review

Individualization of long-term enzyme replacement therapy for Gaucher disease

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Gaucher disease, the most common lysosomal storage disorder, is a heterogeneous condition affecting multiple organ systems. Patients with nonneuronopathic (type 1) Gaucher disease may suffer from hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, skeletal pathology, growth retardation, pulmonary disease, and decreased quality of life. Enzyme replacement therapy (ERT) with mannose-terminated glucocerebrosidase (imiglucerase, Cerezyme, Genzyme Corporation, Cambridge, MA) reverses or ameliorates many of the manifestations of type 1 Gaucher disease. However, due to the variable pattern and severity of disease, and the uncertain manner of progression, implementation of treatment, choice of initial and maintenance imiglucerase dose, and evaluation of the therapeutic response must be tailored to the individual patient. For the past 14 years, the US Regional Coordinators of the International Collaborative Gaucher Group have individually and collectively developed extensive clinical experience in managing patients with Gaucher disease. In this review, we present recommendations for initial imiglucerase treatment and subsequent dose adjustments based on a schedule of regular assessment and monitoring, and achievement and maintenance of defined therapeutic goals. ***Genet Med* 2005:7(2):105–110.**

Key Words: *Gaucher disease, enzyme replacement therapy, therapeutic goals, imiglucerase, dose adjustment.*

Gaucher disease is a multisystemic chronic heterogeneous disorder and as such, requires that an individualized treatment plan be established based on each patient's clinical status. Many variables need to be considered when making treatment decisions including the severity and rate of disease progression and the impact of disease manifestations on quality of life. Enzyme replacement therapy (ERT) with intravenous recombinant, mannose-terminated glucocerebrosidase (imiglucerase, Cerezyme) is the preferred treatment for symptomatic patients with nonneuronopathic (Type 1) Gaucher disease. For the physician prescribing ERT, the clinical challenge is to find the dose that will achieve and sustain the optimal clinical benefit of therapy for each patient. This challenge is best met in the context of a treatment plan that defines specific, evidence-based quantitative and qualitative therapeutic goals (Fig. 1). After an initial comprehensive clinical assessment, pertinent therapeutic goals are established and an initial dosing regimen is selected. Achievement and maintenance of these goals should then be evaluated by thorough and regular monitoring as recommended by the International Collaborative Gaucher Group (ICGG) International and US Regional Coordinators.[1–3] The treatment plan is considered successfully implemented only when all goals are achieved and maintained in all affected organ systems.

The success or failure in achieving and maintaining the therapeutic goals should determine when patients may be considered for dose adjustments. It is recommended that decisions regarding dose management should be made by physicians who are experienced in caring for patients with Gaucher disease.[4,5] For children or patients with severe manifestations of Gaucher disease, such as pulmonary or cardiac involvement, or severe skeletal disease, dose reductions after initial improvement is observed may not necessarily be prudent and require careful scrutiny. Quantitative responses must be evaluated in the context of the patient's overall clinical status. For example, the hemoglobin parameters described below may be insufficient for patients with hypoxic pulmonary disease or those living at high altitude. Similarly, a relapse from an achieved goal may not necessarily indicate the need for a dose escalation

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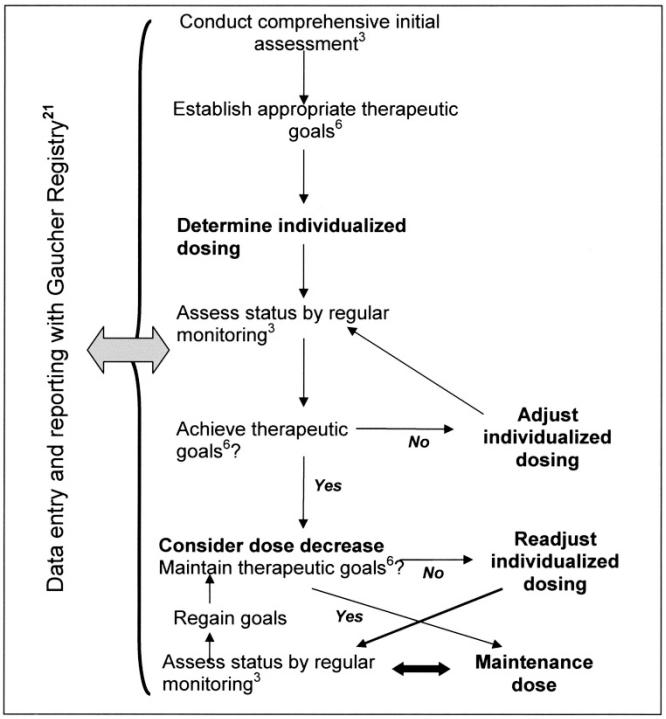

Fig. 1. Schematic treatment model for Gaucher disease incorporating assessment and monitoring guidelines,[3] therapeutic goals,[6] individualized dosing (as the subject of this review, shown in bold), and suggested interaction with the Gaucher Registry.[21] Reprinted from *Seminars in Hematology*, vol. 4, Pastores GM, Weinreb NJ, Aerts H, Andria G, Cox TM, Giralt M, Grabowski GA, Mistry PK, Tylki-Szymanska A, "Therapeutic goals in the treatment of Gaucher disease," 4–14, 2004, with permission from Elsevier.

until potentially confounding intercurrent conditions are excluded (e.g., recurrent anemia due to a bleeding duodenal ulcer).

In 2003, an international panel of Gaucher disease experts met in Amsterdam, the Netherlands, to review the medical literature and their clinical experience for the purpose of developing therapeutic goals for Gaucher disease. The outcome of this panel's work resulted in a article, "Therapeutic Goals in the Treatment of Gaucher Disease,"[6] in which evidence-based goals were established based on the clinical responses observed during the alglucerase/imiglucerase clinical trials and on data from the Gaucher Registry program.[7] In this review, we apply these goals to create guidelines for individualization of dosing for initial and maintenance ERT for type 1 Gaucher disease.

SYNOPSIS OF THERAPEUTIC GOALS

Anemia

The therapeutic goals for anemia were as follows: (1) increase hemoglobin (Hb) concentrations within 12 to 24 months to 11.0 g/dL for women and children and 12.0 g/dL for men; (2) eliminate dependency on blood transfusion; (3) reduce fatigue, dyspnea, and angina; and (4) maintain improved Hb values achieved after the first 12 to 24 months of therapy.

Thrombocytopenia

For thrombocytopenia, the goals are as follows. For all patients, increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding. For splenectomized patients, normalization of platelet count by 1 year of treatment. For patients with an intact spleen, with moderate baseline thrombocytopenia, increase platelet count by 1.5- to 2.0-fold by year 1 and approach low-normal level by year 2, and with severe baseline thrombocytopenia, increase platelet count by 1.5-fold by year 1 and continued slight increase during years 2 to 5 (and doubling by year 2). However, normalization is not usually expected. Also, avoid splenectomy (which may be necessary during life-threatening hemorrhagic events) and maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved.

Hepatomegaly

For hepatomegaly, the goals are as follows: reduce and maintain the liver volume to 1.0 to 1.5 times normal; and reduce the liver volume by 20% to 30% within year 1 to 2 and by 30% to 40% by year 3 to 5.

Splenomegaly

For splenomegaly, the goals are as follows: reduce and maintain spleen volume to $<$ 2 to 8 times normal; reduce the spleen volume by 30% to 50% within year 1 and by 50% to 60% by year 2 to 5; alleviate symptoms due to splenomegaly: abdominal distension, early satiety, and new splenic infarction; and eliminate hypersplenism.

Skeletal pathology

The goals for skeletal pathology are as follows: lessen or eliminate bone pain within 1 to 2 years; prevent bone crises; prevent osteonecrosis and subchondral joint collapse; and improve bone mineral density (BMD) in pediatric patients by attaining normal or ideal peak bone mass at the time of skeletal maturation and increasing cortical and trabecular BMD by year 2, and in adult patients by increasing trabecular BMD by 3 to 5 years.

Growth in pediatric patients

The goals for growth in pediatric patients are as follows: normalize growth such that the patient achieves a normal height according to population standards within 3 years of treatment; achieve normal onset of puberty.

Pulmonary involvement

For pulmonary involvement, the goals are as follows: reverse hepatopulmonary syndrome and dependency on oxygen; ameliorate pulmonary hypertension (ERT plus adjuvant therapies); improve functional performance and endurance; prevent rapid deterioration of pulmonary disease and sudden death; and prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy.

Functional health and well-being

The goals for functional health and well-being are as follows: resolve or lessen pain, discomfort, and fatigue; improve or restore physical function for carrying out normal daily activities and fulfilling functional roles; and improve scores from baseline (using a validated quality-of-life instrument) within 2 to 3 years or less depending on disease burden to near normal levels based on age and sex adjustments, excluding the effects of concomitant diseases.

Biochemical markers

Quantitative goals for biochemical markers are not presented because of insufficient data on clinical correlations. For purposes of clinical decision-making, changes in biomarkers should be consistent over time and must be evaluated relative to trends in other organ system parameters. Serum chitotriosidase, angiotensin-converting enzyme (ACE), and tartrate-resistant acid phosphatase (TRAP) may be useful as an adjunct to clinical observations in the monitoring of the patient's response(s) to ERT. Other biomarkers, such as lysosomal-associated membrane protein (LAMP), soluble CD163, and the chemokine CCL18 are being investigated

The amount of time required for a patient to achieve his or her therapeutic goals is dependent on many factors, including the rate of disease progression and the extent and the severity of disease. Therapeutic goals may be achieved at different rates in the various organ systems. For example, hematologic and visceral compartments may begin to respond within 12 months, with ultimate attainment of the goal requiring 12 to 36 months of treatment. Responses in certain skeletal lesions and growth and development often require at least 24 to 60 months, although a minority may improve earlier.[7–11]

LONG-TERM DOSING PLAN

The initial ERT dose should be determined in the context of the existing severity of disease and the likelihood for continued, progressive, or new-onset complications. The characteristics of increased and lower risk adults and children are shown in Tables 1 and 2. Generally, the recommended initial imiglucerase dose in adults and children at increased risk is 60 units/kg body weight every 2 weeks. Lower risk adults may begin treatment at 30 to 45 units/kg every 2 weeks. Upon achieving the therapeutic goals, a clinician's decision to change the dose should be implemented based on the history and objective evidence of disease status and course. For example, in patients with severe skeletal disease (moderate to severe osteopenia, chronic bone pain, bone crises, avascular necrosis, pathologic fractures, and joint replacements) who remain stable or show only modest improvements, dose reductions may not be appropriate until significant improvements are achieved and maintained for at least 1 year. In the absence of confounding concomitant illness or the very rare development of neutralizing antibodies to imiglucerase, failure to achieve goals may indicate a need for an increase in enzyme dose or frequency of administration. However, alternative strategies should also be considered such as adjuvant therapy with bisphosphonates for adults who fail to achieve significant improvement in osteopenia in the expected time frame.[12]

Table 1
Children (< 18 years) with Gaucher disease: Risk assessment

Increased Risk	All Others
One or more of the following in addition to physical signs:	All children with any relevant physical signs or manifestations of Gaucher disease should be treated with ERT
Symptomatic disease, including manifestations of abdominal or bone pain, fatigue, exertional limitations, weakness, and cachexia	
Growth failure	
Any evidence of skeletal involvement, including Erlenmeyer flask deformity (EFD)	
Platelet count ≤ 60,000 mm^3 and/or documented abnormal bleeding episode(s)	
Hemoglobin ≤ 2.0 g/dL below lower limit of normal for age and sex	
Impaired quality of life (QOL) due to Gaucher disease	

Dose reductions for increased-risk patients

There is as yet no evidence from controlled clinical trials for a schema of dose reductions for patients who have achieved all therapeutic goals. We offer the following recommendations based on our own clinical experience and review of the literature. Adult patients with increased risk at baseline (or at any subsequent time) and who have achieved all therapeutic goals can have the dose decreased in small increments (≈ 15%–25%) until their next scheduled evaluation (in 3–6 months). For patients who maintain all therapeutic goals, similar decrements in dose may then be considered. However, in increased-risk adults with severe disease and all children, the minimum recommended long term maintenance dose is 30 U/kg every 2 weeks. This dose has been reported as a threshold for improving versus worsening radiologic manifestations of skeletal disease.[13]

Of important note, at the time of this writing, insufficient information is available concerning dose reduction in the pediatric population. Caution should be exercised when considering dose reductions in children because it is unknown what the appropriate dose is to prevent long-term Gaucher disease complications.

Dose reductions for lower-risk patients

Adult patients with less severe disease at baseline may tolerate larger dose reductions (e.g., 25%–50% per dose) when on an every other week regimen. However, the minimum recom-

Table 2
Adults with Gaucher disease: Risk assessment

Increased risk	Lower risk
One or more of the following:	Level of disease meets ALL of the following:
Symptomatic skeletal disease	Normal liver, cardiac, lung and renal functions Minimal impairment of QOL No obvious or recent rapid progression of disease manifestations Skeletal disease limited to mild osteopenia and Erlenmeyer flask deformity Hemoglobin > 10.5 g/dL for females and > 11.5 g/dL for males (or not more than 2.0 g/dL below lower limit of normal for age and sex) Platelet count > 60,000 mm^3 on three determinations Liver volume < 2.5 × normal Spleen volume < 15 × normal
Moderate to severe osteopenia	
Chronic bone pain	
Bone crises	
Avascular necrosis	
Pathological fractures	
Joint replacement(s)	
Impaired QOL due to Gaucher disease	
Cardiopulmonary disease, including pulmonary hypertension	
Platelet count ≤ 60,000 mm^3 or documented abnormal bleeding episodes	
Symptomatic anemia or hemoglobin ≤ 8.0 g/dL	
Transfusion dependency	
Significant liver disease	
Hepatomegaly that is 2.5 × normal	
Infarcts	
Portal hypertension	
Hepatitis	
Significant splenic disease	
Splenomegaly that is ≥ 15 × normal	
Infarcts	
Significant renal disease	
Any concomitant medical condition that further complicates or exacerbates Gaucher disease or its signs and symptoms	

mended long-term maintenance dose for adult patients with less severe disease is no < 20 U/kg every 2 weeks.[14] The safety and efficacy of an every 4-week imiglucerase maintenance regimen for lower-risk patients is the subject of an ongoing, randomized clinical trial, compared with the usual every 2-week infusion regimen.

Maintenance of therapeutic goals

Comprehensive monitoring of patients should be conducted on a regular basis to ensure maintenance of therapeutic goals that have been previously attained.[3] The following criteria have been established as a guideline for the treating physician to determine whether the clinical responses achieved in the treated patient are maintained. As such, this guideline should be used by the treating physician in reviewing the patient's overall response and long-term care plan. Patients who do not sustain responses, and meet *any* of the criteria for failure, should be considered for an increase in enzyme dose to the level at which therapeutic goals were previously achieved or maintained.

Failure to maintain therapeutic goals

Patients are considered to have failed maintenance of clinical response if *any* of the following criteria are met. Such patients should be returned to the dose regimen at which therapeutic goals were previously achieved or maintained. (1) Hemoglobin level decreases more than 1.25 g/dL for women and children and 1.5 g/dL for men below the patient's value before dose reduction, and this value is the same or lower when repeated twice, at 2-week intervals. Recurrence of fatigue at-

tributable to anemia.(2) Platelet count decreases below 25% of the patient's level before dose reduction, or declines below 80,000/mm^3 and this value is the same or lower when repeated twice, at 2-week interval. Recurrence of bleeding and bruising that is not associated with the initiation of anticoagulant or platelet antiaggregating treatment or other causes such as initiation of corticosteroids for some concurrent condition. (3) The patient's liver and/or spleen volume(s) has increased by 20% more than the measurement(s) before dose reduction. Recurrence of abdominal pain or decreased appetite. (4) Evidence of progression of bone disease, including an episode of pathologic fracture, medullary infarction, lytic lesion, or avascular necrosis. (5) Increased severity or frequency of bone pain. (6) Recurrence or increased frequency of bone crisis. (7) Deterioration in quality of life not attributed to other causes. (8) Development or any exacerbation of pulmonary symptoms related to Gaucher disease (i.e., pulmonary hypertension or pulmonary fibrosis). (9) Pediatric patients who demonstrate a delay in growth and development and/or a loss of previously achieved milestones.

There are two additional parameters that should be considered when monitoring patients to ensure they are maintaining defined therapeutic goals: (1) a consistent increase in chitotriosidase or other biochemical markers of 20% or more after a dose reduction may indicate an increased risk of deterioration in clinical status and may predate an actual clinical event. Although clinical decisions should not be based on these parameters alone, careful monitoring for other signs of clinical deterioration is advisable. (2) Clinically significant decreases in bone density, detected by DXA, may also be indicative of skeletal deterioration warranting thorough monitoring of the patient's bones. Adult patients with severe osteopenia/osteoporosis may benefit from the use of adjunctive treatments (e.g., bisphosphonates).[12] The use of bone antiresorptive agents in affected children is currently under investigation.

DISCUSSION

Gaucher disease is a highly heterogeneous disorder, necessitating a systematic approach to evaluation and monitoring and an individualized approach to therapy. Decisions regarding dosing of ERT in patients with Gaucher disease should be based on disease severity, clinical course, and response to therapy, and are best made in consultation with experts in the treatment of the disorder. Multiple reports of favorable responses to ERT using a wide range of doses have been published,[7] but a controlled clinical trial defining an optimal initial or maintenance dose has not been reported. Absent that information, this review, which represents a consensus statement by clinicians and investigators with extensive experience in treating patients with type 1 Gaucher disease in the United States, outlines guidelines for dosage selection and adjustment based on a comprehensive assessment of pretreatment disease severity and an empirical evaluation of therapeutic responses that are tied to achievement of carefully defined therapeutic goals. A detailed definition of these goals with supporting evidence has been published elsewhere.[6] The current treatment recommendations rely on the following assumptions:

(1) Treatment should be initiated with an appropriate dose as defined in this review and with optimal patient compliance to mitigate, reduce, or eliminate the development of irreversible pathology and complications. Because of marked clinical heterogeneity, neither genotype nor isolated measurements of currently available biomarkers are sufficiently reliable indicators on which to base treatment decisions. Published reports of successful outcomes with the use of the imiglucerase using doses substantially lower than those we recommend[15,16] lack sufficient comprehensive information about the nature and course of skeletal responses to support a conclusion that is generally applicable, particularly in light of the broad heterogeneity in phenotypic expression that is characteristic of Gaucher disease.

(2) With achievement of therapeutic goals in all affected disease compartments and continued comprehensive serial monitoring, dose adjustments to maintenance levels are generally safe and desirable.

(3) The time required from inception of ERT to achievement of treatment goals varies by organ system involved, but usually requires at least 12 to 36 months.

(4) Realistic therapeutic goals are established based on the published guidelines and individual patient clinical characteristics.[6] The response to ERT, regardless of dose, may be limited in patients with preexistent liver disease including fibrotic scarring, progression to cirrhosis, portal hypertension, and hepatopulmonary syndrome, in patients with severe baseline splenomegaly, especially when associated with postinfarction fibrotic scars or nodule formation, and in patients with irreversible bone pathology.

(5) The pretreatment status of the patient and the age at the time of the proposed dose adjustments are important factors in the decision regarding the amount of change, if any. Any dose reduction in growing children should be carefully considered.

(5) After dose change, patients should be closely monitored for failure to maintain goals that were previously achieved. If patients fail to maintain such goals, then an increase or return to previous dose must be seriously considered unless an alternative explanation can be identified.

In circumstances when therapeutic goals are either not achieved or not sustained, dose adjustment should be recommended only after confounding intercurrent illnesses have been excluded. Examples include bleeding, iron deficiency, vitamin B12 deficiency, multiple myeloma, myelodysplasia, lymphoma, intercurrent viral infections including HIV in high risk populations, and idiopathic thrombocytopenic purpura in patients with anemia and/or thrombocytopenia, viral hepatitis, chronic hepatitis, autoimmune liver disease, and iron overload (in cases with hepatic disease), and vertebral disk disease, spinal stenosis, osteoarthritis, and intermittent claudication in those with apparently refractory bone pain.

The development of antibodies to imiglucerase very rarely contributes to therapeutic failure. Approximately 15% of patients with type 1 Gaucher disease treated with ERT develop

IgG antibodies within the first 6 months of treatment.[9,17,18] Later immune sensitization is very unusual. In most instances, these antibodies have little clinical effect either in terms of neutralization of enzyme activity or as a cause of hypersensitivity infusion reactions, and many antibody-positive patients on therapy tolerize (i.e., show a decrease in serum/plasma antibody titers, resolution of infusion-related adverse events). If suspected as a cause of treatment failure,[19] testing for neutralizing serum antibodies is available to treating physician through Genzyme Corporation. For those rare adult patients with mild to moderate Gaucher disease for whom ERT is not a therapeutic option, due to allergy, hypersensitivity, or lack of venous access, substrate reduction therapy with drugs such as miglustat may be considered.[20]

Enzyme replacement therapy with imiglucerase is generally accepted as the current standard of care for Gaucher disease. Treatment with imiglucerase, given to several thousand patients worldwide, has been shown to lead to substantially improved patient physical and functional well-being and good long-term prognosis. The individualized approach to imiglucerase treatment as described above is the most efficient and cost-effective method for improving the outcome and health of patients with type 1 Gaucher disease.

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