REVIEW ARTICLE

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A Path for Horizing Your Innovative Work

VELAGLUCERASE ALFA: AN ENZYME REPLACEMENT THERAPY IN GAUCHER'S DISEASE

DEVANSHI CHAUDHARI[1], JIGNA SHAH[1]

1. Department of Clinical Pharmacy, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384 001, Gujarat, India.

Corresponding Author Email: devanshi.c72@gmail.com

Accepted Date: 04/04/2012 **Publish Date: 27/04/2012**

Abstract: Gaucher's disease is an inherited metabolic disease that is presented as a multi-system disease. Enzyme replacement aims to reduce the accumulated waste material within these macrophages by augmenting the activity of the enzyme and attempting to restore the cell back to normality. This study increasing focuses on patient satisfaction and preservation of quality of life in patients with Gaucher's Disease who receiving their enzyme replacement therapy with Velaglucerase alfa.

Keywords: Gaucher's disease, enzyme replacement therapy, Velaglucerase alpha.

INTRODUCTION

Lysosomal storage disorders are a group of diseases which occur due to accumulation of glucosylceramide/glucocerebroside and some related compounds within the lysosomes. Gaucher's disease (GD) is the most common amongst the various disorders under this group. GD is a model for applications of molecular medicine to clinical delineation, diagnosis, and treatment. The prevalence of GD is approximately 1/57,000 to 1/75,000 births worldwide,[1, 2] but the disease is more prevalent in individuals of Ashkenazi Jewish descent in whom the incidence is 1/800 births.[3,4] There is a paucity of reported cases in the literature with reference to the Indian subcontinent, possibly due to the rarity of this disease in this part of the world. A series of seven cases from Malabar region in Kerala showing increased incidence in the tribal population of Mappila Muslims has been published.[5]

Historical Aspects

GD was first described by Philippe Gaucher in 1882, two decades prior to the dictum of "Inborn errors of metabolism" given by Sir Archibald Garrod. Gaucher observed large cells in a splenic aspirate during the evaluation of a large spleen and he thought that it was evidence of a primary neoplasm of the spleen.[6] in 1924, Epstein first recognized the storage of glucocerebroside[7], while Brandy et al. delineated that the metabolic defect was due to the deficiency of the enzyme β-glucosidase (GBA).[8]

Genetics

GD is inherited as an autosomal recessive disorder. The protein saposin C presents glucocerebroside to GBA and directly activates the enzyme. Deficiency of saposin C, which is even rarer, results in a severe disorder similar to GD.[9] The GBA gene is located on chromosome 1q21.[10] More than 300 distinct mutations of the GBA gene have been described in which 80% are single nucleotide substitutions while rare or unknown alleles account for the remaining 20%.

Description of GD

GD is one of the most common glycolipid storage disorders, caused by an inherited deficiency of the lysosomal enzyme glucocerebrosidase, leading to accumulation of the substrate glucocerebroside in the cells of the macrophage-monocyte system.[11] accordingly; key disease features are related

to splenomegaly with hypersplenism, hepatomegaly, and bone involvement. Although a single-gene disorder, phenotypic expression is extremely variable, ranging from totally asymptomatic (only detectable by DNA analysis or enzyme deficiency) to a lethal newborn form with hydrops fetalis and ichthyosis. Many manifestations, some not uncommon and others very rare, cannot be explained by storage per se; examples include immunologic abnormalities, increased prevalence of certain malignancies with relative paucity of others, neurologic co morbidities (peripheral neuropathy and Parkinsonism), calcification of cardiac valves, and pulmonary hypertension. Yet, most patients will present or develop signs/symptoms that are commonly managed by hematologists, for example, anemia, thrombocytopenia, and splenomegaly. In the past 2 decades, GD has become a model for other Lysosomal Storage Disorders (LSDs), particularly because of the introduction of safe and effective Enzyme Replacement Therapy (ERT), [12] as well as Substrate Reduction Therapy (SRT), [13] and other modalities. Since the glucocerebrosidase gene was cloned, [14, 15] _ 300 mutations have been identified, [6] partly explaining the great phenotypic heterogeneity. Because many are private mutations and others may be either single or combined mutations in a complex allele, whole-gene sequencing is recommended for accurate genotyping. I underscore this point because, although genotype-phenotype correlations are imperfect, accurate genotyping for individual patients is important to predict probable prognoses.

Table 1.

Classic subtypes of GD

SUBTYPE	Type I	
	Asymptomatic	**Symptomatic**
Common genotype	N370S/N370S or 2 mild mutations	N370S/other or 2 mild mutations
Common presenting Features	None	Hepatosplenomegaly, hypersplenism, bleeding tendency, bone pains, growth retardation
Neurologic Involvement	Early-onset parkinsonism or peripheral neuropathy (rarely)	Early-onset Parkinsonism or peripheral neuropathy (rarely)
Bone involvement	None	Mild to severe (variable)
Lung involvement	None	None to (rarely) severe
Life expectancy (if untreated)	Normal	Normal/near normal
Disease-specific treatment (2010)	None	ERT (or SRT if ERT unsuitable/not a therapeutic option)

SUBTYPE	Type II	
	Neonatal	**Infantile**
Common genotype	2 null or recombinant mutations	1 null and 1 severe mutations
Common presenting Features	Hydrops fetalis; ichthyosis	SNGP, strabismus opisthotonus, trismus
Neurologic Involvement	Lethal	Severe
Bone involvement	None	None
Lung involvement	Severe	Severe
Life expectancy (if untreated)	Fetal/neonatal death	Death before 2 y
Disease-specific treatment (2010)	None	Supportive (ERT not justified ethically)

SUBTYPE	Type III		
	IIIa	**IIIb**	**IIIc**
Common genotype	None	L444P/L444P; 2 severe mutations	D409H/D409H
Common presenting Features	SNGP; myoclonic seizures; mild visceral involvement	SNGP; massive hepatosplenomegaly growth retardation	SNGP; cardiac valve calcifications; mild visceral involvement
Neurologic Involvement	SNGP; slowly progressive neurologic deterioration	SNGP; gradual but progressive cognitive deterioration	SNGP; brachycephalus
Bone involvement	Mild	Moderate to severe; kyphosis (gibbus)	Minimal in most; gibbus in the longest living
Lung involvement	Mild to moderate	Mild to moderate	Minimal
Life expectancy (if untreated)	Death during childhood	Death in mid adulthood	Death in very early adulthood
Disease-specific treatment (2010)	ERT for visceral disease	ERT for visceral disease	Cardiac valve replacement if possible

SNGP indicates supranuclear gaze palsy; ERT, enzyme replacement therapy; SRT, substrate reduction therapy; and PC, pharmacological chaperone.

Management

1) Surgical procedure
   - Splenectomy
   - Orthopedic surgeries
   - Obstetric surgeries

2) Enzyme Replacement Therapy (ERT)
   - Alglucerase
   - Imiglucerase
   - Velaglucerase Alfa
   - Taliglucerase Alfa

3) Substrate Reduction Therapy (SRT)
   - Miglustat
   - Eliglustat

4) Pharmacologic Chaperone Therapy (PC)

FDA approves Velaglucerase Alfa

The U.S. Food and Drug Administration have approved velaglucerase alfa for injection to treat children and adults with a form of the rare genetic disorder Gaucher disease. Gaucher disease occurs in people who do not produce enough of an enzyme called glucocerebrosidase. Without this, harmful amounts of a certain fatty substance (lipid) can build up in the liver, spleen; bones, bone marrow and nervous system, and can prevent cells and organs from working properly. About 1 in 50,000 to 1 in 100,000 in the general population has gaucher disease. Velaglucerase alfa provides long-term enzyme replacement therapy for Type 1 Gaucher disease, the most common form of the genetic disorder. It is an alternative to Cerezyme (Imiglucerase), another enzyme replacement therapy. The safety and effectiveness of velaglucerase alfa was assessed in three clinical studies involving 82 patients with Type 1 Gaucher disease ages 4 years and older. The studies included patients who switched to velaglucerase alfa after being treated with Cerezyme. The most common adverse reactions to velaglucerase alfa are allergic reactions.

Velaglucerase alfa information

Basis of discovery

Before the 1990s, treatment of Gaucher's disease was palliative, involving interventions, such as splenectomy. Although Enzyme Replacement Therapy (ERT) for lysosomal storage disorders, such as Gaucher's disease, was proposed in the 1960s, producing sufficient quantities of β-glucocerebrosidase and targeting it to the appropriate cells proved challenging.[16]

Imiglucerase, a recombinant analogue of β-glucocerebrosidase produced in Chinese hamster ovary cells, [16, 17] was approved by

the FDA in 1994 and largely replaced alglucerase. In addition, miglustat, a small-molecule drug that inhibits the synthesis of sphingolipids, such as glucocerebroside[18], was approved by the FDA in 2003 for patients with mild to moderate type 1 Gaucher's disease for whom ERT is not an option.

Drug properties

Velaglucerase alfa, which is produced by gene-activation technology in a human fibroblast cell line, has the same amino-acid sequence as human glucocerebrosidase. It is manufactured to contain predominantly high mannose-type N-linked glycan chains at the four occupied N-glycosylation sites to facilitate internalization of the enzyme mediated by the mannose receptor on target cells.[19, 20, 21] Velaglucerase alfa catalyses the hydrolysis of glucocerebroside to glucose and ceramide; reducing the amount of accumulated glucocerebroside.[19-22]

Clinical data

The efficacy of velaglucerase alfa was evaluated in three clinical trials involving a total of 99 patients with type 1 Gaucher's disease. Two randomized, double-blind trials involved patients with Gaucher's disease-related anaemia and either thrombocytopenia or organomegaly who were not currently receiving specific therapy for Gaucher's disease.

One of these studies was a 12-month trial involving 25 patients aged 4 years and older who were naive to ERT (defined as having not been treated with ERT for at least 30 months before study entry). Patients were randomized to receive velaglucerase Alfa at a dose of either 45 units per kg or 60 units per kg every other week.[20, 21] In both groups of patients, the mean change in hemoglobin concentration from baseline — the primary end point — was 2.4 g per deciliter, which is considered to be a clinically meaningful increase.[20, 21, 23] In addition, in the group that received the 60 units per kg dose, the mean reduction in liver volume was 17%, the mean reduction in spleen volume was 50% and platelet count increased by 51 × 109 per liter. The corresponding changes in the group that received the 45 units per kg dose were a 6% mean reduction in liver volume, a 40% mean reduction in spleen volume and an increased platelet count of 41 × 109 per liter.

The second study was a 9-month randomized double-blind and non-inferiority trial involving 34 patients aged 3 years and older who were not allowed to have received

disease-specific therapy for at least the previous 12 months. Patients were randomized to receive either 60 units per kg of velaglucerase alfa or 60 units per kg of Imiglucerase every other week. After 9 months of treatment, the mean absolute increase from baseline in haemoglobin concentration for patients treated with velaglucerase alfa was 1.6 g per decilitre. This was clinically and statistically non-inferior to that observed with Imiglucerase; the mean treatment difference in change from baseline to 9 months (Velaglucerase Alfa minus Imiglucerase) was 0.1 g per deciliter. There were no statistically significant differences between the groups receiving velaglucerase Alfa and Imiglucerase in the changes in platelet counts and liver and spleen volumes after 9 months of treatment, and in the time to first hemoglobin response (defined as 1 g per deciliter increase from baseline).[20, 21]

A third 12-month open-label, single-arm trial involved 40 patients aged 9 years and older who had been receiving treatment with Imiglucerase at doses ranging between 15 units per kg to 60 units per kg for a minimum of 30 consecutive months. Patients were also required to have a stable biweekly dose of Imiglucerase for at least 6 months before enrolment. Imiglucerase therapy was stopped and treatment with velaglucerase alfa was administered every other week at the same number of units as the patient's previous Imiglucerase dose. Haemoglobin concentrations and platelet counts remained stable on average throughout the 12 months of treatment with velaglucerase alfa and no patient required dosage adjustment during this period.[20, 21]

Mechanism of Action

Velaglucerase alfa is a human glucocerebrosidase product developed using the company's proprietary gene activation technology. Gaucher disease, caused by deficiency of the enzyme glucocerebrosidase results in accumulation of a toxic glycolipid substrate, called glucocerebroside. Velaglucerase alfa supplements or replaces beta-glucocerebrosidase, the enzyme that catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside and correcting the pathophysiology of gaucher disease.[24]

Therapeutic use

Velaglucerase alfa is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy for pediatric and adult patients with type 1 Gaucher disease. Glucocerebroside can

build up to harmful levels in the liver, spleen, lungs, bone marrow, and brain. This accumulation of fatty material in tissues interferes with the normal functioning of the body's organs and may cause organ enlargement and bone pain.

Recommended dosage

Velaglucerase should be dosed at 60 units/kg infused intravenously over 60 minutes every other week. Dosage adjustments, more specifically decreases in dose, can be made based on achievement and maintenance of each patient's therapeutic goals. Velaglucerase is supplied as a lyophilized powder to be reconstituted and diluted for infusion; it is available in 200-unit and 400-unit single-use vials.

Drug interactions

No studies have been done regarding drug-drug interactions with velaglucerase.

Adverse reactions

The most common adverse reactions associated with velaglucerase are infusion-related reactions (i.e., headache, dizziness, abdominal pain, nausea, back pain, joint pain, upper respiratory tract infection, prolongation of activated partial thromboplastin time, fatigue/asthenia, and pyrexia). Additionally, hypersensitivity can occur with velaglucerase alfa, and care should be exercised.[25–27]

REFERNCES

1. Meikle PJ, Hopwood JJ, Clague AE and Carey WF: Prevalence of lysosomal storage disorders. JAMA 1999; 281: 249–54.

2. Biegstraaten M, van Schaik IN, Aerts JM and Hollak CE: Non-neuronopathic' Gaucher disease reconsidered. Prevalence of neurological manifestations in a Dutch cohort of type I Gaucher disease patients and a systematic review of the literature. J Inherit Metab Dis 2008; 31: 337–49.

3. Beutler E, Nguyen NJ, Henneberger MW, Smolec JM, McPherson RA and West C: Gaucher disease: Gene frequencies in the Ashkenazi Jewish population. Am J Hum Genet 1993; 52: 85–88.

4. Beutler E and Grabowski GA: Glucosylceramide lipidosis–Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D. The metabolic and molecular bases of inherited diseases. 8th Ed. New York: McGraw-Hill (2001). pp. 3635–68.

5. Feroze M, Arvindan KP and Jose L Gaucher's disease among Mappila muslims of Malabar. Indian J Pathol Microbiol 1994; 37: 307–11.

6. Gaucher PC: De l'epithelioma primitive de la rate, hypertrophie idiopathique de la rate sans leukemia. Paris: MD Thesis 1882.

7. Epstein E: Beitrag zurchemie der Gaucherschen krankeit. Biochem Z 1924; 145: 398–402.

8. Brady RO, Kanfer JN and Shapiro D: Metabolism of glucocerebrosides.II: Evidence of an enzymatic deficiency in Gaucher's disease. Biochem Biophys Res Commun 1965; 18: 221–5.

9. Schnabel D, Schroder M and Sandhoff K. Mutation in the sphingolipid activator protein 2 in a patient with a variant of gaucher disease. FEBS Lett 1991; 284: 57–9.

10. Cormand B, Montfort M, Chabas A, Vilageliu L and Grinberg D: Genetic fine localization of the beta-glucocerebrosidase (GBA) and prosaposin (PSAP) genes: Implications for Gaucher disease. Hum Genet 1997; 100: 75–9.

11. Zimran A, Elstein D. Lipid storage diseases. In: Lichtman MA, Kipps T, Seligsohn U, Kaushansky K, Prchal JT, ed.

Williams Hematology. 8th ed; New York, NY: McGraw-Hill (2010):1065-1071.

12. Barton NW, Brady RO and Dambrosia JM: Replacement therapy for inherited enzyme deficiency–macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991; 324:1464-1470.

13. Cox T, Lachmann R and Hollak C: Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT918) to decrease substrate biosynthesis. Lancet. 2000; 355:1481-1485.

14. Sorge J, West C, Westwood B and Beutler E: Molecular cloning and nucleotide sequence of human glucocerebrosidase cDNA. Proc Natl Acad Sci U S A 1985; 82: 7289-7293.

15. Horowitz M, Wilder S, Horowitz Z, Reiner O, Gelbart T and Beutler E: The human glucocerebrosidase gene and pseudo gene: structure and evolution. Genomics. 1989; 4(1): 87-96.

16. Brady RO: Enzyme replacement therapy for lysosomal diseases. Annu. Rev. Med 2006; 57: 283–296.

17. Zimran A: Replacement therapy with imiglucerase for type 1 Gaucher's disease. Lancet 1995; 345, 1479–1480.

18. Cox TM: Management of non-neuronopathic gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring. J. Inherit. Metab. Dis 2008; 31: 319–336.

19. Brumshtein, B: Characterization of gene-activated human acid-b-glucosidase: crystal structure, glycan composition, and internalization into macrophages. Glycobiology 2009; 20: 24–32.

20. US Food and Drug Administration (FDA). FDA labeling information — Vpriv (velaglucerase Alfa). FDA website [online], (2010).

21. European Medicines Agency (EMA). European Public Assessment Report — Vpriv. EMA website [online], (2010).

22. Zimran A: Phase 1/2 and extension study of velaglucerase Alfa replacement therapy in adults with type 1 gaucher disease: 48-month experience. Blood 115, 4651–4656 (2010).

23. Pastores GM: Therapeutic goals in the treatment of gaucher disease. Semin. Hematol 2004; 41: 4–14.

24. Zimran A, Altarescu G, Phillips M, Attias D, Jmoudiak M, Deeb M, Wang N,

Bhirangi K, Cohn GM and Elstein D: Phase I/II and extension study of velaglucerase Alfa (Gene-Activated TM human glucocerebrosidase) replacement therapy in adults with type 1 gaucher disease: 48-month experience. Blood 2010.

25. VPriv™ (velaglucerase Alfa) for injection [product information]. Cambridge, MA: Shire Human Genetic the era pies Inc, Feb 2010.

26. Fong CT. Lysosomal storage disorders. In *Merck Manuals Online Medical Library.* Available from: http://www.merck.com/mmpe/print/sec19/ch296/ch296f.html (Accessed January 25, 2011)

27. Brumshtein B, Salinas P, Peterson B, Chan V, Silman I, Sussman JL, Savickas PJ, Robinson GS and Futerman AH: Characterization of gene-activated human acid-beta-glucosidase: crystal structure, glycan composition, and internalization into macrophages. Glycobiology 2010; 20: 24–32.