

The Therapeutic Potential of High-Density Lipoprotein Mimetic Agents in Coronary Artery Disease

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Low levels of high-density lipoprotein cholesterol (HDL-C) represent a major cardiovascular risk factor that is only modestly influenced by currently available drugs. Consequently, there has been interest in developing new therapeutic agents specifically targeting HDL-C to reduce risk in patients with coronary artery disease. One strategy involves the administration of therapies that mimic HDL-C or its properties, including reconstituted HDL, apolipoprotein A-I (apoA-I), apoA-I Milano, and apoA-I mimetic peptides. The atheroprotective effects of reconstituted HDL, apoA-I, and apoA-I Milano have been well documented in animal studies, and two recent clinical trials also provided encouraging results. The most investigated apoA-I mimetic peptide, D-4F, was shown to significantly reduce atherosclerotic lesions in animal models but data in humans are scarce. HDL-C mimetic agents constitute a promising novel strategy to reduce coronary artery disease risk but require further study in larger clinical trials.

Introduction

Despite the effectiveness of current therapies, including antiplatelet agents, angiotensin-converting enzyme inhibitors, and statins, coronary artery disease (CAD) remains one of the principal causes of morbidity and mortality in developed countries [1]. New treatment strategies are required to further prevent CAD and reduce the risk of coronary events in individuals with preexisting disease. Large cohort studies have repeatedly demonstrated that low levels of high-density lipoprotein cholesterol (HDL-C) are strongly and independently associated with the risk of CAD [2–4]. It is estimated that approximately 40% of

patients with premature CAD have decreased HDL-C, which represents the most common lipoprotein disorder in this population [5]. Based on this evidence, the National Cholesterol Education Program Adult Treatment Panel III guidelines [6] consider low HDL-C (< 1.03 mmol/L or 40 mg/dL) as a major risk factor for CAD and a potential target for therapeutic intervention. However, the idea that raising HDL-C can actually reduce CAD risk remains controversial [7,8]. This may be partly explained by the fact that currently available lipid-modifying therapies, including statins, fibrates, and nicotinic acid (niacin), have only modest HDL-C-raising effects. Accordingly, recent updates of the National Cholesterol Education Program guidelines do not specify a goal value for HDL-C raising [9].

Research in the past two decades has not only greatly enhanced our understanding of HDL-C metabolism but has also offered novel potential therapeutic targets to address low HDL-C. Two main approaches are currently being explored. The first involves the administration of agents that elevate endogenous plasma HDL-C, such as cholesteryl ester transfer protein (CETP) inhibitors and ligands of transcription factors such as peroxisome proliferator-activated receptor α/δ or liver X receptor. Therapies that mimic HDL-C function, including reconstituted high-density lipoprotein (rHDL), apolipoprotein A-I (apoA-I), apoA-I mutants, and apoA-I peptide mimetics, constitute the second strategy and are the focus of this review.

Atheroprotective Effects of HDL-C

HDL is the smallest and densest class of circulating lipoproteins. It is composed of both lipids (free cholesterol, cholesteryl esters, triglycerides, and phospholipids) and proteins (mainly composed of apoA-I), synthesized mainly by the liver. Initially lipid-poor, nascent HDL particles (also called pre- β or discoid HDL) progressively accumulate lipids and become mature or spherical HDL. The atheroprotective effects of HDL-C are attributed in large extent to its ability to transport excess cholesterol from blood vessels and peripheral tissues (skeletal muscle, adipose tissue,

skin, and macrophages) to the liver for biliary excretion, a process termed *reverse cholesterol transport* (RCT). The pathways of RCT are complex and have previously been described in detail [10]. Briefly, free cholesterol is transferred from peripheral tissues to HDL in several regulated steps via different receptors (adenosine triphosphate-binding cassette A1, G1, and G4, and scavenger receptor-B1) and through its conversion to cholesteryl esters by lecithin cholesterol acyltransferase (LCAT). Cholesterol in HDL is then transported back to the liver via one of two routes. Direct RCT involves selective uptake of cholesteryl esters from HDL particles by hepatic and steroidogenic cells through scavenger receptor-B1. Indirect RCT involves CETP, which facilitates the transfer of cholesteryl esters from HDL to very low-density lipoprotein, which is then converted to low-density lipoprotein (LDL), which returns cholesterol to the liver via the hepatic LDL receptor. LDL may also return to peripheral tissues, a process that increases the likelihood of atherosclerotic plaque development.

There is clear evidence that HDL-C possesses biological functions other than RCT. These are known as pleiotropic effects and may independently contribute to the atheroprotective effects of HDL-C. Emerging experimental studies have demonstrated that HDL-C exerts anti-inflammatory, antioxidant, and antithrombotic effects [11,12]. For example, HDL-C impacts the inflammatory pathway through endothelial cell adhesion molecules, which bind inflammatory cells to the vascular wall and promote the development of atherosclerotic lesions. Several *in vitro* and *in vivo* studies have demonstrated that incubation with or infusion of rHDL or apoA-I results in decreases in levels of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 [13–15]. Additionally, a decrease in the number of inflammatory cells in the vessel wall is observed [13]. Oxidation, another important process that contributes to atherosclerotic plaque development, may also be modified by HDL-C. apoA-I is capable *in vitro* and *in vivo* of removing enzymes that oxidize LDL phospholipids (known as LDL lipid hydroperoxides) after injection into mice or humans [16,17]. HDL-C also acts as a carrier of enzymes that destroy lipid hydroperoxides, including paraoxonase-1 [18] and paraoxonase-3 [19], and other enzymes that hydrolyze oxidized phospholipids, such as platelet-activating factor acetyl hydrolase [20] and LCAT [21]. Finally, the antithrombotic properties of HDL-C are mediated via 1) improved endothelial function and platelet inhibition through increased nitric oxide (NO) levels via upregulation of endothelial NO synthase expression [22]; 2) increased prostacyclin release, which acts alongside NO to mediate relaxation of vascular smooth muscle cells, inhibit platelet activation, and inhibit the local proliferation of vascular smooth cells [23]; 3) antiapoptotic effects, which prevent the release of microparticles responsible for precipitating thrombus formation [24]; and 4) a potential anticoagulant effect as a co-factor facilitating the inactivation of coagulation factor Va by activated protein C and protein S, which inhibit thrombin generation and fibrin clot formation [25].

Concept of HDL Mimetic Therapies

rHDL and apoA-I (or its mutant derivative apoA-I Milano) represent the HDL mimetic strategies that have received the most study to date, including their use in phase 2 clinical trials. In contrast, the experience with apoA-I mimetic peptides has so far been limited to preclinical or early-phase clinical studies. Due to their rapid mode of action, these therapies have been proposed for short-term use in patients presenting with acute coronary syndromes (ACS) in addition to conventional medical therapy. The concept of administration of rHDL or apoA-I infusions shortly after ACS aims to reduce plaque burden and increase plaque stability in patients at high risk of recurrent coronary events. Before discussing the clinical studies evaluating HDL mimetics, we first review the main experimental studies.

HDL Mimetics in Experimental Studies

rHDL, apoA-I, and apoA-I Milano

The antiatherosclerotic effects of artificial HDL were first described in cell cultures by Orekhov et al. [26] in 1984, generating enthusiasm for this line of investigation. *In vivo* evaluations were later conducted in a model of cholesterol-fed rabbits developing atherosclerotic-like aortic lesions. Weekly infusions with homologous HDL/very high-density lipoprotein fraction not only reduced the development of atherosclerotic lesions by approximately 60% [27], but they also decreased established atherosclerotic lesions in a separate study [28]. Infusions of purified rabbit apoA-I were administered in similar experimental models and also demonstrated significant effects on the progression of atherosclerosis but not on atherosclerosis regression [29].

ApoA-I Milano is a mutant form of apoA-I (arginine 173 to cysteine) identified in inhabitants of Limone sul Garda, a small village in northern Italy whose inhabitants have a low incidence of CAD despite very low levels of HDL [30]. It has been suggested that the presence of the thiol group in apoA-I Milano confers enhanced antioxidant activity, which may account for the potent antiatherogenic properties of this mutated apolipoprotein [31]. One of the first studies of apoA-I Milano was conducted in cholesterol-fed rabbits using the balloon injury model of atherosclerosis. Injections of rHDL containing apoA-I Milano linked to a phospholipid carrier resulted in a 70% reduction in plaque area and a 50% reduction in macrophage infiltration in iliac artery lesions, demonstrating both atheroprotective and anti-inflammatory effects, all in the absence of a change in circulating cholesterol levels [32]. More recently, infusions of recombinant apoA-I Milano-containing synthetic HDL have demonstrated an ability to inhibit progression and promote regression of atherosclerosis, reverse endothelial dysfunction, induce rapid changes in plaque composition, and reduce *in-stent* restenosis [33–36]. These promising data have led to several clinical trials of HDL and apoA-I infusions.

apoA-I mimetic peptides

Because human apoA-I comprises 243 amino acids, the main limitations of rHDL/apoA-I therapies include their high production cost and logistical difficulties associated with the need for intravenous administration. In 1985, Anantharamaiah et al. [37] designed an 18-amino acid peptide that possessed the class A amphipathic helical motif present in apoA-I lipid-binding domains. Refinement in peptide design led to the development of structural variants of the basic 18AA peptide with increased hydrophobicity and lipid-binding affinity by replacement of nonpolar amino acids with phenylalanine (F) residues. The peptides were called 2F, 3F, 4F, 5F, 6F, and 7F in recognition of the number of newly attached phenylalanine residues [38]. The first in vivo demonstration that apoA-I mimetic peptides possess antiatherosclerotic properties utilized the more hydrophobic peptide 5F [39]. In C57BL/6J mice fed with an atherogenic diet, daily intraperitoneal injection of 5F during 16 weeks significantly reduced aortic atherosclerotic lesion area compared with hyperlipidemic control mice receiving either saline or mouse apoA-I without altering cholesterol levels or lipoprotein profiles. Ex vivo analyses of HDL isolated from 5F-treated mice demonstrated a significantly larger effect in inhibiting LDL-associated lipid hydroperoxide formation and LDL-induced monocyte chemotaxis. More recent investigations of apoA-I mimetic peptides have used the 4F peptide because it displays improved solubility properties, is more effective than 5F in reducing LDL-induced monocyte chemotactic activity [38], and its D-amino acid form (D-4F) is orally active. Oral administration of D-4F in LDL receptor-null mice on a western diet reduced atherosclerotic lesions by 79% and rendered the HDL anti-inflammatory without altering plasma cholesterol or HDL-C levels [40]. Similar results were confirmed in hyperlipidemic rabbits [41] and in studies on mice and monkeys that demonstrated a synergistic effect of low-dose combination therapies of D-4F and statins [42•]. These data suggest that the atheroprotective effects of apoA-I mimetic peptides may not necessarily be due to changes in lipoprotein profiles per se, but rather to an improvement in HDL quality and function and/or direct anti-inflammatory effects of the peptide itself, as proposed by several authors [43]. The use of a D-peptide, however, raises the issue of potential prolonged accumulation in tissues.

HDL Mimetics in Clinical Trials

apoA-I mimetic peptides were recently tested in a phase 1 study that randomly assigned 50 patients with stable CAD or a CAD equivalent to either various single oral doses of unformulated D-4F or placebo [44•]. D-4F had a low bioavailability but appeared safe and improved the HDL anti-inflammatory index in vitro.

Clinical studies of HDL and apoA-I infusions were initiated in the mid 1990s. These early proof-of-concept studies evaluated the effects of infusing recombinant

pro-apoA-I phospholipid complexes and plasma-derived human apoA-I phospholipid discs on a variety of parameters in humans. These studies demonstrated that HDL infusions were associated with increased fecal sterol excretion and normalization of endothelium-dependent vasodilation, suggesting an effect on the RCT pathway and a potential for beneficial vascular effects [45–47].

In 2003, a small phase 2 clinical trial assessed the effects of infusing recombinant apoA-I Milano/phospholipid complexes (ETC-216) on coronary atheroma in patients presenting with ACS [48]. In this double-blind trial, 57 patients were randomly assigned to receive five weekly infusions of placebo (saline) or ETC-216 at 15 mg/kg or 45 mg/kg within 2 weeks of an ACS. Intravascular ultrasound was performed at baseline and after treatment to measure atheroma volume in a single segment of coronary artery with 20% to 50% diameter narrowing. A total of 47 patients completed the protocol (36 in the treatment groups). After 5 weeks of therapy, the mean (SD) percent atheroma volume decreased by 1.06% (3.17%) in the combined ETC-216 group ($P = 0.02$ compared with baseline). In the placebo group, the mean (SD) percent atheroma volume increased by 0.14% (3.09%) ($P = 0.97$ compared with baseline). The absolute reduction in atheroma volume in the combined treatment cohort was 14.1 mm³ or a 4.2% decrease from baseline ($P < 0.0001$). Although this study was limited in size and did not show a statistically significant difference compared with placebo, it raised the possibility that rapid remodeling of atherosclerosis with short-term infusions of HDL may be feasible.

More recently, a form of rHDL consisting of human wild-type apoA-I combined with soybean phosphatidylcholine that mimics chemical and biological properties of native HDL was evaluated in the Effect of rHDL on Atherosclerosis–Safety and Efficacy (ERASE) study [49••]. This multicenter, double-blind, placebo-controlled trial, designed to assess the safety and efficacy of rHDL using intravascular ultrasound and quantitative coronary angiography end points, randomized 183 men and women with recent ACS to receive four weekly infusions of either placebo (saline) or CSL-111 at dose of 40 or 80 mg/kg. Atherosclerotic plaque burden was evaluated by intravascular ultrasound and quantitative coronary angiography (the latter in coronary segments demonstrating at baseline a > 20% diameter stenosis) at baseline and 2 to 3 weeks after the last study infusion. The primary efficacy parameter was the percentage change in atheroma volume. Nominal changes in plaque volume and plaque characterization indexes on intravascular ultrasound and coronary score on quantitative coronary angiography were also prespecified end points. Following the preplanned interim safety analysis, the high-dose CSL-111 group (80 mg/kg) was discontinued because of a high incidence of liver transaminase elevations. Short-term infusion of CSL-111 at 40 mg/kg was safe and well tolerated and resulted in a 3.4% reduction in atheroma volume compared with a 1.6% reduction in the placebo group ($P < 0.0001$ vs baseline for rHDL; $P =$ not significant

vs placebo). The nominal change in plaque volume was -5.3 mm^3 with CSL-111 and -2.3 mm^3 with placebo ($P < 0.0001$ vs baseline for rHDL; $P =$ not significant vs placebo). Changes in plaque characterization indexes and coronary score were significantly different between groups ($P = 0.01$ and 0.03 between rHDL and placebo groups, respectively). Importantly, the benefit of rHDL compared with placebo with respect to coronary score was similar to that observed in previous statin trials after 2 years of treatment [50,51]. These results are encouraging given the known long-term prognostic value of changes in atherosclerosis burden on quantitative coronary angiography [52]. The findings, however, require confirmation in larger trials with clinical end points.

Conclusions

Strategies targeting HDL-C to potentially improve prognosis include those aimed at raising HDL-C and those aimed at improving its quality. However, currently available drugs, such as statins, fibrates, and niacin, have limited HDL-raising capabilities. Newer agents, such as CETP inhibitors, are currently under investigation, although recent clinical trial data regarding torcetrapib have been disappointing. These findings provide the basis for ongoing research into the development of HDL mimetic agents. The data outlined in this review show that HDL mimetics, such as rHDL, apoA-I, or apoA-I Milano, and apoA-I mimetic peptides represent potential new therapeutic paradigms for the treatment of atherosclerosis. These novel strategies may further reduce atherothrombotic cardiovascular events in patients with CAD not only by enhancing RCT but also through their antioxidative, antithrombotic, and anti-inflammatory properties. Larger studies with robust clinical end points are needed to better assess the future role of these agents in the global management of CAD patients.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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