Enzyme Replacement or Substrate Reduction? A Review of Gaucher Disease Treatment Options

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ABSTRACT

Background: Gaucher disease is a rare lysosomal storage disease resulting from a deficiency or reduced activity in the acid β -glucosidase enzyme. Only 1 treatment option was available for 15 years, but several new treatment options have come to market since 2003.

Objective: The article will detail the pathophysiology and review current therapies in the literature for all 3 major clinical types of Gaucher disease, with a focus on considerations for selecting therapy in type 1 disease.

Methods: Extracted and summarized applicable studies and reviews from Cochrane Review, ClinicalTrials.gov, CINAHL, IPA, and PubMed.

Results: Enzyme replacement therapy is preferred for the management of Gaucher disease. Current literature does not favor any enzyme replacement product over another. However, velaglucerase alfa and taliglucerase alfa theoretically have a lower risk of immunogenicity reactions compared with imiglucerase. Alternative treatments for type 1 disease include substrate reduction therapy; however, these treatments require evaluation of patient-specific variables (eg, genotype evaluation, renal function) and consideration of adverse effect and dosing profiles. Evaluation of current literature found no substrate reduction therapy is preferred over another. There are no approved therapies for type 2 and type 3 disease, but enzyme replacement therapy may be used with limited efficacy for symptom management.

Conclusion: Enzyme replacement therapy is preferred for treating type 1 Gaucher disease and substrate replacement therapy may be considered in patients who do not tolerate or cannot receive enzyme replacement therapy.

Key Words—enzyme replacement, Gaucher disease, lysosomal storage disease, substrate reduction

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Gaucher disease is a progressive, lysosomal storage disease (LSD) resulting from an autosomal recessive mutation in the 1q21 chromosome. This mutation causes a deficiency or lack of activity in the acid β -glucosidase enzyme resulting in residual enzyme activity between 5% to 25%.¹ The lack of acid β -glucosidase activity results in pathogenic accumulation of the lipid substrate glucocerebroside or glucosylceramide (GLC) in tissue macrophages.² When macrophages accumulate GLC, they are known as Gaucher cells and gather in several parts

of the body including the bone, bone marrow, liver, lymph nodes, and spleen.² The accumulation of Gaucher cells may result in increased cytokine production contributing to the symptomatic manifestations of Gaucher disease.² Symptoms may include anemia, bone pain or fracture, fatigue, hepatomegaly, leukopenia, lung or kidney abnormalities, splenomegaly, thrombocytopenia, and neurologic abnormalities.^{2,3} Gaucher disease is classified as 1 of 3 major clinical types: type 1 (non-neuropathic), type 2 (acute neuropathic), and type 3 (chronic neuropathic). There are

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also 2 other Gaucher disease subtypes known as perinatal-lethal and cardiovascular.⁴⁻⁶ Type 1 is the most common form of Gaucher disease.⁶ The progression of Gaucher disease symptoms is variable, but patients diagnosed in childhood tend to have a more aggressive progression of symptoms.⁷ Each type has different distinguishing features and symptomology, which are characterized in **Table 1**. This literature review

will summarize evidence from clinical trials and meta-analyses evaluating various US Food and Drug Administration (FDA)–approved treatments for the 3 major clinical types of Gaucher disease. It is important for pharmacists and technicians to understand the benefits and risks associated with these therapies to appropriately care for patients who present with Gaucher disease.

Table 1. Gaucher disease characteristics by condition type^{2,6-8}

Characteristics	Type 1 (non-neuropathic)	Type 2 (acute neuropathic)	Type 3 (chronic neuropathic)		
			3a	3b	3c
Prevalence/ Incidence	90% to 99% of people with Gaucher disease	Fewer than 1 in 100,000 people	Fewer than 1 in 100,000 people		
Commonly affected populations	Ashkenazic Jewish decent	Neonates; No ethnic association	No ethnic association	Norbothnian (region of Sweden), Asian, or Arab decent	Japanese, Arab, or Palestinian decent
Mutation type	N370S genotype mutation	Neonatal (2 mutations) or infantile patients (1 severe mutation)	No associated mutation	L444P/L444P mutation	D409H/D409H mutation
Age at diagnosis	Childhood to adulthood; Typically presents in adolescence	4 to 5 months old	Early childhood	Early childhood	Early childhood
Symptoms	Asymptomatic to debilitating or fatal complications; Bleeding tendencies; Cirrhosis and hepatic failure (rare); Hepatosplenomegaly (80% of patients); Mild to severe lung involvement; Splenomegaly (most common symptom in 95% of patients with spleen up to 75 times normal size); Skeletal involvement (bone pain and growth retardation in 70% to 100% of patients); Peripheral neuropathy or early Parkinsonism (rare)	Those that make it to birth display dysphagia, hydrops, opisthotonus, splenomegaly, strabismus, supranuclear gaze palsy, trismus	Ataxia; Lung involvement; Mild kyphosis; Mild hepatomegaly; Mild splenomegaly; Myoclonic seizures; Progressive neurological failure; Supranuclear gaze palsy	Growth retardation; Massive hepatosplenomegaly; Moderate to severe kyphosis; Moderate to severe lung involvement; Progressive cognitive deterioration; Static supranuclear gaze palsy (most common symptom)	Aortic and mitral valve thickening and calcification (dominant feature); Bradycephalus; Moderate splenomegaly; Supranuclear gaze palsy; Tachyarrhythmias
Life expectancy	Normal to near normal life expectancy in most cases if left untreated	Lethal before birth or very early in life (less than 2 years)	Early childhood without treatment	Mid-adulthood without treatment	Very early adulthood without treatment; responds minimally to enzyme replacement therapy

Males and females are equally affected by Gaucher disease; an estimated 6,000 people in the United States are living with the condition.^{2,8} For individuals of Ashkenazic Jewish decent, the incidence is reported to be as high as 1 in 450 births.^{2,8} For the general population, the incidence is estimated as 1 in 20,000 to 1 in 200,000 live births, and the prevalence is estimated at 1 in 40,000.^{2,8} Gaucher disease is generally diagnosed in patients who present with unexpected anemia, organomegaly, or thrombocytopenia.² The gold standard for Gaucher disease diagnosis is enzyme assays that measure the acid β -glucosidase activity in white blood cells or skin cells and genetic DNA analysis.^{2,8} Another enzyme biomarker, chitotriosidase, is also frequently measured to diagnose Gaucher disease.^{1,2} Chitotriosidase expression is specific to lipid storage tissue macrophages.² Levels of this enzyme are typically elevated 100- to 5,000-fold in Gaucher disease, but they may also be elevated in other lysosomal storage diseases.¹ Levels of chitotriosidase often correlate with disease severity and typically decrease once treatment begins.² Lack of chitotriosidase reduction will often be used as a sign of treatment failure or an indication to increase the medication dose.^{1,2}

In addition, pulmonary and activation-regulated chemokines PARC/CCL18 can be elevated 10- to 40-fold in patients with symptomatic Gaucher disease and is a useful biomarker in patients who do not have chitotriosidase activity.¹ Non-specific biomarkers that may be used to monitor patients include tartrate-resistant acid phosphate and angiotensin-converting enzyme.² Although both of these levels are elevated in Gaucher disease, they are not specific to this condition.¹ In addition, acid phosphate levels do not correlate with disease severity or efficacy of treatment, whereas angiotensin-converting enzyme activity tends to decrease with treatment.¹

METHODS

In this comprehensive literature review, multiple secondary databases were searched, including Cochrane Review, CINAHL, IPA, and PubMed, for studies and reviews on the treatment of Gaucher disease. Additionally, we searched ClinicalTrials.gov for unpublished or ongoing studies. Search terms included Gaucher* disease, enzyme replacement therapy, substrate reduction therapy, imiglucerase, Cerezyme, velaglucerase alfa, Vpriv, taliglucerase alfa, Elelyso, miglustat, Zavesca, eliglustat, and Cerdelga. Medical subject headings and each individual search term were used to identify relevant literature. Filters were

set to English language and human subject articles only. Date ranges were not limited. Both authors conducted independent literature searches reviewing article titles and abstracts. Full reports of experimental study designs comparing current marketed enzyme or substrate replacement therapies against any comparator in patients with type 1, type 2, or type 3 Gaucher disease were evaluated for inclusion. Literature was excluded if enrollment and results included patients with other lysosomal storage diseases (eg, Fabry disease, Huntman disease, Niemann-Pick disease), if primary endpoints did not evaluate symptom relief or control of Gaucher disease with validated disease markers, or if the study focused on medication pharmacokinetics or pharmacodynamics. Article selection discrepancies were resolved through discussion.

RESULTS AND DISCUSSION

Treatment Goals

There are established long-term therapeutic goals for major hematologic (ie, anemia, thrombocytopenia), organomegaly (ie, hepatomegaly and splenomegaly), and skeletal manifestations of Gaucher disease.⁹ The goal when initiating therapy is to achieve long-term therapeutic targets within 1 to 2 years of therapy initiation.⁹

In patients with anemia, the goal is to increase hemoglobin concentration to 11 g/dL or greater in women and children or 12 g/dL or greater in men within 12 to 24 months of starting therapy, eliminate the need for blood transfusions, and reduce symptoms of anemia.⁹ In patients with thrombocytopenia, the therapeutic goal is to increase platelet counts to a level where surgical and obstetric bleeding is not a risk.⁹ A specific goal number or time frame is not defined as platelet response is dependent on the severity of thrombocytopenia, spleen volume, and spleen status (splenectomy vs no splenectomy).⁹

The therapeutic goal for hepatomegaly is to decrease liver volume 1.0 to 1.5 times the normal volume.⁹ In general, liver volume should decrease by 20% to 30% during the first year of treatment and decrease by 30% to 40% during the first 3 to 5 years of treatment.⁹ In patients with splenomegaly, the therapeutic goal is to decrease spleen volume to 2 to 8 times the normal size.⁹ Spleen volume is expected to decrease by 30% to 50% during the first year of treatment and by 50% to 60% during the first 2 to 5 years of treatment.⁹ However, spleen volume response is highly dependent on pretreatment spleen volume, with patients being more responsive if they have moderate splenomegaly.⁹

In patients with skeletal pathologies, the goal is to retain skeletal function by preventing new skeletal complications and relieve and prevent bone pain and bone crisis within 1 to 2 years.⁹ The therapeutic goal in pediatric patients is to attain normal skeletal mass and increase trabecular bone mineral density within the first 2 years of treatment and normalize growth within 3 years of starting therapy.⁹ In adults, the goal is to increase trabecular bone mineral density during the first 3 to 5 years of treatment.⁹

Treatment

Enzyme Replacement Therapy

Enzyme replacement therapy is considered first-line treatment for patients with type 1 Gaucher disease in the 2014 draft joint proposal on treatment of Gaucher disease by European Medicine Agency (EMA) and the FDA.¹⁰ Enzyme replacement therapy can also be used for treatment of visceral symptoms in other types of Gaucher disease.^{1,2} Several studies have shown enzyme replacement therapy to be beneficial in relieving symptoms of type 1 disease including reversing visceral and hematologic manifestations.^{2,4} Enzyme replacement therapy may reduce systematic symptoms of type 2 and 3 Gaucher disease but is not effective for reducing or reversing neurologic symptoms.⁸ While enzyme replacement therapy may reverse inflammation and the hematologic effects of Gaucher disease, it has no impact on complications, such as cell death, necrotic tissue injury, skeletal collapse, and tissue fibrosis. Delay and prevention of these complications can be managed by starting enzyme replacement therapy as soon as possible.⁷

Enzyme replacement therapy works by supplementing the deficient or defective acid β -glucosidase to break down GLC into glucose and ceramide, which accumulates in macrophages in the absence of acid β -glucosidase.^{11,12}

Various patient factors and characteristics of individual enzyme replacement therapy medications should be considered prior to initiating treatment. Enzyme replacement therapy should be given to all pediatric patients diagnosed with type 1 Gaucher disease and should be considered in adults based on symptom severity. Patient-specific factors to consider include hemoglobin level, history of pathologic bone fracture, history or presence of liver or spleen infarct, liver, spleen size, platelet count, and presence and severity of osteopenia and bone pain.^{1,2} Generally, enzyme replacement therapy has a greater impact on patients who have severe organomegaly at baseline.¹³

The first enzyme replacement therapy available to treat Gaucher disease was placenta-derived alglucerase, which was later discontinued and replaced by DNA-recombinant, imiglucerase.^{13,14} Imiglucerase was the only available treatment for Gaucher disease for 15 years; however, shortages and the need for alternative treatments for patients who cannot tolerate imiglucerase or develop allergic reactions to imiglucerase prompted development of additional therapies.¹³ Currently, 3 enzyme replacement therapies (ie, imiglucerase, velaglucerase alfa, and taliglucerase alfa) are available for use in the United States.¹⁴⁻¹⁶ Each medication is produced using a different cell line and contains structural differences associated with improved efficacy. However, each carries a risk of antibody development. Imiglucerase in particular has an antibody development rate of 15%; however, the presence of antibodies is not predictive of a hypersensitivity reaction and patients tend to become tolerant after 24 months of continuous therapy.¹³ Both taliglucerase alfa and velaglucerase alfa have a lower incidence of antibody development than imiglucerase. The newest therapy, taliglucerase alfa, may have an improved safety profile compared with imiglucerase and velaglucerase alfa, because it is produced in plant cells and may be less likely to illicit an immunogenicity response and antibody development.¹³ Taliglucerase alfa and velaglucerase alfa also have more terminal mannose sugars compared with imiglucerase and do not need further modification after macrophage uptake. However, there are mixed data indicating that difference in terminal mannose sugars may impact internalization and result in greater uptake of taliglucerase alfa and velaglucerase alfa by macrophages compared with imiglucerase.⁷ Additionally, velaglucerase alfa is also the only enzyme replacement therapy to be categorized as a Pregnancy Category B. However, data on use of imiglucerase in pregnant humans are lacking; in November 2015, the FDA changed the pregnancy classification of taliglucerase alfa from Category B to state human data are limited in pregnant humans and data are insufficient to determine risk. See **Table 2** for a comparison of imiglucerase, velaglucerase alfa, and taliglucerase alfa considerations.

Imiglucerase Efficacy

Long-term effects of imiglucerase were examined in a retrospective study using data collected in the International Collaborative Gaucher Group Registry including 757 type 1 Gaucher disease patients

Table 2. Comparison of FDA-approved enzyme replacement therapies^{15,23-26}

	Imiglucerase (<i>Cerezyme</i>)	Velaglucerase alfa (<i>Vpriv</i>)	Taliglucerase alfa (<i>Elelyso</i>)
FDA approval	May 1994	February 2010	May 2012
FDA indication	Long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of type 1 Gaucher disease that results in one or more of the following conditions: anemia, bone disease, hepatomegaly or splenomegaly, thrombocytopenia	Long-enzyme replacement therapy for patients with type 1 Gaucher disease	Long-term enzyme replacement therapy for adult and pediatric patients with a confirmed diagnosis of type 1 Gaucher disease
Source	Recombinant DNA technology in Chinese hamster cell ovaries	Recombinant DNA technology in human fibroblast cells	Recombinant DNA technology in genetically modified carrot cells
Dosing	2.5 units/kg 3 times a week to 60 units/kg once every 2 weeks	<ul style="list-style-type: none"> Starting dose of 60 units/kg every 2 weeks and titrate to effect If switching from stable imiglucerase, start at same dose and begin velaglucerase alfa 2 weeks after the last imiglucerase dose 	<ul style="list-style-type: none"> Starting dose of 60 units/kg every 2 weeks If switching from stable imiglucerase, start at same dose and begin taliglucerase alfa 2 weeks after the last imiglucerase dose
Administration	<ul style="list-style-type: none"> Intravenous infusion administered over 1 to 2 hours May be administered through an in-line low-protein-binding filter if flocculation occurs. 	<ul style="list-style-type: none"> Intravenous infusion administered over 1 hour Administer through an in-line low protein-binding filter. 	<ul style="list-style-type: none"> Intravenous infusion over 1 to 2 hours Administer through an in-line low protein-binding filter. Pretreatment with antihistamines or corticosteroids may prevent infusion reactions.
Warnings	<ul style="list-style-type: none"> Approximately 15% of patients develop IgG antibodies to imiglucerase in the first year of treatment. Patients must be monitored for IgG antibody formation during the first year of treatment. Patients with detectable antibodies may experience hypersensitivity symptoms. <1% of patients develop anaphylactic reactions. Most of these patients can continue imiglucerase therapy with pretreatment antihistamines or corticosteroids. 	<ul style="list-style-type: none"> Hypersensitivity reactions including anaphylaxis have occurred. Hypersensitivity reactions may be managed by slowing the infusion rate or treatment with antihistamines or corticosteroids. Pretreatment with antihistamines or corticosteroids may prevent subsequent reactions. 	<ul style="list-style-type: none"> Hypersensitivity reactions including anaphylaxis have occurred. Hypersensitivity reactions may be managed by slowing the infusion rate, administering antipyretics, or antihistamines or corticosteroids. Pretreatment with antihistamines or corticosteroids may prevent subsequent reactions.
Common adverse effects	Angioedema (<1.5%), chest discomfort (<1.5%), coughing (<1.5%), cyanosis (<1.5%), dyspnea (<1.5%), flushing (<1.5%), hypotension (<1.5%), pruritus (<1.5%), urticaria (<1.5%)	Hypersensitivity (52%), headache (35%), dizziness (22%), pyrexia (22%), abdominal pain (19%)	Headache (19%), arthralgia (13%), fatigue (9%), nausea (9%), dizziness (9%)

(continued)

Table 2. Comparison of FDA-approved enzyme replacement therapies^{15,23-26} (CONT.)

	Imiglucerase (<i>Cerezyme</i>)	Velaglucerase alfa (<i>Vpriv</i>)	Taliglucerase alfa (<i>Elelyso</i>)
Interactions	No known significant interactions	No known significant interactions	No known significant interactions
Pregnancy Category	<ul style="list-style-type: none"> • Pregnancy Category C • Animal reproductive studies have not been conducted and it is unknown if imiglucerase can cause fetal harm. 	<ul style="list-style-type: none"> • Pregnancy Category B • Limited evidence in humans and no well-controlled studies conducted in pregnant humans. • No fetal harm was observed in rat or rabbit reproductive studies. 	<ul style="list-style-type: none"> • Limited evidence in humans, which is insufficient to establish drug-associated risk in pregnant humans. • No fetal harm was observed in rat or rabbit reproductive studies.

who received either imiglucerase or alglucerase for 10 years. Data showed a sustained benefit with continued use of imiglucerase over 10 years. Patients with a spleen had a significant improvement at 10 years of treatment compared with baseline in hemoglobin concentrations (11.2 g/dL increased to 13.6 g/dL; $p < .0001$), platelet counts ($95.3 \times 10^3/\text{mm}^3$ increased to $166.6 \times 10^3/\text{mm}^3$; $p < .0001$), liver volume (1.8 multiples of normal [MN] decreased to 1.0 MN; $p < .0001$), and spleen volume (19.4 MN reduced to 5.2 MN; $p < .0001$). Similar results were seen in splenectomy patients with significant improvement at 10 years of treatment compared with baseline in hemoglobin concentration (11.9 g/dL increased to 13.4 g/dL; $p < .0001$), and liver volume (2.2 MN decreased to 1.0 MN; $p < .001$). Both patients with and without spleens reported less bone pain after 10 years of therapy (30.1% and 61.1%, respectively).⁴ Evaluated patients in the registry who received either imiglucerase or alglucerase met long-term treatment goals for hemoglobin levels, liver volume, and spleen volume for those with spleens. Other long-term treatment goals were not reported in this study.

Velaglucerase alfa Efficacy

A 2013 study compared velaglucerase alfa 60 units/kg every other week with imiglucerase 60 units/kg every other week for 9 months in a randomized, double-blind, non-inferiority trial in 35 adult and pediatric treatment naïve patients with type 1 Gaucher disease. Velaglucerase alfa was non-inferior to imiglucerase for the mean difference in hemoglobin (0.14 g/dL; lower bound 97.5% CI, -0.6 g/dL; non-inferiority margin, -1.0 g/dL), liver volume decreased from baseline (-0.07% body weight; 95% CI, -0.43% to 0.29% body weight), spleen volume decreased from baseline (0.08% body weight; 95% CI, -0.52% to 0.68% body

weight), and chitotriosidase change from baseline (1,069 nmol/mL/h; 95% CI -7,446 to 9,583 nmol/mL/h). A similar number of patients in each group developed adverse events related to treatment, and in both groups the most common adverse effect was infusion-related events. No patients in the velaglucerase alfa group developed antibodies compared with 4 patients in the imiglucerase group.¹⁷

Additionally, in a phase 2/3 open-label, prospective trial, 40 adult and pediatric patients on imiglucerase for at least 30 months and a stable dose of imiglucerase for at least 6 months were switched from imiglucerase to velaglucerase alfa at the same dose and were followed for 12 months. By the end of the 12-month study period, all patients remained stable on velaglucerase alfa with a mean hemoglobin decrease of -0.1 g/dL (95% CI, -0.3 to 0.1), platelet count increase of 7% (95% CI, 0.5 to 13.5), spleen volume decrease -5.6% (95% CI, -10.8 to -0.04), and no change in liver volume 0.0% (95% CI, -2.6 to 2.6). Additionally, chitotriosidase activity and CCL18 levels remained stable after 12 months of velaglucerase alfa therapy. No patients developed anti-velaglucerase alfa antibodies. Three patients had anti-imiglucerase antibodies and 2 patients had anti-velaglucerase antibodies present at the beginning of the study despite not having previous exposure to velaglucerase. These antibodies had weak cross-reactivity with the velaglucerase alfa. Velaglucerase alfa treatment was generally well tolerated; however, 4 patients had serious adverse effects with 1 experiencing an anaphylactoid reaction to velaglucerase alfa.¹⁸ The results of these 2 trials indicate that imiglucerase and velaglucerase alfa have similar efficacy in controlling Gaucher disease manifestations either as an initial therapy or as an alternative to imiglucerase with the potential for less antibody development with velaglucerase alfa.

Taliglucerase alfa Efficacy

A prospective, phase 3, randomized, double-blind trial assessed taliglucerase alfa 30 units/kg or 60 units/kg every 2 weeks for 9 months in 31 treatment-naïve patients with type 1 Gaucher disease. During treatment, 2 patients developed non-neutralizing antibodies to taliglucerase alfa and 2 developed hypersensitivity reactions; however, no other serious adverse effects were reported. By the end of 9 months, all patients receiving taliglucerase alfa 30 units/kg and 60 units/kg had statistically significant change from baseline in spleen volume, liver volume, and hemoglobin concentration. Patients in the taliglucerase alfa 30 units/kg group spleen volume decreased by 26.9% from baseline (95% CI, 21.98% to 31.9%; $p < .001$), liver volume decreased by 10.5% from baseline (95% CI, 4.0% to 17.0%; $p = .004$), and hemoglobin concentration increased by 1.6 g/dL from baseline (95% CI, 0.3 to 3.5; $p = .001$). Patients in the taliglucerase alfa 60 units/kg group spleen volume decreased by 38.0% from baseline (95% CI, 32.8% to 43.4%; $p < .001$), liver volume decreased by 11.1% from baseline (95% CI, 7.4% to 15.0%; $p < .001$), and hemoglobin concentration increased by 2.2 g/dL from baseline (95% CI, 0.6 to 3.8; $p < .001$). Increased platelet count was seen in both groups but was only significantly increased from baseline in the 60 unit/kg group with an increase of 41,494/mm³ (95% CI, 17,658 to 65,330; $p = .003$). Although the majority of patients had a significant change in Gaucher disease manifestations from baseline and some patients met the 1-year treatment goals for liver and spleen volume, it is unknown whether all patients met the 1-year treatment goals because of the length of the study.¹³

An additional open-label phase 3 trial evaluated 31 adult and pediatric patients who were switched from imiglucerase to taliglucerase alfa. Patients had received imiglucerase for at least 2 years and had been on a stable dose for at least 6 months. Patients were switched to taliglucerase alfa every 2 weeks at a dose equal to the previous imiglucerase dose. At 3, 6, and 9 months after switching to taliglucerase alfa, average hemoglobin concentrations, platelet counts, and spleen and liver volumes remained stable or were improved. Biomarkers such as chitotriosidase activity and CLL18 concentration also remained stable or improved. Patients receiving higher doses of taliglucerase alfa had more pronounced improvements in disease manifestations; the largest differences were seen in patients receiving greater than 30 units/kg rather than in patients receiving 15 to 30 unit/kg, and the smallest changes were seen in patients receiving

less than or equal to 15 unit/kg. Patients receiving less than or equal to 15 unit/kg were still stable compared with baseline. Statistical analysis was not done to compare changes from baseline or between doses. Patients primarily experienced mild adverse effects. However, 1 patient experienced hypersensitivity and 5 developed IgG anti-taliglucerase alfa antibodies (2 non-neutralizing and 3 neutralizing). None of the patients who developed antibodies experienced treatment-emergent adverse effects. All patients were considered stable at the end of 9 months.¹⁹ The results of these studies emphasize the safety and efficacy of treating Gaucher disease patients with taliglucerase either as an initial therapy or as an alternative to imiglucerase.

Substrate Reduction Therapy

For patients who cannot tolerate enzyme replacement therapy or experience anaphylactic reactions, oral substrate reduction therapy is another option for management of Gaucher disease according to the 2014 draft joint proposal on treatment of Gaucher disease by EMA and FDA.¹⁰ Substrate reduction therapy reduces the GLC influx into the lysosome by inhibiting the GLC-synthase enzyme, resulting in a reduction of the amount of GLC present. This therapy has a higher incidence of adverse effects than enzyme replacement therapy, and long-term reduction of GLC may affect several different cell functions. In addition, substrate reduction therapy should be avoided in pregnant women and in men and women attempting to conceive.¹ Even though both substrate reduction therapies are Pregnancy Category C medications, there are limited data to support safety in pregnancy. However, the option of having an oral therapy available offers an alternative to patients who find management with intravenous enzyme replacement therapy cumbersome.¹² Additionally, substrate reduction therapy offers an alternative for individuals who cannot tolerate or develop allergic reactions to enzyme replacement therapy. See **Table 3** for a comparison of characteristics of substrate reductions therapies.

Miglustat Efficacy

A 12-month open-label trial enrolling 28 adult patients with type 1 Gaucher disease who were unable or unwilling to use enzyme replacement therapy assessed the clinical effect of miglustat 100 mg 3 times daily that could be adjusted down to 100 mg once daily or up to 300 mg 3 times daily. A total of 79% of patients were treatment naïve, and

Table 3. Comparison of substrate reduction therapy medications^{27,28}

	Miglustat	Eliglustat
FDA indication	Monotherapy treatment of adult patients with mild to moderate type 1 Gaucher disease where enzyme replacement therapy is not a therapeutic option	Long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 EM, IM, or PM
Dosing	<ul style="list-style-type: none"> • 100 mg three times daily • Renal dose adjustments: <ul style="list-style-type: none"> ◦ CrCl of 50 mL/min to 70 mL/min: 100 mg twice daily ◦ CrCl 30 mL/min to 50 mL/min: 100 mg once daily ◦ CrCl less than 30 mL/min: not recommended 	<ul style="list-style-type: none"> • 84 mg twice daily in CYP2D6 EM and IM • 84 mg once daily in CYP2D6 PM • Reduce dose if patient is taking concomitant strong or moderate CYP2D6 inhibitors.
Administration	No additional considerations	<ul style="list-style-type: none"> • Oral administration with or without food • Capsules cannot be crushed, dissolved, or opened. • If switching from enzyme replacement therapy, may start 24 hours after the last enzyme replacement therapy dose.
Contraindications	None	<ul style="list-style-type: none"> • Due to the risk of PR, QTc, or QRS prolongation the following patients should not take eliglustat: <ul style="list-style-type: none"> ◦ EM or IM who are also taking a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor ◦ PM taking a strong CYP3A inhibitor
Common adverse effects	Diarrhea (89%), flatulence (44%), abdominal pain (50%), nausea (22%), weight decrease (67%)	Arthralgia (45%), headache (40%), migraine (10%), flatulence (10%), nausea (10%), oropharyngeal pain (10%)
Interactions	May increase clearance of imiglucerase	CYP2D6 and CYP3A inhibitors increase exposure to eliglustat
Pregnancy Category	<ul style="list-style-type: none"> • Pregnancy Category C • No human pregnancy studies • Reproductive animal studies showed decreased live births and decreased fetal weight in rats and maternal death and decreased body weight gain in rabbits. 	<ul style="list-style-type: none"> • Pregnancy Category C • No human pregnancy studies. • Reproductive studies on rats showed anomalies at 6 times the normal human dose. However, no fetal harm was noted in rabbits at 10 times the normal human dose.
Other considerations	<ul style="list-style-type: none"> • Crosses blood-brain barrier • Does not improve neurologic function 	<ul style="list-style-type: none"> • Does not cross blood-brain barrier • Does not improve neurologic function

Note: CrCl = creatinine clearance; EM = extensive metabolizers; IM = intermediate metabolizers; PM = poor metabolizers.

25% had undergone a splenectomy. Additionally, 6 patients withdrew from the study due to gastrointestinal complaints ($n = 2$) and for other non-study-related reasons ($n = 4$); the most common adverse effect was diarrhea occurring in 79% of patients. At the end of 12 months, there was a statistically significant decrease from baseline in glycolipid biosynthesis, chitotriosidase activity (16.4%; 95% CI 9.4 to 23.5; $p < .001$), liver volume (12% decrease; 7.8 to

16.4; $p < .001$), and spleen volumes (19% decrease; 95% CI, 14.3 to 23.7; $p < .001$). There was also a statistically significant increase from baseline at 12 months in platelet counts ($8.3 \times 10^9/L$; 95% CI, 1.9 to 14.7; $p = .014$) but not in hemoglobin concentration. While miglustat significantly decreased spleen volume and liver volume at 1 year of therapy, these changes did not meet 1 year expected decrease for Gaucher disease therapy. Additionally, dose changes

were not reported so it is unknown if higher doses were needed to achieve better results.¹¹

A multicenter, prospective, open-label, non-inferiority study evaluated the effect of switching adult patients who were stable on enzyme replacement therapy for at least 2 years to oral miglustat 100 mg 3 times daily with permitted dose reduction to once or twice daily. Miglustat was considered non-inferior to enzyme replacement therapy if liver volume increased by less than 10% at 24 months. Half of the 42 enrolled patients discontinued therapy prematurely due to adverse effects ($n = 13$), worsening disease ($n = 6$), and other reasons ($n = 2$). At the end of 24 months, miglustat was non-inferior to enzyme replacement therapy for maintaining liver volume with liver volume change of -1.1% (95% CI, -6.0 to 3.9%). Sensitivity analysis had consistent findings between the per-protocol analysis ($n = 18$) and the full analysis ($n = 32$). Additionally, of the patients with liver volume at therapeutic goal at baseline, 91% were deemed to still be within the therapeutic goal at 24 months. At the end of 24 months of miglustat therapy, there was a mean increase in spleen volume (23%; 95% CI, 7% to 39%), mean decrease in hemoglobin (-0.95 g/dL; 95% CI, -1.38 to -0.53 g/dL), and mean decrease in platelets ($-44 \times 10^9/L$; 95% CI, -58 to $-31 \times 10^9/L$). However, of the patients meeting therapeutic goals at baseline 95% still met spleen volume goals, 94% still met hemoglobin goals, and 85% still met platelet count goals at 24 months. Overall, 84% of the patients who completed therapy maintained disease stability at 24 months.¹²

These studies indicate that miglustat may be useful in maintaining a stable liver volume in some Gaucher disease patients and could benefit patients who are unwilling or unable to use enzyme replacement therapy. However, adverse effects may limit the number of patients who can tolerate miglustat therapy, and there was no measure of compliance with the miglustat regimen, which may impact the results of this study.^{11,12}

Eliglustat Efficacy

A phase 2, open-label, single-arm trial evaluated safety and efficacy of eliglustat 50 mg twice daily with permitted adjustment to 100 mg twice daily in 28 treatment-naïve adult patients with type 1 Gaucher disease. After 1 year of eliglustat therapy, 77% of patients met the primary composite outcome of achieving 2 of the 3 following outcomes: 0.5 g/L increase in mean hemoglobin, 15% increase in mean platelet counts, and 15% decrease

in mean spleen volume (95% CI, 58% to 98%), and liver volume significantly decreased by 17.0% ($p < .001$) at 1 year. Adverse effects were experienced in 85% of patients with the majority of adverse effects being mild or moderate and the 2 reported adverse effects deemed unrelated to treatment. During the study, 3 patients stopped therapy due to pregnancy. Two discontinued eliglustat at 3 and 4 weeks gestation and delivered healthy infants, the third miscarried twice; however, the miscarriages were considered unrelated to therapy. Of the 26 patients, 19 elected to continue therapy and longer term effects were reported in a separate study. After 4 years of treatment with eliglustat, all patients met the long-term enzyme replacement goals for hemoglobin and spleen volume, 94% met the long-term goal for liver volume, and 47% met the long-term goal for platelet count. Additionally, the mean bone mineral density T-score for the lumbar spine increased significantly, femur MRI showed stabilized or improved disease, no new bone lytic lesions were present, and no bone crisis were reported after 4 years of eliglustat therapy.^{3,20,21}

In the ENCORE trial, eliglustat was compared with imiglucerase in patients with type 1 Gaucher disease who were receiving enzyme replacement therapy for at least 3 years prior to treatment. This phase 3, randomized, multicenter, open-label, non-inferiority trial randomized 160 patients to receive either eliglustat escalated over 8 weeks to 50, 100, or 150 mg twice daily ($n = 106$) or imiglucerase ($n = 54$) for 12 months. Eliglustat was considered non-inferior to imiglucerase if 75% of patients met the composite primary outcome of hemoglobin concentration that did not decrease more than 15 g/L, platelet count that did not decrease by more than 25%, spleen volume that did not increase by more than 15%, and liver volume that did not increase more than 20% from baseline. Per protocol evaluation found eliglustat ($n = 99$) non-inferior to imiglucerase ($n = 47$) in maintaining hematologic and organ volume stability at 12 months with a between-group difference in the composite endpoint of -8.8% (95% CI, -17.6 to 4.2). More patients in the imiglucerase group (94%) reported stable symptoms (ie, bone mineral density score, hemoglobin concentration, liver size, platelet counts) compared with the eliglustat group (85%). While the study did show that eliglustat was non-inferior to imiglucerase for maintaining stability, the non-inferiority margin used was larger than what was used in other studies, which had non-inferiority margins in the 10% to 15% range.²²

DISCUSSION

Enzyme replacement therapy has been the gold standard for treatment of Gaucher disease with imiglucerase generally used as a first-line therapy. Studies evaluating velaglucerase alfa and taliglucerase alfa either in treatment-naïve patients or in patients who switched from imiglucerase showed that these 2 therapies had similar clinical efficacy in mitigating complications of type 1 Gaucher disease. While these therapies have similar efficacy, the potential for side effects must also be considered. Imiglucerase has a theoretical increased risk for developing antibodies, which can either reduce the efficacy of the medication or cause hypersensitivity reactions. Alternatively, taliglucerase alfa and velaglucerase alfa have shown decreased risk of developing antibodies, however, the impact on clinical safety and efficacy has yet to be determined. Patients who have received imiglucerase therapy have been found also to have velaglucerase alfa and taliglucerase alfa antibodies without ever having exposure to either drug, however, the presence of these antibodies does not seem to impact the efficacy of the medications.^{13,17-19} In addition, the molecular structures of taliglucerase alfa and velaglucerase alfa have theoretical advantages. Taliglucerase alfa and velaglucerase alfa have more terminal mannoses than imiglucerase, potentially resulting in better uptake into macrophages and no further modification of these proteins following uptake. Finally, in women of childbearing potential, taliglucerase alfa has human data but data are insufficient to establish risk in pregnant women and velaglucerase alfa is the only treatment of Gaucher disease with a Pregnancy Category B classification; all other treatments are categorized as Category C, but this may be due to lack of evidence in pregnant women. Although the data for use of these therapies in pregnant women are limited, the experience with imiglucerase makes it the safest option for women who wish to get pregnant. Differences between available enzyme replacement therapy may be taken into consideration when selecting therapy for type 1 Gaucher disease patients. A disadvantage of all enzyme replacement therapy is that administration is only available by an intravenous route, which could impact patient quality of life.

A potential oral alternative to enzyme replacement therapy is substrate reduction therapy. Both miglustat and eliglustat demonstrate efficacy in reducing symptoms of Gaucher disease in patients who either cannot tolerate or refuse treatment with enzyme replacement therapy. Studies are limited that directly compare

enzyme replacement therapy and substrate reduction therapy. Additionally substrate reduction therapy is only approved in adult patients, and acceptability as first-line therapy will likely require additional data. In patients for whom substrate reduction therapy is an option, characteristics of each medication should be taken into consideration prior to initiating therapy. Both medications require close attention to patient-specific factors. Miglustat is dosed on renal function and eliglustat requires genetic testing to determine CYP2D6 genotype prior to beginning therapy. Patients who have ultra-rapid CYP2D6 metabolism are not good candidates for eliglustat. Other considerations for selecting substrate reduction therapy include dosing, interactions, and adverse effects. Miglustat is dosed 3 times each day, whereas eliglustat can be dosed twice daily. Eliglustat has interactions with medications that inhibit CYP2D6 and CYP3A4, whereas miglustat has minimal interactions comparatively. Finally, miglustat has significant gastrointestinal effects such as abdominal pain, diarrhea, and flatulence, whereas eliglustat has a milder side effect profile. All of these factors are important to consider when selecting substrate reduction therapy for patients.

Although there are several options for treatment of type 1 Gaucher disease, there are no FDA-approved medications for treatment of type 2 and type 3 Gaucher disease. Existing treatments for type 1 disease may have a mild effect on symptom management in some type 3 patients. Current options for the treatment of Gaucher disease have progressed over time, with DNA recombinant technology offering safer therapeutic alternatives and oral therapies considered a viable option in patients where traditional intravenous management is not possible.

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