Journal of Clinical Lipidology (2016) 10, 356–367

Journal of Clinical Lipidology

Familial lecithin:cholesterol acyltransferase deficiency: First-in-human treatment with enzyme replacement

Robert D. Shamburek, MD*, Rebecca Bakker-Arkema, PharmD[1], Bruce J. Auerbach, PhD, Brian R. Krause, PhD, Reynold Homan, PhD, Marcelo J. Amar, MD, Lita A. Freeman, PhD, Alan T. Remaley, MD, PhD

Cardiovascular and Pulmonary Branch, National Heart, Lung and Blood Institute, NIH, Bethesda, MD, USA (Drs Shamburek, Amar, Freeman, Remaley); and AlphaCore Pharma, Ann Arbor, MI, USA (Drs Bakker-Arkema, Auerbach, Krause, Homan)

KEYWORDS:
Cholesterol;
HDL;
Triglyceride;
Renal disease;
Lecithin cholesterol acyltransferase;
Lecithin cholesterol acyltransferase deficiency;
LCAT;
Recombinant enzyme replacement;
Lipoprotein-X

BACKGROUND: Humans with familial lecithin:cholesterol acyltransferase (LCAT) deficiency (FLD) have extremely low or undetectable high-density lipoprotein cholesterol (HDL-C) levels and by early adulthood develop many manifestations of the disorder, including corneal opacities, anemia, and renal disease.

OBJECTIVE: To determine if infusions of recombinant human LCAT (rhLCAT) could reverse the anemia, halt progression of renal disease, and normalize HDL in FLD.

METHODS: rhLCAT (ACP-501) was infused intravenously over 1 hour on 3 occasions in a dose optimization phase (0.3, 3.0, and 9.0 mg/kg), then 3.0 or 9.0 mg/kg every 1 to 2 weeks for 7 months in a maintenance phase. Plasma lipoproteins, lipids, LCAT levels, and several measures of renal function and other clinical labs were monitored.

RESULTS: LCAT concentration peaked at the end of each infusion and decreased to near baseline over 7 days. Renal function generally stabilized or improved and the anemia improved. After infusion, HDL-C rapidly increased, peaking near normal in 8 to 12 hours; analysis of HDL particles by various methods all revealed rapid sequential disappearance of preβ-HDL and small α-4 HDL and appearance of normal α-HDL. Low-density lipoprotein cholesterol increased more slowly than HDL-C. Of note, triglyceride routinely decreased after meals after infusion, in contrast to the usual postprandial increase in the absence of rhLCAT infusion.

CONCLUSIONS: rhLCAT infusions were well tolerated in this first-in-human study in FLD; the anemia improved, as did most parameters related to renal function in spite of advanced disease. Plasma lipids transiently normalized, and there was rapid sequential conversion of small preβ-HDL particles to mature spherical α-HDL particles.

Published by Elsevier Inc. on behalf of National Lipid Association.

Introduction

Lecithin:cholesterol acyltransferase (LCAT) is a plasma enzyme that catalyzes the production of cholesteryl esters (CEs) from free cholesterol (FC) and phosphatidylcholine (lecithin).[1] In humans, about 90% of CE in plasma is

[1] Present address. MedImmune, LLC, Gaithersburg, MD, USA.

* Corresponding author. National Institutes of Health, 10 Center Dr. MSC 1666, Bldg. 10/Rm. 8N-202, Bethesda, MD 20892-1666, USA.

E-mail address: bobs@mail.nih.gov

Submitted December 12, 2015. Accepted for publication December 15, 2015.

1933-2874/Published by Elsevier Inc. on behalf of National Lipid Association.
http://dx.doi.org/10.1016/j.jacl.2015.12.007

synthesized by LCAT mainly in high-density lipoprotein (HDL).[2] It is believed that newly formed CE accumulates in the core of HDL particles, resulting in the maturation of HDL particles from small discoidal particles to mature, spherical α-HDL.[3] In humans, the resulting CE in mature HDL are then directly removed by the liver (minor route) or transferred to apolipoprotein B–containing lipoproteins by CE transfer protein (CETP; major route) and cleared via the classical hepatic low-density lipoprotein (LDL) receptor pathway,[2] originally described by Glomset as reverse cholesterol transport.[4]

Inherited mutations in the gene for LCAT result in 2 autosomal recessive forms of LCAT deficiency. Patients with a total loss of LCAT activity are classified as having familial LCAT deficiency (FLD) and have a marked decrease in HDL cholesterol (HDL-C) levels (<10 mg/dL), plasma CE <25% of total cholesterol (TC; normal >70%), mild-to-severe hypertriglyceridemia, lipoprotein-X (Lp-X) in plasma, corneal opacities, normochromic normocytic anemia, and progressive renal disease.[5–8] FLD patients often develop proteinuria as young adults and then go on to develop nephrotic syndrome and end-stage renal disease typically in their 40s and 50s.[1] There is no effective treatment except for dialysis or renal transplantation, and the disease can rapidly reoccur in the transplanted kidney.[9–11] Renal disease may develop secondary to the appearance of Lp-X, which is a vesicular-like abnormal lipoprotein particle rich in phospholipid (PL) and FC that accumulates in the kidney.[12] Patients with fish-eye disease have a partial LCAT deficiency with some residual LCAT activity.[1,8] These patients are relatively asymptomatic with no Lp-X or renal disease but have reduced HDL-C and corneal opacities.

FLD patients have an abnormal distribution of HDL subfractions; most of their plasma apoA-I is found in small, disc-shaped, poorly lipidated preβ-HDL particles and α-4 HDL particles containing PL and FC.[13] Interestingly, patients with LCAT deficiency do not have a markedly increased risk for cardiovascular disease in most studies,[1,14] likely because they also have low levels of LDL cholesterol (LDL-C) because of the decreased formation of CE on HDL, which are normally transferred from HDL to LDL by CETP.

Recently, recombinant human LCAT (rhLCAT; ACP-501) was shown to be safe in a phase I study of subjects with stable cardiovascular disease[15] (ClinicalTrials.gov NCT01554800) and is being developed as a potential therapy for acute coronary syndrome. In this report, we describe the first-in-human use of enzyme replacement therapy (ERT) with rhLCAT in a patient with FLD and its effect on lipoprotein metabolism and hematologic and renal function.

Methods

Study design

This single-center study was approved by the National Heart, Lung and Blood Institute, Institute Review Board, before patient recruitment. The subject provided informed consent before participation in the study. The study was conducted after Food and Drug Administration review under an Investigational New Drug 117100 as an Expanded Access Protocol. This is a first-in-human study of ACP-501 (rhLCAT) in a subject with FLD.

The subject was administered 1-hour intravenous infusions of rhLCAT (ACP-501) during a dose escalation optimization phase (0.9, 3.0, and 9.0 mg/kg over 22 days; Supplementary Fig. 1), followed by a maintenance phase of 10 infusions of each of the 2 higher doses weekly or biweekly over 7 months (Supplementary Table 1).

A detailed Methods section is available in the Supplementary data.

Statistics

Summary statistics were reported as percent change or fold change from prestudy levels or preinfusion baseline levels.

Results

Demographics of subject

A 52-year-old man with FLD and end-stage renal disease previously described[16] was enrolled in an expanded access use protocol (IND 117,100) to determine whether dialysis could be avoided or delayed. Over the 31 months before inclusion, the patient's renal function rapidly declined (creatinine increasing from 2.5 to 5.6 mg/dL), necessitating the placement of a fistula in his arm in anticipation of dialysis within weeks. Baseline labs included: blood urea nitrogen (BUN) 159 mg/dL, creatinine 5.6 mg/dL, estimated glomerular filtration rate (eGFR) 13 mLs/min/1.73 m^2, 24-hour urine protein 2307 mg, hemoglobin (HGB) 8.2 g/dL, hematocrit (HCT) 24.7%, TC 80 mg/dL, LDL-C 46 mg/dL, HDL-C <5 mg/dL, and triglyceride (TG) 147 mg/dL. See full clinical history in Supplementary data.

Summary of safety of rhLCAT

Over the 8-month course of rhLCAT (ACP-501) therapy (Supplementary Fig. 1), the patient received a total of 23 infusions that were well tolerated by the patient. There were no infusion site reactions or infusion toxicities. Other than favorable changes in creatinine, BUN, cystatin C, HGB, and HCT, as summarized in the following sections, there were no other clinically meaningful shifts in clinical laboratory parameters or physical examination during the study. There were 3 adverse events (AEs) (atrial fibrillation, a mild viral syndrome, and elective hemodialysis at the completion of the study) that were not attributed to ACP-501.

Atrial fibrillation, which occurred 72 hours after receiving the third dose of rhLCAT, was classified as an serious adverse event (SAE). The patient had a long history