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Antiatherosclerotic Effects of CSL112 Mediated by Enhanced Cholesterol Efflux Capacity

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ABSTRACT: Approximately 12% of patients with acute myocardial infarction (AMI) experience a recurrent major adverse cardiovascular event within 1 year of their primary event, with most occurring within the first 90 days. Thus, there is a need for new therapeutic approaches that address this 90-day post-AMI high-risk period. The formation and eventual rupture of atherosclerotic plaque that leads to AMI is elicited by the accumulation of cholesterol within the arterial intima. Cholesterol efflux, a mechanism by which cholesterol is removed from plaque, is predominantly mediated by apolipoprotein A-I, which is rapidly lipidated to form high-density lipoprotein in the circulation and has atheroprotective properties. In this review, we outline how cholesterol efflux dysfunction leads to atherosclerosis and vulnerable plaque formation, including inflammatory cell recruitment, foam cell formation, the development of a lipid/necrotic core, and degradation of the fibrous cap. CSL112, a human plasma-derived apolipoprotein A-I, is in phase 3 of clinical development and aims to reduce the risk of recurrent cardiovascular events in patients with AMI in the first 90 days after the index event by increasing cholesterol efflux. We summarize evidence from preclinical and clinical studies suggesting that restoration of cholesterol efflux by CSL112 can stabilize plaque by several anti-inflammatory/immune-regulatory processes. These effects occur rapidly and could stabilize vulnerable plaques in patients who have recently experienced an AMI, thereby reducing the risk of recurrent major adverse cardiovascular events in the high-risk early post-AMI period.

Key Words: acute myocardial infarction ■ apolipoprotein A-I ■ atherosclerotic plaque ■ cholesterol efflux

Within a year of experiencing an acute myocardial infarction (AMI), ≈12% of patients will experience major adverse cardiovascular events (MACEs), with over half of these occurring in the 90-day high-risk period following the index event.[1,2] There is, therefore, an unmet need for effective therapies that reduce the risk of secondary MACEs in this high-risk period post-AMI.

The rupture or erosion of atherosclerotic plaque, caused by cholesterol retention in the arterial wall, is the primary pathophysiological step in AMI.[3,4] Reverse cholesterol transport (RCT) is the mechanism by which cholesterol is removed from atherosclerotic plaque and is transported to the liver for removal from the body. RCT is often impaired among patients with AMI,[5] leading to further cholesterol accumulation in the arterial wall, and recurrent cardiovascular events. The first step in RCT is cholesterol efflux, the transfer of cholesterol from plaque macrophages to apolipoprotein A-I (apoA-I), which is an essential component of high-density lipoprotein (HDL).[6] ApoA-I promotes cholesterol efflux primarily via the ATP-binding cassette transporter-1 (ABCA1).[6] CSL112 is human plasma-derived apoA-I formulated with phosphatidylcholine to form disc-shaped particles suitable for intravenous infusion, and was designed to maximize cholesterol efflux from cells and exhibit favorable pharmacologic properties.[7] CSL112 fuses with native HDL, resulting in HDL remodeling and a rapid dose-dependent increase in lipid-poor

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Nonstandard Abbreviations and Acronyms

ABCA1	ATP-binding cassette transporter-1
CEC	cholesterol efflux capacity
ICAM-1	intercellular adhesion molecule 1
LCAT	lecithin-cholesterol acyltransferase
MACE	major adverse cardiovascular event
RCT	reverse cholesterol transport
VCAM-1	vascular cell adhesion molecule 1

pre-β1 HDL concentration, which increases primarily ABCA1-driven cholesterol efflux.[8] The completed phase 2b Apo-I Event Reduction in Ischemic Syndromes I (AEGIS-I) clinical trial demonstrated that CSL112 robustly and rapidly enhances cholesterol efflux capacity (CEC) in patients with AMI.[9] AEGIS-II is a phase 3 randomized, placebo-controlled trial evaluating the efficacy of CSL112 to reduce the risk of MACEs during the first 90 days after AMI.[10]

In this review, we summarize the role of cholesterol efflux in protecting against the development of atherosclerosis and how enhancement of CEC by CSL112 can reduce vascular inflammation and stabilize vulnerable plaques, potentially reducing the risk of secondary MACEs.

THE CAUSE OF ATHEROSCLEROSIS

The Role of Low-Density Lipoprotein, HDL, and Cholesterol Efflux

Atherosclerosis is a progressive inflammatory condition that develops over a patient's lifetime and predisposes to AMI.[11] The formation of atherosclerotic plaque is elicited by low-density lipoprotein (LDL)–mediated cholesterol deposition in the arterial wall with subsequent inflammatory cell recruitment, vessel remodeling, and ultimately plaque rupture or erosion, which may lead to thrombosis and AMI.[4] Elevated serum LDL cholesterol (LDL-C) is a causative risk factor for atherosclerosis and readily modifiable with a range of established therapeutic approaches, including statins, which have efficacy in reducing plaque size after years of treatment.[12] HDL and apoA-I counteract the pathogenic events leading to the formation and development of atheroma by promoting the removal of cholesterol from the artery wall.[13] HDL and apoA-I have anti-inflammatory effects via decreasing plasma membrane-free cholesterol and lipid raft content in monocytes and neutrophils, causing a dose-dependent reduction in their activation.[14] ApoA-I is able to regulate cholesterol levels, and, in contrast to current LDL-C–lowering agents, can rapidly remove cholesterol over several days.[15]

LDL-C causes atherosclerosis by accumulating in the arterial intima, where it can be modified by oxidation and aggregation.[16,17] Binding of LDL-C to intimal proteoglycans is one of the first steps in disease initiation.[17] LDL-C enters the intimal space where the endothelium is damaged and attracts macrophages to the site. Macrophages engulf LDL-C and become activated, triggering a cascade of events resulting in macrophages and dendritic cells developing into foam cells as a result of excess cholesterol endocytosis.[4,18–20] As foam cells undergo apoptosis, lipid-rich material is released to form a lipid core, also referred to as the necrotic core, as it contains cell debris resulting from the removal of apoptotic cells by efferocytosis.[4] Smooth muscle cell proliferation and increased collagen production below the endothelial cells result in the formation of a fibrotic cap (Figure 1).[3,4,18,19,21–24] Furthermore, oxidized lipids can damage the endothelium, leading to dysfunction and promoting a vicious cycle of vessel vulnerability to atherosclerotic progression.[25,26]

Many atherosclerotic plaques remain stable throughout a patient's life; however, a subset of plaques is vulnerable to rupture or erosion. Plaque disruption subsequently leads to thrombus formation and myocardial infarction (MI).[4,21] The characteristics of a vulnerable plaque include a thin fibrotic cap and a large lipid core.[4,21] Impaired CEC contributes to the development of a vulnerable plaque through plaque lipid accumulation, acute inflammation, and endothelial dysfunction.[26,27] On the other hand, cholesterol efflux reduces plaque cholesterol, inflammation, and apoptosis and increases efferocytosis, resulting in reduction of the lipid core. However, as atherosclerosis progresses, lipid influx outweighs efflux,[28] and consequently, apoptosis increases, efferocytosis is impeded, and apoptotic cells undergo necrosis (Figure 1). The core contains lipids, cytokines, and proteases that contribute to degradation of the plaque fibrous cap, which can then become vulnerable to rupture. When a plaque ruptures, it triggers the development of a thrombus that can block vessels and lead to an MI.[21]

Cholesterol Efflux Is Atheroprotective

Cholesterol deposition incites a progressive macrophage-dominated inflammatory response that could potentially be reversed by the activation of RCT. Cholesterol efflux is one of the counterregulatory mechanisms that oppose cholesterol accumulation and inflammation. Multiple studies have shown that a moderate cholesterol depletion leads to attenuation of the proinflammatory immune responses in various cell types that contribute to atherogenesis. Depletion of cellular cholesterol reduces the response to toll-like

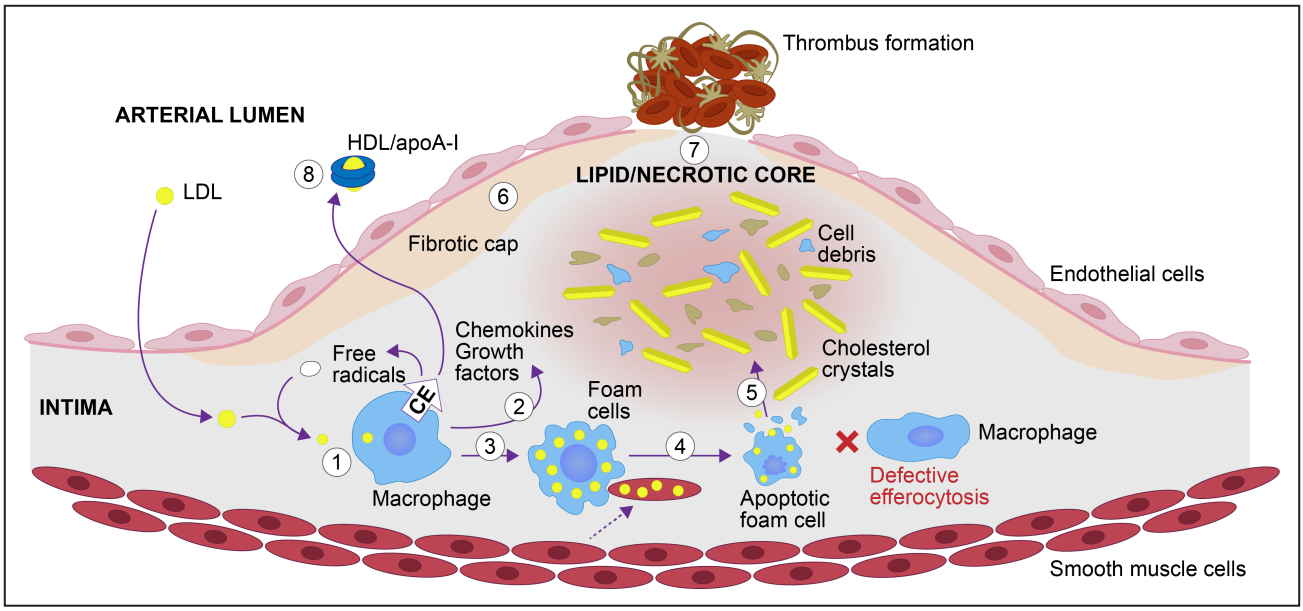

Figure 1. Cholesterol efflux opposes the development of vulnerable plaque.[3,4,18,19,21–24]
(**1**) Macrophages, attracted by low-density lipoprotein (LDL), engulf LDL and become activated. (**2**) Activated macrophages release free radicals, chemokines, and growth factors; LDL is readily oxidized by free radicals, which further amplifies vascular inflammation. (*3*) Chemokines recruit macrophages and smooth muscle cells, which continue to endocytose the excess cholesterol and become foam cells. (**4**) Foam cells undergo apoptosis. (**5**) As efferocytosis is defective, apoptotic cells undergo necrosis and lipid-rich material is released; together with cell debris, they form a lipid/necrotic core. (**6**) Smooth muscle cells continue to proliferate and produce collagen, forming a fibrotic cap. (**7**) Lipids, cytokines, and proteases from the lipid/necrotic core erode the fibrous cap, which becomes thin and susceptible to fissure and thrombosis. (**8**) Cholesterol efflux, mediated by high-density lipoprotein (HDL)/apolipoprotein A-I (apoA-I), opposes the development of a vulnerable plaque by removing cholesterol from macrophages and preventing/reducing the formation of foam cells, reducing foam cell apoptosis, enhancing efferocytosis and lowering lipid content to prevent the formation of the lipid/necrotic core, reducing inflammation, and increasing collagen to stabilize the fibrotic cap. CE indicates cholesterol efflux.

receptor ligands in leukocytes,[29] decreases antigen presentation in dendritic cells,[30] reduces blood leukocyte counts,[31] and lowers platelet activation,[32] whereas elevated blood LDL levels increase adhesion molecule expression (ICAM-1 [intercellular adhesion molecule 1] and VCAM-1 [vascular cell adhesion molecule 1]) in endothelial cells.[33]

Cholesterol efflux is considered one of the most clinically relevant atheroprotective properties of HDL as the inverse relationship between CEC and incident cardiovascular disease has been demonstrated by large prospective studies; the Dallas Heart and the European Prospective Investigation into Cancer (EPIC)-Norfolk studies have shown an association between a high CEC and a reduced risk of cardiovascular events, including incident events.[34–37] A study by Khera et al showed that CEC is a stronger predictor for coronary artery disease than diabetes, hypertension, smoking, and HDL cholesterol levels.[35] CEC is also a predictor of mortality in patients with AMI, independent of lipid levels and traditional cardiovascular risk factors.[5] Furthermore, inflammation/acute-phase response impairs CEC.[38–40] In line with this, CEC is reduced immediately after an AMI for at least 30 days.[41,42] Therefore, the reduction in CEC after AMI may contribute to the high risk of recurrent events, including death during this period. An apoA-I–based treatment approach that increases CEC could, therefore, be highly beneficial to patients post-AMI in reducing the risk of secondary cardiovascular events.

ATHEROPROTECTIVE EFFECTS OF CSL112

Enhanced CEC

CSL112 is designed to enhance CEC during the early post-AMI period, when patients have particularly low CEC and, as such, it is provided as 4 weekly infusions, starting within 5 days of admission for AMI. The enhancement of CEC is hypothesized to reduce the risk of secondary MACEs in the first 90 days post-AMI.[10]

The 7 clinical trials completed to date have shown that CSL112 is well tolerated, with a renal and hepatic safety profile similar to placebo.[9,43–50] Infusion of CSL112 immediately increases apoA-I levels and causes a rapid and marked increase in the capacity of serum to efflux cholesterol via ABCA1, a key transporter that mediates cholesterol efflux from macrophage foam cells (Table).[9,49,51] A 6-g dose was selected

Table. Fold Change in CEC With Infusion of CSL112 in Patients With Stable Atherosclerotic Disease, AMI, and AMI With Renal Impairment[9,44,46]

Study name	Study type	Fold change from baseline	
		Total CEC	ABCA1-dependent CEC
CSLCT-HDL-10-70 (NCT01499420)	Phase 2a SAD study in patients with stable atherosclerotic disease	3.1	…
CSL112_2001 (NCT02742103)	Phase 2 multiple-dose study in subjects with moderate RI and AMI	2.33	3.17
AEGIS-I (NCT02108262)	Phase 2b multiple-dose study in patients with AMI	2.45	4.3

AEGIS indicates Apo-I Event Reduction in Ischemic Syndromes; ABCA1, ATP-binding cassette transporter-1; AMI, acute myocardial infarction; CEC, cholesterol efflux capacity; RI, renal impairment; and SAD, single-ascending dose.

for further development because of favorable pharmacokinetic/pharmacodynamic and safety profiles and a strong 4.3-fold elevation in ABCA1-dependent CEC observed in patients after AMI in a phase 2b trial.[9]

By significantly enhancing cellular cholesterol removal, CSL112 can potentially modulate multiple factors and processes that contribute to unstable plaque formation, such as plaque lipid content/necrotic core, inflammation and macrophage recruitment, and apoptosis of foam cells. In addition, increased cholesterol efflux by CSL112 may enhance foam cell efferocytosis and collagen expression, and improve overall plaque stability, including plaque growth and remodeling (Figure 1).[52–58] Overall, it may lead to a reduction in plaque vulnerability, and, consequently, rates of recurrent cardiovascular events (Figure 2).[9,52–59]

Plaque Stabilization

ApoA-I–based therapies offer the potential for stabilization/remodeling/regression of atherosclerotic plaques in animal models and humans. CSL111 is a predecessor compound formulated with higher phosphatidylcholine/apoA-I molar ratio than CSL112.[43,60] A study by Murphy et al showed that when CSL111 was infused into hypercholesterolemic apolipoprotein

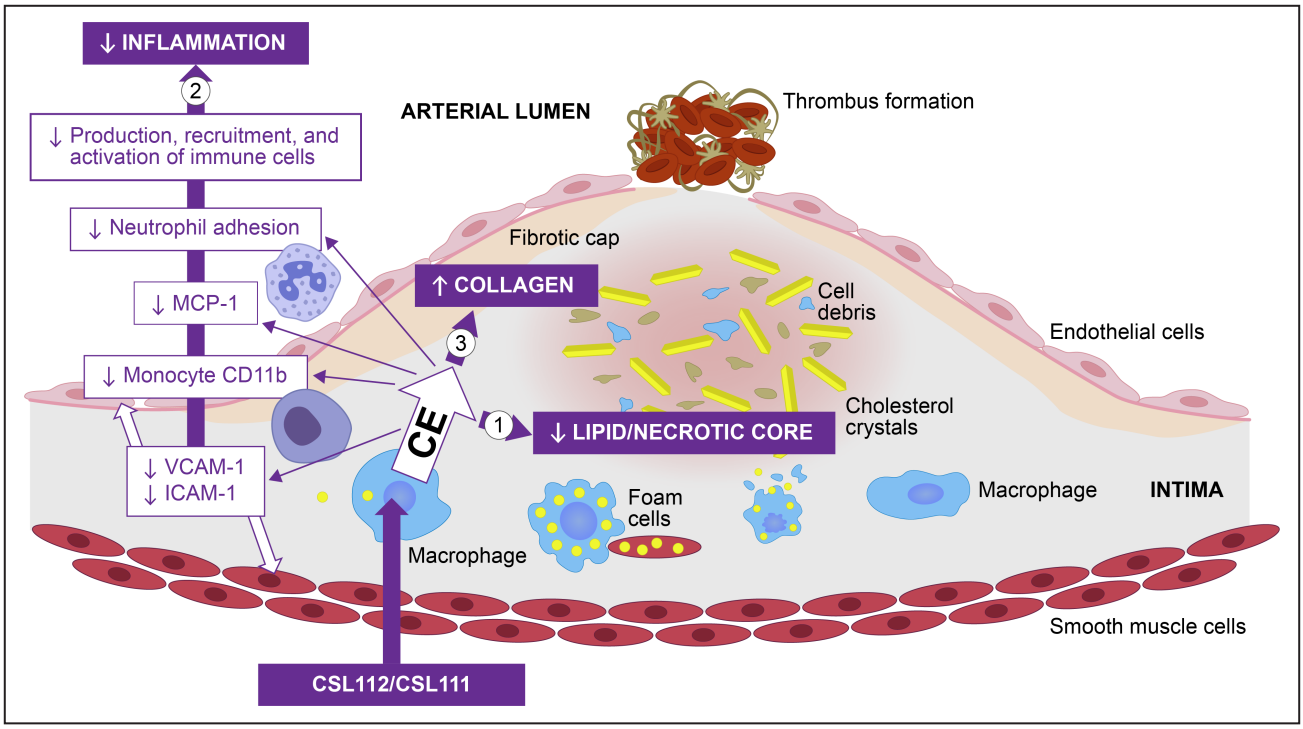

Figure 2. Summary of pathways modulated by CSL112 and its precursor formulation (CSL111).[9,52–59]
CSL112 and its precursor formulation CSL111 promote cholesterol efflux, which (**1**) reduces plaque lipid content and necrotic core; (**2**) inhibits inflammation; and (**3**) increases the collagen content of the plaque fibrous cap. CD11b indicates cluster of differentiation molecule 11b; CE, cholesterol efflux; ICAM-1, intercellular adhesion molecule-1; MCP, monocyte chemoattractant protein; and VCAM-1, vascular cell adhesion protein 1.

E (apoE)$^{-/-}$ mice, the reduction in inflammation was accompanied by reduction in plaque lipid content, a significantly reduced necrotic core size compared with controls, and a significant increase in collagen levels.[53] Similarly, Hewing et al have reported that treating apoE$^{-/-}$ mice with native human apoA-I significantly decreased lipid content and macrophage numbers in advanced aortic root atherosclerotic plaques.[61] This was associated with a reduction in markers of inflammatory M1 macrophages and an increase in anti-inflammatory M2 macrophages within the plaque.[61] These results were similar to a randomized controlled trial that assessed coronary plaque burden using intravascular ultrasound in patients administered 4 weekly infusions of CSL111, 40 mg/kg (n=111), 80 mg/kg (n=12), or saline (n=60).[52] Following CSL111 administration, a statistically significant reduction was seen in plaque characterization index and coronary score.[52] These results were consistent with a preclinical study in mice, which showed beneficial changes in the composition of plaque.[61] The effect seen on the necrotic core was likely attributable to the reduction in both immune cell recruitment and macrophage cell death triggered by enhanced CEC. It has been shown that the removal of certain sterols by cholesterol efflux can protect macrophages from oxidized LDL-mediated cell death.[62] Increasing CEC may, therefore, also restore efferocytosis. In another study, patients with claudication received placebo or one infusion of 80 mg/kg CSL111 5 to 7 days before percutaneous superficial femoral artery revascularization. After CSL111 treatment, both circulating monocyte activation and invasion were lower when assessed by cluster of differentiation molecule 11b (CD11b) expression, and there was evidence of a trend (P=0.05) toward decreased tumor necrosis factor-α. Lipid content, average macrophage size, and VCAM-I expression in the plaques were significantly lower in the CSL111 group versus placebo, demonstrating the potential for CSL111 to induce significant acute changes in plaque morphology consistent with plaque stabilization.[54]

Overall, the improvement in CEC via human plasma-derived apoA-I in both preclinical and clinical studies is associated with plaque stabilization through plausible immune modulatory mechanisms.

Inflammatory Response and Biomarkers of Plaque Instability

Infusions of CSL111 were shown to enhance CEC and reduce systemic and plaque inflammation.[53,55,56,59] In hypercholesterolemic apoE$^{-/-}$ mice, CSL111 infusion reduced the presence of macrophages in plaques, and reduced proliferation of hematopoietic stem and progenitor cells, common myeloid progenitor cells, and granulocyte-monocyte progenitor cells.[53] Moreover, in a mouse model of MI, an infusion of CSL111 suppressed systemic and cardiac inflammation. Cardiac chemokine levels were reduced by 60% to 80%, circulating leukocyte numbers by 30%, and monocyte expression of CD11b by up to 25%.[59]

The endotoxin-neutralizing properties of CSL111 have been demonstrated both in vitro and in animal models.[63,64] Furthermore, in human endotoxemia, CSL111 suppressed the endotoxin-mediated inflammatory response, as measured by reduced inflammatory cytokines, cell activation, and clinical symptoms, such as headache, chills, nausea, vomiting, myalgia, and backache.[65] In patients with type 2 diabetes, a randomized crossover trial showed that compared with placebo, CSL111 infusion led to significant decreases in soluble VCAM-1 levels in patient plasma, reduced CD11b expression on circulating monocytes, and reduced adhesion of patient neutrophils to fibrinogen, indicating an anti-inflammatory effect.[55] In cultured human coronary endothelial cells, HDL isolated from patients treated with CSL111 reduced expression of VCAM-1 and ICAM-1.[55] Richart et al studied blood samples from this trial and found that circulating leukocyte levels were reduced by 12% after CSL111 infusion compared with placebo.[59] Similarly, CSL112 caused an inhibition of phytohemagglutinin-M–induced upregulation of ICAM-1 on both monocytes and neutrophils.[7]

When CSL111 was infused into humans with symptomatic carotid disease (within 1 month of presentation) and the plaques were studied histologically, it was observed that systemic levels of the plasma biomarkers of inflammation associated with plaque instability, matrix metalloproteinase 9, and monocyte chemotactic factor-1 were significantly reduced versus placebo, suggesting a reduction in monocyte activation.[56] Similarly, CSL112 was shown to inhibit the secretion of proinflammatory cytokines, including tumor necrosis factor-α, interleukin-1β, and interleukin-6, and chemokines in phytohemagglutinin-stimulated human blood, with ≈2-fold lower concentrations of CSL112 than native HDL required to achieve a similar inhibition of tumor necrosis factor-α and interleukin-1β.[7,8] These anti-inflammatory actions may contribute to the efficacy of CSL112 given that inhibition of interleukin-1β (and downstream interleukin-6) has been shown to improve cardiovascular outcomes in the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial, where the interleukin-1β antagonist canakinumab reduced the primary composite end point of nonfatal MI, nonfatal stroke, and cardiovascular death by 15% in patients with a previous MI and baseline CRP (C-reactive protein) ≥2 mg/L.[66]

Several studies show a close relation between cholesterol efflux and inflammatory processes. It has been shown that cholesterol homeostasis contributes to hematopoietic stem and progenitor cell quiescence

and, in a rheumatoid arthritis mouse model, defective CEC in hematopoietic stem and progenitor cells led to cholesterol accumulation, which, in turn, increased myelopoiesis.[67,68] In mouse models of autoimmunity, cholesterol accumulation in dendritic cells via defective CEC activated the inflammasome and increased inflammatory cytokine secretion.[69] Finally, a study in rats demonstrated that apoA-I and reconstituted HDL attenuated experimentally induced arthritis and associated inflammation by inhibition of toll-like receptor 2 expression, which can be modulated by cell membrane cholesterol content.[70] In addition to cholesterol efflux, ABCA1 receptors also mediate efflux of sphingomyelin and phosphatidylcholine.[71,72] Thus, it is possible that CSL112 infusion, which increases ABCA1-dependent cholesterol efflux,[7] may alter the phospholipid composition of lipid rafts by increasing cellular efflux of other lipid species. This may also contribute to the observed anti-inflammatory effects of CSL112, especially given that sphingomyelin depletion has been shown to reduce recruitment of toll-like receptor 4 to the cell surface of macrophages and attenuate lipopolysaccharide-induced inflammatory responses.[73,74] Overall, these findings suggest that the immunomodulatory effects of apoA-I infusions are at least in part attributable to enhanced cholesterol efflux reducing the lipid content of immune cells.

CSL112 COMPARED WITH PREVIOUS APOA-I INFUSION THERAPIES

Two other apoA-I infusion therapies, MDCO-216 (recombinant dimeric mutant apoA-I Milano) and CER-001 (recombinant wild-type apoA-I), have been investigated in phase 2 clinical trials.[75,76] However, the development of MDCO-216 has since been discontinued because of a lack of efficacy on plaque regression in an imaging study, and similar results were observed in relation to CER-001.[76,77] In comparison to these products, CSL112 stimulates a far more substantial increase in ABCA1-dependent CEC (as seen in the AEGIS-I trial) than that achieved in phase 2 studies of MDCO-216 and CER-001 (330% versus 80%–90% and 6%, respectively).[9,75,76] Dosing of these 3 agents in clinical studies differed substantially, which may also contribute to the disparate effects on CEC. CSL112 is administered at a total dose of 6 g, corresponding to ≈80 mg/kg based on its pharmacodynamic response, whereas MDCO-216 and CER-001 were dosed at 20 and 3 mg/kg, respectively.[75,76] In addition, CSL112 is the only apoA-I–based product that is capable of activating lecithin-cholesterol acyltransferase (LCAT),[7] with animal model studies showing CSL112 infusion results in an immediate 1.7-fold increase in plasma LCAT activity[7]; in contrast, MDCO-216 and CER-001 have no or inhibitory effects on LCAT, respectively.[7,78–81] LCAT converts free cholesterol into cholesteryl ester, leading to the formation of larger, mature HDL particles, which are then transported to the liver for clearance.[6] The differences observed between CSL112 and these other apoA-I–based infusion therapies could be attributed to differences in particle composition determined by apoA-I and lipid source, and apoA-I/lipid molar ratio. CSL112 contains human plasma-derived apoA-I and soy bean phosphatidylcholine, whereas CER-001 and MDCO-216 are both based on recombinant apoA-I preparations and contain sphingomyelin/dipalmitoylphosphatidylglycerol and palmitoyl oleoyl phosphatidylcholine, respectively.[7,80,82] Although CSL112 has been shown to promote LCAT activation,[7] the other 2 formulations fail to activate LCAT.[7] MDCO-216 contains a disulfide linked homodimer form of apoA-I (apoA-I-Milano), which has a reduced ability to activate LCAT. Lack of LCAT stimulation by CER-001 is attributed to inhibitory effects of sphingomyelin.[7,78,80,82] The potential of CSL112 to reduce future cardiovascular events by enhancing cholesterol efflux and thereby reducing cholesterol content and/or instability of atherosclerotic plaque is being evaluated in the phase 3 AEGIS-II study.[83]

CONCLUSIONS

Cholesterol efflux and RCT are important biological processes that can alter plaque characteristics and strongly modulate immune cell function. Dysfunctional cholesterol efflux underpins atherosclerosis, the development of vulnerable plaque, and cardiovascular events. Enhancing cholesterol efflux holds promise as a therapeutic approach to treating atherosclerosis, particularly in patients who have already experienced an AMI and are at high risk of an early recurrent cardiovascular event in the 90-day high-risk period immediately after an AMI. Human plasma-derived apoA-I infusion enhances plaque cholesterol efflux as well as reduces immune cell recruitment and activation in both preclinical and clinical studies. These effects occur rapidly and could stabilize vulnerable plaques in patients who have recently experienced an AMI. The AEGIS-II clinical outcomes trial with CSL112 apoA-I infusions will definitively evaluate the hypothesis that enhancing CEC during this high-risk period will lead to a reduction in the risk of recurrent MACEs.

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