Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency

Vassili Valayannopoulos[1], Vera Malinova[2], Tomas Honzík[2], Manisha Balwani[3], Catherine Breen[4], Patrick B. Deegan[5], Gregory M. Enns[6], Simon A. Jones[4], John P. Kane[7], Eveline O. Stock[8], Radhika Tripuraneni[9], Stephen Eckert[9], Eugene Schneider[9], Gavin Hamilton[10], Michael S. Middleton[10], Claude Sirlin[10], Bruce Kessler[11], Christopher Bourdon[12], Simeon A. Boyadjiev[13], Reena Sharma[14], Chris Twelves[15], Chester B. Whitley[16], Anthony G. Quinn[9,*]

[1]*Ref Centre IEM, Necker-Enf Malades Hosp, IMAGINE Institute and Paris Descartes University, Paris, France;* [2]*Department of Pediatrics, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic;* [3]*Department of Genetics and Genomic Sciences, The Mount Sinai School of Medicine, New York, NY, United States;* [4]*Manchester Centre for Genomic Medicine, St. Mary's Hospital, Manchester, UK;* [5]*Department of Medicine, Addenbrooke's Hospital, Cambridge, UK;* [6]*Department of Pediatrics, Lucile Packard Children's Hospital, Stanford University, Stanford, CA, United States;* [7]*Divisions of Endocrinology & Metabolism, University of California, San Francisco, CA, United States;* [8]*Divisions of Cardiology, University of California, San Francisco, CA, United States;* [9]*Synageva BioPharma Corp., Lexington, MA, United States;* [10]*University of California, San Diego, CA, United States;* [11]*Eureka Internal Medicine, Eureka, CA, United States;* [12]*Health Sciences North, Sudbury, Ontario, Canada;* [13]*University of California, Davis Medical Center, Department of Pediatrics, Section of Genetics, Davis, CA, United States;* [14]*Salford Royal NHS Foundation Trust, Salford, UK;* [15]*Leeds Institute of Cancer and Pathology, Leeds, UK;* [16]*University of Minnesota, Minneapolis, MN, United States*

Background & Aims: Lysosomal acid lipase deficiency is an autosomal recessive enzyme deficiency resulting in lysosomal accumulation of cholesteryl esters and triglycerides. LAL-CL04, an ongoing extension study, investigates the long-term effects of sebelipase alfa, a recombinant human lysosomal acid lipase.

Methods: Sebelipase alfa (1 mg/kg or 3 mg/kg) was infused every-other-week to eligible subjects. Safety and tolerability assessments, including liver function, lipid profiles and liver volume assessment, were carried out at regular intervals.

Results: 216 infusions were administered to eight adult subjects through week 52 during LAL-CL04. At week 52, mean alanine aminotransferase and aspartate aminotransferase levels were normal with mean change from baseline of −58% and −40%. Mean changes for low-density lipoprotein, total cholesterol, triglyceride and high-density lipoprotein were −60%, −39%, −36%, and +29%, respectively. Mean liver volume by magnetic resonance imaging and hepatic proton density fat fraction decreased (12% and 55%, respectively). Adverse events were mainly mild and unrelated to sebelipase alfa. Infusion-related reactions were uncommon: three events of moderate severity were reported in two subjects; one patient's event was suggestive of a hypersensitivity-like reaction, but additional testing did not confirm this, and the subject has successfully re-started sebelipase alfa. Of samples tested to date, no anti-drug antibodies have been detected.

Conclusions: Long-term dosing with sebelipase alfa in lysosomal acid lipase-deficient patients is well tolerated and produces sustained reductions in transaminases, improvements in serum lipid profile and reduction in the hepatic fat fraction. A randomized, placebo-controlled phase 3 trial in children and adults is underway (ARISE: NCT01757184).

Keywords: Lysosomal storage; Enzyme replacement; Fatty liver; Hepatomegaly; Dyslipidemia.

Received 10 February 2014; received in revised form 21 May 2014; accepted 23 June 2014; available online 30 June 2014

* Corresponding author. Address: Synageva BioPharma Corp., 33 Hayden Street, Lexington, MA 02421, United States. Tel.: +1 781 357 9900; fax: +1 781 357 9901.
E-mail address: Anthony.Quinn@synageva.com (A.G. Quinn).

Abbreviations: LAL, lysosomal acid lipase; LAL D, lysosomal acid lipase deficiency; CE, cholesteryl ester; TG, triglycerides; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GGT, gamma glutamyl transferase; PDFF, proton density fat fraction; AE, adverse event; CTCAE, common terminology criteria for adverse events; IRR, infusion-related reaction; MN, multiples of normal.

Introduction

Lysosomal Acid Lipase (LAL) Deficiency (LAL D) (OMIMD 278000) is an autosomal recessive disease that is associated with significant morbidity and shortened life expectancy. Mutations in the *LIPA* gene markedly decrease LAL enzyme activity leading to

lysosomal cholesteryl ester (CE) and triglyceride (TG) accumulation. Although the *LIPA* gene is expressed in many tissues, lysosomal accumulation of undigested lipids is prominent in cells of the monocyte/macrophage lineage, in the liver and hepatocytes [1]. Common clinical manifestations include serum transaminase elevation, hepatomegaly, hepatic lipid accumulation, and dyslipidemia. This presentation, historically known as cholesteryl ester storage disease, is an underappreciated cause of liver fibrosis with frequent progression to cirrhosis [2]. LAL D is also associated with evidence of premature atherosclerosis in some cases [3–10]. Clinical diagnosis is challenging due to the prevalence (1:40,000 to 1:300,000 [3,11]) and manifestations that overlap with more common liver/lipid disorders.

In contrast to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), where the pathogenesis is not fully understood, LAL D leads to CE and TG accumulation in hepatocytes and liver macrophages with progression to fibrosis. The high frequency of liver fibrosis with cirrhosis development in LAL D, for some as early as 6 months of age, suggests that the accumulation of lysosomal CE and TG is a potent driver of liver fibrosis [2,12–14]. In the rat disease model of LAL D, liver fibrosis also develops rapidly (within 4–8 weeks) in association with abnormal lipid accumulation. Concordant reduction in liver CE, TG, alpha smooth muscle actin staining and fibrosis with sebelipase alfa (a recombinant human LAL enzyme; Synageva BioPharma Corp., Lexington, MA, US) highlights the importance of lysosomal CE and TG accumulation as a driver of fibrosis [15].

Current medical management of LAL D is limited and includes the use of HMG-CoA reductase inhibitors (statins) alone or in combination with other lipid-lowering therapies for disease-associated hypercholesterolemia. Although these agents can reduce serum cholesterol and TG concentrations, these changes are not accompanied by consistent improvements in serum transaminases or substantial reductions in hepatic CE or TG content [2,16]. These findings, and the observed decreases in stellate cell activation and fibrosis concordant with hepatic lipid reduction in the rat model, point to the importance of hepatic lipid reduction in the amelioration of liver disease progression in these patients.

The initial effects of sebelipase alfa in LAL D adults in the LAL-CL01 study and effects up to 12 weeks in the LAL-CL04 study have been reported [17]. We now provide evidence of these beneficial effects on biochemical markers of disease activity up to week 52, describe for the first time improvements in hepatic lipid content, and additionally report longer term safety.

Patients and methods

Study design

LAL-CL04 (trial registration number: NCT01488097) is an ongoing open-label, multicentre, extension study of LAL-CL01 (NCT01307098) involving eight sites in five countries. Subjects who completed the LAL-CL01 study were eligible to enrol in this extension study (Fig. 1).

The dose schedule in the LAL-CL04 study consisted of four once-weekly infusions of sebelipase alfa at the same dose as in the LAL-CL01 study (0.35, 1.0 or 3.0 mg/kg) followed by every-other-week infusions of sebelipase alfa (1.0 or 3.0 mg/kg).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and Good Clinical practice guidelines. Ethics committees and/or institutional review boards at participating institutions reviewed and approved the protocol. All subjects provided informed written consent before undergoing study-specific assessments or procedures.

Investigations

The objectives of LAL-CL04 were to evaluate the long-term safety, pharmacokinetics, pharmacodynamics, and immunogenicity of sebelipase alfa. Pharmacodynamic and clinical effects were assessed by measuring alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, TGs, low-density lipoprotein (LDL), high-density lipoprotein (HDL), alkaline phosphatase, gamma-glutamyl transferase (GGT), C-reactive protein and ferritin. Liver volume was assessed by MRI and the hepatic proton density fat fraction (PDFF), a measure of lipid content, was assessed by MRI (multi-echo gradient-echo sequence imaging) or ^{1}H-MRS (if available) [18–21].

Safety assessments included treatment-related adverse events (AEs), vital signs, physical examination, electrocardiography, and routine laboratory tests at regular intervals. AEs were graded using the National Cancer Institute Common Terminology Criteria for adverse events (CTCAE), version 4.0 or higher. Infusion-related reactions (IRRs) were defined as any AE that occurred during the 2-h infusion or within 4 h after the infusion and assessed by the investigator as at least possibly related to the study drug.

Anti-drug antibody assays

The presence of serum anti-sebelipase alfa antibodies was examined by use of a validated bridging enzyme-linked immunosorbent assay [22,23]. Additional methodological details have been published previously [17].

Statistical analysis

Subjects who received at least one dose of sebelipase alfa in LAL-CL04 were analysed for safety; AEs, vital signs, and laboratory tests were summarized. Statistical comparisons of the dosing cohorts were not performed, as the study was not powered to detect differences between them. Data from the two cohorts were pooled and descriptive statistics were used to compare to baseline parameters from LAL-CL01. Changes and percent changes from baseline in serum transaminases, serum lipids, acute phase reactants, hepatic PDFF and liver volumes were summarized with no specific statistical hypothesis testing. Exploratory statistical analyses were performed to examine the effects of sebelipase alfa on key activity parameters. The Wilcoxon sign-rank test was used for statistical tests of change from baseline, without adjustment for multiplicity. For each measure, only the p value for the absolute change from baseline was calculated; this p value was used to describe the change from baseline regardless of the summary statistic that is displayed (i.e., change from baseline or percentage change from baseline).

Starting with the week 4 visit, laboratory assessments were performed two weeks post-infusion. In order to further investigate the post-infusion increases in LDL and TG an additional serum biochemistry assessment was scheduled one week post-infusion (between week 24 and 28). In the graphs, all 1-week-post-infusion laboratory data are presented one week after the week 24 visit. For end points calculated as change from baseline, the LAL-CL01 study baseline was used, with the exception of the liver volume and hepatic PDFF end points, which were first performed using MRI/MRS at baseline of LAL-CL04. Liver volume is displayed as multiples of normal (MN, where "normal" liver volume in litres was defined as 2.5% of body weight in kg). Hepatic PDFF is reported for the right lobe of the liver using either MRI (n = 4 subjects) or MRS (n = 2 subjects). Percentage change from baseline was computed for all six subjects and combined to form the mean percentage change in hepatic PDFF.

Results

The first subject entered LAL-CL04 on 12 December 2011; the last subject completed the last visit on 15 May 2013. Of the nine subjects who completed LAL-CL01, eight enrolled in LAL-CL04 with a median of 18 weeks (range 9 to 28 weeks) between the last dose of sebelipase alfa in LAL-CL01 and the first dose in LAL-CL04. One subject (#4) did not enrol in LAL-CL04. The subject completed LAL-CL01, but was subsequently lost to follow-up. When the patient made contact with the trial centre again approximately 9 months after completing LAL-CL01, the patient had already developed liver failure, manifested by oedema, fatigue and grade 1 hepatic encephalopathy. The patient was no longer eligible for