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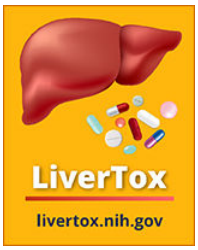

Sebelipase alfa

Updated: March 10, 2016.

OVERVIEW

Introduction

Lysosomal acid lipase deficiency is an inherited condition which underlies Wolman disease and cholesteryl ester storage disease. The current standard treatment for these two conditions is enzyme replacement therapy using infusions of recombinant forms of lysosomal acid lipase. Enzyme replacement therapy is generally well tolerated and has not been linked to serum enzyme elevations or to instances of clinically apparent acute liver injury.

Background

Sebelipase (se" be lye' pase) alfa is a recombinant form of the lysosomal enzyme that is absent or deficient in inherited conditions that are marked by dyslipidemia, early onset of atherosclerosis and fatty liver disease that can progress to cirrhosis. The severe form of lysosomal acid lipase deficiency is known as Wolman disease in which the enzyme is entirely absent. Wolman disease is a severe, progressive disease of infancy marked by severe diarrhea, failure to thrive and progressive hepatic fibrosis and cirrhosis, usually leading to death within the first year of life. The same enzyme defect also appears to be responsible for the milder form of dyslipidemia and liver disease known as cholesterol ester storage disease in which the enzyme is deficient, but not totally absent. Cholesterol ester storage disease typically presents in adolescence or young adulthood, but may go undetected and present with middle age with wide spread complications of atherosclerosis or cirrhosis of unknown cause. The enzyme acts in lysosomes upon cholesterol esters and its deficiency results in accumulation of the cholesterol esters and triglycerides in hepatocytes and diffusely in macrophages in the liver, spleen, adrenals, bone marrow, lymph nodes and intestinal villi. Liver histology demonstrates microvesicular steatosis, foamy macrophages and progressive fibrosis. Serum aminotransferase levels are typically mildly or moderately elevated. Cholesterol lowering agents have been used in an attempt to treat these conditions, but have little effect. Cirrhosis and end stage liver disease can be managed successfully with liver transplantation, and hematopoietic cell transplantation has been reported to reverse some of the manifestations. Recently, infusions of recombinant lysosomal acid lipase have been found to decrease serum enzyme elevations and result in resolution of hepatomegaly in patients with cholesterol ester storage disease. In some cases, the beneficial effects were dramatic with evidence of disease regression. Pilot studies in children with Wolman disease have also had promising results with enzyme replacement. Sebelipase alfa, a recombinant lysosomal acid lipase product extracted from the egg whites laid by transgenic hens, was approved for use in lysosomal acid lipase deficiency in 2015. The recombinant protein is available in solution in single use vials of 2 mg/mL under the brand name Kanuma. The recommended regimen of therapy varies by indication, but is in the range of 1 to 3 mg/kg infused intravenously every 1 to 2 weeks. Side effects are few but can include infusion reactions and hypersensitivity.

Hepatotoxicity

In preregistration controlled trials, lysosomal acid lipase enzyme replacement therapy usually resulted in a rapid improvement in serum enzyme elevations, which was used as a surrogate marker for efficacy in ameliorating the liver disease caused by the lysosomal acid lipase deficiency. No reports of de novo serum aminotransferase elevations or clinically apparent liver injury were reported in trials of sebelipase alfa infusion therapy. Anti-drug reactive antibodies develop in a proportion of patients (particularly those with Wolman disease) and can be associated with hypersensitivity reactions, but these have not been linked to episodes of liver injury and can usually be managed with antihistamines and do not necessitate permanent discontinuation of treatment.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

Sebelipase alfa is a recombinant protein that shares 99% homology with the human enzyme. Proteins are metabolized in multiple organs and tissues into polypeptides and amino acids. There is no reason for these proteins to cause liver disease other than by a hypersensitivity reaction or by their direct enzymatic reactivity.

Outcome and Management

Serum enzyme elevations that occur on enzyme replacement therapies are usually self-limited and mild and generally do not require dose modification or discontinuation of therapy. Persistent or prominent elevations should lead to evaluation for other forms of liver disease. No instances of acute liver failure, chronic hepatitis or vanishing bile duct syndrome due to sebelipase have been reported.

Drug Class: Lysosomal Acid Lipase Deficiency Agents; Enzyme Replacement Therapy

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sebelipase alfa – Kanuma®

DRUG CLASS

Lysosomal Acid Lipase Deficiency Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Sebelipase alfa	1276027-63-4	Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 10 March 2016

Hoeg JM, Demosky SJ Jr, Pescovitz OH, Brewer HB Jr. Cholesteryl ester storage disease and Wolman disease: phenotypic variants of lysosomal acid cholesteryl ester hydrolase deficiency. Am J Hum Genet 1984; 36: 1190-203. PubMed PMID: 6097111.

(Early description of the similarities and differences between Wolman disease and cholesterol ester storage disease points out the near absence of the lysosomal acid lipase in Wolman disease [<4%] and its marked deficiency in cholesterol ester storage disease [23%]).

Pagani F, Pariyarath R, Garcia R, Stuani C, Burlina AB, Ruotolo G, Rabusin M, et al. New lysosomal acid lipase gene mutants explain the phenotype of Wolman disease and cholesteryl ester storage disease. J Lipid Res 1998; 39: 1382-8. PubMed PMID: 9684740.

(Analysis of the variants in the gene of lysosomal acid lipase found mutations that distinguish Wolman disease [missense substitutions] and cholesterol ester storage disease [splicing errors]).

Anderson RA, Bryson GM, Parks JS. Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. Mol Genet Metab 1999; 68: 333-45. PubMed PMID: 10562460.

(Four of 5 patients with cholesterol ester storage disease had a splice junction mutation in at least one allele of the lysosomal acid lipase gene which encoded a shortened form of the enzyme, whereas all 3 with Wolman disease had missense mutations in both alleles accounting for the virtual absence of enzymatic activity).

Krivit W, Peters C, Dusenbery K, Ben-Yoseph Y, Ramsay NK, Wagner JE, Anderson R. Wolman disease successfully treated by bone marrow transplantation. Bone Marrow Transplant 2000; 26: 567-70. PubMed PMID: 11019848.

(6 month old girl with Wolman disease, whose brother had died at age 3 months, underwent bone marrow transplantation with subsequent partial resolution of symptoms and signs, and improved physical and mental development).

Elleder M, Chlumská A, Hyánek J, Poupětová H, Ledvinová J, Maas S, Lohse P. Subclinical course of cholesteryl ester storage disease in an adult with hypercholesterolemia, accelerated atherosclerosis, and liver cancer. J Hepatol 2000; 32: 528-34. PubMed PMID: 10735626.

(51 year old man was found to have advanced artherosclerotic peripheral artery disease, dyslipidemia and micronodular cirrhosis with cholangiocarcinoma, and genetic analysis showed evidence of lysosomal acid lipase deficiency characteristic of cholesterol ester storage disease).

Du H, Schiavi S, Levine M, Mishra J, Heur M, Grabowski GA. Enzyme therapy for lysosomal acid lipase deficiency in the mouse. Hum Mol Genet 2001; 10: 1639-48. PubMed PMID: 11487567.

(In a mouse model of Wolman disease, infusion of mannose terminated human lysosomal acid lipase resulted in uptake of the enzyme in macrophages and decrease in the excessive triglyceride and cholesterol content of the liver, spleen and small intestine).

Fasano T, Pisciotta L, Bocchi L, Guardamagna O, Assandro P, Rabacchi C, Zanoni P, et al. Lysosomal lipase deficiency: molecular characterization of eleven patients with Wolman or cholesteryl ester storage disease. Mol Genet Metab 2012; 105: 450-6. PubMed PMID: 22227072.

(All 8 patients with cholesterol ester storage disease, but none of 3 with Wolman disease, had a splice junction mutation in the lysosomal acid lipase gene, this mutation occurring within a common haplotype suggesting a common "founder" ancestor).

Bernstein DL, Hülkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol 2013; 58: 1230-43. PubMed PMID: 23485521.

(Review of the clinical features of cholesterol ester storage disease based upon 135 patients reported in the literature, found in all races, both sexes with onset ranging from 1 to 68 years; 99% had hepatomegaly and 74% splenomegaly; all had elevations in ALT or AST, mean levels 54 and 52 U/L; cholesterol elevations in all, even with statin use; among 11 deaths, 73% were due to liver failure; liver biopsy findings were diagnostic; genetic analyses show at least 31 distinct mutations accounting for variation in residual enzyme activity and disease presentation: Wolman disease or cholesterol ester storage disease).

Balwani M, Breen C, Enns GM, Deegan PB, Honzík T, Jones S, Kane JP, et al. Clinical effect and safety profile of recombinant human lysosomal acid lipase in patients with cholesteryl ester storage disease. Hepatology 2013; 58: 950-7. PubMed PMID: 23348766.

(Phase 1 and 2 studies of recombinant lysosomal acid lipase [sebelipase alfa] in 9 adults with cholesterol ester storage disease found the infusions to be well tolerated and to result in decreases in serum cholesterol, ALT and AST levels with relapse upon stopping, and sustained improvements with extended therapy).

Grabowski G. Therapy for lysosomal acid lipase deficiency: replacing a missing link. Hepatology 2013; 58: 850-2. PubMed PMID: 23471861.

(Review of the role of lysosomal acid lipase in cholesterol metabolism, the consequences of its deficiency and the possible role of recombinant enzyme replacement therapy).

Valayannopoulos V, Malinova V, Honzík T, Balwani M, Breen C, Deegan PB, Enns GM, et al. Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. J Hepatol 2014; 61: 1135-42. PubMed PMID: 24993530.

(Among 8 adults with cholesterol ester storage disease treated in an open label extension study with infusions of sebelipase every other week for at least one year, serum ALT and AST levels became and remained normal and liver volume and fat content decreased; side effects included 2 hypersensitivity reactions in patients who later tolerated restarting treatment; no mention of liver injury or serum enzyme elevations).

Chuang JC, Lopez AM, Posey KS, Turley SD. Ezetimibe markedly attenuates hepatic cholesterol accumulation and improves liver function in the lysosomal acid lipase-deficient mouse, a model for cholesteryl ester storage disease. Biochem Biophys Res Commun 2014; 443: 1073-7. PubMed PMID: 24370824.

(In a mouse model of cholesterol ester storage disease, ezetimibe led to a decrease in hepatic cholesterol concentrations and improvements in serum ALT levels).

Reiner Ž, Guardamagna O, Nair D, Soran H, Hovingh K, Bertolini S, Jones S, et al. Lysosomal acid lipase deficiency--an under-recognized cause of dyslipidaemia and liver dysfunction. Atherosclerosis 2014; 235: 21-30. PubMed PMID: 24792990.

(Summary of the pathogenesis, genetic basis, clinical features and diagnosis of lysosomal acid lipase deficiency focuses upon need for screening and the frequency with which it is underdiagnosed).

Sun Y, Xu YH, Du H, Quinn B, Liou B, Stanton L, Inskeep V, et al. Reversal of advanced disease in lysosomal acid lipase deficient mice: a model for lysosomal acid lipase deficiency disease. Mol Genet Metab 2014; 112: 229-41. PubMed PMID: 24837159.

(In a mouse model of lysosomal acid lipase deficiency [lal-/-], infusions of recombinant human lysosomal acid lipase resulted in decreases in cholesterol levels in liver and spleen towards normal, less fibrosis accumulation in liver and prolongation of life in comparison to saline infusions).

Shirley M. Sebelipase Alfa: First Global Approval. Drugs 2015; 75: 1935-40. PubMed PMID: 26452566.

(Summary of history of development and approval of sebelipase alfa for therapy of lysosomal acid lipase deficiency mentions that the intravenous infusions result in prompt improvements in serum ALT levels and lessening of hepatomegaly).

Burton BK, Deegan PB, Enns GM, Guardamagna O, Horslen S, Hovingh GK, Lobritto SJ, et al. Clinical features of lysosomal acid lipase deficiency. J Pediatr Gastroenterol Nutr 2015; 61: 619-25. PubMed PMID: 26252914.

(Among 49 patients with lysosomal acid lipase deficiency enrolled in a prospective study, mean age of onset was 9 years; imaging showed hepatomegaly in 77%, splenomegaly 64% and steatosis 51%; ALT elevated in 92%, cholesterol in 63%, triglycerides in 27%).

Burton BK, Balwani M, Feillet F, Barić I, Burrow TA, Camarena Grande C, Coker M, et al. A phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency. N Engl J Med 2015; 373: 1010-20. PubMed PMID: 26352813.

(Among 66 patients [ages 4 to 54 years] with lysosomal acid lipase deficiency [38 with cirrhosis] treated with infusions of sebelipase or placebo every 2 weeks for 20 weeks, serum ALT, AST and cholesterol levels and hepatic volume and fat content improved more with active enzyme therapy than placebo; one patient had a mild hypersensitivity reaction but was able to continue therapy, and there were no hepatic adverse effects mentioned).

Rader DJ. Lysosomal acid lipase deficiency--a new therapy for a genetic lipid disease. N Engl J Med 2015; 373: 1071-3. PubMed PMID: 26352819.

(Editorial in response to Burton [2015] discusses the etiology, pathogenesis and long term consequences of lysosomal acid lipase deficiency and the rationale for a glycosylated, mannose-terminated recombinant enzyme that targets hepatocytes via the mannose-6-phosphate receptor).