

Maintenance Efficacy of Low Dose Imiglucerase for Gaucher Disease

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Research

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Abstract

Background

Imiglucerase is the recommended treatment for Gaucher disease (GD), a hereditary metabolic disease. In high risk adults and all children, the minimum recommended dose for long-term maintenance is 30 U/kg/2 weeks. However, the extremely high cost of this enzyme largely hinders its clinical use. The minimal maintenance dose of imiglucerase has thus been a subject of debate. We aimed to analyze the long-term maintenance outcomes of imiglucerase at dosage < 20 U/kg/2 weeks after standard dose.

Methods

Seventeen patients with GD type 1 or GD type 3 were enrolled for analysis. We evaluated maintenance efficacy of imiglucerase on hemoglobin, platelet, visceral volumes and bone conditions during the 7-year follow-up.

Results

Parameters on hemoglobin, platelet, liver, and spleen volumes of all patients were stabilized or improved. Seven out of 14 patients showed bone mineral density improvement. Three out of 16 patients showed worse bone pain; 6 out of 15 patients showed worse Erlenmeyer flask; 6 out of 15 patients showed worse bone infarction; 1 out of 16 patients showed worse marrow infiltration and 3 out of 15 patients showed worse osteonecrosis.

Conclusions

Imiglucerase less than 20 U/kg/2 weeks is enough to maintain blood and visceral parameters, but is not sufficient to stabilize skeletal conditions.

Background

Gaucher disease, caused by mutations in *GBA1* gene, is one of the most prevalent lysosomal storage diseases. Loss of function mutations in *GBA1* results in decreased glucocerebrosidase's activity and insufficient clearance of glucocerebroside within the lysosomes of various cells and tissues [1]. The pathologic accumulations of glucocerebroside cause splenomegaly, hepatomegaly, anemia, thrombocytopenia, and various skeletal pathologies [2, 3, 4]. Based on the age of onset and involvement of central nervous system (CNS), GD may be classified into 3 types. Type 1 disease (GD1), the most common form, is defined as non-neuronopathic GD, while type 2 is characterized by early onset and rapid progression of neurological symptoms, and type 3 (GD3) is by late onset and neurological involvement [4].

Enzyme replacement therapy (ERT) is the standard treatment of patients with GD1 and GD3. Imiglucerase has been one of the most widely used ERT among the world. It increases blood counts, decreases organ volumes, and improves bone syndromes [5–10]. However, imiglucerase is estimated to cost US \$7000 to US \$38000 per patient per year [11] and its incremental cost-effectiveness ratios are much lower than other rare diseases like Pompe and Fabry disease [12]. The optimal dose regimen balancing clinical effect and economical cost remains to be determined.

After achieving the initial therapeutic goals, the minimum recommended long-term maintenance dose is 30 U/kg/2 weeks for all children and increased risk adults with severe diseases [13]. Imiglucerase has a dose-dependent effect in improving hematological and visceral parameters [14, 15]. However, other study highlighted the importance of high dose enzyme therapy in skeleton complications but not hematological and visceral parameters [11]. But these studies were either focused on initial efficacy or failed to take splenectomy into consideration. Splenectomy is regarded as an important treatment when there are life-threatening complications when ERT is not available [16]. Considering the economic burden of standard imiglucerase administration, what remain to be solved is whether imiglucerase less than 20 U/kg/2 weeks can maintain disease conditions after achieving initial therapy goals.

In China, a group of GD1 and GD3 patients were supported for free ERT treatment by a charity project since 1998. They were treated with standard regimen until 2009. Due to the global supply shortage in 2009, the treatment dose is thereafter less than 20 U/kg/2 weeks until 2018. Here, we retrospectively evaluated patients' hematologic traits, organ volumes and bone diseases during the period of 2012 and 2018.

Methods

Patients

All patients were diagnosed of GD1 or GD3 by measurement of deficient glucocerebrosidase activity and genotyping of *GBA1* at Peking Union Medical College Hospital (PUMCH). They were initially treated with standard dose of imiglucerase (Cerezyme™, Sanofi/Genzyme) and switched to dose < 20 U/kg/2 weeks due to global shortage of imiglucerase. Data were collected from periodic follow-up evaluations and medical records, and stratified by splenectomy status for analysis.

Organ and blood parameters

Spleen and liver volumes were calculated according to abdominal ultrasound measurement [17], and expressed as multiples of normal (MN), where normal spleen volume is 2 mL/kg and normal liver volume is 25 mL/kg. Hemoglobin concentration and platelet count were measured regularly at Peking Union Hospital or local laboratories. Anemia is defined as hemoglobin level < 110 g/L for women and 120 g/L for men, and thrombocytopenia is defined as platelet count < $300 \times 10^9/L$.

Bone conditions

Bone conditions were assessed by MRI (Magnetic Resonance Imaging), X-ray and densitometry (DXA) at baseline and during 2016 and 2019. T score values were used to evaluate bone mass. $-1.0 > T \text{ value} > -2.5$ was defined as osteopenia, and $T \text{ value} < -2.5$ as osteoporosis. Any complains of bone pain or imaging abnormality from 2016 to 2019 were considered as bone involvement in our study.

Results

Demographics

Patient characteristics were described in Table 1. Among 17 patients, 7 were male, and 10 were female. The average diagnosis age was 26.2 years (range, 10–35 years). They were all diagnosed with the GD1 at baseline and 4 patients developed into GD3 later. At baseline, 16 patients were assessed at increased risk and 11 patients underwent splenectomy.

Hemoglobin and platelet count

Values of hemoglobin (Hb) were given in Table 2. For patients with intact spleen (N = 6), Hb concentration at baseline was 92.7 ± 33.3 g/L (range, 37–127 g/L). In 2012, the value was 104.8 ± 5.2 g/L (range, 95–110 g/L) and 4 patients had anemia (range, 95–108 g/L). By 2018, the level rose to 118.8 ± 11.4 g/L and only 2 patients remained anemia (109 and 109 g/L). The values between 2012 and 2018 kept relatively stable, fluctuating between 100 and 120 g/L.

For splenectomy patients, baseline Hb was 115.7 ± 29.5 g/L (range, 67–167 g/L). In 2012, Hb was 128.9 ± 30.1 g/L (range, 89–148 g/L), and above 120 g/L thereafter. Hb was 132.5 ± 25.6 g/L (range, 89–163 g/L) in 2018. Of note, Hb of 3 female patients remained < 110 g/L throughout our observation.

All intact spleen patients had thrombopenia at baseline ($65.8 \pm 25.3 \times 10^9/L$; range, $17-97 \times 10^9/L$) (Table 3). In 2012, the average count was $103.4 \times 10^9/L$ (range, $73-123 \times 10^9/L$) and increased to $167.3 \times 10^9/L$ (range, $90-250 \times 10^9/L$) in 2018. For splenectomy patients, the mean count at baseline was $212.6 \times 10^9/L$ (range, $34-310 \times 10^9/L$). The mean value was $208.1 \times 10^9/L$ (range, $114-447 \times 10^9/L$) in 2012 and $294.5 \times 10^9/L$ (range, $131-624 \times 10^9/L$) in 2018. No patient had thrombopenia from 2012 to 2018.

Visceral volumes

Table 4 Spleen volume of patients of intact spleen (MN)								
Year	Dosage	P1	P2	P4	P6	P13	P17	Mean ± SD
	(U/kg/2 weeks)							
	Mean ± SD							
Baseline	-	18.7	28.9	23.5	12.0	12.5	16.9	18.8 ± 6.0
2012	11.5 (n = 1)	6.4	9.0	8.1	8.8	9.6	-	8.4 ± 1.1
2013	8.2 ± 3.3 (n = 6)	7.4	9.1	8.6	9.3	10.2	11.1	9.3 ± 1.2
2014	13.8 ± 3.0 (n = 6)	6.2	8.0	6.9	8.6	10.2	7.5	7.9 ± 1.3
2015	15.9 ± 2.3 (n = 6)	6.0	8.7	6.7	8.2	8.8	6.4	7.5 ± 1.1
2016	-	-	-	-	-	-	-	-
2017	19.6 ± 5.7 (n = 4)	5.4	7.5	7.0	7.0	9.1	5.4	6.9 ± 1.3
2018	31.7 ± 7.6 (n = 5)	5.3	8.1	7.1	6.9	8.0	5.2	6.8 ± 1.2
-, data unavailable								

Three out of 6 non-splenectomy patients had liver volume > 1.5 MN at baseline. Between 2012 and 2018, no hepatomegaly was observed in these 6 patients in record. For the splenectomy patients, 4 out of 5 patients had hepatomegaly and 2 patients had liver volume > 1.5 MN at baseline. In 2012, still 4 out of 5 patients had hepatomegaly. From 2013 to 2015, the mean liver volume was around 1 MN. In 2015, 4 out of 8 patients had slight hepatomegaly, and only 1 patient had liver volume > 1.5 MN.

Bone conditions

Data of skeleton system manifestations were taken at 2017 or 2018 and compared with baseline (Table 6). For intact spleen patients (N = 5), 2 patients had new appearing bone pain and 1 of them appeared bone infarction and another 1 had osteonecrosis. Besides, 2 patients had osteoporosis and bone marrow infiltration improved. Of note, femoral abnormalities showed in all patients.

In splenectomy patients (N = 11), 6 patients maintained, 2 patients improved, and 1 patient developed bone pain. New appearing bone infarction or osteonecrosis was seen in 5 or 2 new cases respectively. 5 patients had bone density improved and 2 of them had bone marrow involvement improved as well. Erlenmeyer flask deformity showed in 2 new cases.

Discussion

The minimal long-term maintenance dose has been a long-standing question due to its great socioeconomic and medical values. This retrospective study evaluated the efficacy of imiglucerase supply < 20 U/kg/2 weeks in China with 7-year follow-up. During this period, no death was observed. We

found that < 20 U/kg/2 weeks of imiglucerase therapy stabilized hematological levels and organ volumes in GD patients. Therapeutic goals of Gaucher Disease had set out in 2004: 1) increase hemoglobin levels to 110 g/L for women and children, and 120 g/L for men; 2) increase platelet counts sufficiently to prevent surgical, obstetrical, and spontaneous bleeding; 3) reduce and maintain the liver volume to 1.0 to 1.5 MN; 4) reduce and maintain spleen volume to < 2 to 8 MN [18]. Among all 17 patients, only 5 patients had mild anemia (range, 89–109 g/L) and 1 patient had thrombocytopenia ($90 \times 10^9/L$) in 2018. Although some of the organ data unavailable, most of our patients achieved the treatment goals for anemia, thrombocytopenia, hepatomegaly and splenomegaly.

A retrospective analysis compared the efficacy of low dose (7.5–15 U/kg/2 weeks) and high dose (40 U/kg/2 weeks) imiglucerase therapy, and results showed no dose-dependent differences in visceral enlargement and anemia, but highlighted the significance of high dose in skeleton complications. In our study, the effect of < 20 U/kg/2 weeks imiglucerase on bone disease was not optimistic. The treatment goals for skeleton disease require to lessen or eliminate bone pain, prevent bone crises, osteonecrosis and subchondral joint collapse, and improve bone mineral disease (BMD). However, new appearing osteonecrosis, bone infarction, Erlenmeyer flask and bone pain were seen in variable extents in these patients, especially in asplenic patients. Bone density improved in 7 patients, but 5 of them had osteonecrosis which may falsely increase BMD values. Since osteonecrosis, osteosclerosis and vertebral compression may be irreversible and skeletal disease is often the source of significant long-term morbidity [16], thorough and sensitive evaluation and monitoring of Gaucher skeletal involvement are extremely necessary and may allow for timely intervention. We suggest that in condition of < 20 U/kg/2 weeks treatment, regular evaluation and timely dosage adjustment are essential for patients suffered from bone pain, osteonecrosis, bone infarction.

The efficacy of enough dose of imiglucerase has been highlighted previously. However, the dose choice is not merely a matter of seeking the optimized clinical effects, but also of controlling high economic cost. Take a 50 kg adult for example, the treatment dosage increases for each 10 U/kg/ 2 weeks, the cost will increase by about RMB 900,000 per year in China. This is absolute a huge burden for most patients. Therefore, the efficacy of inadequate dosage is worthy of more attention.

In 7 years' < 20 U/kg/2 weeks maintaining treatment, dosage below 10U/kg/2 weeks was sometimes seen. None of the patients died, and most them maintained ideal disease condition. Prior to the presence of ERT, gastrointestinal and CNS bleeding, and cirrhosis/portal hypertension often led to premature death of GD patients and the proportional mortality rate (PMR) of liver disease is high to 4.76, only second to septicemia (PMR 9.22) [16]. Therefore, control of hematologic and visceral conditions is extremely important. Our data suggest that < 20 U/kg/2 weeks is optional to prevent life-threatening disease progression such as anemia, thrombocytopenia and hepatomegaly, though fails to meet the need of high-quality life.

Splenectomy was performed historically to improve hypersplenism before the era of ERT. However, it potentially increased risk of skeleton complications exacerbation, progressive hepatomegaly, bacterial

sepsis and pulmonary hypertension [16, 19–22]. Also, osteonecrosis following total or partial splenectomy may not be prevented by ERT [23]. Thus, splenectomy should be avoided if ERT is available. We found that hepatomegaly and osteonecrosis were more frequently observed in splenectomy patients under treatment < 20 U/kg/ 2weeks. This can be explained by that Gaucher cells that were deposited in the spleen ended up in the skeletal system and liver. With respect to blood parameters, splenectomy doesn't affect the maintenance effect of low dose regimen.

As a rare disease, direct study of GD is often difficult for lacking appropriate sample size and duration. Previous studies usually took data from the International Collaborative Gaucher Group (ICGG) Gaucher Registry and patients were thereby largely heterogenous in country, race, data measurement and treatment course. By analyzing the first-hand clinical records in PUMCH, this study is characterized by low dose treatment and long-time observation. In addition, most of our patients experienced treatment stop and restart. It is a common situation in disease management that patients stop medication for economic burden and restart for disease progression. Our results are significant for managing such patients as well.

Of note, some of the outcomes of this study should be interpreted with caution due to the limited sample numbers. Also, some parameters are missed in specific time point and this affects disease monitor and impairs data integrity and continuity. Nevertheless, our data are enough to make an overall conclusion.

Conclusions

In summary, this 7 years' observation shows that imiglucerase < 20 U/kg/2 weeks following standard dosage regimen is capable to prevent life-threatening complications. Blood and organ parameters maintained well, but skeletal system disease may progress under such dosage. For patients with splenectomy or high risk of bone diseases, higher dose is necessary to prevent irreversible changes. Our study suggested when ideal standard dosage unaffordable, treatment below recommended minimum dose is valuable to sustain life.

Abbreviations

GD: Gaucher disease; GD1: Gaucher disease type 1; GD3: Gaucher disease type 3; CNS: Central nervous system; ERT: Enzyme replacement therapy; MN: Multiples of normal; MRI: Magnetic Resonance Imaging; X-ray and densitometry (DXA); hemoglobin (Hb); BMD: bone mineral density; proportional mortality rate (PMR); International Collaborative Gaucher Group (ICGG); PUMCH: Peking Union Medical College Hospital.

Declarations

Availability of data and materials

All data used or analyzed during this study are available from the corresponding author.

Ethics approval and consent to participate

Consents were obtained from patients and their parents of each patient. This study was approved by the Peking Union Medical College Hospital Ethics Review Board (approval number: S-644).

Consent for publication

Not applicable.

Competing interests

The authors have stated that they had no competing interests.

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Authors' contributions

Zhengqing Qiu followed the patients and collected medical data. Yuting Wu, Baohui Zhang and Yuhang Song analyzed data. Yuting Wu drafted the first version of the manuscript. Qiu zhengqing and Zhang Hongbing revised the manuscript. All the authors approved the final version and publication of the manuscript.

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Tables

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