Torcetrapib

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Introduction

Despite widespread use of HMG-CoA reductase inhibitors in the treatment of hyperlipidaemia, many patients remain at risk of cardiovascular disease due to low levels of high-density lipoprotein cholesterol (HDL-C). There is strong epidemiological evidence to show that lower HDL-C levels, which are a common feature in individuals with type 2 diabetes, predict cardiovascular risk independently of low-density lipoprotein (LDL) cholesterol levels. HDL particles are considered to be atheroprotective via a number of mechanisms which include (i) their facilitation of reverse cholesterol transport, whereby cholesterol is transported from peripheral tissues back to the liver, (ii) anti-oxidative function, and (iii) anti-inflammatory properties.

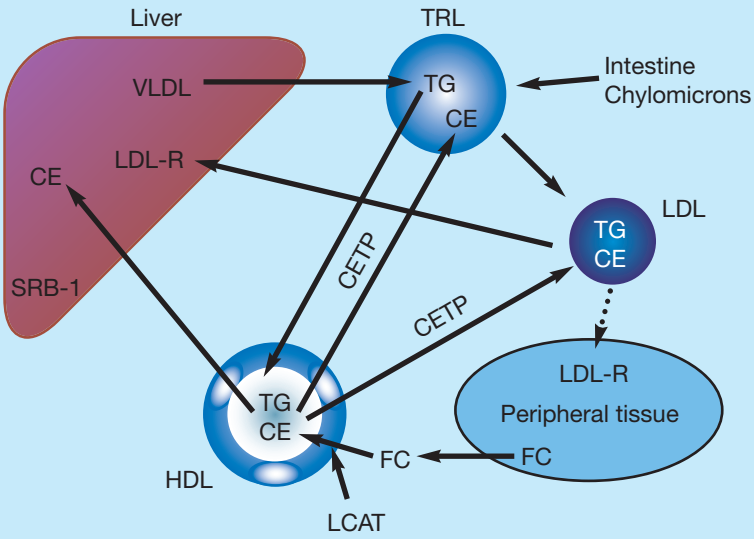
Current trials are studying the use of pharmacological agents in the form of cholesteryl ester transfer protein inhibitors (CETPi) to increase the levels of circulating HDL-C. Torcetrapib was the first CETPi to be trialled. Despite increasing HDL-C levels by over 60%, trials were terminated prematurely due to increased mortality and cardiovascular events associated with the torcetrapib treatment arm.[1] Development of the CETP inhibitors dalcetrapib and anacetrapib is ongoing.

Pharmacology

CETP is a plasma protein that facilitates the transport of cholesteryl esters (CE) and triglycerides between the lipoproteins. As most of the CE in plasma stems from HDL particles (via the enzyme lecithin-cholesterol acyltransferase [LCAT]) and most of the triglyceride stems from triglyceride-rich lipoproteins such as very-low-density lipoproteins (VLDL) from the liver or chylomicrons from the intestine, the net effect of CETP is to collect triglycerides from VLDL or LDL and exchange them for CE from HDL. This process results in lowering of HDL-C levels and thus inhibition of CETP allows HDL-C levels to rise and remain elevated.

Figure 1 demonstrates the role of CETP in lipid exchange, a process during which specific lipid moieties are transferred between HDL, LDL and trigylceride-rich lipoprotein particles with a resultant lowering of HDL-C levels.

Figure 1. The role of cholesteryl ester transfer protein (CETP) in lipid exchange



NOTES. During the process illustrated, and via the actions of CETP, specific lipid moieties are transferred between HDL, LDL and triglyceride-rich lipoprotein particles with a resultant lowering of HDL-cholesterol levels. KEY. CETP: cholesteryl ester transfer protein; CE: cholesteryl esters; TG: triglycerides; HDL: high-density lipoprotein; LCAT: lecithin-cholesterol acyltransferase; TRL: triglyceride-rich lipoproteins; VLDL: very-low-density lipoprotein; SRB-1: scavenger receptor B-1; LDL: low-density lipoprotein; LDL-R: LDL receptor; FC: free cholesterol.

Trials of safety and efficacy

Early efficacy trials of torcetrapib were considered successful with around a 60% rise in HDL-C coupled to around 20% falls in LDL-C. Subsequently, a set of imaging studies (RADIANCE 1 and 2 and ILLUSTRATE)[2–4] were initiated to determine whether inhibition of CETP with torcetrapib, administered with atorvastatin, would provide an additional anti-atherosclerotic benefit, as compared with atorvastatin plus placebo. RADIANCE 1 and 2 examined the impact of torcetrapib on common carotid intima media thickness (cIMT) in 850 subjects with familial hypercholesterolaemia (FH) and 752 individuals with mixed dyslipidaemia. Twenty-one percent of patients in RADIANCE 2 had type 2 diabetes, a

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group commonly presenting with mixed dyslipidaemia, whereas <5% of patients with FH did so. The primary endpoint in both was the yearly rate of change in the maximum common cIMT of 12 carotid segments. However, neither study showed any benefit of torcetrapib on this primary outcome measure. The ILLUSTRATE trial performed intravascular ultrasound of the coronary vessels at baseline and follow up in 910 subjects, of whom 21% had type 2 diabetes. The primary efficacy measure was percentage atheroma volume which increased by 0.19% in the atorvastatin-only group and by 0.12% in the torcetrapib-atorvastatin group (p=0.72), so once again no clear evidence of benefit. Interestingly, each of these trials reported significant elevations in systolic blood pressure (BP) with torcetrapib (between 2.8 to 5.4mmHg as compared to placebo arm).

The ILLUMINATE study[1] was a randomised, double-blind study involving 15,067 patients with manifest cardiovascular disease or type 2 diabetes (~45% of the total). This major phase III secondary prevention morbidity and mortality trial compared torcetrapib plus atorvastatin with atorvastatin alone. Subjects were initially treated with atorvastatin at a dose necessary to reduce LDL levels to 100mg/dl (2.6mmol/L). In addition to atorvastatin, 60mg of torcetrapib or matching placebo was given in a randomised, double-blind fashion. As expected, torcetrapib induced significant changes in the lipid profile with a rise in HDL-C of 72.1%, a decrease in LDL-C of 24.9% and a non-significant decrease in triglycerides of 9%.

However, somewhat against expectations, the trial was terminated in December 2006 at a median follow-up period of only 18 months after findings of a significantly higher all-cause mortality from both cardiovascular and non-cardiovascular events in the torcetrapib arm. The hazard ratio for the primary outcome (major cardiovascular events) was 1.25 in the torcetrapib treatment arm. In addition to the increase in mortality, the rates of non-fatal myocardial infarction, revascularisation, angina and heart failure were also all higher in the torcetrapib arm. Torcetrapib induced significant increases in BP (systolic: 5.4mmHg at 12 months), and small but significant elevations in serum sodium and bicarbonate and a decrease in serum potassium.

Key points

- Cholesteryl ester transfer protein (CETP) is a key protein involved in reverse cholesterol transport, and its inhibition markedly elevates HDL-cholesterol levels
- The first trialled CETP inhibitor, call torcetrapib, increased mortality due to a rise in blood pressure, an effect subsequently proven to be an off-target effect of this compound unrelated to CETP inhibition
- Anacetrapib and dalcetrapib are CETP inhibitors that are in phase III of clinical trials which currently do not appear to have blood pressure-raising effects. Their effects on vascular and other outcomes will determine the future role for this class of drugs

Discussion

There has been much discussion over the reasons for the harm caused by torcetrapib in ILLUMINATE. The main explanations put forward are outlined below.

- CETP is part of a pathway that delivers cholesterol to the liver so that inhibiting CETP may decrease reverse cholesterol transport and consequently act in a proatherogenic manner. There are currently no means by which to confirm or refute this.
- The hypothesised inverse relationship between HDL-C and cardiovascular risk is an epidemiological phenomenon. Many animal studies can exclude this as an explanation, though there is no conclusive evidence from human studies.
- Adverse off-target drug effects not related to CETPi caused the harm. This is currently viewed as the likely explanation.

Several studies have since proven that the off-target adverse effects of torcetrapib are unrelated to CETPi. Torcetrapib causes induction of aldosterone and cortisol synthesis, a finding which helps to explain the changes in serum electrolytes with torcetrapib. Torcetrapib and angiotensin II also share overlapping pathways for adrenal steroid synthesis. In animal models, BP increases with torcetrapib occur regardless of whether they expressed CETP. More recently, genetic studies displayed significant discordance between common CETP genetic variants and pharmacological inhibition of CETP with torcetrapib in relation to BP, sodium and potassium effects despite concordance on effects on lipid levels, further suggesting that the BP-elevating effects of torcetrapib are mechanistically unrelated to CETPi.

Two further CETP inhibitors are currently at phase III of clinical trials neither of which presently appear to have adverse effects on BP or aldosterone levels. Anacetrapib has displayed promising anti-arteriosclerotic properties as has dalcetrapib. The outcome of trials on these CETP inhibitors will determine if CETPi will be used in the clinical management of patients whose lipid profiles remain suboptimal despite aggressive statin use.

Conflict of interest statement

There are no conflicts of interest.

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