Pharmacotherapy of Gaucher Disease: Current and Future Options

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INTRODUCTION

Gaucher disease (GD) is a rare lysosomal storage disease (LSD) affecting fewer than 20,000 people worldwide, some of whom may not be diagnosed.1,2 The disease was first described in 1882 by the French physician Philippe Gaucher.1,2 Patients with GD have a mutation in the GBA1 gene, located on chromosome 1 (1q21), that causes decreased activity of the enzyme acid beta-glucosidase (β-glucocerebrosidase [GCase]) or glucosylceramidase E.C.3.2.1.45). Under normal conditions, GCase is responsible for cleaving lipid substrates, such as glucocerebroside (glucosylceramide [GLC]) into glucose and sphingosine.2 A lack of GCase interferes with the body’s ability to break down GLC. The monocyte-macrophage system is affected the most because of the high amount of GLC in the cell lysosome, causing accumulation of Gaucher cells.2 Under histological staining, Gaucher cells, which are approximately 20–100 mcM in diameter and have small eccentric nuclei and cytoplasm with crinkled striation, accumulate in many organs, particularly bone, bone marrow, the spleen, and the liver.1,4,6 Gaucher cells also cause the production of inflammatory cytokines that can cause enlargement of the spleen and liver, abnormalities of the lung, destruction of bone, and progression of anemia, thrombocytopenia, and leukopenia.3–9

There are more than 50 known LSDs, such as Fabry, Pompe, and Niemann–Pick disease, among others.5,10 GD affects each gender equally. There are three types of GD—type-1 (GD1), type-2 (GD2), and type-3 (GD3)—that are classified based on the presence of neurological deterioration, age at identification, and rate of disease progression.2,8 GD1, the most common form, comprises about 95% of cases and does not affect the central nervous system (non-neuronopathic).7

The incidence of GD1 is estimated to be one in 20,000 to one in 200,000 among people living in the U.S., Europe, and Israel.3,11 However, approximately one in 450 Ashkenazi Jews (i.e., those of Eastern, Central, and Northern European ancestry) have GD1, and one in 10 are carriers of the disease.8,10 The clinical manifestations of GD1 typically include splenomegaly, hepatomegaly, anemia, thrombocytopenia, osteopenia, and osteonecrosis.6 Patients with GD1 bruises and bleed easily; they typically present with chronic fatigue and with bone infarctions or bone fractures due to osteopenia.11

GD2 and GD3 are neuronopathic forms that affect about 5% of GD patients.8,9 GD2, also known as acute neuronopathic GD, occurs in newborns and infants.9,11 The disorder is marked by severe neurological symptoms in the brain that may result from accumulation of GLC.13 Affected newborns and infants first show oculomotor abnormalities, such as involuntary horizontal eye movement, followed by brainstem involvement, which can lead to hypotonia, spasticity, strabismus, seizures, and other muscle-related issues.5 Affected infants may also develop life-threatening complications, such as respiratory distress and pneumonia.8 Children with GD2 usually die within the first two years of life.5

Like GD2, GD3 is neuronopathic, but it is chronic. GD3 is further divided into subgroups 3a, 3b, and 3c. GD3a typically has only mild visceral manifestations but causes severe progressive myoclonic seizures, which can lead to death within the first two decades. GD3b involves more visceral features, such as massive enlargement of the liver and spleen, growth and mental retardation, and supranuclear gaze palsy. Patients with GD3c exhibit rare cardiac mitral and aortic calcification and often die in early adulthood. In Asia, GD2 and GD3 comprise about 60% of all GD cases.2,12–15

Current treatment of GD includes enzyme replacement therapies (ERTs) and substrate reduction therapies (SRTs). Potential treatments under investigation include a newer SRTs, pharmacological chaperone therapies (PCTs), and histone deacetylase inhibitors (HDACIs).

EXPERT CONSENSUS ON MANAGEMENT GOALS FOR GD1

Recently, all 35 members of the European Working Group on Gaucher Disease (EWGGD) were invited to participate in a consensus study using online surveys. Twenty-five EWGGD members who are physicians participated; other members supported the initiative but felt they lacked the necessary clinical experience.16 These physicians from 16 countries on average treated 92 GD1 patients (range, two to 600).16 Three rounds of surveys were executed starting with 65 statements to reach consensus for GD1 management goals. At the end of three rounds after modifying the statements, the experts agreed on 42. The short-term, long-term, and general consensus management goals are presented in Tables 1, 2, and 3, respectively. In general, the consensus panel agreed that physicians should aim to restore normal values, prevent complications, and eliminate or reduce signs and symptoms of anemia, bleeding tendency, bone disease, and liver, spleen, and pulmonary complications.16 The importance of improving quality of life, reducing fatigue, and maintaining normal participation in school or work activities was also included in the consensus. In addition, detection of early malignancies, possible parkinsonism, and prediabetes was cited, as GD patients are likely to benefit from prompt initiation of appropriate care and treatment.16

ENZYME REPLACEMENT THERAPY

For more than a century after the discovery of GD, patients were treated entirely with supportive measures, such as iron

Disclosures: The authors report no commercial or financial interests in regard to this article.
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### Table 1 Short-Term Management Goals for Gaucher Disease Type-1*

<table>
<thead>
<tr>
<th>Category</th>
<th>Management Goals</th>
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</table>
| Anemia-related symptoms   | • Eliminate blood transfusion dependency.  
                          | • Increase hemoglobin levels within 12–24 months to > 11 g/dL for women and children and > 12 g/dL for men.                                                                                                                            |
| Bleeding tendency         | • Increase platelet counts during the first year of treatment to prevent spontaneous, surgical, and obstetrical bleeding.  
                          | • Normalize platelet count during first year of treatment (for patients with splenectomy).  
                          | • Achieve platelet count ≥ 100,000/mm³ within three years of treatment (for patient with intact spleen).                                                                 |
| Mobility                  | • Lessen bone pain not related to irreversible bone disease within one to two years.  
                          | • Decrease bone marrow involvement as measured by Gaucher scoring system bone marrow burden in patients without severe irreversible bone disease at baseline.  
                          | • Increase bone mineral density by second year in adults with T score < –2.5 at baseline.  
                          | • Attain normal or ideal peak skeletal mass in children.  
                          | • Within two years of treatment, normalize growth based on population standard height.                                                                                                           |
| Visceral complications    | • Avoid splenectomy (may be necessary during life-threatening hemorrhagic events).  
                          | • Alleviate symptoms due to splenomegaly: abdominal distention, early satiety, new splenic infarction.  
                          | • Eliminate hypersplenism.  
                          | • Reduce spleen volume to < 2 to 8 times normal by year 1 or 2, depending on baseline spleen volume.  
                          | • Reduce liver volume to 1 to 1.5 times normal by year 1 or 2, depending on baseline liver volume.                                                                                       |
| General well-being        | • Improve scores from baseline of a validated quality-of-life instrument within two to three years, depending on disease burden.  
                          | • Reduce fatigue (not anemia related) as measured by a validated fatigue scoring system.  
                          | • Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles.                                                                                       |

* These goals are adapted with minor modification from the Expert Consensus of the European Working Group on Gaucher Disease.\(^{16}\) The data for this consensus were collected from Pastores et al.,\(^{81}\) literature, and input from patients.

### Table 2 Long-Term Management Goals for Gaucher Disease Type-1*

<table>
<thead>
<tr>
<th>Category</th>
<th>Management Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia-related symptoms</td>
<td>• Maintain improved hemoglobin values achieved after first 12–24 months of therapy.</td>
</tr>
</tbody>
</table>
| Bleeding tendency         | • Maintain platelet count ≥ 100,000/mm³.  
                          | • Reduce bleeding tendency due to low platelet count, platelet defects, or coagulation abnormalities.                                                                                                                             |
| Mobility                  | • Prevent bone complications: avascular necrosis, bone crises, bone infarcts, and fractures.  
                          | • Prevent osteopenia and osteoporosis (maintain BMD T score [DEXA] > 1).  
                          | • Prevent chronic use of analgesics for bone pain.  
                          | • Maintain normal mobility. If impaired at diagnosis, improve mobility.  
                          | • Increase physical activity.                                                                                                                                                    |
| Visceral complications    | • Maintain spleen volume < 2 to 8 times normal after year 1 or 2.  
                          | • Maintain near normal liver volume after year 1 or 2.                                                                                                                        |
| Pulmonary complications   | • Prevent liver fibrosis, cirrhosis, and portal hypertension.  
                          | • Prevent or improve pulmonary disease: pulmonary hypertension, hepatopulmonary syndrome.                                                                                      |
| General well-being        | • Maintain good quality of life as measured by a validated instrument.  
                          | • Maintain normal participation in school and work activities.  
                          | • Minimize psychosocial burdens of life-long treatment.  
                          | • Achieve normal onset of puberty.  
                          | • Normalize life expectancy.                                                                                                                                                    |
| Pregnancy and delivery    | • Prevent Gaucher disease complications during pregnancy and delivery.                                                                                                           |

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BMD = bone mineral density; DEXA = dual energy x-ray absorptiometry.
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### Table 3: General Management Goals for Gaucher Disease Type-1*

<table>
<thead>
<tr>
<th>Category</th>
<th>Management Goals</th>
</tr>
</thead>
</table>
| Long-term complications   | • Early detection of hematologic malignancies: multiple myeloma, lymphoma, amyloidosis.  
                              • Early detection of solid tumors: hepatocellular carcinoma, renal cell carcinoma.  
                              • Early detection of parkinsonism/Parkinson’s disease.  
                              • Early detection of insulin resistance and type-2 diabetes mellitus. |
| General                   | • Proper education of the patient and family about the disease and therapy.  
                              • Early detection of signs and symptoms indicative of GD3, such as eye movement abnormalities.  
                              • Other associated conditions, but not specific for GD1: iron deficiency anemia, serum vitamin D, cholelithiasis, cholecytitis. |

* These goals are adapted with minor modification from the Expert Consensus of the European Working Group on Gaucher Disease.16 The data for this consensus were collected from Pastores et al.,11 literature, and input from patients.

GD1 = Gaucher disease type-1; GD3 = Gaucher disease type-3.

or blood transfusions to treat bleeding due to low hemoglobin levels or with splenectomy.19 In 1991, the first intravenous (IV) ERT—alglucerase (Ceredase, Genzyme)—was introduced to reduce the accumulation of GLC by supplementing defective GCase enzymes with active ones.18 This approach has been effective in reducing the systemic manifestations of GD, such as splenomegaly.19

Alglucerase was manufactured using human placental tissue collected as a byproduct of human serum albumin manufacture. Although the treatment was effective, the number of placenta needed to make enough drug for one patient treatment per year was estimated at 50,000 (10–12 metric tons).20,21 Genzyme then introduced imiglucerase (Cerezyme), which is produced in Chinese hamster ovary cells as a recombinant analogue of GCase. The Food and Drug Administration (FDA) approved imiglucerase in 1994, and alglucerase was discontinued in 1998 after nearly all patients had been switched.21 Imiglucerase is administered by IV infusion over one to two hours. The dosage is individualized for each patient and ranges from 30 to 60 units/kg every two weeks.2,22

In June 2009, Genzyme announced a viral contamination at its manufacturing site, which caused a dramatic reduction in the global supply of imiglucerase.23 In 2010, the FDA approved velaglucerase alfa (Vpriv, Shire Human Genetic Therapies), an analogue of recombinant GCase that is produced in human fibrosarcoma cell lines.24 Two years later, the FDA approved taliglucerase alfa (Elelyso, Pfizer), which is manufactured using genetically modified carrot plant root cells.2,25–27

There are some differences in the amino acid structure and glycosylation of these three ERTs. The amino acid composition of imiglucerase and taliglucerase alfa differs from human GCase, while velaglucerase has the same amino acids found in humans. Taliglucerase alfa differs from velaglucerase alfa and imiglucerase in its glycosylation due to α-(1,2)-xylose and α-(1,3)-fucose, which are unique to plant-derived proteins. Imiglucerase has a mannose structure, while velaglucerase alfa contains longer-chain high mannose-type glycans. Based on x-ray crystallography of the structures and in vitro study of various expressions of mannose receptor binding, all three ERTs are similar in macrophage uptake of the drugs, with velaglucerase having greater cellular uptake than imiglucerase.3,28–30

Imiglucerase, velaglucerase, and taliglucerase are indicated for the treatment of pediatric and adult patients with GD1.22–30 Within four years of initiating imiglucerase therapy, 93% of patients in studies showed significant improvement. Taliglucerase has resulted in significant improvements in liver volume, platelet counts, and hemoglobin.27–30 In clinical trials, 2% of the patients treated with taliglucerase experienced urticaria, hypotension, flushing, wheezing, chest tightness, nausea, vomiting, and dizziness.26 Table 4 lists adverse effects and other characteristics of the ERTs.

Approximately 15% of patients treated with imiglucerase develop immunoglobulin G (IgG) antibodies during the first year of treatment.24 These antibodies usually develop in the first six months of therapy, but in rare cases they appear after 12 months. Velaglucerase and taliglucerase also have the potential for development of immunogenicity. In clinical studies, one of the 54 ERT-naïve patients treated with velaglucerase developed IgG antibodies to the drug, but did not experience hypersensitivity reactions. Patients who are switched to velaglucerase should be monitored for the development of antibodies to velaglucerase.30 In general, many patients treated with ERTs eventually develop tolerance to the antibodies. Prior to infusions, pretreatment with antihistamines or sometimes steroids can decrease the reaction.23–30

The average wholesale prices (AWPs) of these ERTs are $1,903 per vial for imiglucerase (400 units), $1,652 per vial for velaglucerase (400 units), and $935 per vial for taliglucerase (200 units). Patients are often administered 60 units/kg every two weeks. As this dosage, the approximate annual costs for imiglucerase, velaglucerase, and taliglucerase would be $544,260, $472,475, and $510,510, respectively, for a 70-kg adult, or $148,435, $128,860, and $145,860 for an 18-kg child.31 However, discounts may lower these costs for individual patients depending on their health insurance plans. The cost of the nurses or doctors who administer the drug and other hospital expenses, as well as the potential costs of managing GD complications, have not been factored into these costs.

### SUBSTRATE REDUCTION THERAPY

Although ERTs are beneficial for the treatment of GD, there is still a need to find drugs that are less costly, easier to administer, less immunogenic, and capable of treating GD2 or GD3 subtypes. SRT was first proposed in 1972 as a possible approach for the treatment of GD.52 The principle mechanism of action of SRT is to inhibit the enzyme UDP-glucose ceramide
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Table 4 Enzyme Replacement Therapy for Gaucher Disease

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Imiglucerase (Cerezyme, Genzyme Corp.)</th>
<th>Velaglucerase Alfa (Vpriv, Shire Human Genetic Therapies, Inc.)</th>
<th>Taliglucerase Alfa (Elelyso, Pfizer, Inc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard care for GD1, non-neuronopathic GD3</td>
<td>Pediatric (age 4–17 years) and adult GD1, severe GD</td>
<td>Adults and children with GD1</td>
</tr>
<tr>
<td>Switching between</td>
<td>Patients treated with imiglucerase can switch to velaglucerase alfa or taliglucerase alfa with same dose.</td>
<td>Patients on imiglucerase or taliglucerase alfa can be switched to velaglucerase alfa at same dose.</td>
<td>Patients on eliglustat can be switched to velaglucerase and taliglucerase alfa at the same dose.</td>
</tr>
<tr>
<td>medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>Recommended dose: 60 units/kg IV every 2 weeks. Clinical trials ranged from 2.5 units/kg to 60 units/kg every 2 weeks.</td>
<td>Recommended dose: 60 units/kg IV every 2 weeks. Clinical trials ranged from 15 units/kg to 60 units/kg every 2 weeks.</td>
<td>Recommended dose: 60 units/kg IV every 2 weeks. Clinical trials ranged from 11 units/kg to 73 units/kg once every 2 weeks.</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Plasma half-life, 3–11 minutes; plasma clearance, 0.6–1.2 L/h/kg; volume of distribution, 0.09–0.15 L/kg</td>
<td>Plasma half-life, 11–12 minutes; plasma clearance, 6.72–7.56 mL/min/kg; volume of distribution, 82–108 mL/kg</td>
<td>Plasma half-life, 18.9–28.7 minutes; plasma clearance, 20–30 L/h/kg; volume of distribution, 7.3–11.7 L/kg</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, tachycardia, and infusion-related reactions.</td>
<td>Adverse reactions more commonly seen in pediatrics: upper respiratory tract infection, rash, prolonged aPTT, pyrexia. Other adverse reactions: nausea, abdominal pain, back pain, joint pain, diarrhea, rash, fatigue, headache, dizziness, pyrexia, asthenia, fatigue, and infusion-related reactions.</td>
<td>Upper respiratory tract infection/nasopharyngitis, pharyngitis/throat infection, headache, arthralgia, influenza, urinary tract infection, pyelonephritis, back pain, extremity pain, infusion-related reactions.</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time; GD = Gaucher disease; GD1 = GD type-1; GD3 = GD type-3; IV = intravenous.

Eliglustat, the first enzyme in the pathway for glycosylating sphingolipids, is used as a second-line treatment in the U.S., Europe, and Israel for patients who are unable to take IV ERTs or are intolerant of them. The structure of eliglustat differs from miglustat in that it is a D-threo-1-phenyl-2-decanoylamino-3-morpholino-propanol, a ceramide analogue. During the clinical trials in GD1 patients, mean spleen and liver volumes decreased by 63% and 28%, respectively, and mean hemoglobin level and mean platelet count increased by 2.3 g/dL and 95%, respectively. Improvements in bone marrow score and bone mineral density and reduction of glucosylsphingosine were also observed. The adverse effects of eliglustat include arthralgia, headache, nausea, fatigue, back pain, and pain in the extremities. Other occasional adverse effects include upper abdominal pain, diarrhea, migraine, flatulence, oropharyngeal pain, dizziness, asthenia, reflux disease, constipation, palpitation, and rash. Although eliglustat’s pregnancy category is C and miglustat’s is X, based on expert opinion, pregnant or breastfeeding women or male patients who are trying to have children should discuss this with the physicians who treat their GD.

Eliglustat is dosed according to patient cytochrome P450 (CYP) 2D6 genotype, which is determined by an FDA-approved test. The recommended dosing of eliglustat is 84 mg twice a day for CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs) or 84 mg once daily for CYP2D6 poor metabolizers (PMs). A specific dose cannot be recommended for patients whose CYP2D6 genotype is unknown (indeterminate metabolizers).

Eliglustat is contraindicated in ultrarapid metabolizers, EMs, or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor, or in IMs or PMs taking a strong CYP3A inhibitor. Eliglustat may cause prolongation of the PR, QT, and/or QRS intervals; its use is not recommended in patients with pre-existing cardiac disease or long QT syndrome or in those taking class IA or
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Table 5  Substrate Reduction Therapy for Gaucher Disease

<table>
<thead>
<tr>
<th></th>
<th>Miglustat (Zavesca, Actelion Pharmaceuticals)</th>
<th>Eliglustat (Cerdelga, Genzyme Corporation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient type</td>
<td>Patients with mild GD who are unable to receive ERT; use as second treatment option.</td>
<td>Patients with GD1.</td>
</tr>
<tr>
<td>Dosing</td>
<td>100-mg capsule three times a day. For patients with severe diarrhea and/or tremor, reduce dose to one or two capsules per day. For patients with CrCl of 30–50 mL/min, one capsule per day. Not recommended if CrCl &lt; 30 mL/min.</td>
<td>100-mg capsule (equivalent of 84 mg) twice a day for IMs and EMs of CYP2D6 genotypes or once daily for PMs. Administer FDA-approved genotype testing before use.</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Half-life, 6–7 hours; bioavailability, 97%; excretion, renal unchanged.</td>
<td>Half-life, 6.5 hours (EMs) to 8.9 hours (PMs); low oral bioavailability due to significant first-pass metabolism; excretion: fecal, 51.4%; urine, 41.8%.</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Peripheral neuropathy, weight loss, diarrhea, tremor, flatulence, abdominal pain, dyspepsia, headache, paresthesia, influenza-like symptoms, cramps, visual disturbances, thrombocytopenia.</td>
<td>Incidence of 10% or greater: arthralgia, headache, nausea, fatigue, back pain, pain in extremities. Occasional: upper abdominal pain, diarrhea, migraine, flatulence, oropharyngeal pain, dizziness, asthenia, reflex disease, constipation, palpitation, rash.</td>
</tr>
</tbody>
</table>

CrCl = creatinine clearance; CYP = cytochrome P450; EMs = extensive metabolizers; ERT = enzyme replacement therapy; GD = Gaucher disease; GD1 = GD type-1; IMs = intermediate metabolizers; PMs = poor metabolizers.

class III antiarrhythmics. The use of eliglustat is also contraindicated in patients with moderate-to-severe renal impairment or hepatic impairment. Miglustat and eliglustat are provided in monthly dose packs with an AWP of $32,184 (90 capsules) and $29,131 (56 capsules), respectively. At recommended dosages (which may vary based on genotype or other patient-specific issues), the approximate annual AWPs of miglustat and eliglustat are $336,210 and $349,575, respectively. These prices do not reflect discounts that may apply under various health insurance plans.

**GD3 TREATMENT**

None of the currently available therapies is effective in treating the neuropathic forms of GD. In GD2, disease progression involving the central nervous system is usually overwhelming; fatality occurs in infancy with little to no impact of ERTs seen in these patients. In GD3, where phenotypic variability and progression of neurological manifestations is slower, ERTs have the potential for favorable outcomes by alleviating the visceral and hematologic aspects of the disease, therefore improving the quality of life. Due to the rarity of GD3, reports of ERTs’ efficacy in treating hematologic and visceral problems had been limited to a small single-center, off-label study. However, the International Collaborative Gaucher Group (ICGG) Gaucher Registry has now collected the largest set of data on the use of imiglucerase in GD3 patients during their childhood or adolescent years. As of September 2015, there were 289 GD3 patients in the ICGG Registry who had their first imiglucerase treatment before the age of 18 years. A total of 253 GD3 patients were treated with imiglucerase for up to five years. The majority have GBA mutations of L444P (77%) and D409H (7%). At baseline, these GD3 patients exhibited early onset of severe hematologic and visceral disease and growth failure. During the first year of imiglucerase treatment, hemoglobin levels and platelet counts increased (decreased anemia), liver and spleen volumes decreased (decreased thrombocytopenia and hepatosplenomegaly), and linear growth accelerated. The life span of untreated GD3 patients was a median of 12 years. The probability of surviving for at least five years after starting imiglucerase was 92%. Of the GD3 deaths reported in the registry after imiglucerase treatment, some were due to progression of neurological, cardiac, or pulmonary complications. The GD3 patients who died of cardiac causes were mostly D409H homozygous, with manifestation of cardiac valvular, coronary, or aortic calcifications.

Several combination therapies using ERT and SRT for the treatment of GD3 have also shown success. Patients exhibited marked improvement of neurological signs, such as reductions in seizure frequency and improved ability to move around without a wheelchair. Early combination treatment using SKT and ERT might prevent or delay neurological onset, but among patients who already have neurological impairment, it might be more difficult to treat and take more time to see marked improvement. Currently, four clinical trials are recruiting GD3 patients. An open-label, multicenter, multinational clinical trial recruiting GD3 patients is ongoing with completion expected by 2022. This phase 2 trial is studying the safety, tolerability, pharmacokinetics, and pharmacodynamics of venglustat (GZ/SAR 402671).

**BONE MARROW TRANSPLANT**

In an early study of GD, investigators used allogeneic bone marrow transplant (BMT) to treat an 8-year-old boy with GD3, but the result was disappointing. Infiltration of the bone marrow by Gaucher cells remained unchanged, and the patient died from sepsis. In another case report, a 2-year-old girl with neuronopathic GD underwent BMT. During the subsequent 24 months, there was no improvement of her neuronopathic manifestations, hepatic size, enzyme levels, or histology. This patient also died of sepsis at 24 months post-BMT. Because BMT appears to have little or no effect on the neuropaagnostic aspects of GD and because of its inherent risks (including high morbidity and high mortality), this procedure is not generally recommended for GD patients who have advanced neurological symptoms. Since the introduction of ERTs and SRTs, BMTs are rarely performed in GD patients in the U.S.
INVESTIGATIONAL TREATMENTS

Lucerastat is the newest SRT under investigation. Lucerastat, or N-butyldeoxygalactonojirimycin ((2R, 3S, 4R, 5S)-1-buty1-2-[hydroxymethyl] piperidine-3, 4, 5-triol), is a soluble, low-molecular-weight oral iminosugar. It was able to cross the blood–brain barrier in a mouse model of GM2 gangliosidosis, reducing accumulation of GM2 in the brain and improving neuromotor performance and survival in the mouse model. Safety, tolerability, and pharmacokinetics of lucerastat were investigated in two randomized, double-blind, placebo-controlled studies. A single ascending-dose study recruited 39 patients and a multiple ascending-dose study recruited 37 patients. The participants received oral doses of 100 mg, 300 mg, 500 mg, or 1,000 mg of lucerastat. Some of the adverse effects noted were constipation, dyspepsia, headache, rash, and increased alanine aminotransferase and aspartate aminotransferase levels. No severe or serious adverse effects or clinically relevant abnormalities of vital signs and 12-lead electrocardiograms were observed.

In addition to conducting further evaluations of the available ERTs and SRTs, researchers continue to look for new therapeutic alternatives for GD1, GD2, or GD3. Potential future treatments include pharmacological chaperone therapy (PCT), PCT, also known as enzyme enhancement therapy, uses chemicals to stabilize or reactivate misfolded GCase within cells. One of these agents is ambroxol, an over-the-counter expectorant used in many parts of the world to treat various airway infections, such as pneumonia or cystic fibrosis. In laboratory studies, ambroxol was found to increase the enzymatic activity of various misfolded mutant forms of GCase in the endoplasmic reticulum, making the enzyme fold properly and amending its function. Because ambroxol can cross the blood–brain barrier, it provides a promising option for GD3. High-dose ambroxol given at 25 mg/kg per day to a maximum daily dose of 1,300 mg in a study of five patients produced remarkable improvement in neurological symptoms, including reduction of myoclonus seizures and pupillary light reflex dysfunction. Ambroxol may also be useful for GD1 with neurological complications such as parkinsonism or peripheral neuropathy. Another PCT, isoformagamine tartrate, developed by Amicus Therapeutics, was designed to bind and stabilize misfolded GCase from mutation of the N370S gene. However, initial clinical trials failed to show improvements, and further development of the drug was halted in 2009.

HDACIs, such as valproic acid, are another class of medications being investigated to treat GD. HDACIs have been used to treat inflammatory diseases, psychiatric/neurological disorders, and cancer. They also have been tried in in vitro studies of inherited diseases that arise from protein misfolding, such as cystic fibrosis, Huntington’s, and type C Niemann–Pick disease. Approximately 360 missense mutations have been identified in GD. This mutation causes GCase to fold improperly. In vitro study using fibroblasts from GD patients showed that an HDACI (LB-205) modulated molecular chaperones, such as heat shock protein (Hsp) 90 and Hsp 70, restoring the activity of GCase.

While preclinical findings involving PCT or HDACIs have been promising, it remains unknown clinically if these compounds can effectively reduce GLC accumulation in GD patients.

CONCLUSION

Intravenous ERTs are the standard care for most patients with GD, but these drugs have no effect on GD2 or GD3 patients because of their inability to cross the blood–brain barrier. At 60 units/kg every two weeks, the annual AWP of therapy using available ERTs imiglucerase, taliglucerase, and velaglucerase ranges from $128,860 to $148,435 for an 18-kg child or $472,475 to $544,260 for a 70-kg adult. Currently, there is no evidence for a clinician to recommend any one ERT over the others.

Orally administered SRT offers an alternative treatment for GD. Two SRTs approved by the FDA are miglustat and eliglustat. Miglustat is indicated for the treatment of mild-to-moderate GD1 patients for whom ERT is not a therapeutic option. Miglustat warnings and precautions include peripheral neuropathy, tremors, and diarrhea. Eliglustat is indicated for treatment-naive GD1 and for patients who are stable on ERTs but seek the convenience of oral dosing. FDA-approved testing to determine the genotype of patients should be conducted prior to prescribing eliglustat. GD1 patients who are CYP2D6 EMs, IMs, or PMs should take eliglustat only after adjustment of the dose. Patients who are CYP2D6 ultrarapid metabolizers may not achieve adequate concentrations of eliglustat. Clinicians should monitor drug interactions, pregnancy status, patient compliance, and cardiac, renal, and liver status. Depending on the dose, the average yearly cost ranges from $349,575 to $386,210.

Tables 4 and 5 list therapeutic options for GD and summarize important information for practicing clinicians, including dosing, pharmacokinetics, pregnancy category, and adverse effects, and describe the administration of all three available ERTs.

Investigational approaches for GD treatment include ambroxol and HDACIs. Further clinical studies are needed to learn more about the safety, tolerability, and pharmacokinetics of these agents.

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