Trying to harness the potential of HDL: wishful thinking or sound strategy?

Alan M. Fogelman*

Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1736, USA

Online publish-ahead-of-print 12 May 2014

This editorial refers to 'Effects of the high-density lipoprotein mimetic agent CER-001 on coronary atherosclerosis in patients with acute coronary syndromes: a randomized trial, by J.-C. Tardif et al., on page 3277.'

Almost four decades have passed since the Framingham Study reported that HDL cholesterol was a protective factor against coronary heart disease.1 It has been nearly a quarter of a century since Badimon et al.2 demonstrated that i.v. infusion of HDL into cholesterol-fed rabbits caused regression of atherosclerotic lesions. Since then there have been many attempts to harness the potential of HDL as a therapeutic strategy. The latest attempt is described by Tardif et al.3 who report the results of the CHISQUARE study, which is the largest randomized clinical trial to date testing the efficacy of serial HDL infusions in patients with a recent acute coronary syndrome.

The study used an engineered lipoprotein particle mimicking pre-beta HDL and consisting of a recombinant human apolipoprotein A-I [apoA-I; produced in Chinese hamster ovary (CHO) cells and then purified by column chromatography] combined with two phospholipids. Between March 2011 and August 2012, patients with a clinical indication for coronary angiography and a research-mandated intravascular ultrasound (IVUS) recording approved by the IVUS core laboratory were randomized to receive either placebo or an infusion of the HDL mimetic (CER-001). Qualifying patients in this randomized, double-blinded, placebo-controlled, ascending dose trial were randomly assigned to receive six weekly volume-matched infusions of either CER-001 or placebo in a 3:1 ratio in three consecutive cohorts (CER-001 3 mg/kg vs. placebo, then 6 mg/kg vs. placebo, and finally 12 mg/kg vs. placebo), resulting in similar numbers of patients randomized to the four study arms.

The primary efficacy endpoint was the nominal change in total atheroma volume (follow-up minus baseline) on IVUS. Secondary and exploratory efficacy measures included the nominal change in percentage atheroma volume on IVUS, and the nominal changes in coronary artery score (defined as the per-patient mean of minimum lumen diameter for all lesions measured) and in cumulative coronary stenosis score on quantitative coronary angiography (QCA). The cumulative coronary stenosis score is an index of the anatomical extension and severity of disease in all coronary arteries.

There were 417 and 461 patients with paired IVUS and QCA measurements, respectively. The percentages of patients who received all six planned study drug infusions in the primary analysis were 97.5, 100, 96.7, and 91.4% in the placebo, CER-001 3 mg/kg, 6 mg/kg, and 12 mg/kg groups, respectively.

Despite increasing the plasma level of free cholesterol by ~45% at 2 h after the start of the infusion of CER-001 at a dose of 12 mg/kg, which suggests that the infusion of this dose of the HDL mimetic did in fact mobilize tissue cholesterol, the study failed to show a significant reduction in coronary atherosclerosis on IVUS and QCA as compared with placebo.4

Despite initial enthusiasm following a pilot study,4 this study3 is the fourth that has failed to show significant improvement in the primary efficacy parameter (atheroma volume) compared with placebo after infusion of HDL in humans with coronary artery atherosclerosis.3–6

Despite the failure in the primary efficacy parameter, in one of the studies, the mean changes in the plaque characterization index on IVUS and mean changes in coronary score on QCA were significantly different from placebo. Additionally, in a small study of patients with peripheral vascular disease that received infusions of reconstituted HDL prior to surgery, there was a significant reduction in plaque cholesterol and inflammatory markers in specimens of superficial femoral artery taken at surgery.7

The current study3 was well designed and was powered to detect a difference between placebo and the primary efficacy parameter. What are possible reasons for the failure to see a significant difference? Some of the possible reasons are shown in Figure 1. Perhaps the dose was too low, or the mimetic needs to be given much more frequently (e.g. needs to be given daily instead of weekly). Perhaps the infused apoA-I was inactivated by the systemic and local tissue inflammation that is known to be present in these patients. Stan Hazen and his colleagues recently reported that apoA-I recovered from human atheroma is dysfunctional and extensively oxidized by myeloperoxidase.8 Perhaps the techniques for measuring changes

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.


* Corresponding author. Tel.: +1 310 825 6058, Fax: +1 310 206 3489, Email: afogelman@mednet.ucla.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please email: journals.permissions@oup.com.
Whether the peptides were given orally or by injection, they were found to exert their action primarily in the small intestine and plasma.11 Decrease the levels of unsaturated lysophosphatic acid in the aortic atherosclerosis in mice seems to be related to their ability to decrease systemic inflammation and dysfunctional apolipoprotein A1 in human atheroma.9 The ability of these peptides to decrease very high plasma levels. Surprisingly, in mice, the peptides were found to exert their action primarily in the small intestine regardless of whether the peptides were given orally or by injection.10 The ability of these peptides to decrease systemic inflammation and aortic atherosclerosis in mice seems to be related to their ability to decrease the levels of unsaturated lysophosphatic acid in the small intestine and plasma.11

HDL is not like other lipoproteins; it is much more complex.12 The failure of the study by Tardif et al. 9 to achieve its primary efficacy parameter is likely to be multifactorial. It is also probably too soon to determine if trying to harness the potential of HDL is wishful thinking or a sound strategy.

**Funding**

This work was supported by the National Heart, Lung, and Blood Institute at the National Institutes of Health (HL 30568) and a Network Grant from the Leducq Foundations.

**Conflict of interest:** A.M.F. reports grants from NHLBI, during the conduct of the study; he is a principal and officer in Bruin Pharma, outside the submitted work. In addition, he is listed as an inventor on many apoA-I mimetic peptide patents owned by the University of California and licensed to Bruin Pharma.

**References**


