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Coronary Atheroma Regression From Infusions of Autologous Selectively Delipidated Preβ-HDL-Enriched Plasma in Homozygous Familial Hypercholesterolemia

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Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels. Despite aggressive therapy with multiple LDL-lowering therapies, patients face premature mortality, needing additional therapies beyond LDL reduction to improve outcomes. Preβ–high-density lipoprotein (HDL) is the only form of HDL that is effective in removing cholesterol from lipid-laden macrophages, the initial step in reverse cholesterol transport; however, preβ-HDL is present in very low concentrations in plasma. To increase the levels of preβ-HDL and turbocharge reverse cholesterol transport, HDL Therapeutics, Inc., has developed a novel plasma delipidation system (PDS-2) to selectively delipidate plasma HDL and convert α-HDL to preβ-HDL. Autologous plasma is collected via plasmapheresis, processed offline using the PDS-2 System, and then reinfused back into the patient.

In a previous 28-subject acute coronary syndrome (ACS) study, we have documented that 7 weekly infusions of autologous delipidated preβ-HDL–enriched plasma can reduce coronary plaques assessed by intravascular ultrasound (1). In the present study, we determined the effects of 7 weekly infusions of autologous delipidated preβ-HDL–enriched plasma on coronary atheroma assessed by coronary computed tomography angiography (CCTA) in 6 HoFH patients (5 male, 1 female, >17 years of age) studied at baseline and after 7 weekly infusions. Inclusion criteria required the clinical phenotypic diagnosis of HoFH and having ≥20% luminal stenosis on CCTA at base-line and being on stable lipid-lowering therapy. The primary endpoint was change in total coronary atheroma cross-sectional area. Secondary endpoints were changes in atheroma of differing composition. A total of 16 coronary plaques were identified and compared between baseline and follow-up by quantitative CCTA imaging analyzed in a blinded fashion (2). The study protocol was approved by the human investigation review committees of Ecogene-21 (Advarra Institutional Review Board Services, Aurora, Ontario, Canada), Cedars-Sinai Medical Center (Los Angeles, California), and Boston Children's Hospital (Boston,Massachusetts). Written informed con-sent was obtained from each study subject.

All infusions were well tolerated with no significant adverse reactions, including effects on laboratory parameters including hematology and metabolic profile. Analysis of median pre- and post-infusion lipoprotein values revealed reductions in LDL-C (−19%) and HDL-C (−18%) and marked increases (+66%) in percentage of preβ-HDL ($P < 0.0001$). The study met its primary endpoint with a significant reduction in the total atheroma cross-sectional area (−18%; $p = 0.023$). This decrease was driven by a reduction of low-density (−38%; $p = 0.005$) and necrotic core (−33%; $p = 0.007$) plaques. Similarly, the volume of low-density (−42%; $p = 0.003$) and necrotic core (−35%; $p = 0.003$) plaques were significantly reduced (Table 1). Virtually identical changes and levels of statistical significance were noted when plaques were analyzed on a per patient basis (Table 1).

TABLE 1 Effect of Delipidated-HDL Infusion on Atheroma in Familial Hypercholesterolemia

	Baseline	Follow-Up	Absolute Change*	Relative Change	p Value†	p Value‡
Atheroma cross-sectional area, mm^2§						
Total	9.9 ± 3.5	8.2 ± 2.4	-1.8 ± 2.8	-18%	0.023	0.011
Noncalcified	9.0 ± 3.5	7.2 ± 1.9	-1.8 ± 2.5	-20%	0.015	0.003
Low-density NCP	1.6 ± 0.8	1.0 ± 0.5	-0.6 ± 0.6	-38%	0.005	<0.001
Necrotic core	1.5 ± 0.7	1.0 ± 0.5	-0.5 ± 0.6	-33%	0.007	<0.001
Fibrofatty	4.0 ± 1.9	3.2 ± 0.8	-0.8 ± 1.7	-20%	0.121	0.053
Volume, mm^3						
Low-density NCP	35.2 ± 38.1	20.6 ± 22.9	-14.6 ± 17.5	-42%	0.003	0.001
Necrotic core	31.6 ± 32.2	20.4 ± 22.7	-11.2 ± 14.2	-35%	0.003	0.001

Values are mean ± SD. n = 16 plaques. Analysis software used was Autoplaque (Cedars-Sinai Medical Center, Los Angeles, California). *Absolute change calculated as the difference between follow-up and baseline. †Significant differences between pre- and post-infusion measurements per plaque were assessed by Wilcoxon signed rank test, using STATA 14.0. ‡Significant differences between pre- and post-infusion measurements per patient were assessed by univariable multilevel mixed-effects regression adjusting for within-patient correlation, using STATA 15.0. §Atheroma cross-sectional area was calculated as follows: plaque volume/plaque length.

HDL = high-density lipoprotein; NCP = noncalcified plaque.

Recent reports of other types of HDL infusions by Nicholls et al. (3,4) have been negative. Five weekly infusions of a reformulated apoA-I Milano preparation in statin-treated ACS patients did not reduce percent coronary atheroma volume as assessed by intravascular ultrasound and a negative result was also reported for ACS patients in the Coronary Angioplasty and Rotablator Atherectomy (CARAT) trial who received 10 weekly infusions of a recombinant HDL mimetic (3,4). In contrast, preβ-HDL generated by PDS-2 is similar to normal preβ-HDL in electrophoretic mobility, chemical composition, and metabolism with preserved lecithin-cholesterol acyltransferase activity.

In our study, 7 weekly infusions of preβ-HDL-enriched autologous delipidated plasma in HoFH patients resulted in significant regression in total atheroma cross-sectional area, low-density, and necrotic core plaques. A large CCTA trial documented that low-density and necrotic core plaque types are the strongest predictor of fatal or nonfatal myocardial infarction (5).

Limitations of this study are the small sample size, which is due to the rare nature of the HoFH disease, and the lack of an untreated arm. However, the baseline CCTA analysis served as a comparator for the results after therapy. This study provides the first clinical proof for a functional reverse cholesterol pathway in humans. The marked reduction in low-density and necrotic core plaques, with preβ-HDL infusions fills a long-sought HDL-targeted treatment gap for high-risk patients with cardiovascular disease.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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