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Glucocerebrosidase

Updated: March 5, 2018.

OVERVIEW

Introduction

The current standard treatment for type 1 Gaucher disease is enzyme replacement therapy using infusions of natural or recombinant forms of glucocerebrosidase, the lysosomal enzyme that is deficient in Gaucher disease. 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

Glucocerebrosidase is a lysosomal enzyme that is deficient or defective in the inherited condition known as Gaucher disease. The enzyme acts in lysosomes upon the sphingolipid glucocerebroside, catalyzing its conversion to glucose and ceramide. Glucocerebrosidase is an important step in the metabolism of glycolipids and its absence leads to accumulation of glycosylceramide in macrophages, giving rise to "foam cells" particularly in the spleen, liver and bone, leading to splenomegaly, hepatomegaly and bone dysplasia. In type 1 Gaucher disease, the most common form of this disease, the tissue damage is mostly limited to liver, spleen and bone, but sometimes involves lung and kidney. In types 2 and 3 Gaucher disease, there is also neurologic accumulation of foam cells and damage, leading to severe neurologic outcomes in infancy or childhood. Infusions of glucocerebrosidase have been shown to increase the activity of this enzyme intracellularly, to decrease foam cells and to ameliorate the signs of symptoms of type 1 Gaucher disease. The initial forms of glucocerebrosidase (alglucerase) used to treat patients were prepared from human tissue, largely placentas. Subsequently, recombinant forms of glucocerebrosidase were developed (imiglucerase, velaglucerase, taliglucerase) that have improved and more prolonged activity, allowing for less frequent infusions with better tolerance. All forms of glucocerebrosidase used clinically have been generally well tolerated with only mild adverse events, largely due to local or hypersensitivity reactions. None of the natural or recombinant forms of the enzyme have been linked to liver injury.

Alglucerase (al gloo' ser ase) is a placenta-derived form of purified glucocerebrosidase that was approved for use in type 1 Gaucher disease in the United States in 1991, the first drug approved as an enzyme replacement therapy. Alglucerase was typically administered three times weekly, and was withdrawn from use when recombinant forms of glucocerebrosidase became available that could be administered every 1 to 4 weeks, and appeared to have equal if not superior efficacy and similar or fewer side effects. Alglucerase is no longer commercially available.

Imiglucerase (im" i gloo' ser ase) was the first recombinant form of glucocerebrosidase approved for therapy of type 1 Gaucher disease. Imiglucerase is prepared by recombinant techniques using Chinese hamster ovary cells. It differs from the native enzyme in one amino acid (histidine at position 495 instead of arginine) and by

modification of the glycosylation sites so that they terminate in mannose sugars, which are specifically recognized and taken up by macrophages. Imiglucerase was approved for use in the United States in 1994 and soon became the most widely used enzyme replacement therapy for Gaucher disease. It is available as a lyophilized powder in vials of 200 and 400 Units. The typical dose is 60 Units/kg given by intravenous infusion over 1 to 2 hours every two weeks. Side effects are uncommon and generally mild, but can include local infusion site reactions, fatigue, headache, dizziness, abdominal pain, nausea, diarrhea, back pain, fever and rash. Rare, but potentially severe adverse reactions include hypersensitivity reactions and anaphylaxis.

Velaglucerase (vel" a gloo' ser ase) alfa was the second recombinant form of glucocerebrosidase approved as therapy of Gaucher disease. Velaglucerase is produced in a human cell line using gene activation technology, resulting in production of a recombinant protein with the identical amino acid sequence as the native, human enzyme. The glucocerebrosidase producing cells are treated with enzymes that modify glycosylation and result in high-mannose type glycans which increase uptake of the velaglucerase by macrophages. Velaglucerase was approved for use as enzyme replacement therapy of type 1 Gaucher disease in the United States in 2010. It is available as a lyophilized powder in single use vials of 400 Units under the brand name Vpriv. The typical initial dose is 60 Units/kg intravenously every 2 weeks. Side effects are not common and usually mild, but can include local infusion reactions, fatigue, headache, dizziness, abdominal pain, nausea, back pain, joint pain and fever. Rare, but reported severe adverse reactions include hypersensitivity reactions and anaphylaxis.

Taliglucerase (tal" i gloo' ser ase) alfa was the third recombinant form of glucocerebrosidase approved for therapy of type 1 Gaucher disease. Taliglucerase is prepared in plant cell cultures transfected with the human glucocerebrosidase gene. Taliglucerase differs from the native enzyme by two amino acids at the N terminal and 7 amino acids at the C terminal end. It is glycosylated and the oligosaccharide chains have terminal mannose sugars, which increase its uptake by macrophages. Taliglucerase was approved for use as enzyme replacement therapy for type 1 Gaucher disease in the United States in 2011. It is available as lyophilized powder in single use vials of 200 Units. The typical dose is 60 Units/kg every two weeks administered intravenously over 1 to 2 hours. Side effects are not common and usually mild, but can include local infusion reactions, fatigue, headache, dizziness, abdominal pain, nausea, back pain, joint pain and fever. Rare, but reported severe adverse reactions include hypersensitivity reactions and anaphylaxis.

Hepatotoxicity

In preregistration controlled trials, liver test abnormalities were no more common with glucocerebrosidase enzyme replacement therapy than with placebo or other treatments. What abnormalities occurred were mild and resolved spontaneously, usually without need for dose interruption. During premarketing clinical trials and since its more widespread clinical availability, no reports of acute liver injury with jaundice attributable to natural or recombinant forms of glucocerebrosidase have been published.

LIkelihood score: E (unlikely to cause clinically apparent liver injury).

Mechanism of Injury

The natural and recombinant forms of glucocerebrosidase are proteins and are metabolized in multiple organs and tissues to 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 enzyme replacement therapy of Gaucher disease have been reported.

Drug Class: Gaucher Disease Agents, Enzyme Replacement Therapy

Other Drugs in the Class: Eliglustat, Miglustat

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Imiglucerase – Cerezyme®

Taliglucerase – Elelyso®

Velaglucerase – Vpriv®

DRUG CLASS

Gaucher Disease Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Imiglucerase	154248-97-2	Protein	Not Available
Taliglucerase alpha	37228-64-1	Protein	Not Available
Velaglucerase alpha	884604-91-5	Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 05 March 2018

Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 397-416.

(Textbook of pharmacology and therapeutics; glucocerebrosidase is not discussed).

Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002; 113: 112-9. PubMed PMID: 12133749.

(Among 1028 patients in a worldwide Gaucher registry [53% from the US], 88% had at least one N370S allele and 26% were homozygous; long term results of enzyme replacement therapy demonstrated major improvements by 1 year and stability thereafter; no discussion of adverse events).

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).

Gonzalez DE, Turkia HB, Lukina EA, Kisinovsky I, Dridi MF, Elstein D, Zahrieh D, et al. Enzyme replacement therapy with velaglucerase alfa in Gaucher disease: Results from a randomized, double-blind, multinational, Phase 3 study. Am J Hematol 2013; 88: 166-71. PubMed PMID: 23386328.

(Among 25 treatment naïve patients with type 1 Gaucher disease treated with velaglucerase [45 or 60 U/kg every 2 weeks for 12 months], hemoglobin and platelet counts improved and spleen size decreased, and there were no serious adverse events attributable to therapy, common side effects being headache, nasopharyngitis, arthralgias, cough and pain; no mention of ALT elevations or hepatotoxicity).

Zimran A, Pastores GM, Tylki-Szymanska A, Hughes DA, Elstein D, Mardach R, Eng C, et al. Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase. Am J Hematol 2013; 88: 172-8. PubMed PMID: 23339116.

(Among 40 patients with type 1 Gaucher disease on long term imiglucerase enzyme replacement therapy who were switched to one of 4 doses of velaglucerase for 12 months, one developed an anaphylactic reaction to the first infusion, the others tolerated it well with stable indices of disease and no other serious or severe adverse events attributable to the velaglucerase).

Starzyk K, Richards S, Yee J, Smith SE, Kingma W. The long-term international safety experience of imiglucerase therapy for Gaucher disease. Mol Genet Metab 2007; 90: 157-63. PubMed PMID: 17079176.

(Among 2931 spontaneous adverse event reports made to the sponsor of imiglucerase between 1997 and 2004, 852 were considered related [or unknown]; the major category of adverse events were injection site reactions, urticarial and rash, but 34 were designated "hepatobiliary"; no further details provided).

Kishnani PS, DiRocco M, Kaplan P, Mehta A, Pastores GM, Smith SE, Puga AC, et al. A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1. Mol Genet Metab 2009; 96: 164-70. PubMed PMID: 19195916.

(Among 95 patients with type 1 Gaucher disease switched from every 2 to every 4 week infusions [same total dose], adverse events were similar and no patient required discontinuation for side effects; no mention of ALT elevations or hepatotoxicity).

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).

Weinreb NJ, Goldblatt J, Villalobos J, Charrow J, Cole JA, Kerstenetzky M, vom Dahl S, et al. Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment. J Inherit Metab Dis 2013; 36: 543-53. PubMed PMID: 22976765.

(Analysis of 757 patients participating in the Gaucher disease registry on long term imiglucerase therapy [every 2 weeks for 10 years or more] showed sustained improvements in all clinical features; no discussion of adverse events).

Pastores GM, Petakov M, Giraldo P, Rosenbaum H, Szer J, Deegan PB, Amato DJ, et al. A Phase 3, multicenter, open-label, switchover trial to assess the safety and efficacy of taliglucerase alfa, a plant cell-expressed recombinant human glucocerebrosidase, in adult and pediatric patients with Gaucher disease previously treated with imiglucerase. Blood Cells Mol Dis 2014; 53: 253-60. PubMed PMID: 24950666.

(Among 31 patients with type 1 Gaucher disease on long term imiglucerase who were switched to taliglucerase given every 2 weeks for 9 months, clinical features were stable and there were no severe adverse events related to therapy; no mention of ALT elevations or hepatotoxicity).

Pastores GM, Rosenbloom B, Weinreb N, Goker-Alpan O, Grabowski G, Cohn GM, Zahrieh D. A multicenter open-label treatment protocol (HGT-GCB-058) of velaglucerase alfa enzyme replacement therapy in patients with Gaucher disease type 1: safety and tolerability. Genet Med 2014; 16: 359-66. PubMed PMID: 24263462.

(Among 211 patients with type 1 Gaucher disease treated with velaglucerase [15-60 U/kg every 2 weeks for up to 1.5 years], infusion reactions occurred in 13% and values for clinical chemistry results were "unremarkable").

Zimran A, Wang N, Ogg C, Crombez E, Cohn GM, Elstein D. Seven-year safety and efficacy with velaglucerase alfa for treatment-naïve adult patients with type 1 Gaucher disease. Am J Hematol 2015; 90: 577-83. PubMed PMID: 25903392.

(Among 10 patients with type 1 Gaucher disease treated with velaglucerase every 2 weeks for up to 7 years, no patient stopped therapy because of adverse events; no mention of ALT elevations or hepatotoxicity).

Hughes DA, Gonzalez DE, Lukina EA, Mehta A, Kabra M, Elstein D, Kisinovsky I, et al. Velaglucerase alfa (VPRIV) enzyme replacement therapy in patients with Gaucher disease: Long-term data from phase III clinical trials. Am J Hematol 2015; 90: 584-91. PubMed PMID: 25801797.

(Among 57 patients with type 1 Gaucher disease enrolled in an extension study of velaglucerase [60 U/kg every 2 weeks for 1.2 to 4.8 years], no serious drug related adverse events occurred; no specific mention of ALT elevations or hepatotoxicity).

Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, Lukina E, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. Lancet 2015; 385 (9985): 2355-62. PubMed PMID: 25819691.

(Among 106 patients with stable type 1 Gaucher disease on long term enzyme replacement therapy who were switched to eliglustat or maintained on imiglucerase for 12 months, clinical features were stable in both groups while side effects more frequent with eliglustat included diarrhea, fatigue, nausea, headache, dyspepsia and abdominal pain; no mention of ALT elevations or hepatotoxicity, but one patient developed hepatocellular carcinoma).

Zimran A, Durán G, Giraldo P, Rosenbaum H, Giona F, Petakov M, Terreros Muñoz E, et al. Long-term efficacy and safety results of taliglucerase alfa through 5 years in adult treatment-naïve patients with Gaucher disease. Blood Cells Mol Dis 2016 Jul 18 pii. [Epub ahead of print]. PubMed PMID: 27499018.

(Among 19 adults with Gaucher disease enrolled in a clinical trial of twice vs once daily dosing of taliglucerase, 17 finishing 5 years of treatment, adverse events were mild-to-moderate and all were considered unrelated to therapy: "Most laboratory test values remained normal through study end. No abnormal values were clinically meaningful").

Zimran A, Wajnrajch M, Hernandez B, Pastores GM. Taliglucerase alfa: safety and efficacy across 6 clinical studies in adults and children with Gaucher disease. Orphanet J Rare Dis 2018; 13: 36. PubMed PMID: 29471850.

(A summary analysis of 6 clinical trials of taliglucerase alfa in at least 59 adults and 16 children with Gaucher disease treated for up to 5 years found that adverse events were mild and transient including arthralgia, headache and pruritus and de novo anti-taliglucerase antibodies; no mention of ALT elevations or hepatotoxicity).

Charrow J, Fraga C, Gu X, Ida H, Longo N, Lukina E, Nonino A, Gaemers SJM, Jouvin MH, Li J, Wu Y, Xue Y, Peterschmitt MJ. Once- versus twice-daily dosing of eliglustat in adults with Gaucher disease type 1: The

Phase 3, randomized, double-blind EDGE trial. Mol Genet Metab 2018; 123: 347-56. PubMed PMID: 29358012.

(Among 170 adults with Gaucher disease treated with once or twice daily eliglustat for a median of 3.3 years, all deaths were unrelated and there were no liver related severe adverse events or liver adverse event related discontinuations).

Zimran A, Belmatoug N, Bembi B, Deegan P, Elstein D, Fernandez-Sasso D, Giraldo P, et al.; GOS Study group. Demographics and patient characteristics of 1209 patients with Gaucher disease: Descriptive analysis from the Gaucher Outcome Survey (GOS). Am J Hematol 2018; 93: 205-12. PubMed PMID: 29090476.

(Summary of clinical features of 1209 patients [95% type 1] enrolled in an international Gaucher disease registry between 2010 and 2017, including 887 [73%] who received at least one therapy, most commonly imiglucerase [66%], velaglucerase [57%], alglucerase [12%], taliglucerase [10%] and miglustat [10%], does not mention adverse events or liver related complications of treatment).