

Novel treatment options for lysosomal acid lipase deficiency: critical appraisal of sebelipase alfa

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Abstract: Lysosomal acid lipase deficiency (LAL-D) is a rare disorder of cholesterol metabolism with an autosomal recessive mode of inheritance. The absence or deficiency of the LAL enzyme gives rise to pathological accumulation of cholesterol esters in various tissues. A severe LAL-D phenotype manifesting in infancy is associated with adrenal calcification and liver and gastrointestinal involvement with characteristic early mortality. LAL-D presenting in childhood and adulthood is associated with hepatomegaly, liver fibrosis, cirrhosis, and premature atherosclerosis. There are currently no curative pharmacological treatments for this life-threatening condition. Supportive management with lipid-modifying agents does not ameliorate disease progression. Hematopoietic stem cell transplantation as a curative measure in infantile disease has mixed success and is associated with inherent risks and complications. Sebelipase alfa (Kanuma) is a recombinant human LAL protein and the first enzyme replacement therapy for the treatment of LAL-D. Clinical trials have been undertaken in infants with rapidly progressive LAL-D and in children and adults with later-onset LAL-D. Initial data have shown significant survival benefits in the infant group and improvements in biochemical parameters in the latter. Sebelipase alfa has received marketing authorization in the United States and Europe as long-term therapy for all affected individuals. The availability of enzyme replacement therapy for this rare and progressive disorder warrants greater recognition and awareness by physicians.

Keywords: sebelipase alfa, LAL deficiency, Wolman disease

Introduction

Lysosomal acid lipase deficiency (LAL-D) is an ultra-rare autosomal recessive lysosomal storage disorder. It is progressive in nature and characterized by the absence or deficiency of LAL. This enzyme is responsible for the metabolism of cholesterol esters and triglycerides derived from low-density lipoproteins (LDLs). Impaired activity of LAL results in pathological accumulation of cholesterol in various tissues.^{1,2} The severe infantile form of the disease presents as gross intestinal malabsorption, adrenal calcification, hepatomegaly, and early mortality.¹⁻⁴ The late-onset presentation in children and adults includes dyslipidemia and liver fibrosis with associated consequences of premature atherosclerosis and liver cirrhosis.^{4,5} Traditionally, there have been no curative therapies for LAL-D, and treatment strategies are supportive in nature, centering upon optimizing nutritional status, the use of lipid-modifying agents to minimize atherosclerosis, and managing the consequences of disease progression (eg, liver transplantation for end-organ failure).

The development of enzyme replacement therapies (ERTs) for lysosomal storage disorders was first exemplified in the development of treatment for type 1 Gaucher

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disease.^{6,7} ERTs are currently available for other lysosomal storage disorders, but until recently, there has been no ERT equivalent for LAL-D.

Sebelipase alfa (Kanuma; Alexion Pharmaceuticals, Cheshire, CT, USA) is a recombinant human LAL that has gained marketing authorization for the treatment of LAL-D in Europe and the United States. The availability of enzyme replacement for this condition will fundamentally change management strategies for physicians treating patients with LAL-D. Although this is a rare condition and likely underrecognized in the health care setting, the existence of replacement therapy necessitates increased awareness of the clinical manifestations of LAL-D from the general and specialist physician. Here, we review the pathophysiology, clinical features, and treatment of LAL-D, as well as provide an overview of sebelipase alfa and future directions in LAL-D management.

Pathophysiology of LAL-D

LAL is a glycoprotein located in the lysosomal compartment of mammalian cells, most prominent in macrophages and hepatocytes. LAL catalyzes the hydrolysis of cholesterol esters and triglycerides, providing cells with a source of free cholesterol. The underlying pathophysiology of LAL-D relates to disturbed lysosomal cholesterol metabolism. The resultant accumulation of cholesterol in affected tissues gives rise to accompanying clinical phenotypes, such as hepatomegaly and liver fibrosis from hepatic infiltration, or malabsorption secondary to gastrointestinal involvement.¹⁻⁵

Cholesterol is essential in many physiological processes. These include its role as a precursor molecule in steroid hormone synthesis, bile acid synthesis, and as a component of cellular membranes. The LAL enzyme is able to generate free cholesterol for cellular use through metabolizing exogenously derived cholesterol. Exogenous cholesterol is obtained from LDL, which enters hepatocytes via receptor-mediated endocytosis. Upon reaching the lysosomal compartment, LAL catalyzes the hydrolysis of cholesterol esters and triglyceride components into free cholesterol and free fatty acids, respectively.⁸ The generation of free cholesterol inhibits *de novo* cholesterol synthesis through feedback inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the key limiting factor in cholesterol synthesis. Free cholesterol end products also inhibit the activation of sterol regulatory element-binding proteins, transcription factors that activate genes responsible for cholesterol synthesis.⁹

In the absence or reduction of LAL activity, higher levels of cholesterol esters and triglycerides accumulate in

the lysosome, with resultant reduction in intracellular free cholesterol. This impairs the negative feedback mechanism acting upon HMG-CoA reductase and sterol regulatory element-binding protein, with resultant synthesis of cholesterol and accumulation in organs giving rise to pathological effects that manifest clinically as either infantile LAL-D or cholesterol ester storage disease (CESD).¹⁰

Genetics of LAL-D

LAL-D is an autosomal recessive condition. The *LIPA* gene, consisting of a 2.5 kb cDNA sequence spanning ten exons and nine introns, encodes this enzyme. The *LIPA* gene localizes to the long arm of chromosome 10 at position 10q23.31.¹¹⁻¹³ LAL-D may manifest in homozygotes or compound heterozygotes harboring mutations in the *LIPA* gene. Currently over 40 mutations have been described in LAL-D, with differing functional defects including instability at the messenger RNA (mRNA) level, altered protein/catalytic site structure, and reduced or complete absence of enzyme activity.¹⁴

Phenotype severity in LAL-D has been linked with the activity of *LIPA* gene product. Early-onset LAL-D in infancy, also known as Wolman disease, is more severe and associated with rapid progression and early mortality. *LIPA* mutations seen in infantile LAL-D are associated with complete absence or severely diminished LAL activity.^{10,13,14} There is a larger repertoire of mutations in infantile LAL-D, for example, complete inactivation of catalytic function due to truncation mutations or the absence of correctly spliced mRNA. This contrasts with LAL-D of later onset, historically known as CESD, which is associated with residual LAL enzyme activity and may present with a more variable phenotype. In contrast to infantile LAL-D, over 50% of described *LIPA* mutations in CESD are associated with an exon 8 splice junction mutation (E8SJM). This mutation encodes a defective LAL with no enzymatic activity, but a small fraction of normally spliced mRNA is present, giving rise to residual LAL activity.⁵

Epidemiology of LAL-D

Epidemiological data are limited owing to the rarity of diagnoses and few reported cases in the literature. Studies into the prevalence of LAL-D reveal disparity between the frequency of *LIPA* mutations reported in the literature and the number of reported cases. Underdiagnosis is likely.¹⁵

LIPA mutations in infantile LAL-D are heterogeneous. Unlike the E8SJM in CESD, there is no dominant *LIPA* mutation in this phenotype. Increased frequency of Wolman disease in the Los Angeles Iranian Jewish community has

been reported based on the screening of an exon 4 mutation.¹⁶ The carrier frequency was estimated to be 3%, with an estimated 1 in 4,200 live births predicted to be homozygous of the mutation. In contrast to this, an Australian study estimated the prevalence of Wolman disease to be 1.9 per million.¹⁷ These two populations are ethnically distinct from each other, and it is possible that high prevalence in certain groups is due to founder effect. Further studies will be highly relevant in establishing the prevalence of LAL-D in different populations and across ethnicities.

In the CESD phenotype, prevalence and carrier frequency of the most common E8SJM *LIPA* mutation has been estimated for different populations (Table 1), with highest estimates in Caucasian populations. Although the authors found no African-American individuals with this mutation, there are case reports of *LIPA* mutations associated with the infantile phenotype in African individuals.¹⁸ Again, further epidemiological data will be significant for verification of the existing data.

Clinical presentation of LAL-D

The differences in LAL activity associated with infantile LAL-D and late-onset CESD give rise to a spectrum of clinical phenotypes. The rarity of cases means that our knowledge is predominantly based on published case reports, and long-term survival data are lacking. Manifestation in infancy is severe and associated with absent or severely reduced LAL activity with early mortality.^{6,11,20–23} *LIPA* gene mutations that retain greater residual activity give rise to milder phenotypes (CESD) presenting later in childhood or adulthood. LAL-D can be overlooked or misdiagnosed when presenting features are indistinguishable from nonalcoholic fatty liver disease (NAFLD) or dyslipidemia.^{24–26}

Clinical presentation in infancy

Characterization of early-onset LAL-D presenting in infancy was first described by Dr Wolman in the 20th century.¹

Table 1 Estimated E8SJM allele frequency and CESD prevalence among different populations

Population	E8SJM allele frequency	CESD population prevalence (per million)
Germany ¹⁵	1 in 200	25
USA ¹⁹		
Caucasian	1 in 300	8
Hispanic	1 in 300	8
Ashkenazi Jewish	1 in 500	3
Asian	1 in 1,000	1

Abbreviations: CESD, cholesterol ester storage disease; E8SJM, exon 8 splice junction mutation.

Clinical features are severe and manifest within the first few weeks of life. It is associated with rapid clinical deterioration and early mortality, usually by 1 year of age. Symptoms in infantile LAL-D may manifest as malabsorption, growth failure, vomiting, diarrhea/steatorrhea, adrenal failure, and abdominal distention. Examination and biochemical findings include hepatosplenomegaly, adrenal calcification, dyslipidemia, abnormal liver function tests (LFTs), and anemia. Histological findings in affected patients reveal pathological accumulation of cholesterol and triglycerides in multiple organs.^{1–3}

Survival beyond 1 year of age is rare in infantile disease, although in certain cases survival has been prolonged in those who have undergone liver transplantation and/or hematopoietic stem cell transplantation (HSCT). A recent study reported median survival of 3.7 months in patients with LAL-D diagnosed before the age of 2. Those who underwent treatment (HSCT and/or liver transplant) reported median survival of 8.6 months, but in the untreated group this was only 3 months. Of those who survived beyond 12 months, the majority had received HSCT or liver transplantation and HSCT.³

Other rare lysosomal and nonlysosomal disorders such as Niemann–Pick disease A, Gaucher’s disease, galactosemia, hemophagocytic lymphohistiocytosis, and disorders of amino acid metabolism are to be considered in differential diagnoses while considering LAL-D presenting in infancy.³

Clinical presentation in childhood and adulthood

Longitudinal case reviews of LAL-D diagnosed beyond infancy reveal that LAL-D is predominantly a pediatric condition, with paucity of diagnoses in those over the age of 40.^{4,5} Presentation of LAL-D in childhood and adulthood is most variable, in contrast with the infantile variant.

Given the spectrum of phenotypes, CESD may present to endocrinologists/cardiologists with dyslipidemia, or to gastroenterologists with deranged LFTs or frank liver cirrhosis and associated complications.^{24–27} Physicians in metabolic, cardiovascular, and gastrointestinal disciplines (as well as the wider pool of physicians) are encouraged to be aware of this condition, especially pertinent now that enzyme replacement is available in order to reduce delay or misdiagnosis of what may now be a treatable condition.

LAL-D should be considered in differential diagnosis when the detection of abnormal liver function may be noted on chance routine testing in asymptomatic individuals or for viral hepatitis screening.²⁸ Hepatomegaly is commonly present, and patients may possess features (including histological) that are

reminiscent of NAFLD/nonalcoholic steatohepatitis (NASH), or cryptogenic cirrhosis with associated complications.^{24,29}

LAL-D has been described in the setting of patients presenting with hyperlipidemia or type IIb hyperlipoproteinemia and may be misdiagnosed as familial hyperlipidemic disorders.^{25,26,30}

Histological abnormalities

Widespread histological abnormalities are seen in the tissues of patients with LAL-D. The earliest case reports documented autopsy findings of cholesterol and triglyceride deposits in various organs, with changes most marked in the liver, spleen, gastrointestinal tract, adrenals, lymph nodes, and bone marrow.^{1,2,31}

The cholesterol content of the liver and spleen is increased. Liver cholesterol content can be markedly elevated, and histology may range from the presence of cholesterol ester crystals within hepatocytes and reticuloendothelial cells (Kupffer cells, macrophages) to microvesicular steatosis, fibrotic scarring, and frank cirrhosis (Figures 1–3). The use of specific lysosomal markers cathepsin D, lysosomal associate membrane protein 1 and 2 in liver immunohistochemistry may be of diagnostic benefit in differentiating LAL-D from other forms of liver disease given that microvesicular steatosis is not a reliable marker for CESD.³²

In the spleen, reticuloendothelial cells become transformed into lipid-laden foam cells, manifesting as splenomegaly.

Changes in the gastrointestinal tract are seen in the mucosa and, to lesser extent, the submucosa of the small intestines. Prominence of foam-laden vacuolated macrophages infiltrating the lamina propria occurs, with distortion of the architecture and dysfunction in absorptive and enzymatic activity of the small intestinal enterocytes.

Adrenal gland enlargement is seen in infantile disease, with lipid accumulation, necrosis, and calcification of zona reticularis.

Biochemical derangements

Commonly noted biochemical derangements in LAL-D include deranged LFTs with elevated alanine transaminase (ALT) and/or aspartate aminotransferase (AST), which can deteriorate as disease progresses. Hyperbilirubinemia and elevated gamma glutamyl transferase may also be seen. Dyslipidemia is a common feature, with elevated levels of triglycerides, total cholesterol, and low high-density lipoprotein. High-density lipoprotein levels may be reduced.³

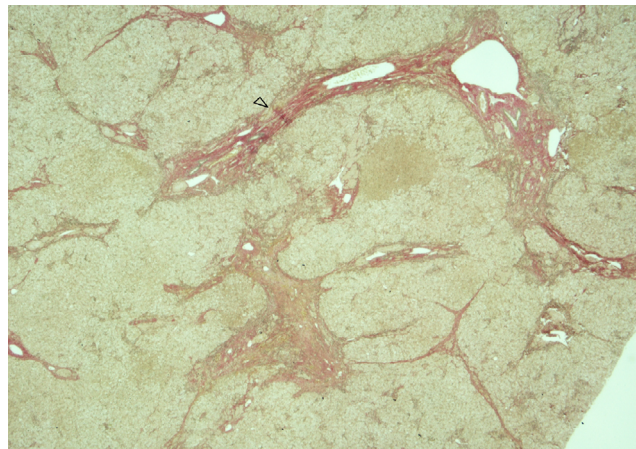


Figure 1 Bridging fibrosis on Von Giesson (elastic) stain.

Notes: Liver biopsy from a patient diagnosed with lysosomal acid lipase deficiency at the age of 40 years. The arrowhead denotes bridging fibrosis.

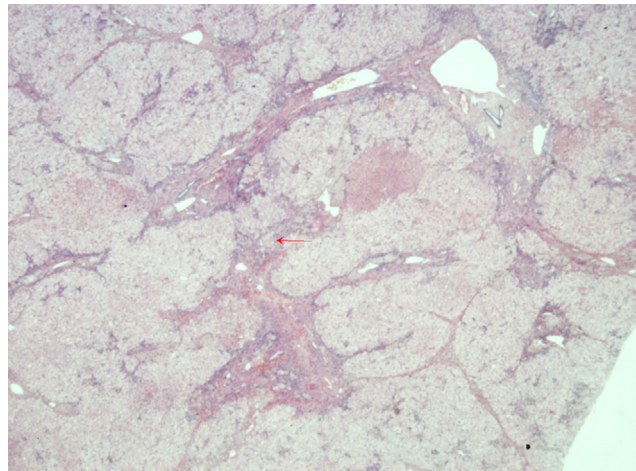


Figure 2 Bridging fibrosis H and E stain.

Notes: Liver biopsy from a patient diagnosed with lysosomal acid lipase deficiency at the age of 40 years. The red arrow denotes bridging fibrosis.

Abbreviation: H and E, hemotoxylin and eosin.

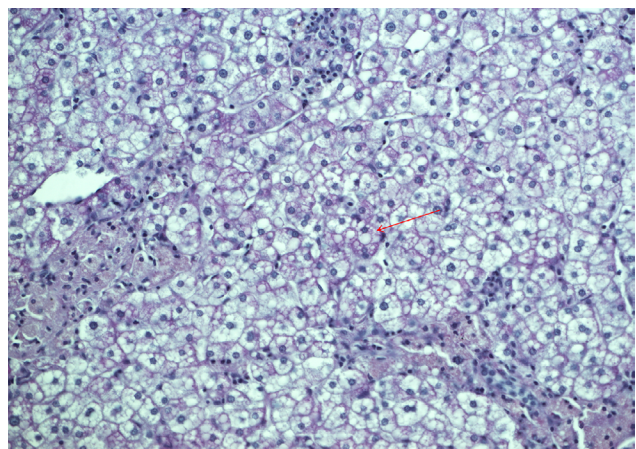


Figure 3 Microvesicular steatohepatosis on PAS stain.

Notes: Liver biopsy from a patient diagnosed with lysosomal acid lipase deficiency at the age of 40 years. The red arrow denotes microvesicular steatosis.

Abbreviation: PAS, periodic acid–Schiff.

Radiological abnormalities

The earliest case studies of infantile disease reported adrenal gland calcification on X-ray imaging. Computed tomography (CT) and magnetic resonance imaging scan can identify adrenal enlargement necrosis and calcification. The radiological imaging can demonstrate hepatomegaly (low attenuation on CT indicates fat infiltration, but this is not diagnostic as it is also seen in NAFLD and NASH), splenomegaly, and lymphadenopathy (Figure 4).³³ Ultrasound scan in pediatric case reports have demonstrated bowel wall thickening in the small intestines.³⁴

Survival and morbidity

One study has reported mean time from clinical/biochemical abnormalities to diagnosis was 9 years (median: 5.8 years). In contrast to the NAFLD/NASH population, this cohort of patients has accelerated progression to fibrosis: of 31 patients with liver biopsies, 85% had features of fibrosis and/or cirrhosis, and all were under 18 years of age.⁵ The finding of significant liver fibrosis contrasts with the adult NAFLD population: an estimated 3%–15% of NAFLD will progress to NASH.³⁵ The high proportion of LAL-D patients who may have significant liver disease is also reflected in the acid lipase replacement investigating safety and efficacy (ARISE) trial:³⁶ 25 out of 32 (78%) liver biopsies revealed bridging fibrosis and/or cirrhosis (Ishak score ≥ 3). Significantly eight of the ten cirrhotic subjects did not have a diagnosis of cirrhosis, showing that advanced liver disease can remain



Figure 4 Hepatosplenomegaly and liver steatosis on MRI scan of an adult patient diagnosed with cholesterol ester storage disease.

Abbreviation: MRI, magnetic resonance imaging.

asymptomatic.³⁶ There is no longitudinal survival data for LAL-D, although there are reports of individuals diagnosed in old age (80 years), presumably with milder phenotypical variants of LAL-D.³⁰

Dyslipidemia is a common biochemical abnormality in CESD, but definitive studies of increased cardiovascular mortality in LAL-D are not available. There are documented cases of premature atherosclerosis and cardiovascular disease in patients with CESD, but these are observed associations.^{24,29,37}

Clinical diagnosis of LAL-D

In individuals where LAL-D is a differential, diagnosis can be made on a blood spot³⁸ or peripheral leukocyte LAL activity. Liver biopsy is not the first-line diagnostic investigation for LAL-D. However, biopsies are undertaken if there is clinically suspected liver disease or to exclude other etiologies of chronic liver disease. Liver biopsies are often obtained in confirmed LAL-D prior to treatment, and may be repeated if clinical deterioration is noted. Genetic analysis of *LIPA* mutations is not a compulsory part of the diagnostic workup. There is no genotype–phenotype correlation in CESD: the *LIPA* mutation does not predict the clinical course/outcome.

Clinical management of LAL-D

Current management of LAL-D is largely supportive. Nutritional supplementation has been used in infantile disease, including fat-free enteral and parenteral nutrition, but with no morbidity or mortality benefits. Low cholesterol/reduced saturated fat diets have been used in pediatric and adult CESD, although this has also demonstrated low efficacy.^{39,40}

Lipid-modifying agents

HMG-CoA reductase inhibitors (statins) have been administered to reduce endogenous cholesterol synthesis in pediatric and adult cases of CESD. These have been used alone or in conjunction with other lipid-modifying agents (ezetimibe, cholestyramine), but results have been variable.⁴¹

Some case reports have noted improved lipid profile with statin therapy (predominantly lovastatin although simvastatin has also been administered). Evaluation of lipid parameters on statin therapy has varied from 6 months to 9 years post-commencement. The addition of ezetimibe to lovastatin has demonstrated additional improvements to total cholesterol and LDL levels in certain cases.^{40,42,43}

However, despite their apparent lipid-modifying properties, it remains unclear whether statins ameliorate premature atherosclerosis or reduces cardiovascular disease in this group of patients. Importantly, statins have shown no benefit in modifying the progression of liver disease

associated with CESD.⁴ Although some reports have noted improved liver histology such as reduced hepatocyte vacuolation, no comment was made on the progression or otherwise of liver fibrosis.²⁴ Others have reported reduced fat infiltration on radiological imaging, but without coexisting liver histology.⁴² Clinical improvement of hepatosplenomegaly has been reported, but methods of assessment vary between reports.³⁹ Furthermore, others have shown no CT-based improvement in liver volumes with statin therapy.²⁴ Repeated liver histology during statin treatment has been undertaken in several cases, but all revealed progression of underlying disease.⁴

Hematopoietic stem cell therapy

Stem cell/bone marrow transplantation for LAL-D is potentially curative, as normal LAL activity will be derived from donor cells. Stem cell/bone marrow transplantation for LAL-D is potentially curative as normal LAL activity will be derived from donor cells, but outcomes of HSCT have been mixed.⁴⁴ Successful cases of bone marrow and umbilical cord blood transplantation have been documented up to 4 and 11 years posttransplantation, with normalization of LAL, improved lipid parameters, resolution of symptoms, regression of hepatosplenomegaly, and histological improvement in the liver.^{45,46}

Deaths have also been reported after transplantation: two of four patients in one case series died due to sinusoidal obstruction syndrome.⁴⁶ Another revealed normalization of peripheral LAL levels, but death occurred secondary to progression of underlying LAL-D, with subsequent histology revealing failure of engraftment in the liver.⁴⁷

Although HSCT has proved successful in select cases, this is not a ubiquitous treatment strategy. Failure of engraftment, risks associated with the procedure, and emergence of post-transplant complications means that alternatives are needed.

Liver transplantation

Similar to HSCT, liver transplantation is also associated with risks and complications. This procedure has been undertaken in LAL-D patients (in both infants and adults). Liver transplantation for an infant with infantile LAL-D was undertaken prior to bone marrow transplantation, but recurrence of cirrhosis in the graft and delayed bone marrow transplantation were felt to have contributed to death.⁴⁸

Liver transplantation undertaken for later-onset LAL-D (CESD) has been undertaken in cases complicated by end-stage cirrhosis.⁴⁹⁻⁵¹ Follow-up of affected children and adolescents who had undergone this procedure has been

documented, varying from 10 months to 4 years postprocedure. These cases demonstrated good clinical progress, normalization of LFTs, and improved lipid parameters. One case of transplantation in an adult female with LAL-D reported satisfactory graft function 2 years postprocedure and improved lipid profile, although peripheral LAL levels remained low. Evidence for long-term mortality and morbidity post-transplantation are currently limited.⁵²

Current strategies remain unsatisfactory in halting the progress of LAL-D. Finite resources, specific criteria for transplantation, and the risks posed by these procedures preclude their universal availability to affected individuals.

There is also concern that transplanted grafts can potentially develop liver disease, as the total amount of peripheral LAL activity continues to be low in patients who have received liver transplantation.³⁷

Enzyme replacement strategies and preclinical data

The development of an LAL enzyme replacement enables correction of metabolic defects that characterize LAL-D and reduce pathological accumulation of cholesterol in affected tissues. Preclinical studies have shown that this is feasible. In vivo models of LAL deficiency have demonstrated that LAL replacement targets the enzyme to the destined compartment and ameliorates the pathological effects of LAL deficiency. In the mouse model of LAL-D, infusion of recombinant human LAL revealed histological improvement in several organs (liver, spleen, and intestines), with histological improvement noted in Kupffer cells.⁵³

Other methods of targeting recombinant human LAL in in vivo systems have been published. These include the production of human LAL in Chinese hamster ovary cells and adenovirus-mediated transfer of the LAL cDNA into hepatocytes.^{54,55} These systems have not progressed beyond preclinical stages.

Sebelipase alfa

Sebelipase alfa (Kanuma) is the first enzyme replacement developed by Synageva Biopharma Ltd (now Alexion Pharmaceuticals) for LAL-D. Clinical trials have been conducted in infants displaying the rapidly progressive form of LAL-D and in children and adults with later-onset phenotype. Data show significantly enhanced survival in affected infants and correction of biochemical abnormalities in older subjects.

Sebelipase alfa is a recombinant human LAL; hence, the amino acid sequence is identical to that of the human protein. It is a glycoprotein with a molecular weight of 55

kDa. Carbohydrate-containing moieties of the drug include *N*-acetylglucosamine, mannose-6-phosphate (M6P), and other mannose-terminated *N*-linked glycan structures. The presence of glycan moieties confers specificity, allowing targeted delivery of LAL to the lysosomal compartment by means of the macrophage mannose receptor on reticuloendothelial cells and the M6P receptor. The recombinant protein is synthesized in genetically modified hens (*Gallus gallus*) with secretion of the protein into the egg white.^{56,57}

Sebelipase alfa licensing and indications

Currently, sebelipase alfa has received marketing authorization in Europe, the United States, and Japan.⁵⁸ It is classified as an orphan medicine owing to the rarity of LAL-D. Treatment can be initiated upon the diagnosis of LAL-D in affected individuals of all ages. It is administered as an intravenous infusion, and the recommended dose for infants under 6 months is 1 mg/kg every week, while in adults and older children with later-onset LAL-D (CESD), this is 1 mg/kg every 2 weeks.

Pharmacodynamics

Sebelipase alfa localizes to the lysosomal compartment via receptor-mediated uptake by reticuloendothelial cells and other cells expressing the M6P receptor. The therapeutic effect of the drug is evidenced by the effect on liver transaminases and lipid profile in trial subjects. LAL-CL01, the first-in-human sebelipase alfa study, revealed a significant reduction in ALT and AST levels from baseline in 100% and 67% of subjects, respectively, at day 28.⁵⁷

Preclinical data

Data derived from preclinical models have demonstrated the efficacy and acceptable safety profile in mammals.

In the rat model of LAL deficiency, sebelipase alfa-treated animals showed improved parameters compared to placebo. Sebelipase alfa (5 mg/kg) administration weekly for 4 weeks resulted in reduced lipid content in Kupffer cells and hepatocytes, improved transaminases, and reduced liver weight in the treatment group.⁵⁹

Toxicology studies reveal no significant findings after short-term (4 weeks) administration or long-term (6 months) repeated dosing. Short-term dosing at up to 50 mg/kg per week has been used in murine and primate models (human equivalent doses of ~8 and 16 mg/kg respectively), while 30 mg/kg per week long-term dosing in primates (human equivalent dose of ~10 mg/kg) did not reveal concerning findings based on clinical observations.

Initial clinical data

The first-in-human Phase I/II study of sebelipase alfa (LAL-CL01) was conducted in nine adult subjects with clinical manifestations of LAL-D (deranged ALT/AST, lipid profile, and/or hepatomegaly).⁵⁷ Three dosing regimens (0.35, 1, and 3 mg/kg) infused intravenously on a weekly basis were investigated in sequential cohorts. Results were encouraging and revealed good safety profile and significant reduction in ALT and AST levels from baseline in 100% and 67% of subjects, respectively, at day 28.

Efficacy

In infant-onset LAL-D

Sebelipase alfa has shown significant survival benefit in infants with LAL-D. LAL-CL03 is an open-label, single-arm, Phase II/III trial conducted in nine infants under 6 months of age, with the primary outcome measure of survival at 12 months.⁶⁰ Six subjects (67%) receiving sebelipase alfa achieved the primary end point; this was compared with a historical cohort of patients with similar characteristics of which 0% survived to 12 months. Clinical features in these nine infants included deranged ALT and AST (median 145 and 125 IU/L, respectively), hepatomegaly (nine subjects), splenomegaly (eight subjects), and adrenal calcification (six subjects) at baseline. Resolution of symptoms, reduced organomegaly, and improved biochemical parameters were all noted in the treatment group. Deaths occurred in four patients, but none were attributed to the drug.

Children and adults

LAL-CL04 was a continuation of LAL-CL01 over a period of 52 weeks, with a total of eight subjects (one subject was no longer eligible for the study due to development of decompensated liver disease).⁶¹ This study revealed that the initial improvement in transaminases was sustained over the longer dosing period (Table 2). Sebelipase alfa was infused weekly in three dosage groups (0.35 mg/kg, 1 mg/kg or 3 mg/kg).

Table 2 LAL-CL04 biochemical parameters at 52 weeks

Parameter	Baseline mean \pm SD	Mean change at 52 weeks ^a
ALT (U/L)	83 \pm 22	-49 \pm 21
AST (U/L)	53 \pm 12	-23 \pm 11
Total cholesterol (mg/dL)	169 \pm 39	-71 \pm 31
HDL cholesterol (mg/dL)	40 \pm 9	9 \pm 6
LDL cholesterol (mg/dL)	145 \pm 76	-73 \pm 31
Triglycerides (mg/dL)	147 \pm 85	-71 \pm 66

Note: ^aOne subject received sebelipase for 38 weeks.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

Table 3 Primary and secondary end points in ARISE study

Outcomes	Closed-label period		P value	
	Treatment arm (number of patients)	Sebelipase alfa (36)		Placebo (30)
Primary end point				
ALT normalization – number of patients (%)		11 (31)	2 (7)	0.03
Secondary end points				
AST normalization – number of patients (%)		15 (42)	1 (3)	<0.001
Reduction in LDL cholesterol – percentage ± SD		28.4±22.3	6.2±13.0	<0.001
Reduction in non-HDL cholesterol – percentage ± SD		28.0±18.6	-6.9±10.9	<0.001
Reduction in triglyceride level – percentage ± SD		25.5±29.4	11.1±28.8	<0.05
Increased HDL cholesterol – percentage ± SD		19.6±16.8	-0.3±12.4	<0.05
Reduction in baseline hepatic fat content as assessed by MRI (%) [*]		32.0±26.8	4.2±15.6	<0.05
Number of patients with reduction in steatosis by morphometric assessment of hepatic fat content on histology (%)		10/16 (62)	4/10 (40)	0.42

Notes: ^{*}Total number of patients =57 (sebelipase alfa =32; placebo =25). From *N Engl J Med*, Burton BK, Balwani M, Feillet F, et al. A Phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency, 2015;373(11):1010–1020. Copyright© 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.³⁶

Abbreviations: ALT, alanine transaminase; ARISE, acid lipase replacement investigating safety and efficacy; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; SD, standard deviation.

Thereafter two dosing groups (1 mg/kg or 3 mg/kg) were administered on a fortnightly basis for up to 52 weeks. At 52 weeks, ALT and AST in all subjects had normalized (mean ALT 34 IU/L, mean AST 32 IU/L), and improvements in lipid profiles were seen (after an initial rise at the end of LAL-CL01 period). No differences between 1 and 3 mg/kg doses could be distinguished.

The Phase III of ARISE/LAL-CL02 trial was a double-blind, placebo-controlled trial conducted with 66 subjects (children and adults) comparing sebelipase alfa (dosage 1 mg/kg every 2 weeks) to placebo.³⁶ At the end of the 20-week closed-label period, all subjects received sebelipase alfa in the open-label extension. The primary end point of ALT normalization at the end of the 20-week closed-label period was reached in 33% of the treatment group, compared to 7% in the placebo group. Other secondary outcomes were also significantly improved in the treatment group (Table 3). During the open-label period, the former placebo group experienced statistically significant falls in ALT and LDL cholesterol and elevation in high-density lipoprotein levels.

Safety profile of sebelipase alfa

Current information derived from clinical trials of sebelipase alfa has revealed it is relatively well tolerated. Additional trials in infants and adults remain ongoing and will supplement existing data (Table 4).

LAL-CL01, the first-in-human Phase I/II study of sebelipase alfa, was conducted in nine subjects with three dosing regimens (0.35, 1, and 3 mg/kg) infused intravenously on a weekly basis. Each subject received four doses of the drug, and monitoring revealed it to be well tolerated with no reported serious adverse events. Adverse events in two subjects were felt to be treatment-related.⁵⁷

Table 4 Known adverse drug reactions for sebelipase alfa

Adverse reactions in infants	
Very common (≥10%)	
General pyrexia, chills	
Dermatological eczema, maculopapular rash, pruritus, urticarial rash	
Gastrointestinal diarrhea, gastroesophageal reflux, vomiting	
Respiratory tachypnea, respiratory distress, wheezing, cough, rhinitis, nasal congestion, sneezing, reduced oxygen saturation	
Cardiovascular tachycardia, hypertension	
Immune system eyelid edema	
Central nervous system/psychiatric hypotonia, agitation, irritability	
Adverse reactions in children and adults	
Common (1%–9%)	
General infusion-related reaction, infusion site induration, chills, chest discomfort, edema, fatigue, pyrexia	
Dermatological eczema, urticaria, papular rash, pruritic rash, pruritus	
Gastrointestinal diarrhea, abdominal pain/distension, nausea	
Respiratory laryngeal edema, dyspnea	
Cardiovascular tachycardia, hypotension, hyperemia	
Immune system anaphylactoid reaction, eyelid edema, urinary tract infection	
Central nervous system/psychiatric anxiety, insomnia, dizziness	
Serious adverse events	% (Number of affected of total subjects)
Anaphylaxis	3 (3/106)
Hypersensitivity	20 (21/106)
	9/14 infants
	12/92 children/adults

Note: Data from a previous study.⁶²

The LAL-CL04 extension to this trial reported one subject having experienced an infusion-related reaction, although subsequent reintroduction of sebelipase did not have any further adverse effects.⁶⁰ Additional trials also support the acceptable safety profile of sebelipase alfa. ARISE/LAL-CL02 reported three serious adverse reactions, including one infusion-associated event. Most hypersensitivity reactions were recorded in infant subjects.³⁶

Immunogenicity

Experience with other ERTs in other lysosomal diseases suggest that ERTs are immunogenic, and the development of antidrug antibodies can affect drug efficacy.⁶²⁻⁶⁴ In the case of sebelipase alfa, this seems more common in infants. Four infants in LAL-CL03 developed antidrug antibodies, mainly within the first 2 months of exposure. Antibodies in two of these subjects showed *in vitro* inhibition of enzyme activity and inhibition of cellular uptake of LAL. In three of the subjects, antidrug titers decreased to undetectable levels over the study period. Adult subjects participating in LAL-CL04 trial did not demonstrate antidrug antibodies over the study period of 52 weeks.⁶⁰

Five subjects in ARISE had detectable antidrug antibodies, mostly within 3 months of exposure, but antibody titers were low and did not affect efficacy or impact safety.³⁶

Discussion

The availability of ERT for LAL-D is promising. Initial studies have shown survival improvement in infantile disease and improvement in biochemical parameters for late-onset disease in children and adults. However, several aspects relating to long-term outcome are unknown. We do not know the effect of ERT on the progression of liver fibrosis. The primary end point of the ARISE trial was normalization of serum ALT, but LFTs are not reliable correlates of fibrosis or cirrhosis, and transaminases in advanced liver disease may be within the normal range. Cirrhosis may take years to develop, and longitudinal data will be valuable in this assessment. Regression of fibrosis has been shown in other liver diseases with treatment of the underlying etiology.⁶⁵ It will be interesting to know if this is the case with sebelipase alfa.

LAL-D subjects with decompensated cirrhosis and severe liver disease (Child-Pugh Score C) were not included in trials. The burden of end-stage liver disease in this group is significant, with limited treatment options.^{66,67} In addition, subjects with liver comorbidities were not part of the inclusion criteria for these trials. It would be of interest to know the additive effect of LAL-D upon liver disease progression given that steatosis is known to act synergistically with other factors in fibrosis progression.⁶⁸

Available sebelipase alfa trials have demonstrated significant improvements in the lipid profiles of participating subjects. Whether this will ameliorate premature atherosclerosis and significantly affect mortality and/or morbidity in terms of cardiovascular disease remains to be seen. No studies have addressed the effects of lipid-lowering agents on LAL-D progression/mortality.

There are no recommendations for sebelipase alfa dosing in pregnancy, and the effects of this drug in human fetal

development are unknown. However, data derived from animal studies have shown no detrimental effects on fetal development.⁶²

Not surprisingly, some patients especially in infantile LAL-D group have shown antibody response. Like other ERTs, sebelipase alfa being a foreign protein is potentially immunogenic, and this aspect of treatment should always be considered by treating clinicians.

Currently ongoing clinical trials are seeking to address some of the issues raised. An open-label, single-arm, Phase II study in infants under 8 months with rapidly progressive LAL-D (NCT02193867, sponsored by Alexion) seeks to assess long-term parameters (up to 3 years). Primary outcome measures include safety profile, changes in biochemical and physical parameters, and the use of concurrent medications. Secondary outcomes include survival at 12 months and beyond, growth status, and pharmacokinetic characterization.

Another Phase II, open-label trial (NCT02112994, sponsored by Alexion) seeks to assess the safety and efficacy of sebelipase alfa in a broader population of infants over 8 months, children, and adults. Secondary outcome measures include assessment of liver severity (Child-Pugh and United Kingdom End Stage Liver Disease [UKELD] score as well as histopathology) up to 96 weeks, immunogenicity, and effect of concurrent medications.

Conclusion

Sebelipase alfa is the first of its kind for ERT in LAL-D. Current data demonstrate significant survival impact in infants with rapidly progressive disease and marked improvements in biochemical parameters in the older LAL-D group. Longitudinal data will be relevant in assessing long-term impact on disease progression and mortality, as well as in characterization of adverse events and immunogenicity. Although LAL-D is an uncommon condition and rarely described in the literature, genetic analyses estimate a higher prevalence than case reports would suggest. The rarity and clinical spectrum of the LAL-D phenotype makes it likely that it is underdiagnosed. Enhancing awareness of LAL-D in physicians is essential given the availability of ERT for a life-threatening disorder and may considerably impact detection rates and supplement existing knowledge of the natural history, progression, and epidemiology of this uncommon condition.

Disclosure

Dr Reena Sharma is principle investigator for sebelipase alfa CL04 trial and has received travel grants and bursaries from Synageva and Alexion. The other authors report no conflicts of interest in this work.

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