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Treatment-naïve Gaucher disease patients achieve therapeutic goals and normalization with velaglucerase alfa by 4 years in phase 3 trials

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ABSTRACT

Gaucher disease is an inherited metabolic disease characterized by β-glucocerebrosidase deficiency and commonly treated with enzyme replacement therapy (ERT). The efficacy of ERT with velaglucerase alfa was assessed based on the achievement of published therapeutic goals and the normalization of disease parameters in 39 treatment-naïve patients with type 1 Gaucher disease, 6 to 62 years of age, enrolled in phase 3 clinical trials. After 4 years of ERT, therapeutic goals for thrombocytopenia and splenomegaly had been achieved in 100% of patients; goals for anemia and hepatomegaly had been achieved in 95% and 94% of patients, respectively. Consistent with the goal for bone mineral density, lumbar spine bone density improved in 87% of patients ≥18 years of age. At year 4, compared with clinical ranges for healthy individuals, 86% of patients with a low baseline hemoglobin concentration had normalized, 60% with a low baseline platelet count had normalized, 67% with baseline splenomegaly had normalized, 58% with hepatomegaly had normalized, and lumbar spine bone density had normalized in 53% of adults. The decade-old therapeutic goals do not reflect the potential for normalization of clinical parameters in ERT-treated patients. Goals consistent with normalization or near-normalization should be considered. ClinicalTrials.gov identifiers: NCT00430625, NCT00553631, NCT00635427.

1. Introduction

Type 1 Gaucher disease (GD) is a rare inherited metabolic disease that leads to thrombocytopenia, anemia, hepatosplenomegaly, delayed growth in children, and various skeletal abnormalities. The severity of the disease and the age at which symptoms start differs considerably between patients [1].

Long-term enzyme replacement therapy (ERT) is indicated in symptomatic patients to replace the lysosomal enzyme that is deficient in GD. Of three currently available exogenous enzymes for ERT, imiglucerase, velaglucerase alfa, and taliglucerase alfa, velaglucerase alfa is the only one that is produced by gene activation in a human cell line and results in a protein with the identical amino acid sequence as the naturally occurring human enzyme [2]. The two other enzymes are produced in a Chinese hamster ovary mammalian or plant-based expression system and have primary structures that differ from the natural human enzyme by one amino acid residue (imiglucerase) or 10 amino acid residues (taliglucerase alfa) [3–5]. The glycosylation patterns between these three enzymes also are different [6]. It is unclear whether these product differences affect their relative efficacy and safety profiles.

Long-term ERT is expected to lead to improvements in the signs and symptoms of type 1 GD. Pastores and colleagues defined a number of therapeutic goals for the treatment of GD, which were published over 10 years ago and were based on data from the medical literature and the collective clinical experience of an international panel of physicians [7]. The goals took into account common observations in treated patients, including the realization that in patients with GD, anemia and hepatomegaly were more multifactorial than thrombocytopenia and splenomegaly. It was appreciated that severely enlarged spleens were unlikely to be completely corrected to volumes seen in healthy individuals, and also that the severity of thrombocytopenia before treatment helped predict the extent to which the platelet count improved [8].

Abbreviations: BMD, bone mineral density; ERT, enzyme replacement therapy; GD, Gaucher disease; MN, multiples of normal.

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A benchmark post hoc therapeutic goals analysis was conducted in eight adult patients treated with velaglucerase alfa in a phase 1/2 study; five long-term goals were met in all eight patients by 4 years of velaglucerase alfa treatment [9]. Furthermore, normal or near-normal clinical values were achieved in this adult cohort [10].

In a subsequent long-term phase 3 extension study of velaglucerase alfa ERT (study name, HGT-GCB-044), the efficacy of velaglucerase alfa was evaluated using therapeutic goals. A total of 93 patients with type 1 GD from three separate clinical trials were enrolled in the extension study, which included both pediatric and adult patients. The therapeutic goals analysis was a post hoc efficacy analysis to determine whether or not goals of GD treatment were achieved within specific time periods after the initiation of treatment. The primary efficacy analysis [11] showed significant continued improvements in patients who were treatment naïve before their first velaglucerase alfa dose and who received 2.3 to 5.8 years of velaglucerase alfa treatment. We present the therapeutic goals analysis conducted in this study population and a further post hoc analysis designed to explore how much more was achieved clinically, beyond the therapeutic goals and toward normal-range values, in patients receiving velaglucerase alfa.

2. Methods

2.1. Extension study HGT-GCB-044

HGT-GCB-044 was a multicenter, open-label, phase 3 extension study (ClinicalTrials.gov identifier NCT00635427) into which patients from three separate clinical trials were enrolled. Only patients who were treatment naïve upon enrolling in the seminal trials were included in this analysis; these were patients from two phase 3, double-blind, randomized controlled trials [12,13]. All studies received institutional review board or independent ethics committee approval at the sites where they were conducted and followed local regulations and International Conference on Harmonisation Good Clinical Practice guidelines, including obtaining written informed consent for each patient.

The two randomized controlled studies have been described in detail elsewhere (ClinicalTrials.gov identifiers NCT00430625, NCT00553631) [12,13]. Briefly, treatment-naïve patients with type 1 GD over 2 years of age and with clinical signs of GD were enrolled and randomized to one of two treatment groups: velaglucerase alfa 60 U/kg and either imiglucerase 60 U/kg in a 9-month noninferiority trial [12], or velaglucerase alfa 45 U/kg in a 12-month two-dose trial [13]. All patients had a 60-min ERT intravenous infusion every other week regardless of the drug or dose to which they were randomized.

Patients who completed one of the seminal trials could enroll in the extension study in which all patients received velaglucerase alfa at a dose of 60 U/kg (at least in the first year, after which dose reduction was allowed) and they could continue participating in the extension study until commercial velaglucerase alfa was available to them [11].

Efficacy assessments in both the extension and seminal studies included blood sampling for hemoglobin concentration and platelet counts every 2 or 12 weeks; abdominal magnetic resonance imaging for visceromegaly assessment at baseline, 6 months, 9 months (noninferiority trial only), 12 months, and every year thereafter; dual-energy X-ray absorptiometry of the proximal femurs and the lumbar spine every year in patients ≥18 years of age to measure bone mineral density (BMD); and height measurements approximately every 3 months in patients <18 years of age.

Organ volumes were expressed as a percentage of body weight and as multiples of normal (MN), where 0.2% body weight is 1 MN for the spleen and 2.5% body weight is 1 MN for the liver. BMD and height measurements were converted to age- and sex-matched Z-scores, and height percentiles also were calculated as previously described [11,14].

3. Analysis

The data were analyzed by Shire's Biostatistics and Statistical Programming department and all authors had access to the primary clinical trial data.

Only patients who received velaglucerase alfa in both the seminal and extension studies were included in this analysis; therefore, we analyzed a group who received velaglucerase alfa throughout and did not switch from imiglucerase.

The treatment response was evaluated against the therapeutic goals for hemoglobin concentration, platelet count, spleen and liver volumes, BMD, and height for age (Table 1). We assessed the achievement of therapeutic goals at baseline and at yearly intervals after the initiation of ERT. Results presented here are after 1 year of ERT (or 3 years for BMD and height) and after 4 years of ERT.

We used shift tables to show the numbers of patients meeting the therapeutic goal at a particular time point in the patients in whom the goal was already met at baseline and patients whose clinical values at baseline were outside the therapeutic goal range. Analogous shift tables were drawn to show the numbers of patients whose clinical values fell within a healthy (normal reference) range (Table 2) at the same time points. Severely enlarged spleens appear to have a limited capacity to reduce in volume and in previous publications, 5 MN has been identified as the upper limit of mild splenomegaly [7,8,15], so spleen volumes that fell to ≤5 MN were considered to have normalized. We used −1 as the cutoff for normal BMD Z-scores, which meant that Z-scores no >1 standard deviation below the age- and sex-matched reference population mean were considered to be within normal limits (similar to the categorization of BMD T-scores of at least −1 as normal [16]). Analyses of liver volume were repeated after excluding splenectomized patients, because hepatomegaly is generally greater in splenectomized patients. We did not perform data imputation for missing values, so in a few instances where baseline data were missing, those patients were excluded from the analysis of that variable.

To show the extent of improvement achieved by year 4 in each individual patient, we also plotted individual patients' clinical values at baseline and at 4 years on the same graph.

4. Results

Ninety-three patients with type 1 GD received the study drug velaglucerase alfa in the extension study. Thirty-nine of these patients were treatment naïve before receiving their first dose of velaglucerase alfa in the preceding trial. All 39 patients were included in this analysis (Table 3): eight pediatric patients 6 to 16 years of age, and 31 adults 18 to 62 years of age.

Twelve patients had a baseline platelet count $<60 \times 10^9$/L and four of eight pediatric patients were below the fifth height percentile. The duration of velaglucerase alfa exposure from baseline to the end of the extension study in the analysis group ranged between 2.3 and 5.8 years (mean dose, 56.6 U/kg). Thirty of 39 patients received ≥4 years of treatment with the study drug, but most patients had completed or discontinued from the extension study by 5 years, including patients who stopped participating in the study once commercial velaglucerase alfa became available [11].

4.1. Hematology and organ volumes after 1 year of ERT

4.1.1. Therapeutic goals

Short-term therapeutic goals (within 1–2 years; Table 1) for hemoglobin concentration, platelet count, and spleen and liver volume were achieved in patients receiving velaglucerase alfa (Table 4). The goal for hemoglobin was achieved in 23 of 24 (96%) patients who had a hemoglobin level below the therapeutic goal for age and sex at baseline, and the short-term goal for platelet count was achieved in 15 of 25 (60%) patients who had a platelet count $<120 \times 10^9$/L at baseline

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Table 1
Goals for Gaucher disease treatment according to time from initiation of enzyme replacement therapy.

	Characteristic	At 1 year	At 2–5 years	At baseline[a]
Hemoglobin	Female or ≤12 years of age	≥11 g/dL	Same as 1 year	≥11 g/dL
	Male and >12 years of age	≥12 g/dL	Same as 1 year	≥12 g/dL
Platelet count	Nonsplenectomized	≥50% increase (or ≥120 × 10^9/L)	2 years and after: ≥100% increase if baseline was <60 × 10^9/L ≥100 × 10^9/L if baseline was ≥60 and <120 × 10^9/L ≥120 × 10^9/L if baseline was ≥120 × 10^9/L	≥120 × 10^9/L
	Splenectomized	≥120 × 10^9/L	Same as 1 year	≥120 × 10^9/L
Spleen volume	Nonsplenectomized	≥30% decrease (or ≤8.0 MN)	2 years and after: ≥50% decrease compared with baseline (or ≤8.0 MN)	≤8.0 MN
Liver volume	All patients	≥20% decrease (or ≤1.5 MN)	3 years and after: ≥30% decrease compared with baseline (or ≤1.5 MN)	≤1.5 MN
BMD	≥18 years of age	n/a	3 years and after: Z-score change >0	n/a
Linear growth	<18 years of age	n/a	3 years and after: above fifth height percentile	Above fifth height percentile

BMD, bone mineral density; MN, multiples of normal; n/a, not applicable.
The criteria shown here are consistent with the therapeutic goals defined by Pastores and colleagues [7].
[a] Values considered to be within therapeutic goal range before treatment.

(outside the therapeutic goal range). The therapeutic goals for organ volumes were met in 22 of 23 (96%) patients with spleen volumes >8 MN (which would be the cutoff as per the therapeutic goals) at baseline and 14 of 18 (78%) patients with liver volumes >1.5 MN at baseline.

4.1.2. Normalization

When we analyzed the group at baseline and at 1 year post baseline using clinical ranges for healthy individuals (Table 2), we observed a low baseline hemoglobin level in 33 patients (of 36 patients with data at both time points) even though only 24 patients were considered to be below the therapeutic goal. We observed a low platelet count in 25 of 34 patients, splenomegaly in 27 of 28 nonsplenectomized patients, and hepatomegaly in 33 of 35 patients (Table 5).

At 1 year, normalization of hemoglobin concentration was observed in the vast majority of patients who had a low hemoglobin level at baseline (27 of 33; 82%). As early as year 1, platelet counts normalized in 9 of 25 (36%) patients who had a low baseline platelet count. At 1 year, spleen volume normalized in 9 of 27 (33%) patients with baseline splenomegaly and liver volume normalized in 11 of 33 (33%) patients who had hepatomegaly. After excluding splenectomized patients, 8 of 26 (31%) patients who had hepatomegaly were found to have normalized.

Table 2
Clinical criteria considered to represent normalization.

	Criteria
Hemoglobin concentration	
6–12 years of age	11.2–15.5 g/dL
12–59 years of age	
Female	11.6–16.4 g/dL
Male	12.7–18.1 g/dL
≥59 years of age	
Female	11.5–15.8 g/dL
Male	12.5–17.0 g/dL
Platelet count	
6–12 or ≥60 years of age	130–394 × 10^9/L
12–60 years of age	140–400 × 10^9/L
Spleen volume	≤5.0 MN
Liver volume	≤1.0 MN
BMD	Z-score ≥ −1.0

BMD, bone mineral density; MN, multiples of normal.
Hemoglobin and platelet reference ranges were from the central laboratory (Covance Central Laboratory Services, Indianapolis, IN, and Geneva, Switzerland).

4.2. Hematology and organ volumes after 4 years of ERT

4.2.1. Therapeutic goals

Of the patients who had clinical values outside the therapeutic goal range at baseline, the goal for hemoglobin concentration was achieved in 19 of 20 (95%) patients, the long-term goal for platelet count was achieved in all 20 (100%) patients, and the goals for spleen and liver volume were achieved in all 16 (100%) patients and in 15 of 16 patients (94%), respectively (Table 4). One patient's liver volume and another patient's hemoglobin concentration at 4 years did not meet the long-term therapeutic goals, although the goals were met at the subsequent volumetric assessment and hematology test.

4.2.2. Normalization

Normalization of hemoglobin concentration was observed in 24 of 28 (86%) patients who had a low hemoglobin level at baseline; platelet count normalized in 12 of 20 patients (60%). At year 4, 12 of 18 (67%) patients with baseline splenomegaly experienced normalization and 15 of 26 (58%) patients with hepatomegaly experienced normalization (or 11 of 19 [also 58%] patients, after excluding splenectomized patients).

4.3. BMD in adults: therapeutic goal and normalization

Consistent with the therapeutic goal for BMD in adults [7], the lumbar spine BMD Z-score was increased compared with baseline in 26 of 27 (96%) patients at year 3 and 20 of 23 (87%) patients at year 4. The femoral neck BMD Z-score was increased in 20 of 28 (71%) patients at year 3 and 16 of 23 (70%) patients at year 4. The Z-score change observed varied between patients (Fig. 1), but on average, there was a mean 66% increase in lumbar spine BMD Z-scores from baseline to 4 years and an 11% increase in femoral neck Z-scores.

At year 4, lumbar spine BMD had normalized (from Z-score below −1 to Z-score of at least −1) in 10 of 19 (53%) patients; normalization was not observed in the femoral neck in any of the 6 patients who had a low baseline femoral neck Z-score.

4.4. Patients with normal values at 4 years

At 4 years, normalization of hemoglobin concentration, platelet count, spleen volume, liver volume, and lumbar spine BMD (abnormal to normal value) had been observed in 80%, 41%, 63%, 56%, and 43%, respectively, of all patients with data, while 7%, 28%, 5%, 4%, and 13% of patients had remained normal (normal both at baseline and after treatment) for the same variables (Table 6).

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Table 3
Patient characteristics at baseline or 4 years ($N = 39$).

Characteristic	Baseline		4 years	
	Patients with data	Median (range) or no. (%)	Patients with data	Median (range)
Age, years	39	29 (6, 62)		
<18 years of age, no. (%)	39	8 (21)		
Male, no. (%)	39	21 (54)		
Splenectomized patients, no. (%)	39	9 (23)		
Hemoglobin, g/dL	39	10.9 (7.1, 14.4)	30	14.1 (10.4, 17.3)
Platelet count, $\times 10^9$/L	38	82.5 (13, 310)	29	170 (108, 439)
Spleen volume, MN	29	13.6 (4.8, 65.1)	19	4.2 (1.8, 15.0)
Liver volume, MN	38	1.5 (0.8, 3.2)	27	1.0 (0.7, 1.6)
Lumbar spine BMD,[a] Z-score	31	−1.73 (−4.20, 0.78)	23	−0.74 (−2.90, 2.33)
Femoral neck BMD,[a] Z-score	31	−0.59 (−2.77, 2.37)	23	−0.54 (−2.37, 3.12)
Height for age,[b] Z-score	8	−1.54 (−2.70, −0.37)	5	−0.57 (−1.77, 0.12)

BMD, bone mineral density; MN, multiples of normal.
[a] Patients ≥18 years of age.
[b] Patients <18 years of age.

4.4.1. Height for age: therapeutic goal

World Health Organization growth reference data were used in this study, which are available for children and adolescents ≤19.0 years of age. Seven of eight pediatric patients were <19 years of age (between 9.2 and 17.3 years) after 3 years of study participation. All seven patients were above the fifth height percentile at 3 years and thus met the therapeutic goal for linear growth, including three patients who were below the fifth height percentile at baseline. Baseline height percentiles were 0.9, 2.0, 4.0, 9.2, 12.9, 14.0, and 35.6, and year 3 percentiles were 8.1, 26.4, 14.7, 12.7, 29.5, 56.4, and 59.5, respectively.

The eighth patient was 16.8 years of age at baseline with a height percentile of 0.3; at 17.8 years of age (month 12), his height percentile was 3.1 and at 18.9 years of age (month 27), it had improved further to 5.7.

Five pediatric patients had height-for-age data at 4 years (Table 3), four of whom remained above the fifth height percentile. One 7-year-old patient who improved from a height percentile of 0.9 at baseline to the eighth percentile by 3 years was subsequently at percentile 3.8 at 4 years, although this was still an improvement from baseline.

5. Discussion

The therapeutic goals of GD treatment are meant to indicate what can reasonably be anticipated in the first few years of ERT; for five clinical variables, our study suggests that normalization or near-normalization is not an unreasonable expectation and the goals should change to reflect this.

The therapeutic goals for four hematological and visceral variables and BMD were achieved by year 4 or maintained in 100% (n = 8) of patients receiving velaglucerase alfa in a phase 1/2 study wherein normalization of clinical variables also was observed [9,10]. In the present study, 60% to 96% of patients achieved short-term therapeutic goals for the same four hematological and visceral variables in the first year of ERT, and 94% to 100% achieved the individual long-term goals for the same variables at 4 years. At the same time, therapeutic goals were maintained in 100% of the patients in whom the goals were considered already met at baseline (overall, 96–100% of all patients at 4 years had clinical measurements that met the individual hematological and visceral goals). We also observed the achievement of the BMD goal in the lumbar spine in 87% of adults. Therefore, the results of our therapeutic goal analyses support those from the phase 1/2 study. We also can add a further observation that height for age improved in pediatric patients receiving velaglucerase alfa who had a median height Z-score of −1.54 at baseline.

In a retrospective study of patients who enrolled in a disease registry, 92%, 80%, 79%, and 91% of patients met the goals for hemoglobin concentration, platelet count, spleen volume, and liver volume,

Table 4
Number of patients who met the therapeutic goals at baseline and after treatment.

Goal met at baseline, no.	Goal met at 1 y (3 y for BMD), no.		Goal met at 4 y, no.	
	Yes	No	Yes	No
Hemoglobin				
Baseline yes	12	0	10	0
Baseline no	23	1	19	1
Platelet count				
Baseline yes	9	0	9	0
Baseline no	15	10	20	0
Spleen volume				
Baseline yes	5	0	3	0
Baseline no	22	1	16	0
Liver volume				
Baseline yes	17	0	11	0
Baseline no	14	4	15	1
Lumbar spine BMD				
Baseline no	26	1	20	3
Femoral neck BMD				
Baseline no	20	8	16	7

BMD, bone mineral density.
The BMD goal (a Z-score improvement compared with baseline) was not applicable at baseline, so no patients met the BMD goal at baseline.

Table 5
Number of patients who had normal clinical values at baseline and after treatment.

Normal at baseline, no.	Normal at 1 y (3 y for BMD), no.		Normal at 4 y, no.	
	Yes	No	Yes	No
Hemoglobin				
Baseline yes	3	0	2	0
Baseline no	27	6	24	4
Platelet count				
Baseline yes	8	1[a]	8	1[a]
Baseline no	9	16	12	8
Spleen volume				
Baseline yes	1	0	1	0
Baseline no	9	18	12	6
Liver volume				
Baseline yes	1	1	1	0
Baseline no	11	22	15	11
Lumbar spine BMD				
Baseline yes	4	0	3	1
Baseline no	9	14	10	9
Femoral neck BMD				
Baseline yes	20	1	15	2
Baseline no	0	7	0	6

BMD, bone mineral density.
[a] Normal platelet count at baseline and a higher-than-normal platelet count after treatment.

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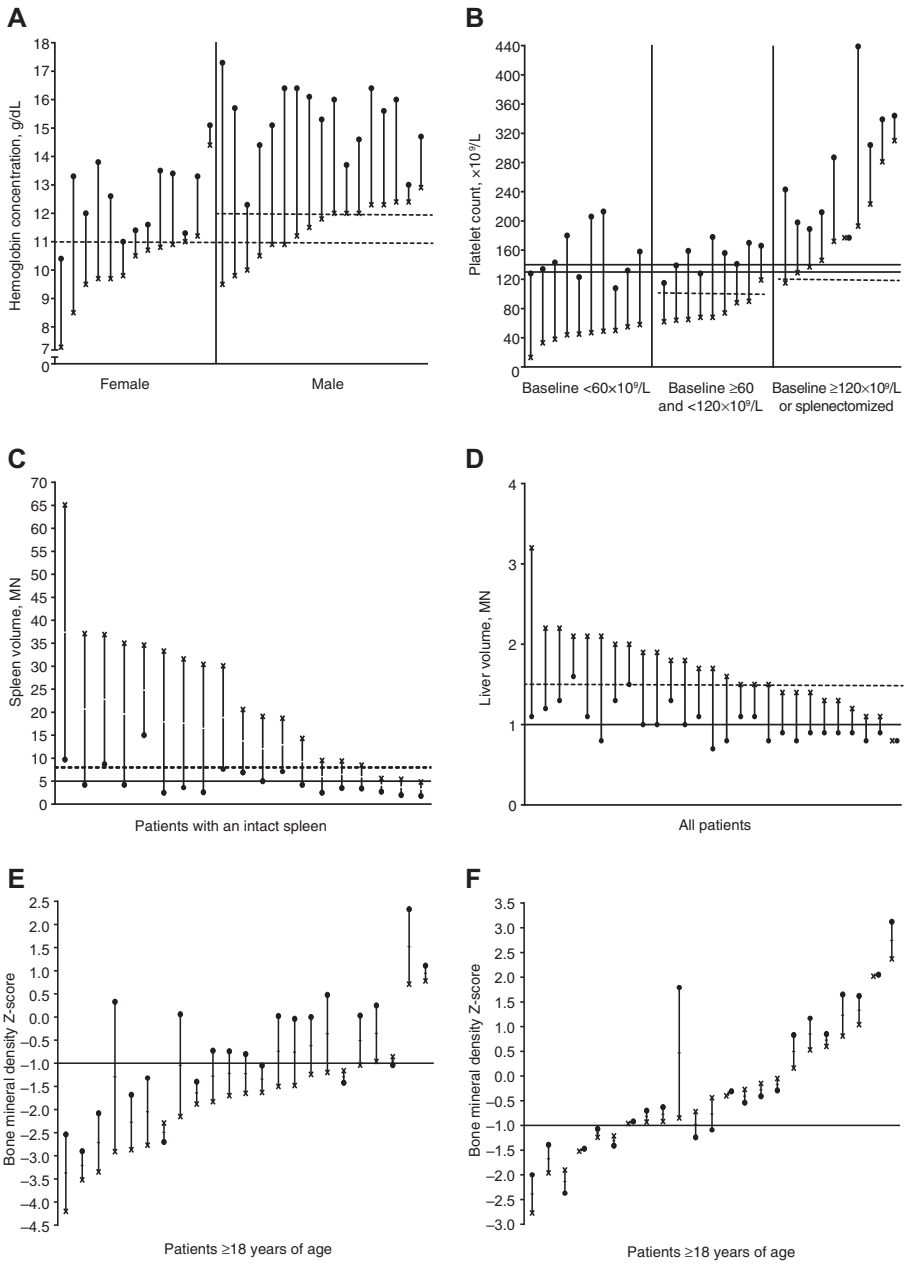

Fig. 1. Achievement of therapeutic goals and/or normal clinical values in individual patients. Panels show data for (A) hemoglobin concentration, (B) platelet count, (C) spleen volume, (D) liver volume, (E) lumbar spine BMD, and (F) femoral neck BMD. Each vertical line plotted represents a single patient; crosses indicate the baseline values and dots indicate the values after 4 years of velaglucerase alfa enzyme replacement therapy. Long-term therapeutic goals are defined in Table 1 and are shown as dashed horizontal lines in panels A–D. Normal clinical values are defined in Table 2 and are shown as solid horizontal lines in panels B–F. BMD, bone mineral density; MN, multiples of normal.

respectively, after 4 years of ERT with imiglucerase (N = 195) [17]. Respectively, 100%, 47%, 100%, and 94% of patients met the goals for the same variables after 4 years of treatment with eliglustat, which is not an ERT but an oral substrate reduction therapy, in a phase 2 study (N = 19) [18]. In a single-center study by Tukan and colleagues, 53% to 82% of patients met these goals by 4 years of low-dose imiglucerase treatment (N = 164) and 100% of a pediatric subgroup who were < 14 years of age at baseline achieved the goal for height in the same period [19].

The results of the above studies may not be comparable with the present study. For example, the study design and completeness of

Table 6
Proportion of whole study group who normalized after 4 years of ERT by clinical parameter.

	Hemoglobin	Platelets	Spleen volume	Liver volume	Lumbar spine BMD	Femoral neck BMD
Total patient number	30	29	19	27	23	23
Abnormal → normal (normalized)	24 (80%)	12 (41%)	12 (63%)	15 (56%)	10 (43%)	0
Normal → normal (remained normal)	2 (7%)	8 (28%)	1 (5%)	1 (4%)	3 (13%)	15 (65%)
Abnormal → abnormal (remained abnormal)	4 (13%)	8 (28%)	6 (32%)	11 (41%)	9 (39%)	6 (26%)
Normal → abnormal	0	1 (3%)	0	0	1 (4%)	2 (9%)

BMD, bone mineral density.

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data collection in a disease registry are generally very different from clinical trials. Also, unlike the present study, splenectomized patients were excluded from both the eliglustat and registry studies, and a wide or lower range of unit/kg ERT doses were used in the imiglucerase studies. However, these previous studies suggest that a significant number of patients can have an incomplete treatment response, or improvement in some clinical variables but not others.

Although we did not expect the same proportion of patients who met the therapeutic goals to experience normalization, normalization was observed in up to 86% of patients for the five disease parameters evaluated. This follows two previous reports in which patients with type 1 GD treated with ERT experienced normalization of disease variables, particularly hemoglobin concentration and liver volume [10,15], and other reports showing a substantial treatment response that tended to normalization [20]. The production of velaglucerase alfa in a human cell line, as a product with the native human amino acid sequence, may have contributed to the results observed in this cohort; further research is needed to explore this further.

In this study, patients considered to have met a therapeutic goal at baseline, or after ERT, did not necessarily have normal clinical values, so there was potentially room for further improvement. In the case of spleen volume, volume reduction is sometimes limited by the presence of splenic lesions [21]. Nevertheless, our results suggest that normalization of important disease parameters is generally likely to be achieved; at least, values that are closer to normal can reasonably be considered the goals of GD treatment. The current therapeutic goals were based on results that were seen mostly in patients exposed to one particular GD-specific therapy over well-defined but arbitrary time frames of 1 to 2, 3, or 5 years. Considering the current evidence, perhaps we should expect normalization or near-normalization of values in most cases, and also for some patients who are “slow responders” to continue to improve gradually after the arbitrary cutoff points of 1 year, 2 years, and so on.

5.1. Limitations of analysis

Clinical reference ranges are not without controversy, because clinical values that are slightly outside normal ranges can sometimes still meet a person's physiologic needs. The benefits of achieving specific therapeutic goals on a patient's long-term clinical outcomes have not been demonstrated, and if patients achieve more than the currently established therapeutic goals, we cannot yet link this directly to better outcomes, quality of life, or patient satisfaction, although anemia and low lumbar spine BMD may be risk factors for skeletal complications of GD (avascular necrosis and fractures) [22]. Above 1500 to 2000 mL, spleen volumes may not make a significant difference to the function of the spleen [23,24] (we calculated that 100% of patients in our study had spleen volumes below 2000 mL at year 4). Further research, including outcomes research (most feasibly done via disease registries), even assessing surrogate outcomes, is needed.

Composite analyses including multiple disease variables may be required to best assess the effect of ERT on GD [25], rather than analyses of individual variables as presented here.

Finally, this analysis was limited by the attrition in patient numbers over time because of the availability of and switching to commercial velaglucerase alfa, meaning that there was missing follow-up data for some patients; however, 30 of 39 (77%) patients were still participating in the study at 4 years.

6. Conclusions

The therapeutic goals for GD treatment that are now over a decade old do not reflect the potential for normalization of clinical parameters in ERT-treated patients. Our results suggest that goals consistent with normalization or near-normalization should be considered instead.

Authorship contributions

AZ, DE, DEG, EAL, and HB were investigators in the clinical trials. AZ, DE, and QD contributed to the analysis plan and interpreted data. YQ analyzed and checked the data. All authors revised the manuscript and gave final approval of the manuscript.

Conflict of interest disclosures

Research supported by company (AZ: Shire). Current or recent participation in a clinical trial sponsored by company (AZ: Shire). Honoraria (AZ: Genzyme, Pfizer, Shire). Employed as contractor for Shire (DE). Consulting fees (EAL: Genzyme, Shire). Membership on advisory board or committee (EAL: Genzyme, Shire). Contracted research (EAL: Genzyme, Shire; HB: Shire). Employee of Shire (YQ, QD). DEG has no potential competing interests to declare.

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