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Patients with type 1 Gaucher disease in Spain: A cross-sectional evaluation of health status

Pilar Giraldo [a,b,*], Jordi Pérez-López [c], Ramiro Núñez [d], Rafael Fernández de la Puebla [e], Elisa Luño [f], Salvador Saura-Grau [g], Juan Carlos Bureo [h], Sylvia Plaza [i], Javier de la Serna [j]

[a] Translational Research Unit, Miguel Servet University Hospital, IIS Aragón, CIBER de Enfermedades Raras (CIBERER), Aragon Institute of Health Sciences (IACS), Zaragoza, Spain
[b] Spanish Foundation for the Study and Therapy of Gaucher Disease (FEETEG), Spain
[c] Department of Internal Medicine, Vall d'Hebron Hospital, Barcelona, Spain
[d] Department of Hematology, Virgen del Rocío Hospital, Sevilla, Spain
[e] Department of Internal Medicine, Reina Sofía Hospital, Córdoba, Spain
[f] Department of Hematology, Central de Asturias Hospital, Oviedo, Spain
[g] Department of Medical Oncology, Dr. Negrín Hospital, Las Palmas, Spain
[h] Department of Internal Medicine, Infanta Cristina Hospital, Badajoz, Spain
[i] Medical Affairs, Shire Pharmaceuticals Ibérica, Madrid, Spain
[j] Department of Hematology, 12 de Octubre Hospital, Madrid, Spain

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ABSTRACT

A multicentre, cross-sectional epidemiological survey was conducted to describe the health status of patients with type 1 Gaucher disease (GD1) in Spain. Patient data were collected retrospectively from clinical records. Therapeutic goals for seven clinical parameters were chosen as primary outcome measures. 108 GD1 patients (mean age 44.8 years; 53% male) were recruited from 28 hospitals. Ninety-five patients (88%) were receiving treatment for GD1. Hemoglobin concentration was the therapeutic goal with the highest level of achievement, being met by 105 of 108 patients (97%), followed by the goals for liver volume (86/98 patients; 88%), spleen volume (67/77 patients; 87%) and platelet count (81/108 patients; 75%). The goal for bone mineral density (BMD) was met by 48 of 75 patients (64%), and the goal for quality of life was met by 65 of 103 patients (63%). Bone pain was the parameter with the lowest level of achievement (goal met by 50/94 patients; 53%). The clinical information most often missing from patient records was the BMD Z-score (missing for 31% of patients). These data suggest that most Spanish GD1 patients have good control over hematological and visceral parameters, but there is a need to improve monitoring and treatment of GD-related bone disease.

1. Introduction

Gaucher disease (GD; OMIM #230800) is an autosomal recessive disorder caused by deficient activity of the glucocerebrosidase enzyme (GBA; EC 3.2.1.45) required for the degradation of glycosphingolipids. GBA deficiency leads to accumulation of the enzyme's substrate in the lysosomes of monocyte-lineage cells which develop into pathologic "Gaucher cells" in visceral tissues [1,2]. GD has been classified into three subtypes according to the presence or absence of neurological features. Type 1 Gaucher disease (GD1) is the most common, and is characterized by the lack of central nervous system involvement. GD2 and GD3 are characterized by acute and chronic neurologic symptoms, respectively. More than 350 mutations have been described in the *GBA* gene region as the cause of GD [3]. The most common *GBA* genotype in GD1 patients is N370S/N370S, which tends to result in milder disease, followed by N370S/L444P [4–6].

The prevalence of GD in the Iberian Peninsula is estimated to be 1:149,000, similar to that of other European populations [7]. Approximately 88% of the affected population have GD1, with the most common *GBA* mutations being N370S/L444P (32%) and N370S/N370S (17%). The Spanish Foundation for the Study and Treatment of Gaucher Disease (FEETEG) reports that there are currently 342 GD1 patients in Spain [8].

Clinical manifestations of GD1 commonly include anemia, thrombocytopenia, hepatomegaly, splenomegaly and bone disease [9–12].

Abbreviations: ANOVA, one-way analysis of variance; BMD, bone mineral density; BMI, body mass index; CCL18, chemokine (C-C motif) ligand 18; EC, Enzyme commission number; ERT, enzyme replacement therapy; GBA, glucocerebrosidase; GD, Gaucher disease; DXA, dual energy X-ray absorptiometry; IQR, interquartile range; MAP Tool®, monitor, action and progress tool; MN, multiples of normal; MRI, magnetic resonance imaging; OMIM, Online Mendelian Inheritance in Man; QoL, quality of life; SD, standard deviation; SRT, substrate reduction therapy; VAS, visual analog scale.

* Corresponding author at: Translational Research Unit, Miguel Servet University Hospital-IACS, P° Isabel La Catolica 1-3, 50009, Zaragoza, Spain.
E-mail addresses: giraldocastellano@gmail.com (P. Giraldo), jordperez@vhebron.net (J. Pérez-López), ramirojosenv@gmail.com (R. Núñez), fdezpuebla@gmail.com (R.F. de la Puebla), eluno@uniovi.es (E. Luño), ssauragrau@hotmail.com (S. Saura-Grau), splaza@shire.com (S. Plaza), drjdelaserna@gmail.com (J. de la Serna).

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Pulmonary involvement and other manifestations such as coagulation abnormalities and secondary neurologic disease are also observed [13–15].

There are currently two main types of treatment for GD1: enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), which have both been shown to be effective in improving key disease parameters [16].

The clinical heterogeneity of GD1 requires an individualized approach to disease management. In 2004, an international consensus on the therapeutic goals for GD1 treatment was published to aid in therapeutic decision-making [17]. The primary objective of the present study was to describe the clinical characteristics and current health status of GD1 patients managed in Spanish hospitals, particularly with regard to the achievement of therapeutic goals. The secondary objectives of the study included describing patients according to differences in their disease management, such as by treatment and splenectomy status.

2. Materials and methods

2.1. Study design and patients

This was a multicenter observational, cross-sectional epidemiological study designed and conducted by investigators managing GD1 patients in Spanish hospitals (Study identification number: SHI-TSE-2011-01, Vall d'Hebron University Hospital). The study protocol was reviewed and approved by ethics committees of the participating hospitals, and was conducted in accordance with the Helsinki Declaration of 1975 as revised in 2008. All patients were required to sign an informed consent form. Patients younger than 18 years of age provided informed consent via a parent or legal representative.

The study recruitment period lasted 7 months (June 2012 to January 2013) and data were gathered in a central database until April 2013. Involvement in the study was proposed to investigators by the study sponsor if they were identified as managing GD1 patients in Spanish hospitals or specialized centers. GD1 patients attending a routine clinical visit during the study recruitment period were invited to participate. Patients who agreed to participate and signed the consent form were included in the study. Patients were excluded if they were considered by the investigator to have limited cognitive abilities or impaired capacity to complete the study documentation.

The therapeutic goals MAP (Monitor, Action and Progress) Tool®, an application designed to collect and collate clinical data in one simple visual output, was used for data collection. Data were collected retrospectively from the clinical records of participating patients during a single study visit. These data included information recorded in the 6 to 12 months prior to the study visit, with the exception of the quality of life (QoL) questionnaire that was supplied at the study visit.

2.2. Outcome measures

The therapeutic goals based on a published concensus [17] for seven clinical parameters were the primary outcome measures for the study. One measurement per parameter was collected for each patient where available. The therapeutic goals for each parameter were defined as: 1) hemoglobin concentration ≥ 12 g/dL for men or ≥11 g/dL for women and children <18 years old; 2) platelet count ≥120 × 10^9/L; 3) spleen volume ≤ 8 multiples of normal (MN) as measured by magnetic resonance imaging (MRI) or ultrasound; 4) liver volume ≤ 1.5 MN as measured by ultrasound; 5) bone pain ≤1 as a patient-reported level of pain in the last 24 h according to the visual analog scale (VAS; 0–10) where 0–1 is little or no pain, 2–4 is mild, 5–7 is moderate, and 8–10 is severe or extreme pain; 6) bone mineral density (BMD) Z-score ≥ −1, measured by dual energy X-ray absorptiometry (DXA), with the ability to distinguish where the scan was performed (in the lumbar spine, femoral neck or distal forearm); 7) QoL SF-36 score ≥ 70, obtained from the physical component of the SF-36 questionnaire [18] by averaging the scores for vitality and physical function (scored from 0 to 100).

Additional information collected included sociodemographic and physical characteristics, as well as clinical data. Data collected from clinical records included details of GD1 disease history, disease features, and treatment.

2.3. Statistical analysis

Patient characteristics were summarized for the whole study population, and also analyzed according to treatment status (on treatment vs. untreated) and splenectomy status (splenectomized vs. non-splenectomized). Primary clinical parameters were analyzed in groups according to treatment status, splenectomy status, time since diagnosis (<10 years vs. 10–20 years vs. >20 years), or time since treatment initiation (<10 years vs. ≥10 years). A focused analysis of BMD was also conducted, classifying patients according to their BMD age-, sex- and race-matched DXA Z-scores (retrieved from patients' medical records).

As this was a cross-sectional study and some data were missing for the primary parameters, two independent analysis populations were defined for sensitivity analysis: the Full Analysis Set comprising all enrolled patients who met the enrolment criteria and gave informed consent (n = 108), and the Complete Data Analysis Set comprising patients in the Full Analysis Set with complete data for all seven primary parameters (n = 65). No imputation was performed for missing values and instances of missing data are indicated in the results tables.

Categorical variables were summarized by calculating the patient frequencies and percentages. Comparisons of categorical variables between two or more groups were made through Fisher's exact and Chi-square tests, respectively. Continuous variables were descriptively summarized with means, standard deviations, medians and interquartile ranges (IQRs). Comparison of continuous variables between two groups was made using the Mann–Whitney U test or Student's *t*-test, and between three or more groups using the Kruskal-Wallis test. The two-sided significance level for all statistical tests was 0.05.

All statistical analyses were performed using the SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

Approximately 50 investigators at 50 hospitals were invited to be involved in the study; 35 investigators at 28 hospitals accepted, and recruited patients into the study. One hundred and eight GD1 patients geographically representing 10 of Spain's 17 autonomous communities were enrolled (Fig. 1).

3.2. Patient characteristics

Patients had a mean age of 44.8 ± 16.6 years, and nine (8%) were children (5–17 years of age). Fifty-seven patients (53%) were male (Table 1). The most frequent *GBA* mutation was N370S, seen in 95 of 105 patients (90%). The median age of onset of GD1 symptoms was 20.7 (IQR 8.2–33.0) years, with diagnosis occurring at a median age of 28.0 (IQR 14.2–38.0) years. Pre-existing bone complications were recorded for 23 patients (21%).

Ninety-five patients (88%) were receiving treatment for GD1, of whom 68 (72%) were receiving ERT (46 on imiglucerase, 22 on velaglucerase alfa) and 20 (21%) were receiving SRT (miglustat). At the study visit, the mean time on treatment for all patients was 10 years (119.0 ± 73.4 months; data not shown). Adverse events were identified in the clinical records of three patients: impotence, migraine and facial erythema, and pain during infusion. The latter was an infusion-related reaction and was the only adverse event considered

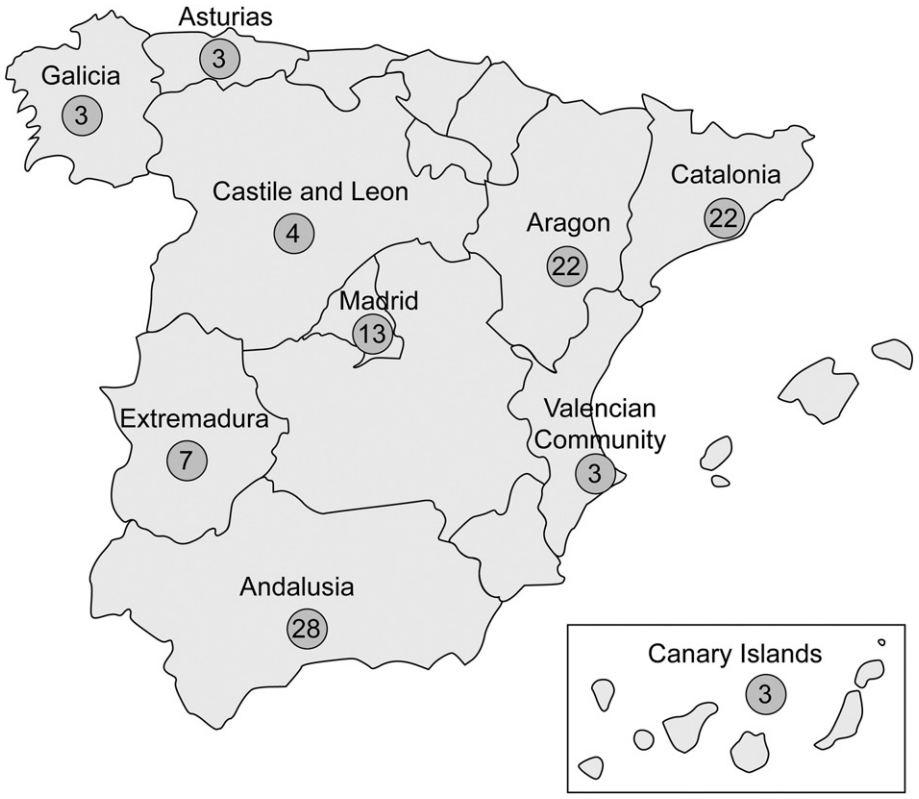

Fig. 1. Geographic distribution of GD1 study patients. One hundred and eight patients from 28 hospitals across 10 of Spain's 17 autonomous communities were recruited to the study. The dark gray circles on the map display the number of patients recruited from each community. The study population represents approximately a third of all GD1 patients in Spain, currently reported to be 342 by the Spanish Foundation for the Study and Treatment of Gaucher Disease (FEETEG).

related to treatment (velaglucerase alfa). None of the patients had positive test results for anti-drug antibodies. Patients on treatment had a younger median age at diagnosis compared with untreated patients (25.2 [IQR 12.2–34.2] years vs. 37.2 [IQR 31.5–49.1 years; $p = 0.007$] and showed less bleeding tendency (6% vs. 23%; $p = 0.040$) (Table 1).

Twenty-seven patients (25%) had undergone splenectomy. Splenectomized patients had an older mean age at study visit compared with non-splenectomized patients (50.9 ± 13.8 years vs. 42.7 ± 17.1 years; $p = 0.0262$), and were less likely to have a family history of GD1 (22% vs. 49%; $p = 0.0134$) (Table 1); they also showed more comorbidities (67% vs. 30%; $p = 0.0006$) and a higher percentage of osteonecrosis (30% vs. 12%; $p = 0.037$).

3.3. Achievement of therapeutic goals

3.3.1. Full analysis set

Therapeutic goals for the seven parameters were met by the majority of patients (Table 2). Hemoglobin concentration was the therapeutic goal with the highest level of achievement, being met by 105 of 108 patients (97%), followed by the goals for liver volume (86/98 patients; 88%), spleen volume (67/77 patients; 87%) and platelet count (81/108 patients; 75%). Bone pain in the past 24 h was the parameter with the lowest level of goal achievement, with the goal being met by 50 of 94 patients (53%).

Median platelet count was higher for patients on treatment compared with untreated patients (Table 2). Patients on treatment also showed a lower median CCL18 level and chitotriosidase activity.

No statistically significant differences were observed for therapeutic goal achievement when splenectomized patients were compared with non-splenectomized patients. However, splenectomized patients had a significantly higher mean platelet count and higher median CCL18 level (Table 2).

Analyses according to time since diagnosis or treatment initiation showed that patients whose diagnosis occurred 10 to 20 years ago were more likely to have smaller values for liver volume compared with those diagnosed more than 20 years ago, or less than 10 years ago (1.1 ± 0.3 MN vs. 1.1 ± 0.2 MN vs. 1.4 ± 0.4 MN; $p = 0.005$). Mean liver volume was also smaller for patients who started treatment 10 or more years ago, compared with those who started treatment less than 10 years ago (1.1 ± 0.3 MN vs. 1.2 ± 0.3 MN; $p = 0.010$), although no statistically significant differences were seen in the percentages of patients meeting the therapeutic goal for liver volume (89.7% for ≥10 years vs. 88.6% for <10 years).

3.3.2. Complete data analysis set

We analyzed patients who had complete data for all seven primary outcome measures ($n = 65$). The parameters with the most missing values were BMD (missing data for 33 patients; 31%) and bone pain (missing for 14 patients; 13%) (Table 2).

The mean values for each of the primary parameters for the Complete Data Analysis Set were displayed on the MAP Tool® chart for a visual indication of this group's health status (Fig. 2). Analysis of the Complete Data Analysis Set did not reveal notable differences in the observed values for the primary parameters, nor in the percentages of patients achieving the therapeutic goals when compared with the Full Analysis Set (Table 3). The therapeutic goals met by the lowest percentage of patients in the Complete Data Analysis Set were those related to bone disease (Fig. 3).

3.3.3. Assessment of bone mineral density

Of the patients in the Full Analysis Set with available BMD data, 48 (48/75; 64%) had Z-scores in the normal range and 27 (36%) were categorized as osteopenic or osteoporotic (Table 4). There was little difference between the treated and untreated patient groups in the percentages of patients with missing BMD data (29/95; 30.5% vs. 4/13;

Table 1
Patient characteristics of the Full Analysis Set (n = 108).

			All patients	By treatment status			By splenectomy status		
				Untreated	On treatment	p-value	Non splenectomized	Splenectomized	p-value
			n = 108	n = 13	n = 95		n = 81	n = 27	
Age (years)		n (missing)	107 (1)	13 (0)	94 (1)		80 (1)	27 (0)	
		Mean (SD)	44.8 (16.6)	48.7 (19.8)	44.3 (16.2)	ns[T]	42.7 (17.1)	50.9 (13.8)	0.0262[T]
Gender	Male	n (%)	57 (53)	9 (69)	48 (51)	ns[C]	41 (51)	16 (59)	ns[C]
	Female	n (%)	51 (47)	4 (31)	47 (50)		40 (49)	11 (41)	
Height (m)		n (missing)	96 (12)	11 (2)	85 (10)		71 (10)	25 (2)	
		Median (IQR)	1.7 (1.6–1.7)	1.7 (1.6–1.7)	1.7 (1.6–1.7)	ns[U]	1.7 (1.6–1.7)	1.7 (1.6–1.7)	ns[U]
Weight (kg)		n (missing)	103 (5)	11 (2)	92 (3)		76 (5)	27 (0)	
		Median (IQR)	67 (58–75)	70 (55–76)	67 (58–75)	ns[U]	66 (55–75)	70 (61–74)	ns[U]
BMI[a]	Underweight (<18.5)	n (%)	3 (3)	1 (9)	2 (2)		3 (4)	0 (0)	
	Normal (18.5–24.99)	n (%)	64 (67)	5 (46)	59 (70)		48 (69)	16 (64)	
	Overweight (≥25.0)	n (%)	22 (23)	5 (46)	17 (20)	ns[F]	15 (21)	7 (28)	ns[F]
	Obese (≥30.0)	n (%)	6 (6)	0 (0)	6 (7)		4 (6)	2 (8)	
	Missing	n	13	2	11		11	2	
Age at symptom onset (years)		n (missing)	88 (20)	7 (6)	81 (14)		61 (20)	27(0)	
		Median (IQR)	20.7 (8.2–33.0)	32.0 (10.0–39.0)	20.0 (8.0–33.0)	ns[U]	22.7 (6.3-33.9)	18.6 (9.0–32.0)	ns[U]
Age at diagnosis (years)		n (missing)	105 (3)	12 (1)	93 (2)		78 (3)	27 (0)	
		Mean (SD)	27.5 (16.4)	39.7 (14.7)	25.9 (16.0)		27.8 (16.5)	26.6 (16.3)	ns[T]
		Median (IQR)	28.0 (14.2–38.0)	37.2 (31.5–49.1)	25.2 (12.2–34.2)	0.007[U]	28.2 (14.2-38.0)	24.0 (12.2–38.0)	
Family history of Gaucher disease[b]	Yes	n (%)	46 (43)	7 (54)	39 (41)	ns[C]	40 (49)	6 (22)	0.0134[C]
Pre-existing bone complication	Yes	n (%)	23 (21)	3 (23)	20 (21)	ns[F]	16 (20)	7 (26)	ns[C]
Osteonecrosis	Yes	n (%)	18 (17)	2 (15)	16 (17)	ns[F]	10 (12)	8 (30)	0.037[C]
Comorbidities	Yes	n (%)	42 (39)	4 (31)	38 (40)	ns[C]	24 (30)	18 (67)	0.0006[C]
Transfusion dependency	Yes	n (%)	1 (1)	0 (0)	1 (1)	ns[F]	0 (0)	1 (4)	
Bleeding tendency	Yes	n (%)	9 (8)	3 (23)	6 (6)	0.040[C]	7 (9)	2 (7)	ns[F]
Pulmonary involvement	Yes	n (%)	3 (3)	2 (15)	1 (1)	0.0377[F]	2 (3)	1 (4)	ns[F]
Neurological symptoms	Yes	n (%)	3 (3)	0 (0)	3 (3)	ns[F]	3 (4)	0 (0)	ns[F]
Splenectomy	Yes	n (%)	27 (25)	2 (15)	25 (26)	ns[F]	0 (0)	27 (100)	NA
Genotype	N370S/N370S	n (%)	29 (27)	4 (33)	25 (27)		24 (31)	5 (19)	
	N370S/L444P	n (%)	36 (33)	2 (17)	34 (37)		27 (35)	9 (33)	
	N370S/RECNCI1	n (%)	1 (1)	0 (0)	1 (1)		1 (1)	0 (0)	
	N370S/Other	n (%)	29 (27)	2 (17)	27 (29)		17 (22)	12 (44)	
	L444P/Other	n (%)	1 (1)	0 (0)	1 (1)	0.0472[F]	0 (0)	1 (4)	ns[F]
	D409H/D409H[c]	n (%)	1 (1)	0 (0)	1 (1)		1 (1)	0 (0)	
	D409H/Other	n (%)	5 (5)	2 (17)	3 (3)		5 (6)	0 (0)	
	Other/Other	n (%)	3 (3)	2 (17)	1 (1)		3 (4)	0 (0)	
	Missing	n	3	1	2		3	0	
Treatment	Yes	n (%)	95 (88)	NA	95 (100)		70 (86)	25 (93)	ns[F]
Type of treatment	Imiglucerase	n (%)	46 (43)	–	46 (48)		35 (50)	11 (44)	
	Velaglucerase alfa	n (%)	22 (20)	–	22 (23)		15 (21)	7 (28)	
	Alglucerase	n (%)	0 (0)	–	0 (0)		0 (0)	0 (0)	
	Miglustat	n (%)	20 (19)	–	20 (21)		14 (20)	6 (24)	
	Imiglucerase + miglustat	n (%)	3 (3)	–	3 (3)		3 (4)	0 (0)	
	Other	n (%)	4 (4)	–	4 (4)		3 (4)	1 (4)	
Adverse events	Yes	n (%)	3 (3)	NA	3 (3)	NA	3 (4)	0 (0)	ns[F]
Infusion related reactions	Yes	n (%)	1 (1)	NA	1 (1)	NA	1 (1)	0 (0)	ns[F]

[F]Fisher's exact test.
[C]Chi-square test.
[T]Student's *t*-test.
[U]Mann–Whitney U test.
SD, standard deviation; IQR, interquartile range; ns, non-significant; NA, not applicable.
[a] Adults were classified according to the WHO Global Database on BMI classifications [25] as defined in the table. For children <18 years old, percentiles for BMI were calculated according to age and sex, and classified according to Underweight (<15th percentile), Normal (15–85th percentile), Overweight (>85–97th percentile) and Obese (>97th percentile).
[b] No information on the number of siblings in the study population is available as data were collected anonymously.
[c] Patient reclassified after finalization of the study as having GD type 3c due to clinical evolution of their disease.

30.8%). The distribution of patients across the three BMD categories was similar for the Complete Data Analysis Set.

In the Full Analysis Set, a higher percentage of splenectomized patients was categorized as osteoporotic (5 of 17 patients; 29%) compared with non-splenectomized patients (3 of 58 patients; 5%). Furthermore, a higher percentage of splenectomized patients had low BMD Z-scores <— 1 even if they were on treatment, though the number of untreated patients was too small to draw any conclusions (Table 4).

4. Discussion

We conducted a cross-sectional observational study to assess the clinical characteristics and health status of Spanish GD1 patients. This is the first study where therapeutic goals have been used to evaluate the health status of GD1 patients in Spain. Although GD1 is a rare disease, 108 patients participated in the study, accounting for approximately one third of all GD1 patients included in the Spanish GD

Table 2
Status and achievement of therapeutic goals in the Full Analysis Set (n = 108).

		All patients	By treatment status			By splenectomy status		
			Untreated	On treatment	p-value	Non-splenectomized	Splenectomized	p-value
		n = 108	n = 13	n = 95		n = 81	n = 27	
Hemoglobin concentration (g/dL)	n (missing)	108 (0)	13 (0)	95 (0)		81 (0)	27 (0)	
	Mean (SD)	13.6 (1.5)	13.3 (1.3)	13.6 (1.5)	0.459[T]	13.6 (1.5)	13.5 (1.3)	
	Median (IQR)	13.6 (12.8–14.6)	13.1 (12.8–14.3)	13.6 (12.8–14.6)		13.6 (12.9–14.6)	13.5 (12.5–14.5)	0.586[U]
Goal achievers (♂≥12 and ♀≥11)	*n (%)*	*105 (97)*				*79 (98)*	*26 (96)*	*1.000[F]*
Platelet count (10^9/L)	n (missing)	108 (0)	13 (0)	95 (0)		81 (0)	27 (0)	
	Mean (SD)	177 (89.1)	134 (57.3)	183 (91.2)		148 (50.1)	264 (120.0)	<0.001[T]
	Median (IQR)	164 (117–200)	135 (87–150)	167 (120–201)	0.048[U]	144 (110–186)	247 (170–351)	
Goal achievers (Platelet count ≥120)	*n (%)*	*81 (75)*				*57 (70)*	*24 (89)*	*0.054[C]*
Splenomegaly (MN)	n (missing)	77 (4)	11 (0)	66 (4)		77 (4)	27 (0)	
	Median (IQR)	1.3 (1.0–4.0)	1.3 (1.0–5.0)	1.4 (1.0–4.0)	0.965[U]	1.3 (1.0–4.0)	-	NA
Goal achievers (Spleen volume ≤8 MN)	*n (%)*	*67 (87)*				*67 (87)*	-	*NA*
Hepatomegaly (MN)	n (missing)	98 (10)	13 (0)	85 (10)		75 (6)	23 (4)	
	Median (IQR)	1.0 (1.0–1.3)	1.1 (1.0–1.7)	1.0 (1.0–1.3)	0.192[U]	1.0 (1.0–1.2)	1.0 (1.0–1.5)	0.3225[U]
Goal achievers (Liver volume ≤1.5 MN)	*n (%)*	*86 (88)*				*67 (89)*	*19 (83)*	*0.468[F]*
Bone pain in the last 24 hours (VAS 0–10)	n (missing)	94 (14)	13 (0)	81 (14)		71 (10)	23 (4)	
	Median (IQR)	1.0 (0.0–3.0)	1.5 (0.0–2.0)	1.0 (0.0–3.0)	0.813[U]	1.0 (0.0–3.0)	2.0 (0.0–3.0)	0.365[U]
Goal achievers (VAS ≤1)	*n (%)*	*50 (53)*				*41 (58)*	*9 (39)*	*0.120[C]*
Bone pain among patients having pain[a] (VAS >0)	n (%)	59 (63)	8 (62)	51 (63)		43 (61)	16 (70)	
	Median (IQR)	2.0 (1.0- 4.0)	2.0 (1.8–6.5)	2.4 (1.0–4.0)	0.525[U]	2.0 (1.0–4.0)	3.0 (2.0–3.5)	0.643[U]
Bone mineral density (DXA Z-score)	n (missing)	75 (33)	9 (4)	66 (29)		58 (23)	17 (10)	
	Mean (SD)	-0.7 (1.3)	-0.7 (1.6)	-0.8 (1.2)	0.931[T]	-0.6 (1.2)	-1.1 (1.5)	0.157[T]
Goal achievers (DXA Z-score ≥-1)	*n (%)*	*48 (64)*				*39 (67)*	*9 (53)*	*0.28[C]*
Physical Component Score of SF-36 (0 - 100)	n (missing)	103 (5)	13 (0)	90 (5)		78 (3)	25 (2)	
	Median (IQR)	80 (60–85)	75 (63–80)	80 (60–85)	0.823[U]	80 (60–88)	75 (60–83)	0.684[U]
Goal achievers (PCS ≥70)	*n (%)*	*65 (63)*				*49 (63)*	*16 (64)*	*0.915[C]*
CCL18 (ng/mL)	n (%)	67 (62)	10 (77)	57 (60)		49 (61)	18 (67)	
	n (missing)	59 (8)	9 (1)	50 (7)		44 (5)	15 (3)	
	Median (IQR)	259 (136–543)	515 (310–967)	215 (131–448)	0.018[U]	215 (116–419)	631 (152–877)	0.034[U]
Chitotriosidase (nmol/mL/h)	n (%)	88 (82)	12 (92)	76 (80)		65 (80)	23 (85)	
	n (missing)	81 (7)	12 (0)	69 (7)		59 (6)	22 (1)	
	Median (IQR)	1257 (553–3150)	2896 (164-–8491)	987 (456–2800)	0.002[U]	1143 (380–3150)	1729 (818–3505)	0.3529[U]
Number of goals achieved (0–7)	n	108						
	Mean (SD)	4.6 (1.4)						
Patients achieving goals								
7	n (%)	10 (9)						
6	n (%)	21 (19)						
5	n (%)	33 (31)						
4	n (%)	21 (19)						
3	n (%)	11 (10)						
2	n (%)	12 (11)						

[F], Fisher's exact test; [C], Chi-square test; [T], Student's *t*-test; [U], Mann-Whitney U test.
SD, standard deviation; IQR, interquartile range; NA, not applicable.
[a] VAS pain value of patients who declared having any level of pain in the past 24 h.

Registry [8]. The MAP Tool® is currently not widely recognized by the Gaucher community as an effective tool. Therefore, statistical analyses independent from the MAP Tool® were conducted to analyze all data collected.

Our data share similarities with a previous report describing the distribution, clinical and genetic characteristics of GD1 patients in the Iberian Peninsula (Spain and Portugal) [7]. The age at diagnosis was comparable (27.5 vs. 28.7 years), and splenectomy was more common in older patients. The genotypes reported were consistent with those found in our cohort, with N370S being the most frequent *GBA* mutation. They also reported GD1 patients with the D409H mutation, an allele that has been linked to cardiovascular and neurological symptoms, and is seen in GD3; six GD1 patients in our study had the D409H mutation, though only one patient was homozygous for this allele. The D409H homozygous patient was reclassified after the finalization of the study as having GD type 3c, due to clinical evolution of their disease. This reclassification does not compromise the final results of the study.

Compared with other countries, our study population had a high average age at diagnosis which has been reported to be 17 years in Latin America [19] and 22 years in France [20] though these studies included patients with all types of GD. The study in Latin America reported a much lower percentage of splenectomized patients compared with our study (7% vs. 25%), but a similar percentage of patients receiving treatment (89% vs. 88%). The study in France had a similar number of splenectomized patients compared with our study (19% vs. 25%), but a lower percentage of patients receiving treatment (78% vs. 88%).

Nearly all patients in our study (>85%) were meeting the therapeutic goals for hemoglobin concentration, hepatomegaly and splenomegaly, and three-quarters of patients were meeting the goal for platelet count.

Most patients (88%) were receiving ERT or SRT as treatment for GD1. Patients on treatment had significantly lower CCL18 levels and

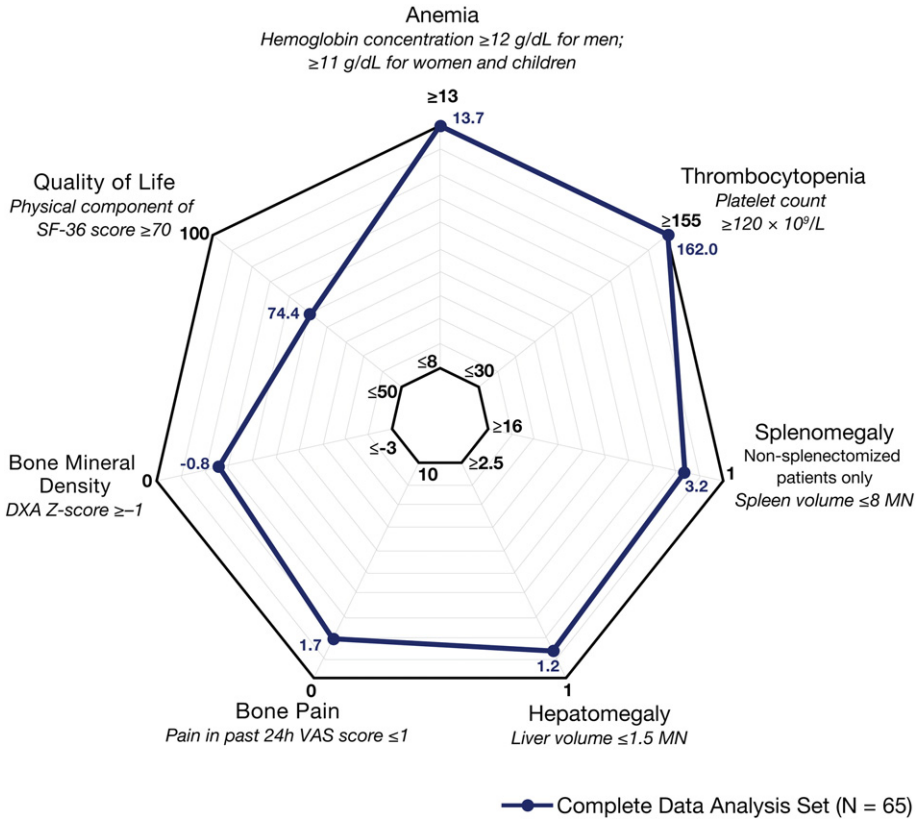

Fig. 2. Graphical display of health status in the Complete Data Analysis Set. The mean observed values for primary parameters for the Complete Data Analysis Set are visualized using the MAP Tool® chart. Values indicating better health status appear toward the outermost ring of the chart, while those indicating poorer health status are plotted toward the innermost ring.

chitotriosidase activity than untreated patients. These plasma biomarkers are markedly elevated in GD1 patients and are viewed as a reflection of the overall body burden of Gaucher cells [21].

Three adverse events were found in the clinical records of our study patients. One of these events was considered to be treatment-related where the patient experienced diffuse abdominal pain during and after intravenous infusion with velaglucerase alfa. The patient discontinued treatment due to poor tolerance.

The most important finding of this study is evidence that patients are not being followed appropriately for bone disease. Clinical or radiographic evidence of bone disease is found in 70–100% of GD1 patients and ranges from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis [12]. Furthermore, bone disease commonly develops without obvious symptoms and although ERT may be effective for skeletal pathology, the response can take longer than the time taken to ameliorate other symptoms [22,23]. It is also possible for bone disease to develop during treatment [20]. In our study, a third of patients were not routinely followed for BMD, and 36% of those who were followed had a Z-score in the osteopenic or osteoporotic range. Low BMD of the lumbar spine has been reported as a strong risk factor for fractures in GD1 patients [24]. We found that splenectomy was associated with low BMD Z-scores <-2.5, which is consistent with previous data suggesting that deterioration of bone disease often occurs after splenectomy [13].

A limitation of our study is, as in every rare disease, the low number of accessible patients and geographical dispersion, resulting in a low power to detect differences and a decreased ability to generalize due to potential selection bias. As this was an observational study based on data collected from routine clinical practice, there was no randomization, nor a sampling procedure to assure representativeness. Furthermore, only one measurement per parameter was collected from each patient. This may impact the study results since patients had varying degrees of disease severity, and different lengths of time on treatment and time since undergoing splenectomy. No adjustments were made for these factors when making comparisons between groups and the data reflect the heterogeneity observed in clinical practice.

5. Conclusions

GD1 patients in Spain appear to have good control of hematologic and visceral parameters and most patients are meeting the established therapeutic goals [17] for these clinical parameters. Bone disease in GD1 patients is not always followed up by physicians in Spain despite its high prevalence. Monitoring and treatment of GD-related bone disease must be improved and further prospective studies are needed to better assess the impact of treatment on bone parameters.

Authorship contribution

PG, JP, RN, RF, EL, SS and JS contributed to the design of the study, and they were investigators in the study who recruited patients and collected data. All authors contributed to the development of the manuscript, critically reviewed the manuscript during development and approved the final draft prior to submission. Dr. Juan Carlos Bureo passed away on 29 August 2014. The outline of this manuscript was seen and agreed to by him in early August 2014.

Conflict-of-interest disclosure

PG receives consultancy fees and research funding from Actelion, Genzyme and Shire. JP receives consultancy fees and research funding from Shire. RN receives consultancy fees from Shire. SP is an employee of Shire. RF, EL, SS, and JS have no competing interests to declare.

Table 3
Status and achievement of therapeutic goals in the Complete Data Analysis Set (n = 65).

		All patients	By treatment status			By splenectomy status		
			Untreated	On treatment	p-value	Non-splenectomized	Splenectomized	p-value
		n = 65	n = 9	n = 56		n = 50	n = 15	
Hemoglobin concentration (g/dL)	n	65	9	56		50	15	
	Mean (SD)	13.7 (1.3)	13.1 (1.4)	13.8 (1.2)		13.8 (1.3)	13.2 (1.1)	ns[T]
	Median (IQR)	13.6 (12.9–14.5)	13.1 (12.4–13.9)	13.6 (12.9–14.5)	ns[U]	13.6 (13.0–14.6)	13.2 (12.5–14.2)	
Goal achievers (♂≥12 and ♀≥11)	*n (%)*	*64 (99)*				*50 (100)*	*14 (93)*	*ns[F]*
Platelet count (10^9/L)	n	65	9	56		50	15	
	Mean (SD)	162 (60.3)	108 (38.2)	171 (58.8)	0.003[T]	150 (51.1)	205 (70.8)	0.002[T]
Goal achievers (Platelet count ≥120)	*n (%)*	*48 (74)*				*35 (70)*	*13 (87)*	*ns[F]*
Splenomegaly (MN)	n	50	8	42		50	15	
	Median (IQR)	1.2 (1.0–4.0)	2.8 (1.2–5.4)	1.1 (1.0–3.0)	ns[U]	1.2 (1.0–4.0)	–	NA
Goal achievers (Spleen volume ≤8 MN)	*n (%)*	*45 (90)*				*45 (90)*	–	*NA*
Hepatomegaly(MN)	n	65	9	56		50	15	
	Median (IQR)	1.1 (1.0–1.5)	1.2 (1.1–2.0)	1.0 (1.0–1.5)	ns[U]	1.0 (1.0–1.5)	1.5 (1.0–1.7)	ns[U]
Goal achievers (Liver volume ≤1.5 MN)	*n (%)*	*55 (85)*				*44 (88)*	*11 (73)*	*ns[F]*
Bone pain in the last 24 hours (VAS 0–10)	n	65	9	56		50	15	
	Median (IQR)	1.0 (0.0–2.5)	2.0 (1.5–7.0)	2.4 (1.0–4.1)	ns[U]	1.0 (0.0–2.4)	1.0 (0.0–3.0)	ns[U]
Goal achievers (VAS ≤1)	*n (%)*	*38 (59)*				*30 (60)*	*8 (53)*	*ns[C]*
Bone pain among patients having pain (VAS >0)	n (%)	37 (56.9)	6 (66.7)	31 (55.4)		28 (56.0)	9 (60.0)	
	Median (IQR)	2.0 (1.0–4.1)	2.0 (1.5–7.0)	2.4 (1.0–4.1)	ns[U]	2.0 (1.0–5.0)	3.0 (2.0–3.0)	ns[U]
Bone mineral density (DXA Z-score)	n	65	9	56		50	15	
	Mean (SD)	−0.8 (1.3)	-0.7 (1.6)	−0.8 (1.2)	ns[T]	−0.7 (1.2)	−1.2 (1.5)	ns[T]
Goal achievers (DXA Z-score ≥-1)	*n (%)*	*40 (62)*				*33 (66)*	*7 (47)*	*ns[C]*
Physical component score of SF-36 (0–100)	n	65	9	56		50	15	
	Median (IQR)	80 (68–85)	75 (63–80)	81 (68–88)	ns[U]	80 (63–85)	80 (68–85)	ns[U]
Goal achievers (PCS ≥70)	*n (%)*	*46 (71)*				*36 (72)*	*10 (67)*	*ns[F]*
Number of goals achieved (0–7)	n	65						
	Mean (SD)	5.2 (1.2)						
Patients achieving goals								
7	n (%)	10 (15)						
6	n (%)	15 (23)						
5	n (%)	24 (37)						
4	n (%)	10 (15)						
3	n (%)	4 (6)						
2	n (%)	2 (3)						

[F], Fisher's exact test; [C], Chi-square test; [T], Student's *t*-test; [U], Mann–Whitney U test.
SD, standard deviation; ns, non-significant; NA, not applicable.

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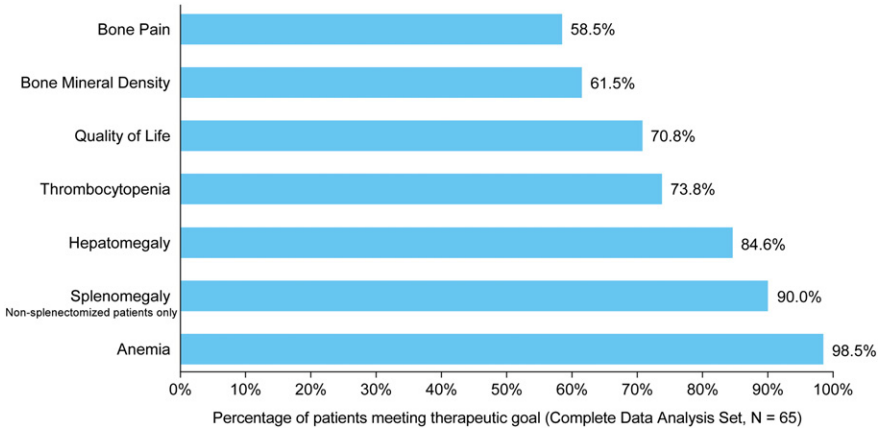

Fig. 3. Achievement of therapeutic goals in the Complete Data Analysis Set. Nearly all patients in the Complete Data Analysis Set met the therapeutic goal for hemoglobin concentration, whereas bone pain was the therapeutic goal with the lowest level of achievement.

Table 4
Bone mineral density classification in the Full (n = 108) and Complete Data (n = 65) Analysis sets.

		All patients	By treatment status			By splenectomy status			Non-splenectomized		Splenectomized	
			Untreated	On treatment	p-value	Non-splenectomized	Splenectomized	p-value	Untreated	On treatment	Untreated	On treatment	p-value
Full Analysis Set		n = 108	n = 13	n = 95		n = 81	n = 27		n = 11	n = 70	n = 2	n = 25	
Normal: Z-score ≥-1	n (%)	48 (64)	5 (56)	43 (65)		39 (67)	9 (53)		4 (50)	35 (70)	1 (100)	8 (50)	
Osteopenia:: −2.5 ≤ Z-score < −1	n (%)	19 (25)	3 (33)	16 (24)	ns[F]	16 (27)	3 (18)	0.026[F]	3 (38)	13 (26)	0	3 (19)	0.039F[a]
Osteoporosis: Z-score < −2.5	n (%)	8 (11)	1 (11)	7 (11)		3 (5)	5 (29)		1 (13)	2 (4)	0	5 (31)	
Missing	*n*	33	*4*	*29*		*23*	*10*		*3*	*20*	*1*	*9*	
Complete Data Set		n = 65	n = 9	n = 56		n = 50	n = 15		n = 8	n = 42	n = 1	n = 14	
Normal: Z-score ≥ −1	n (%)	40 (62)	5 (56)	35 (62)		33 (66)	7 (47)		4 (50)	29 (69)	1 (100)	6 (43)	
Osteopenia:: −2.5 ≤ Z-score < −1	n (%)	17 (26)	3 (33)	14 (25)	ns[F]	14 (28)	3 (20)	0.03[F]	3 (38)	11 (26)	0	3 (21)	0.045F[a]
Osteoporosis: Z-score < −2.5	n (%)	8 (12)	1 (11)	7 (12)		3 (6)	5 (33)		1 (13)	2 (5)	0	5 (36)	

[F], Fisher's exact test for overall distribution.
ns, non-significant.
[a] Results from the comparison of three groups of patients: non-splenectomized untreated, non-splenectomized on treatment and splenectomized on treatment. Splenectomized untreated patients were not considered due to low numbers.

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