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The Management of Gaucher Disease in Developing Countries: A Successful Experience in Southern Brazil

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Key Words
Clinical protocols · Gaucher disease · Guideline · Imiglucerase · Therapeutics

Abstract
Objective: Gaucher disease (GD) is a genetic disease caused by glucocerebrosidase deficiency. GD is treated by enzyme replacement therapy (ERT) with imiglucerase, a high-cost drug provided by the Brazilian Ministry of Health (BMH). This study reports the implementation of the BMH guidelines for GD in the southernmost state of the country. ***Methods:*** We review the clinical and laboratorial data for patients seen at the reference center for GD from Rio Grande do Sul, Brazil (July 2003 to June 2006). ***Results:*** Twenty-five patients were included in this study. At baseline, 19/20 were on ERT (mean dosage of imiglucerase = 51.8 U/kg/infusion), 3/17 presented anemia, and 5/16 thrombocytopenia. The amount of imiglucerase prescribed to these patients was adjusted according to the guidelines in July 2003; out of them, 18 were receiving ERT in the reference center at month 36 (mean dosage of imiglucerase = 27.5 U/kg/infusion), 2/18 presented anemia, and 4/18 presented thrombocytopenia. The analysis of the liver, spleen, and bone data presented some limitations, but the available information suggests that patients did not deteriorate. GD patients who initiated ERT after July 2003 (n = 5) received lower dosage of imiglucerase since the beginning of the treatment; most of them demonstrated clinical and laboratorial response. From baseline to month 36, the consumption of imiglucerase by the reference center showed a significant reduction, which represented savings of USD 3 million to the public health system. ***Conclusions:*** The model of care of GD patients suggested by the BMH guidelines appears to be cost-effective and could be an example for management of rare diseases in underdeveloped countries.

Gaucher disease (GD) is an autosomal recessive lysosomal storage disease (LSD) caused by glucocerebrosidase deficiency [1]. The deficient activity of this enzyme leads to the accumulation of glucocerebrosides in the lysosomes of macrophages, mainly in the spleen, liver, and bone marrow [2–4]. In more severe cases, it may affect the lungs, kidneys, and the central nervous system [5]. GD is a heterogeneous disorder and can be classified into 3 types: type I (or non-neuronopathic disease), which accounts for over 90% of all cases and is associated with hematological disorders, hepatosplenomegaly, and bone involvement [6]; type II (or acute neuronopathic disease), which is more severe and results in death within the first 2 years of life [7]; and type III (or chronic neuronopathic disease), which may cause slow and progressive neurological dysfunction [8]. The incidence of type I GD in the general population is 1:40,000 to 1:60,000 live births [9].

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GD was the first LSD to be efficiently treated by enzyme replacement therapy (ERT) with imiglucerase (recombinant glucocerebrosidase) [10]. This treatment is crucial for the improvement of the quality of life of patients, and in Brazil it is granted by the Brazilian Ministry of Health [11]. In 2004 the treatment of 425 Brazilian patients cost USD 48.56 million to the Brazilian Ministry of Health, rising to USD 58.79 million for 458 patients in 2005 [12].

Given the clinical heterogeneity and the multisystemic profile of GD, ERT should be administered on a patient-by-patient basis according to the severity of the disease [6]. In 2002, aiming to promote the rational use of imiglucerase in the country, the Brazilian Ministry of Health published the clinical protocol and therapeutic guidelines for GD (CPTG-GD), in which they recommend the implementation of reference centers at state levels, where patients should be clinically followed up in order to have the lowest clinically effective dose of imiglucerase prescribed [6]. As GD usually requires lifelong treatment, the reduction or the increase in the amount of imiglucerase received depends on the clinical response to the actual dosage. Clinical response was defined as any improvement in clinical and laboratorial variables. The highest dose of imiglucerase allowed by CPTG-GD is 60 U/kg/infusion every 15 days (children with severe GD), and the lowest is 10 U/kg/infusion every 15 days (adults with stable mild disease). Treatment for asymptomatic patients and for patients presenting type II GD is not recommended.

The aim of the present study was to describe and to evaluate the implementation of the CPTG-GD at a reference center for GD in the state of Rio Grande do Sul, Brazil, focusing on the assessment of clinical outcomes and costs for the public health system over a 36-month period (from July 2003 to June 2006).

Methods

Rio Grande do Sul is the southernmost state of Brazil with a population of about 10 million inhabitants. At the time this study was performed, 25 patients presenting GD were known to be alive in the state. In July 2003 a reference center for GD was implemented at the Hospital de Clínicas de Porto Alegre (HCPA) in the city of Porto Alegre, Rio Grande do Sul. Since then, patients have been scheduled similar days to receive their infusion simultaneously in order to allow the sharing of vial content (e.g., if one patient needs 5.5 vials of imiglucerase per infusion and another one needs 4.5, 10 vials are shared between them).

All patients seen at the reference center (n = 25) had their diagnosis confirmed by the glucocerebrosidase enzyme assay and/or by DNA analysis and were followed up according to the CPTG-GD: (1) An initial dosage of imiglucerase is established as follows: adult patients, older than 18 years, without criteria for severe disease: 15 U/kg/infusion every 15 days; patients up to 12 years old without criteria for severe disease and patients aged 12–18 years with failure to thrive: 30 U/kg/infusion every 15 days; patients with severe disease or type III disease: 60 U/kg/infusion every 15 days. (2) Severity criteria were defined as advanced bone disease or pathological fracture, liver size representing 9% or more of body weight, spleen size representing 10% or more of body weight, portal hypertension, platelet count $\leq 50{,}000/mm^3$, hemoglobin level <8 mg/dl, renal or cardiopulmonary involvement, and severe functional limitation characterized by disabling disease (dyspnea or pain on minimal exertion). (3) Maintenance dosage of imiglucerase was established according to the clinical response to ERT. Clinical response was characterized as the presence of one or more of the following items after at least 6 months of treatment, assuming that none of these parameters showed deterioration: any increase in hemoglobin or platelet count; any reduction in liver or spleen size; relief of bone pain. (4) The minimal clinical and laboratory follow-up included a complete blood and platelet count performed every 3 months, abdominal ultrasound performed every 6 months to determine the size of the longest cranial-caudal axis of the liver and the spleen, and a skeletal assessment (lumbar spine, hip, and femur X-ray) performed annually.

For this study, patients were categorized into 2 groups: group 1 – patients who had received treatment before the implementation of the CPTG-GD; and group 2 – patients diagnosed after July 2003, e.g., throughout the 36-month follow-up period. Clinical and laboratory assessments were grouped into months 0, 12, 24, and 36; month 0 refers to the evaluations performed immediately before implementation of the CPTG-GD (for group 1 patients) or immediately before onset of treatment (for group 2 patients), whereas months 12, 24, and 36 correspond to the subsequent assessments. Anemia was defined according to the Gaucher Registry: Hb <12.0 g/dl for males older than 12 years; Hb <11.0 g/dl for females older than 12 years; Hb <10.5 g/dl for children 2–12 years; Hb <9.5 g/dl for children aged 0.5–2 years; and Hb <10.1 g/dl for infants aged less than 6 months [6]. Thrombocytopenia was defined by platelet count less than $120{,}000/mm^3$, whereas leukopenia was defined as leukocyte count less than $3{,}600/\mu l$. All X-rays were evaluated by the same blinded radiologist and only patients who had X-rays of the same bones taken at month 0 and 36 were considered for analysis. Each X-ray showed one or more abnormal findings.

A questionnaire specially developed for evaluation of the patient's satisfaction, including questions regarding his/her perception of his/her medical and pharmaceutical care, quality of life, and quality of care provided by the reference center was applied at 12, 24, and 36 months. The patient (or his/her caretaker if the patient was a child or mentally compromised) answered the questions anonymously. The evaluation and monitoring of clinical and laboratory findings were managed by a customized Access database.

Statistical Analysis

The statistical analysis was made using the SPSS 15.0 software. The descriptive analysis included absolute and relative frequencies for qualitative variables, percentages, and means ± standard

deviation for quantitative variables. The scores for hematological parameters and liver and spleen size at different assessment times were analyzed by one-way ANOVA. A significance level of 5% was considered statistically significant.

Ethical Aspects

This study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre, Brazil.

Results

The characteristics of the 25 Gaucher patients included in this study are shown in table 1.

Group 1 Patients

In month 0, twenty Gaucher patients were seen at the reference center. Of those, 19 were being treated with imiglucerase for a mean time of 4.4 years (0.3–9 years). One patient declined treatment for personal reasons. Ten patients (50%) were male; 17 (85%) had type I GD, and 3 (15%) type III. One patient moved to another Brazilian state in late 2005 and therefore his data were collected only until then.

Most treated patients were clinically stable at month 0 (tables 1–4; fig. 1, 2). The mean dosage of imiglucerase prescribed is shown in table 3. Weight and height assessments revealed that children's growth was preserved, while for adults it was stable, irrespective of imiglucerase dose reduction (table 3). The hemoglobin levels and leukocyte and platelet counts (of non-splenectomized and splenectomized patients) did not change throughout the study period (table 2). Liver and spleen sizes for non-splenectomized (fig. 1, 2) and splenectomized patients remained stable throughout the period. We noticed that the variation in liver and spleen sizes was not significant, although there was a tendency towards an increase in the long axis measurement accordantly to the children's growth. The bone assessments also remained stable (table 4). With regard to skeletal assessment, bone infarct was the most frequent finding. Erlenmeyer flask deformity, the most common finding described in most studies, was not observed in patients treated at the reference center [9]. Only 2 splenectomized patients with abnormal bone findings on radiological examination complained of bone pain, possibly suggesting greater severity of this variable in splenectomized patients.

Group 2 Patients

From month 0 to month 36, five new GD patients were diagnosed (fig. 3, 4):

Table 1. Characteristics of the 25 patients with Gaucher disease followed up at the reference center in Rio Grande do Sul, Brazil; the study started with 20 patients in July 2003 and ended in June 2006 with 23 patients

	Patients
Type of the disease[a]	
Type I	21 (84%)
Type II	1 (4%)
Type III	3 (12%)
Gender	
Male	15 (60%)
Female	10 (40%)
Age at diagnosis (years)	
<12	15 (60%)
12–17	3 (12%)
≥18	7 (28%)
Median	10
Age at the beginning of treatment with imiglucerase (years)[b]	
<12	14 (58%)
12–17	4 (17%)
≥18	6 (25%)
Median	10
Treatment status at month 36	
On ERT	21 (84%)
Not on ERT	2 (8%)
Moved to other Brazilian state	1 (4%)
Dead	1 (4%)
Splenectomized patients	6 (24%)
Age at month 36, mean ± SD	33.8 ± 15.2

[a] None of the patients with type I disease is related. Among the 3 patients with type III disease, 2 are siblings.
[b] One patient declined treatment for personal reasons.
ERT = Enzyme replacement therapy.

Patient 1 (time on ERT: 24 months): male; age at diagnosis: 27 years; main clinical symptoms at diagnosis: avascular necrosis of proximal femur, femoral bone infarct, bone pain, hepatomegaly, and history of splenectomy. ERT with imiglucerase started with 30 U/kg/infusion soon after the diagnosis was established. The dose was reduced to 15 U/kg/infusion at month 6 due to improvement in bone pain. The patient remains without hematological alterations (fig. 3, 4), had a slight reduction in liver size, and will be submitted to a hip replacement surgery.

Patient 2 (time on ERT: 6 months): male; age at diagnosis: 1 month; main clinical symptoms at diagnosis: liver disease and thrombocytopenia, being initially classified as having type III GD. ERT with imiglucerase started with 60 U/kg/infusion in the 3rd month of life lasting un-

Table 2. Annual assessment of hemoglobin level, leukocyte count, and platelet count in group 1 patients (n = 19) with Gaucher disease treated at the reference center in Rio Grande do Sul, Brazil

	Month 0[a] (n = 19)	Month 12 (n = 19)	Month 24 (n = 19)	Month 36 (n = 18)[b]	p value
Hemoglobin (g/dl)	12.34 ± 1.26 (17/19)	12.16 ± 1.44 (19/19)	12.31 ± 1.41 (19/19)	12.80 ± 1.33 (18/18)	0.875
Anemia[c]	3/17	4/19	3/19	2/18	
Leukocytes (/μl)	6,389 ± 2,134 (15/19)	6,077 ± 2,901 (17/19)	6,335 ± 2,711 (19/19)	6,721 ± 2,533 (18/18)	0.573
Leukopenia[d]	0/15	1/19	1/19	0/18	
Platelets (/mm³)	178,688 ± 109,004 (16/19)	226,868 ± 168,275 (19/19)	213,105 ± 136,895 (19/19)	211,888 ± 118,012 (18/18)	0.970
Non-splenectomized patients	158,333 ± 75,023 (15/16)	156,333 ± 62,942 (15/19)	155,733 ± 60,483 (15/19)	168,866 ± 68,806 (15/18)	
Splenectomized patients	484,000 (1/16)	421,100 ± 222,779 (4/19)	370,600 ± 171,798 (4/19)	353,500 ± 151,352 (3/18)	
Thrombocytopenia[e]	5/16	5/19	4/19	4/18	

Figures are number or mean ± SD with number in parentheses.
[a] Month 0 corresponds to the data of patients collected immediately before the implementation of the reference center.
[b] One patient moved to another state in Brazil and, therefore, does not belong to the reference center in Rio Grande do Sul.
[c] Anemia is defined according to age-specific and gender-specific mean hemoglobin levels: Hb <12 g/dl for males >12 years; Hb <11 g/dl for females >12 years; Hb <10.5 g/dl for children 2–12 years; Hb <9.5 g/dl for children aged 0.5–2 years; Hb <10.1 g/dl for infants <6 months.
[d] Leukopenia is defined as a leukocyte count <3,600/μl.
[e] Thrombocytopenia is defined as a platelet count <120,000/mm³.

Table 3. Follow-up of group 1 patients (n = 19) with Gaucher disease at the reference center in Rio Grande do Sul, Brazil, considering weight, height, and annual dose of imiglucerase

	Month 0[a] (n = 19)	Month 12 (n = 19)	Month 24 (n = 19)	Month 36 (n = 18)[b]
Weight (kg)	43 ± 16 (17/19)	45 ± 15 (18/19)	48 ± 14 (19/19)	49 ± 11 (16/18)
Patients <18 years	36 ± 13 (12/17)	39 ± 13 (13/19)	41 ± 11 (12/19)	46 ± 11 (12/16)
Patients ≥18 years	59 ± 7 (5/17)	61 ± 4 (5/19)	62 ± 7 (7/19)	57 ± 4 (4/16)
Height (cm)	146 ± 19 (15/19)	149 ± 15 (18/19)	153 ± 14 (19/19)	156 ± 13 (18/18)
Patients <18 years	138 ± 19 (10/15)	143 ± 5 (12/18)	148 ± 15 (12/19)	154 ± 15 (12/18)
Patients ≥18 years	162 ± 6 (5/15)	162 ± 5 (6/18)	161 ± 6 (7/19)	160 ± 5 (6/18)
Mean imiglucerase (U/kg/infusion)	51.8 ± 17.4 (19/19)[c]	30.5 ± 14.9 (19/19)	27.9 ± 13.8 (19/19)	27.5 ± 14.0 (18/18)
Patients <18 years	52.6 ± 19.3 (14/19)	36.9 ± 13.1 (13/19)	35.0 ± 11.7 (12/19)	33.3 ± 13 (12/18)
Patients ≥18 years	49.6 ± 12.1 (5/19)	16.7 ± 6.8 (6/19)	15.7 ± 6.7 (7/19)	15.8 ± 7.4 (6/18)
Type I patients	47.6 ± 11.9 (16/19)	25.0 ± 7.7 (16/19)	23.7 ± 8.5 (16/19)	23.0 ± 8.2 (15/18)
Type III patients	74.0 ± 27.8 (3/19)	60.0 (3/19)	50.0 ± 17.3 (3/19)	50.0 ± 17.3 (3/18)

Figures are mean ± SD with number in parentheses.
[a] Month 0 corresponds to the data of patients collected immediately before the implementation of the reference center.
[b] One patient moved to another state in Brazil and, therefore, does not belong to the reference center in Rio Grande do Sul.
[c] This value corresponds to the mean dose of imiglucerase prescribed to patients immediately before the implementation of the reference center. Soon after the implementation of the reference center, the dose was readjusted to 33.2 ± 12.8.

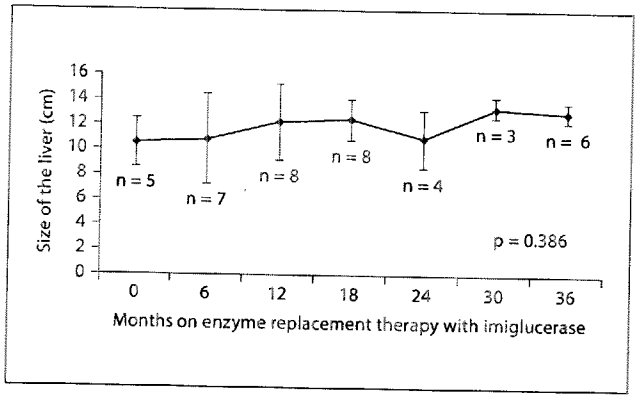

Fig. 1. Liver size assessment (cranial-caudal axis) in patients with spleen under treatment before (month 0) and after implementation of clinical protocol and therapeutic guidelines at the reference center in Rio Grande do Sul, Brazil (n = 19/20).

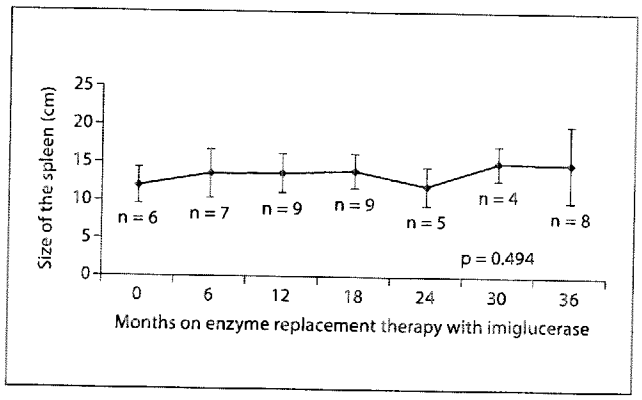

Fig. 2. Spleen size assessment (cranial-caudal axis) in patients with spleen under treatment before (month 0) and after implementation of clinical protocol and therapeutic guidelines at the reference center in Rio Grande do Sul, Brazil (n = 15/19).

Table 4. Radiological assessment of the hip, spinal column, and femur of 19 group 1 patients with Gaucher disease treated at the reference center of Rio Grande do Sul, Brazil

	Month 0 (n = 16/19)	Month 12 (n = 19)	Month 24 (n = 19)	Month 36 (n = 18)[a]
Normal	13	13	14	14
Abnormal	3	6	5	4

[a] One patient moved to another state in Brazil.

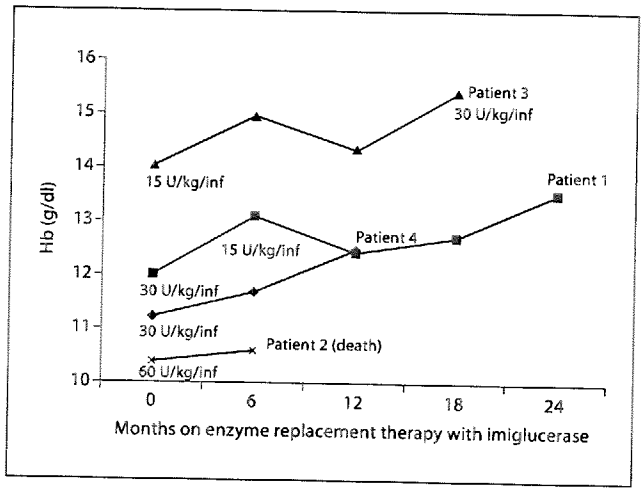

Fig. 3. Hemoglobin count assessment in 4 Gaucher disease patients (group 2) after implementation of the clinical protocol and therapeutic guidelines.

til the patient was 8 months when he died due to pneumonia and neurological involvement. Even though, liver condition and platelets improved with ERT (fig. 3, 4), and his evolution was compatible with type II GD.

Patient 3 (time on ERT: 18 months): male; age at diagnosis: 56 years; main clinical symptoms at diagnosis: thrombocytopenia and splenomegaly. ERT with imiglucerase started with 15 U/kg/infusion as soon as the diagnosis was established. At month 6 and 12, there was a reduction in splenomegaly and a slight improvement in platelets. At month 18, the dosage of imiglucerase was increased to 30 U/kg/infusion aiming to improve the platelets count. However, this patient presented a severe infusion reaction at this dosage and was later shown to present a positive intradermal test to imiglucerase. He has not been on ERT since then.

Patient 4 (time on ERT: 12 months): male; age at diagnosis: 8 years; main clinical symptoms at diagnosis: anemia, thrombocytopenia, hepatosplenomegaly, femoral bone infarct, and 2 previous non-pathological fractures. ERT with imiglucerase started with 30 U/kg/infusion as soon as the diagnosis was established. The patient improved on visceral and hematological parameters (fig. 3, 4) and did not present other fractures.

Patient 5: male; age at diagnosis: 49 years; main clinical symptoms at diagnosis: hepatomegaly and abnormal liver functions tests. For personal reasons, the patient has not started ERT yet.

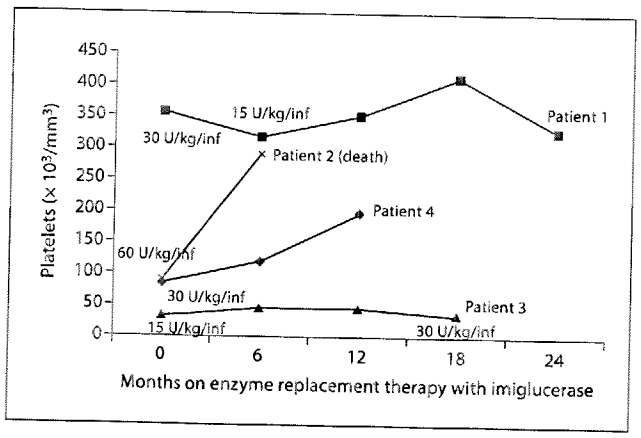

Fig. 4. Platelet count assessment in 4 Gaucher disease patients (group 2) after implementation of the clinical protocol and therapeutic guidelines.

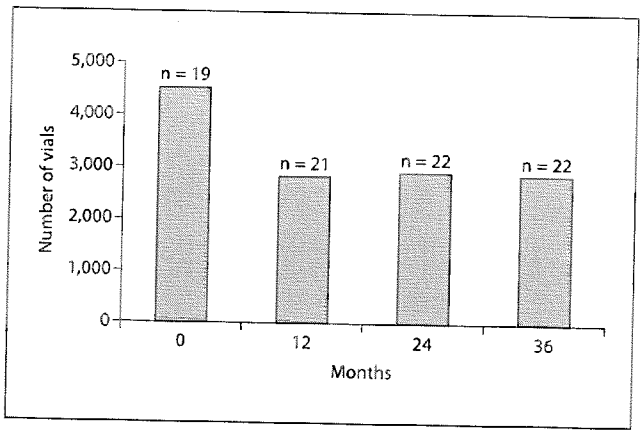

Fig. 5. Imiglucerase consumption before implementation of clinical protocol and therapeutic guidelines (month 0) and after (months 12, 24, 36) at the reference center in Rio Grande do Sul, Brazil. Number of patients (n) under treatment is shown for each period.

Patient Satisfaction Survey

The satisfaction survey conducted at months 12 (n = 16/20), 24 (n = 19/22), and 36 (n = 16/22) showed that all patients were very satisfied with the care provided by the reference center in Porto Alegre, RS, Brazil.

Treatment Compliance

Treatment compliance (e.g., the proportion between the number of received and expected infusions per year) before the implementation of the reference center was possible to be retrieved only for 9/19 patients. For these patients, compliance rose from 67.6% before to 89.6% after its implementation. The compliance was 100% for group 2 patients after the implementation of the reference center. Patients with persistent anemia and thrombocytopenia throughout the 36-month follow-up period (n = 2) showed the lowest treatment compliance (table 2). One of those patients who was treated with an infusion of 30 U/kg has been investigated for the possibility of other related blood disorders.

Imiglucerase Costs to the Brazilian Public Health System

Figure 5 shows the annual consumption of imiglucerase 200 U vials in Rio Grande do Sul before and after creation of the reference center. From month 0 to 36 there was a reduction of 38% in the necessary number of vials to treat patients, which was not associated with a reduction in the number of patients. This finding represents savings of USD 3 million.

Discussion

All known living Gaucher disease patients of Rio Grande do Sul were included in this study. There is no data about the true incidence of Gaucher disease in Brazil and specifically in Rio Grande do Sul, but comparing the available data with the data from other countries, this disease is probably under-diagnosed in our country [9, 12].

Given the rarity, heterogeneity, and multisystemic nature of GD, coupled with treatment costs and lack of evidence regarding effectiveness of high doses, imiglucerase should be administered on a patient-by-patient basis, always seeking the lowest clinically effective loading and maintenance doses [13, 14].

Recent long-term follow-up studies using low imiglucerase doses (mean dose of 15–30 U/kg every 4 weeks) and high doses (mean dose of 80 U/kg every 4 weeks) in adult patients were retrospectively compared, and the increase in hemoglobin level and in platelet count as well as the improvement in visceral parameters did not differ between groups [15]. In our study, after implementation of the reference center and adjustment of the imiglucerase dosage according to the clinical protocol and therapeutic guidelines for GD, we also noted that all parameters analyzed (hematological, visceral, and skeletal) remained stable.

Although the variation in liver and spleen sizes was not significant, the interpretation of these variables had some limitations. The abdominal ultrasound showed

only one axis of the liver and spleen, not allowing a volume estimation of these organs. Moreover, some tests were not performed at the reference center and were not assessed by the same physician, which may have produced an assessment bias.

The bone assessments also remained stable. However, the most interesting findings are that bone abnormalities did not deteriorate; none of the patients had a pathological fracture or complained of worsening bone pain, even with the dose reduction after implementation of the CPTG-GD. The analysis of this variable was limited since many patients did not have the same bones evaluated at the recommended time intervals. More sensitive technologies can be used to assess bone disorders, such as magnetic resonance and computed tomography, but radiological examination has also proved effective [16].

The outcomes of the 3 new patients diagnosed after implementation of the reference center, although they initially received lower doses, are similar to those of patients who received higher doses initially and lower doses later.

In addition to the maintenance of clinical parameters with the use of lower doses, the implementation of the reference center allowed continued treatment with 100% adhesion, thus improving treatment compliance and patient satisfaction. Together with these outcomes, the rational use of imiglucerase led to cost savings of approximately USD 3 million in 36 months of follow-up, resulting in a better use of public resources with improvement of patients' health and care. This model of care and follow-up should be an inspiring example for other Brazilian states and for other countries.

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