Long-term hematological, visceral, and growth outcomes in children with Gaucher disease type 3 treated with imiglucerase in the International Collaborative Gaucher Group Gaucher Registry

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A B S T R A C T

In Gaucher disease (GD), deficiency of lysosomal acid β-glucosidase results in a broad phenotypic spectrum that is classified into three types based on the absence (type 1 [GD1]) or presence and severity of primary central nervous system involvement (type 2 [GD2], the fulminant neuropathic form, and type 3 [GD3], the milder chronic neuropathic form). Enzyme replacement therapy (ERT) with imiglucerase ameliorates and prevents hematological and visceral manifestations in GD1, but data in GD3 are limited to small, single-center series. The effects of imiglucerase ERT on hematological, visceral and growth outcomes (note: ERT is not expected to directly impact neurologic outcomes) were evaluated during the first 5 years of treatment in 253 children and adolescents (<18 years of age) with GD3 enrolled in the International Collaborative Gaucher Group (ICGG) Gaucher Registry. The vast majority of GBA mutations in this diverse global population consisted of only 2 mutations: L444P (77%) and D409H (7%). At baseline, GD3 patients exhibited early onset of severe hematological and visceral disease and growth failure. During the first year of imiglucerase treatment, hemoglobin levels and platelet counts increased and liver and spleen volumes decreased, leading to marked decreases in the number of patients with moderate or severe anemia, thrombocytopenia, and hepatosplenomegaly. These improvements were maintained through Year 5. There was also acceleration in linear growth as evidenced by increasing height Z-scores. Despite devastating disease at baseline, the probability of surviving for at least 5 years after starting imiglucerase was 92%. In this large, multinational cohort of pediatric GD3 patients, imiglucerase ERT provided a life-saving and life-prolonging benefit for patients with GD3, suggesting that, with proper treatment, many such severely affected patients can lead productive lives and contribute to society.

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1. Introduction

Gaucher disease (GD) is a pan-ethnic lysosomal storage disorder caused by autosomal recessive mutations in GBA, which encodes acid β-glucosidase (EC 3.2.1.45; glucocerebrosidase) [1]. GD was the first lysosomal storage disorder to be described, and the metabolic defect was identified from seminal studies by Dr. Roscoe Brady and colleagues at the National Institutes of Health in the 1960s [2,3]. The enzymatic defect in GD results in lysosomal accumulation of substrates, primarily glucosylceramide and its lysolipid derivative, glucosylsphingosine, that in turn lead to lysosomal dysfunction, cellular dysfunction, and immune activation [4], giving rise to a complex multisystemic disorder. Lipid substrates accumulate most prominently in macrophages, which assume a characteristic ultrastructural appearance eponymously...
described as Gaucher cells that infiltrate the spleen, liver, bone marrow, and occasionally the lungs. In addition, neuronal death in perivascular regions of the brain is a primary pathologic process in the type 2 (GD2) and type 3 (GD3) variants [5]. Accumulation of glucosylceramide-laden macrophages in the spleen, liver, and bone marrow are directly associated with visceral and hematological manifestations, but in GD2 and GD3, neuronal injury initiated by Gaucher lipids is implicated in disease pathophysiology [4].

GD has traditionally been classified into three broad clinical phenotypes based on the absence or presence and severity of primary central nervous system (CNS) involvement [6]. Type 1 (GD1) is characterized by splenomegaly, blood dyscrasias, orthopaedic complications and lack of neurologic involvement. GD2 is characterized by CNS involvement with onset within the first months/year of life, hepatosplenomegaly, and rapidly progressive neurodegenerative disease typically leading to death by 2 years of age. In contrast in GD3, there is early onset of milder neurologic involvement that progresses slowly. Patients with GD3 typically have marked visceral and hematological disease, and some exhibit cardiac complications [7,8]. While all forms of GD exist along a clinical spectrum, GD3 shows wide phenotypic variation, ranging from early onset of severe neurological manifestations that are reminiscent of GD2 to late-onset neurological manifestations [9–11]. Neuronopathic GD (GD2 and GD3) is rare, with a prevalence estimated at <1 in 100,000 individuals [12], however, the worldwide prevalence varies substantially. In GD patients having predomnantly from the United States, Europe and Israel, 5% were classified as GD3 and 1% as GD2 [13], whereas in countries such as Egypt, Korea, Taiwan, and China where GD1 is rare, at least one-third of GD patients had GD2 or GD3 phenotypes [14–18].

All forms of GD were considered life-limiting until the pioneering studies of Dr. Roscoe Brady and colleagues led to the approval of macrophage-targeted enzyme replacement therapy (ERT) in 1991 with pla-cental mannose-terminated glucocerebrosidase (alglucerase, Ceredase®, Genzyme Corporation, Cambridge, MA) [19] and in 1994 with the recombinant form (imiglucerase, Cerezyme®, Genzyme), which was shown to have similar clinical effect and likely equivalent pharmacokinetics to alglucerase [20]. In GD1 patients, ERT is highly effective at reversing the visceral and hematologic manifestations as well as certain aspects of skeletal disease, including the risk of avascular osteonecrosis, osteopenia, bone pain and growth failure [19,21–29]. More recently, oral substrate reduction therapy (i.e., miglustat and eliglustat) has become available with similar therapeutic effects reported for eliglustat (Cerdelga®, Sanofi Genzyme) [30–36]. None of the currently available therapies, however, are effective in treating the neuronopathic disease manifestations. In GD2, progression of CNS involvement is overwhelming, with fatigue in infancy and little impact of ERT. In GD3, where phenotypic variability is wide and progression of neurological manifestations far slower, ERT has the potential to lead to favorable outcomes by alleviating the visceral and hematological aspects of the disease and improving quality of life. Due to the rarity of GD3, reports of hematological and visceral efficacy of ERT in GD3 have been limited to small single-center series [14,37–47]. The long-term clinical effects of imiglucerase in GD3 have not yet been evaluated in a large, multinational cohort such as the International Collaborative Gaucher Group (ICGG) Gaucher Registry.

Here, imiglucerase ERT outcomes are provided for the largest GD3 cohort to date who began treatment during childhood or adolescence. The primary objectives of the current study were to: (1) characterize the genotypes, phenotypes and demographics of the current ICGG Registry cohort of GD3 patients treated with imiglucerase, (2) describe the visceral, hematological, and growth outcomes reported for these patients within the first 5 years of treatment, and (3) evaluate survival and cause of death in this cohort. Neurological manifestations in the ICGG Registry population have been reported previously [48].

2. Methods
2.1. The ICGG Registry
Established in 1991, the ICGG Registry (www.clinicaltrials.gov, NCT00358943) is the largest ongoing, longitudinal, international database of demographic, biochemical and clinical outcome data from patients with GD. The Registry is governed by an international group of experts in Gaucher disease with operational support provided by Sanofi Genzyme. The Registry is strictly observational; patients in the Registry undergo clinical assessments and receive care as determined by their treating physicians. Participation in the Registry is voluntary and open to all patients worldwide, irrespective of treatment status or choice. As of 2015, physicians from >60 countries have submitted anonymized data on >6000 patients representing some 54,000 patient-years of follow-up experience [49].

2.2. Study design
We identified all GD3 patients in the ICGG Registry as of 4 September 2015. Patients meeting the inclusion criteria for the current study were diagnosed as having GD3 by the reporting physician; had received alglucerase/imiglucerase as the initial primary therapy for Gaucher disease; had initiated treatment before 18 years of age; and had data reported for birth date, gender, splenectomy status, date of splenectomy (among splenectomized patients), date of diagnosis, date of first infusion, and initial treatment dose. In this report “imiglucerase” is used to denote patients who received ERT with either imiglucerase (recombinant enzyme) or alglucerase (placental-derived enzyme), as they have been shown to be therapeutically equivalent treatments [20]. Patients were evaluated for hematological parameters, visceral parameters, and height, at baseline (i.e., pre-treatment up to +2 wks after initiation of treatment) and in the five years following treatment initiation; patients were included if they had a baseline assessment, plus one or more follow-up assessments in the 5 years following treatment initiation.

This study was conducted according to the principles of the Declaration of Helsinki (2013) [50]. Informed consent was obtained from all subjects or their parent(s) or guardian(s). The data are reported in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [51].

2.3. Study assessments
Demographic information for the GD3 study cohort includes gender, age at diagnosis, age at treatment initiation, splenectomy status (i.e., intact spleen or total or partial splenectomy) and country of enrollment into the Registry. Genotypes are reported by the treating physicians. Information on the exact method of genotyping is not collected by the ICGG Registry, and includes methods ranging from specific allele amplification to full GBA sequencing [52]. The time-weighted average dose of imiglucerase was calculated by taking an average of the reported doses at the different time points multiplied by the length of time on that dose within the 5-year evaluation period. The length of time on a dose was calculated by the difference in days from the start of one dose to the start of a new dose.

Anemia is reported as “present” or “absent,” according to the following age and gender norms for hemoglobin concentration: <12 g/dL for males older than 12 years; <11 g/dL for females older than 12 years; <10.5 g/dL for children ages >2 to 12 years; <9.5 g/dL for children ages 6 months to 2 years; <10.1 g/dL for children younger than 6 months of age. Thrombocytopenia is reported categorically as “mild or none” (≥120 × 10^9/L), “moderate” (60 to <120 × 10^9/L) and “severe” (<60 × 10^9/L).

Liver and spleen volumes were measured volumetrically by magnetic resonance imaging, computed tomography, or ultrasonography and...
reported as multiples of normal (MN) organ size predicted for body weight [19]. A standard formula was used to convert ultrasound measurements to volume equivalents [53]. Hepatomegaly is reported categorically as “mild or none” (≤ 1.25 MN), “moderate” (> 1.25 to ≤ 2.5 MN) or “severe” (> 2.5 MN). For patients with intact spleens, splenomegaly is reported categorically as “mild or none” (≤ 5 MN), “moderate” (> 5 to ≤ 15 MN) and “severe” (> 15 MN).

Age and gender-adjusted height Z-scores were calculated based upon individual patient height compared with normative reference growth charts from United States Centers for Disease Control (CDC) Prevention [54].

Vital status, date of death, and cause of death were voluntarily reported by the treating physician. A Kaplan-Meier survival analysis was performed to evaluate survival from treatment initiation until death, study withdrawal, or last recorded medical assessment.

2.4. Statistical analysis

All analyses were descriptive in nature with no inferential testing. Hematological parameters, visceral parameters, and height were evaluated at six time points based on the duration of imiglucerase treatment: baseline (value closest to initiation of treatment up to +2 wk after initiation of treatment); > 0 to ≤ 1 year; > 1 to ≤ 2 years; > 2 to ≤ 3 years; > 3 to ≤ 4 years; > 4 to ≤ 5 years. If more than one assessment was reported within a time period, the most recent value was used. Included patients had baseline values as well as values during one or more of the five possible follow-up periods. Thus, the number of patients represented in the follow-up periods varies based on the available assessments. Kaplan-Meier survival estimates were calculated extending up to 20 years after initiation of treatment; while treatment status was not evaluated within a time period, the most recent value was used. Included patients had baseline values as well as values during one or more of the five possible follow-up periods. Thus, the number of patients represented in the follow-up periods varies based on the available assessments. Kaplan-Meier survival estimates were calculated extending up to 20 years after initiation of treatment; while treatment status was not evaluated

3. Results

3.1. Patient disposition

As of 4 September 2015, 289 GD3 patients in the ICGG Registry had their first imiglucerase treatment at <18 years of age. Of these patients, 36 were excluded from this analysis because they were missing a diagnosis date (n = 7), had undergone partial or total splenectomy after their first ERT treatment or were splenectomized but missing the date of splenectomy (n = 5), or had no information reported on their splenectomy status (n = 1) or initial ERT dose (n = 23). A total of 253 patients met the inclusion criteria and were included in the present analysis. The average number of follow-up values reported per patient was as follows (non-splenectomized, splenectomized): hemoglobin/anemia (3.5, 4.0), platelet count/thrombocytopenia (3.5, 4.0), liver volume/hepateomegaly (3.1, 2.8), spleen volume/splenomegaly (3.1), and height Z-scores (3.4, 4.1).

3.2. Demographic, genotypic, and treatment characteristics

Table 1 summarizes the demographic, geographic, and genotypic characteristics of the GD3 patient cohort. Both genders were equally represented, and most patients (87%) had intact spleens. More than half (57%) of patients were diagnosed before 2 years of age (median 1.7 years) and received their first imiglucerase infusion at a median age of 2.3 years. The majority of patients began treatment soon (median 0.3 years) after being diagnosed, though the interval from diagnosis to first infusion ranged from 0.3 to 12.4 years. The time-weighted mean (standard deviation) biweekly dose was 66.4 (29.12) U/kg with a median of 60.0 U/kg (range 12.0 to 240 U/kg). Of the 34 countries represented, the majority of patients were from European countries (32.4%), the United States (26.9%) and Egypt (20.9%). Patients from the JAPAC region (China, India, Japan, Korea, Malaysia, Philippines) and Latin America accounted for 10.3% and 5.9% of patients, respectively. Among the 202 patients with GBA genotype data reported, 163 (80.7%) had at least one L444P allele, with 122 (60.4%) being homozygous for L444P. Thirty (14.9%) patients with genotype data had at least one D409H allele, with 11 (5.4%) being homozygous for D409H. Overall, nearly 90% (n = 180) of patients with genotype data reported were homozygous or compound heterozygous for L444P or D409H. The majority (93%) of splenectomized patients had at least one L444P allele, and none had a D409H allele.

The wide range of disease severity in this population of GD3 patients is illustrated in box plots of hemoglobin level, platelet count, spleen volume, liver volume and height Z-score (Online Supplemental Figs. 1–9).

3.3. Hematologic outcomes

Baseline hemoglobin levels were reported for 163 non-splenectomized (mean 9.6 ± 1.92 g/dL) and 30 splenectomized (mean 10.1 ± 1.90 g/dL) patients (Table 2). Among non-splenectomized patients, mean hemoglobin levels increased to 11.4 ± 1.68 g/dL (n = 143) in Year 1 and reached 12.0 ± 1.46 g/dL (n = 96) in Year 5. Anemia was present in 62.6% of non-splenectomized patients at baseline, which decreased to 11.6% at Year 3 (n = 95) and 11.5% at Year 5 (n = 96) (Fig. 1A). Similar trends were seen in splenectomized patients, with an increase in hemoglobin to 11.8 ± 1.68 g/dL (n = 26) in Year 1 that was maintained at or above this level through Year 5 (12.0 ± 1.87, n = 25). At baseline, 46.7% of splenectomized patients were considered anemic, which decreased to 19.2% at Year 1 and was maintained at or below 20% through Year 5 (Fig. 1A).

Baseline platelet counts were reported for 161 non-splenectomized (mean 127.4 ± 99.24 × 10^9/L) and 30 splenectomized (mean 286.9 ± 162.59 × 10^9/L) patients (Table 2). Among non-splenectomized patients, mean platelet counts increased to 182.0 ± 94.32 × 10^9/L (n = 139) during Year 1 and 218.0 ± 79.60 × 10^9/L (n = 95) by Year 5. The proportion of non-splenectomized patients with severe or moderate thrombocytopenia decreased from 62.7% at baseline to 9.5% at Year 5 (Fig. 1B). Among splenectomized patients, mean platelet counts increased to 447.7 ± 127.94 × 10^9/L (n = 26) during Year 1 and were maintained at 382.9 ± 125.36 × 10^9/L (n = 24) at Year 5. Among the 16.7% of splenectomized patients (n = 5) who had moderate or severe thrombocytopenia at baseline, all had mild or no thrombocytopenia at Years 1 through 5 (Fig. 1B).

3.4. Visceral outcomes

Baseline liver volumes were available for 49 non-splenectomized (mean 2.4 ± 1.28 MN) and 9 splenectomized (mean 2.4 ± 1.45 MN) patients (Table 2). Mean liver volume decreased during Year 1 to 1.7 ± 0.80 MN in non-splenectomized patients (n = 33) and 1.7 ± 1.17 MN in splenectomized patients (n = 7) and continued to decrease over time to 1.2 ± 0.33 MN in non-splenectomized patients (n = 25) and 0.8 ± 0.09 MN in splenectomized patients (n = 3) at Year 5. The proportion of non-splenectomized and splenectomized patients with severe or moderate hepatomegaly decreased steadily from baseline to Year 5 (Fig. 1C). Baseline spleen volumes were available for 63 of the non-splenectomized patients (mean 34.6 ± 15.26 MN). >90% (n = 57) of these patients had severe splenomegaly at baseline. Spleen volume steadily decreased from baseline to Year 5 with the mean reaching 11.9 ± 5.86 MN (n = 33, Table 2) and only 27.3% (n = 9) of patients remaining with severe splenomegaly (Fig. 1D).

3.5. Height Z-scores

Baseline height Z-scores were available for 140 non-splenectomized patients (mean − 1.8 ± 1.43) and 26 splenectomized patients (mean
−3.0 ± 1.81) (Table 2). Short stature (Z-score < −2.0) at baseline was present in 37.9% and 76.9% of patients, respectively. Following imiglucerase treatment, there was an increase in growth (i.e., “catch-up growth”) as evidenced by a progressive increase in height Z-scores in both groups. Non-splenectomized and splenectomized patients achieved mean Z-scores of −1.2 ± 1.20 (n = 82) and −1.5 ± 1.32 (n = 21), respectively, after 5 years of treatment. The corresponding proportions of patients with short stature after 5 years decreased to 24.4% and 42.9%, respectively.

3.6. Survival

The survival analysis included 253 patients with a total of 2111.6 patient-years of follow-up. Thirty-seven (14.6%) patient deaths were reported during up to 20 years of follow-up with a median duration of 7.5 person-years. The age at death ranged from 0.9 to 29.0 years, with a mean (SD) of 9.5 (6.91) years for nonsplenectomized patients (n = 21) and 19.1 (4.18) years for splenectomized patients (n = 4); age at death was not specified for n = 2 patients. In the Kaplan-Meier survival analysis, the probability of surviving for at least 5 years after starting ERT was 92%. Similarly, the probability of surviving 10 years after starting ERT was 82% and surviving 20 years after starting ERT was 76% (Fig. 2). The most common causes of death were progression of neurological disease (n = 8; all patients had at least one L444P allele) and cardiac disease (n = 6; 4 were D409H homozygotes and 2 were L444P homozygotes). Table 3 shows the mean age at diagnosis, age at first infusion, age at death and splenectomy status at first infusion for each category of cause of death.

Among the 36 patients excluded from this analysis, 7 (19.4%) died. The difference in proportion of patient deaths between included and excluded patients was not statistically significant by chi-square test.

3.7. Age at treatment initiation

At the time of their first ERT infusion, non-splenectomized patients were younger than splenectomized patients (mean 3.5 versus 7.4 years) (Table 1). In a secondary analysis, non-splenectomized and splenectomized patients were stratified by age at treatment initiation.
(≤2 or >2 years of age) to investigate whether these groups had different degrees of severity in clinical manifestations. The general trends towards improved hematologic, visceral and growth outcomes were similar between both age groups and similar to the overall GD3 cohort (Online Supplemental Tables 1 and 2).

### 4. Discussion

This analysis from the ICGG Registry evaluated the largest multinational cohort to date of pediatric GD3 patients who initiated imiglucerase at <18 years of age stratified by years on ERT. The study depicts the uniformly devastating nature of GD3 in this global cohort with mean age at presentation of only 2.7 years and with massive organomegaly and cytopenia. Imiglucerase ERT resulted in rapid improvements in hematological, visceral and growth parameters among both non-splenectomized and splenectomized patients within the first year of treatment and incrementally through 5 years. Hemoglobin levels and platelet counts increased markedly, underscored by striking decreases in the percentages of patients with moderate or severe anemia and thrombocytopenia. Liver and spleen volumes decreased as did the percentages of patients with moderate or severe anemia and thrombocytopenia.

**Table 2**

<table>
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<th>Parameters</th>
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<td>&gt;1 to ≤2</td>
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<tr>
<td></td>
<td>&gt;2 to ≤3</td>
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<tr>
<td>Hemoglobin (g/dL), n</td>
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<td>143</td>
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<tr>
<td>Mean (SD)</td>
<td>9.6 (1.92)</td>
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<tr>
<td>Median</td>
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<td>Min, Max</td>
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<td>6.1 , 16.7</td>
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<td>Hemoglobin (g/dL), n</td>
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<td>Mean (SD)</td>
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<td>Median</td>
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<td>Min, Max</td>
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<td>Mean (SD)</td>
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Our findings in a large global GD3 cohort are in line with outcomes in small single-center series [14,37–47]. The majority of our cohort (almost 90%) was either homozygous or compound heterozygous for L444P or D409H, further confirming the high prevalence of these mutations among GD3 patients. Both L444P and D409H mutations occur in the normal pseudogene sequence and can be transferred to GBA by gene conversion events [56]. Given the high frequency of gene conversion events that result in L444P mutations [57], L444P may actually be the most frequent GD mutation, underscoring the importance of neuronopathic GD worldwide [6] despite much of the scientific literature focusing on the N370S mutation in the European GD1 population.

The age at GD3 diagnosis in prior studies ranged widely, from 6 months to 51 years, as did the age at initiation of ERT, ranging from 1 year to 70 years [14,37–47]. Since our analysis was limited to patients under the age of 18 who began ERT before 18 years of age, the ranges of age at diagnosis (0 to 16.8 years) and age at first ERT infusion (0 to 16.8 years) were smaller. The larger size and geographic diversity of our study underscores the hematologic and visceral benefits [14,37–47] and growth normalization [38,39,44] in response to imiglucerase ERT in a multinational GD3 population.

In our cohort, anemia persisted in 10–20% of patients during the 2 to 5 years after starting imiglucerase treatment, despite mean and median hemoglobin levels exceeding 12 g/dL in both non-splenectomized and splenectomized patients at 5 years. It is known that mild anemia may persist in patients with severe anemia (≤8 g/dL) at baseline, especially in the ICGG Registry [26] and nearly as good as treatment responses in pediatric GD1 patients after 8 years of imiglucerase treatment [55].
among those with hypersplenism associated with massive splenomegaly [58]. Further assessments may be needed in such patients to rule out co-morbidities contributing to anemia. Other important factors contributing to residual anemia and thrombocytopenia on long term ERT are likely to be marrow and splenic fibrosis [59,60]. In GD1 patients, focal splenic lesions reflecting fibrotic disease have been linked to poor platelet and splenic responses to ERT, and such lesions are more prevalent in patients with severe splenomegaly, a feature of the cohort reported herein [59]. It should be noted, however, that previous studies on splenic lesions and marrow fibrosis have only focused on adult patients; bone marrow and splenic response to Gaucher disease in pediatric patients may be different and merit future studies. In a large study of GD1 patients with intact spleens, the most severe splenomegaly before ERT initiation was associated with treatment-refractory thrombocytopenia in some patients and platelet counts appeared to increase only when spleen volume had decreased substantially [60]. Our pediatric patient population with GD3 presented earlier and with more severe hematological/visceral disease compared to a large ICGG Registry pediatric population reported previously by Andersson et al. [55] Comparison of our severe patient population with a similarly severely affected subgroup of GD1 pediatric patients in Andersson et al. suggests that the response of visceral and hematologic disease to ERT are broadly similar in these two patient populations [55].

The long-term outcomes in splenectomized patients should be interpreted with caution due to the small number of splenectomized patients in this study, particularly at later time points. In the short-term, however, response of thrombocytopenia in asplenic patients to ERT was excellent, as has been reported in other studies. For example, there were about 20% of patients with moderate to severe thrombocytopenia at baseline and after one year of imiglucerase ERT, there were no patients with moderate or severe thrombocytopenia (Fig. 1B). Prior to the advent of ERT, splenectomy was performed to treat thrombocytopenia in GD (i.e., to normalize platelet count and lessen hepatomegaly), but it is no longer recommended as it has been shown to lead to more aggressive bone disease, pulmonary hypertension, liver disease and a predisposition to malignancy in GD1 patients [62], and has been

Fig. 1. Hematologic and visceral parameters of GD3 patients in the ICGG Gaucher Registry who initiated imiglucerase at < 18 years of age by splenectomy status and years on ERT. (A) anemia; (B) thrombocytopenia; (C) hepatomegaly; (D) splenomegaly.
associated with increased accumulation of Gaucher lipids in the brains of neuronopathic GD patients [63].

The life spans of untreated GD3 patients have been reported to be variable, ranging from death in childhood or adolescence to survival into adulthood [64]. In 1986, a natural history study of 12 pediatric Norrbottian GD3 patients reported death at a median age of 12 years and a survival rate of just 5% during 22 years of follow up [64]. In contrast in our study, the probability of a GD3 patient started on ERT before age 18 years surviving for at least 5 years is 92%, provided the patient has a genotype similar to the predominant ones in this ICGG study population. Similarly, the probability that such a patient will be alive 20 years after starting ERT is 76%. Our findings show that imiglucerase increases survival, although late deaths do still occur. Of the 37 (14.6%) deaths reported in the Registry GD3 cohort, the most common causes were progression of neurological disease (n = 8) and cardiac complications (n = 6), both inherent in GD3 [18,65]. Four of the patients who died of cardiac causes were D409H homozygotes, a genotype in which cardiac valvular, coronary and aortic calcifications are prominent features of the phenotype [65–72]. There were also 3 deaths from pulmonary complications; however, this analysis did not include data extraction on pulmonary disease manifestations. Future studies on the natural history of GD3 should address the important issue of whether there is any response of established pulmonary infiltration at baseline to ERT and whether progressive pulmonary infiltrative disease occurs despite ERT.

As an observational database that relies upon physicians to voluntarily enter data, interpretation of ICGG Registry analyses requires certain considerations. For example, although the collective data is by far the largest described to date, data on each parameter are not available for every patient. In addition, this cohort is not proportionally representative by country based upon the expected prevalence of GD3 per population size. Several factors may contribute to this reporting bias including a lack of Registry sites in some regions. In very young children, neurological signs are often missed, leading to an initial diagnosis of GD1. Such patients may be reclassified later as GD3 when they are older and the neurological signs more obvious, but the Registry data for such patients may not have been revised, which will result in underreporting. The Registry data do not specify whether kyphosis and other skeletal deformation, which develop in some GD3 patients, were accounted for when evaluating growth improvement. Furthermore, height Z-scores were calculated using United States normative data, which may differ from height norms in other areas of the world.
Data inaccuracies are inherent in observational studies; for example, the several patients who died before 2 years of age may have had GD2 and one patient reportedly had the N370S/Rare Allele genotype. The presence of a N370S allele typically precludes neuronopathic GD [73]. Due to the nature of the database, it cannot be verified whether these were diagnostic or data entry errors. Likewise, the causes of death reported could not be confirmed.

Genetic reporting has undergone significant change during the years for which this study reports, primarily due to the presence of a pseudogene located 16 kb downstream from the functional GBA gene that shares 96% exonic sequence identity [57,73–75]. The most frequently encountered disease-causing allele in neuronopathic GD patients is L444P [56], which can be present either as a single base substitution in GBA or as part of a complex recombinant allele involving GBA and its pseudogene [76]. Many laboratories do not distinguish between the point mutation and the recombinant alleles that include this mutation [77], such that the latter may not be reported. In a large genotyping study of GD1 and GD3 patients, 5 (21%) GD3 patients deemed heterozygous for L444P instead had a recombinant allele and not a single nucleotide change [73]. Since the ICGG Registry does not specifically delineate reporting of recombinant alleles, these may be underreported in the current study.

Although not evaluated in this study, neurologic disease is a prominent feature in GD3 [48] and a treatment to alleviate neurologic manifestations remains an important unmet need for GD3 patients. Improved or stabilized neurologic manifestations in ERT-treated GD3 patients have been reported anecdotally [43–46,78], despite the inability of macrophage-targeted ERT to penetrate the blood-brain barrier. These improvements may be secondary neurologic and behavioral benefits that result when overwhelming visceral and hematological manifestations are reversed by ERT in these chronically sick children. Other potential contributors may include reductions in systemic inflammation, cytokine/chemokine storm, and Gaucher cell burden following ERT. Future evaluation of large GD3 cohorts in the ICGG Registry may help shed light on such associations.

In conclusion, the current study in a large, pediatric GD3 cohort of the ICGG Registry provides clear evidence that imiglucerase ERT improved even severe hematologic and visceral manifestations in a worldwide population of children and adolescents with GD3 within the first 5 years of treatment and often after only 12 months. With early inception of imiglucerase ERT, the survival of patients with GD3 was substantially longer than is commonly believed by both clinicians and regulatory authorities. ERT can provide a crucial life-saving and life-prolonging benefit for patients with GD3 in whom neurological deterioration is not invariable and in whom, with proper treatment, many can lead productive lives and contribute to society. Given the rarity of GD3 and the scarcity of data on the natural history and benefits of ERT in this population, observational studies derived from the ICGG Registry

### Table 3
Demographic and genotypic characteristics and cause of death for GD3 patients in the ICGG Registry who initiated imiglucerase at < 18 years of age.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Status epilepticus and/or progressive neurological disease</th>
<th>Cardiac complications</th>
<th>Infection, sepsis, shock</th>
<th>Pulmonary failure and/or lung disease</th>
<th>Other cause or unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Age at diagnosis (years), n</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.4 (0.79)</td>
<td>4.2 (4.94)</td>
<td>5.9 (7.04)</td>
<td>1.2 (0.83)</td>
<td>3.5 (4.40)</td>
</tr>
<tr>
<td>Median</td>
<td>1.2</td>
<td>1.6</td>
<td>3.4</td>
<td>0.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.4, 2.6</td>
<td>1.0, 13.5</td>
<td>0.7, 19.5</td>
<td>0.6, 2.1</td>
<td>0.5, 16.7</td>
</tr>
<tr>
<td>Age at infusion (years), n</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.0 (1.77)</td>
<td>8.7 (4.43)</td>
<td>6.2 (6.98)</td>
<td>1.7 (1.57)</td>
<td>4.4 (4.74)</td>
</tr>
<tr>
<td>Median</td>
<td>1.8</td>
<td>8.0</td>
<td>3.9</td>
<td>1.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.2, 3.9</td>
<td>2.3, 13.9</td>
<td>1.0, 16.0</td>
<td>0.6, 1.3</td>
<td>0.6, 16.8</td>
</tr>
<tr>
<td>Age at death (years), n</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.2 (4.97)</td>
<td>19.2 (6.53)</td>
<td>12.3 (7.27)</td>
<td>6.7 (3.54)</td>
<td>8.6 (6.79)</td>
</tr>
<tr>
<td>Median</td>
<td>6.8</td>
<td>17.7</td>
<td>11.4</td>
<td>6.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Min, Max</td>
<td>3.3, 18.9</td>
<td>12.9, 29.0</td>
<td>4.7, 21.5</td>
<td>1.4, 12.5</td>
<td>0.9, 19.9</td>
</tr>
<tr>
<td>Splenectomy status at first infusion, n (%)</td>
<td>1 (12.5)</td>
<td>1 (16.7)</td>
<td>1 (25.0)</td>
<td>0</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Splenectomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsplenectomized</td>
<td>7 (87.5)</td>
<td>5 (83.3)</td>
<td>3 (75.0)</td>
<td>3 (100.0)</td>
<td>14 (87.5)</td>
</tr>
</tbody>
</table>
are critical for enhancing the understanding of GD and its response to treatment, as well as bolstering the foundation for evidenced-based treatment guidelines.

Contributions
AEB, ATS, AV, NB, GAG, EHK, GFC and PKM designed the study and JLB performed the statistical analysis. Laurie LaRusso drafted the manuscript with PKM. All authors interpreted the results, reviewed early and final drafts of the manuscript and were fully responsible for the content and editorial decisions related to this manuscript.

AEB has received honorarium and travel reimbursement and served on advisory boards for Novartis, ApoPharma and Sanofi Genzyme. ATS has received speaker fees and travel fees from Sanofi Genzyme and Shire, as well as fees for participation on advisory boards and scientific committees for the ICGG Registry (Sanofi Genzyme). AV has no financial relationships to disclose. NB has received fees from Sanofi Genzyme and Shire for lectures, travel reimbursement, and participation on advisory boards and scientific committees for the ICGG Registry (Sanofi Genzyme) and the Gaucher Outcome Survey (Shire).

GAG was an employee of the Cincinnati Children’s Hospital Medical Center during the time this study was conducted and the Chief Scientific Officer of Synageva BioPharma Corp. and then Kiniksa Pharmaceuticals, Ltd. when the paper was written.

EHK is a member of the North American ICGG Registry Advisory Board (Sanofi Genzyme) and is a consultant for the SIFAP study sponsored by Shire Human Gene Therapies.

JLB is an employee of Sanofi Genzyme. GFC was an employee of Sanofi Genzyme at the time this study was conducted and the paper was written.

PKM is a member of the North American and International ICGG Registry Advisory Boards (Sanofi Genzyme) and has received a research grants from Sanofi Genzyme and honoraria and travel support for lectures.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jmgme.2016.12.001.

References


