Inhibition of CETP as a novel therapeutic strategy for reducing the risk of atherosclerotic disease

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Lowering low-density lipoprotein cholesterol (LDL-C) levels with statins is a proven strategy for reducing the risk of atherothrombotic cardiovascular disease (CVD). Yet, despite the success of statins in reducing cardiovascular event rates in at-risk patients, many will still experience further events. There is, therefore, a need to develop suitable therapies to reduce this residual risk. Low high-density lipoprotein cholesterol (HDL-C) levels are an important independent risk factor for CVD. Though fibrates, niacin, and statins have been shown to modestly raise HDL-C, there is increasing recognition of the need to develop therapies that can increase HDL-C more robustly. Such therapies may help supplement the LDL-C-lowering benefits of statins. Inhibition of cholesteryl ester transfer protein (CETP) has been identified as a possible strategy for substantially increasing HDL-C levels and CETP inhibitors have demonstrated clinical efficacy, in terms of increasing HDL-C, in preliminary clinical trials, and clinical trials based on outcomes are ongoing. Two CETP inhibitors, JTT-705 and torcetrapib, are now being evaluated more extensively.

Introduction

Statins have become the gold standard treatment for patients with, or at risk for, cardiovascular disease (CVD) due to their ability to produce significant reductions in the risk of death or cardiovascular events through reductions in low-density lipoprotein cholesterol (LDL-C) levels. However, despite the impressive benefits of statins, there remains a significant proportion of treated patients for whom cardiovascular events are not prevented. Clearly, other CVD risk factors, beyond LDL-C, need to be targeted to achieve further reductions in cardiovascular events.

Epidemiological studies have demonstrated that a low level of high-density lipoprotein cholesterol (HDL-C) is a strong and independent risk factor for coronary heart disease (CHD). Indeed, estimates based on data from four large studies have suggested that, for every 0.03 mmol/L (1 mg/dL) increase in HDL-C, there is a 2–3% decrease in cardiovascular risk. In simple terms, HDL-C levels are a measure of the cholesterol content of HDL particles and, therefore, are an indirect measure of the numbers of circulating HDL particles. Most available treatments that raise levels of HDL-C, or that increase the numbers of HDL particles, are only modestly effective (Table 1). Hence, there is a need for new therapies with more potent HDL-elevating activity. One such approach is by infusion of recombinant HDL-associated lipoproteins or lipoprotein mimetics. An alternative method, which appears particularly promising and is the focus of this review, is via inhibition of the cholesteryl ester transfer protein (CETP)—a key player in cholesterol metabolism.

Reverse cholesterol transport and the role of CETP

The atheroprotective nature of HDL particles is due to a composite of multiple mechanisms including antioxidative, anti-inflammatory, antithrombotic, and antiapoptotic effects. Additionally, HDL particles play a pivotal role in reverse cholesterol transport (RCT), the process by which excess cholesterol in peripheral tissues is returned to the liver for excretion. It is this process that is frequently cited as the primary mechanism by which HDL protects against atherosclerosis and may induce plaque regression. Cholesterol efflux from peripheral tissues to HDL—the first stage of RCT—occurs by a number of routes: via the ATP-binding cassette transporter A1 (ABCA1) to poorly lipidated apolipoprotein AI (apoA-I); via the scavenger receptor B1 (SR-B1) to both discoidal and larger, spherical HDL particles; or via passive diffusion. During the second stage of RCT, cholesterol is delivered to the liver, either by direct interaction of HDL with the hepatic SR-B1 receptors, mostly in the form of free cholesterol, or by transfer of cholesteryl ester (CE) to apoB-containing particles [very-low-density lipoprotein (VLDL) and LDL], and subsequent uptake by hepatic LDL receptors (Figure 1). After delivery to the liver, cholesterol can be excreted from the body as a component of bile.
A key regulator of RCT is CETP, a hydrophobic glycoprotein produced in the liver and secreted into plasma, where it is found primarily bound to HDL.\(^26\) CETP promotes the transfer of CE from HDL to VLDL and LDL in exchange for triglycerides and the transfer of triglycerides from VLDL to LDL and HDL in exchange for CE.\(^27\)

As a regulator of cholesterol flux through the RCT system, CETP may be viewed as potentially having both proatherogenic and antiatherogenic properties. By shifting CE from HDL to apoB-containing lipoproteins (LDL and VLDL), CETP may decrease direct RCT via the HDL/hepatic SR-B1 route. Additional proatherogenic effects of CETP activity may include a reduction in overall HDL levels, potentially reducing cellular cholesterol efflux from the arterial wall, and an increase in atherogenic LDL levels. However, the potentially proatherogenic activities of CETP may, to a large extent, be neutralized by an increase in indirect RCT via the LDL/hepatic LDL receptor route. Clearly, the question of whether the sum effect of CETP activity is pro- or antiatherogenic is a complicated one and there is no certainty that CETP inhibition will be a viable strategy for protecting against atherosclerosis.\(^28\)–\(^31\) So far, evidence that CETP inhibition can reduce atherosclerosis is limited to data from rabbit models of atherosclerosis.\(^32\) However, as the following brief review of the cumulative evidence from epidemiological and observational studies of the link between CETP, HDL-C, and CHD risk shows, there is cautious optimism that inhibition of CETP may have potential as a novel therapy.

**CETP, HDL-C, and cardiovascular risk**

Understanding of the link between CETP, HDL-C, and cardiovascular risk has, to a large part, been advanced through the study of a range of mutations in the CETP gene; a comprehensive list of which, along with a description of their link to HDL-C levels, is provided by Barter et al.\(^27\) This review limits discussion to the evidence provided by the best studied of these mutations.

**CETP gene mutations**

Initial evidence of a link between CETP and HDL-C levels came from studies that demonstrated that a mutation in the CETP gene, resulting in CETP protein deficiency, was the underlying cause of elevated HDL-C levels in Japanese individuals with familial hyperalphalipoproteinaemia (HALP).\(^32\)

The genetic trait in question was identified as a splicing mutation at the +1 position of intron 14 (G\(^+\)1A/In14) of the CETP gene, resulting in a nucleotide substitution from G to A. This splicing mutation is present in up to 2% of the general population of Japan and is present in 27% of people in the Omagari region.\(^33\)–\(^35\) Because it occurs so frequently in the Japanese population, there are appreciable numbers of individuals who are homozygous for G\(^+\)1A/In14. Such individuals have no measurable CETP activity and, consequently, have less markedly raised HDL-C levels than do homozygous G\(^+\)1A/In14 individuals.\(^35\)

Inazu et al.\(^34\) subsequently identified a second mutation in the CETP gene, also causing CETP protein deficiency, that occurs in exon 15 and results in a D to G substitution at amino acid 442 (D442G). This gene mutation is even more common than G\(^+\)1A/In14, being present in up to 7% of the Japanese population. Interestingly, individuals who are homozygous for D442G retain partial CETP activity and, consequently, have less markedly raised HDL-C levels than do homozygous G\(^+\)1A/In14 individuals.

In HALP subjects homozygous for G\(^+\)1A/In14 and lacking detectable CETP activity, radiolabelling experiments showed...
that the inability to transfer CE from HDL to other lipoproteins, such as apoB-containing lipoproteins, led to an accumulation of CEs in the HDL fraction, with associated increases in apoA-I, apoA-II, and apoE. Increases in apoA-I and apoA-II were due to reduced catabolic rates, and not increased production, as apolipoprotein synthesis remained unaltered.

CETP protein deficiency may not only affect overall levels of HDL-C but may also result in qualitative changes in HDL particles that may impact their functionality. CETP protein deficiency appears to favour accumulation of larger, CE-rich HDL particles, and at least two studies have previously raised questions about the ability of these larger HDL particles to promote cholesterol efflux from macrophages. However, a more recent study by Tall et al. provides evidence that HDL particles from subjects with homozygous CETP gene mutations may actually have enhanced ability to promote cholesterol efflux from macrophages via an ABCG1-dependent pathway due to an increased content of lecithin cholesterol acyltransferase (LCAT) and apoE.

Not surprisingly, individuals who are homozygous for CETP gene defects also display other changes to their lipid profile. Most notably, there may be substantial reductions in LDL-C and apoB, and the LDL particles that are present are more heterogeneous, deficient in CE, triglyceride-rich, and have a low affinity for the LDL receptor. Furthermore, metabolic turnover of LDL and apoB may be substantially increased, perhaps due to upregulation of the LDL receptor pathway.

Clearly, mutations in the CETP gene can produce significant changes in lipid and lipoprotein metabolism and the precise nature of these changes varies between different mutations. Consequently, the role played by underlying CETP mutations on an individual’s cardiovascular risk is complex and ill-defined. Evidence suggests that overall cardiovascular risk may be dependent on subsidiary factors affecting the metabolic setting of the CETP gene mutation. For example, in a study of 201 patients with highly elevated levels of HDL-C (>2.58 mmol/L (100 mg/dL)) who were expected to be at low risk of CHD, 12 patients were nevertheless observed to have clinically evident CHD. All 12 subjects had reduced CETP function but in conjunction with reduced hepatic triglyceride lipase activity.
Mixed findings on the link between CETP protein deficiency and CHD risk have also emerged from the Honolulu Heart Study. Initial results showed that men of Japanese descent with low or moderately increased HDL-C levels [1.05–1.54 mmol/L (41–60 mg/dL)], who were heterozygous for the D442G CETP gene mutation, had a 50% increased risk of CHD compared with men who had similar HDL levels, but who had no CETP gene mutations. However, men with elevated levels of HDL-C (>1.54 mmol/L (60 mg/dL)) had less risk of CHD, irrespective of CETP gene deficiency. Subsequently, a prospective analysis of 7-year data from the Honolulu Heart Study has shown a trend towards a lower incidence of cardiovascular events in subjects with heterozygous CETP gene mutations compared with those without a mutation. Another study investigating the link between CHD risk and CETP activity in Japanese subjects showed that individuals with HDL-C levels >2.05 mmol/L (80 mg/dL) had very low risk of CHD, irrespective of whether they had a G-i1A/in14 or D442G CETP gene mutation.

Thus, from the results of studies on individuals with CETP protein deficiency arising from genetic mutations, the relationship between CETP and the risk of CHD is difficult to interpret. However, it seems likely that a deficiency in CETP may protect against atherosclerosis, provided that the CETP deficiency is also associated with an increase in HDL-C and that the HDL particles are functional.

Not all CETP gene mutations have as dramatic an effect on CETP protein levels as those described above. Various single nucleotide polymorphisms (SNPs) of the CETP gene have also been reported that are associated with only small changes in plasma CETP levels and HDL-C levels. However, since the frequencies of these mutations among populations are generally higher than more dramatic gene defects, they have also been studied in an attempt to delineate the relationship between CETP function and the progression of atherosclerosis. As yet, a clear and unambiguous relationship between CETP activity and cardiovascular risk has not been borne out by these additional studies of CETP SNPs, most of which have not consistently shown an association between genotype and CHD risk.

Studies of the most well-characterized CETP SNP, Taq1B (located in intron 1 of the CETP gene), have provided evidence that high CETP activity is associated with low HDL-C levels and increased CHD risk, although this effect may to some degree be dependent on gender. For example, in the Framingham Offspring Study, higher plasma CETP concentrations and lower levels of HDL-C were found in subjects homozygous for the B1 allele of the Taq1B SNP compared with heterozygous subjects and subjects homozygous for the B2 allele. The lower level of CETP activity and higher levels of HDL-C in men with either one or two copies of the B2 allele appeared to be associated with reduced risk of CHD, although there was no significant association in women. Recently, the relationship between the Taq1B CETP SNP and HDL-C levels and CHD risk has been strengthened by the results from a large meta-analysis of patient data from seven population-based studies (each >500 individuals) and three randomized, placebo-controlled, pravastatin trials.

The A405V CETP gene polymorphism has also been the subject of much investigation. A study of a genetically homogeneous population of Ashkenazi Jews (who tend to have exceptional longevity), showed that the incidence of homozygosity for the 405V allele was significantly higher than in a control group consisting of Ashkenazi Jews and individuals from the Framingham Offspring Study. This homozygous genotype was associated with reduced CETP levels and a unique lipoprotein profile, characterized by larger HDL and LDL particles, and was suggested to confer a survival advantage leading to longevity. Yet, previous studies of the A405V CETP gene polymorphism have provided contradictory findings. In the Copenhagen City Heart Study, women who were heterozygous or homozygous for the 405V allele had increased levels of HDL, but also had an increased risk of ischaemic heart disease. In a study of Hawaiian men of Japanese ancestry, plasma CETP concentrations were reduced and HDL-C levels increased in those who were homozygous for the 405V allele compared with those who were heterozygous or homozygous for the 405I allele. In this study, men who were homozygous for the 405V allele and who had high triglyceride levels had a higher prevalence of CHD.

Thus, in keeping with CETP protein deficiency studies, the cumulative evidence from CETP polymorphism studies on the link between CETP activity and CHD risk is not entirely conclusive. At best, it may be surmised that genotypes regularly associated with low CETP activity and high HDL-C levels are more likely to be associated with a lower risk of CVD.

Emerging clinical trial data

Though relatively limited, there is accumulating evidence emerging from clinical trials to show that high CETP concentration or activity is associated with an increased risk of CVD.

The REGRESS study evaluated the effect, over 2 years, of once-daily treatment with pravastatin 40 mg vs. placebo on atherosclerosis progression in 674 men with CHD. Analysis of baseline CETP concentrations demonstrated that individuals with levels in the highest quintile had significantly greater progression of atherosclerosis after 2 years vs. those with baseline concentrations in the lowest quintile. Similarly, analysis of data from 281 patients with familial hypercholesterolaemia who participated in the atorvastatin vs. simvastatin on atherosclerosis progression (ASAP) study revealed a positive correlation between baseline CETP concentration and atherosclerotic progression as measured by change in carotid intima-media thickness after 2 years. Perhaps the most compelling data supporting a link between CETP concentration and CHD risk were provided recently in the form of a nested case–control study of participants in the EPIC–Norfolk Population Study. Results showed that CETP levels in baseline plasma were inversely related to HDL-C levels and were slightly higher in patients who developed fatal or non-fatal CHD during follow-up than in control subjects. Subjects in the highest quintile for CETP mass (≥4.9 mg/L) had an increased relative risk of CHD with an odds ratio (OR) of 1.43 (95% CI: 1.03–1.99, P = 0.03) compared with the lowest quintile (<2.4 mg/L), a relationship that was augmented [1.87-fold increase in OR (95% CI: 1.06–3.30, P = 0.02)] in patients with triglycerides above the median level [1.7 mmol/L (151 mg/L)]. The observation that triglyceride levels inflated the effect of CETP concentration on CHD risk in this study, again suggests
that the metabolic background may be important in determining the relationship between CETP activity and CHD risk. This may be explained by the fact that in the presence of high triglyceride there is enhanced triglyceride transfer to HDL and LDL from VLDL. This leads to triglyceride-rich LDL, which is more susceptible to the action of triglyceride lipases, generating small dense LDL and a more atherogenic lipid profile.59,60

Inhibition of CETP for the prevention of CVD

Although by no means conclusive, the evidence accumulated to date generally supports the inhibition of CETP as a potential new strategy for decreasing cardiovascular risk.27 Accordingly, several inhibitors of CETP are now in development. CETi-1 is an anti-CETP vaccine developed by linking a B-cell epitope of human CETP to a T-cell epitope of the tetanus toxin, thereby eliciting a sufficient antibody response against CETP to inhibit its function. JTT-705 and torcetrapib are small molecule inhibitors that act by directly binding CETP to inhibit CE transfer activity. Both JTT-705 and torcetrapib have demonstrated significant anti-atherosclerotic effects in preclinical studies. In cholesterol-fed rabbits, JTT-705 increased levels of HDL-C, decreased levels of non-HDL-C, and produced a 70% decrease in lesions of the aortic arch.29 A similar study with torcetrapib, also in cholesterol-fed rabbits, resulted in elevations in HDL-C from week 1, which remained elevated throughout the treatment period. These elevated levels of HDL-C were associated with a significant reduction in aortic atherosclerotic area compared with control rabbits.31 The findings from preliminary clinical trials of CETP inhibitors are described below.

Clinical trials with CETP inhibitor monotherapy

CETi-1

Results from a phase II study, in which 203 patients received either placebo or CETi-1 in one of three doses, have been published.61 After an initial inoculation, subjects received further injections at 4 weeks, 8 weeks, and 6 months. Results were encouraging, showing that CETi-1 was well tolerated, produced an appropriate immunogenic response and resulted in an increase in HDL-C levels. After 1 year, CETi-1 had elicited anti-CETP antibodies in 90% of patients and increased HDL-C by 8%. However, the increase in HDL-C was not statistically significant compared with placebo and was observed only in patients who were not receiving concurrent statin therapy.

JTT-705

The efficacy and safety of JTT-705 has been evaluated in a randomized, phase II dose–response trial in 198 healthy individuals with mild hyperlipidaemia.62 Subjects with HDL-C levels ≤1.6 mmol/L (60 mg/dL) and triglyceride levels ≤4.5 mmol/L (400 mg/dL) (no defined exclusion criteria for LDL-C) were randomized to treatment groups receiving either JTT-705 300, 600, or 900 mg, or placebo. After 4 weeks, there was a dose-dependent decrease in CETP activity, with a 37% decrease from baseline in the 900 mg group. At the highest dose of JTT-705, HDL-C levels were increased by 34% and there was a 7% decrease in LDL-C.

Although a reduced flux of CE from HDL to LDL following CETP inhibition would be expected to reduce LDL-C levels (as observed in this phase II trial), this reduction in LDL-C appears smaller than those typically reported with statin therapy.10

Torcetrapib

A 14-day, phase I study conducted by Clark et al. assessed the effect of torcetrapib on both CETP activity and lipid levels across a range of doses in 40 healthy normolipidaemic subjects.63 Dose-dependent decreases in CETP activity led to elevations in HDL-C of 16% (10 mg daily) to 91% (120 mg twice daily) and changes in LDL-C from a 9% increase (10 mg daily) to a 42% decrease (120 mg twice daily). At the 120 mg twice-daily dose, apoA-I and apoE increased by 27% and 66%, respectively, and apoB decreased by 26%. In CETP-deficient individuals, CE-enriched HDL has been reported to be less efficient at promoting cholesterol efflux38,39 and may not be protective against atherosclerosis.64 The high (but incomplete) level of CETP inhibition in this study led to the production of HDL with a higher free cholesterol/CE ratio than has been observed in subjects with complete CETP deficiency.39,65 Thus, changes in cholesterol metabolism with torcetrapib treatment appear to be more similar to those observed in subjects with partial, rather than complete, CETP deficiency. This residual low level of CETP activity may be important in preventing accumulation of very large dysfunctional apoE-rich HDL and abnormal polydisperse LDL.

Combination therapy with CETP inhibitors and statins

Given the continuing emphasis of CVD prevention guidelines on LDL-C lowering, it is probable that, clinically, the HDL-C elevating benefits of CETP inhibition would be used to augment the established benefits from intensive LDL-C lowering with statins.66 With this in mind, recent clinical studies of CETP inhibitors have evaluated concomitant treatment with a statin.

JTT-705 and pravastatin

A randomized, double-blind, phase II study investigated the lipid effects of a combination of JTT-705 and pravastatin in 155 individuals with LDL-C >4.1 mmol/L (160 mg/dL).67 Subjects were already taking pravastatin 40 mg daily at entry to the study, and were randomized to receive placebo or JTT-705 300 mg or 600 mg daily, while continuing with pravastatin treatment. After 4 weeks, the combination of JTT-705 600 mg and pravastatin 40 mg led to a 30% decrease from baseline in CETP activity, together with a 28% increase from baseline in HDL-C, and a 5% decrease from baseline in LDL-C (i.e. in addition to the LDL-C lowering already achieved with pravastatin). The combination was reported to be safe and well tolerated with no notable safety concerns.

Torcetrapib and atorvastatin

A phase II, single-blind study investigated the effects of torcetrapib alone or in combination with atorvastatin on...
plasma lipoprotein levels in 19 subjects with low HDL-C levels (<1.03 mmol/L (40 mg/dL)). Subjects received torcetrapib at a dose of 120 mg/day, with or without atorvastatin 20 mg/day, for 4 weeks, and a subgroup of subjects in the torcetrapib monotherapy group received torcetrapib 120 mg twice daily for a further 4 weeks. HDL-C increased by 46% in the torcetrapib 120 mg/day group, 61% in the torcetrapib 120 mg/day plus atorvastatin 20 mg/day group, and 106% in the subgroup receiving twice-daily torcetrapib 120 mg/day for an additional 4 weeks. LDL-C decreased by 8, 17, and 17% in these three groups, respectively. Importantly, the 17% LDL-C decrease in the group receiving torcetrapib 120 mg/day along with atorvastatin 20 mg/day was additional to the LDL-C decrease in the placebo group receiving atorvastatin 20 mg/day. In this study, torcetrapib was well tolerated and there were no major adverse events. Again, inhibition of CETP with torcetrapib therapy was partial (28–65%).

Two further phase II, multicentre, double-blind trials, have investigated the lipid modifying effects of torcetrapib with and without atorvastatin in patients with low HDL-C [men <1.13 mmol/L (44 mg/dL); women <1.38 mmol/L (54 mg/dL)]. In patients treated with torcetrapib alone 10–90 mg/day (n = 162), the mean increase in HDL-C levels from baseline relative to placebo after 8 weeks ranged from 9.0–54.5% (P< 0.0001 for 30, 60, and 90 mg doses). Additionally, the mean LDL-C level decreased by as much as 16.5% (P< 0.01 for the 90 mg dose). In subjects treated with torcetrapib 10–90 mg/day with concomitant treatment with atorvastatin 20 mg/day, mean HDL-C levels increased by 8.3–40.2% (P< 0.0001 for 30, 60, and 90 mg doses) and mean LDL-C levels decreased by up to 18.9% (P< 0.01 for 60 and 90 mg doses) relative to baseline values following an atorvastatin run-in phase. Notably, torcetrapib treatment was associated with increases in LDL and LDL particle sizes, irrespective of the presence of background atorvastatin treatment.

Most recently, a phase II dose-ranging trial in 493 patients with LDL-C levels >3.33 mmol/L (130 mg/dL) showed that treatment with torcetrapib 60 mg/atorvastatin 10–80 mg (the doses selected for further clinical development) resulted in elevations in HDL-C levels of 44–66% (P< 0.0001) in conjunction with decreases in LDL-C levels of −41 to −60% (P< 0.0001). Treatment was generally well tolerated, however, dose-related, reversible increases in blood pressure were reported (4% subjects had greater than 15 mmHg increase), which will require further investigation in larger clinical trials.

Conclusions

A wealth of evidence suggests that elevated levels of HDL-C are beneficial in CVD, and low HDL-C levels are recognized as a significant cardiovascular risk factor. The activity of CETP is known to relate to HDL-C levels. However, the precise role of CETP in atherogenesis and CHD risk in humans is not yet fully understood, but is likely to be dependent on a combination of metabolic, genetic, and environmental factors.

Data from CETP-deficient subjects have suggested that therapeutic inhibition of CETP may be advantageous in raising HDL-C levels and that this may lead to reductions in CVD risk. Intriguingly, recent results from a study on the efflux capability of HDL particles from CETP-deficient subjects suggest that the large lipid-rich HDL-2 particles found in these individuals have increased potential to promote efflux via the ABCG1 receptor. This implies that the potential benefits from CETP inhibition may lie not only in the quantitative changes to HDL levels but also in qualitative changes that render the resultant particles more efficient at promoting cholesterol efflux.

Several compounds that inhibit CETP activity are now in clinical development and these have been shown to produce large increases in HDL-C and modest decreases in LDL-C. Although studies in rabbits have shown that CETP inhibition can protect from atherosclerotic progression, whether CETP inhibition in humans will mirror the effect seen in rabbit models remains to be seen.

The combined use of statins with CETP inhibitors has the potential to reduce the risk of CVD beyond the reductions achievable with statin therapy alone. However, further data are required to confirm this hypothesis and several clinical trials employing surrogate endpoints (such as coronary intravascular ultrasound and carotid intima-media thickness measurement) are underway. These trials, as well as future clinical endpoint trials, will help to answer some of the remaining questions surrounding the potential of CETP inhibitors to reduce cardiovascular risk and augment existing CVD treatments.

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