Pharmacology Report

Enzyme Replacement Therapy for Lysosomal Storage Diseases

Susan Kleppin, RPh, FASHP

Susan Kleppin, RPh, FASHP, Director of Pharmacy, Chartwell Midwest Wisconsin

Lysosomes are the major digestive units in cells. Enzymes within lysosomes break down certain complex carbohydrates and fats. Lysosomal storage disorders are genetic disorders resulting in a lack of the enzymes that break down these substances. Without the enzymes, the substances accumulate in cell lysosomes, disrupting the normal cell function and causing the lysosomal storage disorders.[1]

More than 40 types of lysosomal storage disorders have been identified. Most are autosomal recessive disorders, meaning that both parents must carry the abnormal gene that prevents the body from making an enzyme with normal activity. Individually, the lysosomal storage diseases are quite rare, but taken together, they affect roughly 1 in 7700 births, making them a relatively common health problem.[1]

All of the lysosomal storage diseases are progressive. The rate of progression, severity of symptoms, and organs affected vary among disorders and even within each disorder type. There are no known cures for these diseases, but progress continues to be made in identifying treatment options. The most common treatment option is enzyme replacement therapy.

Enzyme replacement therapy involves intravenous (IV) infusions to correct the underlying enzyme deficiency that causes disease. This article focuses on 2 enzyme replacement therapy agents: imiglucerase and agalsidase beta, used to treat the most common types of lysosomal storage disease–Gaucher disease and Fabry disease, respectively.

IMIGLUCERASE

Imiglucerase is used to treat Gaucher disease. Gaucher disease is an autosomal recessive genetic disease as described previously. It is a lipid storage disorder that affects up to 1 in 40 000 live births although it has a higher prevalence in Ashkenazi Jews, occurring in approximately 1 in 450 in this population.[2]

This metabolic disorder is caused by a deficiency of the enzyme glucocerebrosidase that results in the accumulation of harmful quantities of glycolipid glucocerebroside throughout the body, but especially within the bone marrow, spleen, and liver.[3] Symptoms vary significantly from patient to patient.

Clinical signs and symptoms may include easy bruising and bleeding, fatigue, anemia, weak bones and fractures, bone and joint pain, and hepatosplenomegaly. Neurologic symptoms can include oculomotor abnormalities, limb rigidity, seizures, and cognitive problems.[3] There are 3 major types of Gaucher disease that are differentiated based on the absence (type 1) or presence of neurologic symptoms (types 2 and 3).[4] Individuals with Gaucher disease type 2 have a short life span because there is no known treatment; it is usually fatal, with death occurring before the age of 2.[1]

Imiglucerase is approved to treat the symptoms of Gaucher disease type 1.[5] This is a modified form of the enzyme glucocerebrosidase and this works to reduce the build up of glucoserebroside (GL-1) in the body. It breaks down the accumulated GL-1 into its more basic elements, glucose and ceramide, that can be naturally removed from the body.[4] The drug is given intravenously every 2 weeks, with the dose individualized based on patient weight and the severity of their symptoms. The most common dose is 60 units/kg intravenously every 2 weeks and the dose for which the most data are available.[6] The dose is administered over 1 to 2 hours after preparation. Efficacy has been shown in multiple long-term studies.[7] Reductions in spleen and liver volume, improvements in hemoglobin and platelet count, and a decrease in patient-reported bone pain have all been demonstrated.

Author Affiliations: *Chartwell Midwest Wisconsin, Middleton, Wisconsin.*

Susan Kleppin, RPh, FASHP, *is director of pharmacy at Chartwell Midwest Wisconsin.*

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Genzyme, the manufacturer of this product, has maintained a worldwide post-marketing database of adverse events since the drug's US Food and Drug Administration (FDA) approval in 1994.[5] Approximately 13.8% of patients experience adverse events; these include discomfort at the injection site; hypersensitivity symptoms, including pruritis, dyspnea, and hypotension; nausea; abdominal pain; fatigue; and headache.[5]

Approximately 15% of patients have developed immunoglobulin G (IgG) antibodies to imiglucerase during the first year of therapy; most in the first 6 months.[5] Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity reaction. Anaphylactoid reactions occur in <1% of patients. The use of antihistamines and/or steroids before administration can mitigate the hypersensitivity symptoms. Slowing of the infusion rate can also help.[5]

Another FDA-approved preparation of glucocerebrosidase is also available–velaglucerase alfa.

AGALSIDASE BETA

Agalsidase beta (Fabrazyme) is used to treat Fabry disease, which is caused by a lack of or absent activity of the lysosomal enzyme α-galactosidase A.[8] This results in the accumulation of 2 glycolipids–globotriaosylceramide (GL-3) and globotriaosylsphingosine (Lyso-GL-3) in lysosomes. The accumulation starts in utero, causing cellular damage that can lead to organ damage and premature death.[9]

The disease is classified into 2 main phenotypes, classic and nonclassic, both of which can lead to organ failure and serious complications in adulthood.[10] Fabry disease can occur in males and females; it is estimated that the classic type 1 Fabry disease affects approximately 1 in 40 000 males, and type 2 in 1 in 1000 to 4000 males.[9]

In patients with the classic phenotype, symptoms typically begin in childhood or adolescence.[7] They increase with age and may include burning pain in hands and feet, decreased or absent sweat production, angiokeratomas, gastrointestinal problems, chronic fatigue, dizziness, and headache. Over time, patients can develop heart or kidney disease.[9]

Treatment with agalsidase beta should be used in the following patients[11]:

- In asymptomatic male patients with classic phenotype as soon as there are early clinical signs of kidney, heart or brain involvement, but may be considered in patients 16 years or older in the absence of clinical signs or symptoms of organ involvement.
- In females with classic phenotype and males with nonclassic phenotype, who should be treated as soon as there are early clinical signs of kidney, heart, or brain involvement, while treatment could be considered in females with nonclassic phenotype with early clinical signs considered to be due to Fabry disease.

The greatest benefit of enzyme replacement therapy for Fabry disease have been reported in patients who have milder impairment of renal or cardiac function at the start of therapy.[12]

The recommended dose is 1 mg/kg body weight intravenously every 2 weeks at a rate of 15 mg/hour.[13] The most commonly reported adverse reactions include upper respiratory tract infections, chills, fever, cough, fatigue, peripheral edema, dizziness, and rash.[12]

Infusion-associated reactions occurred in 59% of patients treated with agalsidase beta in clinical trials.[12] Fever, chills, dyspnea, vomiting, hypotension, and paresthesias have occurred. The use of antihistamines and/or steroids before administration can mitigate the hypersensitivity symptoms. Slowing of the infusion rate can also help.[12] If anaphylaxis or severe allergic reactions occur, the infusion should be stopped and emergency medical care sought.

Patients can develop IgG antibodies to agalsidase beta; most do so within the first 3 months of exposure. Ninety-five of 121 (79%) of adult patients and 69% of pediatric patients in clinical trials developed IgG antibodies.[12]

CONSIDERATIONS FOR SITE OF TREATMENT ADMINISTRATION

Treatment with imiglucerase and agalsidase beta should be initiated in the clinic setting due to the risk of infusion-related reactions. Home therapy with either agent could be considered as a reasonable option after several months of uneventful infusions in the clinic setting. Home infusion would potentially be more convenient for a patient.

Home infusion of these agents presents several issues that need to be addressed:

- Home infusion would be easier if a patient had a long-term vascular access device placed.

TABLE 1

Average Wholesale Price of Enzyme Replacement Therapy

Enzyme replacement therapy	Estimated dose for 80-kg patient	AWP per dose
Imiglucerase	4800 units (60 units/kg) every 2 weeks	$24,118 per dose ($627,061 annually)
Agalsidase beta	80 mg (1 mg/kg) every 2 weeks	$17,148 per dose ($445,854 annually)

Abbreviation: AWP, average wholesale price.

- The stability of diluted imiglucerase and agalsidase beta is limited to 24 hours with refrigeration if immediate use is not possible. This usually necessitates preparation in the home by the home health nurse.
- Both imiglucerase and agalsidase beta have very specific preparation instructions detailed in the prescribing information. Because these products are proteins, they cannot be shaken during reconstitution. Multiple vials will need to be reconstituted to make up each dose. Careful attention to preparation is necessary.
- Both products are extremely expensive (Table 1) and require refrigeration. Loss of product during shipping to a patient's home would be costly.
- The risk of infusion-related reactions must be considered, and pretreatment with antihistamines and antipyretics should be considered.
- Consideration should be given to having an epinephrine auto-injector on hand in case of anaphylaxis or a severe infusion-related reaction.

SUPPORT FOR PATIENTS

Sanofi Genzyme, the manufacturer of these 2 products, has support services available to patients who require enzyme replacement therapy. Case managers are available to help coordinate care and handle insurance issues, and patient education liaisons are available to provide disease information. The company also has a copay assistance program to help eligible individuals pay for their qualifying out-of-pocket expenses and a charitable access program.

CONCLUSION

Enzyme replacement therapy does not correct the underlying genetic defect that causes lysosomal storage disease but increases the concentration of the enzyme that is lacking. This therapy is lifelong and expensive. The distribution of the enzyme in the body after the IV infusions is not uniform, and thus symptoms of the lysosomal storage disease remain untreated, especially neurological symptoms.[14] Other treatments for enzyme deficiencies continue to be explored, including substrate reduction therapy, gene therapy, and hematopoietic stem cell transplantation.

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