Cholesteryl Ester Transfer Protein Inhibition Reduces Cardiovascular Events

Subjects: Cardiac & Cardiovascular Systems

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Cholesteryl ester transfer protein (CETP) is a glycoprotein synthesized in the liver that is present in all primates (including humans), rabbits and hamsters. The CETP molecule has a boomerang shape, with a tunnel that forms between spaces at each end for binding cholesteryl esters and triglycerides (TG). It is responsible for the exchange of TG from very low-density lipoprotein (VLDL) particles with cholesteryl esters from high-density lipoprotein (HDL) particles and low-density lipoprotein (LDL) particles. The net effect of this exchange is to enrich VLDL and LDL particles with cholesteryl esters and deplete them of TG while simultaneously enriching HDL particles with TG and depleting them of cholesteryl esters.

Keywords: cholesteryl ester transfer protein ; obicetrapib ; apoB

1. Introduction

Epidemiological evidence that elevated HDL cholesterol (HDL-C) is inversely associated with atherosclerotic cardiovascular disease (ASCVD) [1][2][3][4][5], combined with the discovery of mutations in the *CETP* gene that are associated with increased HDL-C and reduced LDL cholesterol (LDL-C) concentrations [6][7], launched interest in the development of agents to pharmacologically inhibit CETP. CETP inhibitors reduce the rate of transfer of cholesteryl ester from HDL into TG-rich lipoproteins. This leads to the formation of larger, cholesteryl ester-enriched HDL particles that are slowly catabolized, and, as a consequence, depletion of cholesterol in the TG-rich and apolipoprotein (apo) B-containing lipoproteins, i.e., VLDL, LDL, intermediate density lipoproteins (IDL), chylomicrons, and their remnants [8].

To date, no CETP inhibitor has ever achieved marketing authorization. The first CETP inhibitors were primarily developed to increase HDL-C, which at the time was believed to be a pathway for ASCVD risk reduction [1][2][3][4][5]. However, randomized controlled trials (RCTs) of agents that primarily raise HDL-C have not shown HDL-C as a causative factor in the reduction of the risk of ASCVD [9]. This includes the cardiovascular outcome trials of the first CETP inhibitors, torcetrapib, dalcetrapib (CETP modulator/functional CETP inhibitor), and evacetrapib, which all failed to reduce ASCVD risk for a variety of agent-specific reasons [10][11][12]. However, the Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) trial demonstrated a significant reduction in major coronary events with anacetrapib, a potent CETP inhibitor that not only raised HDL-C, but also lowered LDL-C by 17% and apoB by 18%, relative to placebo [13][14]. The absolute LDL-C difference between the anacetrapib and placebo arms amounted to 11 mg/dL (0.28 mmol/L) which places the REVEAL primary endpoint exactly on the Cholesterol Treatment Trialists' meta-regression line for non-HDL-C and major adverse cardiovascular events (MACE) [15]. The causality of LDL-C and VLDL-C with increased ASCVD risk is supported by a large body of evidence from observational investigations, RCTs, and Mendelian randomization studies, but the relationship loses significance when apoB is accounted for, supporting the view that it is the number of circulating apoB-containing lipoprotein particles that drives risk [16][17][18][19][20].

2. Obicetrapib—The Newest Cholesteryl Ester Transfer Protein Inhibitor

Obicetrapib (also known as TA-8995) is a new selective CETP inhibitor designed specifically to reduce LDL-C and apoB [21][22][23]. It is the most polar of all CETP inhibitors, and its biochemical structure is suggested to have improved binding and specificity [23][24]. It has been shown to inhibit the activity of CETP by up to 97% [23]. Obicetrapib was shown to have a mean terminal half-life at steady-state of ~130–150 h after 5 and 10 mg repeated daily dosing [23]. The CETP Inhibition by Obicetrapib in Patients with Mild Dyslipidemia (TULIP) phase 2 trial evaluated obicetrapib at several doses alone and in combination with moderate-intensity statins in 364 participants with mild dyslipidemia (LDL-C > 2.5 mmol/L [96.7 mg/dL] and <4.5 mmol/L [173 mg/dL], HDL-C < 1.8 mmol/L [69.6 mg/dL] and >0.8 mmol/L [30.9 mg/dL], and TG < 4.5 mmol/L [399 mg/dL]) [22]. Subjects received placebo or obicetrapib at doses of 1, 2.5, 5, or 10 mg alone and obicetrapib 10 mg

with atorvastatin 20 mg or rosuvastatin 10 mg once daily for 12 weeks [22]. LDL-C measured by beta-quantification was significantly reduced by 27.4%, 32.7%, 45.3%, and 45.3% with the 1, 2.5, 5, and 10 mg obicetrapib doses, respectively, and by 68.2% and 63.8% with obicetrapib plus atorvastatin and plus rosuvastatin, respectively. Similarly, apoB was significantly reduced by 20.0%, 24.6%, 33.6%, and 33.7% with the 1, 2.5, 5, and 10 mg obicetrapib doses, respectively, and by 50.1% and 46.3% with obicetrapib plus atorvastatin and plus rosuvastatin, respectively. Obicetrapib also significantly reduced non-HDL-C and lipoprotein(a) and increased HDL-C. In contrast to anacetrapib, obicetrapib is more hydrophilic and was undetectable in plasma within 120 h after discontinuation of dosing.

The Randomized Study of Obicetrapib as an Adjunct to Statin Therapy (ROSE) administered obicetrapib 5 mg and 10 mg once daily compared with placebo as an adjunct to high-intensity statin therapy (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) for an 8-week treatment period to 120 subjects with LDL-C > 70 mg/dL (1.81 mmol/L) and TG < 400 mg/dL (4.52 mmol/L) [21]. In ROSE, the primary LDL-C analysis was performed using the Friedewald formula to calculate LDL-C, which demonstrated median LDL-C reductions from baseline of 42.9% and 45.7% for the obicetrapib 5 mg and 10 mg groups, respectively, compared with 0.0% for placebo. LDL-C results using beta-quantification were comparable to those from Friedewald, −41.5% and −50.8% for 5 mg and 10 mg obicetrapib, respectively, compared with −6.50% with placebo. ApoB was significantly reduced by 24.4% and 29.8%, non-HDL-C by 38.9% and 44.4%, and lipoprotein(a) by 33.8% and 56.5%, respectively, and HDL-C was increased by 135% and 165% and apoA1 by 44.6% and 47.8%, respectively, for 5 mg and 10 mg obicetrapib ($p < 0.0001$ compared with placebo). To date, obicetrapib has consistently been shown to be safe and well tolerated at all doses alone and in combination with statins [21][22][23]. The PREVAIL cardiovascular outcome trial is administering 10 mg obicetrapib vs. placebo to 9000 participants with ASCVD and LDL-C ≥ 70 mg/dL (1.80 mmol/L) and TG < 400 mg/dL (4.52 mmol/L), despite taking maximal tolerated lipid-lowering therapy [25]. Because obicetrapib reduced LDL-C and apoB in ROSE by approximately three times the level shown for anacetrapib in REVEAL, it could potentially result in a greater reduction in ASCVD risk.

3. Modulation of ApoB as the Basis for Cholesteryl Ester Transfer Protein Inhibitor Reduction of Cardiovascular Events

As described previously, CETP inhibition reduces the rate of transfer of cholesteryl ester from HDL into TG-rich lipoproteins, thereby increasing the overall cholesterol content in HDL and the formation of larger HDL particles that are more slowly catabolized, while also depleting the cholesterol content of the apoB lipoproteins, including VLDL, LDL, chylomicrons and their remnants [8]. CETP inhibitors also improve cholesterol efflux capacity, the first step in reverse cholesterol transport [12][22][26], and reduce lipoprotein(a) [21][22][27]. During the initial development of CETP inhibitors, their action on HDL-C was the primary focus. However, the focus of CETP inhibitors has now shifted to their ability to reduce LDL-C and apoB [28]. An examination of apoB kinetics in 19 subjects with dyslipidemia who received 120 mg torcetrapib with or without atorvastatin for 4 weeks demonstrated that torcetrapib reduced VLDL, IDL, LDL and apo B levels primarily by increasing the rate of apoB100 clearance, whereas, when added to atorvastatin, torcetrapib reduced apoB levels mainly by enhancing VLDL apoB100 clearance and reducing production of IDL and LDL apoB100 [29]. A study of apoB kinetics in 39 mildly hypercholesterolemic subjects who received 100 mg anacetrapib added to their background treatment of atorvastatin for 8 weeks demonstrated that anacetrapib reduced LDL-C levels by increasing the LDL-apoB100 fractional clearance, both when anacetrapib was given alone or on background statin treatment [30]. This suggests a common mechanism of action of anacetrapib and statins to enhance LDL-apoB clearance, thereby reducing the total number of LDL particles as well as LDL-C and apoB concentrations [8][30].

There is universal agreement, supported by prospective observational investigations, RCTs, and Mendelian randomization studies that LDL-C, non-HDL-C, and apoB are causal factors for ASCVD [16][31]. In conventional statistical tests, the three markers are treated as independent variables. However, they are not metabolically and biologically independent. On the contrary, they are metabolically and biologically tightly related, thereby underpinning their statistical correlations. However, they are not identical because the mass of cholesterol within apoB particles is variable. When apoB particles contain more cholesterol than average, LDL-C and non-HDL-C overestimate the number of apoB particles, whereas, when apoB particles contain less cholesterol than average, LDL-C and non-HDL-C underestimate the number of apoB particles. Because there is one molecule of apoB per apoB particle, plasma apoB equals the total number of atherogenic particles in plasma, the great majority of which, generally 90% or more, are LDL particles.

LDL-C remains the most common lipid measure in clinical care, notwithstanding all the evidence that both non-HDL-C and apoB are more accurate markers of cardiovascular risk and acknowledged to be so by the major European and American Guidelines [19][20]. Their superiority over LDL-C is axiomatic since both incorporate VLDL as well as LDL and both VLDL and LDL particles are atherogenic. The real contest is between non-HDL-C and apoB. Multiple, well-conducted, prospective observational studies and randomized clinical trials have shown non-HDL-C and apoB to have similar

predictive power, while many have shown apoB is superior to non-HDL-C [32]. One meta-analysis of randomized clinical trials showed non-HDL-C to be statistically, but not clinically, superior to apoB [33] whereas another showed that apoB was superior to non-HDL-C [34]. This mixed picture of results reflects the fact that the conventional statistical methods were not designed to compare highly correlated variables such as non-HDL-C and apoB.

Discordance analysis was created to overcome this limitation [35]. Because the cholesterol content of apoB particles is variable, discordant groups can be created in which the non-HDL-C/apoB ratio is either high or low. In both cases, non-HDL-C and apoB will make opposite predictions about risk. Discordance analyses in the Framingham Heart Study [36], INTERHEART [37], the Women's Health Study [38] and UK Biobank [39] have all shown that apoB, not HDL-C, correctly predicts cardiovascular risk when the two markers are discordant. Similarly, discordance analysis in the Coronary Artery Risk Development in Young Adults (CARDIA) study has shown apoB correctly predicts the risk of coronary artery calcification whereas non-HDL-C does not [40]. Moreover, Johannesen et al. in a discordance analysis of subjects on statin therapy demonstrated that apoB was superior to non-HDL-C as a marker of cardiovascular risk overall and cardiovascular mortality specifically [41].

The uniform outcome in favor of apoB in discordance analyses establishes, therefore, that when LDL-C or non-HDL-C differ in prediction of cardiovascular risk from apoB, apoB is right and LDL-C or non-HDL-C is wrong. Moreover, clinically significant discordance is common. Framingham [36], INTERHEART [37], and the Women's Health Study [38] all demonstrated that significant discordance between LDL-C and apoB and between non-HDL-C and apoB is present in up to two-thirds of the population. In individuals with significant discordance, apoB and the cholesterol markers will make different predictions as to risk even if the HRs for the whole population are the same [42]. This follows because a HR is the increase in risk per standard deviation increase in the risk of the marker. Thus, if the level of apoB in an individual, relative to the population, is higher than the level of LDL-C or non-HDL-C, the hazard predicted in this patient will be higher than the hazard predicted by LDL-C or non-HDL-C, even if the HRs calculated for the population are the same. Thus, even in the studies in which the overall HRs for non-HDL-C, LDL-C and apoB were the same, such as the Emerging Risk Factor Collaboration [5], apoB will offer significant advantages to a substantial number of subjects.

Strong evidence in favor of apoB is now available from multiple Mendelian randomization analyses. A de novo genome-wide association study was conducted to examine lipid-related traits (apoB, LDL-C, TG, HDL-C, and apoA1) associated with risk of CHD using data from the UK Biobank (~440,000 participants) followed by Mendelian randomization analysis using data from the CARDIoGRAMplusC4D consortium with over 60,000 cases of CHD [43]. Mendelian randomization indicated that LDL-C, TG, and apoB were associated with increased risk of CHD, and that HDL-C and apoA1 were associated with decreased CHD risk. However, in multivariable Mendelian randomization, only apoB was robustly related to increased CHD risk (odds ratio 1.92; 95% CI 1.31–2.81), whereas the relationships for each of the other lipid-related traits when included with apoB in the model were either attenuated to the null or changed direction. The primacy of apoB as a risk determinant for ASCVD was confirmed in another Mendelian randomization analysis, which also demonstrated that apoB was the most significant lipid-related causal factor for peripheral arterial disease [44].

Recently, a prospective cohort analysis of data from the UK Biobank and from two large clinical trials, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and IMPROVE-IT, was undertaken to examine whether the cholesterol content or the TG content of lipoproteins is associated with ASCVD risk beyond the number of apoB-containing lipoproteins [45]. Among nearly 400,000 primary prevention individuals and over 40,000 patients with established ASCVD, apoB, non-HDL-C, and TG were each individually shown to be associated with incident myocardial infarction, but, when assessed together, only apoB was significantly associated with increased risk (HR per 1 standard deviation 1.27; 95% CI 1.15–1.40; $p < 0.001$ for the primary prevention analysis). Finally, apoB has now been shown to be a more accurate marker of atherosclerotic cerebrovascular disease than non-HDL-C or LDL-C [46]. None of this contradicts the masses of evidence linking LDL-C and non-HDL-C to the risk of cardiovascular disease. ApoB is simply a more complete measure of the cardiovascular risk associated with the apoB lipoproteins than LDL-C and non-HDL-C.

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Nat. Med. 2022; in press.

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