Efficacy and Safety of Taliglucerase Alfa for the Treatment of Gaucher Disease: A 9-Year Experience

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Livia d'Avila Paskulin[1,2], Rodrigo Tzovenos Starosta[1,3], Filippo Pinto e Vairo[4,5], Bárbara C. Krug[6], Paulo Picon[6,7] and Ida Vanessa Doederlein Schwartz[1,2,8]

Abstract

Gaucher disease (GD) is one of the most common lysosomal disorders, occurring in approximately 1 in 40,000 live births worldwide. Since 2014 enzyme replacement therapy (ERT) with taliglucerase alfa has been the treatment of choice for adult patients with GD in Brazil. The aim of this study was to evaluate the long-term efficacy and safety of taliglucerase alfa in a cohort of Brazilian patients treated at a referral center for inborn errors of metabolism. All patients who received at least one infusion of the enzyme at the study center were considered eligible to participate. Patients were followed for adverse reactions and events throughout the study period. Platelets, hemoglobin, chitotriosidase activity, bone marrow burden (BMB) score, bone mineral density, and the severity score index (SSI) were analyzed. For patients who were switched to taliglucerase alfa from imiglucerase, the same variables were compared before and after the switch. At 9-year follow-up, all parameters of interest had remained stable or improved. The overall rate of adverse events was lower than in other studies that evaluated long-term ERT with taliglucerase, and no serious adverse events were considered related to treatment. Based on our findings, ERT with taliglucerase alfa is an effective and safe approach for treatment of patients with GD.

Keywords

Gaucher disease, *GBA*, taliglucerase alfa, enzyme replacement therapy.

Introduction

Gaucher disease (GD) is one of the most common lysosomal disorders, with an overall prevalence of 1 in 40,000 live births worldwide [1]. It is caused by deficient activity of the lysosomal enzyme glucocerebrosidase encoded by *GBA*. Accumulation of glucocerebrosides such as glucosylceramide and glucosylsphingosine within macrophages triggers a proinflammatory state [2], as well as cell engorgement leading to symptoms such as hepatosplenomegaly, thrombocytopenia, osteonecrosis, and, in some patients, neurological impairment. GD is categorized into three types, according to the presence and extent of neurological involvement: type 1 GD is characterized by no overt neurological symptoms; type 2 GD, also referred as acute neuronopathic, by neurological compromise which is fatal at an early age; and type 3 GD, the chronic neuronopathic form with onset in late childhood or adulthood.

GD was the first metabolic disorder to be treated successfully with enzyme replacement therapy (ERT) – alglucerase,

[1] Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Genética e Biologia Molecular, Porto Alegre, RS, Brazil.
[2] Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Serviço de Genética Médica, Porto Alegre, RS, Brazil.
[3] Washington University in Saint Louis, Saint Louis Children's Hospital, Division of Clinical Genetics, Saint Louis, MO, USA.
[4] Mayo Clinic, Center for Individualized Medicine, Rochester, MN, USA.
[5] Mayo Clinic, Department of Clinical Genomics, Rochester, MN, USA.
[6] Hospital de Clínicas de Porto Alegre, COMEX, Porto Alegre, RS, Brazil.
[7] Universidade Federal do Rio Grande do Sul, Departamento de Medicina Interna, Porto Alegre, RS, Brazil.
[8] Hospital de Clínicas de Porto Alegre, Laboratório BRAIN, Porto Alegre, RS, Brazil.

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Corresponding Author:
Ida Vanessa D. Schwartz, ischwartz@hcpa.edu.br

a mannose-terminated form of glucocerebrosidase extracted from human placental tissue which was approved by the US Food and Drug Administration (FDA) in 1991 [3]. In 1995, the first recombinant human glucocerebrosidase analogue was developed: imiglucerase, which is expressed in Chinese hamster ovary cells [4–5]. Twenty-five years later, velaglucerase alfa—an enzyme derived from cultured human cells—obtained regulatory approval by the FDA, the European Medication Agency (EMA), and the Brazilian National Health Surveillance Agency (ANVISA) [6].

In 2010, after a worldwide shortage of imiglucerase due to viral contamination in the production facilities [7–8], taliglucerase alfa (a plant-derived recombinant enzyme which had yet to be approved at the time [9–10]), entered emergency use to ensure continuity of care for patients previously treated with imiglucerase. Taliglucerase alfa was approved in 2012, and, since 2014 is the first-line treatment for adult patients with GD in Brazil [11].

Taliglucerase alfa does not require deglycosylation to expose the mannose residues in vitro [12], which both simplifies and reduces the cost of production. On the other hand, as it is plant-derived, it can cause more adverse reactions than mammalian-derived enzymes. Imiglucerase differs from native glucocerebrosidase at amino acid residue 495, where it has a histidine instead of an arginine in the C-terminus. Taliglucerase alfa differs from native glucocerebrosidase by 2 amino acid residues at the C-terminus and up to 7 amino acid residues at the N-terminus. Velaglucerase alfa has an identical secondary structure to native glucocerebrosidase. All three therapeutic enzymes have four exposed N-glycosylation sites which are modified to end in mannose residues. In clinical trials [10], taliglucerase alfa appeared to have similar safety and efficacy profiles compared to imiglucerase [13] and velaglucerase [14]. Cravo et al [15] published a description of a Brazilian experience with taliglucerase alfa in which patients remained stable after switching from imiglucerase, although 85% of the patients experienced at least one adverse event during 3.5 years of follow-up.

Within this context, the present study was conducted to evaluate the long-term efficacy and safety of taliglucerase alfa in a cohort of Brazilian patients with GD.

Methods

This is a retrospective cohort study with a convenience sampling strategy (i.e., only individuals already seen and treated at the Hospital de Clínicas de Porto Alegre were enrolled). Data were collected from January 2012 to January 2021 (Figure 1). The study protocol was approved by the ethics committee of the Hospital de Clínicas de Porto Alegre under the number #13-0537, and all patients provided written informed consent.

Patients

Patients with a biochemical and genetic diagnosis of GD (types 1 or 3) who had received at least one infusion of taliglucerase alfa at the Gaucher Disease Referral Center (GDRC) of Porto Alegre, Brazil, were eligible to participate in the study. Patients were naïve to treatment or have been treated with imiglucerase. All patients had a confirmed pathogenic *GBA* genotype.

Taliglucerase alfa has been prescribed to 18 patients at the GDRC. However, only patients who had been on regular treatment with taliglucerase alfa for more than 6 months (n=9) were included in the efficacy analysis.

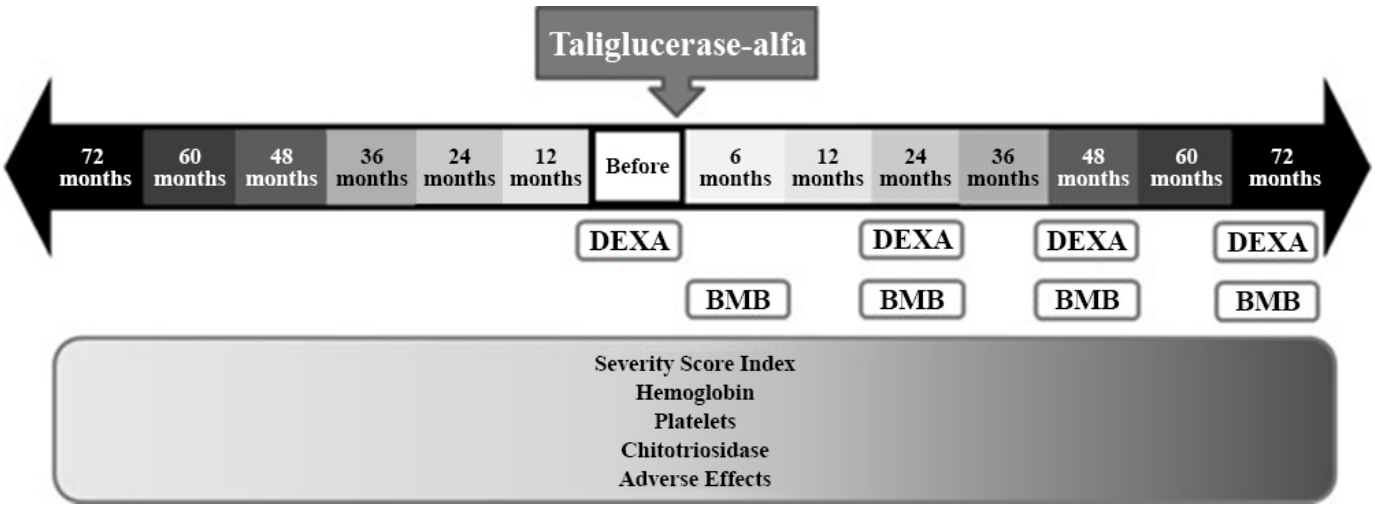

Figure 1. Schematic diagram of study protocol. DEXA was performed before ERT with taliglucerase alfa and every other year thereafter; MRI for BMB score was performed during the first year of treatment and every other year thereafter; Severity Score Index, hemoglobin, platelets, and chitotriosidase were assessed every 3 months; Adverse events were evaluated throughout the study period. BMD = bone mineral density; BMB = Bone Marrow Burden score.

Safety

Patients were followed for adverse reactions (defined as happening during the infusion or before 24 hours of completion of an infusion) and adverse events (defined as happening with no temporal association with infusions) throughout the study period (Figure 1). Adverse events and reactions were categorized as mild, moderate, or severe according to physician's judgement [16].

Efficacy

Severity score index (SSI) [17], hemoglobin, platelets, chitotriosidase activity, and bone parameters were assessed during the study period. For patients who had switched to taliglucerase alfa, the same variables were compared before and after the switch (Figure 1).

SSI, hemoglobin, platelets, and chitotriosidase were assessed every 3 months. Mineral bone disease was assessed through dual-energy X-ray absorptiometry (DXA) measurement of bone mineral density (BMD), classified as normal (T- or Z-score higher than -1.0), osteopenia (T- or Z-score between -1.0 and -2.5), or osteoporosis (T- or Z-score lower than -2.5) in accordance with the International Society of Bone Densitometry 2015 guidelines [18]. Bone marrow involvement was assessed through the bone marrow burden score (BMB) as described by Maas in 2003, where values between 0 and 4 are mild, 5 and 8 are moderate, and 9 and 16 denote severe involvement [19]. Bone parameters were assessed during the first year of treatment with taliglucerase alfa, and subsequently every other year or as clinically indicated (Figure 1).

Statistical Methods

Descriptive statistics were used. Sample size, mean, standard deviation, standard error, and range were used for continuous variables. Number and percentage of patients were used for categorical variables.

Results

Of the 18 patients included, 10 were male. The mean age at the end of follow-up was 46.5 years (range, 23-66 years). Seventeen patients have type 1 GD, and one have type 3 GD. Data regarding age, gender, *GBA* genotype, time on imiglucerase or miglustat treatment before ERT with taliglucerase alfa, and whether the patient was included in the efficacy analysis are described in Table 1.

Safety

Eight patients (8/18, 44.4%) had at least one adverse reaction during treatment with taliglucerase alfa: 4/18 (22.2%) had mild reactions, 3/18 (16.6%) had moderate reactions, and 1/18 (5.6%) had severe reactions. Tables 2 and 3 display the adverse reactions and the adverse events experienced by each patient, together with type of intervention needed, need for hospitalization, severity, and relation to ERT. Two patients had severe adverse reactions: patient J, a 55-year-old man previously treated with imiglucerase and previously diagnosed with multiple myeloma (MM), who died of complications of MM after 21 months on ERT with taliglucerase alfa; and patient K, 62-year-old man naïve to treatment with severe acute-on-chronic hepatic failure who, after the first minutes of infusion, developed hypotension later diagnosed as due to sepsis, progressing to cardiogenic shock and death after 2 days. Both reactions were classified as unrelated to taliglucerase alfa. Patient P, a 14-year-old male with type 3 GD (complicated by epilepsy, severe muscular kyphoscoliosis, and global developmental delay) developed a moderate adverse reaction of anaphylaxis despite premedication with ranitidine, loratadine, and intravenous hydrocortisone; the infusion was discontinued, and hydrocortisone and promethazine were administered intravenously, with resolution of symptoms. This patient was described by Vairo *et al* in 2013 [20] as having previously developed a severe IgE-mediated adverse reaction to imiglucerase after 9 years of treatment. He is currently receiving ERT with velaglucerase and has not experienced further reactions.

Patient G was found to be pregnant after her first infusions of taliglucerase alfa. At the time, there were no recommendations regarding treatment with this enzyme during pregnancy. After discussion with the patient and her family, ERT was maintained. She was referred to a specialized hospital for prenatal care and did not experience any complication during pregnancy. She gave birth to a healthy child through spontaneous vaginal delivery at 39 weeks of pregnancy.

Efficacy

Nine patients completed at least 6 months of treatment with taliglucerase alfa and were included in the efficacy analysis. Hemoglobin, platelets, SSI, and chitotriosidase activity before and after switch to or initiation of taliglucerase alfa are displayed in Figure 2.

BMD results are shown in Table 4. Patient A had osteoporosis with a T-score of -3, which did not improve despite 137 months of ERT with imiglucerase. After switching to taliglucerase alfa, the patient remained stable, with slight improvement of T-score after dose increase. Patient C had a normal BMD at inclusion with a Z-score of -0.6, with worsening to a Z-score diagnostic for osteopenia after 24 months on taliglucerase. It is noticeable, however, that this patient had poor adhesion to treatment (only 27 out of 52 infusions in this period were completed, data not shown). Patients D and E had a Z-score in the osteopenia range before switching to taliglucerase, with improvement to the normal range after switching to taliglucerase. Patient F was naïve to treatment and experienced improvement of BMD T-score from osteopenia to normal after 50 months of taliglucerase alfa treatment. The other patients remained stable on treatment with taliglucerase alfa.

Table 1. Patients' demographic and clinical characteristics.

Patient	Age (years)	Gender	GD Type	GBA Genotype	Time on Imiglucerase (months)	Imiglucerase dose pre-switch (IU/kg/2 weeks)	Time on Miglustat (months)	Miglustat dose pre-switch (mg/day)	Taliglucerase dose post-switch (IU/kg/2 weeks)	Time on Taliglucerase post-switch (months)	Current Dose (IU/kg/2 weeks)	Efficacy Analysis	Safety Analysis
A	65	F	1	p.(Asn409Ser)/ RecNciI	138	15	0	–	30	108	30	+	+
B	53	F	1	p.(Asn409Ser)/ p.Leu483Pro	114	15	0	–	30	106	45	+	+
C	47	M	1	p.(Asn409Ser)/ RecNciI	152	15	0	–	15	76	15	+	+
D	33	M	1	p.(Asn409Ser)/ RecNciI	123	45	0	–	30	107	45	+	+
E	40	M	1	p.(Asn409Ser)/ p.(Leu483Pro)	4	15	0	–	15	108	30	+	+
F	66	M	1	p.(Asn409Ser)/ p.(Asn409Ser)	24	15	0	–	15	108	15	+	+
G	**25**	**F**	**1**	**p.(Asn409Ser)/ p.Leu483Pro**	**0**	**–**	**0**	–	**15**	**60**	**30**	**+**	**+***
H	**54**	**F**	**1**	**p.(Glu388Lys)/ p.(Ser405Asn)**	**0**	**–**	**41**	**300**	**30**	**40**	**15**	**+**	**+**
I	30	M	1	p.(Asn409Ser)/ p.(Leu483Pro + p.Ala495Pro)	238	15	0	–	15	22	15	+	+
J	66	M	1	p.(Asn409Ser)/ p.(Asn409Ser)	35	30	0	–	30	57	30***	–	+

Table 1. Cont

Patient	Age (years)	Gender	GD Type	GBA Genotype	Time on Imiglucerase (months)	Imiglucerase dose pre-switch (IU/kg/2 weeks)	Time on Miglustat (months)	Miglustat dose pre-switch (mg/day)	Taliglucerase dose post-switch (IU/kg/2 weeks)	Time on Taliglucerase post-switch (months)	Current Dose (IU/kg/2 weeks)	Efficacy Analysis	Safety Analysis
K	**62**	**M**	**1**	**p.(Asn409Ser)/ RecNciI**	**0**	**-**	**0**	**–**	**60**	–	–	–	**+**
L	55	M	1	p.(Asn409Ser)/ RecNciI	34	15	0	–	15	–	–	–	+
M	54	M	1	p.(Asn409Ser)/ p.(Leu483Pro)	6	15	0	–	15	–	–	–	+
N	42	F	1	p.(Asn409Ser)/ p.(Leu483Pro)	16	15	0	–	15	–	–	–	+
O	32	F	1	p.(Asn409Ser)/ RecNciI	17	15	0	–	15	–	–	–	+
P	23	M	3	p.(Leu483Pro)/ p.(Leu483Pro)	108 **	60	0	–	60	–	–	–	+
Q	**51**	**F**	**1**	**p.(Glu388Lys)/ p.(Ser405Asn)**	**0**	**–**	**10**	**300**	**30**	–	–	–	**+**
R	39	F	1	p.(Asn409Ser)/ p.(Leu483Pro)	21	30	0	–	30	–	–	–	+
Mean	46.5				52.2	22.5	25.5	300	25.8	45.4	23.9		

+: patient included in the analysis; -: patient excluded from the analysis; * Pregnant during ERT with taliglucerase; ** 34 months with no treatment after severe adverse reaction to imiglucerase; ***last dose before death. Patients highlighted in **bold** are naïve to ERT. Age at end of follow-up or age at death presented. Historically, p.(Asn409Ser) has been called N370S, and p.(Leu483Pro) L444P.

Table 2. Adverse reactions, severity, and relationship to treatment.

Patient	Adverse reaction	Fatal	IV medication	Oral medication	ERT discontinued	Hospitalization required	Severity	ERT-related
G	Nausea, abdominal pain	No	No	Yes	No	No	Mild	Yes
K	Cardiogenic shock secondary to sepsis	Yes	Yes	Yes	Yes	Yes	Severe	No
M	Hyperemia, edema (infusion site reaction)	No	Yes	No	No	No	Mild	Yes
N	Nausea, vomiting, abdominal pain	No	No	Yes	No	No	Mild	Yes
O	Nausea, vomiting, abdominal pain	No	Yes	Yes	Yes	No	Moderate	Yes
P	Anaphylaxis, headache, nausea, vomiting, abdominal pain	No	Yes	Yes	Yes	No	Moderate	Yes
Q	Hyperemia, edema, pruritus, respiratory distress	No	Yes	Yes	Yes	No	Moderate	Yes
R	Nausea, vomiting, abdominal pain	No	Yes	Yes	No	No	Mild	Yes

ERT, enzyme replacement therapy.

Table 3. Adverse events, severity, and relationship to treatment.

Patient	Adverse event	Fatal	Treatment at event	Treatment discontinued	Hospitalization required	Severity	Treatment-related
A	Parkinsonism	No	Tali	No	No	Moderate	No
C	Short PR interval	No	Tali	No	No	Mild	No
F	Arterial coronary disease, heart failure	No	Tali	No	No	Moderate	No
H	Hepatic steatosis	No	Tali	No	No	Mild	Unclear*
J	Progression of multiple myeloma	Yes	Tali	No	Yes	Severe	No
L	Metastatic hepatocellular carcinoma	Yes	Imi	No	Yes	Severe	No
N	Hepatic steatosis	No	Eli	No	No	Mild	Unclear*
O	Hepatic adenoma	No	Imi	No	No	Mild	No
P	Mixed restrictive-obstructive ventilatory disease	No	Vela	No	No	Moderate	No
R	First-trimester intrauterine demise	No	Imi	No	Yes	Severe	No

*a possible causal correlation between treatment and hepatic steatosis has been proposed [30]. Tali = taliglucerase; imi = imiglucerase; eli = eliglustat; vela = velaglucerase

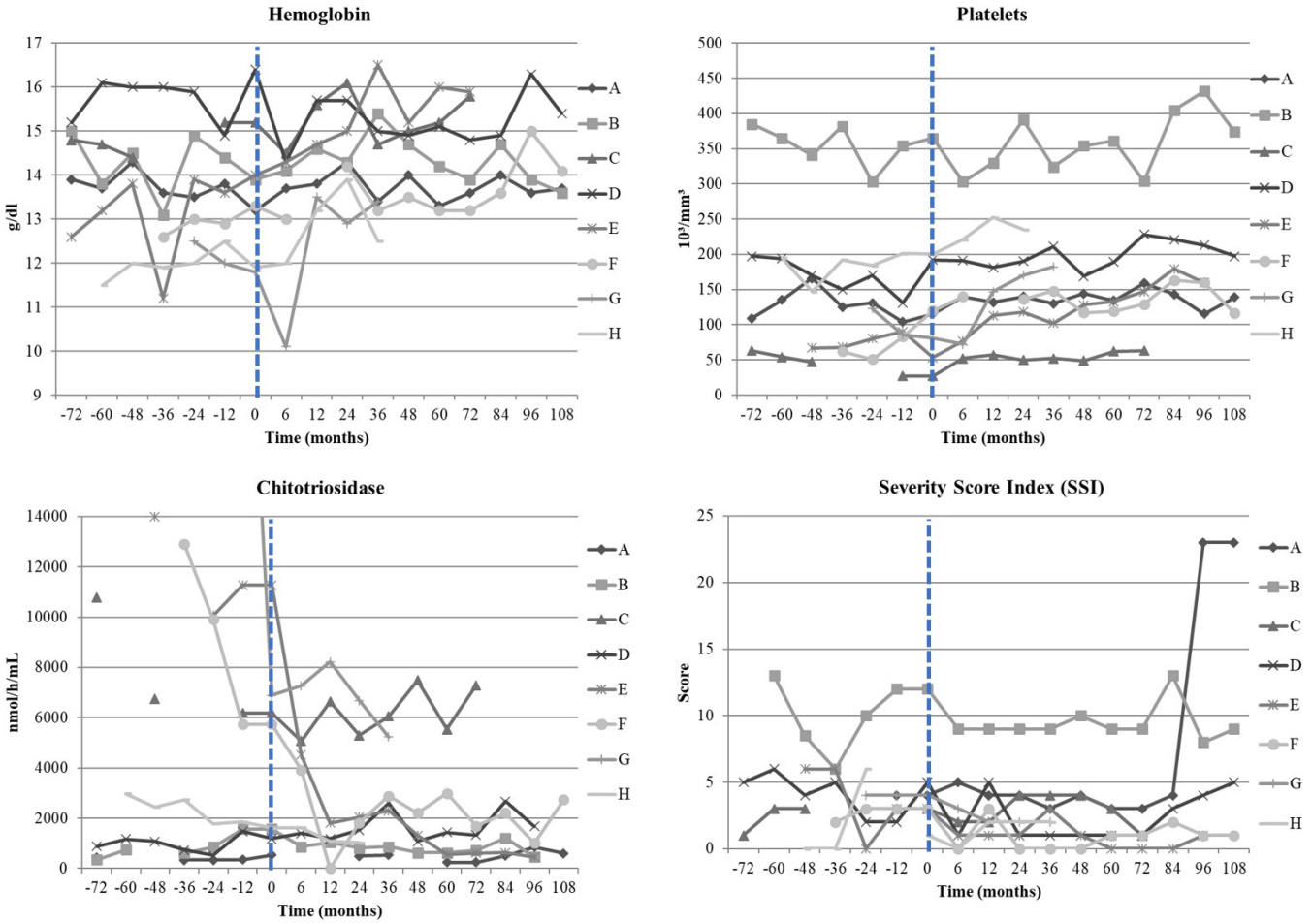

Figure 2. Disease parameters before and during ERT with taliglucerase alfa. Each line represents a different patient. Dashed blue line (Time = 0 months) marks the initiation of ERT with taliglucerase alfa. Patients G and H were treatment-naïve.

Table 4. DEXA bone mineral density prior to switch (BMD1) and after the switch to taliglucerase alfa.

PATIENT (T or Z score)	DEXA Bone Mineral Density (L1-L4)							
	BMD1		BMD2		BMD3		BMD4	
	Time on imiglucerase	Score	Time on taliglucerase	Score	Time on taliglucerase	Score	Time on taliglucerase	Score
A (T)	137	-3	21	-3.3	43	-2.6	56	-2.8
B (T)	104	0.1	28	0.9	49	0.7	83	-0.4
C (Z)	152	-0.6	2	-0.6	24	-1.4	57	-1.3
D (Z)	114	-1.4	41	-0.4	68	-0.5	92	-0.5
E (Z)	0	-1.6	6	0.2	28	0.3	154	-0.9
F (T)	16	-2.3	16	-1.6	50	-1.4	79	-1.4
G (Z)	0	-0.5	22	-0.4	NE	NE	NE	NE

NE = not evaluated.

BMB scores are shown in Table 5. One patient had an increase in BMB score during ERT with taliglucerase alfa: patient B, a 52-year-old splenectomized woman with history of osteonecrosis of the right proximal and distal femur and right proximal humerus who presented with acute bone pain on the left proximal femur after 192 months on ERT (132 months on imiglucerase and 60 months on taliglucerase; median dosage 30 IU/kg biweekly). MRI detected osteonecrosis of the left proximal femur, increasing her total BMB score from 3 to 6. ERT dosage was then increased to 45 IU/kg biweekly.

Table 5. Bone Marrow Burden (BMB) score measured during first year of ERT with taliglucerase alfa and every 2 years thereafter.

PATIENT	BONE MARROW BURDEN					
	BMB1		BMB2		BMB3	
	Time on taliglucerase (months)	Score	Time on taliglucerase (months)	Score	Time on taliglucerase (months)	Score
A	9	3	33	3	59	3
B	7	3	45	3	67	6*
C	3	8	NE	NE	NE	NE
D	8	8	23	8	63	8
E	10	12	23	12	34	12
F	9	6	21	6	52	6

NE = not evaluated; *Femoral osteonecrosis. Mild = 0-4; Moderate = 5-8; Severe = 9-16

Discussion

Treatment-naïve patients experienced improvement in clinical and laboratory parameters, while previously treated patients remained stable after 9 years of ERT with taliglucerase alfa. Only one individual (patient G) had a clinically significant decrease in hemoglobin during the 6th month of treatment; however, this occurred one day after delivery; therefore, it most likely represents an immediate post-partum finding unrelated to inefficiency of taliglucerase alfa, as noticed by the catch-up of hemoglobin levels on follow-up.

One patient had slight improvement in BMD after switching from imiglucerase to taliglucerase alfa, however a concomitant dose change renders this result difficult to interpret; two patients on imiglucerase and one treatment-naïve normalized the BMD after taliglucerase alfa was initiated. The other patients had normal BMD and remained stable. Our findings are consistent with other reports of bone disease in GD, which showed that BMD is usually the slowest treatment target to be achieved [21]. Bone marrow infiltration remained stable for most patients, as expected since patients who had at least two consecutive BMB measurements had already been on ERT for over 5 years [22–24].

Only 8/18 of the patients had adverse reactions and 10/18 had adverse events, a rate lower than that reported by Zimran *et al* in 2019 and by Cravo *et al* in 2018. Zimran *et al* evaluated 17 patients prospectively over 5 years and found that 14 had at least one mild adverse event of which none were related to taliglucerase-alfa treatment according to the physicians' impressions [25]. Cravo *et al* analyzed 35 Brazilian patients for 3.4 years and found that 27 experienced adverse events; unfortunately, this study did not establish whether adverse events were related to ERT [15]. Pastores *et al* (2014) followed 31 patients for 9 months and reported that 32% of the adults (n=8) had at least one adverse event considered related to ERT with taliglucerase alfa [26]. In our cohort, the only severe adverse events were considered unrelated to ERT, and no severe adverse reactions occurred; the treatment-related reactions were mild (n=4) or moderate (n=3). In comparison, velaglucerase has an adverse reaction rate of 12.5-13.3% [27–28]. The adverse reaction rate of imiglucerase is uncertain but has been reported to be as low as 3% [29]. Based on the current study and the available data, it is not possible to directly compare the rate of adverse reactions in different ERT modalities.

Conclusion

Based on our long-term experience, ERT with taliglucerase alfa is an effective and safe approach for treatment of patients with GD. Platelets, hemoglobin, chitotriosidase activity, BMB score, BMD, and SSI remained stable or improved after 6 years of treatment. The overall rate of adverse events was low, and no serious adverse events were considered to be treatment-related.

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Declaration of Conflicting Interests

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