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Enzyme Replacement Therapy

Updated: March 10, 2016.

OVERVIEW

Introduction

Enzyme replacement therapy refers to treatment of congenital enzyme deficiencies using purified human, animal or recombinant enzyme preparations. The enzymes are given parenterally, usually by intravenous infusion. The diseases treated are generally rare genetic disorders which lead to severe disability and premature death.

Background

Enzyme replacement therapy is typically used to replace a missing or deficient enzyme in a person with an inherited enzyme deficiency syndrome. The missing enzyme is replaced by infusions of an enzyme that is purified from human or animal tissue or blood or produced by novel recombinant techniques. Typically, the enzyme is modified to allow for a longer half-life, more potent activity, resistance to degradation or targeting to a specific organ, tissue or cell type. The first successful enzyme replacement therapies were for alpha-1-antitrypsin (A1AT) deficiency using plasma derived purified human A1AT. A1AT deficiency is associated with early onset emphysema attributed to the lack of leukocyte elastase inhibitor which leads to progressive pulmonary damage. Small prospective studies suggested a benefit from augmentation therapy, raising the levels of A1AT in serum by infusing the enzyme purified from human serum. This therapy was eventually shown to be beneficial, particularly in patients with early or intermediate pulmonary dysfunction and was quite safe, without the occurrence of viral hepatitis, despite being prepared from human plasma.

A second form of successful enzyme replacement therapy was established for Gaucher disease, an inherited deficiency of lysosomal acid β-glucocerebrosidase that leads to accumulation of the substrate (glucocerebroside and its other breakdown products such as ceramide) in lysosomes. The major tissues affected are liver, spleen and bone. The glucocerebrosidase was initially prepared from placental tissue and was modified to allow its specific uptake by macrophages and delivery into lysosomes. Subsequently, recombinant forms of glucocerebrosidase have been developed and now constitute the standard of care for type 1 Gaucher disease.

Subsequently, similar or related approaches have been taken to treat other enzyme deficiency syndromes such as adenosine deaminase deficiency, lysosomal acid lipase deficiency, Fabry disease, Pompe disease, Hurler and Hunter syndrome and several of the rarer forms of mucopolysaccharidoses. A list of enzymes approved for use in enzyme replacement therapy in the United States, the year of first approval, the generic and brand names of the product and the disease for which they are used are given in the Table.

Natural purified and recombinant enzymes are generally well tolerated with minimal systemic adverse reactions. The usual major reactions to enzyme replacement therapy are local infusion reactions and hypersensitivity reactions. Hypersensitivity can be a difficult problem, not just in causing allergic symptoms but also in causing

inactivity of the enzyme by cross reacting antibodies. Hypersensitivity reactions are generally more common and more severe in patients with total absence of the enzyme, rather than a deficiency or minor amino acid mutation that inactivates the protein. Hypersensitivity reactions can be severe with rash, fever, hypotension, angioneurotic edema, bronchospasm, anaphylaxis and cardio-pulmonary collapse. Most reactions, however, are mild and transient and may be prevented by premedication with antihistamines, antipyretics or corticosteroids.

Enzyme Replacement Therapies

Generic Name	Brand Name	Enzyme	Year	Disease
Alpha1-Proteinase inhibitor	Prolastin-C Glassia	Alpha1-Antitrypsin	2009 2010	A1AT Deficiency
Alglucerase alfa	Ceredase*	β-Glucocerebrosidase	1991	Gaucher
Imiglucerase	Cerezyme	β-Glucocerebrosidase	1995	Gaucher
Taliglucerase alfa	Elelyso	β-Glucocerebrosidase	2012	Gaucher
Velaglucerase alfa	VPRIV	β-Glucocerebrosidase	2010	Gaucher
Pegademase	Adagen	Adenosine Deaminase	2000	ADA Deficiency
Agalsidase beta	Fabrazyme	Alpha-Galactosidase A	2003	Fabry
Alglucosidase alfa	Lumizyme	Acid alpha-Glucosidase	2010	Pompe
Laronidase	Aldurazyme	α-L-Iduronidase	2003	Hurler, MPS I
Idursulfase	Elaprase	Iduronate-2-Sulfatase	2006	Hunter, MPS II
Elosulfase alfa	Vimizim	N-Acetylgalactosamine-6 Sulfatase	2014	Morquio Snydrome A, MPS IVA
Galsulfase	Naglazyme	N-Acetylgalactosamine-4 Sulfatase	2005	Maroteaux-Lamy, MPS VI
Sebelipase alfa	Kanuma	Lysosomal Acid Lipase	2015	Wolman, LAL Deficiency

* Withdrawn from market.

MPS=Mucopolysaccharidosis.

Hepatotoxicity

Enzyme replacement therapies generally cause little evidence for liver injury. Minor, transient elevations in serum enzymes occur with some agents, but none of the current enzyme replacement therapies have been associated with severe liver test abnormalities or clinically apparent liver injury with jaundice. None of the replacement therapies have been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. Indeed, many enzyme replacement therapies can lead to an improvement in liver injury associated with the underlying condition, and improvement in hepatic function or serum enzyme elevations has been used as a surrogate endpoint for efficacy of some treatments (such as lysosomal acid lipase deficiency).

Likelihood score for Enzyme Replacement Therapies: E (unlikely causes of liver injury).

Mechanism of Injury

Some enzyme replacement therapies are recombinant proteins that share a high degree of 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 possibly by their direct enzymatic reactivity acting upon the liver.

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: Genetic Disorder Agents; Gaucher Disease Agents; Sebelipase alfa

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Agalsidase beta – Fabrazyme®

Alglucosidase alfa – Lumizyme®

Imiglucerase – Cerezyme®

Pegademase – Adagen®

DRUG CLASS

Enzyme Replacement Therapy

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Various	Not Applicable	Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 10 March 2016

Overview

Baldo BA. Enzymes approved for human therapy: indications, mechanisms and adverse effects. BioDrugs 2015; 29: 31-55. PubMed PMID: 25648140.

(Review of enzymes that are approved for use in the US including those used for enzyme replacement therapy [for Gaucher, Fabry, Pompe, and several MPS] as well as those for specific diseases [dornase for cystic fibrosis, alteplase for myocardial infarction and stroke, L-asparaginase for cancer, and pegloticase for gout]; no mention of ALT elevations or hepatotoxicity except for L-asparaginase).

Gaucher Disease

Elstein D, Zimran A. Review of the safety and efficacy of imiglucerase treatment of Gaucher disease. Biologics 2009; 3: 407-17. PubMed PMID: 19774208.

(Review of the pathogenesis and clinical features of Gaucher disease, types 1, 2 and 3, as well as the development of enzyme replacement therapy and long term efficacy and safety of imiglucerase, a human recombinant form of glucocerebrosidase that was given intravenously every 2 weeks and largely replaced the placental tissue derived product [alglucerase] which was given 3 times weekly).

Velaglucerase (Vpriv) for Gaucher's disease. Med Lett Drugs Ther 2010; 52 (1337): 36. PubMed PMID: 20508578.

(Concise review of the mechanism of action, efficacy and cost of velaglucerase, shortly after this second recombinant form of glucocerebrosidase was approved as therapy of type 1 Gaucher disease; no discussion of adverse events).

Lysosomal Acid Lipase Deficiency (Cholesterol Ester Storage Disease, Wolman 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 patient, who later tolerated restarting treatment; no mention of liver injury or serum enzyme elevations).

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).

Alpha-1-Antitrypsin (A1AT) Deficiency

Seersholm N, Wencker M, Banik N, Viskum K, Dirksen A, Kok-Jensen A, Konietzko N. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin

deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. Eur Respir J 1997; 10: 2260-3. PubMed PMID: 9387950.

(Analysis of changes in lung function [FEV1] in 198 German patients with A1AT deficiency receiving weekly infusions of A1AT [purified from human plasma] compared to 97 Danish patients who were not being treated, found less decrease in FEV1 in treated subjects; no mention of adverse events).

Wencker M, Banik N, Buhl R, Seidel R, Konietzko N. Long-term treatment of alpha1-antitrypsin deficiency-related pulmonary emphysema with human alpha1-antitrypsin. Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL)-alpha1-AT-study group. Eur Respir J 1998; 11: 428-33. PubMed PMID: 9551749.

(Among 443 patients with A1AT deficiency treated with weekly infusions of human A1AT [plasma derived], 65 had adverse events, but these were largely infusion reactions which were repeated and severe in 3 [fever, chills]; no patient developed viral hepatitis, but there was no mention of ALT levels).

Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Am J Respir Crit Care Med 1998; 158: 49-59. PubMed PMID: 9655706.

(Among 1048 patients with A1AT deficiency followed in a natural history study, showed a decreased mortality in those receiving A1AT infusions and those with intermediate baseline declines in FEV1 had less decline if they were receiving A1AT infusions; no mention of adverse events).

Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS, Skovgaard LT, et al. A randomized clinical trial of alpha (1)-antitrypsin augmentation therapy. Am J Respir Crit Care Med 1999; 160: 1468-72. PubMed PMID: 10556107.

(Among 56 patients with A1AT deficiency treated with A1AT or placebo infusions every 4 weeks for 3 years, the loss of lung tissue as measured by CT was less with the enzyme infusions while changes in FEV1 were not; "no adverse effects of treatment or placebo were observed").

Campos MA, Lascano J. α1 Antitrypsin deficiency: current best practice in testing and augmentation therapy. Ther Adv Respir Dis 2014; 8: 150-61. PubMed PMID: 25013223.

(Review of the genetics, clinical features, diagnosis and management of A1AT deficiency mentions that adverse reactions to A1AT infusion therapy are rare, usually transitory and may include headache, nausea and dizziness; no mention of ALT elevations or hepatotoxicity).

Adenosine Deaminase (ADA) Deficiency

Booth C, Gaspar HB. Pegademase bovine (PEG-ADA) for the treatment of infants and children with severe combined immunodeficiency (SCID). Biologics 2009; 3: 349-58. PubMed PMID: 19707420.

(Review of efficacy and safety of pegademase mentions that more than 150 patients have been treated with this enzyme which allows for disease stabilization and "no toxic or hypersensitivity reactions have been reported" with its use, the main side effect being development of antibodies to bovine ADA in up to 80% of recipients, but is rarely clinically significant; no mention of ALT elevations or hepatotoxicity).

Pompe Disease

Broomfield A, Fletcher J, Davison J, Finnegan N, Fenton M, Chikermane A, Beesley C, et al. Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy. J Inherit Metab Dis 2016; 39: 261-71. PubMed PMID: 26497565.

(Among 33 children with Pompe disease [lysosomal acid maltase deficiency] who were treated with every other week infusions of recombinant alglucosidase for 0.5 to 13.5 years, 13 [40%] died and 13 [40%] survived

ventilation-free, factors associated with poor outcome being older age at starting therapy, cross reactive antibodies and failure to thrive; adverse events included severe infusion reactions [25%]; no mention of ALT elevations or hepatotoxicity).

Stepien KM, Hendriksz CJ, Roberts M, Sharma R. Observational clinical study of 22 adult-onset Pompe disease patients undergoing enzyme replacement therapy over 5years. Mol Genet Metab 2016 Feb 4. [Epub ahead of print] PubMed PMID: 26873529.

(Among 22 adults with Pompe disease treated with alglucosidase [20 mg/kg every other week] for at least 5 years, there was continued increase in ventilation requirement and wheel chair dependence; therapy was "well tolerated" and there were no deaths from liver disease or mention of ALT elevations or hepatotoxicity).

Fabry Disease

Goláň L, Goker-Alpan O, Holida M, Kantola I, Klopotowski M, Kuusisto J, Linhart A, et al. Evaluation of the efficacy and safety of three dosing regimens of agalsidase alfa enzyme replacement therapy in adults with Fabry disease. Drug Des Devel Ther 2015; 9: 3435-44. PubMed PMID: 26185417.

(Among 44 adults with Fabry disease treated with weekly infusions of agalsidase, 25% had infusions reactions, but none were severe; no mention of ALT elevations or hepatotoxicity).

Schiffmann R, Pastores GM, Lien YH, Castaneda V, Chang P, Martin R, Wijatyk A. Agalsidase alfa in pediatric patients with Fabry disease: a 6.5-year open-label follow-up study. Orphanet J Rare Dis 2014; 9: 169. PubMed PMID: 25425121.

(Among 11 children with Fabry disease treated for up to 6 years with agalsidase, 6 had infusion reactions but all were able to continue therapy; there were no drug related serious adverse events and no mention of ALT elevations or hepatotoxicity).

Wilcox WR, Banikazemi M, Guffon N, Waldek S, Lee P, Linthorst GE, Desnick RJ, et al.; International Fabry Disease Study Group. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet 2004; 75: 65-74. PubMed PMID: 15154115.

(Among 58 patients with Fabry disease treated with agalsidase for 30 to 36 months, 8 had serious infusion reactions; no mention of ALT elevations or hepatotoxicity).

Mucopolysaccharidoses, types I (Hurler), II (Hunter), IVA (Morquio A), and VI (Maroteaux-Lamy).

Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics 2009; 123: 229-40. PubMed PMID: 19117887.

(Among 40 patients with MPS-1 treated with laronidase in a 3.5 year extension study, infusion reactions occurred in 53% which was associated with anaphylaxis in one patient; hepatomegaly decreased with treatment and there was no mention of ALT elevations or liver related adverse events).

Muenzer J, Beck M, Eng CM, Giugliani R, Harmatz P, Martin R, Ramaswami U, et al. Long-term, open-labeled extension study of idursulfase in the treatment of Hunter syndrome. Genet Med 2011; 13: 95-101. PubMed PMID: 21150784.

(Among 94 patients with Hunter syndrome treated long term with weekly, intravenous idursulfase infusions, improvements in FEV1, walking distance and mean liver and spleen volumes were sustained, and while 53% of children had infusion related adverse events, these decreased with time and were not dose limiting; no mention of ALT elevations or hepatotoxicity).

Horovitz DD, Magalhães TS, Acosta A, Ribeiro EM, Giuliani LR, Palhares DB, Kim CA, et al. Enzyme replacement therapy with galsulfase in 34 children younger than five years of age with MPS VI. Mol Genet Metab 2013; 109: 62-9. PubMed PMID: 23535281.

(Among 34 Brazilian children with MPS VI started on weekly infusions of galsulfase before the age of 5 years, there were no severe infusion reactions or adverse events considered treatment related; no mention of ALT elevations or hepatotoxicity).

Hendriksz CJ, Giugliani R, Harmatz P, Lampe C, Martins AM, Pastores GM, Steiner RD, et al.; CSP Study Group. Design, baseline characteristics, and early findings of the MPS VI (mucopolysaccharidosis VI) Clinical Surveillance Program (CSP). J Inherit Metab Dis 2013; 36: 373-84. PubMed PMID: 22127392.

(Among 123 patients with MPS VI [ages 1 to 59 years] receiving enzyme replacement therapy, height and weight increased and liver and spleen size decreased; infusion reactions were the most common adverse event and some required corticosteroids or antihistamines; no mention of ALT elevations or hepatotoxicity and no deaths were due to liver disease).

Giugliani R, Hwu WL, Tylki-Szymanska A, Whiteman DA, Pano A. A multicenter, open-label study evaluating safety and clinical outcomes in children (1.4-7.5 years) with Hunter syndrome receiving idursulfase enzyme replacement therapy. Genet Med 2014; 16: 435-41. PubMed PMID: 24202085.

(Among 28 boys with Hunter syndrome treated with idursulfase infusions, liver volume decreased by 17% and spleen volume by 21% and, while 17 children had infusion reactions [57%], there were "no clinically important changes in laboratory parameters").

Hendriksz CJ, Burton B, Fleming TR, Harmatz P, Hughes D, Jones SA, Lin SP, et al. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study. J Inherit Metab Dis 2014; 37: 979-90. PubMed PMID: 24810369.

(Among 176 patients with Morquio A syndrome [ages 5 to 57] treated with placebo or elosulfase weekly or every other week, modest improvements occurred with weekly elosulfase infusions; infusion reactions were common but did not necessitate permanent discontinuation; no mention of ALT elevations or hepatotoxicity).

Giugliani R, Lampe C, Guffon N, Ketteridge D, Leão-Teles E, Wraith JE, Jones SA, et al. Natural history and galsulfase treatment in mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome)--10-year follow-up of patients who previously participated in an MPS VI Survey Study. Am J Med Genet A 2014; 164A: 1953-64. PubMed PMID: 24764221.

(Among 59 patients enrolled in a multinational survey of MPS VI who had long term follow up [55 receiving galsulfase], there was modest improvements in walking distance and pulmonary function; data on side effects were not collected).

Burton BK, Berger KI, Lewis GD, Tarnopolsky M, Treadwell M, Mitchell JJ, Muschol N, et al. Safety and physiological effects of two different doses of elosulfase alfa in patients with Morquio A syndrome: A randomized, double-blind, pilot study. Am J Med Genet A 2015; 167A: 2272-81. PubMed PMID: 26069231.

(Among 25 patients with Morquio A syndrome treated with elosulfase [2 or 4 mg/kg weekly] exercise capacity improved slightly with treatment, infusion reactions were frequent, but did not require permanent discontinuation, and there were "no clinically meaningful changes in …clinical chemistry ...results").