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Long-term bone outcomes in Italian patients with Gaucher disease type 1 or type 3 treated with imiglucerase: A sub-study from the International Collaborative Gaucher Group (ICGG) Gaucher Registry

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ABSTRACT

Background: Gaucher disease (GD) is a lysosomal storage disorder. We evaluated the "real-world" effectiveness of first-line imiglucerase on long-term bone outcomes in Italian patients in the International Collaborative Gaucher Group (ICGG) Gaucher Registry.

Methods: Patients treated with imiglucerase for ≥2 years and with bone assessments at baseline and during follow-up were selected. Data on bone pain, bone crises, marrow infiltration, avascular necrosis, infarction, lytic lesions, Erlenmeyer flask deformity, bone fractures, mineral density, and imiglucerase dosage were evaluated.

Results: Data on bone manifestations were available for 73 of 229 patients (31.9 %). Bone crises frequency decreased significantly from baseline to the most recent follow-up ($p < 0.001$), with some improvement observed in bone pain prevalence. Bone pain and bone crises prevalence decreased significantly from baseline at 2 to <4 and 4 to <6 years (all $p < 0.05$). A low median (25th, 75th percentile) baseline imiglucerase dosage was identified in patients reporting bone pain or bone crises (15.0 [13.7, 30.0] and 22.8 [17.5, 36.0] U/kg once every 2 weeks, respectively).

Conclusion: Our study suggests that the management of GD in Italy, with regards to imiglucerase dosage, is suboptimal and confirms the need for clinicians to monitor and correctly treat bone disease according to best practice guidelines.

1. Introduction

Gaucher disease (GD) is a rare, progressive, lysosomal storage disorder caused by mutations in the *GBA1* gene, which encodes acid glucocerebrosidase (also known as acid β-glucosidase). Deficient activity of this enzyme leads to the accumulation of glucosylceramide, typically in the liver, spleen, and bone marrow. GD is classified into three sub-types according to neurological involvement and the progression rate of central nervous system (CNS) symptoms. Type 1 GD (also known as non-neuronopathic GD) is the most common form and is distinguished by the lack of CNS involvement, type 2 GD (acute neuronopathic GD) has an early onset CNS involvement and rapid neurological progression, while type 3 GD (chronic neuronopathic GD) has a slower neurological progression and later CNS onset than type 2 GD, although a continuum of

Abbreviations: BMD, bone mineral density; CNS, central nervous system; DXA, dual X-ray absorptiometry; ERT, enzyme replacement therapy; EWGGD, European Working Group on GD; GD, Gaucher disease; ICGG, International Collaborative Gaucher Group; MRI, magnetic resonance imaging; q2w, once every 2 weeks; SD, standard deviation.

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phenotypes has been described [1,2]. Symptoms can include anemia, tiredness, a tendency to bleed or bruise easily, enlarged spleen and liver, and bone disease.

Bone disease is prevalent in patients with GD and can occur at any age causing pain, disability, and reduced quality of life; prevention of severe bone complications is recognized as an unmet need (see Hughes et al. 2019 [3] for a comprehensive review). The clinical manifestations of bone disease are heterogeneous and can include bone pain, bone crises, bone marrow infiltration, Erlenmeyer flask deformity, loss of bone mineral density (BMD), bone infarction, lytic lesions, osteosclerosis, osteonecrosis, and fractures [4,5].

Bone marrow infiltration by Gaucher cells may cause ischemia, inflammation, plasma cell dyscrasias, and compression, whereas mineralization defects result from abnormal bone remodeling, osteoblast dysfunction, and inflammation-driven bone resorption [3]. Imbalance between bone formation and breakdown induces disordered trabecular and cortical bone modeling, cortical bone thinning, fragility fractures, and osteolytic lesions. An altered cytokine- and prostaglandin-expression profile (the inflammatory secretome) is a key pathogenetic factor of bone disease in GD [3]. Several methods are used to evaluate bone disease in the Gaucher patient: magnetic resonance imaging (MRI) is recommended to study bone marrow infiltration, lytic lesions, osteonecrosis, and infarction; T1- and T2-weighted MRI images can be scored to evaluate bone marrow burden of GD; X-rays are useful to detect fractures, bone deformities, and sclerosis; BMD is best assessed by dual X-ray absorptiometry (DXA) [3].

For Gaucher patients, bone pain is considered one of the six most relevant management goals for the disease by the European Working Group on GD (EWGGD) [6]. Indeed, timely diagnosis of GD and early initiation of effective treatment are essential to prevent progressive skeletal disease. Notably, 80–95 % of patients with type 1 GD present with some form of bone involvement at diagnosis [5], while the presence of bone pain or other bone symptoms may cause diminished health-related quality of life [7]. Although bone pain can be caused by bone crises and altered mineralization, it may also be a consequence of previous irreversible bone damage, in which case therapy is not effective.

Current treatments, including enzyme replacement therapy (ERT) and substrate reduction therapy, aim to compensate for the underlying enzyme deficiency in GD. Imiglucerase (the first available ERT) is approved in the European Union for the long-term treatment of patients with type 1 or type 3 GD [8]. Its effectiveness on bone symptoms is dose-dependent. For example, imiglucerase 15 U/kg once every 2 weeks (q2w) improved hematological parameters and organomegaly, but not bone parameters, whereas 60 U/kg/q2w improved hematological and visceral parameters within 6 months and halted progression of or improved bone disease with continued use [8]. Studies have also shown that while bone manifestations, including bone pain and bone crises, may improve with imiglucerase, the risk of bone events is not completely alleviated [9–17].

Started in 1991, the International Collaborative Gaucher Group (ICGG) Gaucher Registry (NCT00358943, sponsored by Sanofi Genzyme), is a worldwide, observational, longitudinal, international database of the clinical, demographic, genetic, biochemical, and therapeutic characteristics of patients with GD, irrespective of disease severity, treatment status or treatment choice.

The objectives of this study were to evaluate the "real-world" effectiveness of first-line imiglucerase on long-term bone outcomes, analyzing data of Italian patients with type 1 or type 3 GD enrolled in the ICGG Gaucher Registry.

2. Methods

2.1. Study population

The study population included all Italian patients with type 1 or type 3 GD who received imiglucerase as first-line therapy among patients enrolled in the ICGG Gaucher Registry as of April 2, 2021. Data on demographic and clinical characteristics, including GD type, sex, age at Gaucher diagnosis, age at initiation of Gaucher treatment, and splenectomy status, were assessed.

Table 1
Demographic and clinical characteristics of Italian patients with type 1 or type 3 Gaucher disease reported in the ICGG Gaucher registry as having received first-line imiglucerase as of April 2, 2021 (n = 229 unless stated otherwise).

Parameter	
Gaucher disease type[a], n (%)	
Type 1	214 (93.4)
Type 3	15 (6.6)
Sex, n (%)	
Male	111 (48.5)
Female	118 (51.5)
Age at diagnosis[b] (years)	
Mean ± SD	23.2 ± 18.8
Median (25th, 75th)	20.8 (6.4, 35.5)
Min, max	0.1, 76.6
Age at initiation of imiglucerase (years)	
Mean ± SD	28.8 ± 18.9
Median (25th, 75th)	28.5 (11.9, 42.0)
Min, max	0.5, 76.8
Splenectomy status at imiglucerase initiation[c], n (%)	
Non-splenectomized	175 (77.8)
Splenectomized	50 (22.2)
Splenectomy status at end of follow-up[d], n (%)	
Non-splenectomized	175 (77.1)
Splenectomized	52 (22.9)

[a] Disease type reported by physicians.
[b] Data missing for 7 patients (n = 222).
[c] Data missing for 4 patients (n = 225).
[d] Data missing for 2 patients (n = 227).

Patients treated with first-line imiglucerase for at least 2 years and with bone assessments at baseline and during follow-up were selected for analysis. Data on clinical bone manifestations, bone marrow, and BMD were assessed. Bone pain and bone crises were evaluated as 'yes' or 'no', and marrow infiltration, avascular necrosis, infarction, lytic lesions, Erlenmeyer flask deformity, and fractures as 'absent' or 'present'. BMD was evaluated using DXA, and total lumbar vertebrae BMD Z-scores and total femur BMD Z-scores were calculated. Patients with BMD Z-scores >-1, >-2.5 to ≤-1, or ≤-2.5, respectively, were categorized as 'mild or none,' 'moderate,' or 'severe' BMD loss. Outliers <-4 or >4 were excluded from the analysis.

Bone pain and bone crises were also assessed at baseline and at follow-up in specific post-baseline time intervals: 2 to <4 years, 4 to <6 years, 6 to <8 years, 8 to <10 years, and 10+ years. For each time interval, only patients who had a baseline assessment and a follow-up assessment in the specific post-baseline time interval were included. Therefore, these results are not directly comparable over time as the patient population differed at each time interval.

The prescribed imiglucerase dosage was assessed in patients who reported the absence or presence of bone pain or bone crises at baseline and follow-up using the most recent imiglucerase dosage reported in the ICGG Gaucher Registry at the last follow-up. Doses ≥60 U/kg/q2w were excluded.

For all parameters, baseline was defined as the data point closest to imiglucerase initiation using a window of no more than −2 years to +6 weeks (inclusive) from imiglucerase initiation. The most recent follow-up assessment was defined as the most recent data point while still receiving first-line imiglucerase and at least 2 years between baseline and follow-up. If patients switched from imiglucerase or discontinued imiglucerase, assessments after switch or discontinuation were not considered.

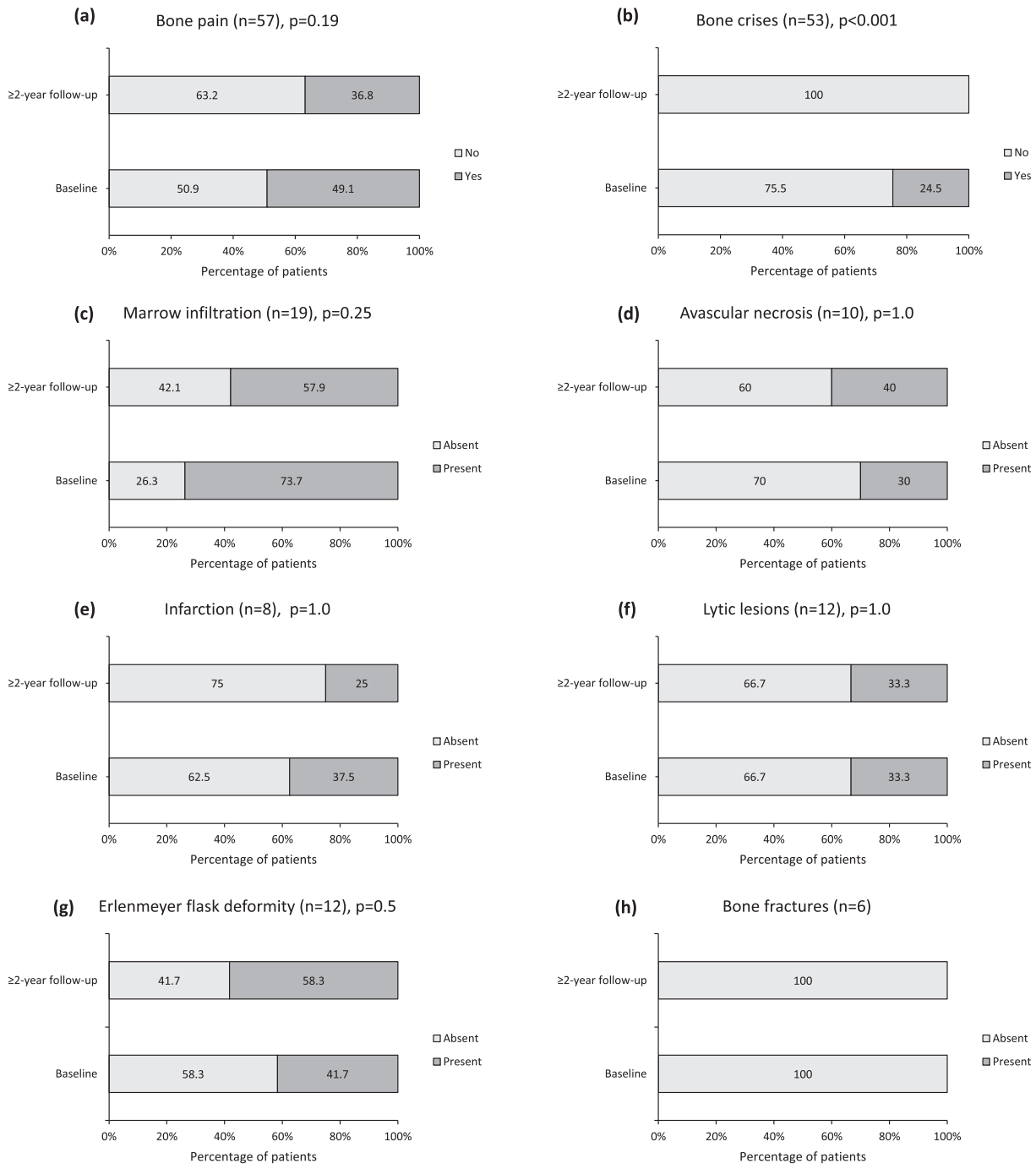

Fig. 1. Bone manifestations of (a) bone pain, (b) bone crises, (c) marrow infiltration, (d) avascular necrosis, (e) infarction, (f) lytic lesions, (g) Erlenmeyer flask deformity, and (h) bone fractures at baseline and the most recent follow-up assessment among Italian patients with type 1 or type 3 Gaucher disease reported in the ICGG Gaucher registry (McNemar's exact test was used to compare baseline and follow-up data).

2.2. Statistical analysis

The frequency and percentage of patients reporting bone manifestations and the follow-up time (in years) for each bone parameter were assessed. For descriptive analyses, continuous data are presented as mean ± standard deviation (SD), median (25th, 75th percentile), and/or min and max. Categorical data are presented as frequency and percentage.

The McNemar's exact and Wilcoxon signed-rank tests compared results at baseline and the most recent follow-up for bone manifestations and BMD Z-scores, respectively. p-Values <0.05 were considered statistically significant.

3. Results

3.1. Patients

As of April 2, 2021, 229 Italian patients with type 1 or type 3 GD enrolled in the ICGG Gaucher registry received imiglucerase as first-line treatment (Table 1). Over 90 % of patients had type 1 GD, and 48.5 % were male. The mean ± SD age at Gaucher diagnosis and imiglucerase initiation were 23.2 ± 18.8 years and 28.8 ± 18.9 years, respectively.

Table 2
Length of follow-up (in years) of bone parameters among Italian patients with type 1 or type 3 Gaucher disease reported in the ICGG Gaucher registry as having received first-line imiglucerase for ≥2 years.

Parameter	n	Mean ± SD	Median (25th, 75th)	Min, max
Bone pain	57	9.2 ± 6.7	6.2 (4.8, 11.0)	2.1, 25.5
Bone crises	53	9.0 ± 6.3	6.3 (4.9, 11.0)	2.2, 25.5
Marrow infiltration	19	8.5 ± 6.0	6.2 (3.9, 9.7)	3.1, 24.5
Avascular necrosis	10	8.6 ± 7.3	5.8 (3.5, 11.2)	2.9, 24.5
Infarction	8	4.6 ± 2.0	4.6 (2.9, 6.0)	2.1, 7.7
Lytic lesions	12	11.9 ± 7.6	11.2 (5.4, 16.3)	2.1, 24.8
Erlenmeyer flask deformity	12	9.6 ± 8.7	7.0 (2.8, 14.5)	2.1, 26.6
Fractures	6	4.2 ± 1.8	4.5 (2.1, 5.8)	2.1, 6.1
Total lumbar vertebrae BMD Z-score[a]	26	7.0 ± 3.4	6.4 (5.4, 7.9)	2.3, 16.8
Total femur BMD Z-score[a]	19	6.2 ± 2.6	6.0 (3.5, 7.9)	2.3, 11.0

[a] Outliers <−4 or >4 were excluded from the analysis.

One-hundred and seventy-five patients (77.8 %) were not splenectomized at imiglucerase initiation, with splenectomy status unknown for 4 patients. Two of these patients reported splenectomy during follow-up, but the date of splenectomy was unknown, and it could not be determined whether these patients were splenectomized at baseline.

3.2. Bone outcomes

Data on bone manifestations at baseline and the most recent follow-up, with a minimum of 2 years between assessments, were available for 73 patients (31.9 %). A statistically significant decrease in the percentage of patients reporting bone crises from baseline to follow-up (24.5 % versus 0 %; $p < 0.001$; N = 53) was observed (mean ± SD follow-up of 9.0 ± 6.3 years; range 2.2–25.5 years) (Fig. 1b, Table 2). Similarly, fewer patients reported bone pain at mean follow-up of 9.2 (±6.7) years (range 2.1–25.5 years) versus baseline (36.8 % versus 49.1 %; $p = 0.19$; n = 57) (Fig. 1a, Table 2).

No bone fractures were reported at baseline or ≥2-year follow-up (mean follow-up of 4.2 ± 1.8 years; range 2.1–6.1 years; n = 6) and fewer patients had marrow infiltration (57.9 % versus 73.7 %; n = 19) or infarction (25 % versus 37.5 %; n = 8) at follow-up than at baseline (Fig. 1h, c, and e, respectively; Table 2). While the percentage of patients with lytic lesions (33.3 %) remained unchanged (Fig. 1f) (n = 12), more patients had avascular necrosis (40 % versus 30 %; n = 10) or Erlenmeyer flask deformity (58.3 % versus 41.7 %; n = 12) at follow-up than baseline (Fig. 1d and g, respectively). However, none of these differences in bone parameters between baseline and follow-up reached statistical significance. It should also be noted that bone complications that have already occurred cannot be reversed.

Significant decreases were observed in bone pain at 2 to <4 years (n = 45, Fig. 2a) and 4 to <6 years (n = 34, Fig. 2b) and in bone crises at 2 to <4 years (n = 41, Fig. 2f) and 4 to <6 years (n = 33, Fig. 2g) compared with baseline (all $p < 0.05$). For both time intervals, bone pain frequency decreased from approximately 45 % at baseline to around 20 % at follow-up, and bone crises frequency fell from approximately 25 % at baseline to 0 % at follow-up.

Trends in bone pain and bone crises were less clear after 6 or more years of follow-up. Fewer patients reported bone pain at 6 to <8 years (33.3 % versus 38.1 %; n = 21), 8 to <10 years (36.4 % versus 45.5 %; n = 11), and 10+ years (41.2 % versus 52.9 %; n = 17) than at baseline, although these comparisons did not reach statistical significance (Fig. 2c, d, and e). Similarly, the frequency of bone crises fell to 0 % for all time intervals after baseline, although the difference between baseline and follow-up after 6+ years did not reach statistical significance (Fig. 2h, i, and j). However, these analyses were limited by small sample sizes (n = 19, n = 8, and n = 16, respectively, at 6 to <8 years, 8 to <10 years, and 10+ years).

Compared with baseline, mean (± SD) lumbar vertebrae and femur BMD Z-scores improved with imiglucerase treatment at the most recent follow-up, although the increases in BMD Z-scores were not statistically significant (from −0.7 ± 1.2 to −0.3 ± 1.3 for lumbar vertebrae BMD Z-scores and −0.4 ± 0.9 to −0.2 ± 1.1 for femur BMD Z-scores; $p = 0.24$ and $p = 1.00$, respectively). More patients were categorized as having mild or no BMD loss and fewer patients were categorized as moderate BMD loss at the most recent follow-up than baseline for lumbar vertebrae BMD Z-scores, while the percentage of patients categorized as severe BMD loss was unchanged (Fig. 3a). The distribution of femur BMD Z-score categories was the same at baseline and follow-up (Fig. 3b).

3.3. Imiglucerase dosage

The imiglucerase dosage received by patients with bone pain or bone crises data at baseline and the most recent follow-up are shown in Table 3.

For patients with bone pain data at baseline and follow-up (n = 57), the median (25th, 75th percentile) imiglucerase dosage was 20.5 (15.0, 30.0) U/kg/q2w and 28.0 (15.0, 31.0) U/kg/q2w, respectively. For patients with data on bone crises at baseline and follow-up (n = 53), the median (25th, 75th percentile) imiglucerase dosage was 20.5 (15.0, 30.0) U/kg/q2w and 28.0 (15.0, 30.0) U/kg/q2w, respectively. The baseline imiglucerase dosage was not known for 5 patients.

The median (25th, 75th percentile) imiglucerase dosage for patients reporting bone pain doubled from 15.0 (13.7, 30.0) U/kg/q2w at baseline (n = 26) to 30 (20.0, 35.0) U/kg/q2w at follow-up (n = 21). Baseline median imiglucerase dosage was higher for patients without bone pain than for those with bone pain (23.5 versus 15.0 U/kg/q2w, respectively), although this was reversed at follow-up (22.9 versus 30.0 U/kg/q2w, respectively).

For the 12 patients with bone crises at baseline, the median (25th, 75th percentile) imiglucerase dosage was 22.8 (17.5, 36.0) U/kg/q2w. At follow-up, no patients reported bone crises, while the median dosage was 28.0 (15.0, 30.0) U/kg/q2w (n = 53).

Among patients reporting bone pain or bone crises, the minimum imiglucerase dosage reported was 7.5 U/kg/q2w at baseline and 14.3 U/kg/q2w at follow-up for bone pain, and 12.0 U/kg/q2w at baseline for bone crises; no patients reported bone crises at follow-up.

4. Discussion

Our study intended to describe the long-term bone response to imiglucerase in a real-world setting in Italy. To this end, we retrieved and analyzed data from the ICGG Gaucher Registry pertaining to Italian patients with type 1 or type 3 GD who received imiglucerase as first-line therapy. We identified significant responses to imiglucerase in terms of the amelioration of both bone pain and bone crises, especially during the initial 6 years of treatment, with skeletal disease stability, or at least no other bone disease worsening, observed, and no bone fractures reported.

Our study shows that the initial prescribed imiglucerase dosage in some patients with bone pain or bone crises was lower than the recommended dosage (i.e., 60 U/kg/q2w, as per the Summary of Product Characteristics [8]). Specifically, at least one Gaucher patient received imiglucerase 7.5 U/kg/q2w despite reporting bone pain at baseline, while at least one Gaucher patient with bone crises received imiglucerase 12.0 U/kg/q2w. Unfortunately, we were unable to stratify patient response according to imiglucerase dosage. Hence, although our results demonstrated clinically meaningful results for imiglucerase, with no further reports of bone crises after treatment initiation in any of the follow-up time intervals, we are unable to comment on whether low

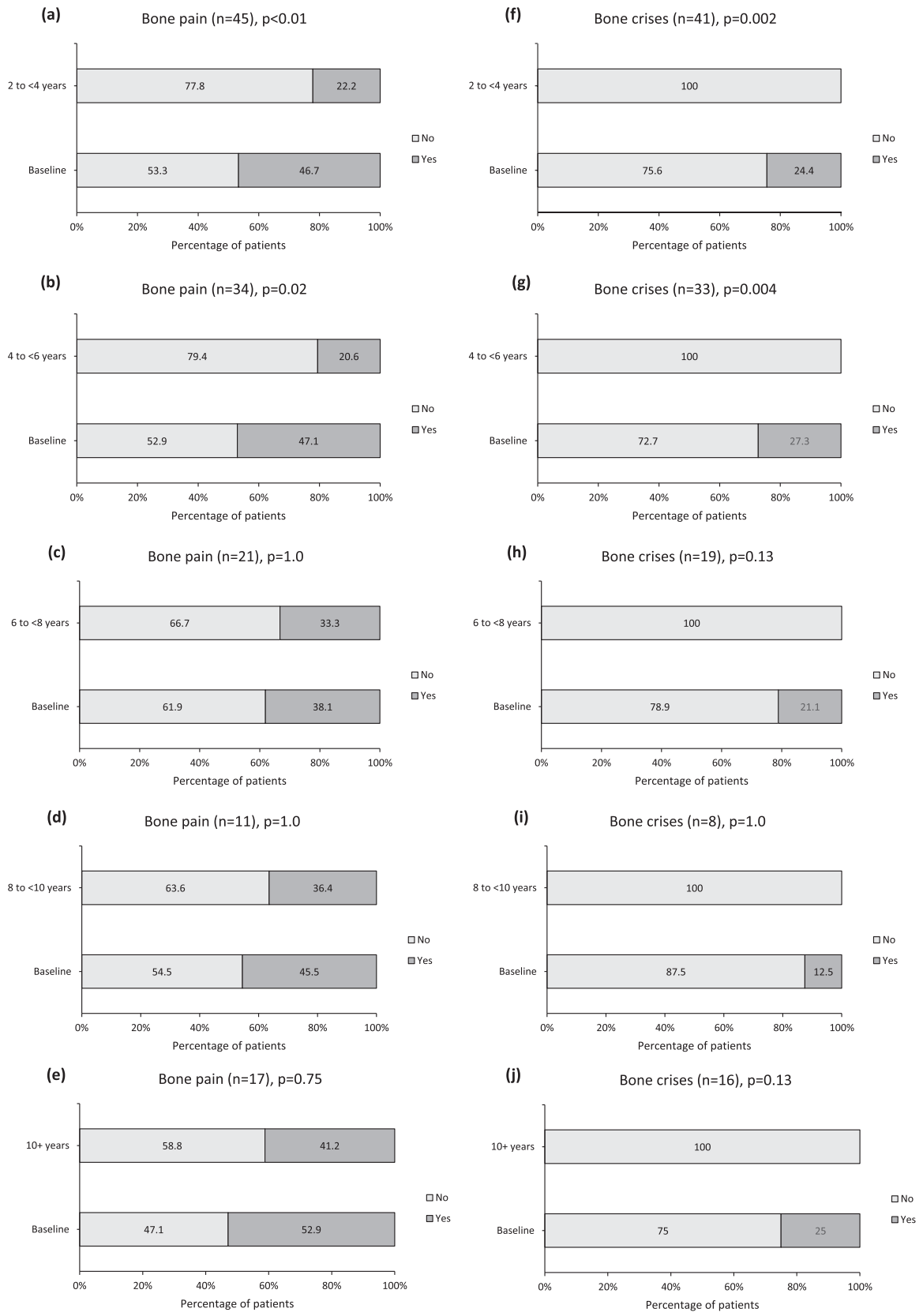

Fig. 2. Bone manifestations of (a–e) bone pain and (f–j) bone crises at baseline and at specific post-baseline time intervals among Italian patients with type 1 or type 3 Gaucher disease reported in the ICGG Gaucher registry (McNemar's exact test was used to compare baseline and follow-up data). Note: For each time interval, only patients who had a baseline assessment and a follow-up assessment in the specific post-baseline time interval were included. Therefore, these results are not directly comparable over time as the patient population differed at each time interval.

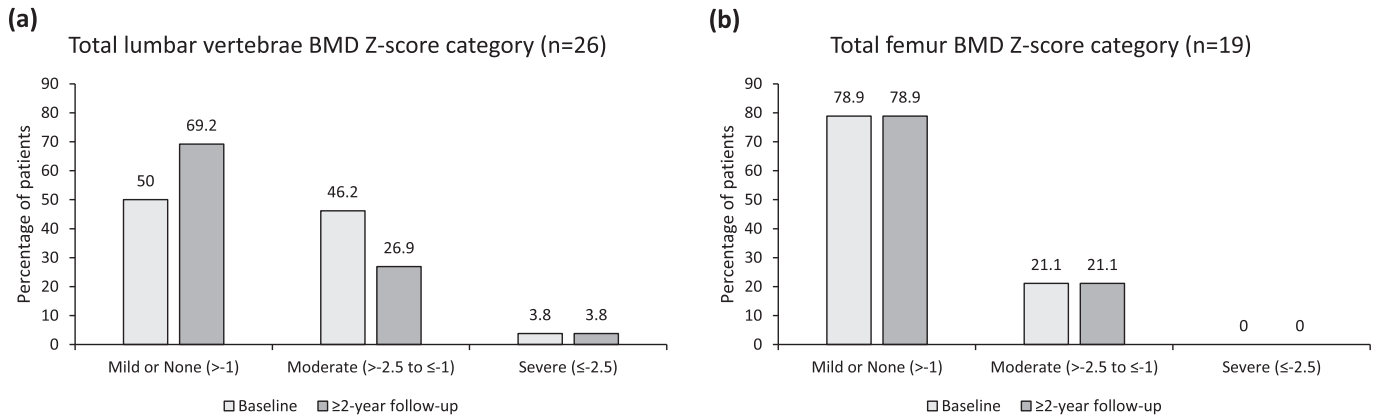

Fig. 3. Bone mineral density assessments of (a) total lumbar vertebrae BMD Z-score and (b) total femur BMD Z-score at baseline and the most recent follow-up assessment among Italian patients with type 1 or type 3 Gaucher disease reported in the ICGG Gaucher registry.

Table 3
Imiglucerase dosage among Italian patients with type 1 or type 3 Gaucher disease reported in the ICGG Gaucher registry as having received first-line imiglucerase and with bone pain or bone crises records at baseline and the most recent follow-up assessment while still receiving imiglucerase, and with ≥2 years between baseline and follow-up.

Parameter	Bone pain at baseline[a]			Bone pain at follow-up[b]		
	Yes	No	Total	Yes	No	Total
No. pts[c]	28	29	57	21	36	57
Imiglucerase dosage[d] (U/kg/q2w)						
Mean ± SD	25.0 ± 17.0	25.2 ± 12.4	25.1 ± 14.7	29.2 ± 11.5	26.4 ± 16.0	27.4 ± 14.4
Median (25th, 75th)	15.0 (13.7, 30.0)	23.5 (15.0, 30.0)	20.5 (15.0, 30.0)	30.0 (20.0, 35.0)	22.9 (15.0, 30.0)	28.0 (15.0, 31.0)
Min, max	7.5, 60.0	12.0, 60.0	7.5, 60.0	14.3, 60.0	7.2, 60.0	7.2, 60.0
No. pts	26	26	52	21	36	57

Parameter	Bone crises at baseline[a]			Bone crises at follow-up[b]		
	Yes	No	Total	Yes	No	Total
No. pts[c]	13	40	53	0	53	53
Imiglucerase dosage[d] (U/kg/q2w)						
Mean ± SD	28.8 ± 16.5	23.4 ± 13.2	24.8 ± 14.1	–	25.9 ± 14.1	25.9 ± 14.1
Median (25th, 75th)	22.8 (17.5, 36.0)	16.3 (15.0, 30.0)	20.5 (15.0, 30.0)	–	28.0 (15.0, 30.0)	28.0 (15.0, 30.0)
Min, max	12.0, 60.0	8.0, 60.0	8.0, 60.0	–	7.2, 60.0	7.2, 60.0
No. pts	12	36	48	0	53	53

[a] Baseline was defined as the data point closest to initiation of therapy with imiglucerase using a window of no more than −2 years to +6 weeks (inclusive) from initiation of therapy for all parameters.

[b] Most recent follow-up assessment was defined as the most recent data point while taking imiglucerase as first primary Gaucher therapy and at least 2 years apart from baseline.

[c] Total number of patients in population of interest.

[d] Imiglucerase dosage at baseline assessment was defined using the dosage at imiglucerase initiation. Imiglucerase dosage at follow-up assessment was defined using the most recent imiglucerase dosage reported in the ICGG Gaucher Registry at the time of the bone follow-up assessment.

dose imiglucerase is generally an optimal approach for treating most patients (at least initially) or whether it is a generally sub-optimal treatment that is only occasionally effective.

The ICGG Gaucher Registry aims to characterize the GD population and enhance the overall understanding of GD. In addition, this large database can enable the Gaucher medical community to optimize patient care by developing recommendations for monitoring patients and reporting long-term patient outcomes to evaluate the long-term effectiveness of imiglucerase and other therapies. To achieve these goals, the Registry must be regularly updated so that researchers can have confidence in the accuracy of the data. Disappointingly, the data for Italian patients in Registry appears incomplete and non-homogenous, suggesting that the Registry data entry fields have been inadequately completed. Indeed, the only usable data are subjective (bone pain and bone crises) and seem to correlate with low imiglucerase doses, while data on objective measurements, such as BMD Z-scores, were limited.

Consequently, our data cannot be compared with those in the international literature, i.e., BMD Z-scores, which correlate with high ERT doses. Indeed, the superior effects of high- versus low-dose ERT on bone marrow involvement and bone disease manifestations in patients with type 1 GD were demonstrated in a retrospective comparative cohort study [18]. Imiglucerase 60 U/kg/q2w also had a significant positive impact on health-related quality of life in patients with bone involvement comprised of infarctions, lytic lesions, and avascular necrosis, including patients with advanced disease [19], and improved patient-reported bone pain as early as 3 months after initiation and decreased bone crises within 12 months of treatment [15]. These results suggest that a higher imiglucerase dosage (i.e., 60 U/kg/q2w) may be more appropriate when bone disease is present.

Although clear patterns in bone manifestations were not observed with longer treatment times (i.e., 6+ years of follow-up), our analysis was limited by small sample sizes and overlapping but inconsistent patient populations at the follow-up time intervals. In addition, our study was restricted by limitations associated with using ICGG Gaucher Registry data, including the impact of possible confounders on treatment outcomes. Therefore, our results do not provide the complete picture of reality for all patients.

There were also limitations in the data used for our study. For example, data on concomitant therapy with bisphosphonates are available in the ICGG Gaucher Registry, but were not requested for this analysis. No data were available on biomarkers of bone reabsorption and bone formation or comorbidities, while bone pain may result from previous irreversible bone damage, which complicates bone disease and worsens the clinical picture. The baseline imiglucerase dosage was not known for 5 patients, therefore comparisons between baseline and follow-up doses should be made with caution.

5. Conclusion

Our study suggests that the management of GD in Italy, with regards to imiglucerase dosage, is suboptimal and confirms the need for clinicians to monitor and correctly treat bone disease according to the current best practice guidelines. In addition, registries, such as the ICGG Gaucher Registry, must be filled in correctly. Otherwise, as with our study, the data are of limited value.

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CRediT authorship contribution statement

Maria Domenica Cappellini: Conceptualization, Methodology, Validation, Writing – review & editing. **Francesca Carubbi:** Conceptualization, Methodology, Validation, Writing – review & editing. **Maja Di Rocco:** Conceptualization, Methodology, Validation, Writing – review & editing. **Fiorina Giona:** Conceptualization, Methodology, Validation, Writing – review & editing. **Gaetano Giuffrida:** Conceptualization, Methodology, Validation, Writing – review & editing.

Declaration of competing interest

MDC declares having served on advisory boards for Sanofi/Genzyme, BMS/Celgene, Vifor, Vertex/CRISPR, Novonordisk, Ionis, Agios, and Silence.

FC declares funding from Sanofi, Amgen, and Amicus in the last 3 years.

MDR declares having served on advisory boards for/received honoraria for lecturing or moderating meetings from Sanofi, Takeda, Orchad, Alnylan, and Ultragenix.

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Data availability

The data that support the findings of this study are available to Registry participants in aggregate format, and can be requested through a Data Analyses Request form. The data are not publicly available due to privacy or ethical restrictions. For additional information, please contact rarediseaseregistries@sanofi.com. The ICGG Gaucher Registry is sponsored by Sanofi.

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