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Impact of velaglucerase alfa on bone marrow burden score in adult patients with type 1 Gaucher disease: 7-Year follow-up

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ABSTRACT

Background: Bone marrow infiltration by substrate-engorged "Gaucher" cells manifests early in Gaucher disease (GD). The impact of velaglucerase alfa on bone marrow burden (BMB) was evaluated as an exploratory assessment.
Methods: BMB scores were assessed using T1- and T2-weighted magnetic resonance images of the lumbar spine (LS) and femora among symptomatic GD patients who participated in the 9-month Phase I/II trial and long-term extension study for velaglucerase alfa. A post-hoc assessment of marrow involvement was performed. BMB scores per site are 0–8 (0/1 = normal; 8 = severe infiltration).
Results: The median LS-BMB score at baseline was 6 (n = 12; range 3–8); at 9 months, compared with baseline, there was a median change of −2 (n = 11; two-sided p-value = 0.0078). LS-BMB scores continued to decrease through 5 years (n = 8; median change from baseline −5 [p = 0.0078], median score 1 [range 1–4]) and were subsequently sustained through 7 years (n = 8). LS-BMB decreases of ≥2 points occurred in 6/11 patients at 9 months, and in all assessable patients (8/8) by 5 years. Long-term femoral BMB (F-BMB) assessment was possible for three patients; all experienced reductions of ≥2 points at 5 years with a total score (LS-BMB + F-BMB) decrease ≥4.
Conclusions: This post hoc analysis suggests improvement in BMB scores through 5 years that was sustained through 7 years, despite dose reduction from 15 months. Prospective studies in a large cohort are needed to validate these findings.

Introduction

Gaucher disease, the most common lysosomal storage disease, is characterized by the presence of glucocerebroside-filled 'Gaucher cells' most abundantly in the spleen, liver, and bone marrow [1]. Since the advent of disease-specific enzyme replacement therapy (ERT) [2], most patients have benefited substantially because of improvements in anemia, thrombocytopenia, and hepatosplenomegaly, yet the response of treatment in bone (e.g., improved bone density and cortical thickness) lagged behind that of the visceral and hematological parameters [3].

Skeletal involvement, such as osteopenia/osteoporosis, osteonecrosis, and bone pain, which may occur without any obvious correlation to genotype, gender, age, or severity of other disease parameters, remains one of the unmet needs of patients with Gaucher disease. ERT with imiglucerase (Cerezyme®, Genzyme-Sanofi, Cambridge, MA, USA), a recombinant ERT, has been shown to reduce the incidence of bone crises, bone pain, and some bone pathology including osteopenia and osteoporosis [4–9]. In addition, radiological studies using T1- and T2-weighted magnetic resonance imaging (MRI) and quantitative chemical shift imaging (QCSI) showed that long-term ERT correlated with imaging results suggestive of decreased bone marrow glycolipid infiltration and increased bone mineral density (BMD) [4]. QCSI of the lumber spine (LS) is considered by some to be the most accurate imaging modality to quantitatively assess bone marrow involvement in Gaucher disease, with low values (<0.23) indicative of 'bone at risk' [10–12]. Current availability of QCSI is limited to a single center (Amsterdam, The Netherlands). Therefore, as a possible alternative, a semi-quantitative MRI-based bone marrow burden (BMB) score was developed which correlates well with QCSI scores and shows good correlation with some demographic and clinical characteristics of Gaucher disease [13–15]. In addition, BMB scoring includes both axial and appendicular bone marrow burdens, corresponding to LS and femurs (F) [15].

Velaglucerase alfa (VPRIV®; Shire, Lexington, MA, USA) is a human β-glucocerebrosidase produced in HT-1080, a human cell-line, using gene-activation technology [16,17]. The safety and tolerability of

Abbreviations: BL, baseline; BMB, bone marrow burden; BMD, bone mineral density; CCL18, chemokine (C–C motif) ligand 18; EOW, every other week; ERT, enzyme replacement therapy; F, femur; F-BMB, femoral bone marrow burden; FN, femoral neck; GD, Gaucher disease; LS, lumbar spine; MRI, magnetic resonance imaging; QCSI, quantitative chemical shift imaging.

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Table 1
Study population at baseline (n = 12).

Demographics	
Median age, years (range)	39.3 (18.8, 69.8)
Female sex, n (%)	7 (58)
Clinical parameters	Median (range)
Hemoglobin concentration, g/dL[a]	11.1 (9.8, 13.3)
Platelet count, $\times 10^9$/L[a]	60.3 (37.0, 98.5)
Spleen volume, % of body weight	3.7 (2.2, 6.5)
Liver volume, % of body weight	4.4 (2.6, 5.8)
Chitotriosidase, nmol/mL/h[b]	19,772 (7391, 68,552)
Plasma CCL18 level, ng/mL[a]	1978 (1563, 5247)
Lumbar spine BMB score	6 (3, 8)

Normal spleen volume = 0.2% of body weight.
Normal liver volume = 2.5% of body weight.
[a] Baseline and week 1 (prior to first dose) values averaged if both were available.
[b] The raw chitotriosidase concentrations are reported because there was no information on chitotriosidase genotype.

velaglucerase alfa in clinical trials and its efficacy on key disease parameters in type 1 Gaucher disease have been reported [18–22], including improvement of BMD [23]. Herein, we report a post hoc analysis of the effect of velaglucerase alfa on serial measurements of BMB (an exploratory endpoint) in patients with type 1 Gaucher disease during 7 years of the Phase I/II and extension studies using standardized data capture and monitoring protocol.

Material and methods

Patients with type 1 Gaucher disease (based on biochemical and molecular criteria) who were ≥18 years of age, who had Gaucher-related anemia, thrombocytopenia, had an intact spleen, and who had not received Gaucher-specific treatment for ≥12 months before enrolling, were eligible to enroll in TKT025, a single-center study. In TKT025, patients received 60 units/kg body weight of velaglucerase alfa intravenously every other week (EOW) for 9 months. Patients who completed TKT025 were eligible to enroll in the extension study, TKT025EXT, and allowed a step-wise dose reduction after 3 months (1 year from start of TKT025) to 30 units/kg/EOW if patients met at least two of four therapeutic goals for hemoglobin concentration, platelet counts, spleen volume, and liver volume [18,24].

T1- and T2-weighted MR images of the LS in the sagittal plane and femur in the coronal plane were obtained at baseline (start of TKT025; prior to the first dose), at 9 months (end of trial), and during TKT025EXT at cumulative months 15, 24, 33, 45, 57, 69, and 81, with months 24, 33, 45, 57, 69, and 81 considered years 2, 3, 4, 5, 6, and 7, respectively.

To evaluate the exploratory endpoint for BMB score, a radiologist experienced in BMB scoring [15] (blinded to the patients' identity, age, gender, clinical parameters, velaglucerase alfa dose, and the sequence of the MR images) scored all the images using the BMB scoring method described by Maas et al. [13]. Up to eight points each for the LS and F sites (0/1 considered normal; 8 considered severe) is assigned for a maximum composite BMB score (LS-BMB + F-BMB) of 16 points.

Statistical analysis

This was a post hoc statistical analysis of the 12 patients who received at least one dose of velaglucerase alfa in the 9-month study TKT025. Available data from study TKT025 and the corresponding long-term extension study TKT025EXT were incorporated in each analysis. The mean and median BMB scores for the LS and F were summarized at each protocol-scheduled assessment. The proportion of patients whose BMB score was reduced by ≥2 points, or ≥3 points, was calculated. Median within-patient changes from baseline were also calculated. The Wilcoxon signed-rank test was used to test the null hypothesis that the median difference between pairs of observations (baseline; post baseline) was zero. p values obtained from the Wilcoxon signed-rank test are two-sided. No adjustment was made for multiple comparisons. p values ≤0.05 were deemed statistically significant.

A post hoc analysis of the correlation between baseline LS-BMB scores and baseline hemoglobin concentration, platelet counts, normalized (percent of body weight) liver and spleen volumes, chemokine (C–C motif) ligand 18 (CCL18) levels, and LS-BMD Z-scores (matched for age and sex) was performed using the Spearman rank correlation coefficient. At 9 months and years 2 and 7, a descriptive assessment of the association between a response in LS-BMB scores (≥2-point reduction) and a response in hemoglobin concentration (≥1 g/dL improvement), platelet counts (≥20% improvement), normalized liver and spleen volumes (≥15% reduction), and CCL18 levels (≥20% reduction) was performed.

Results

Detailed patient characteristics of the 12 adult patients who enrolled in the 9-month Phase I/II clinical trial, including the 10 patients who subsequently entered the long-term extension trial (of which 8 patients completed 7 years), have been reported previously [18]. Table 1

Table 2
Individual, median, and mean lumbar spine BMB scores at each time point.

Patient	BMB score							
	Baseline	9 months	2 years	3 years	4 years	5 years	6 years	7 years
0001	6	6	5	4	5	4	5	4
0002	4	3	3	3	1	1	1	1
0003	8	8	5	4	3	1	1	1
0005[a]	7	7	–	–	–	–	–	–
0006[b]	5	–	–	–	–	–	–	–
0007	6	4	1	1	1	1	1	1
0008[c]	6	5	5	1	4	–	–	–
0009	6	3	4	1	–	1	1	1
0010	3	1	1	1	1	1	1	1
0011	6	1	1	1	–	1	1	1
0012[d]	6	4	–	–	–	–	–	–
1003	6	2	1	1	1	1	1	1
n	12	11	9	9	7	8	8	8
Median (range)	6 (3, 8)	4 (1, 8)	3 (1, 5)	1 (1, 4)	1 (1, 5)	1 (1, 4)	1 (1, 5)	1 (1, 4)
Mean (95% CI)	5.8 (4.9, 6.6)	4.0 (2.4, 5.6)	2.9 (1.4, 4.3)	1.9 (0.8, 2.9)	2.3 (0.7, 3.9)	1.4 (0.5, 2.3)	1.5 (0.3, 2.7)	1.4 (0.5, 2.3)

– Indicates missing BMB score.
[a] Discontinued from study before 2 years.
[b] Discontinued from TKT025 after three infusions.
[c] Discontinued from study after 4 years.
[d] Completed TKT025 but did not enroll in TKT025EXT.