Rationale for cholesteryl ester transfer protein inhibition

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Abstract

Purpose of review—Raising HDL cholesterol (HDL-C) has become an attractive therapeutic target to lower cardiovascular risk in addition to statins. Inhibition of the cholesteryl ester transfer protein (CETP), which mediates the transfer of cholesteryl esters from HDL to apolipoprotein B-containing particles, leads to a substantial increase in HDL-C levels. Various CETP inhibitors are currently being evaluated in phase II and phase III clinical trials. However, the beneficial effect of CETP inhibition on cardiovascular outcome remains to be established.

Recent findings—Torcetrapib, the first CETP inhibitor tested in a phase III clinical trial (ILLUMINATE), failed in 2006 because of an increase in all-cause mortality and cardiovascular events that subsequently were attributed to nonclass-related off-target effects (particularly increased blood pressure and low serum potassium) related to the stimulation of aldosterone production. Anacetrapib, another potent CETP inhibitor, raises HDL-C levels by approximately 138% and decreases LDL cholesterol (LDL-C) levels by approximately 40%, without the adverse off-targets effects of torcetrapib (DEFINE study). The CETP modulator dalcetrapib raises HDL-C levels by approximately 30% (with only minimal effect on LDL-C levels) and proved safety in the dal-VESSEL and dal-PLAQUE trials involving a total of nearly 600 patients. Evacetrapib, a relatively new CETP inhibitor, exhibited favorable changes in the lipid profile in a phase II study.

Summary—The two ongoing outcome trials, dal-OUTCOMES (dalcetrapib) and REVEAL (anacetrapib), will provide more conclusive answers for the concept of reducing cardiovascular risk by raising HDL-C with CETP inhibition.

Keywords

atherosclerosis; cholesteryl ester transfer protein; inhibitor; lipid metabolism

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In a press release from May 7, 2012 Roche announced the stop of dal-OUTCOMES (the dalcetrapib clinical phase III trial) due to a lack of clinically meaningful efficacy in an interim analysis of the study. Roche has decided to terminate all studies in the dal-HEART program including dal-OUTCOMES, dal-OUTCOMES 2, dal-PLAQUE 2 and dal-ACUTE. The dal-PLAQUE and dal-VESSEL studies were completed already (Roche Inc., Roche provides update on Phase III study of dalcetrapib; media release).

Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The introduction of cholesterol-lowering statins over 20 years ago significantly reduced the morbidity and mortality of atherosclerosis, but intervention trials have consistently shown substantial residual cardiovascular risk [even after the reduction of LDL cholesterol (LDL-C) levels <70 mg/dl] [1]. The inverse relationship of HDL cholesterol (HDL-C) levels and the risk for coronary artery disease in epidemiological studies and preclinical data demonstrating the atheroprotective role of HDL have made it an attractive therapeutic target to provide additional benefit to statins in lowering the risk of cardiovascular disease [2]. HDL is a central component in reverse cholesterol transport, in which it transfers excess cholesterol from peripheral cells, including foam cell macrophages in the arterial wall, to the liver for intestinal excretion [3]. Furthermore, HDL exhibits anti-inflammatory, antithrombotic and antioxidant effects and improves endothelial function [4]. Currently available HDL-raising drugs comprise niacin, fibrates and PPAR-gamma agonists, and in some trials there has been risk reduction for these agents. Even in these, attributing the benefits to HDL elevation has been problematic because of the multiple metabolic effects of each drug.

Other HDL-targeted agents in preclinical and clinical studies include purified apoA-I, apoA-I mimetic peptides, liver X receptor (LXR) agonists, antimiR33 and cholesteryl ester transfer protein (CETP) inhibitors [2,5]. In this review, we will discuss currently tested CETP inhibitors and modulators and their progress in clinical trials.

CHOLESTERYL ESTER TRANSFER PROTEIN INHIBITORS

CETP is synthesized in the human liver and the adipose tissue, and secreted into the circulation. CETP mediates the transfer of cholesteryl ester from HDL to apolipoprotein B (apoB)-containing lipoproteins (mainly VLDL and LDL) in exchange for triglycerides (heterotypic transfer). Subsequently, the apoB-containing lipoproteins deliver the cholesterol to the liver by binding to the hepatic LDL receptor (indirect pathway of the reverse cholesterol transport) [6,7]. Structural imaging of the interaction of CETP with HDL and LDL suggests that CETP forms a tunnel to transfer the cholesterol from donor to acceptor lipoproteins [8■■]. CETP also mediates the transfer of cholesteryl ester between HDL subtypes (homotypic transfer) generating large HDL_2 particles and lipid-free apoA-I (preβ HDL) from HDL_3 particles [9]. CETP inhibitors such as torcetrapib and anacetrapib inhibit the homotypic and heterotypic transfer, whereas dalcetrapib selectively inhibits the heterotypic transfer without affecting the homotypic transfer [7].

Individuals with a deficiency of CETP activity due to genetic mutations have substantially increased HDL-C levels [10]. However, results from association studies of genetic CETP deficiency and cardiovascular risk, though tending to support protection, have not been conclusive [10]. More definite answers on the effect of CETP inhibition are expected from the two ongoing outcome trials dal-OUTCOMES (dalcetrapib) and REVEAL (anacetrapib) involving a total of around 45 000 patients [11].

TORCETRAPIB

Torcetrapib (Pfizer, New York, NY, USA), the first CETP inhibitor tested in a phase III study [Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE); www.clinicaltrials.gov identifier NCT00134264], exhibited a remarkable increase in HDL-C (72.1%) and reduction in LDL-C (24.9%) levels. Despite these favorable changes in the lipid profile, the all-cause mortality (specifically cancer and infection related) and major cardiac events were significantly higher in the torcetrapib compared with the placebo group, leading to the premature termination of ILLUMINATE in

December 2006. The torcetrapib group had a mean increase of systolic blood pressure of 5mmHg, increase in serum aldosterone, reduction of serum potassium and an increase in serum bicarbonate and sodium levels [12]. The results of the ILLUMINATE study challenged the concept of reducing cardiovascular risk by raising HDL with CETP inhibition. The underlying mechanisms for the adverse effects of torcetrapib are still not completely determined. However, subsequent studies indicated that the observed off-target effects are unrelated to CETP inhibition and are rather molecule specific [13,14]. Another argument against a class-related toxicity is that CETP inhibitors such as anacetrapib, evacetrapib or CETP modulator dalcetrapib do not exhibit these adverse effects [11,15■]. Furthermore, individuals with genetic variants of CETP do not show hypertension [16]. There is also evidence for beneficial effects of torcetrapib: the post hoc analysis of ILLUMINATE found that cardiovascular events were lower in the torcetrapib-treated group with higher increase in HDL-C and apoA-I [12]. The functionality of HDL particles was shown to be normal or even enhanced: the cholesterol efflux from human macrophages was found to be normal with the treatment of 60mg torcetrapib daily (same dose as used in ILLUMINATE) or even increased with 120mg torcetrapib daily *in vitro* [17]. Another indication of potential benefit was a post hoc analysis of the ILLUSTRATE study showing regression of coronary atheroma [assessed by intravascular ultrasound (IVUS)] in patients with HDL-C levels in the upper quartile after treatment with torcetrapib [18].

ANACETRAPIB

Anacetrapib (Merck, Whitehouse Station, NJ, USA) is a potent CETP inhibitor that induces a substantial increase of HDL-C and reduction of LDL-C plasma levels. HDL particles isolated from anacetrapib-treated patients exhibited an increased cholesterol efflux capacity from macrophages and an increased ability to reduce the inflammatory response to macrophage toll-like receptor 4 *in vitro* [19]. The efficacy and safety of anacetrapib was evaluated in the Determining the EFficacy and tolerability of CETP INhibition with anacEtrapib (DEFINE) study (www.clinicaltrials.gov, identifier NCT00685776). A total of 1623 patients with coronary heart disease (CHD) or at high risk for CHD and LDL-C levels of 50–100 mg/dl on statin treatment were randomized to either anacetrapib (100mg daily) versus placebo for 18 months. In addition to the statin effect, anacetrapib led to a 39.8% decrease in LDL-C from baseline beyond that seen with placebo at 24 weeks, resulting in average LDL-C levels of 45mg/dl. HDL-C levels rose by 138.1% compared to placebo from an average of 41mg/dl at baseline to 101 mg/dl after 24 weeks of treatment. Anacetrapib was well tolerated and did not exhibit adverse cardiovascular effects as seen with torcetrapib. Through 76 weeks, no significant changes were noted in blood pressure, electrolytes or serum aldosterone with anacetrapib treatment compared to placebo. Noteworthy, there were no significant changes in C-reactive protein (CRP) levels despite raising HDL by 138% with anacetrapib [20], similar to the findings from the dal-VESSEL trial [21■■].

Randomized EValuation of the Effects of Anacetrapib through Lipid-modification (REVEAL) (www.clinicaltrials.gov identifier NCT01252953) is the large clinical phase III outcome trial for anacetrapib involving approximately 30 000 patients with established atherosclerotic vascular disease in North America, Europe and Asia. The aim of the study is to evaluate whether lipid modifications with anacetrapib reduce the risk of coronary death, myocardial infarctionor coronary revascularization over a follow-up of 4 years. The patients are randomized to either anacetrapib (100 mg/daily) versus placebo on top of a standard therapy. In addition to established cardiovascular disease, the patients need to be likely to achieve total cholesterol levels less than 135mg/dl on statin treatment to be eligible for the study. The study was initiated in 2011 and the completion is expected to be in January 2017.

DALCETRAPIB

Unlike torcetrapib and anacetrapib, dalcetrapib (Roche, Pleasanton, CA, USA) does not inhibit the homotypic intra-HDL transfer of cholesteryl ester from smaller HDL_3 to larger HDL_2 and is therefore termed by Roche as a modulator of CETP activity rather than an inhibitor. This HDL remodeling process is important for the formation of preβ HDL particles, which are the preferred acceptors of ATP-binding cassette transporter 1 (ABCA-1)-mediated cholesterol efflux in the reverse cholesterol transport [7].

The Dalcetrapib HDL Evaluation, Atherosclerosis and Reverse cholesterol Transport (dal-HEART) Program includes a series of clinical phase II and III trials to evaluate the efficacy and safety of dalcetrapib in humans. The dal-VESSEL (www.clinicaltrials.gov, identifier NCT00658515) study established the safety and the vascular effect of dalcetrapib in patients with or at risk of CHD. A total of 466 patients with low HDL-C levels were randomized to dalcetrapib (600mg daily) versus placebo over a period of 36 weeks. Dalcetrapib inhibited CETP activity by a mean of 56%, accompanied by a 31% increase in HDL-C [21▪▪]. There were no differences in the outcome measures – flow-mediated dilatation (FMD) (as a parameter for endothelial function) and blood pressure – between the dalcetrapib and the placebo group. HDL has been shown to improve endothelial function by activating the L-arginine/nitric oxide pathway [22]. The lack of improvement of FMD after raising HDL with dalcetrapib might be because of the relatively moderate extent of the HDL increase (approximately 30%). Furthermore, the majority of patients in dal-VESSEL were already treated with an angiotensin receptor blocker, angiotensin-converting enzyme inhibitor and statin, agents that have been shown to improve FMD [23]. There were no significant changes in the levels of inflammatory and oxidative stress markers, such as high-sensitive CRP, interleukin-6 (IL-6) and myeloperoxidase (MPO) between the groups, similar to the findings with CRP in the DEFINE trial [20]. However, dal-VESSEL proved the safety of dalcetrapib and confirmed that hypertension is not related to CETP inhibition itself.

The phase II study dal-PLAQUE (www.clinicaltrials.gov identifier NCT00655473) evaluated the efficacy and safety of dalcetrapib in atherosclerosis by using a dual-imaging approach of MRI (for the assessment of morphological changes of the vessel wall) and PET-CT (for the assessment of vascular inflammation). A total of 130 statin-treated patients with or at high risk for coronary artery disease were randomized to either dalcetrapib (600mg daily) or placebo treatment for 24 months. Over the treatment period, levels of HDL-C increased by 31% and those of apoA-I by 10% compared to baseline. Both imaging techniques did not show evidence of a pathological effect of dalcetrapib on the arterial wall. There was a significantly lower increase in carotid total vessel area in the dalcetrapib-treated group versus placebo at 24 months, suggesting a beneficial vascular effect of dalcetrapib. There were no significant changes in blood pressure after 24 months with dalcetrapib and fewer cardiovascular events in the dalcetrapib versus the placebo group (2 versus 7 events, respectively) [24▪].

The dal-PLAQUE-2 (www.clinicaltrials.gov identifier NCT01059682) is a phase III study on the effect of dalcetrapib (600mg daily) versus placebo on atherosclerotic disease progression in 900 patients with proven coronary artery disease over a 24-month treatment period. Progression of atherosclerosis is being determined using IVUS and quantitative coronary arteries angiography for the coronary arteries, and by the measurement of the intima-media thickness (IMT) by ultrasound in the carotid arteries.

dal-OUTCOMES [25] (www.clinicaltrials.gov, identifier NCT00658515) is the large phase III outcome study involving approximately 16 000 patients that evaluates the effect of CETP modulation with dalcetrapib on cardiovascular morbidity and mortality in patients with

recent acute coronary syndrome (ACS). Four to 12 weeks after an acute coronary event, patients are randomized to dalcetrapib (600mg daily) or placebo in addition to standard therapy. The expected treatment period is (at least) 2 years. The primary outcome measure is the time to first occurrence of any component of the composite cardiovascular event (coronary artery disease death, nonfatal myocardial infarction, unstable angina requiring hospital admission, resuscitated cardiac arrest or atherothrombotic stroke). There are no exclusions based on the baseline levels of LDL-C or HDL-C, but on treatment with HDL-raising agents such as niacin, fibrates or bile acid sequestrants.

Similar to dal-OUTCOMES, the phase III study dal-ACUTE (www.clinicaltrials.gov identifier NCT01323153) evaluates the effect of dalcetrapib (600mg daily) versus placebo in approximately 300 patients with ACS. In contrast to dal-OUTCOMES with randomization of patients beginning 4–12 weeks after an acute event, patients in dal-ACUTE are randomized only 1 week after the ACS. The study completion is expected to be in October 2012.

EVACETRAPIB

Evacetrapib (Eli Lilly, Indianapolis, IN, USA), a relatively new CETP inhibitor, was evaluated in a phase II study (www.clinicaltrials.gov identifier NCT01105975) involving almost 400 patients with elevated LDL-C or low HDL-C. The patients were randomized to one of 10 treatment groups: placebo; evacetrapib monotherapy 30mg daily, 100mg daily, or 500mg daily; or statin therapy (simvastatin 40mg daily, atorvastatin 20mg daily, or rosuvastatin 10mg daily) with or without evacetrapib 100mg daily over a treatment period of 12 weeks. CETP activity was inhibited with evacetrapib dose dependently up to 90%. Evacetrapib monotherapy led to a dose-dependent increase in HDL-C by 54–129% and decrease of LDL-C by 14–36% compared to placebo. In combination with statins, evacetrapib (100 mg daily) raised the HDL-C levels comparable to evacetrapib monotherapy, but led to an additional decrease of LDL-C by 11–14% compared to the treatment with statins alone. There were no significant differences in blood pressure, aldosterone, cortisol and electrolyte levels with evacetrapib monotherapy compared to placebo [15▪], although these safety data need to be confirmed in larger clinical trials with higher patient numbers and a long-term follow-up. Furthermore, the dose dependency of the CETP inhibition by evacetrapib could be used to evaluate the association of the degree of CETP inhibition and cardiovascular risk reduction.

CONCLUSION

On the basis of primarily epidemiological and preclinical studies, raising HDL-C by CETP inhibition and modulation appears to be an attractive therapeutic approach to provide additional benefit to statins in the reduction of cardiovascular risk. The results from the various outcome studies to establish CETP inhibition clinically are, therefore, highly anticipated. While waiting for these results, and even beyond them, some issues to consider include the relationship between the degree of CETP inhibition and cardiovascular risk reduction; whether the benefits are more pronounced in patients with low HDL-C levels, or will those with normal or high starting levels also benefit?; the impact of concomitant metabolic conditions for the effect of CETP inhibition on cardiovascular risk, given, for example, that in genetic studies the protection of a CETP mutation was attenuated in those with high triglycerides [26]; the composition and functionality of HDL particles derived from CETP inhibition in the reverse cholesterol transport and the impact of restored HDL remodeling with CETP activity modulation. Also, it should be kept in mind that for anacetrapib, the large decrease in LDL cholesterol with monotherapy may make it difficult to attribute reduced risk to the HDL-raising effect. This would seem to make the dalcetrapib

studies easier to interpret from a purely HDL standpoint, but if it fails to show an effect in the outcome studies, this could be not because the concept was a failure, but that the HDL elevation was not high enough.

In summary, the rationale for raising HDL to reduce cardiovascular risk is strongly based on epidemiological and animal studies, with some clinical support coming from HDL-infusion trials. Whether CETP inhibition, which certainly raises HDL, will translate to reduced cardiovascular risk remains to be seen, however. In favor of this approach are some human genetic studies, limited subanalyses of the ILLUMINATE trial, in-vitro experiments on the function of HDL isolated from individuals treated with CETP inhibitors and a recent imaging trial. The substantial residual risk with even aggressive statin treatment has driven interest in the CETP inhibitor outcome trials to an understandably high level, and we join our colleagues in hoping for a new and potent clinical weapon.

Acknowledgments

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪▪of special interest

▪▪of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 391).

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KEY POINTS

- HDL is an attractive therapeutic target because of its central role in reverse cholesterol transport and its anti-inflammatory, antioxidant and antithrombotic properties.

- CETP inhibitors and modulators substantially increase HDL-C levels, but the benefit on cardiovascular outcome remains to be conclusively confirmed.

- The adverse off-target effects of torcetrapib have not been found in phase II and III clinical trials for the CETP inhibitors anacetrapib and evacetrapib or CETP modulator dalcetrapib.