



In the name of GOD

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Gaucher Disease Treatment

Gaucher Disease Treatment



- Several pharmacologic agents have been approved by FDA for the treatment of type 1 or 3 Gaucher disease
- They may be classified as enzyme replacement therapy (ERT) or substrate reduction therapy (SRT)
- **Enzyme replacement therapy**
- First line & gold standard for treatment in children & adult
- ERT with glucocerebrosidase purified from human placenta (**alglucerase**) in 1991
- In 1994, **imiglucerase**, a recombinant form of the enzyme produced in cultured Chinese hamster ovary

Gaucher Disease Treatment



- In 2010, **velaglucerase alfa**, a recombinant enzyme produced in cultured human cells
- velaglucerase alfa is associated with fewer hypersensitivity reactions and fewer antibodies than the other enzymes
- In 2012, **taliglucerase alfa**, a plant (carrot) cell-based ERT was approved
- all used to treat type 1 Gaucher disease
- Historically, most patients have been treated with imiglucerase. This preparation is highly effective in reversing the visceral and hematologic manifestations of Gaucher disease

Gaucher Disease Treatment



- Treatment is typically administered once every other week in a dose of 30-60 U/kg
- All doses are administered via intravenous (IV) infusion once every 2 weeks
- **Duration time:** 1 to 2 hr for > 20 kg & 2 hr for < 20 kg
- Pre – medication: antihistamine or corticosteroid in hypersensitive reaction
- most suitable initial and maintenance dosages remains controversial
- Severity and rate of disease progression vary widely, especially in adults
- This makes treatment decisions extremely difficult in some patients

Gaucher Disease Treatment



- **European consensus working group on gaucher disease:**
- ERT dosing for pediatric and adolescent patients with Gaucher disease based on disease severity
- **Severe Disease**
- Recommended Dose: 60 U/kg every 2 weeks.
- **Pediatric Indications:**
- 1) Severe acute bone involvement (bone crises, avascular necrosis, pathological fractures).
- 2) Massive splenomegaly or hepatomegaly.
- 3) Severe cytopenias (severe anemia or thrombocytopenia).
- 4) Significant growth failure and pubertal delay.
- 5) All patients with Type 3 Gaucher disease..

Gaucher Disease Treatment



- **Moderate Disease**
- Recommended Dose: 30 to 45 U/kg every 2 weeks.
- **Pediatric Indications:**
- Moderate splenomegaly or hepatomegaly.
- Mild-to-moderate cytopenias without severe bone crises.
- Minor growth velocity decline on growth curves.
- **Mild Disease**
- Recommended Dose: 15 to 30 U/kg every 2 weeks.
- **Pediatric Indications:**
- Mildly symptomatic or screening-identified pediatric patients presenting with mild organ enlargement or minimal reductions in platelet count or hemoglobin.
- **Uptodate: 30 – 60 U/kg in mild & moderate disease**

Gaucher Disease Treatment



- **Key Clinical Considerations in Pediatrics:**
- Preference for Higher Starting Doses:
- Because pediatric patients have active growth plates and risks of irreversible skeletal morbidity and developmental delays, most clinical guidelines favor initiating treatment at 30 to 60 U/kg.
- Dose Titration: Once therapeutic goals are reached (normalization of hematologic parameters, organ volume reduction, Lyso-Gb1 biomarker clearance, and improvement in bone mineral density), the dose may be gradually titrated down to a maintenance regimen.

Gaucher Disease Treatment



- children who present symptomatically, may have severe disease manifestations that require early treatment.
- newborn screening
- This is leading to a new subclass of Gaucher disease patients, often asymptomatic
- lack of a prognostic correlation between genotype and disease severity
- high cost of the therapy
- **Presymptomatic treatment** with ERT remains controversial

Gaucher Disease Treatment



The response of patients to ERT is highly variable and does not correlate with genotype, disease severity, splenectomy, or age

- some patients describing symptomatic improvement within the first year of treatment
- reducing liver and spleen volumes, reversing cytopenias (anemia and thrombocytopenia), clearing bone marrow involvement, improving bone mineral density, and lowering biomarker levels (Lyso-Gb1)
- Other effects of ERT in children with Gaucher disease include increased growth velocity, weight gain, increased energy levels, and correction of both delayed puberty and a hypermetabolic state

Gaucher Disease Treatment



- **poor response factors to therapy, including:**
- cirrhosis and portal hypertension
- extensive infarction and fibrosis of the spleen
- lung involvement
- associated hematologic malignancies (respond relatively)
- Mesenteric lymphadenopathy is relatively resistant to the enzyme
- Skeletal disease is the slowest to respond
- much longer period of ERT is required to achieve a radiologic response

Gaucher Disease Treatment

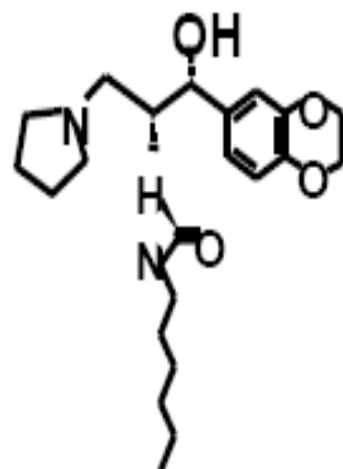


- To overcome these difficulties, increases in the dosage of enzyme infusions have been attempted
- The symptoms of patients with decompensated liver disease do not appear to respond well to ERT, and these patients remain at risk for life-threatening hemorrhage resulting from variceal bleeding
- No evidence shows that ERT results in neurologic improvement
- Although the enzyme affects the visceral involvement in types 2 and 3 disease, the associated brain involvement may persist or progress
- In January 2026, **imiglucerase** was approved for treatment of type 3 Gaucher disease in both adult and pediatric patients

Gaucher Disease Treatment



- **Substrate reduction therapy**
- miglustat
- Eliglustat
- inhibit glucosylceramide synthase
- Inhibit of synthesis glucosylceramide
- Decrease of accumulation in gaucher cells



Genz-112638



Glucosylceramide
Synthase

Ceramide + Glucose



Glucocerebrosidase

Glucosylceramide

Deficient in
Gaucher
Disease

↑
Accumulates
in Gaucher
Disease

Gaucher Disease Treatment



- amount of glucocerebroside is reduced to a level that allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective
- **Miglustat** was approved in 2003 as monotherapy for adults with mild-to-moderate type 1 Gaucher disease for whom ERT is not an option
- mild-to-moderate adverse effects with miglustat
- the most frequently reported side effects being gastrointestinal

Gaucher Disease Treatment



- **Eliglustat** was approved in August 2014 as first-line oral treatment for the long-term treatment of adults with Gaucher disease type 1
- The dose of eliglustat is determined by establishing the patient's CYP2D6 phenotype (ie, extensive metabolizers [EM], intermediate metabolizers [IM], or poor metabolizers [PM])
- EM:84 mg BID
- IM :84 mg QD or BID
- PM:84 mg QD

Gaucher Disease Treatment



- in adult patients with GD1, Imiglucerase and Eliglustat demonstrate equivalent clinical efficacy
- Clinical trials (including the ENCORE and ENGAGE studies) have established that both agents achieve comparable outcomes in reducing liver and spleen volumes, reversing cytopenias (anemia and thrombocytopenia), clearing bone marrow involvement, improving bone mineral density, and lowering biomarker levels (Lyso-Gb1)
- the choice between them depends on patient age, disease subtype, pharmacogenomic profile, route preference, and drug interaction potential

Gaucher Disease Treatment



- **When Imiglucerase (ERT) is Mandatory or Preferred:**
- Pediatric and Adolescent Patients (< 18 years)
- Type 3 Gaucher Disease
- Pregnancy and Breastfeeding: ERT is the standard of care to maintain stability during pregnancy
- CYP2D6 Ultra-Rapid Metabolizers : Eliglustat clears too quickly to reach therapeutic levels and is contraindicated
- Patients with Complex Polypharmacy: Patients taking strong CYP2D6 or CYP3A4 inhibitors (e.g., cardiac medications, antidepressants) where SRT risks toxicity

Gaucher Disease Treatment



- **When Eliglustat (SRT) is Preferred:**
- **Patient Convenience & Quality of Life:**
Eliminates lifelong biweekly IV infusions in stable adult patients
- **Venous Access Complications:**
Ideal for patients with poor peripheral veins or severe needle phobia
- **ERT Resistance or Hypersensitivity:**
Eliglustat is Excellent alternative for patients who develop neutralizing anti-imiglucerase IgG antibodies or severe recurrent infusion-related reactions

Gaucher Disease Treatment



- **Key differences between imiglucerase and eliglustat**
- **Feature:**
 - Imiglucerase (Cerezyme)
 - Eliglustat (Cerdelga)
- **Therapy Class:**
 - Enzyme Replacement Therapy (ERT)
 - Substrate Reduction Therapy (SRT)
- **Mechanism of Action:**
 - beta-glucocerebrosidase to break down accumulated glucosylceramide
 - Inhibits glucosylceramide synthase to reduce substrate synthesis

Gaucher Disease Treatment



- **Route & Frequency:**
 - IV infusion every 2 weeks
 - Oral capsule daily (once or twice daily based on CYP2D6 status)
- **Approved Age Group:**
 - All ages (infants, pediatric, and adult patients)
 - Adults (> 18 years) only
- **Indicated Phenotypes:**
 - Type 1 and Type 3 Gaucher disease
 - Type 1 Gaucher disease only

Gaucher Disease Treatment



- **Required Pre-Testing:**
- None required
- Mandatory CYP2D6 pharmacogenomic testing prior to initiation
- **Pregnancy / Lactation:**
- Safe and recommended
- Not recommended / Contraindicated
- **Drug Interactions:**
- Minimal to none
- High (significant interactions via CYP2D6 and CYP3A4 pathways)
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Gaucher Disease Treatment



- Eliglustat possesses a decisive clinical advantage over Miglustat and serves as the primary first-line oral therapy for eligible adult patients with Type 1 Gaucher disease
- **Comparison: Eliglustat vs. Miglustat**
- **Feature:**
- Eliglustat (Cerdelga)
- Miglustat (Zavesca)
- **Therapeutic Generation**
- Second-generation (highly selective)
- First-generation (non-selective)
- **Target Selectivity:**
- High: Specifically inhibits glucosylceramide synthase
- Low: Inhibits glucosylceramide synthase as well as intestinal disaccharidases

Gaucher Disease Treatment



- **Clinical Efficacy:**
 - High (ERT-equivalent): Comparable to Imiglucerase in controlling organomegaly and cytopenias
 - Moderate: Lower efficacy compared to ERT and Eliglustat
- **Guideline Status:**
 - First-line oral therapy for adult Type 1 Gaucher disease
 - Second-line / Alternative therapy (reserved for patients unable to receive ERT or Eliglustat)
- **Gastrointestinal Tolerability:**
 - Excellent; mild and infrequent GI effects
 - Poor: Osmotic diarrhea, abdominal cramps, and weight loss in over 80% of patients

Gaucher Disease Treatment



- **Neurological Risks:**
- None
- Risk of peripheral neuropathy and fine hand tremors
- **Dosing Regimen:**
- 84 mg oral capsule once or twice daily (based on CYP2D6 status)
- 100 mg oral capsule three times daily
- **Mandatory Pre-testing:**
- CYP2D6 pharmacogenomic testing required
- No CYP2D6 genotyping required
- **Metabolism & Elimination:**
- Hepatic metabolism via CYP2D6 / CYP3A4
- Renal elimination unchanged (requires dose adjustment in renal impairment)

Gaucher Disease Treatment



- **Superior Safety & Tolerability Profile:**
- Miglustat's off-target inhibition of gut disaccharidases leads to carbohydrate malabsorption, persistent osmotic diarrhea, weight loss, and potential peripheral neuropathy, frequently causing patients to discontinue treatment. Eliglustat avoids these intestinal and neurological toxicities.
- **Patient Adherence & Dosing Convenience:**
- Eliglustat is administered once or twice daily, whereas Miglustat requires a three-times-daily schedule.

Gaucher Disease Treatment



- **Efficacy Equivalent to ERT:** Clinical trials demonstrate that Eliglustat achieves organ volume reduction, hematologic recovery, and bone density improvements equivalent to intravenous Imiglucerase. Miglustat yields significantly lower clinical response rates
- **Where Miglustat May Be Considered:**
 - In adult Type GD1 who are CYP2D6 Ultra-rapid Metabolizers (where Eliglustat is ineffective/contraindicated)
 - cannot receive intravenous ERT
 - In patients with complex polypharmacy involving severe, unmanageable CYP2D6 or CYP3A4 drug-drug interactions

Gaucher Disease Treatment



- **Pharmacologic chaperone therapy**
- is a new strategy to increase residual activity by stabilizing misfolded mutant proteins, preventing endoplasmic-reticulum–associated degradation in proteosomes and allowing trafficking to lysosomes
- a real advantage to oral therapy and in the case of SRTs and PCs can envision these in combination with ERT or developed as maintenance options. It is to be hoped that among these medications there will be at least one that will ameliorate neuronopathic features.
- **Gene therapy**
- No gene therapies have yet been approved for Gaucher disease
- **Hematopoietic Stem Cell Transplantation (HSCT):**
- high procedure-related morbidity and mortality

Gaucher Disease Treatment



- **Supportive Measures and Special Precautions**
- **Avoidance of Splenectomy**
- Surgical removal of the spleen must be avoided whenever possible.
- Splenectomy eliminates the primary reservoir for Gaucher cell sequestration
- excess substrate accumulation into the bones and liver
- This significantly accelerates avascular necrosis (AVN), acute bone crises, and hepatic cirrhosis.
- increases the long-term risk of developing severe Pulmonary Arterial Hypertension

Gaucher Disease Treatment



- **Management of Acute Bone Crises & Skeletal Involvement:**
 - must be carefully differentiated from acute osteomyelitis
 - aggressive intravenous hydration
 - potent analgesia (including opioids)
 - temporary escalation of the ERT dose.
- **Skeletal Micronutrient Optimization:** In conjunction with DEXA monitoring and **bisphosphonates**, routine assessment and correction of Vitamin D and calcium deficiencies are required to preserve bone mineral density.
- **Surgical Referral:** Prompt referral to an orthopedic specialist in the event of avascular necrosis or pathological fractures.

Gaucher Disease Treatment



- **Role of Biomarkers in Gaucher Disease:**
- Diagnosis, Severity Assessment, and Therapeutic Monitoring
- **1. Glucosylsphingosine (Lyso-Gb1 / Lyso-GL1)**
- The Gold Standard
- **Properties & Nature:** The deacylated form of glucosylceramide (the primary accumulating substrate in Gaucher disease).
- **Sensitivity & Specificity:** Exceptionally high (>99%); currently the most sensitive and specific biomarker for Gaucher disease.

Gaucher Disease Treatment



- **Clinical Application:**
- Direct Correlation with Disease Burden
- Serum Lyso-Gb1 levels correlate precisely with liver and spleen volumes, bone marrow infiltration, and overall disease severity.
- **Optimal Therapeutic Indicator:**
- Following initiation of ERT or SRT, Lyso-Gb1 levels drop rapidly along a predictable trajectory.
- Failure to decline or a secondary elevation indicates subtherapeutic dosing or non-adherence.

Gaucher Disease Treatment



- **2. Chitotriosidase (ChT)**
- **Properties & Nature:**
- An enzyme secreted directly and in massive quantities (100- to 1,000-fold above normal) by lipid-laden macrophages (Gaucher cells).
- **Clinical Application:**
- Classical biomarker used to monitor the reduction of systemic Gaucher cell burden during treatment.
- **Major Limitation:**
- Approximately 5–6% of the general population carries a homozygous null mutation in the CHIT1 gene, resulting in total enzyme deficiency. Additionally, ~30% are heterozygous . It cannot be used in these individuals.

Gaucher Disease Treatment



- **3. Chemokine CCL18**
- **Properties & Nature:**
 - A chemokine protein secreted by Gaucher cells into systemic circulation (levels are elevated 10- to 50-fold).
- **Clinical Application:**
 - The primary alternative biomarker for patients with genetic chitotriosidase deficiency.
- **Limitation:** Less specific than Lyso-Gb1; levels may also rise in pulmonary fibrotic disorders or other active inflammatory states.

Gaucher Disease Treatment



- 4. Serum Ferritin
- Properties & Nature:
 - An iron-storage protein and acute-phase reactant.
- Clinical Application:
 - Markedly elevated in most patients with Type 1 Gaucher disease (even in the absence of systemic iron overload), reflecting marked macrophage activation.
 - Gradually decreases toward normal physiological levels following initiation of ERT.

Gaucher Disease Treatment



- 5. Tartrate-Resistant Acid Phosphatase (TRAP) and Angiotensin-Converting Enzyme (ACE)
- Properties & Nature:
- TRAP: Secreted by Gaucher cells and osteoclasts.
- ACE: Produced by activated macrophages.
- Clinical Application:
- Elevated TRAP reflects active disease and bone turnover.
- Both parameters are non-specific adjunctive markers evaluated alongside primary biomarkers.
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Gaucher Disease Treatment



- **Summary of Clinical Practice**
- In modern clinical management, Lyso-Gb1 testing is the first-line, preferred biomarker.
- Where Lyso-Gb1 testing is unavailable, a combination of Chitotriosidase (after ruling out genetic deficiency) or CCL18, together with Serum Ferritin, is utilized to track treatment response.
- **Monitoring Frequency:**
- Titration Phase: Assess biomarkers (especially Lyso-Gb1) every 3 to 6 months to evaluate the rate of response and dose adequacy.

Gaucher Disease Treatment



- **Maintenance Phase:**
- Assess annually (every 12 months) to ensure treatment adherence and sustained stability
- **Expected Treatment Response:**
- Following ERT/SRT initiation, Lyso-Gb1 levels should decrease by at least 50% within the first year. An absent or inadequate decline warrants evaluation for under-dosing, neutralizing anti-drug antibody formation (in ERT), or patient non-adherence.
- **Pre-treatment Screening:**
- Baseline measurement prior to therapy is required if Chitotriosidase is used, to identify potential homozygous or heterozygous CHIT1 gene mutations

Gaucher Disease Treatment



Table 3: Gaucher disease: risk assessment model for children

Increased risk	Patient has more than one of the following parameters with physical signs: • Symptomatic disease • Growth retardation • Evidence of skeletal involvement • Platelet count of less than 60,000 mm³ and/or bleeding • Hemoglobin of 2.0 g/dL below LLN • Impaired QoL	Other risk Children with relevant signs of Gaucher disease should be treated with enzyme replacement therapy
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*Defined as <18 years old. ERT=Enzyme replacement therapy; ICGG=International Collaborative Gaucher Group; LLN=Lower limit of normal; QoL=Quality of life

Gaucher Disease Treatment



Amirjazi, et al. Gaucher disease diagnosis algorithms for hematologists

Table 2: Risk assessment model for adults with Gaucher disease frequency of assessment and monitoring

High risk

Patient has ≥ 1 of the following:

- Symptomatic skeletal disease
- Impaired QoL
- Cardiopulmonary involvement
- Platelet count of less than or equal to $60,000 \text{ mm}^3$ or abnormal bleeding
- Symptomatic anaemia or haemoglobin $\leq 8.0 \text{ g/dL}$
- Transfusion dependency
- Significant liver disease by MRI
- Significant spleen disease by MRI
- Significant kidney disease
- Any concomitant medical condition that further complicates or exacerbates Gaucher disease

Low risk

Patient with all the following:

- Normal cardiac, liver, lung, and renal function
- No apparent or rapid progression of disease manifestations
- Skeletal disease like mild osteopenia and Erlenmeyer flask deformity
- Haemoglobin more than 10.5 g/dL (female patients) or more than 11.5 g/dL (male patients)
- Platelet count of more than $60,000 \text{ mm}^3$
- Liver volume of less than $2.5 \times$ normal by MRI
- Spleen volume of less than $15 \times$ normal by MRI

Table 1: Gaucher disease: Short- and long-term management goals^[19]

	Short-term goals	Long-term goals
Anemia	Eliminate transfusion dependency Improve hemoglobin levels within 1-2 years to more than 11.0 g/dL (women and children) and more than 12.0 g/dL (men)*	Maintain improved hemoglobin
Bleeding tendency	Increase platelet counts during the 1 st year of treatment Splenectomized: Normalize by 1 year Nonsplenectomized: $\geq 100 \times 10^9/L^\dagger$ within 3 years	Maintain a platelet count of at least $100 \times 10^9/L$ Reduce increased bleeding tendency
Visceral	Avoid splenectomy Alleviate splenomegaly Eliminate hypersplenism Reduce spleen and liver volumes to less than 2-8 times and 1-1.5 times normal, respectively, by 1-2 years	Keep spleen volume of <2-8 times of normal Normal liver volume after 1-2 years Prevent liver fibrosis, cirrhosis, hepatocellular carcinoma, and portal hypertension
Mobility	Lessen bone pain within 1-2 years Decrease bone marrow involvement Increase BMD by 2 years tested by MRI Normalize growth within 2 years of treatment	Prevent bone complications Prevent osteopenia and osteoporosis Prevent chronic use of analgesic medication Improve impaired mobility and physical activity
General wellbeing	Improve QoL scores within 2-3 years of treatment Reduce fatigue Improve or restore physical function	Maintain QoL and participation in school or work activities Achieve normal onset of puberty
Pulmonary	No recommendations	Prevent or improve pulmonary disease
Pregnancy	No recommendations	Prevent Gaucher disease-related complications

*Normal hemoglobin range: 120.0-155 g/day (women), 135-175 g/L (men); [†]Normal platelet count: $150-450 \times 10^9/L$. BMD=Bone mineral density; ERT=Enzyme replacement therapy; SRT=Substrate reduction therapy; QoL=Quality of life.

Table 4: Frequency of assessment and monitoring for Gaucher patients in Saudi Arabia^[20]

Aspects	Patients not on ERT		Patients on ERT		
			Not achieved therapeutic goals		At time of dose change or significant clinical complication
	Every 3-6 months	Every 12-24 months	Every 3-6 months	Every 12 months	Every 6-12 months
Comprehensive physical examination	Yes		Yes		Yes (annual)
QoL survey	Yes			Yes	Yes (annual)
Blood tests					
Hemoglobin	Yes		Yes		Yes
Platelet count	Yes		Yes		Yes
Biomarkers*	Yes		Yes		Yes
Further blood tests			Based on patient's age and clinical status		
Visceral Aspect					
Spleen volume		Yes		Yes	Yes
Liver volume		Yes		Yes	Yes
Skeletal					
MRI of femora		Yes		Yes	Yes
Radiography†		Yes		Yes	Yes
DXA		Yes		Yes	Yes
Pulmonary	Recommended every 12-24 months for patients with borderline or above normal pulmonary pressures				

*Hyaluronidase, lyso-Gb1 - a should be consistently monitored every 12 months and in conjunction with other clinical assessments of disease activity and response to treatment; †Optional in absence of new symptoms or evidence of disease progression. DXA= Dual-energy X-ray absorptiometry; ERT=Enzyme replacement therapy; ICGG=International Collaborative Gaucher Group; MRI=Magnetic resonance imaging; QoL=Quality of life; SF-36=Short-form 36 item; TRAP=Tartrate-resistant acid phosphatase

Thank you

