

Effect of serial infusions of reconstituted high-density lipoprotein (CER-001) on coronary atherosclerosis: rationale and design of the CARAT study

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Background: High-density lipoprotein (HDL) is believed to have atheroprotective properties, but an effective HDL-based therapy remains elusive. Early studies have suggested that infusion of reconstituted HDL promotes reverse cholesterol transport and vascular reactivity. The CER-001 Atherosclerosis Regression Acute Coronary Syndrome Trial (CARAT) is investigating the impact of infusing an engineered pre-beta HDL mimetic containing sphingomyelin (SM) and dipalmitoyl phosphatidylglycerol (CER-001) on coronary atheroma volume in patients with a recent acute coronary syndrome (ACS).

Methods: The CARAT is a phase 2, multicenter trial in which 292 patients with an ACS undergoing intracoronary ultrasonography and showing percent atheroma volume (PAV) greater than 30% are randomly assigned to treatment with ten infusions of CER-001 3 mg/kg or matching placebo, administered at weekly intervals. Intracoronary ultrasonography is repeated at the end of the treatment period.

Results: The primary endpoint is the nominal change in PAV. Safety and tolerability will also be evaluated.

Conclusions: CARAT will establish whether serial 3 mg/kg infusions of an engineered pre-beta HDL mimetic containing SM and dipalmitoyl phosphatidylglycerol (CER-001) will regress atherosclerotic plaque in patients with a recent ACS.

Keywords: Atherosclerosis; high-density lipoproteins (HDLs); CER-001; intravascular ultrasound; clinical trial

Submitted Jun 05, 2016. Accepted for publication Oct 20, 2016.

doi: 10.21037/cdt.2017.01.01

View this article at: <http://dx.doi.org/10.21037/cdt.2017.01.01>

Introduction

For more than a quarter century, lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins has formed a foundation for risk reduction strategies in patients

with established coronary heart disease. However, residual risk of patients with acute coronary syndrome (ACS) remains high despite effective statin treatment (1), and some of this residual risk may be modifiable by additional

lipoprotein interventions (2).

High-density lipoprotein (HDL) as a target and experience with new therapies

Population studies consistently demonstrate an inverse, curvilinear relationship between HDL-C levels and cardiovascular risk, regardless of atherogenic lipid levels (3,4), while patients suffering from HDL deficiency resulting from genetic defects in gene coding for proteins involved in HDL synthesis or maturation present an increased risk for cardiovascular disease (5). In addition, meta-analyses of trials of statins indicate that an inverse association of HDL-C concentration with cardiovascular risk persists among patients treated with statins (4,6,7), although there are some exceptions to these observations (8,9). Favorable effects of HDL have been attributed to its role in lipid transport and to beneficial effects on inflammatory, oxidative, apoptotic and thrombotic pathways implicated in atherosclerosis (10). Intervention studies in animal models have demonstrated that direct infusion of HDL-like particle or transgenic expression of its major proteins has a favorable impact on the extent and histologic phenotype of experimental atherosclerosis (11-13). Small studies in human have indicated favorable effects of HDL-like particle infusion on endothelial function and atherosclerosis (14-17).

Orally bioavailable drugs that increase HDL-C concentration, including niacin, fibrates, and cholesteryl ester transfer protein (CETP) inhibitors have not been found to provide clinical benefit when added to statins (18-23). At least to date, these findings suggest that raising HDL-C may not be sufficient to further reduce cardiovascular risk in statin-treated patients. In contrast, favorable effects of infusing delipidated forms of HDL on lipid transporting factors, endothelial function and atherosclerotic plaque volume (14-17) suggest that administering an engineered HDL particle, as opposed to indirectly altering its production or remodelling, might provide a more effective therapeutic approach. This would be consistent with recent reports that increasing the number of HDL particles, as opposed to HDL-C, may be more relevant to reducing cardiovascular risk (24).

Emergence of plaque imaging to evaluate anti-atherosclerotic drugs

Advances in arterial wall imaging have extended the ability to visualize the extent and progression of atherosclerosis,

in addition to the dimensions of the arterial lumen. In particular, serial application of intraarterial ultrasonography has evolved to assess the impact of medical therapies on disease progression (16,25-36). Serial IVUS imaging within an epicardial coronary artery enables precise quantitation of the volumetric burden of atherosclerotic plaque within an anatomically matched coronary segment, defined by the location of fiducial side branches, after treatment. Using this approach, studies have demonstrated the benefits of LDL-C lowering with statins (26-28) and antihypertensive agents (29) in CAD patients and use of pioglitazone in patients with type 2 diabetes and CAD (30). Subsequent analyses revealed that HDL-C raising contributes to the benefits of statins (37) and pioglitazone (38) and identified patients who were more likely to have atherosclerosis regression under treatment with the CETP inhibitor, torcetrapib (39). The clinical relevance of these findings is supported by observations that plaque burden at baseline and its progression on serial imaging both associate with cardiovascular events (40,41).

Experience with HDL infusions and imaging

Several studies have utilized IVUS to determine a potential benefit of engineered HDL mimetics of different compositions. In a study of 57 patients with an ACS, weekly intravenous infusions of saline or reconstituted HDL containing palmitoyl-oleyl phosphatidylcholine and apolipoprotein A-I Milano dimer (ETC-216) at a concentration of 15 or 45 mg/kg for 5 weeks was evaluated. Coronary IVUS imaging was performed at baseline and 2 weeks following the final infusion. Administration of both doses of ETC-216 was associated with regression of coronary atherosclerosis compared to baseline. In fact, there was no greater regression at the higher dose, suggesting a potential for relative saturation of lipid mobilization (16). Subsequent analyses revealed the greatest degree of regression at sites containing the largest amount of atheroma at baseline and that regression was accompanied by reverse remodeling of the artery wall (42).

The Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) study aimed to determine the effect of infusing HDL particles that contained wild-type apoA-I (CSL-111) and soy bean lecithin in 183 patients who received weekly infusions of either saline or CSL-111 at a dose of 40 or 80 mg/kg. The higher dose was terminated due to unacceptably high rates of liver enzyme elevation. Significant reductions in plaque burden compared with

baseline were observed in the CSL-111 treated patients, although a placebo-controlled comparison failed to meet statistical significance. The investigators also reported favorable effects of infusing CSL-111 on surrogate ultrasonic measures of plaque composition and quantitative coronary angiography (36).

An alternative approach to administration of HDL involves the infusion of autologous HDL after it has undergone selective delipidation. An early, proof-of-concept study in 28 patients with an ACS demonstrated a non-significant trend towards greater regression with seven autologous delipidated HDL infusions compared with placebo (43). The findings of these studies suggested that it was the infusion of lipid-deplete forms of HDL, as opposed to the specific protein, that appeared to exert a favorable effect on the artery wall. These programs continue to undergo clinical development.

CER-001

CER-001 is an engineered negatively-charged lipoprotein particle mimicking pre-beta HDL containing recombinant human apoA-I and the natural phospholipids, sphingomyelin (SM) and dipalmitoyl phosphatidylglycerol (DPPG) in a molar ratio of 32.3:1, and with a protein:phospholipid weight ratio of 1:2.7. The particles are synthesized with the same negative charge as observed with natural pre-beta HDL particles. In this respect, CER-001 is quite distinct from other reconstituted HDL particles undergoing clinical development. The presence of a negative charge added to the SM prevents fusion between particles and promotes more rapid and sustained cholesterol and lipids mobilization. Animal studies using both LDL receptor knockout mice and carotid flow cessation in apoE knockout mice demonstrated a reduction in arterial wall cholesterol content with CER-001 infusions (44,45). Phase 1 studies in healthy volunteers demonstrated that CER-001 promoted increases in cholesterol content of circulating HDL particles, consistent with lipid mobilization, at doses as low as 3 mg/kg (46).

A number of studies were subsequently performed to evaluate the impact of infusing CER-001 on atherosclerotic plaque in humans. A small open-label study of infusing CER-001 8 mg/kg in patients with familial hypoalphalipoproteinemia demonstrated an increase in cellular cholesterol efflux and cholesterol content of circulating HDL and reductions in both magnetic resonance imaging derived measures of aortic and carotid

plaque burden and positron emission tomography detected fluorodeoxyglucose signalling as a measure of plaque inflammatory activity (47). Similarly, a small open-label study evaluating the effect of infusing CER-001 8 mg/kg in patients with homozygous familial hypercholesterolemia demonstrated similar reductions in aortic and carotid plaque burden on magnetic resonance imaging (48).

The Can HDL Infusions Significantly Quicken Atherosclerosis Regression (CHI-SQUARE) study evaluated the effect of infusing CER-001 at a dose of 3, 6 or 12 mg/kg or placebo weekly on six occasions in 507 patients with an ACS. The primary analysis of the study demonstrated that the primary endpoint, total atheroma volume, decreased by 3.13, 1.50 and 3.05 mm³ in the 3, 6, and 12 mg/kg groups of CER-001 respectively, compared with 2.85 mm³ with placebo, failing to meet statistical significance. However, a subsequent blinded analysis by a different core laboratory focusing on anatomically matched arterial segments in patients with suitable image quality demonstrated disease regression with the 3 mg/kg dose. In intention to treat analysis, total atheroma volume declined by -4.76 mm³, compared with -2.85 mm³ with placebo. There was a trend towards diminishing regression with increasing CER-001 dose. Per protocol analysis supported these findings, with significantly greater plaque regression (-6.28 *vs.* -3.63 mm³ with CER-001 3 mg/kg compared with placebo, *P*=0.03). A similar observation for plaque regression at the lowest CER-001 dose was found on examination of percent atheroma volume (PAV), which in previous trials has associated more closely with clinical outcomes (46). The mechanism underlying the diminishing effect with increasing CER-001 dose remains uncertain. Whether this reflects saturation of cholesterol efflux transporters or the effects of increasing administration of the lipid contents of CER-001 is unknown.

Further analysis demonstrated much greater regression with CER-001 3 mg/kg in those patients whose baseline PAV was greater than 30%, suggesting a more substantial effect on regression in patients with a greater burden of atherosclerotic plaque at baseline (49). In composite, these findings suggest that CER-001 may have an anti-atherosclerotic effect in humans, which appears to be more robust in patients with a greater baseline plaque burden and is observed at lowest tested dose. An adequately powered placebo-controlled trial is therefore required to test the hypothesis that serial, low-dose infusions of CER-001 promote coronary plaque regression.

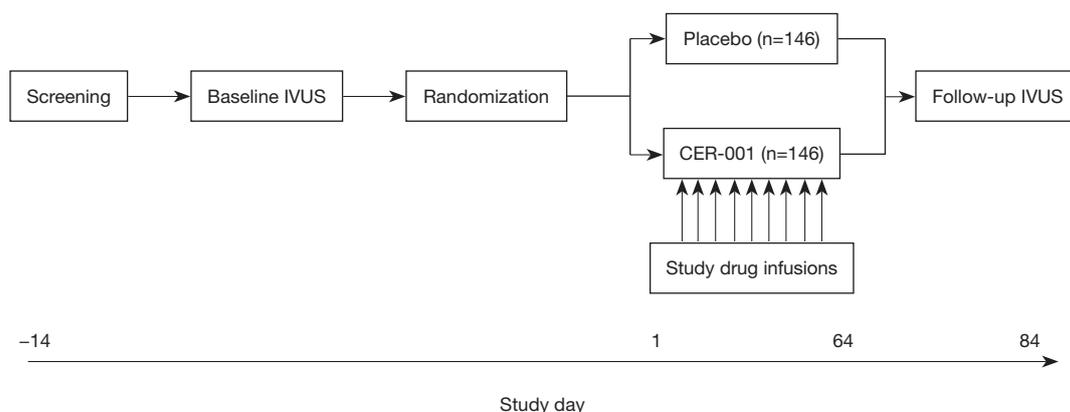


Figure 1 Study schematic for patients throughout the trial.

Methods

Study design

The CER-001 Atherosclerosis Regression Acute Coronary Syndrome Trial (CARAT) study (NCT02484378) is a double-blind, randomized, placebo-controlled trial performed in up to 40 sites in Australia, Hungary, Netherlands and the United States. The study (*Figure 1*) includes a screening period up to 14 days and up to 84 days from randomization to the end of study IVUS imaging. Institutional review board approval was obtained from each site prior to commencement. The study compares the effects of ten weekly intravenous infusions of CER-001 (3 mg/kg) with matching placebo infusions on coronary atheroma volume in patients with an ACS and higher plaque burden. Study patients are adults of at least 18 years of age, who undergo clinically indicated coronary angiography within 7 days of presentation with an ACS. The ACS can be either biomarker positive or negative, although the latter group will be limited to 25% of the study cohort. In addition, qualifying patients must have a PAV of at least 30% in the proximal 10-mm of the target artery at baseline, suitable image quality obtained with an approved IVUS catheter (Boston Scientific OptiCross; Volcano Revolution, Natick, MA, USA) to undergo plaque analysis, and be able to be randomized within 14 days of index event presentation. This minimum plaque burden requirement was selected on the basis of observations that CER-001 may produce greater disease regression in patients with the greatest plaque burden at baseline. The vessel chosen for imaging must not be a bypass graft, have undergone revascularization, have luminal stenosis greater than 50%, or be deemed the culprit vessel for the index or

a previous myocardial infarction. Major exclusion criteria include HbA1c greater than 10%, fasting triglycerides >500 mg/dL, significant heart failure, liver or kidney disease and the presence of imaging within a vessel that is deemed not acceptable for the study by the core laboratory. Patients who meet all inclusion and no exclusion criteria are randomly assigned in 1:1 ratio to receive ten weekly infusions of CER-001 or placebo. Patients receive evidence-based background therapy, including anti-platelet drugs and maximally tolerated intensive statin treatment in accordance with national guidelines, as determined by treating physicians. IVUS imaging is repeated within the same coronary artery within 7–21 days following the final infusion.

Results

The primary endpoint of the study is the nominal change from baseline to follow up in PAV compared with placebo. This analysis is performed by the core laboratory using cross-sectional IVUS images spaced 0.5-mm apart in a matched arterial segment, defined by the presence of a proximal and distal side branch. In each cross-sectional image, the leading edges of the lumen and external elastic membrane will be traced by analysts, blinded to treatment status. Where calcification causes an acoustic shadow extending at least 90°, the external elastic membrane leading edge is not defined and thus that image is not included for analysis. Additional imaging endpoints include the nominal change in total atheroma volume throughout the vessel and within the 10-mm segment found to contain the largest burden of plaque at baseline. Cases with less than 15 matched, evaluable images at both time points will not

be included in the primary analysis. Exploratory efficacy parameters include systemic lipoprotein and inflammatory markers (such as C-reactive protein) and surrogate measures of plaque composition. A sample size of 292 patients is chosen under the assumption of a 15% non-completion rate, yielding 248 patients with evaluable IVUS imaging at both time points. This sample size provides 86% power to demonstrate a difference in the change in PAV between the treatment groups of 1.0% with a standard deviation of 2.6%. In addition, adverse events and major adverse cardiovascular events will be collected.

CARAT is an academically led trial involving a partnership between the academic research organizations South Australian Health and Medical Research Institute (SAHMRI) and Cleveland Clinic Coordinating Center for Clinical Research (C5Research), contract research organizations (InterEuropa), and the pharmaceutical sponsor Cerenis SA. The study is led by an academic executive steering committee that will oversee all aspects of the trial. All imaging analysis will be performed by the core laboratory located within the Vascular Research Center at SAHMRI, with data management and statistical analysis provided by SAHMRI Clinical Research.

Conclusions

Despite the failure to date of oral, small molecule approaches that target HDL-C to provide cardiovascular benefit when added to statins, infusion of a simple, engineered HDL particle is an alternative with substantial supporting evidence from preclinical and early clinical studies. CER-001 has a number of properties that suggest that it should have a favorable impact on coronary atherosclerosis in humans. The CARAT study will draw on the information obtained from prior studies in humans to determine whether CER-001 promotes coronary plaque regression after ACS.

Acknowledgements

The study was sponsored by Cerenis.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Institutional review board approval was

obtained from each site prior to commencement (No. HREC/15/RAH/172) and written informed consent was obtained from all patients.

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Cite this article as: Andrews J, Janssan A, Nguyen T, Pisaniello AD, Scherer DJ, Kastelein JJ, Merkely B, Nissen SE, Ray K, Schwartz GG, Worthley SG, Keyserling C, Dasseux JL, Butters J, Girardi J, Miller R, Nicholls SJ. Effect of serial infusions of reconstituted high-density lipoprotein (CER-001) on coronary atherosclerosis: rationale and design of the CARAT study. *Cardiovasc Diagn Ther* 2017;7(1):45-51. doi: 10.21037/cdt.2017.01.01