



ELSEVIER

# Therapeutic Goals in the Treatment of Gaucher Disease

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Gaucher disease, the most common lysosomal storage disorder, is a heterogeneous multisystem condition. Patients with non-neuronopathic (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 reverses or ameliorates many of the manifestations of type 1 Gaucher disease. However, the variable disease pattern and severity, and the uncertain manner of progression, render the decision to initiate ERT difficult. Thus, implementation of treatment and evaluation of the therapeutic response must be tailored to the individual patient. To obtain an evidence-based consensus on contemporary therapeutic goals, an international panel of physicians with extensive clinical experience in Gaucher disease met to review the extant literature on its treatment. The panel adopted an integrated system-based approach to arrive at a comprehensive guide to individualized management. Here we establish goals of treatment in Gaucher disease and propose a comprehensive schedule of monitoring of all relevant aspects to confirm the achievement, maintenance, and continuity of the therapeutic response.

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Gaucher disease, the most common lysosomal storage disorder,<sup>1</sup> is a multisystem condition that results from autosomal recessive mutations in the gene encoding glucocerebrosidase (acid  $\beta$ -glucosidase, EC 3.2.1.45).<sup>2</sup> More than 300 discrete mutant alleles have been identified.<sup>3</sup> Deficient glucocerebrosidase activity leads to the accumulation of its

major substrate, glucocerebroside (glucosylceramide), in a variety of tissues, but principally within the lysosomes of macrophages, resulting in characteristic storage cells, commonly known as Gaucher cells. Infiltration of organs by the pathologic macrophages accounts for disease in the liver, spleen, bone marrow, skeleton, lungs, and occasionally, in lymph nodes.<sup>2</sup> The relationship between glucocerebroside storage and brain damage in central nervous system disease is less clear.<sup>4</sup>

Gaucher disease is a clinically heterogeneous disorder. Three main phenotypes are traditionally distinguished: non-neuronopathic disease (also known as type 1 disease), which is the most common variant accounting for more than 90% of all cases, acute neuronopathic disease (type 2), and chronic neuronopathic disease (type 3).<sup>2,5</sup> Patients with neuronopathic disease usually have extensive systemic involvement, but neurologic manifestations may vary greatly in severity. Death is common in infancy (type 2), or in childhood or early adulthood (type 3). The clinical course and life expectancy are considerably more variable for patients with type 1 disease, encompassing a spectrum ranging from fulminant disease presenting early in childhood to an indolent, or even asymptomatic disorder discovered fortuitously in elderly adults. Most often, however, the disease is progressive, albeit

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at different rates,<sup>6</sup> and symptomatic patients may die prematurely due to sequelae of severe skeletal disease, bleeding complications, infection, liver failure, and severe pulmonary disease.<sup>7</sup> Phenotypic expression cannot reliably be predicted by genotype, as severity may vary among siblings or even in identical twins.<sup>8</sup> Disease progression may be inexorable, or may be slow and erratic, punctuated by periods of rapid exacerbation and clinical crises interspersed with sometimes lengthy periods of quiescence lasting for months or even many years. Furthermore, for each patient, disease severity may be unevenly distributed according to organ compartments. For example, some patients suffer primarily from the effects of splenic enlargement, often but not invariably accompanied by cytopenias, whereas others have little organomegaly, but severe and crippling skeletal disease.<sup>2</sup>

The heterogeneity of Gaucher disease requires an individualized approach to treatment that begins with a comprehensive multisystemic initial assessment of all possible disease manifestations to accurately stage disease burden. From the outset, it is clearly desirable to identify the principal therapeutic goals for each manifestation of disease. Each goal should include a quantitative or qualitative objective and an expected timeframe for response that is consistent with accepted standards of care. Achievement and maintenance of therapeutic goals is predicated on ongoing, regular, and systematic monitoring of all aspects of the disease. This comprehensive approach is designed to provide treatment that is individualized and takes the patient's personal circumstances and life-quality needs into account.

Enzyme replacement therapy (ERT) with mannosylated glucocerebrosidase (imiglucerase, Cerezyme®, Genzyme Corporation, Cambridge, MA) effectively reverses or ameliorates many of the manifestations of type 1 Gaucher disease.<sup>9</sup> Recently, substrate inhibition therapy with miglustat (Zavesca, Actelion Pharmaceuticals US, San Francisco, CA) has been licensed in countries of the European Union for symptomatic patients with mild to moderate disease for whom ERT is unsuitable,<sup>10</sup> and in the United States for symptomatic patients with mild to moderate disease for whom ERT is not a therapeutic option.<sup>11</sup> Miglustat is not indicated for use with imiglucerase or instead of imiglucerase. Many patients also require adjunctive medication or intervention, eg, bisphosphonates for osteopenia; pain relief, orthopedic surgery, and physical therapy for pre-existent irreversible skeletal complications; specific therapies to ameliorate portal hypertension; and vasodilator treatment for pulmonary hypertension.<sup>5,12</sup> However, the preferred treatment providing the best standard of care for all patients with clinically significant manifestations of type 1 Gaucher disease is ERT with imiglucerase.<sup>10</sup> Using the cumulative experience with ERT in more than 3,000 patients worldwide, particularly as documented in the International Gaucher Registry,<sup>5,12</sup> we propose a set of outcome-based therapeutic goals as a guide for clinicians treating patients with type 1 Gaucher disease and as reference standards for future clinical trials in this condition.

## Methods

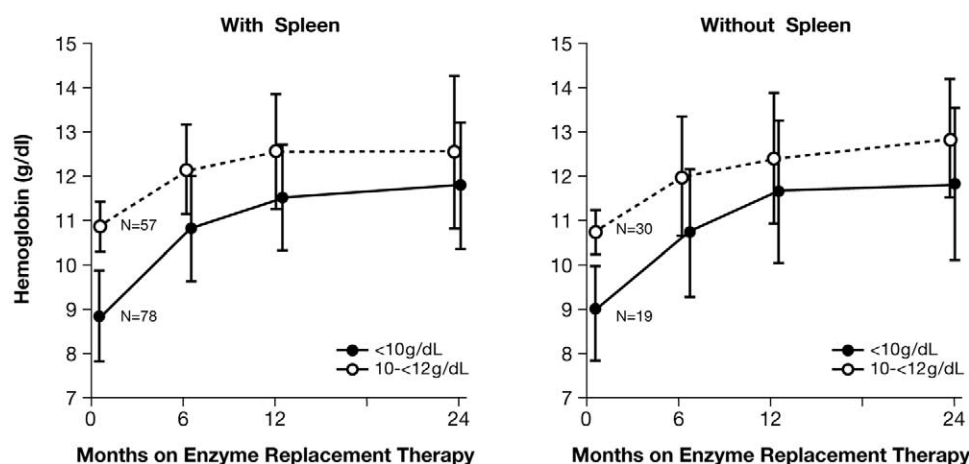
On October 23, 2003, a Global Experts Meeting on Therapeutic Goals for the Treatment of Gaucher Disease was convened in Amsterdam, The Netherlands. An international panel of physicians with extensive clinical experience in the treatment of patients with Gaucher disease met for the purpose of reaching consensus on evidence-based, therapeutic goals with reference to each organ system. Based on a pre-assigned responsibility for a specific disease manifestation, each participant presented a summary of the pertinent medical literature (including relevant data from the International Gaucher Registry, an observational database established in 1991 including, as of September 30, 2003, 3,254 patients), reviewed their own extensive clinical experience and outcomes, and proposed a list of therapeutic goals. After discussion, designed to capture the collective clinical experience of the panel, a consensus was achieved for each therapeutic goal. These goals are set out in this report.

## Results

### Anemia

Anemia is defined according to age and gender-specific mean hemoglobin (Hb) concentrations: Hb < 12.0 g/dL in males over 12 years of age; Hb < 11.0 g/dL for females over 12 years of age; Hb < 10.5 g/dL for children over 2 years and less than 12 years of age; Hb < 9.5 g/dL for children between the ages of 6 months and 2 years, and <10.1 g/dL for children under 6 months of age. Data from the International Gaucher Registry (Fig 1) demonstrate rapid and sustained improvements in anemia with ERT regardless of spleen status.<sup>9</sup> Patients in the Spanish Gaucher Registry,<sup>13</sup> whose mean pretreatment Hb concentrations were lower than those in the International Gaucher Registry, responded similarly, but with a steeper rise in Hb during the first 6 months of therapy. After 60 months of ERT, mean changes in hemoglobin were similar among patients in both registries.

Therefore, evidence-based goals for treating anemia in patients with Gaucher disease are to increase hemoglobin levels to  $\geq 11.0$  g/dL for women and children and  $\geq 12.0$  g/dL for men within 12 to 24 months (in the absence of iron deficiency), eliminate the need for blood transfusions, and reduce symptoms of anemia, namely, commonly fatigue, and occasionally in older patients, dyspnea or angina (Table 1). Even in severely affected patients (Hb < 8.0 g/dL), significant increases in Hb levels are expected during the first 6 months of therapy, eliminating transfusion dependency with amelioration of symptoms of anemia. However, in this subgroup, mild anemia may persist, especially among those with hypersplenism associated with massive splenomegaly. Anemic patients with Gaucher disease, particularly those who fail to respond adequately to ERT, require comprehensive hematologic evaluation to rule out coexistent etiologies, including iron deficiency, vitamin B<sub>12</sub> deficiency, anemia of chronic disease, and, especially in older individuals, myelodysplasia or immunoproliferative disorders. A drop in Hb concentra-



**Figure 1** Changes in hemoglobin concentration during the first 2 years of ERT among patients in the ICGG Gaucher Registry. Reprinted with permission from Excerpta Medica.<sup>9</sup>

tion (acute or gradual) should prompt investigation to rule out blood loss due to an intercurrent condition.

## Thrombocytopenia

Thrombocytopenia of sufficient magnitude to justify initiation of ERT is defined by repeated platelet counts less than  $100,000/\mu\text{L}$ . The magnitude and time course of the platelet response to ERT is influenced by the initial severity of thrombocytopenia and the pretreatment spleen volume. In the Gaucher Registry database, platelet responses were seen in patients with moderate thrombocytopenia (platelet counts  $<120,000/\mu\text{L}$  and  $>60,000/\mu\text{L}$ ), as well as those with more pronounced thrombocytopenia ( $<60,000/\mu\text{L}$ ). However, patients with moderate severity at baseline achieved a higher mean platelet level and were more likely to achieve a platelet count greater than  $120,000/\mu\text{L}$  (Fig 2).<sup>9</sup> Patients with an intact spleen were more likely to have lower pretreatment platelet counts than patients who had undergone splenectomy.<sup>14</sup> Patients with intact spleens who were severely thrombocytopenic at baseline tended to remain somewhat thrombocytopenic despite a doubling of their platelet count. This observation is most likely attributable to persistent hypersplenism combined with severe bone marrow infiltration and resulting decreased platelet production.

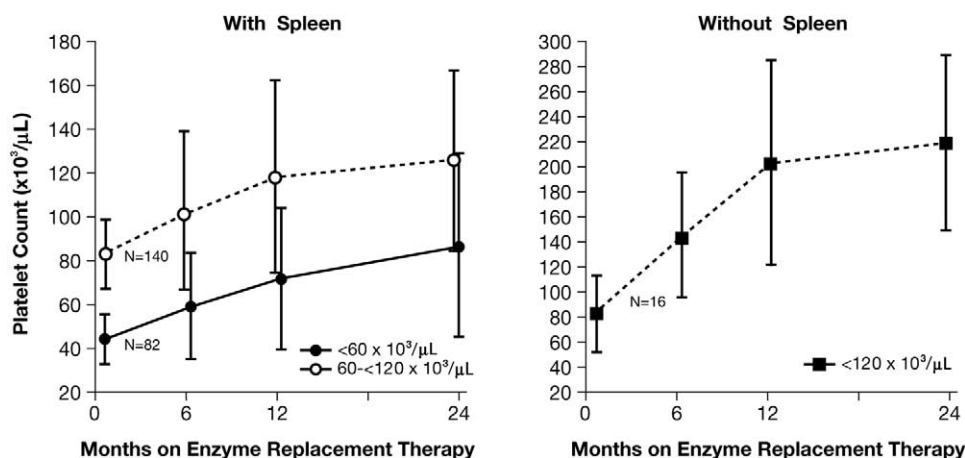
The most important therapeutic goal for patients with thrombocytopenia is to increase platelet counts to a level sufficient to prevent surgical or obstetrical bleeding. When the platelet count exceeds  $30,000/\mu\text{L}$ , spontaneous bleeding is rarely observed in patients with Gaucher disease. However,

some patients with Gaucher disease may have intrinsic or iatrogenic defects of platelet function or concurrent abnormalities in coagulation factors that can increase the risk of bleeding irrespective of the platelet count.<sup>15,16</sup> Therefore, prevention of spontaneous bleeding should also be a goal. Another important goal of ERT is to avoid splenectomy for the purpose of correcting thrombocytopenia. Splenectomy was used historically to treat hypersplenism in Gaucher disease. With the availability of ERT, splenectomy is very rarely indicated and should be avoided if possible, because of potential exacerbation of skeletal disease,<sup>17</sup> the increased risk of overwhelming bacterial sepsis,<sup>18</sup> and the enhanced risk of pulmonary hypertension.<sup>12</sup> However, in some, fortunately rare, emergency circumstances, when hemostasis must be rapidly achieved to prevent catastrophic, irreversible complications, splenectomy (followed by ERT) may still be necessary. One such situation would be when low platelet levels are accompanied by other risk factors for intracranial hemorrhage (eg, advanced age and hypertension) and marked splenomegaly with extensive fibrosis or nodule formation that proves resistant to enzyme therapy.

The specific quantitative therapeutic goals for improvement in platelet count depend on pretreatment spleen status, degree of splenic enlargement, and the initial degree of thrombocytopenia (Table 2). Platelet counts in previously splenectomized patients should normalize within the first year of treatment. Platelet counts in patients with an intact spleen and moderate baseline thrombocytopenia ( $>60,000/\mu\text{L}$  to  $120,000/\mu\text{L}$ ) should increase 1.5- to 2.0-fold by year 1 and approach low-normal counts by year 2 of treatment. In patients with more severe thrombocytopenia before institution of treatment ( $<60,000/\mu\text{L}$ ), platelet counts should increase 1.5-fold by year 1, and continue to increase slightly during years 2 to 5 (doubling by year 2) of treatment; in these circumstances, restoration of platelet counts to the normal range is not expected. Some patients will have a minimal or highly attenuated platelet response because of a limited reduction in initial massive splenomegaly<sup>19</sup> and/or severe bone marrow infiltration.<sup>20</sup>

**Table 1** Therapeutic Goals for Anemia

- Increase hemoglobin levels within 12 to 24 months to
  - $\geq 11.0$  g/dL for women and children
  - $\geq 12.0$  g/dL for men
- Eliminate blood transfusion dependency
- Reduce fatigue, dyspnea, angina
- Maintain improved Hb values achieved after the first 12 to 24 months of therapy



**Figure 2** Changes in platelet counts during the first 2 years of ERT among patients in the ICGG Gaucher Registry. Reprinted with permission from Excerpta Medica.<sup>9</sup>

## Hepatomegaly

Hepatomegaly is assessed by quantitative imaging of the liver volume, preferably using magnetic resonance imaging (MRI) or computed tomography (CT), and not merely by physical examination.<sup>14,21</sup> Hepatomegaly is defined as a liver mass greater than 1.25 times the normal 2.5% of total body weight in kilograms. Data from the International Gaucher Registry demonstrated significant reductions in liver volume in patients with either moderate (liver volume  $>1.25$  and  $\leq 2.5$  times normal) or severe ( $>2.5$  times normal volume) pre-treatment hepatomegaly with ERT (Fig 3A).<sup>9</sup> In these patients, hepatomegaly decreased by 20% to 30% within 12 months and by 30% to 40% over 2 to 5 years. Patients with moderate hepatomegaly were more likely to achieve liver volume normalization: 50% to 58% of patients with moderate hepatomegaly achieved a liver volume less than 1.25 times normal by month 24 of ERT compared with 6% to 9% of patients with severe hepatomegaly. The reduction in hepatomegaly was greatest during the first 2 years of ERT, but

liver volumes in those with enlarged livers continued to decrease at a slower rate during years 3 to 5.

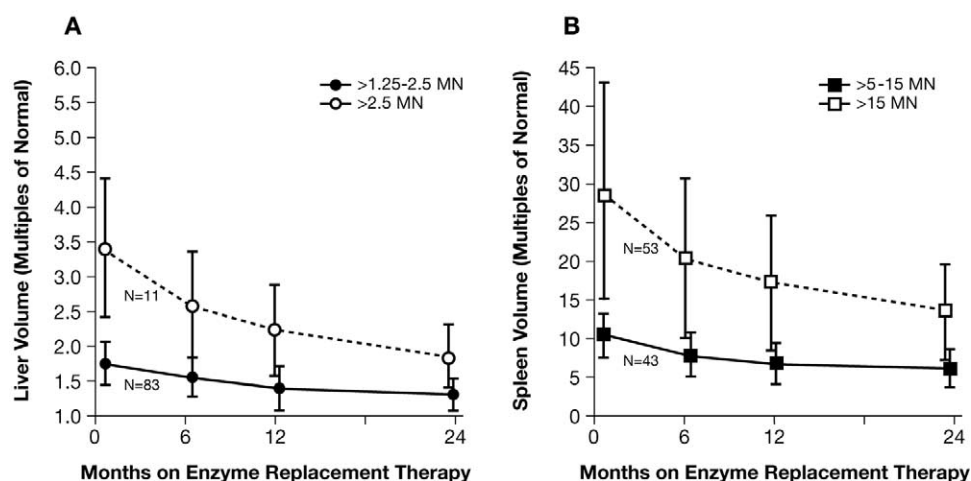
Therapeutic goals for patients with hepatomegaly are to reduce the liver volume to 1.0 to 1.5 times normal (Table 3). Liver volume should decrease by 20% to 30% within year 1 to 2 and by 30% to 40% by year 3 to 5.<sup>9</sup> Volume normalization is generally not possible when hepatomegaly is severe, presumably due to the presence of fibrosis.<sup>9</sup> Grossly abnormal liver function test results and/or advanced liver disease should prompt screening for an intercurrent condition (eg, viral hepatitis, chronic hepatitis, autoimmune liver disease, iron overload). Current data are insufficient to draw conclusions on the impact of treatment for the prevention of hepatic infarction, fibrotic scarring, progression to cirrhosis, portal hypertension, and hepatopulmonary syndrome. Manifestations of portal hypertension (eg, ascites, varices) may occasionally improve,<sup>22</sup> especially when the liver disease is accompanied by massive infiltration of the spleen. Intraparenchymal fibrosis may be associated with the hepatopulmonary syndrome. Case reports indicate that hepatopulmonary syndrome may show dramatic improvement with ERT (see Pulmonary Involvement). Some patients with established cirrhosis and hepatic failure will require allogeneic hepatic transplantation.

**Table 2** Therapeutic Goals for Thrombocytopenia

- All patients: increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding.
- Patients with splenectomy: normalization of platelet count by 1 year of treatment
- Patients with an intact spleen:
  - Moderate baseline thrombocytopenia: the platelet count should increase by 1.5- to 2.0-fold by year 1 and approach low-normal level by year 2
  - Severe baseline thrombocytopenia: the platelet count should increase by 1.5-fold by year 1 and continue to increase slightly during years 2 to 5 (doubling by year 2), but normalization is not expected
  - Avoid splenectomy (may be necessary during life-threatening hemorrhagic events)
  - Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved

## Splenomegaly

Splenomegaly is assessed by quantitative imaging of the spleen volume, preferably using MRI or CT.<sup>14,21</sup> Splenic imaging by ultrasonography is also useful for identifying nodular Gaucher cell infiltration of the spleen<sup>23</sup> and areas of splenic infarction, and, by Doppler flow imaging, the presence of portal hypertension and reversed portal venous blood flow. Splenomegaly is defined as a splenic mass greater than the normal 0.2% of total body weight in kilograms. The pre-treatment spleen volume exceeds five multiples of normal in about 90% of all symptomatic nonsplenectomized patients with type 1 disease. International Gaucher Registry data demonstrated substantial decreases in spleen volume in pa-



**Figure 3** Changes in liver volume (A, patients with spleen) and spleen volume (B) according to baseline size during the first 2 years of ERT for patients in the ICGG Gaucher Registry. Reprinted with permission from Excerpta Medica.<sup>9</sup>

tients with either moderate (spleen volume  $>5$  and  $\leq 15$  times normal) or severe ( $>15$  times normal volume) pretreatment splenomegaly with ERT (Fig 3B). Overall, splenomegaly decreased by 30% to 50% within 12 months and by 50% to 60% over 2 to 5 years. Responses were influenced by pretreatment volume: reduction in spleen size to less than five times the normal volume by month 24 was seen in about half of patients with moderate pretreatment splenomegaly and in less than 5% of patients with severe pretreatment splenomegaly.<sup>9</sup>

Therapeutic goals for patients with splenomegaly are to reduce spleen volume to  $\leq 2$  to 8 times normal, alleviate discomfort due to splenic enlargement (abdominal distension, early satiety) and abdominal pain due to recurrent episodes of splenic infarction, and eliminate hypersplenism (Table 4). Volume normalization is not expected in patients with severe baseline splenomegaly.<sup>9</sup> Many patients will have some residual enlargement with long-term treatment, probably as a result of pre-existing postinfarction fibrotic scars or nodule formation.

Currently, there are insufficient data regarding the effects of enzyme therapy on the development of fibrotic scarring, risk for rupture, and development of intrasplenic sanctuary sites that may be associated with a risk for hematologic malignancy (eg, lymphoma, myeloma). However, the panel was unanimous in recognizing the likely benefit of enzyme therapy on these long-term parameters of risk related to splenic infiltration in Gaucher disease.

## Skeletal Pathology

Skeletal pathology in Gaucher disease is multifaceted. Three, often coexistent, pathologic presentations have been identi-

fied: focal disease (lytic and/or sclerotic lesions associated with infarction, thrombosis, and inflammatory processes that can progress to osteonecrosis), local disease (remodeling defects and long bone deformities such as Erlenmeyer flask deformity, and cortical bone thinning), and generalized osteopenia and osteoporosis.<sup>24</sup> Osteoporosis is associated with an increased risk of pathologic fracture.<sup>24</sup>

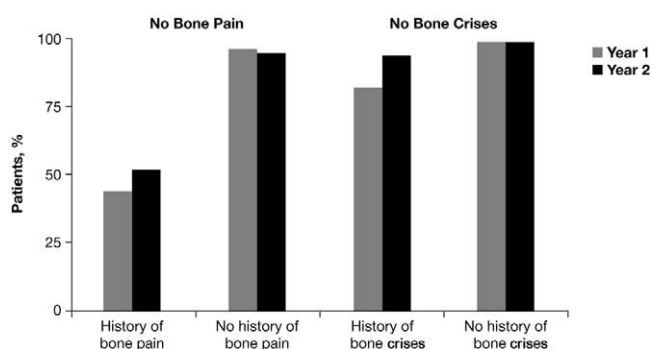
The functional effects of these osseous manifestations of Gaucher disease can include loss of skeletal function (due to fractures and subsequent joint deformity from subchondral, humeral, or femoral head collapse or fragmentation and degeneration) and various combinations and fluctuations of acute and chronic bone pain. Acute, excruciating episodic bone pain is characteristic of Gaucher bone crisis, which typically causes debilitation lasting several days or longer and requires treatment with immobilization, hydration, and opioid analgesics. Bone crises may also be accompanied by periosteal elevation, leukocytosis, and fever, and can mimic osteomyelitis. Untreated patients with skeletal symptoms, and patients whose treatment with ERT began after an irreversible skeletal complication, often require joint replacement or other orthopedic intervention, suffer functional disability and impaired quality of life, and, at times, have earlier than expected mortality.<sup>25</sup> Skeletal pathology and severe clinical symptoms can occur in patients with relatively minor organomegaly and normal hematologic parameters. From the International Gaucher Registry data, 66% of patients receiving ERT had a pretreatment complaint of bone pain, 29% had suffered prior bone crises, 50% had osteopenia, 35% had

**Table 3** Therapeutic Goals for Hepatomegaly

- Reduce and maintain the liver volume to 1.0 to 1.5 times normal
- Reduce the liver volume by 20% to 30% within year 1 to 2 and by 30% to 40% by year 3 to 5

**Table 4** Therapeutic Goals for Splenomegaly

- Reduce and maintain spleen volume to  $\leq 2$  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, new splenic infarction
- Eliminate hypersplenism



**Figure 4** Bone pain and bone crises among patients in the ICGG Gaucher Registry receiving ERT for 2 years according to previous history of bone pain and bone crises. Reprinted with permission from Excerpta Medica.<sup>9</sup>

infarction, 34% had avascular necrosis, 28% had new fractures before ERT, and 14% had undergone joint replacement.<sup>14</sup> Because skeletal pathology is often progressive, yet unpredictable, treatment should be started as early as possible to prevent the development of irreversible pathology.<sup>24</sup>

After inception of ERT, bone pain resolved in 50% of symptomatic patients within 1 to 2 years, and new onset of bone pain in asymptomatic patients occurred in only 4%. Eighty percent to 90% with prior bone crises had no recurrences during the first 2 years of ERT, and the incidence of de novo crises during the first 2 years of ERT was less than 1% (Fig 4).<sup>9</sup> After 2 to 4 years of ERT, physician assessment of overall bone involvement (clinical and radiologic) indicated improvement in 30% to 40% of pediatric patients (age <18 years), progression in less than 5% of pediatric patients, improvement in 20% to 30% of adult patients, and progression in 5% to 10% of adult patients. Bone mineral density (BMD) has been shown to improve with ERT, although the response may take at least 2 years to manifest in children and longer in adults.<sup>26</sup> For some adult patients, adjuvant therapy with bisphosphonates may be required for those who fail to demonstrate clinically significant improvement in BMD after 2 to 4 years of ERT.<sup>27-29</sup> An additional response of BMD is achieved by adding bisphosphonates in significantly osteopenic/osteoporotic patients on ERT.<sup>30</sup> Decreased bone marrow infiltration, as assessed experimentally by MRI and quantitative chemical shift imaging (QCSI), has been observed after as little as 1 year of ERT, but this more commonly takes at least 3 years<sup>26,27,31-34</sup> and is more apparent in more active bone, ie, vertebral marrow.<sup>35</sup> However, these techniques are not yet standardized or correlated with clinical outcomes.

The all-encompassing goal for children and adults with skeletal pathology is to retain skeletal function by preventing the onset of new skeletal complications and to relieve and prevent recurrence of acute and chronic bone pain and bone crises. Pediatric and adult patients have differences in skeletal physiology that must be taken into consideration when therapeutic goals are set. For children the aim should be to achieve ideal peak skeletal mass and prevent skeletal pathology, whereas in adults the aim is to maintain or improve the

skeleton and retain, preserve, or improve function. Patients with advanced bone disease at the time of ERT initiation also may benefit from orthopedic intervention, physiotherapy, and adjunctive treatment (eg, bisphosphonates for severe BMD loss).<sup>30</sup>

The specific therapeutic goals for skeletal disease are to lessen or eliminate bone pain within 1 to 2 years of treatment, to eliminate bone crises within 1 to 2 years of treatment, to prevent osteonecrosis and subsequent subchondral joint collapse, and with respect to BMD, to attain peak or ideal skeletal mass for pediatric patients and to achieve quantitative improvement in BMD for adults (Table 5).

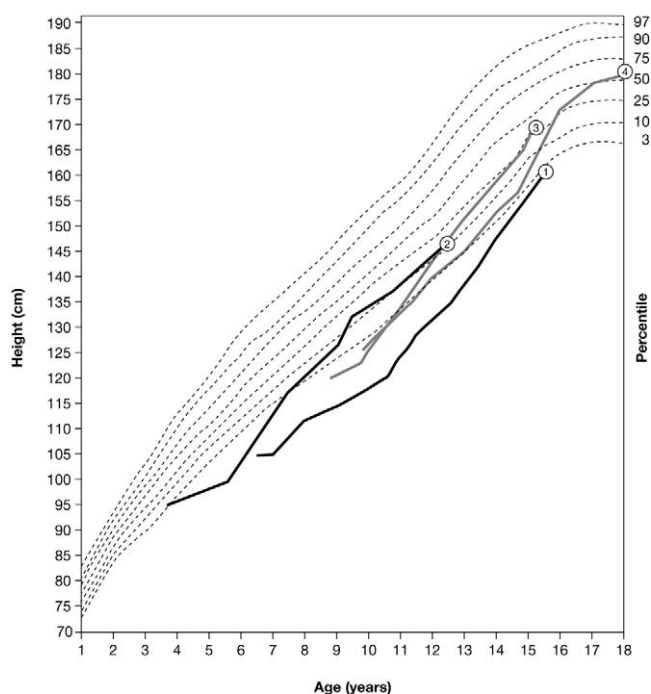
The skeletal pathologies of Gaucher disease, which affect most patients with non-neuronopathic disease,<sup>14</sup> can be the most debilitating aspect of the disease because of the associated pain along with the occurrence of fractures and joint collapse. Skeletal pathology is often progressive, so treatment should be started as early as possible to prevent the progression to irreversible pathology. The onset or development of bone pathology in a patient receiving ERT should prompt investigation for the possibility of loss of mechanical bone integrity requiring changes in therapy with orthopedic intervention and/or increasing the dose of ERT.

## Growth

Approximately half of the children with Gaucher disease exhibit growth retardation<sup>36-38</sup> and approximately 25% are shorter than expected compared with mid-parental height.<sup>14,39</sup> Children with Gaucher disease who exhibit markedly stunted growth also tend to have severe visceral involvement and may experience delayed puberty.<sup>38</sup> In otherwise mildly affected children, growth retardation should prompt appropriate assessments by an endocrinologist. Studies indicate that with ERT, children with Gaucher disease exhibiting growth retardation can achieve normal height, according to population averages. In one study, eight of nine patients who were at or below the fifth percentile at baseline and received ERT normalized growth rates within 4 to 30 months.<sup>37</sup> Another study found that growth normalization was observed after 36 months of treatment.<sup>40</sup> Experience at the Children's Memorial Health Institute in Warsaw, Poland, also showed that patients receiving ERT achieved normal growth. Figure 5 shows growth patterns of four boys during treatment with alglucerase (Ceredase®, Genzyme Corporation). Each line indicates a different child. The therapeutic goal for children with Gaucher disease is to normalize growth such that a

**Table 5** Therapeutic Goals for Skeletal Pathology

- Lessen or eliminate bone pain within 1 to 2 years
- Prevent bone crises
- Prevent osteonecrosis and subchondral joint collapse
- Improve BMD
  - Pediatric patients
    - Attain normal or ideal peak skeletal mass
    - Increase cortical and trabecular BMD by year 2
  - Adult patients
    - Increase trabecular BMD by 3 to 5 years



**Figure 5** Growth chart showing growth patterns before and during ERT. Patients 1 and 2 have type 3 Gaucher disease; patients 3 and 4 have type 1 Gaucher disease. Patients 1 and 3 underwent splenectomy. All four patients received ERT at a dose of 30 to 40 U/kg/2 wk. Treatment was initiated at age 4.5 years, 6.5 years, 9 years, and 10 years for patients 1, 2, 3, and 4, respectively.

normal height is achieved according to population standards within 3 years of starting ERT (Table 6).

## Pulmonary Involvement

The lungs represent one of the sites for accumulation of pathologic macrophages in Gaucher disease. However, only 1% to 2% of patients with type 1 Gaucher disease exhibit overt pulmonary manifestations in the form of interstitial lung disease or pulmonary vascular disease (ie, severe pulmonary hypertension and/or hepatopulmonary syndrome).<sup>12,41</sup>

The risk factors for severe pulmonary hypertension include asplenic patients naive to ERT, asplenic patients suboptimally treated with ERT, female sex, glucocerebrosidase mutations other than N370S, positive family history, and an angiotensin-converting enzyme (ACE) I gene polymorphism.<sup>12</sup> Development of pulmonary hypertension is a grave sign, because it is recognized to be an important cause of premature death in patients with type 1 Gaucher disease.<sup>7,42,43</sup> Pulmonary hypertension responds to ERT in combination with vasodilators (eg, prostacyclin and bosentan).

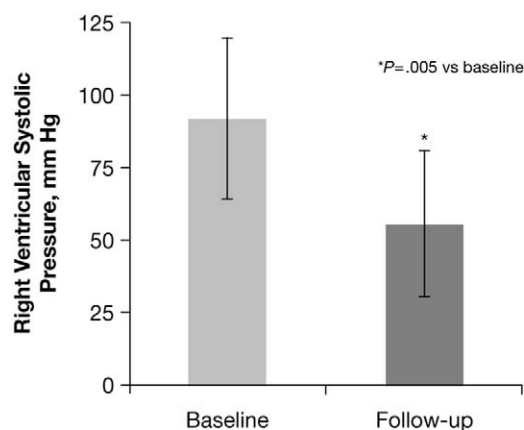
### Table 6 Therapeutic Goals for Growth in Pediatric Patients

- Normalize growth such that patient achieves a normal height according to population standards within 3 years of treatment.
- Achieve normal onset of puberty

Figure 6 shows mean baseline and follow-up right ventricular systolic pressure among nine patients with severe pulmonary hypertension receiving ERT with or without vasodilators and anticoagulants, demonstrating significant improvement with treatment compared with baseline.<sup>12</sup>

Interstitial lung disease also responds to ERT in some patients with Gaucher disease.<sup>44</sup> Additionally, there are reports of dramatic reversal of hepatopulmonary syndrome with ERT.<sup>41</sup> The vascular lesions underlying hepatopulmonary syndrome may coexist with plexogenic vasculopathy that causes severe pulmonary hypertension,<sup>45</sup> and therefore reversal of hepatopulmonary syndrome may unmask underlying pulmonary hypertension.<sup>41</sup> The latter observations underscore the importance of maintaining optimal ERT with adjuvant therapies as required after the resolution of hepatopulmonary syndrome. There is evidence that cellular uptake of imiglucerase in the lungs is not as avid as in other disease compartments;<sup>29,44</sup> therefore, high-dose ERT may be required in some patients. If the clinical signs of hepatopulmonary syndrome fail to resolve with ERT, underlying cirrhosis or presence of large anatomic intrapulmonary shunts should be excluded.

Patients with overt, symptomatic pulmonary involvement may suffer from sudden life-threatening deterioration. The goal of ERT and adjuvant therapies is to prevent sudden death or rapid and inexorable clinical deterioration, and to improve the patient's functional capacity and quality of life (Table 7). For hepatopulmonary syndrome and interstitial disease, the goal of ERT is to reverse this syndrome and obviate dependency on oxygen. The goal of treatment of severe pulmonary hypertension with ERT and adjuvant therapies is to improve hemodynamic and functional status as well as to prolong life. Almost all cases of severe pulmonary involvement in type 1 Gaucher disease in the literature and in our collective experience relate to splenectomized patients. An important goal of ERT is prevention of these complica-



**Figure 6** Baseline and follow-up right ventricular systolic pressure among nine patients with severe pulmonary hypertension receiving ERT with or without other treatments; mean follow-up was  $4.6 \pm 4$  years (range, 1 to 12 years). Two patients were receiving ERT as monotherapy, one patient had been receiving ERT but had poor compliance, and six patients were receiving ERT, vasodilators, and coumadin.<sup>12</sup>

**Table 7** Therapeutic Goals for Pulmonary Involvement

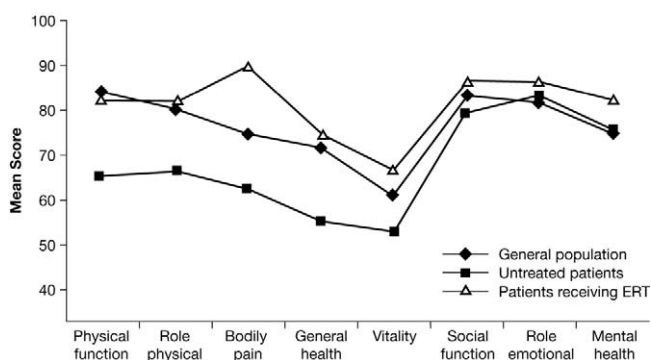
- Reverse hepatopulmonary syndrome and dependency on oxygen
- Ameliorate pulmonary hypertension (ERT plus adjuvant therapies)
- Improve functional status and quality of life
- Prevent rapid deterioration of pulmonary disease and sudden death
- Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy

tions through timely institution of ERT and avoidance of splenectomy.

### Functional Health and Well-being

The World Health Organization defines health as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.” When quality of life is considered in clinical situations, the focus is on the perception of the impact of disease and treatment on multiple dimensions of health including physical and psychological well-being, and role-activities.

In a retrospective study of 212 patients with Gaucher disease (mean age,  $45.1 \pm 17$  years) receiving ERT, health-related quality of life was assessed using the SF-36 Health Survey.<sup>46</sup> Scores for Physical Functioning, Role Physical, Bodily Pain, General Health, and Vitality were significantly lower for patients with Gaucher disease compared with those for age- and sex-matched control subjects ( $P < .05$ ). Domains related to psychological health (Social Function, Role Emotional, and Mental Health) were similar between the patients and the general population. The benefits of ERT can be observed from the results of a recent survey involving 55 patients (mean age, 46.8 years) with Gaucher disease (Fig 7). Scores for most domains approximated those of the general population and were better than those reported by patients who were not receiving ERT (Fig 7).<sup>46,47</sup> Patients receiving ERT had better scores for domains related to physical health (Physical Function, Role Physical, Bodily Pain, General



**Figure 7** Domains of the SF-36 Health Survey for the general population,<sup>64</sup> untreated patients with Gaucher disease ( $n = 212$ ),<sup>46</sup> and patients receiving ERT ( $n = 55$ ; mean duration, 6.3 years; range, 0.1 to 11.8 years) for Gaucher disease.<sup>47</sup> Adapted with kind permission of Kluwer Academic Publishers.<sup>46</sup>

Health, and Vitality). Domains related to psychological health (Social Function, Role Emotional, and Mental Health) were similar for the untreated patients and the general population.

The therapeutic goals for health-related quality of life are to improve and restore physical function so that patients are able to carry out their normal daily activities and fulfill their functional roles within their families and society. Patients should show improvement in scores from baseline of a validated quality-of-life instrument such as the SF-36 (Table 8).

### Physical Examination and Biomarkers

The physical examination is a highly important and readily accessible clinical assessment that should not be overlooked. Significant information about the severity, rate of progression, and response to therapy may be derived through observation of the patient's general physical appearance and demeanor, mood, affect, weight and height, gait, range of motion, muscle strength, bone tenderness, cardiopulmonary and abdominal findings, skin, and sexual development. Thorough initial and serial neurologic and eye movement examinations are important for detecting evidence of neuropathic disease in patients with suspect genotypes, and for identifying phenomena such as tremor and other extrapyramidal movement abnormalities, peripheral neuropathy, and age-inappropriate cognitive dysfunction that may possibly be part of the natural history even in patients believed to be free of neurologic risk.<sup>48</sup> Serial quantification of pain using a recognized “pain assessment tool” is also highly recommended. As for all patients with a sustained, chronic illness, periodic examination for clinical depression is also indicated.

Many endogenous serum proteins are variably elevated in patients with Gaucher disease. Chitotriosidase, ACE, and tartrate-resistant acid phosphatase (TRAP)<sup>49,50</sup> appear to correlate with disease involvement and may be useful as an adjunct to clinical observations for monitoring patient responses to ERT.<sup>21</sup> Additional potentially useful biomarkers for Gaucher disease, such as lysosomal-associated membrane protein (LAMP) and the chemokine CCL18, are being investigated.<sup>51,52</sup>

Of these serum proteins known to be elevated in Gaucher disease, chitotriosidase has been studied the most. Chitotriosidase is secreted by activated macrophages,<sup>53</sup> and its activity in plasma is markedly increased in patients with Gaucher disease.<sup>54</sup> Chitotriosidase activity has been seen to decrease in response to ERT,<sup>49,55</sup> and the decrease was related to dose and correlated with other indicators of positive clinical responses (eg, improvements in hematologic and visceral parameters).<sup>49,55</sup> In a study reported by Giraldo et al, patients

**Table 8** Therapeutic Goals for Functional Health and Well-being

- Improve or restore physical function for carrying out normal daily activities and fulfilling functional roles
- Improve scores from baseline of a validated quality-of-life instrument within 2 to 3 years or less depending on disease burden



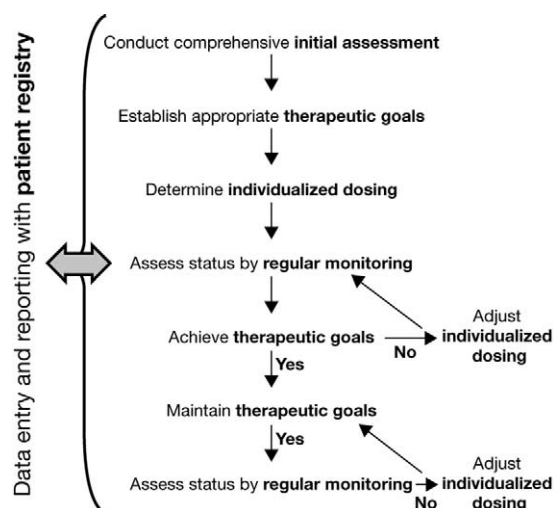
receiving ERT at a dose of 60 to 120 U/kg every 2 weeks for 2 years demonstrated a mean decrease in chitotriosidase activity of 40% to 70% (depending on dose).<sup>55</sup> In a study reported by Hollak et al, 12 months of treatment (usually at low dose) was associated with a mean decrease in chitotriosidase activity of 32%; 78% of patients demonstrated a decrease of at least 15%, and the patients whose chitotriosidase activity decreased by less than 15% had inferior visceral or skeletal responses compared with the other patients.<sup>49</sup>

Chitotriosidase activity is absent in a small proportion of patients (6% to 8%) because of a mutation in the chitotriosidase gene. For such patients, assessment of ACE or TRAP activity can be substituted. Absolute levels of chitotriosidase (or other biochemical markers) are not indicative of disease severity in individual patients, are not useful for comparisons among patients, and have no prognostic significance. Single measurements should not be included among criteria for starting ERT or selecting the initial dose. For some patients, serial increases in chitotriosidase activity may be an early indicator of clinical relapse following dose reduction or after a treatment interruption.<sup>56</sup> Increases in chitotriosidase activity should prompt investigation of the patient's disease status and compliance with therapy (if the patient is receiving ERT). However, alterations to therapy must be supported by a complete assessment of disease status and are not to be made solely on the basis of change in chitotriosidase activity. Quantitative goals for biochemical markers are not presented because of insufficient data on clinical correlations.

## Discussion

Gaucher disease is a highly heterogeneous disorder, requiring an individualized treatment plan for each patient designed to achieve a maximal response in all affected disease compartments. The construction of a comprehensive treatment plan by defining specific treatment goals is an approach that is useful not only for guiding the treating physician, consulting specialists, and allied health personnel, but also for educating patients and families, establishing reasonable expectations, and creating a partnership in caring. Most patients will have multiple therapeutic goals that must be achieved within the expected timeframes and maintained throughout their lives. Successful application of this method requires a comprehensive initial assessment of all potentially affected organ systems and regular ongoing monitoring to assess the global response to therapy, to adjust the treatment plan when goals are not met, and to ensure the maintenance of attained goals. This treatment approach is similar to that for other chronic diseases with heterogeneous manifestations and responses to therapy, thus requiring individualized dosing and ongoing assessment and monitoring. A patient registry, such as the Gaucher Registry, provides a platform to track the progress of patients individually and collectively. Such an approach is summarized in Fig 8.

Enzyme replacement therapy with imiglucerase is, at present, the core of any therapeutic plan. Dose and dosing frequency of ERT can and should be individualized to achieve and maintain the relevant therapeutic goals within



**Figure 8** A schematic treatment model for Gaucher disease incorporating assessment and monitoring guidelines, therapeutic goals, individualized dosing, and a patient registry.

the expected timeframes. The rate and degree of response to therapy may vary due to several factors, including age at presentation, concurrent medical conditions, specific organ compartments affected and extent of involvement, and the presence of irreversible pathology. Hematologic and visceral disease therapeutic goals can generally be met more rapidly than designated goals for skeletal or pulmonary compartments. However, ERT doses should not be arbitrarily decreased on the basis of hematologic or organ volume successes while potentially reversible skeletal or pulmonary disease persists. Dose increases may help patients to achieve their therapeutic goals in some cases, or may be indicated for patients who relapse following dose reduction. However, dose increases are unlikely to be effective with certain types of irreversible pathology such as fibrosis of the liver, spleen, and lung, and avascular necrosis of the bone. In all cases, within the limitations of prognostic accuracy, it is wise to initiate an effective treatment regimen sufficiently early in the course of the disease to minimize the risk of developing any irreversible long-term complications.

Treatment of Gaucher disease is life-long, and the establishment of therapeutic goals may encourage compliance with treatment and minimization of treatment interruptions. Compliance with ERT during long-term therapy has been approximately 90% and even higher for patients who receive home care.<sup>57</sup> Some patients may desire a temporary break from treatment because of personal issues or changes in lifestyle. Although some patients may remain stable during treatment interruptions, many patients experience disease progression (eg, varying combinations of decreased platelet counts and/or hemoglobin levels, increasing organomegaly, recurrent or heightened pain, exacerbation of skeletal pathology, reversal of quality-of-life gains, and progressively increased biomarkers when treatment is stopped).<sup>58-63</sup> Few patients, if any, are expected to maintain therapeutic goals in the prolonged absence of treatment, and there are no proven methods for identifying these patients.<sup>61</sup> Therefore, treat-

ment interruptions are not recommended, and, when unavoidable, necessitate close monitoring of the patients. Therapeutic goals, once achieved, require continued compliance with treatment to maintain the goals over time.

The achievement of therapeutic goals also can serve as a benchmark for assessing the consequences of changes or adjustments in the treatment regimen. Modifications such as dose reductions or decreases in dosing frequency should be considered only after all relevant therapeutic goals have been achieved. All therapeutic goals should be maintained with any modification in the treatment regimen. Maintenance of the goals should be monitored according to a regular comprehensive monitoring schedule such as outlined in the Gaucher Registry guidelines.<sup>21</sup> Reversal of the attainment of any therapeutic goal indicates a failure of the treatment modification, although the possibility of an intercurrent condition that may confound the course of Gaucher disease should be considered as well. Inadequate long-term maintenance therapy may be first noticed by changes in biomarkers, decreased hematologic parameters, fatigue, and increases in organ volumes. The effects of suboptimal treatment in the skeleton may not become apparent until the development of an irreversible complication such as an osteonecrotic joint collapse. Therefore, any changes in the treatment regimen of an otherwise stable patient should be made cautiously.

ERT is expensive, but it has dramatically improved the function and well-being of several thousand patients worldwide with type 1 Gaucher disease. The goal-oriented, individualized approach to ERT with imiglucerase described above, when combined with the appropriate use of adjuvant pharmacologic and nonpharmacologic interventions under the guidance of an experienced multidisciplinary team at an established center for the treatment of this disorder, 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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