of a mortality imbalance, is discussed in a paper published online today (Monday 5 November, 2007) in the *New England Medical Journal*.

The Pfizer-funded ILLUMINATE trial into the CETP inhibitor drug, torcetrapib, was ended in December 2006 after the trial's Steering Committee informed Pfizer that the Independent Data Safety Monitoring Board (DSMB) overseeing the study reported an adverse imbalance of mortality, cardiovascular and cancer events in the torcetrapib arm.

In the interest of patient safety, the investigators and Pfizer accepted this recommendation and terminated the ILLUMINATE study and all other trials with torcetrapib. They contacted all clinical investigators to request that they inform patient participants to stop taking study medication immediately. Pfizer informed the FDA and other regulatory authorities of the outcome. No one in Pfizer had access to the data prior to 2 December 2006 and as recently as one month before, the company had received an official communication from the Data Safety Monitoring Board that there was no reason to stop the study. Pfizer announced that it would discontinue the development of torcetrapib.

15,067 subjects at high risk from major cardiovascular disease events were randomised to receive torcetrapib plus atorvastatin (T/A) or atorvastatin alone. The difference in the number of deaths was statistically significant - 82 in the torcetrapib/atorvastatin arm compared to 51 deaths in the atorvastatin arm. Deaths resulted from both cardiovascular and non-cardiovascular causes. Studies running alongside ILLUMINATE, and recently reported, have found that torcetrapib had no effect on atheroma burden in coronaries or intima-medial wall thickness in the carotid arteries.

Professor Mark Caulfield from Barts and The London School of Medicine and Dentistry was the UK investigator on the Steering Committee, and second author on today's NEJM paper. No deaths occurred among the 148 patients who took part in the trial at this centre.

Professor Caulfield has been integral in conducting a series of exploratory analyses in an attempt to gain some insight into what may have occurred, and inform the decision about what to do with good cholesterol raising drugs. Two possible mechanistic explanations for the mortality associated with torcetrapib exist; a side-effect of torcetrapib unrelated to CETP inhibition (perhaps an increase in blood pressure, for example); or a pharmacologic effect of CETP inhibition itself (perhaps the resulting HDL does not work normally).

Torcetrapib had been known to increase blood pressure in earlier phase 2 trials. The increase seen in the ILLUMINATE trial after 12 months of treatment was a mean of 5.4 mmHg in the T/A group compared with 0.9 mmHg in the atorvastatin group alone, and this was greater than the increases seen in previous studies. However, the excess deaths appeared to be among patients whose blood pressure had been less than the median, making it difficult to interpret the

relationship without further analysis. Also observed in the T/A group

was a reduction in potassium and increase in sodium and bicarbonate levels in comparison to the atorvastatin alone group. This, coupled with the cardiovascular event hazard raised the possibility that the increase in blood pressure may have been a manifestation of mineralocorticoid excess. But, whilst cardiovascular risk caused by an increase in aldosterone associated with the use of torcetrapib is one possible explanation for the adverse reactions in the ILLUMINATE trial, it does not rule out other un-known side effects of the drug.

The second possibility to explain the results is that CETP inhibition compromised the function of HDL particles. Cholesterol ester transfer protein (CETP) is involved in the removal of HDL cholesterol and transfer of the cholesterol onto the LDL cholesterol pathway (thus turning good cholesterol into bad cholesterol). The current study does not address the issue of how torcetrapib impacts HDL functionality, although it was noted that within the TA group mortality was lower than in those whose increase in HDL level was was greater than the median, compared with those whose increases were below the level of change.

The ILLUMINATE trial has shown that torcetrapib caused an excess of cardiovascular and non-cardiovascular deaths. Why is not known. Initial exploratory analyses are consistent with a side effect of the drug which may be unrelated to CETP inhibition. The possibility that blockade of CETP may be beneficial remains hypothetical until it is tested in a trial with a CETP inhibitor that does not share the pharmacologic side effects of torcetrapib. Whilst the epidemiological evidence that good (HDL) cholesterol is beneficial, is convincing, raising HDL artificially with drugs has still to prove benefit. At present, being a woman (especially before the menopause), increasing exercise levels and modest consumption of alcohol are the things most associated with protective levels of HDL cholesterol. Low levels of HDL cholesterol are especially common in patients of Bangladeshi origin in parts of the east end of London, for whom premature heart disease is common. For this reason

the loss of torcetrapib is felt more keenly in this part of London.

Despite the unexpected outcome of the trial the Food and Drug Administration (FDA) in the United States has praised Pfizer for running a long-term outcome trial so early in the development of torcetrapib. Patients taking part in the study have been heartened that by taking part in a trial before the drug was licensed for general use, they have helped to prevent what might have been far more damage—most new drugs enter the market without a long-term outcome trial. Novel drugs to alter cholesterol such as torcetrapib, once licensed, would have initially been given to patients at the very highest level of risk, in whom heart attack or stroke would not have been unexpected and so detecting a bad effect of the drug would have been difficult outside the setting of a clinical trial—and might have caused many hundreds, if not thousands of deaths.

Source: William Harvey Research Institute