Imiglucerase in the management of Gaucher disease type 1: an evidence-based review of its place in therapy

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Introduction: Gaucher disease is the first lysosomal disease to benefit from enzyme replacement therapy, thus serving as model for numerous other lysosomal diseases. Alglucerase was the first glucocerebrosidase purified from placental extracts, and this was then replaced by imiglucerase – a Chinese hamster ovary cell-derived glucocerebrosidase.

Aim: The aim was to review the evidence underlying the use of imiglucerase in Gaucher disease type 1

Evidence review: Data from clinical trials and Gaucher Registries were analyzed.

Conclusion: Imiglucerase has been prescribed and found to have an excellent efficacy and safety profile. We report herein the evidence-based data published for 26 years justifying the use of imiglucerase.

Keywords: Gaucher disease, lysosomal disease, imiglucerase, treatment, therapeutic goals, safety

Core evidence place for imiglucerase in the treatment of Gaucher disease type 1

Outcome measure	Evidence	Implication
Hematological parameters	Clear	In treatment-naïve patients, hemoglobin and platelets increased significantly with enzyme replacement therapy.[1] In maintenance studies, no difference was seen when imiglucerase was administrated every 2 weeks or every 4 weeks with the same total dose.[2]
Visceral parameters	Clear	In treatment-naive patients, liver and spleen volume reduced after 9 months of treatment with imiglucerase.[3]
Bone disease	Clear	Imiglucerase has a positive impact on bone manifestations mainly on bone marrow density, bone pain and bone marrow infiltration.[4-6] However, the risk of bone events does not totally disappear despite imiglucerase treatment.[7]
Biomarkers	Clear	Imiglucerase significantly reduces all known biomarkers in particular glucosylsphingosine.[8-10]
Therapeutic goals	Clear	Most of the therapeutic goals are reached with imiglucerase, and low-dose imiglucerase helps achieve hematological and visceral goals.[11,12]
Growth	Suggestive	Imiglucerase has a corrective effect on height.[13]
Quality of life	Suggestive	Imiglucerase has a significant positive impact on health-related quality of life of type 1 GD patients with skeletal disease.[14,15]

Introduction

Gaucher disease (GD) is a rare genetic lysosomal storage disorder inherited in an autosomal recessive pattern.[16] GD occurs due to the deficiency of a lysosomal enzyme, acid β-glucosidase (or glucocerebrosidase)[17] or in rare cases its activator, saposin C.[18,19] The prevalence of the disease worldwide is 1/60,000, while prevalence in Europe is 1/140,000 and in Israel is 1/6,000.[20,21,22] GD diagnosis is confirmed by the detection of low glucocerebrosidase activity (<30%) in peripheral leukocytes.[23] Mutations of the gene coding for glucocerebrosidase lead to an accumulation of the sphingolipid glucocerebroside within macrophages.[24]

Three different types of GD have been described: type 1 (GD1) is characterized by thrombocytopenia, anemia, an enlarged spleen and liver as well as bone complications (Erlenmeyer flask deformity, osteoporosis, lytic lesions, pathological and vertebral fractures, bone infarcts and avascular necrosis [AVN] leading to degenerative arthropathy).[25] GD1 accounts for 90% of all cases.

Type 2 GD is the acute neuronopathic form, and is viewed as a rapidly progressive neurodegenerative disorder of late infancy, resulting in death within the first year or two of life. Massive hepatosplenomegaly and lung involvement are usually seen.[26,27] Type 3, or chronic neuronopathic, GD is a "catch all" encompassing patients who survive infancy but have some form of neurologic involvement. Frequently the only neurologic manifestation is the slowing of horizontal saccadic eye movements, but other patients develop neurodegeneration, myoclonic epilepsy, or psychiatric manifestations.[28] It is now recognized that there is an overlap among these phenotypes and so GD is actually considered as a continuum between these three phenotypes.[29]

In 1991, the first enzyme replacement therapy (ERT) changed the outlook of patients with GD1. This first ERT used glucocerebrosidase purified from human placental tissues, and was called alglucerase (Ceredase; Genzyme Corporation, Cambridge, MA).[30] Alglucerase was later replaced by the Chinese Hamster ovary cell-derived recombinant glucerebrosidase, imiglucerase (Cerezyme; Sanofi Genzyme Corporation, Cambridge, MA, USA). Then, two others ERTs received marketing authorization: velaglucerase, a fibroblast cell-derived glucocerebrosidase (V PRIV; Shire Human Genetics Company, Cambridge, MA, USA)[31] and taliglucerase, a plant-derived glucocerebrosidase (Uplyso; Pfizer Inc, New York, NY, USA).[32]

GD1 can also be treated with substrate reduction therapies (SRT). The first SRT was miglustat (Zavesca; Actelion, Basel, Switzerland), which was only indicated when ERT was not suitable.[33] Numerous side effects restricted the prescription of miglustat. More recently, a new generation of potent and selective glucosyl ceramide synthase inhibitors has received marketing authorization in the US and Europe, namely eliglustat (Cerdelga; Sanofi Genzyme Corporation).[34]

This review summarizes the evidence for the use of imiglucerase to treat patients with GD1.

Learning from the past

In 1964, De Duve[35] suggested that lysosomal diseases should be treated by ERTs. Among lysosomal diseases, GD appeared to be the best candidate.

Proof of concept of replacement therapy for inherited enzyme deficiency diseases was suggested first in GD by Brady, in 1974,[36] with the administration of purified placental glucocerebrosidase. Glucocerebrosidase, a lysosomal acid -glucosidase, catalyzes the hydrolysis of glucosylceramide to glucose and ceramide. In vivo, glucocerebrosidase activity is modulated by saposin C, a glycoprotein that helps the formation of a complex between glucocerebrosidase and lysosomal membrane. Two patients were infused with the enzyme: this was well tolerated in both cases and the glucocerebrosidase infusion resulted in a significant reduction in the quantity of glucocerebroside within erythrocytes and the liver. Further trials to treat GD1 by ERT after 1970 were unsuccessful, maybe because of an inadequate supply of the enzyme.[37,38] Modification in the mannose residues improved its targeting to tissue macrophages and in 1990,[1] Barton et al[30] reported the first results with repeated infusions of mannose-terminated human placental glucocerebrosidase in a child with GD; they demonstrated an improvement in anemia, thrombocytopenia and skeletal manifestations. In 1991, Beutler et al[39] treated two patients and obtained good hematological and visceral results, with a low dose of glucocerebrosidase infused either every other day or three times a week. This placental glucocerebrosidase (alglucerase) became commercially available in 1991.

The limitations to the use of enzyme purified from the placenta was the availability and to a lesser extent the possibility of infective contaminants. The enzyme that was then produced by heterologous expression of human cDNA for glucocerebrosidase in eukaryotic cells was aimed at eliminating both of these limitations. Another genetically engineered glucocerebrosidase can now be expressed in mutant Chinese hamster ovary cells of Lec 1 strain. In this case, recombinant glycoproteins are synthesized with N-glycans with mannose residues present at all N-glycan sites. It differs from placental glucocerebrosidase by one amino acid. The generic name for

this form of the enzyme is imiglucerase. The first randomized double-blind parallel trial with mannose-terminated glucocerebrosidase from both human placental and enzyme produced in Chinese hamster ovary cells was published in 1995.[3]

The US Food and Drug Administration licensed alglucerase and imiglucerase under the Orphan Drug Act in 1983. This approval was followed by a post-approval surveillance that led to the creation of the International Collaborative Gaucher Group (ICGG)[40] and to a pharmacovigilance program.[41] Publications from the registry have contributed to the knowledge of the therapeutic effects of ERT.

Drug formulation and dosing

Imiglucerase is available as a lyophilisat powder for reconstitution, with 400 units of enzymatic activity per vial. Imiglucerase is administrated every other week (eow), by 1 hour intravenous infusion.[42] Dose is usually 60U/kg eow, but can vary between 15 U/kg eow and 120 U/kg eow. The time for starting ERT is always controversial.[43,44]

Clinical trials, and data from the ICGG Gaucher Registry

Most of the relevant efficacy and safety data for imiglucerase have been derived from clinical trials and Gaucher Registries (ICGG Gaucher Registry[17] and French Gaucher Disease Registry).

Hematological parameters
Results from clinical trials
In a pivotal clinical trial by Barton et al, twelve non-splenectomized patients were enrolled to investigate the efficacy of mannose-terminated glucocerebrosidase.[30] By 6 months hemoglobin concentration increased in all the treated patients ($P<0.003$), and after 9–12 months of treatment the hemoglobin concentration had risen to within the normal reference range in 7/12 patients. A significant increase in platelet count was noted by 6 months in 7/10 thrombocytopenic patients.

- Imiglucerase versus alglucerase 60U/kg eow: Thirty patients with untreated GD1 were enrolled in a trial comparing alglucerase and imiglucerase, given at 60U/kg eow over 9 months. The study was a double-blind parallel trial with random assignment to alglucerase or imiglucerase.[3] Hemoglobin increased by a mean of 1.71 g/dL at 6 months with no difference between the two groups. In both groups, the authors observed a lesser degree of response in patients with higher initial hemoglobin levels. Thrombocytopenia increased by 20% at 6 months

and 40% at 9 months, and this response was the same in both groups and was unrelated to the initial level of thrombocytopenia.

In an early French report of 108 patients with GD, hemoglobin levels increased rapidly by 1g/dL after 6 months of treatment and by 1.5 g/dL after 12 months (+ 24%), while platelets increased by 61% after 6 months and by 88% after 12 months.[45]

- Imiglucerase 15U/kg eow versus imiglucerase 2.5 U/kg thrice weekly: A second clinical trial compared imiglucerase at 15U/kg eow and imiglucerase at 2.5U/kg thrice weekly over 12 months, with the aim of finding cost-effective alternative regimens.[4] The mean hemoglobin increase at 12 months was 1.35 and 1.41 g/dL in each group, respectively. Similarly, the mean increase in platelet counts were + 18% and + 33.4% in each group.
- Imiglucerase every 4 weeks versus imiglucerase eow: Maintenance studies comparing the efficacy of imiglucerase every 4 weeks versus imiglucerase every 2 weeks at the same total monthly dose, revealed no statistically significant differences in hemoglobin concentration and in platelet counts between the two groups.[46]

In order to reduce the burden of ERT, eleven patients were randomly assigned either to continue ERT once every week or fortnight or to lower the frequency to once every 4 weeks at the same cumulative dose.[2] The mean changes in hemoglobin levels and platelet count were not significantly different between the two groups.

- Imiglucerase versus velaglucerase: In a study comparing imiglucerase and velaglucerase, at the same dose, in treatment-naive patients, hemoglobin increased by 1.88g/dL and platelets by 146.7 giga/L after 9 months of therapy with no statistically significant difference between the two enzymes.[47]

Results from the ICGG Gaucher Registry
In 2012, Weinreb et al reported the long-term clinical outcomes after 10 years of treatment with imiglucerase. Data were extracted from the ICGG Gaucher Registry.[48]

Five hundred and fifty seven non-splenectomized patients and 200 splenectomized patients met the inclusion criteria: of receiving imiglucerase and having clinical and dose data at the first infusion and after 10 years of follow-up. Compared with non-splenectomized patients at first infusion, splenectomized patients had lower rates of anemia and thrombocytopenia.

In non-splenectomized patients, mean hemoglobin statistically increased from 11.2 to 13.6 g/dL ($P<0.0001$) and platelet

count increased from 95.3 $\times 10^3/mm^3$ to 166.0 $\times 10^3/mm^3$ ($P<0.0001$).

In splenectomized patients, hemoglobin level improved significantly from 11.9 to 13.4 g/dL ($P<0.0001$) and platelet count increased from 237.8 $\times 10^3/mm^3$ to 311.2 $\times 10^3/mm^3$ ($P<0.0001$).

After 10 years of treatment, 90% of patients (splenectomized and non-splenectomized) had normalized hemoglobin levels. At the same time point, 90% of patients (but representing only 6/7 patients) with severe thrombocytopenia (platelets $<60 \times 10^3/mm^3$) had improved platelet count. Despite consistent improvement in platelet count in non-splenectomized patients, fewer had normal platelet count than patients who had normal hemoglobin concentrations. But all splenectomized patients with thrombocytopenia at the first infusion had normalized platelet count after 10 years of treatment.

Pediatric population: In 2008, Andersson et al[49] analyzed the clinical responses to ERT in a large international cohort of 884 children with GD1 from the ICGG to determine the effects of long-term ERT with alglucerase or imiglucerase on hemoglobin levels and platelet counts.

Among those 884 young patients, thrombocytopenia (platelet count lower than 100,000/mm^3) was present in more than half the population at baseline. More than 95% had platelet counts above this level after the study duration. Thus, these longitudinal data demonstrate the benefits of continuous ERT on both biological as well as clinical parameters for children with GD1.

Summary for hematological parameters: In treatment-naive patients, hemoglobin and platelets increased significantly with ERT. No significant difference was seen on hemoglobin and platelet concentration at 9 months when comparing imiglucerase and alglucerase at 60 U/kg eow and when imiglucerase was administrated at 15U/kg eow or 2.5 U/kg three times a week. Even if platelets increased significantly, this normalization in non-splenectomized patients was less frequent than normalization of hemoglobin level.

In maintenance studies, no difference in hemoglobin level and platelet count were seen when imiglucerase was administrated every 2 weeks or every 4 weeks with the same total dose.

Visceral parameters
Results from clinical trials
In the pivotal clinical trial, spleen volume was reduced by a mean of 33% in all patients after 6 months of ERT while hepatic volume decreased significantly by 16%–22% in most treated patients.[30]

- Imiglucerase versus alglucerase 60U/kg every eow: In the clinical trial published by Grabowsky comparing alglucerase and imiglucerase, hepatic volume decreased by 21.4% ±10.8% with imiglucerase and by 16.4% ±8.8% with alglucerase after 9 months of treatment; splenic volume decreased by 47.1% ±13.7 with imiglucerase and by 42.2% ±6.9 with alglucerase.[3] The greatest changes were seen in patients with largest initial spleen and hepatic volumes.

In the French cohort, spleen size reduced by 44% after 6 months and by 51% after 12 months, and liver size reduced by 10% after 6 months and by 12% after 12 months of ERT.[45]

- Imiglucerase 15U/kg eow versus imiglucerase 2.5 U/kg thrice weekly: In the clinical trial performed at Shaare-Zedek Medical Centre, the mean reduction in spleen volume was 38% in the group receiving 15U/kg eow and 35% in the group receiving 2.5U/kg thrice weekly ($P=0.06$). The mean reduction of liver volume was 14% and 15% in each group respectively ($P=0.06$).[4]

- Imiglucerase every 4 weeks versus imiglucerase eow: In stabilized patients, comparing imiglucerase eow or every four weeks[46] (with same total dose), no significant difference was seen between the two groups of patients. However, in the de Fost et al study, one patient with low dose therapy experienced a liver ratio that increased by 12%, and he also complained about fatigue and abdominal discomfort; so, the initial dosing regimen had to be retaken.[2]

- Imiglucerase versus velaglucerase: In the study comparing imiglucerase and velaglucerase, liver volume was reduced from a median range of 1.6% of the body weight at baseline to 1.2 at month 9 for imiglucerase while spleen volume was reduced from a median of 7.0% of body weight at baseline to 4.5 at month 9 with no difference between imiglucerase and velaglucerase.[47]

- Imiglucerase versus eliglustat: In a Phase III, randomized, multinational, open-label, non-inferiority trial, comparing oral eliglustat or imiglucerase infusions over a 12 month period in patients already treated with intravenous ERT, the authors concluded that oral eliglustat maintained hematological and organ volume stability in adults with GD1.[50]

Results from ICGG Gaucher Registry
With regard to liver volumes, results from ICGG Gaucher Registry show a statistically significant decrease in splenectomized patients ($P<0.001$) with mean volume decreasing

from 2.2 multiple of normal (MN) to a median of 1.0 MN.[25] The response was similar to that seen in non-splenectomized patients, with volume decreasing from 1.8 to 1MN. Moreover, non splenectomized GD1 patients demonstrated significant improvement in spleen size from 19.4 to 5.2 MN after 10 years of imiglucerase infusion ($P<0.0001$).

Pediatric population: In the pediatric subgroup, visceral manifestations were also evaluated. Among these 884 children, liver and spleen volumes decreased concurrently with biological improvement. Thus, these longitudinal data illustrate the benefits of continuous ERT on both biological and clinical parameters for children with GD1.[49]

Summary for visceral parameters: In treatment-naive patients, liver and spleen volume reduced after 9 months of treatment with imiglucerase. The greatest changes were seen in patients with largest initial spleen and hepatic volumes. In some cases, this decrease was also observed with low dose of ERT, and was maintained when ERT was perfused every 4 weeks.

Bone disease
Results from clinical trials
In the first clinical trial with placental glucocerebrosidase, published in 1990, Barton et al showed radiographic skeletal improvement (with increased mineralization) in a child with GD1.[1]

He also published a series in 1991, in which there was an increase in trabecular bone in the metaphyseal areas and a resolution of endosteal scalloping in three out of 12 patients. He was the first to observe that the skeletal response took the longest to develop.[30]

However, Beutler et al, in 1991, did not find any change in radiological appearance in any of the patients. One of the patients continued to have fleeting bone pains, and one who had been subject to severe bone pain still suffered from moderate pain after 4 months of treatment.[39]

- Imiglucerase versus alglucerase 60U/kg eow: Grabowski et al in 1995, did not mention any skeletal results after 9 months of comparing alglucerase and imiglucerase.[3]
- Imiglucerase 15U/kg eow versus imiglucerase 2.5 U/kg thrice weekly: Unlike the first results on bone by Grabowski et al, Zimran in 1995, showed improvement in the fatty signal after 12 months of treatment, either at 15U/kg once fortnightly, or 2.5 U/kg thrice weekly.[51]

More recently, Sims et al described the evolution of bone disease with imiglucerase.[5] This was a multicenter, open-label, single cohort, prospective study using within-patient

to baseline comparisons to evaluate the effectiveness of imiglucerase in treating skeletal manifestations of GD1 in patients who had not previously received enzyme therapy. Patients had to have had at least one bone crisis, osteoarticular necrosis, medullary infarction, lytic lesions, pathological fractures, fractures related to GD, marrow infiltration, a T score <-1.0 or Z score <-1.5 or Erlenmeyer flask deformity. Thirty three patients were included and 27 had a late evaluation at 24 months. This prospective study confirmed that ERT with imiglucerase improved the major symptomatic manifestations of Gaucher skeletal disease, bone crisis and bone pains, decreased the risk of skeletal events (infarction, lytic lesions, and fracture), and increased lumbar spine and femoral neck bone marrow density (BMD) during the first 4 years of treatment. These results suggested that early initiation of treatment in symptomatic patients can substantially alleviate discomfort and may prevent potentially disabling bone complications and overall morbidity.

Maas et al also demonstrated a decreased bone marrow burden score in 11/12 patients treated with imiglucerase.[6]

In the de Fost et al maintenance study, one patient with low frequency maintenance therapy experienced a reduction of quantitative chemical shift imaging.[2]

ICGG and French Gaucher Registry
Mistry et al, in 2011, reported data from ICGG Gaucher Registry consisting of patients between the ages of 5 and 50 years treated with imiglucerase.[52] Lumbar spine bone mineral density at baseline and for up to 10 years on imiglucerase were analyzed in patients with GD1, and four groups were determined: children, adolescents, young adults, and older adults. Pretreatment, low BMD was prevalent in all age groups, most strikingly in adolescents. In children with dual energy X-ray absorptiometry (DXA) Z scores ≤-1 at baseline, imiglucerase therapy for 6 years resulted in improvement of mean DXA Z scores from -1.38 (95% confidence interval [CI], -1.73 to -1.03) to -0.73 (95% CI, -1.25 to -0.21); in young adults DXA Z scores improved from -1.95 (95%CI, -2.26 to -1.64) to -0.67 (95% CI, -1.09 to -0.26). BMD also improved in older adults, but the magnitude of improvement was lower compared to younger patients.

The effect of ERT with imiglucerase on BMD in GD1 was studied using BMD data from the ICGG Gaucher Registry.[53] Data were analyzed for 160 untreated patients and 342 ERT-treated patients. Imiglucerase significantly improved BMD in patients with GD, with 8 years of ERT leading to normal BMD.

In the 10 year analysis published by Weinreb et al, imiglucerase also positively affected skeletal symptoms. For non-splenectomized GD1 patients with bone pain, 57.1% no longer reported bone pain after 10 years of imiglucerase use. For patients with bone crisis before initiation of treatment, 92.6% did not report a bone crisis after 10 years of treatment. For splenectomized patients, the percentage of patients with bone pain decreased by 27%, and by 32% for bone crisis.[48]

In 2009, Mistry et al, assessed the relationship between ERT with imiglucerase and incidence of AVN in GD1, and determined whether the time interval between diagnosis and initiation of ERT influences the incidence rate of AVN. He observed a decreased incidence of 50% of de novo posttreatment AVN in GD1 patients in whom imiglucerase infusions were initiated within 2 years of diagnosis. Moreover, in some patients, he concluded that later initiation of therapy following diagnosis could potentially result in skeletal pathology that may cause irreversible morbidity and disability.[43]

In 2010, Stirnemann et al analyzed a cohort of 73 GD1 patients. Among them, 62 were treated with imiglucerase. The aim of the study was to evaluate the frequency of bone events during two periods: diagnosis to ERT and from ERT to the closing date. The authors determined that the probability of bone events occurring at 10 years was 22.4% before treatment and 20.0% during ERT.[7]

In the pediatric subgroup from ICGG, median height Z score was −1.4 at baseline. After 8 years of treatment the mean bone mineral density Z score was −0.34 at baseline, and values normalized within 6.6 years of treatment; 70% of patients reported a bone crisis before treatment and in the first 2 years of treatment, but no bone crises were reported after 2 years of ERT. Less than 2.5% of patients experienced bone crises during ERT.[49]

Summary for bone disease: Imiglucerase has a positive impact on bone manifestations in GD1, mainly on BMD, bone pain and bone marrow infiltration. However, the risk of bone events does not totally disappear despite imiglucerase treatment.

Biomarkers

Several biomarkers are in widespread use for monitoring GD, such as: tartrate-resistant acid phosphatase (TRAP), angiotensin-converting enzyme (ACE), chitotriosidase,[54] ferritin,[55] pulmonary and activation-regulated chemokine (PARC/CCL18/macrophage inhibitory protein-4)[56] and more recently glucosylsphingosine.[9,57] Recently a link between lysolipids, immune activation and GD associated gamopathies or B cell lymphoma has been shown.[58,59]

The earlier clinical trials did not mention these tests as they were not available at that time.

In 1998, Czartoryska et al presented the results of monitoring ERT with chitotriosidase for up to 27 months in seven patients with GD1. They showed a decrease dependent on continuation of treatment.[10]

Data from the French Gaucher Disease Registry[7] reported that imiglucerase decreased all biomarkers tested (chitotriosidase, TRAP, ACE, ferritin). For patients who received the full treatment dose (ie 60U/kg eow), ferritin and TRAP decreased faster but chitotriosidase and ACE declined more slowly.

These results were confirmed by those of Cabrera-Salazar et al.[60]

More recently, Dekker et al explored a new biomarker, plasma glucosylsphingosine, and its relation to phenotype, storage cell markers and therapeutic response. Imiglucerase resulted in rapid decrease of glucosylsphingosine (chitotriosidase and CCL18 were comparably reduced).[61]

In patients naive to treatment, chitotriosidase, CCL18 and glucosylsphingosine decreased comparably upon eliglustat and ERT treatment (imiglucerase or velaglucerase) while the response to miglustat was less.[8] After 2 years, median decrease of chitotriosidase was 89%, 88% and 37% for eliglustat, ERT and miglustat treatment respectively; decrease of CCL18 was 73%, 54%, and 10%; decrease of glucosylsphingosine was 86%, 78%, and 48%.

Summary for biomarkers: Imiglucerase significantly reduced all known biomarkers, in particular glucosylsphingosine, which seems to be one of the more sensitive and specific biomarkers.

Therapeutic goals

Therapeutic goals were established in 2004.[62] For GD1, therapeutic goals were believed to be meaningful but not necessarily in the normal range (Table 1). For example, the aim is to obtain a 50% reduction of the spleen volume but not necessarily to normalize it.

As of June 1, 2007, of the 4187 patients with GD1 enrolled in the ICGG Gaucher Registry, complete data for six therapeutic goals at first infusion and at 4±1 years were available for 195 patients.[11] The proportion of patients who achieved therapeutic goals increased from the initiation of therapy to 4 years. Patient who reached goals for all six parameters increased from 2.1% at first infusion to 41.5% at 4 years. Patients who reached goals for five parameters increased from 12.8% to 76.9%. On average, patients receiving at least 31U/kg during a 4-week period were more likely to achieve a greater number of therapeutic goals at year 4, than those receiving lower dose.

Table 1 Therapeutic goals

Parameter	Goal
Hemoglobin	Increase hemoglobin levels within 12–24 months: • ≥11.0 g/dL for women and children • ≥12.0 g/dL for men • Reduce dyspnea, fatigue, angina
Platelets	Increase platelet count during first year of treatment to prevent surgical, obstetrical and spontaneous bleeding Patients with splenectomy: • Normalization of platelet count after 1 year Patients with intact spleen • Moderate thrombocytopenia: increase by 1.5–2.0 fold by year 1 • Severe thrombocytopenia: increase by 1.5 fold by year 1, doubling by year 2
Hepatomegaly	Reduce and maintain the liver volume to 1.0–1.5 times normal Reduce liver volume by 20%–30% within year 1–2, and by 30%–50% by year 3–5
Splenomegaly	Reduce and maintain spleen volume to ≤ 2 to 8 times normal Reduce spleen volume by 30%–50% within year 1, and by 50%–60% by year 2–5
Skeletal pathology	Lessen or eliminate bone pain within 1–2 years Prevent bone crises Prevent osteonecrosis and subchondral joint collapse Improve BMD
Growth (pediatry)	Normalize growth within 3 years of treatment Achieve normal onset puberty
Pulmonary involvement	Reverse hepatopulmonary syndrome and dependency on oxygen Improve pulmonary hypertension
Functional health	Improve physical function for carrying out normal daily activities
Well-being	Improve scores from baseline of a validated quality of life instruments within 2–3 years

Note: Adapted from Pastores.[62]
Abbreviation: BMD, bone marrow density.

However, in a single-center experience, low-dose imiglucerase achieved most of the hematology and visceral goals. The authors reported results from 164 patients who received 4 years of uninterrupted treatment with imiglucerase at a constant dosage of 15U/kg eow for adults and 30U/kg eow for children. At the end of the 4 years, there was a significant improvement in each of the parameters from the baseline (P=0.000), and 15.2% achieved therapeutic goals in both hematological and visceral parameters within 4 years.[12]

Summary for therapeutic goals: Most of the therapeutic goals were reached with imiglucerase, and low-dose imiglucerase helped achieve hematological and visceral goals.

Growth

GD1 is associated with a high prevalence of failure to thrive, being underweight and reduced height in children and adolescents.[63] Growth deceleration occurs between 3 and 5 years of age and height increase diminishes in later childhood; however at the end of the growth period the difference between the final and the target height were not significant.[13] Therefore, numerous studies have investigated the impact of imiglucerase on growth retardation.[64] In 2008, Andersson et al determined the effects of long-term ERT with alglucerase or imiglucerase on linear growth.[49] Among the 884 patients, median height Z score was –1.4 at baseline. After 8 years of treatment, the median height approximated the median value for the normal population.

Moreover, treatment interruption led to growth retardation, and this was demonstrated by Drelichman et al.[65] In this study, five of 32 children experienced treatment interruptions. Before ERT, four children had growth retardation. After 1–7 years of ERT, all children were growing normally. After 15–36 months of ERT interruption, three children experienced growth retardation.

Summary for growth: Imiglucerase has an important corrective effect on height.

Quality of life

Health-related quality of life (HRQOL) can be diminished in patients with GD1 owing to the debilitating clinical manifestations of this chronic disease.[66] The effect of ERT on HRQOL was investigated with alglucerase in 1999, and results indicated significant improvement in 7 of 8 Short Form scale scores beginning at 18 months of therapy (P<0.05 to 0.001). The Short Form-36 Health Survey (SF 36) scale that showed improvement first was vitality (energy level and fatigue) at 6 months of therapy (P<0.01).[67]

Patients who had been receiving ERT experienced four times more improvement in general HRQOL in comparison with recalled changes over a 4 year period among adults in the general population (P<0.001).[68]

Weinreb et al investigated the role of imiglucerase on HRQOL of patients with GD1 and bone involvement. Thirty-two GD1 patients with skeletal manifestations were evaluated for HRQOL before and after biweekly imiglucerase (at 60 U/kg). Mean baseline SF-36 physical component summary scores were diminished relative to the US general population norms. Low scores were more common in patients with medullary infarction or lytic lesions. Statistically significant improvements were observed for all eight SF-36 subscales after 2 years of treatment. Imiglucerase had a significant positive impact on HRQOL of GD1 patients with skeletal disease, including those with bone infarcts, lytic lesions, and osteonecrosis.[14]

Moreover, in this study evaluating some aspects of HRQOL during the availability shortage of imiglucerase, patients reported a worsening in selected aspects of their life (energy, work or school performance, concentration, memory, and social life). More than 50% of patients declared at least one subjective problem that arose 3, 6, 9 and 12 months after the drug reduction (56%, 65%, 70%, 58%, respectively).[15]

Summary for quality of life: Imiglucerase had a significant positive impact on HRQOL of GD1 patients especially in patients with skeletal disease.

Lung involvement

Symptomatic lung involvement in GD is rare and is associated with patients having more severe disease. To explore the impact of imiglucerase on this manifestation, Goitein et al described eight of 411 patients with lung involvement.[69] The authors concluded that if some patients benefited significantly from ERT, they did not show a normalization in pulmonary function or lung architecture. In some cases, imiglucerase associated with a specific therapeutic seemed to improve pulmonary hypertension, but this effect was inconsistent.[70]

Safety and tolerability

The Genzyme Corporation maintains a global post-marketing adverse event reporting system and a voluntary immuno-surveillance program to detect any previously unrecognized safety concerns and to understand the long-term safety and immunogenicity profile of imiglucerase.[41]

No serious adverse events were reported either in clinical trials or in the ICGG Gaucher Registry.[1,30,39] During the pivotal clinical efficacy trial,[30] the treatment induced no antibody responses to the exogenous glucocerebrosidase.

In the comparative trial between alglucerase and imiglucerase, antiglucocerebrosidase antibodies developed in six patients out of 15 receiving alglucerase and in three out of 15 receiving imiglucerase. Patients in the imiglucerase group developed antibodies by 3–6 months but no major immunologic effects occurred in either group. Moreover, diminished therapeutic response was not apparent in patients positive for antibodies.[3] This excellent safety profile was confirmed by all the other clinical trials.[4,41]

Adverse events considered to be related to imiglucerase were usually mild to moderate. Among them, chills, pyrexia, pruritus, rashes, urticaria, and dyspnea were commonly observed. Between 1994 and 2004, only three patients needed to stop therapy because of infusion reactions.[41] Infusion related side effects were managed by lowering infusion rate or pretreatment with antihistamines.[71] Diminished therapeutic response was not apparent in patients positive for antibodies. Arthritic-like pain in the small joints of the hands and/or feet after initiation of imiglucerase treatments has been reported.[72] No link between imiglucerase and pulmonary hypertension has been established.

Switch and non-inferiority studies comparing imiglucerase and other ERTs such as velaglucerase and taliglucerase confirmed that imiglucerase was well tolerated.[73,74,75]

This excellent tolerance has allowed home therapy in many countries to improve patients' quality of life.[76]

Pregnancy

Imiglucerase has been assigned to pregnancy category C by the US Food and Drug Administration.[77] Animal studies have not been conducted with imiglucerase. There are no controlled data regarding the use of this drug in human pregnancy. Limited experience from 150 pregnancy outcomes suggest that use of imiglucerase is beneficial to control the underlying GD in pregnancy.[71,78] Furthermore, these data indicate no malformative toxicity for the fetus by imiglucerase although the statistical evidence is low. It is not known whether imiglucerase passes via the placenta to the developing fetus. Enzyme therapy may have benefits in reducing menorrhagia, spontaneous abortions and complications associated with delivery and the postpartum period.[79] In pregnant Gaucher patients and those intending to become pregnant, a risk-benefit treatment assessment is required for each pregnancy. Patients who have GD and become pregnant may experience a period of increased disease activity during pregnancy and the puerperium.[80] Treatment naive women should be advised to consider commencing therapy prior to conception in order to attain optimal health. In women receiving imiglucerase, continuation of therapy throughout pregnancy should be considered. Close monitoring of the pregnancy and clinical manifestations of GD is necessary.

There have been no published reports regarding the excretion of imiglucerase into human breast milk and regarding its effects on the nursing infant. One case report mentioned that a small amount of imiglucerase was found to be excreted into human breast milk, but only in the first milk produced after infusion.[81]

Conclusion

Imiglucerase is still the current standard treatment for GD1. Recently developed ERTs and SRT have not shown better results (nor less good) on hematological, visceral, and bone parameters. Imiglucerase also enhances quality of life, and reverses growth retardation. It is safe and well tolerated.

Individualized dosing will probably be implemented in the near future owing to the better understanding of GD1 pathophysiology and mechanism of action of imiglucerase. Imiglucercase will also improve patients' quality of life and help in decreasing the therapeutic cost.

Disclosure

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