High-Density Lipoprotein Infusions

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KEYWORDS

• High-density lipoproteins • Lipids • Cardiovascular risk • Atherosclerosis

KEY POINTS

- High-density lipoproteins (HDLs) have presented an attractive target for development of new therapies in cardiovascular prevention on the basis of epidemiology and preclinical studies demonstrating their protective properties.
- Infusion of HDL mimetics has advanced to clinical development.
- Despite promising results of early clinical studies, more recent trials have failed to demonstrate a beneficial effect of infusing HDL mimetics in statin-treated patients.

INTRODUCTION

The consistent benefit of lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins on cardiovascular events in large outcomes trials has led to widespread use of these agents in preventive approaches for treatment of patients determined to be at high cardiovascular risk.[1–3] However, as many clinical events continue to occur, despite use of statin therapy, there has been increasing interest in developing additional approaches that target other factors to achieve greater risk reduction.[4] By virtue of reports suggesting that HDLs play a protective role against atherosclerotic cardiovascular disease, there has been considerable interest in the development of therapies targeting HDL functionality.[5] Among these approaches, infusion of HDL mimetics has advanced to clinical development. The progress of these studies will be reviewed.

HIGH-DENSITY LIPOPROTEIN AND PROTECTION

Epidemiology studies consistently demonstrate an inverse relationship between HDL-C levels and the prospective risk of cardiovascular disease.[6] This is further evidenced within clinical trials, in which low HDL-C levels continue to be associated with an increase in cardiovascular risk in patients with low LDL-C levels.[7,8] Animal studies demonstrate that targeting HDL functionality via direct infusion or transgenic expression of its major apolipoproteins exerts favorable effects on the burden and composition of atherosclerotic plaque.[9–13] In addition to the central role of HDL in promotion of cholesterol efflux and reverse cholesterol transport, laboratory studies have also demonstrated that HDL impacts favorable effects on inflammatory, oxidative, apoptotic, and thrombotic factors implicated in atherosclerosis.[14] Systemic measures of cholesterol efflux capacity and paroxonase, as a measure of anti-inflammatory activity, are associated with the risk of cardiovascular events.[15–17] More recently, factors such as inflammation, smoking, and dysglycemia have been reported to impair HDL functionality, with potential consequences for cardiovascular risk.[18–20] These observations suggest that therapeutic approaches promoting HDL functionality may be a useful strategy for

Disclosure: Nicholls disclosures are research support from AstraZeneca, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron and LipoScience and a consultant for AstraZeneca, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, Boehringer Ingelheim. Other authors have no disclosures.

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Cardiol Clin ■ (2017) ■–■

https://doi.org/10.1016/j.ccl.2017.12.012

treatment of high-risk patients in addition to statins.

HIGH-DENSITY LIPOPROTEIN EFFECTS OF EXISTING LIPID THERAPIES

The challenge to date has been the ability to demonstrate that favorably targeting HDL translates to cardiovascular benefit. Some evidence has emerged from study of current lipid-modifying therapies to suggest that HDL effects are associated with their benefit. Modest HDL-C raising is associated with the ability of statins to slow disease progression and reduce cardiovascular events.[21] Elevating small HDL particles is associated as an independent predictor of the ability of gemfibrozil to reduce cardiovascular events.[22] Niacin, the most effective HDL-C raising agent currently used in clinical practice, has been reported to produce regression of angiographic disease in the setting prior to use of more intensive statin therapy.[23] The failure to demonstrate benefit of adding niacin to more contemporary statin therapy has raised concerns with regards to its clinical utility for reducing cardiovascular risk.[24,25]

The development of cholesteryl ester transfer protein (CETP) inhibitors was primarily based on their ability to substantially raise HDL-C levels more than current therapies. However, the findings of these agents in clinical trials have been largely disappointing, with reports of toxicity and clinical futility.[6] Even when anacetrapib was demonstrated to have a modest clinical benefit, it was uncertain whether this had anything to do with HDL-C raising, and the agent was not moving forward to regulatory approval.[26] Considerable interest has focused on the potential to use HDL infusions as a treatment for patients with established atherosclerotic disease. Translating reports in animal studies, early human studies have demonstrated that infusing HDL-related mimetics increases fecal sterol excretion, a surrogate measure of reverse cholesterol transport, and improves endothelial function, suggesting potentially favorable effects on the artery wall.[27–29] These findings have provided the impetus for clinical development of a range of HDL mimetics in human studies.

ApoA-I MILANO

Variants of apoA-I have been reported to be of potential clinical utility in HDL therapeutics. In the Italian hamlet of Limone sul Garda, the naturally occurring apoA-I Milano (AIM) variant has been reported to associate with prolonged life expectancy despite the presence of low HDL-C levels.[30,31] This mutant involves an arginine-to-cysteine mutation, generating a protein that can form heterodimers and exert cholesterol efflux and anti-inflammatory properties in preclinical studies.[32,33] When incorporated into an HDL mimetic containing phospholipid (ETC-216), this has been demonstrated to have favorable effects on vascular function, atherosclerosis, and in stent neointimal hyperplasia in mouse and rabbit models.[34–36]

A small early human study demonstrated that infusing either 15 or 45 mg/kg of ETC-216 produced rapid regression of coronary atherosclerosis on serial intravascular ultrasound imaging in patients following an acute coronary syndrome.[37] The lack of difference in therapeutic effect between the 2 doses suggested a potential ability to saturate cholesterol transport pathways at the lower dose. Subsequent reports found greater regression in lesions containing the highest plaque burden at baseline and that regression was accompanied by reverse remodeling of the artery wall.[38] Although this mimetic was well tolerated within the course of this study, it became apparent that it was difficult to generate large quantities in a standardized manner required to perform larger clinical trials. Refinement of the manufacturing process produced a mimetic (MDCO-216) that retained the favorable effects on cholesterol efflux and anti-inflammatory activity.[39–41] However, a repeat imaging study in patients following an acute coronary syndrome failed to replicate evidence of plaque regression.[42] Whether this represents an inability of MDCO-216 to regress disease in patients treated with more intensive statin therapy than used in the earlier study remains unknown. Nevertheless, the inability to demonstrate a favorable impact on atherosclerosis in addition to standard medical therapy suggests that clinical development of this mimetic will not advance.

CER

CER-001 is an HDL mimetic containing wild-type apoA-I and sphingomyelin as its predominant lipid species. This particle is negatively charged in a similar manner to native pre-β HDL, distinguishing it from other HDL mimetics in clinical development.[43] This may underscore the observation of greater cholesterol transport activity in vivo, with favorable impacts on atherosclerotic plaque in animal models.[44,45] Small, single-center studies demonstrated beneficial effects on carotid atherosclerotic plaque burden using magnetic resonance and inflammatory activity using positron emission tomography.[46,47] The Can HDL Infusions