

Effects of Reconstituted High-Density Lipoprotein Infusions on Coronary Atherosclerosis

A Randomized Controlled Trial

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DESPITE HIGHLY EFFECTIVE contemporary treatment regimens, the majority of vascular events are not prevented, particularly in high-risk individuals.^{1,2} Therefore, further strategies to decrease atherosclerosis burden and improve cardiovascular outcomes are needed. There is a strong inverse association between high-density lipoprotein (HDL) cholesterol and risk of coronary heart disease in epidemiological studies.^{3,4}

Efforts to increase HDL cholesterol levels have included administration of oral compounds that interfere with lipid metabolic pathways and result in sustained increase in HDL levels over time or short-term infusion of reconstituted HDL to take advantage of its potent biological properties.⁵ A provocative clinical study has suggested

Context High-density lipoprotein (HDL) cholesterol is an inverse predictor of coronary atherosclerotic disease. Preliminary data have suggested that HDL infusions can induce atherosclerosis regression.

Objective To investigate the effects of reconstituted HDL on plaque burden as assessed by intravascular ultrasound (IVUS).

Design and Setting A randomized placebo-controlled trial was conducted at 17 centers in Canada. Intravascular ultrasound was performed to assess coronary atheroma at baseline and 2 to 3 weeks after the last study infusion.

Patients Between July 2005 and October 2006, 183 patients had a baseline IVUS examination and of those, 145 had evaluable serial IVUS examinations after 6 weeks.

Intervention Sixty patients were randomly assigned to receive 4 weekly infusions of placebo (saline), 111 to receive 40 mg/kg of reconstituted HDL (CSL-111); and 12 to receive 80 mg/kg of CSL-111.

Main Outcome Measures The primary efficacy parameter was the percentage change in atheroma volume. Nominal changes in plaque volume and plaque characterization index on IVUS and coronary score on quantitative coronary angiography were also prespecified end points.

Results The higher-dosage CSL-111 treatment group was discontinued early because of liver function test abnormalities. The percentage change in atheroma volume was -3.4% with CSL-111 and -1.6% for placebo ($P=.48$ between groups, $P<.001$ vs baseline for CSL-111). The nominal change in plaque volume was -5.3 mm^3 with CSL-111 and -2.3 mm^3 with placebo ($P=.39$ between groups, $P<.001$ vs baseline for CSL-111). The mean changes in plaque characterization index on IVUS (-0.0097 for CSL-111 and 0.0128 with placebo) and mean changes in coronary score (-0.039 mm for CSL-111 and -0.071 mm with placebo) on quantitative coronary angiography were significantly different between groups ($P=.01$ and $P=.03$, respectively). Administration of CSL-111 40 mg/kg was associated with mild, self-limiting transaminase elevation but was clinically well tolerated.

Conclusions Short-term infusions of reconstituted HDL resulted in no significant reductions in percentage change in atheroma volume or nominal change in plaque volume compared with placebo but did result in statistically significant improvement in the plaque characterization index and coronary score on quantitative coronary angiography. Elevation of HDL remains a valid target in vascular disease and further studies of HDL infusions, including trials with clinical end points, appear warranted.

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that short-term infusions of HDL containing a naturally occurring variant of apolipoprotein A-I (Milano) can induce regression of coronary atherosclerosis.⁶ However, interpretation of

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this study was limited by the small sample size and imbalances among groups in plaque burden at baseline.

CSL-111 is reconstituted HDL consisting of apolipoprotein A-I from human plasma combined with soybean phosphatidylcholine and chemically and biologically resembles native HDL. The primary objective of the current study was to assess the safety and efficacy of CSL-111 on coronary atherosclerosis as assessed by intravascular ultrasonography (IVUS) and quantitative coronary angiography. Based on prior observations of biological activity in clinical studies,⁷⁻⁹ we hypothesized that CSL-111 would rapidly decrease atherosclerotic plaque burden when administered as a series of weekly infusions to patients with recent acute coronary syndromes.

METHODS

Study Design and Population

Between July 2005 and October 2006, 183 patients with a clinical need for coronary angiography were randomly assigned to receive either placebo (normal saline) or CSL-111 infusions within 2 weeks of having an acute coronary syndrome defined as unstable angina, or non-ST-segment or ST-segment elevation myocardial infarction. Eligible patients were women (without childbearing potential) and men between the ages of 30 and 75 years. Patients had to have at least 1 narrowing of 20% or more on coronary angiography at baseline.

Patients with greater than 50% stenosis in the left main coronary artery, renal insufficiency, liver disease (aspartate aminotransferase or alanine aminotransferase more than 1.5 times the upper limit of normal), active cholecystitis or gallbladder symptoms, uncontrolled diabetes mellitus, New York Heart Association class III or IV heart failure, known soybean allergy, history of alcohol or drug abuse, planned treatment with warfarin or heparin during the study infusion period, or previous or planned coronary bypass graft surgery were excluded from study participation. Institutional ethics commit-

tees approved the protocol at all 17 Canadian study centers, and all trial patients provided written informed consent.

The Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) study was a randomized, double-blind, placebo-controlled trial. Qualifying patients were randomly assigned to receive 4 weekly volume-matched infusions of either placebo or 40 mg/kg or 80 mg/kg of CSL-111.

Prior to the first infusion, a baseline IVUS examination of the designated target coronary artery was performed and delivered to the Montreal Heart Institute core IVUS laboratory for a quality assessment. The proximal 4 cm of the target coronary artery in which IVUS was performed at baseline needed to have a reference diameter of 2.5 mm or more, be free of filling defects suggestive of thrombosis, not have more than a 50% reduction in lumen diameter by visual angiographic estimation at baseline, and not have undergone previous percutaneous coronary intervention nor have been a candidate for intervention at the time of the baseline catheterization. Because the acute coronary syndrome-related artery often undergoes percutaneous coronary intervention, this artery could not be chosen when an intervention was performed. Two to 3 weeks after the last study infusion, a follow-up IVUS was performed in the same segment of the target artery studied at baseline.

Patient safety was monitored throughout the trial with particular emphasis on liver function test results. An independent, unblinded safety review committee met at intervals during the trial. Liver function test data were monitored on an ongoing basis throughout the study.

Intervention and Blinding

CSL-111 (CSL Ltd, Parkville, Australia) consists of apolipoprotein A-I isolated from human plasma and phosphatidylcholine derived from soybean in a molar ratio of 1:150. The viral safety of plasma-derived apolipoprotein A-I is

based on the use of screened blood donations and virus elimination and inactivation steps used in its preparation.¹⁰ CSL-111 is presented as a lyophilisate in 250-mL infusion bottles and reconstituted with 50 mL of sterile water for injection, yielding 62.5 mL of clear, pale yellow solution, pH 7.5, and 10% sucrose concentration as a stabilizing agent.

The site pharmacist and clinical staff member infusing the study drug were unblinded to individual patient treatment allocation but had no other role in study conduct. All other site personnel, patients, blinded study monitor, study management team, and sponsor were blinded to treatment allocation. To ensure adequate blinding, both the placebo saline solution and CSL-111 solutions were shrouded after preparation by the pharmacist and remained shrouded until the infusions were administered and returned to the pharmacy.

IVUS and Coronary Angiography

The methods for IVUS image acquisition and measurement in atherosclerosis studies have been previously described.¹¹⁻¹⁵ Intravascular ultrasound examinations were performed using 40-MHz catheters at baseline and follow-up. The same dose of intracoronary nitroglycerin (0.15 mg) was administered prior to IVUS performed at both time points. All IVUS examinations were analyzed at the Montreal Heart Institute core laboratory by experienced technicians supervised by a cardiologist blinded to treatment assignment, according to published standards.¹⁶

The lumen and external elastic membrane borders were manually traced on digitized cross-sections at every 1 mm in the 30-mm segment of interest at baseline and follow-up. Plaque, lumen, and total vessel volumes were computed for the entire length of the analyzed segments by multiplying the corresponding areas of each cross-section by the distance between neighboring slices and then adding all the products.

We also performed an analysis of plaque characterization on baseline and follow-up IVUS examinations, as previously described.^{13,15,17} A total of 6 matched IVUS cross-sections were selected at every 5 mm in the 30-mm segment. Every chosen cross-section was divided into 5 regions, according to types of plaque present (calcific, fibrotic, fibrohypoechoic, hypoechoic, and normal). The arc of each region was measured in degrees centered on lumen and the inner perimeter was measured at the lumen-to-wall interface. Arc and inner perimeter plaque characterization scores were calculated for each cross-section, by means of weighting factors^{13,15}:

$$([0 \times \text{Normal}] + [1 \times \text{Hypoechoic}] + [1.5 \times \text{Fibrohypoechoic}] + [2 \times \text{Fibrotic}] + [3 \times \text{Calcific}] / (\text{Normal} + \text{Hypoechoic} + \text{Fibrohypoechoic} + \text{Fibrotic} + \text{Calcific}).$$

The arc and inner perimeter plaque characterization indexes were created by summation of the respective scores from each cross-section, divided by the number of cross-sections analyzed.

Meticulous care was taken to ensure identical conditions during the angiographic examinations at baseline and follow-up (catheters, contrast media, projections). Intracoronary nitroglycerin (0.15 mg) was administered into each coronary artery before angiographic injection. The segments of interest were visualized in multiple transverse and sagittal views to clearly separate stenoses from branches, minimize foreshortening, and obtain views as perpendicular as possible to the long-axis of the segments to be analyzed.

All angiograms were analyzed at the Montreal Heart Institute quantitative coronary angiography core laboratory using the clinical measurements solutions system (MEDIS, Leiden, the Netherlands).¹⁸ Quantitative coronary angiography was performed by experienced technicians who were blinded to treatment groups and supervised by an expert physician in matched projections from baseline and follow-up angiograms.¹⁸ For each lesion, an end-

diastolic frame from both angiograms was selected with identical angulations that best showed the stenosis at its most severe degree with minimal foreshortening and branch overlap. All intervened coronary arteries were excluded from the analysis.

Efficacy Parameters

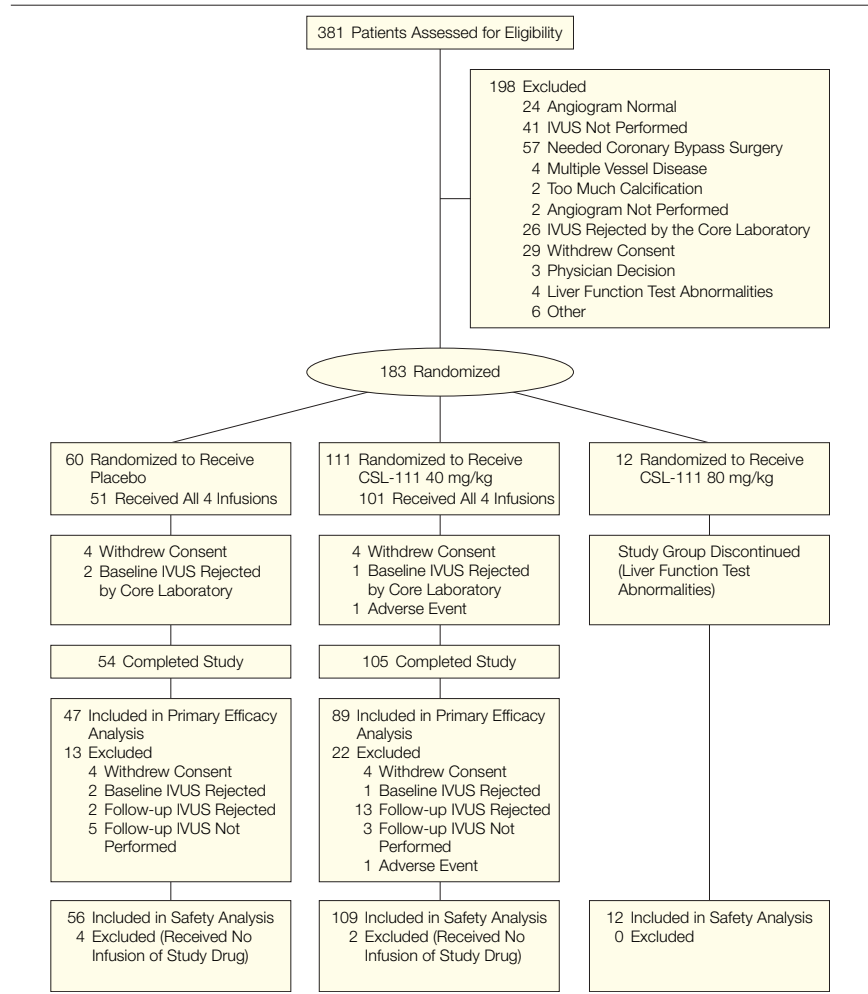
The primary efficacy end point was the percentage change in atheroma volume ($[(\text{follow-up} - \text{baseline})/\text{baseline}] \times 100$) on IVUS. Secondary efficacy measures included the absolute (nominal) change in plaque volume, the change in plaque characterization indexes on IVUS, and the change in coronary score (defined as the per-patient

mean of the minimal lumen diameter for all lesions measured) on quantitative coronary angiography.

Safety Evaluations

Patient safety was assessed by monitoring adverse events, physical examinations, electrocardiograms, and clinical laboratory results. All blood-related analyses were carried out centrally (Mayo Trial Services, Rochester, Minn). Local transaminases values were obtained immediately prior to study infusions, and these samples were also sent for central laboratory analysis. If the local values were 1.5 times or more above the upper limit of normal, the infusion was not administered and was

Figure. Disposition of Patients in the Trial



IVUS indicates intravascular ultrasound.

Table 1. Baseline Characteristics

	Placebo (n = 60)	CSL-111 (Reconstituted HDL)		Total No. of Patients (N = 183)
		40 mg/kg (n = 111)	80 mg/kg (n = 12)	
Age, mean (SD), y	57.4 (9.1)	57.5 (8.6)	60.5 (9.0)	57.7 (8.8)
Men, No. (%)	50 (83.3)	92 (82.9)	10 (83.3)	152 (83.1)
Weight, mean (SD), kg	85.4 (16.2)	84.6 (17.1)	87.6 (18.8)	85.1 (16.9)
Risk factors, No. (%)				
Current smoking	4 (6.7)	15 (13.5)	0	19 (10.4)
Dyslipidemia	59 (98.3)	110 (99.1)	12 (100)	181 (98.9)
Hypertension	33 (55.0)	64 (57.7)	7 (58.3)	104 (56.8)
Diabetes	8 (13.3)	26 (23.4)	3 (25.0)	37 (20.2)
Prior MI	14 (23.3)	18 (16.2)	5 (41.7)	37 (20.2)
Prior PCI	3 (5.0)	10 (9.0)	3 (25.0)	16 (8.7)
Lipid-lowering agent at baseline	54 (90.0)	101 (91.0)	12 (100)	167 (91.3)
Cholesterol, mean (SD), mg/dL				
LDL	82.6 (29.0)	81.9 (34.0)	78.0 (30.8)	81.9 (32.0)
HDL	41.7 (10.3)	42.5 (11.2)	43.2 (13.1)	42.1 (10.8)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention.
SI conversion: To convert HDL and LDL from mg/dL to mmol/L, multiply by 0.0259.

rescheduled for the following week. The infusions could be delayed more than once during the trial for transaminase abnormalities, but patients were discontinued from the study if they were not eligible for infusion at 2 consecutive visits. Patients returned to the clinic 24 hours after each infusion for a blood draw. When transaminase values were more than 5 times the upper limit of normal, patients were asked to return for follow-up blood tests within 72 hours after the prior samples were obtained.

Statistical Analysis

The prospective primary analysis was initially planned to be carried out by comparing changes between study groups. A sample size of 180 patients was required to provide a power of 80% to detect a 3% difference in percentage change in plaque volume (standard deviation of percentage change in plaque volume 6%) between the placebo group and the 2 active combined groups with a 2-sided significance level of .05, assuming a 20% loss to follow-up.

However, after a planned interim review of safety data in December 2005, the safety review committee recommended that the CSL-111 80-mg/kg

treatment group be discontinued based on marked abnormalities in liver function. At the time, 12 patients had been randomly assigned to the 80-mg/kg group. It was hypothesized that the early discontinuation of the 80-mg/kg group could diminish the study's ability to detect significant differences between the active and control groups.

The protocol was therefore amended while all investigators and study personnel remained blinded to focus the primary analysis on the percentage change from baseline in the active group. As specified in the study protocol, additional patients were randomly assigned to either the CSL-111 40-mg/kg or placebo groups until the original target number of patients was reached. The original sample size of 180 patients would provide a power of 80% to detect a change from baseline in atheroma volume of 1.74% in the active treatment groups with a 2-sided significance level of 5%, assuming a standard deviation of 6% and a dropout rate of 20%.

Efficacy results are presented by modified intention-to-treat analysis while safety data are provided for all patients who received at least 1 study infusion. The primary efficacy end point was the percentage change in atheroma volume measured by IVUS. For this analysis of

comparison within groups from baseline to follow-up, a Wilcoxon signed rank test was performed. Comparison between treatment groups was carried out with a Mann-Whitney test. Absolute change in plaque volume was analyzed similarly. The protocol-specified primary analysis was based on modified intent-to-treat population for randomized patients with complete data for the primary end point. In order to determine the effect of missing follow-up data on the primary end point, the last-observation-carried-forward approach including all randomized patients with evaluable baseline data was used as a sensitivity analysis.

For change in plaque characterization indexes and change in coronary score on quantitative coronary angiography, an analysis of covariance model was used adjusting for baseline value and IVUS site. No adjustments for multiple comparisons were carried out. All statistical analyses were performed using SAS statistical software version 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Demographics

One hundred eighty-three patients were randomized: 60 in the placebo group, 111 in the CSL-111 40 mg/kg group, and 12 in the 80 mg/kg group (FIGURE). One hundred forty-five patients remained in the study and had evaluable IVUS examinations at both baseline and follow-up (47 for placebo, 89 for CSL-111 40 mg/kg, and 9 for 80 mg/kg). Baseline patient characteristics were similar between groups (TABLE 1).

Efficacy Results

Intravascular ultrasound results are described in TABLE 2. Plaque volume at baseline was similar in both groups: mean values were 158.3 mm³ for placebo and 151.0 mm³ for CSL-111 40 mg/kg. The interval between baseline and follow-up IVUS examinations was a mean (SD) of 43.5 (6.4) days in the placebo group and 43.4 (6.4) days in the CSL-111 group. The difference between study groups for the percentage change in atheroma volume was not statistically sig-

nificant ($P = .48$). The percentage change in atheroma volume in the CSL-111 40-mg/kg group was -3.41% (interquartile range [IQR], -6.55 to 1.88 ; $P < .001$ vs baseline). For the placebo group, the corresponding change was -1.62% (IQR, -5.95 to 1.94 ; $P = .07$ vs baseline). The difference in absolute change in plaque volume was not statistically significant between groups ($P = .39$). The absolute change in plaque volume was -5.34 mm^3 (IQR, -9.11 to 2.25) in the CSL-111 40-mg/kg group ($P < .001$ vs baseline). The corresponding change was -2.33 mm^3 for placebo (IQR, -9.41 to 3.31 ; $P = .04$ vs baseline).

The baseline characteristics of the 38 patients not included in the primary analysis did not differ from the characteristics of the 145 patients included in the primary analysis. In an additional analysis, a 0% change in plaque volume was imputed for patients with missing plaque volume at follow-up. The results were similar for the sensitivity and primary analyses. In the sensitivity analysis, the difference between study groups was not statistically significant ($P = .48$); the percentage change in atheroma volume was -1.1% for CSL-111 ($P < .001$ vs baseline) and -0.1% for placebo ($P = .07$ vs baseline).

In a sensitivity analysis assuming a 0- mm^3 change in plaque volume for patients with missing follow-up data, the absolute change in plaque volume was -1.2 mm^3 (IQR, -8.3 to 0.8 mm^3) in the 40-mg/kg CSL-111 group ($P < .001$ vs baseline) and -0.1 mm^3 (IQR, -6.4 to 2.3 mm^3) in the placebo group ($P = .04$). The difference between study groups was not statistically significant ($P = .42$).

The evolution of both plaque characterization indexes (arc and inner perimeter) on IVUS was significantly different between study groups ($P = .01$ for both, Table 2). With quantitative coronary angiography assessment of all coronary arteries, there was a significant interaction between coronary score at baseline and

the study treatment ($P = .03$). The mean (SD) number in the placebo group was 6.90 (4.05) segments per patient and in the CSL-111 group it was 6.60 (3.18) segments per patient. Estimated means were therefore tested at specific values (first quartile, median, and third quartile) of the coronary score at baseline (TABLE 3). For

Table 2. Intravascular Ultrasound Results

	Placebo (n = 47)	CSL-111 (Reconstituted HDL) (n = 89)
Plaque volume, mm^3		
Baseline, mean (SD)	158.3 (66.3)	151.0 (64.1)
Baseline, median (IQR)	151.4 (118.2 to 201.3)	146.0 (105.2 to 195.1)
Follow-up, mean (SD)	154.6 (65.7)	147.1 (62.5)
Follow-up, median (IQR)	144.2 (116.4 to 193.3)	136.6 (98.2 to 189.5)
Median change (IQR)	-2.33 (-9.41 to 3.31)	-5.34 (-9.11 to 2.25)
P value vs baseline	.04	<.001
P value vs placebo		.39
Change in atheroma volume, %		
Median change (IQR)	-1.62 (-5.95 to 1.94)	-3.41 (-6.55 to 1.88)
P value for change	.07	<.001
P value vs placebo		.48
Intravascular Ultrasound Assessment of Plaque Characterization Indexes		
Change in arc plaque characterization index		
Baseline, mean (SD)	1.0818 (0.4158)	1.0383 (0.4131)
Follow-up, mean (SD)	1.0963 (0.4134)	1.0347 (0.4111)
LSM change (95% CI)	0.0137 (0.0001 to 0.0273)	-0.0083 (-0.0193 to 0.0027)
Median change (IQR)	0.0022 (-0.0096 to 0.0231)	-0.0001 (-0.0187 to 0.0120)
P value vs baseline	.05	.14
P value vs placebo		.01
Change in inner perimeter plaque characterization index		
Baseline, mean (SD)	1.0736 (0.4147)	1.0296 (0.4125)
Follow-up, mean (SD)	1.0866 (0.4126)	1.0237 (0.4085)
LSM change (95% CI)	0.0128 (-0.0009 to 0.0266)	-0.0097 (-0.0208 to 0.0015)
Median change (IQR)	0.0032 (-0.0068 to 0.0189)	-0.0034 (-0.0210 to 0.0164)
P value vs baseline	.07	.09
P value vs placebo		.01

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; IQR, interquartile range; LSM, least square means.

Table 3. Changes in Coronary Score on Quantitative Coronary Angiography From Baseline to Follow-up*

Coronary Score at Baseline on QCA	Placebo (n = 48)	CSL-111 40 mg/kg (n = 102)	Estimated Difference Between Groups (95% CI)	P Value Between Groups
Overall No. of arterial segments per patient, mean (SD)	6.90 (4.05)	6.60 (3.18)		
Change in score, LSM (SE) [95% CI]				
1.763 mm (25th percentile)	-0.034 (0.012) [-0.059 to -0.010]	-0.035 (0.010) [-0.055 to -0.016]	0.001 (-0.029 to 0.031)	.95
2.004 mm (50th percentile)	-0.052 (0.011) [-0.074 to -0.030]	-0.037 (0.008) [-0.054 to -0.020]	-0.015 (-0.041 to 0.011)	.26
2.265 mm (75th percentile)	-0.071 (0.013) [-0.097 to -0.046]	-0.039 (0.009) [-0.057 to -0.021]	-0.032 (-0.062 to -0.003)	.03

Abbreviations: CI, confidence interval; LSM, least square means; QCA, quantitative coronary angiography. Blank spaces indicate not applicable.

*There was a significant interaction between study treatment and baseline coronary score on QCA ($P = .03$), indicating that the difference between the 2 study groups is not constant across values of baseline coronary score. Estimated means were therefore tested at specific values (first quartile, median, and third quartile) of the coronary score at baseline. Values (in mm) are presented as least square means (SE).

Table 4. Adverse Events in Patients Who Received at Least One Infusion of Study Drug

Adverse Event	No. (%) of Patients		
	Placebo (n = 56)	CSL-111 (Reconstituted HDL)	
		40 mg/kg (n = 109)	80 mg/kg (n = 12)
Nausea or vomiting	6 (10.7)	7 (6.4)	1 (8.3)
Diarrhea	8 (14.3)	9 (8.3)	2 (16.7)
Abdominal pain	1 (1.8)	4 (3.7)	0
Headache	7 (12.5)	15 (13.8)	1 (8.3)
Fatigue	10 (17.9)	11 (10.1)	3 (25.0)
Arthralgia	4 (7.1)	6 (5.5)	0
Hypotension	4 (7.1)	15 (13.8)	0
Death	0	0	0
Myocardial infarction	1 (1.8)	0	1 (8.3)
Unstable angina	2 (3.6)	2 (1.8)	1 (8.3)
Resuscitated cardiac arrest	0	1 (0.9)	0
Stroke or TIA	1 (1.8)	0	0
Liver function tests			
Alanine aminotransferase			
>3 × ULN	3 (5.4)	9 (8.3)	7 (58.3)
>5 × ULN	0	3 (2.8)	6 (50.0)
>10 × ULN	0	1 (0.9)	4 (33.3)
Aspartate aminotransferase			
>3 × ULN	2 (3.6)	8 (7.3)	6 (50.0)
>5 × ULN	0	2 (1.8)	4 (33.3)
>10 × ULN	0	1 (0.9)	3 (25.0)
Bilirubin*			
>2 × ULN	1 (1.8)	2 (1.8)	5 (41.7)
>3 × ULN	0	1 (0.9)	1 (8.3)

Abbreviations: HDL, high-density lipoprotein; TIA, transient ischemic attack; ULN, upper limit of normal.

*Increased total bilirubin is due mostly to elevation in unconjugated fraction.

a coronary score of 2.265 mm at baseline, the least squares mean (SE) change in coronary score was -0.039 mm (0.009 mm) in the CSL-111 40-mg/kg group and -0.071 mm (0.013 mm) with placebo ($P = .03$).

Safety Results

Major adverse events are shown in TABLE 4. CSL-111 was generally well tolerated and clinical events were generally mild or moderate, and there was no difference in overall frequency between treatment and placebo groups. Liver function test abnormalities occurred in both CSL-111 dose groups and in a small number of placebo patients. All increases in liver function tests were self-limiting and returned to normal without clinical consequence or intervention. Alanine aminotransferase levels exceeded 100-fold the upper limit of normal in some patients receiving 80 mg/kg

of CSL-111. Increases in transaminases peaked the day following study drug administration, consistently declined on subsequent days, and were reversible in all patients. Elevation in bilirubin was almost entirely related to increase in the unconjugated fraction.

No patient experienced major clinical adverse events as a result of these elevations. In particular, the liver function test abnormalities in the high-dose group were not associated with hepatic failure or encephalopathy. The only adverse event of note with a higher incidence in the CSL-111 40-mg/kg group than placebo was hypotension (13.8% vs 7.1%).

COMMENT

This study showed differences in coronary atheroma volume after 4 weekly infusions of CSL-111 or placebo (-3.4% vs -1.6% , -5.3 mm³ vs -2.3 mm³, respectively), but the differences between these

groups were not statistically significant. However, CSL-111 may nevertheless potentially induce some favorable vascular effects as seen in the significant reductions of atheroma volume of 3.4% or 5.3 mm³ with active infusions in the analysis comparing follow-up to baseline values. Although the latter finding is not significantly different when compared with placebo and is only suggestive of a possible favorable treatment effect, both the plaque characterization indexes on IVUS and coronary score on quantitative coronary angiography revealed statistically significant differences between CSL-111 and placebo groups that support this analysis.

Good correlations have been observed between histology and IVUS findings for the different atherosclerotic plaque types.¹⁹ The significantly different evolution of plaque characterization indexes^{13,15,17} between treatment groups, along with the other IVUS and quantitative coronary angiography results, suggests that short-term CSL-111 infusions had effects on atherosclerotic plaque (and vascular biology) that were different from those of placebo (statin alone). In contrast, the increase in plaque echogenicity that we have observed in the placebo group was likely due to the effects of statin therapy as this has previously been shown.²⁰

Coronary score is an angiographic measurement that has been used as a valid marker of atherosclerosis progression-regression in studies over the past 15 years.²¹ The benefit of CSL-111 compared with placebo in terms of improved coronary score (0.032 mm) in those patients with a higher baseline measure is not unlike that observed after 2 years of statin treatment.^{21,22} Given the known longer-term prognostic value of changes on quantitative coronary angiography,²³ our results also contribute to the rationale for larger, longer, and more definitive clinical studies of CSL-111 with morbidity and mortality end points. However, these results do not yet provide the rationale for clinical application. Such larger clinical outcomes trials will also help to validate the imaging end points.

The results from this study compare favorably with those from a similar one conducted with reconstituted HDL containing apolipoprotein A-I Milano (ETC-216).⁶ However, there are important differences between studies. Our study was 3 times larger; had administered 4 rather than 5 infusions; included patients with a substantially lower plaque burden shown on baseline IVUS; and used an agent, CSL-111, that contains wild-type apolipoprotein A-I rather than a mutant form. These latter 3 factors might be expected to make detecting plaque reduction more challenging in the current study. Nevertheless, the reduction in atheroma volume in our study (albeit not statistically significant vs placebo in either study) was relatively similar, -3.4% with CSL-111 vs -4.2% for ETC-216. Even though the absolute reduction in plaque volume appeared to be greater with apolipoprotein A-I Milano, there were important baseline differences with much larger plaque volumes in the active group than in the placebo group (268.4 vs 172.6 mm³) in the apolipoprotein A-I Milano study. This raises the possibility that regression to the mean may have contributed to the apparent effect in that study.

Reduction in atheroma volume from baseline was observed in the placebo groups in both studies (-2.9 mm³ or -1.6% in the Milano study). The reason for this is unclear but may be in part due to the relatively small number of placebo-treated patients. Alternatively, this observation may perhaps explain in part the rapid clinical benefits (within a few months) associated with intensive statin therapy in patients with acute coronary syndromes.^{24,25} Indeed, more than 90% of patients in our study were taking a statin.

Although the exact mechanism by which HDL positively influences coronary heart disease has not been fully elucidated, enhancement of cholesterol efflux and reverse cholesterol transport is considered an important target for anti-atherosclerotic therapy.²⁶⁻³¹ High-density lipoprotein may also protect LDL from oxidation and decrease the expression of adhesion molecules and chemo-

kines, which contribute to the formation of atherosclerotic plaques.²⁹ High-density lipoprotein may improve the stability of existing plaques and reduce the susceptibility for plaque rupture.²⁹

Several strategies are being used to leverage the effects of HDL and the reverse cholesterol transport mechanism in the development of new therapeutic agents.⁵ The disappointing results recently reported with torcetrapib despite large increases in HDL cholesterol illustrate the difficulties and risks associated with attempting to demonstrate clinical efficacy and safety of novel therapies.³² Although a larger trial with CSL-111 may have helped to address some of the issues discussed above, we thought that a larger study would have been premature as an early assessment in patients with coronary disease, especially considering the levels of safety (numbers of visits and blood draws) and efficacy (2 invasive procedures within a short period) evaluations involved in our study. CSL-111 (reconstituted HDL) administered at a dose of 80 mg/kg was associated with a high incidence of liver function test abnormalities and led to the early discontinuation of this study group. These changes returned toward normal after stopping the treatment, and there was no evidence of liver failure or permanent damage. Although minor changes in liver function commonly occurred in patients given 40 mg/kg of CSL-111, these were mild to moderate, self-limiting, and not associated with hepatic dysfunction indicators, such as increase in conjugated bilirubin or prothrombin time. CSL-111 was otherwise well tolerated.

In conclusion, short-term infusions of reconstituted HDL resulted in no significant reductions in percentage change in atheroma volume or nominal change in plaque volume compared with placebo but did result in statistically significant improvement in the plaque characterization index and coronary score on quantitative coronary angiography. The clinical significance of these findings is not known. Elevation

of HDL remains a valid target in vascular disease and further clinical evaluation of HDL infusions with longer follow-up appears warranted.

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