De-risking the clinical development of cholesteryl ester transfer protein inhibitors: how much is good enough?

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Online publish-ahead-of-print 31 October 2011

This editorial refers to ‘Torcetrapib impairs endothelial function in hypertension’†, by B. Simic et al., on page 1615

Modification of HDL cholesterol (HDL-C) metabolism is the next frontier in cardiovascular drug development, and modulation of cholesteryl ester transfer protein (CETP) is an important addition to our armamentarium in this field. Clinical trials have shown that CETP inhibitors substantially improve blood lipid profiles by raising plasma levels of HDL-C while simultaneously lowering LDL-C over and above what can be achieved with statin therapy.1–3 The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial was the first phase III trial testing the efficacy of the CETP inhibitor torcetrapib (Pfizer, New York, NY, USA) in reducing the risk of cardiovascular events. ILLUMINATE had to be halted in late 2006 after an interim analysis by the Data Safety and Monitoring Board had indicated a statistically significant increase in total mortality in the torcetrapib arm. 4 Almost simultaneously, the entire clinical development programme of torcetrapib was stopped. This unexpected finding has called into question the validity of CETP as a potential therapeutic target, but it has also challenged the concept of raising HDL-C levels to reduce cardiovascular disease risk. Despite suffering from this unprecedented set back, CETP is still considered by many to be a viable therapeutic target, and other CETP inhibitors are being developed by a robust number of pharmaceutical companies.

Following the publication of ILLUMINATE, analyses of the imaging trials with torcetrapib, in vitro and in vivo experiments, genetic epidemiology studies, and phase II studies with other CETP inhibitors have been used to clarify whether torcetrapib’s unexpected detrimental effects were an off-target side effect of the compound itself, or a phenomenon putatively associated with CETP inhibition and thus a class effect that could be anticipated with other CETP inhibitors as well.2,3,5–8 These studies have unequivocally shown that torcetrapib has off-target side effects that impact the renin–angiotensin–aldosterone system (RAAS) leading to increased aldosterone levels and an increase in systolic blood pressure.

In ILLUMINATE, the risk of mortality appeared to be increased in patients whose increase in systolic blood pressure was less than the median, which is counterintuitive if activation of the RAAS were the sole pathway leading to torcetrapib’s detrimental cardiovascular effects.4 Consequently, investigators are now looking outside the RAAS at other targets that may be negatively affected by torcetrapib.

Simic et al. have now identified the vascular endothelium as an alternative target for torcetrapib’s toxicity.9 The investigators studied spontaneously hypertensive rats (SHRs) and Wistar–Kyoto rats (WKRs), species that do not express CETP, in order to rule out the potential contribution of CETP inhibition per se and focus on the adverse effects of the compound itself. One of the main findings of the study is that torcetrapib leads to an impairment of endothelium-dependent vasorelaxation, which paralleled a decrease in endothelial nitric oxide gene expression and protein level as well as the generation of reactive oxygen species in the SHRs. In WKRs, such changes were not observed. Additional in vitro experiments in cultured aortic endothelial cells revealed that torcetrapib treatment reduced nitric oxide release. Concomitant pharmacological endothelin receptor blockade prevented the impact of torcetrapib-induced endothelial dysfunction, which suggests that this harmful effect of torcetrapib is to a certain extent driven by the potent vasoconstrictor endothelin-1 (Figure 1). Overall, this study presents insightful and unexpected evidence that the off-target toxicity of torcetrapib goes beyond its...
deleterious impact on the RAAS and that direct effects of torcetrapib on the endothelium cannot be ruled out. Moreover, torcetrapib is unlikely to have affected the nature of the HDL particle in these animal models lacking CETP, thereby limiting any speculation about the impairment of vascular reactivity being the result of a torcetrapib-mediated shift of HDL towards a proinflammatory phenotype.

While it is tempting to claim that the observed changes in vascular reactivity are specific to torcetrapib, this study cannot rule out the possibility of a class effect for CETP inhibition per se. This is an extremely important issue since several other CETP inhibitors are currently being tested in clinical trials in humans. However, a previous study using ultrasound imaging in vivo has suggested that torcetrapib, in contrast to the structurally distinct CETP inhibitor JNJ-28545595, may impair endothelial function in rabbits, a species that does express CETP. Which of torcetrapib’s off-target effects, impaired vascular function or increased blood pressure, correlates more with clinical outcomes is unknown. However, given the documented predictive value of endothelial dysfunction, and the absence of a relationship between blood pressure changes and cardiovascular outcomes in the ILLUMINATE trial, the unsuspected role of endothelial dysfunction as a mediator of cardiovascular risk in this trial should be seriously considered.

As suggested by the authors, it appears to be an appropriate proposition to assess the potential vascular toxicity of CETP inhibitors carefully before they are tested in humans, and assessment of vascular reactivity in animal models is a sound first step to rule out potential harmful effects. Nevertheless, it might be prudent to incorporate studies with short-term drug exposure on surrogate outcomes before jumping to large-scale phase III trials that could potentially put large numbers of patients at risk. Potential surrogate outcomes might be endothelial function as measured by flow-mediated dilatation (FMD), carotid intima-media thickness (IMT) measured by ultrasound, progression of coronary atherosclerotic plaque burden as quantified by intravascular ultrasound (IVUS), and atherosclerotic plaque characteristics as quantified by carotid magnetic resonance (MRI) and/or positron emission tomography (PET) imaging.

The study of Simic et al. does provide additional support for the dal-Vessel trial, which has recently shown that dalcetrapib (Basel, Switzerland) treatment had no deleterious effects on endothelial function in a large sample of stable coronary patients with low HDL-C levels. Studies such as dal-Vessel might be considered as an additional precautionary step in the de-risking strategy of the clinical development of CETP inhibitors. Needless to say, no novel CETP inhibitor can escape a well-powered cardiovascular outcomes trial such as REVEAL HPS-3 TIMI-55 for anacetrapib (Merck & Co, Whitehouse Station, NJ, USA) or Dal-Outcomes I for dalcetrapib. Together, these two studies currently hold the destiny of the concept of CETP inhibition in their hands.

The quest to unravel all the potential off-target side effects does not stop with this study, and additional work is warranted to

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**Figure 1** Schematic representation of the detrimental effects of torcetrapib on endothelial function. Torcetrapib (TOR) increases gene expression of endothelin-1 (ET-1) and aldosterone in the adrenal glands, thereby increasing their respective blood levels. Torcetrapib also increases gene expression of ET-1 in the endothelium. ET-1 in turn decreases genetic expression of endothelial nitric oxide synthase (eNOS). Intracellular ET-1 and blood-derived ET-1 (through its interaction with the ET₄ and ET₅ receptors) induces the production of reactive oxygen species (ROS). Through its interaction with the mineralocorticoid receptors (MRs), blood-derived aldosterone also increases ROS production via the stimulation of NADPH oxidase. ROS species are directly secreted by the endothelium into the bloodstream and also decrease eNOS-induced nitric oxide release, one of the most fundamental regulator of vasorelaxation.
understand fully the atherogenicity of torcetrapib. In this context, the latest technological advances in genomics will also be useful tools to identify additional potentially harmful effects of CETP inhibition in a bias-free manner and help in guiding a safe and efficacious development of such compounds.

In summary, this study is an important contribution to the field of CETP inhibition, which may have direct impact on the development programmes of such drugs. It also re-emphasizes the importance of testing drugs extensively in various animal models and in early clinical trials using intermediate outcomes to prevent the exposure of large numbers of patients to novel drugs with an unknown safety profile. After all, the safety of our patients is of paramount importance and a replay of the torcetrapib tragedy should be avoided at all cost. ‘That which does not kill us, makes us stronger’, quoted German philosopher Friedrich Nietzsche (1844–1900). The failure of torcetrapib has provided, and will continue to provide, valuable lessons regarding the concept of CETP inhibition. With the recently published results of phase II and III clinical trials with dalcetrapib13 and anacetrapib,2 respectively, the concept of CETP inhibition again has the wind in its sails.

Conflict of interest: J.J.P.K. is a consultant to Roche, Merck, Eli Lilly, and Boehringer Ingelheim for the development of CETP inhibitors. The other authors declare no conflict of interest.

References