Reductions in glucosylsphingosine (lyso-Gb1) in treatment-naïve and previously treated patients receiving velaglucerase alfa for type 1 Gaucher disease: Data from phase 3 clinical trials

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ABSTRACT

Gaucher disease (GD), an autosomal recessive lipid storage disorder, arises from mutations in the GBA1 (β-glucocerebrosidase) gene, resulting in glucosylceramide accumulation in tissue macrophages. Lyso-Gb1 (glucosylsphingosine, lyso-GL1), a downstream metabolic product of glucosylceramide, has been identified as a promising biomarker for the diagnosis and monitoring of patients with GD. This retrospective, exploratory analysis of data from phase 3 clinical trials of velaglucerase alfa in patients with type 1 GD evaluated the potential of lyso-Gb1 as a specific and sensitive biomarker for GD. A total of 22 treatment-naïve patients and 21 patients previously treated with imiglucerase (switch patients) were included in the analysis. Overall, demographics between the two groups were similar. Mean lyso-Gb1 concentrations were reduced by 302.2 ng/mL from baseline to week 209 in treatment-naïve patients and by 57.3 ng/mL from baseline to week 161 in switch patients, corresponding to relative reductions of 82.7% and 52.0%, respectively. In both the treatment-naïve and switch groups, baseline mean lyso-Gb1 was higher for patients with at least one N370S mutation (363.9 ng/mL and 90.7 ng/mL, respectively) than for patients with non-N370S mutations (184.6 ng/mL and 28.3 ng/mL, respectively). Moderate correlations between decreasing lyso-Gb1 levels and increasing platelet counts, and with decreasing spleen volumes, were observed at some time points in the treatment-naïve group but not in the switch group. These findings support the utility of lyso-Gb1 as a sensitive and reliable biomarker for GD, and suggest that quantitation of this biomarker could serve as an indicator of disease burden and response to treatment.

1. Introduction

Gaucher disease (GD) is an autosomal recessive lipid storage disorder of highly variable severity, with a clinical presentation that includes hepatosplenomegaly, skeletal deformities, hematologic complications, and, in some cases, neurological disease [1]. The condition stems from mutations in the GBA1 gene, which encodes lysosomal β-glucocerebrosidase (β-GC; glucosylceramidase; EC 3.2.1.45). β-GC deficiency results in the accumulation of glucosylceramide in various tissue macrophages, leading to the formation of pathologic Gaucher cells. These cells have a very high lipid load and are known to secrete a number of unique proteins, the quantitation of which is useful for monitoring GD progression and response to treatment [2].

Traditionally, progression of GD and response to treatment is followed by monitoring the clinical parameters of the disease, with additional monitoring of the levels of a range of surrogate markers. These markers include tartrate-resistant acid phosphatase, angiotensin-converting enzyme, ferritin, and alkaline phosphatase [3–5]. Although the expression of these proteins has been shown to correlate with GD activity and to shift in response to GD-specific treatments [6,7], they are not specific to GD, and are only moderately elevated compared with controls, and can be influenced by other factors [3,8]. Thus, biomarkers...
that reflect the pathophysiology of GD and are consequently more specific to GD status/burden would be valuable.

Chitotriosidase and chemokine (C-C motif) ligand 18 (CCL18) are secreted by activated macrophages, including Gaucher cells, and are thus indicative of Gaucher cell burden in the body. However, although both markers are elevated in patients with GD compared with controls, and decrease during treatment with disease-specific therapies, including enzyme replacement therapy (ERT) and substrate reduction therapy, neither marker is involved in the pathophysiology of the disease [9–11]. Elevated chitotriosidase activity has also been observed in patients with a range of lysosomal storage disorders and systemic inflammatory disorders such as sarcoidosis [12–18]. Furthermore, a genetic deficiency of chitotriosidase occurs in approximately 6%–35% of individuals (depending on ethnicity) and thus patients with GD who are chitotriosidase deficient cannot be monitored using this biomarker [19]. CCL18 levels are also elevated in a number of pathologies such as malignancies and inflammatory disorders [20]. As such, the utility of chitotriosidase and CCL18 for monitoring GD activity and treatment response is restricted.

Lyso-Gb1 (glucosylsphingosine, lyso-GL1) has been identified as a promising biomarker for the diagnosis and monitoring of patients with GD [21]. In healthy subjects, glucosylceramide undergoes de-glucosylation β-GC to glucose and ceramide. However, in the absence of functional β-GC in GD, glucosylceramide is instead deacylated to form lyso-Gb1 [11]. Elevations of lyso-Gb1 were first reported in brain tissue from patients with neuronopathic (types 2 and 3) GD [22] and in the plasma of symptomatic patients with nonneuronopathic (type 1) GD [21, 23–25]. Studies suggest that lyso-Gb1 levels correlate with the clinical symptoms of GD, including hepatomegaly and splenomegaly, as well as with chitotriosidase and CCL18 levels, and are reduced upon ERT and substrate reduction therapy [21, 23, 24, 26–27], suggesting that lyso-Gb1 may underlie the clinical symptoms of GD. Plasma lyso-Gb1 levels correlate with disease burden according to genotype, and a threshold of 12 ng/mL has been used to differentiate patients with GD from healthy probands, from patients with other lysosomal storage diseases, and from GD carriers, with 100% sensitivity and 100% specificity [21].

In this study, we evaluated lyso-Gb1 as a specific and sensitive biomarker for GD in a retrospective, exploratory analysis of data from phase 3 clinical trials of velaglucerase alfa in patients with type 1 GD [9, 28, 29].

2. Methods

2.1. Patients and treatments

This analysis included patients who participated in one of two velaglucerase alfa phase 3 clinical studies (TKT032 [NCT00430625] [9] or TKT034 [NCT00478647] [28]) and who then enrolled into HGT-GCB-044, a multicenter, open-label, phase 3 extension study (NCT00635427) [30], in which patients continued to receive velaglucerase alfa for up to 5 years, with dose adjustments permitted at the discretion of the principal investigator (Fig. 1) [29, 31]. In the TKT032 two-dose study, treatment-naïve patients received velaglucerase alfa every other week at 45 U/kg (n = 13 completed) or 60 U/kg (n = 12 completed) for 12 months [9]. These patients comprise the “treatment-naïve” group. Patients enrolled in the TKT034 switch study, who had been receiving a stable imiglucerase regimen for ≥ 2 years at study entry, received velaglucerase alfa every other week at the same dose as imiglucerase prior to switching (15–60 U/kg) for 12 months (n = 38 completed) [28]. These patients comprised the “switch” group.

Patients who participated in these phase 3 clinical trials were contacted by participating study sites for additional consent to allow for the measurement of lyso-Gb1 levels in the samples that were originally collected to measure CCL18 and chitotriosidase. Samples from only those patients who provided further consent were analyzed. All study patients, or their parent(s)/legal representative, provided written informed consent or assent as appropriate. All studies were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Local country regulations were followed along with International Conference on Harmonisation Good Clinical Practice guidelines.

2.2. Sample collection and analysis

Blood samples were collected at baseline, defined as prior to receiving the first dose of velaglucerase alfa in TKT032 or TKT034. Samples were measured for free lyso-Gb1 levels in plasma using high-pressure liquid chromatography–tandem mass spectrometry at Centogene AG, Rostock, Germany as described previously [21]. Briefly, an API 4000 MS/MS system (SCIEX, Concord, ON, Canada) using electrospray ionization in MRM mode in positive mode at 500 °C was used, with a limit of detection of 0.48 ng/mL and a limit of quantification of 0.97 ng/mL. Normal range was defined as 1.7–4.9 ng/mL, and a pathological cut-off of ≥ 12 ng/mL was applied. Blood platelet counts were analyzed by Covance (Indianapolis, IN, USA or Geneva, Switzerland). Spleen volume was measured by quantitative abdominal magnetic resonance imaging at annual intervals. Radiographs were analyzed by a single independent reviewer who was blinded to patient identity and the timing of the imaging in relation to the study (Biomedical Systems, St. Louis, MO, USA). The measurements were normalized to the patient’s body weight. For all patients (regardless of prior treatment history), a blood sample for genotyping β-GC was obtained at study screening if genotype information was not available in the patient’s medical history. Genotyping was performed at Emory Genetics Laboratory, Emory University (Atlanta, GA, USA) [9].

2.3. Statistical analysis

For both the treatment-naive and switch groups, changes in lyso-Gb1 levels over time from baseline were calculated on an individual patient basis. These changes were also summarized with descriptive statistics by visit for treatment-naïve and switch patients. Wilcoxon signed-rank tests were conducted to investigate whether the median percentage was significantly different from baseline in lyso-Gb1 at each post-dose visit. Similar analyses were performed based on genotype subgroups. For these exploratory analyses, these subgroups were defined by the presence of the N370S (c.1226A > G) mutation (those with at least one N370S allele vs. those without the N370S mutation). In addition, Spearman correlation coefficient and p-values were calculated to assess the relationship between lyso-Gb1 concentrations and 1) platelet counts and 2) spleen volume (multiples of normal [MN]) at those time points with data from at least five patients.

3. Results

3.1. Demographic characteristics

A total of 25 patients from TKT032 (treatment-naive patients) and 38 patients from TKT034 (switch patients, previously treated with imiglucerase) were enrolled into HGT-GCB-044. Of these, 44 gave consent for the analysis of lyso-Gb1 concentrations and 43 patients (22 from TKT032 and 21 from TKT034) were included in the analysis. This population included a single splenectomized patient, who was excluded from the analysis based on the anticipated impact of the splenectomy on both the clinical characteristics and biomarkers included in this analysis. In a previous study, lyso-Gb1 levels have been shown to be significantly higher in splenectomized patients than in those with intact spleens [24].

Overall, demographic characteristics between the two groups were similar. Patient ages ranged from 6 to 69 years, approximately three-quarters (76.7%) of whom were adults (≥ 18 years). More patients in
the treatment-naïve group were male compared with the switch group (59.1% vs. 38.1%). The majority of patients in both the treatment-naïve and switch groups had at least one N370S mutation (77.3% and 85.7%, respectively). Disease parameters were milder in the switch group compared with the treatment-naïve group, most likely reflecting prior treatment; however, the range of disease severity was broad in both groups (Table 1).

3.2. Reduction in lyso-Gb1 during treatment with velaglucerase alfa

Blood samples were collected throughout the study period and were analyzed for lyso-Gb1 levels. A total of 176 blood samples were collected from 22 treatment-naïve patients and 153 samples were collected from 21 switch patients (Fig. 1). Mean ± SE decreases in lyso-Gb1 levels were observed in all 22 treatment-naïve patients overall (Fig. 2A), from 323.2 ± 29.9 ng/mL at baseline to 60.4 ± 11.3 ng/mL at week 209, with an overall mean reduction of 302.2 ± 40.4 ng/mL (82.7%; Fig. 2B). Median values decreased from 290.5 ng/mL at baseline to 43.6 ng/mL at week 209, with a median overall reduction of 327.0 ng/mL (85.7%; Fig. 2B). Individual reductions ranged from 123.6 ng/mL to 482.6 ng/mL (78.0% to 95.4%) from baseline to patients’ last available time point. Nearly one-third of the total reduction in lyso-Gb1 levels occurred within the first 3 months after initiation of treatment with velaglucerase alfa, with a mean 30.7% reduction from baseline to week 13 (n = 22). For those patients who completed 209 weeks of treatment (n = 12), median absolute lyso-Gb1 concentrations were reduced from 370.5 ng/mL at baseline to 43.6 ng/mL at week 209, a median decrease from baseline of 327.0 ng/mL, corresponding to a relative reduction of 85.7%. One patient from the treatment-naïve group tested positive for anti-velaglucerase alfa antibodies at week 53 only. This patient achieved a reduction in lyso-Gb1 levels of 434.1 ng/mL from 509.0 ng/mL at baseline to 74.9 ng/mL at week 209, a relative reduction of 85.3%. In addition, decreases in liver and spleen volume (25% and 62%, respectively, from baseline to week 209) and increases in hemoglobin levels (34% to week 197) and platelet counts (300% to week 134) were reported for this patient.

In switch patients, decreases in lyso-Gb1 levels from baseline to each patient’s final visit were observed in all but one patient, who had a small increase in lyso-Gb1 of 1.9 ng/mL (9.4%) from baseline to week 101 (Fig. 2C). No substantial changes in clinical parameters were observed for this patient over time. Overall, mean ± SE lyso-Gb1 levels were reduced from 81.8 ± 15.8 ng/mL at baseline to 52.8 ± 15.2 ng/mL at week 161, a mean decrease from baseline of 57.3 ± 16.2 ng/mL (52.0%). Median values decreased from 53.6 ng/mL at baseline to 26.6 ng/mL at week 161, with a median reduction of 48.7 ng/mL (57.3%; Fig. 2D). Lyso-Gb1 levels fell rapidly upon initiation of treatment with velaglucerase alfa, with a mean reduction of 16.5% from baseline to week 13 (n = 21). For those patients who completed 161 weeks of treatment (n = 10), median absolute lyso-Gb1 concentrations were reduced from 77.0 ng/mL at baseline to 26.6 ng/mL at week 161, a median decrease from baseline of 48.7 ng/mL, corresponding to a relative reduction of 57.3%. Absolute and relative reductions reached statistical significance at weeks 101 and 161 (Fig. 2D).
Five patients in the switch group reported lyso-Gb1 values below the proposed 12 ng/mL diagnostic cut-off for GD [21] at their last available visit, only one of whom had a baseline value below this threshold (individual reductions in lyso-Gb1 from 53.6 to 11.5 ng/mL, 33.9 to 8.6 ng/mL, 22.3 to 10.2 ng/mL, 16 to 7.9 ng/mL, and 9.6 to 9.3 ng/mL, from baseline to last visit). One patient from the switch group tested positive for anti-velaglucerase alfa antibodies at week 77 and all time points thereafter (last visit, week 161). This patient achieved a reduction in lyso-Gb1 levels of 27.0 ng/mL, from 50.0 ng/mL at baseline to 23.0 ng/mL at week 161, a relative reduction of 54.0%, while platelet counts increased by 20% from baseline to week 161. However, liver volume and hemoglobin levels were unchanged and a small increase in spleen volume (11% from baseline to week 157) was reported for this patient. This and one other patient also tested positive for anti-imi-glucerase antibodies at baseline only.

3.3. Impact of genotype on lyso-Gb1 concentrations

In the treatment-naïve population, baseline lyso-Gb1 concentrations (mean ± SD) were higher for patients with at least one allele with the N370S mutation (N370S/N370S or N370S/other: 363.9 ± 133.3 ng/mL; n = 17) than for patients with non-N370S mutations (184.6 ± 38.3 ng/mL; n = 5; Fig. 3A). However, there were no apparent differences between genotype groups in terms of the relative reduction in lyso-Gb1 levels during velaglucerase alfa treatment from baseline to week 161 (82.0% [n = 16] vs. 86.8% [n = 5], respectively; Fig. 3B). Median values at baseline were 315.0 ng/mL and 179.0 ng/mL for N370S and non-N370S mutations, respectively, with median percentage reductions of 82.3% and 86.0% (Fig. 3B). For the 16 patients with the N370S mutation who completed 161 weeks of treatment, median lyso-Gb1 levels were reduced by 82.3%.

Similarly, for switch patients, mean ± SE baseline lyso-Gb1 concentrations were higher in patients with at least one N370S mutation than for patients with non-N370S mutations (90.7 ± 74.5 ng/mL [n = 18] vs. 28.3 ± 15.8 ng/mL [n = 3], respectively; Fig. 3C), but relative reductions in lyso-Gb1 from baseline to week 101 were lower for patients with N370S mutations than with non-N370S mutations (30.2% [n = 18] vs. 42.2% [n = 3], respectively; Fig. 3D). Median values at baseline were 66.1 ng/mL and 22.8 ng/mL for N370S and non-N370S mutations, respectively, with median percentage reductions from baseline to week 101 of 27.9% and 50.6% (Fig. 3D).

3.4. Correlations between lyso-Gb1 concentrations and clinical disease parameters during velaglucerase alfa treatment

In treatment-naïve patients, median platelet counts rose during velaglucerase alfa treatment from 63.0 × 10^9/L at baseline (n = 22) to 146.5 × 10^9/L at week 209 (n = 10), an increase of 132.5%, while median spleen volume decreased from 16.6 MN at baseline (n = 22) to 4.2 MN at week 209 (n = 12), a reduction of 75.0%. For those patients
who completed 209 weeks of treatment, platelet counts increased from $60.0 \times 10^9/L$ at baseline to $146.5 \times 10^9/L$ at week 209 ($n = 10$), while mean spleen volume decreased from $24.4 \text{ MN}$ at baseline to $4.2 \text{ MN}$ at week 209 ($n = 12$). Overall, there was a moderate, statistically significant correlation between decreasing lyso-Gb1 levels and increasing platelet counts at weeks 13, 25, and 53 ($r = -0.530, p = 0.0112$; $r = -0.654, p = 0.0010$; and $r = -0.503, p = 0.0171$, respectively; Fig. 4A), and between decreasing lyso-Gb1 levels and decreasing spleen volumes at weeks 25 and 101 ($r = 0.621, p = 0.0235$ and $r = 0.459, p = 0.0318$, respectively; Fig. 4B). For those patients who completed treatment to week 209, there were no significant correlations between decreasing lyso-Gb1 levels and increasing platelet counts at any time point, although there was a moderate, statistically significant correlation between decreasing lyso-Gb1 levels and decreasing spleen volumes at week 209 ($r = 0.713, p = 0.0093$).

In switch patients, median platelet counts decreased during velaglucerase alfa treatment, from $150.0 \times 10^9/L$ at baseline ($n = 21$) to $121.0 \times 10^9/L$ at week 161 ($n = 9$), while median spleen volume increased from $2.8 \text{ MN}$ at baseline ($n = 19$) to $3.1 \text{ MN}$ at week 161 ($n = 8$). For those patients who completed treatment to week 161, there was a reduction in platelet counts from $145.0 \times 10^9/L$ at baseline to $121.0 \times 10^9/L$ at week 161 ($n = 9$), while spleen volume decreased from $3.8 \text{ MN}$ to $3.1 \text{ MN}$ ($n = 8$). There were no statistically significant correlations between lyso-Gb1 levels and platelet counts or spleen volumes in switch patients overall, with the exception of a moderate correlation between lyso-Gb1 and platelet counts at week 77 ($r = -0.661, p = 0.0376$) (Fig. 4C and D), or for those who completed 161 weeks of treatment.

4. Discussion

The advent of effective therapies for GD has highlighted a need for specific, sensitive biomarkers to aid diagnosis and disease management and monitor responses to treatment. Although chitotriosidase and CCL18, the two most established biomarkers for GD, can offer useful guidance, these biomarkers are not involved in the pathophysiology of the disease and therefore do not offer a true reflection of disease progression or response to therapy. Further, no biomarkers in routine use in the clinical setting are specific to GD. Lyso-Gb1 is being explored as a potential biomarker for GD diagnosis and response to treatment based on evidence for its involvement in disease pathology, specificity to GD, and straightforward method of analysis [21,23,24,32]. Here, we report findings from a retrospective, exploratory analysis of lyso-Gb1 measured in plasma samples from patients with type 1 GD participating in phase 3 clinical trials of velaglucerase alfa.

Although the treatment-naïve and switch groups originated from different phase 3 studies, baseline demographics were generally comparable. However, there was considerable heterogeneity in the patient population for clinical variables at baseline, both between and within groups, because patients were not selected for these clinical studies on
the basis of specific clinical parameters. Overall, patients in the treatment-naïve group demonstrated more severe disease characteristics than switch patients, most likely owing to their untreated status; indeed, the lowest platelet counts and largest spleen sizes observed in treatment-naïve patients in this analysis were at the extremes of values previously reported in patients with GD. Despite prior GD-specific treatment, inter-patient variability in clinical parameters was particularly marked among patients in the switch group, suggestive of variation in the extent of remaining disease, being minimal for some patients but not for others.

Evaluation of baseline plasma lyso-Gb1 revealed higher levels in the treatment-naïve group compared with the switch group, with mean values of 323.2 ng/mL and 81.8 ng/mL, respectively, consistent with an association between disease severity and levels of this biomarker. All treatment-naïve patients had baseline lyso-Gb1 levels above 143 ng/mL, the median value previously reported for N370S homozygotes [21], while 81% of switch patients had lyso-Gb1 levels below 143 ng/mL. However, despite ≥2 years of prior imiglucerase treatment, all but one switch patient still had levels of lyso-Gb1 above the 12 ng/mL threshold proposed for diagnosing GD [21] at the time of switching to velaglucerase.

Reductions in plasma lyso-Gb1 levels over time were achieved in both treatment-naïve and previously treated patients (switch group), consistent with previous reports on the effect of ERT on plasma lyso-Gb1 levels [21,23,24]. Absolute reductions in lyso-Gb1 were greater in the treatment-naïve group than in the switch group. These results may be explained in part by the more severe disease characteristics and higher baseline plasma lyso-Gb1 levels observed in the treatment-naïve group compared with the switch group, suggesting that the potential for improvement was reduced in the switch group. Additionally, patients in the treatment-naïve group received higher average doses of velaglucerase alfa than patients in the switch group (mean 52.4 U/kg vs. 28.9 U/kg, respectively), which may have contributed to a smaller treatment effect in the switch group. An additional hypothesis is the rapid cellular uptake of velaglucerase alfa contributing to a “booster” effect in switch patients [33], although further work is needed to support this. Nonetheless, these findings indicate that despite prolonged previous GD-specific treatment, further reductions in lyso-Gb1 can be achieved after switching to velaglucerase alfa. In the present study, lyso-Gb1 levels fell rapidly upon initiation of treatment with velaglucerase alfa, reaching a 30.7% reduction from baseline to week 13 in the treatment-naïve group and a 16.5% reduction in the switch group. These rapid changes in biomarker levels can be beneficial, as they give an early indication of whether or not a patient is responding to treatment. These findings are in line with previous studies that have reported rapid and significant reductions in plasma lyso-Gb1 levels upon ERT initiation [21,24,32].

On the basis of its proposed role in the pathophysiology of GD, reductions in lyso-Gb1 levels with ERT are predicted to be reflective of the clinical response to treatment. Previous studies have found that reductions in lyso-Gb1 levels correlate with improvements in disease parameters, including liver volume [23,24], spleen volume, and platelet counts [24]. Here, we found a moderate correlation between lyso-Gb1 levels and changes in platelet counts and spleen volume overall in the treatment-naïve group, but there were no correlations between lyso-Gb1 and either platelet count or spleen volume in the switch group, most likely owing to low patient numbers and the smaller changes observed in the switch group. Further, a subset of patients with high
levels of lyso-Gb1 (≥ 100 ng/mL) after 2 years of velaglucerase alfa treatment showed smaller improvements in clinical parameters and smaller percentage changes in lyso-Gb1 levels over this time period than patients reaching lyso-Gb1 levels < 100 ng/mL at 2 years. The development of anti-drug antibodies is a known risk with biological therapies, and, at high titers, may result in a reduction of treatment efficacy [34]. A previous report of data from six clinical studies with velaglucerase alfa, including the extension study from this analysis, found no changes in platelet counts, hemoglobin levels, or levels of the CCL18 or chitotriosidase biomarkers in patients who developed anti-velaglucerase antibodies, consistent with low antibody titers reported in these patients [35]. Similarly, anti-velaglucerase antibody titers were low for both patients who developed anti-drug antibodies in the present study, with reductions in lyso-Gb1 levels consistent with mean values for their respective populations and no evidence of deterioration of treatment effects as indicated by clinical parameters.

Different GD genotypes have been associated with variations in disease severity, prompting evaluation of lyso-Gb1 levels in relation to the presence of the N370S genotype. Here, we found higher baseline plasma lyso-Gb1 levels in patients with at least one N370S mutation in both the treatment-naive and switch groups compared with patients with non-N370S mutations. Although these findings appear to disagree with previous associations of mild disease with the N370S genotype, the wide variability in clinical parameters at baseline and low patient numbers, combined with limited information regarding other mutations present in these patients, means that the values reported in this study may not be representative of these genotypes in the broader GD population. Nonetheless, similar percentage reductions in plasma lyso-Gb1 levels were achieved, regardless of genotype, in both the treatment-naive and switch groups, suggesting that genotype may have minimal impact on response to ERT with velaglucerase.

Studies have demonstrated that elevated plasma lyso-Gb1 is specific to GD within the family of lysosomal storage disorders, supporting the utility of lyso-Gb1 as a biomarker for the diagnosis and monitoring of response to therapy in patients with GD. However, raised levels have also been reported in patients with action myoclonus–renal failure syndrome [36], a progressive myoclonic epilepsy associated with reduced β-GC enzyme activity, stressing the need for further research to fully understand the role of lyso-Gb1 in the disease pathophysiology, in particular its relationship with disease characteristics and disease severity, and the impact of different GD genotypes.

5. Conclusions

Results from phase 3 studies present evidence for the utility of lyso-Gb1 as a sensitive and reliable biomarker for GD, and suggest that quantitation of this biomarker can serve as a direct indicator of disease burden and response to treatment. Lyso-Gb1 levels significantly and rapidly decreased after the initiation of therapy with velaglucerase alfa in both treatment-naive patients and in patients who had received at least 2 years’ previous treatment with imiglucerase. Although this study included patients enrolled into phase 3 clinical trials, thereby forming a defined population of patients with type 1 GD, patients were not selected on the basis of specific clinical parameters and so presented with a broad spectrum of disease burden. Further investigation of lyso-Gb1 for use as a biomarker for GD prognosis and disease monitoring is underway (LYSO-PROVE; NCT02416661), and additional studies to validate lyso-Gb1 as a primary diagnostic parameter are warranted.

Conflicts of interest

D.E. is employed as a contractor for Shire. B.M., Q.D., L.L., and Y.Q. are employees of Shire and own stocks/options. C.C. and S.E. are employees of Centogene AG.

T.B. is an employee of Centogene AG and has received speaker’s honoraria from Shire, Sanofi-Genzyme, Biogen, Actelion, and Novartis, and travel compensations from TEVA and Merck-Serono.

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