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Safety and efficacy of eliglustat combined to enzyme replacement therapy for lymphadenopathy in patients with Gaucher disease type 3

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ABSTRACT

Patients with Gaucher disease type 3 (GD3), especially those with *GBA* p.L444P homozygous mutation, often suffer from complications including lymphadenopathy even under regular enzyme replacement therapy (ERT). In order to improve their outcome, we administrated eliglustat, a substrate reduction therapy (SRT), in combination with ERT to four patients, age ranged 9–18 years, for two years. The results revealed that patients' plasma glucosylsphingosine (lyso-GL1) level and chitotriosidase activity both decreased after adding eliglustat. In three patients who completed follow-up MRI scanning, sizes of lymph nodes all decreased. No severe adverse events were attributed to eliglustat. Therefore, our data suggest that a combined SRT and ERT treatment may improve the ERT-resistant symptoms in patients with GD3.

1. Introduction

Gaucher disease (GD) is a sphingolipid storage disease, resulting from a deficiency in β-glucocerebrosidase (EC 3.2.1.45, acid β-glucosidase, GBA) activity [1], which leads to accumulation of glucocerebroside in macrophages (Gaucher cell) in the bone marrow, liver, spleen, and brain. GD can be classified into the non-neuropathic type 1 disease (GD1; MIM #230800), the acute neuropathic type 2 disease (GD2; MIM #230900), and the subacute neuropathic type 3 disease (GD3; MIM #231000) [2]. Patients with GD1 usually manifest hepatosplenomegaly and bone crisis during adulthood, and enzyme replacement therapy (ERT) with recombinant human GBA (rhGBA) is effective to relieve the symptoms. [3]. Patients with GD2 exhibit neurodegeneration early in age and cannot be treated [4]. GD3 was originally reported from Sweden [5]. The p.L444P mutation was then found to be the predominant mutation in GD3 patients from other countries [6–8]. Patients with homozygous p.L444P mutation frequently manifest severe systemic involvements but only mild neurological abnormalities including supranuclear horizontal gaze palsy, mental retardation, and seizure.

In a report of 55 GD3 patients (40 with homozygous p.L444P mutation) [9], the effects of ERT were variable, but there was considerable variation in the dose of ERT, as well as an uneven distribution of risk factors including age, genotype, and splenectomy. We have reported seven GD3 patients with homozygous p.L444P mutation treated starting from early childhood (1–2.9 years of age), and both visceral and hematological manifestations subsided after ERT [10]. However, a portion of these patients developed horizontal gaze palsy, seizures, mental retardation, kyphosis, and lymphadenopathy during the treatment. Lymphadenopathy was reported in 5% to 52% of GD patients, with ages from 7 months to 58 years, and was more prevalent in GD3 [11–13]. Lymphadenopathy can lead to life threatening protein-losing enteropathy in GD3 patients [12,14].

Eliglustat is a small molecules substrate inhibitor and has been approved for treatment of adult GD1 patients. Eliglustat shows good efficacy to increase bone mineral density, probably due to a better penetration to soft tissues [15,16]. In this study, we wanted to explore if eliglustat combined to ERT could relieve lymphadenopathy in patients with GD3.

Abbreviations: AEs, Adverse events; ERT, Enzyme replacement therapy; GD, Gaucher disease; LAPs, Lymphadenopathies; SRT, Substrate reduction therapy.

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Table 1
Demographic information of patients.

Patient	1	2	3	4
Gender	F	M	F	M
Age at diagnosis	2y3m	1y2m	2y7m	1y10m
Age at ERT start	2y4m	1y 2 m	2y9m	2y
GBA Genotype	L444P/L444P	L444P/L444P	L444P/L444P	L444P/L444P
CYP2D6 genotype	EM	EM	IM	EM
Dose of ERT (U/kg/2 wks)	60	120	60	60
Body weight at baseline (kg)	42	21	37	20
Dose of eliglustat	42 mg bid	21 mg bid	42 mg bid	21 mg bid
Age at baseline	18y2m	10y0m	14y3m	9y3m
Baseline status				
Symptoms	kyphosis, seizure, mental retardation, protein losing enteropathy	kyphosis, oculomotor apraxia	kyphosis	kyphosis
Hb (g/dl)	14.1	15.3	12.1	12.8
Platelet (k/cumm)	287	245	191	250
Lymph node index	26.9	fail	4.1	5.9
104 week status				
Hb (g/dl)	13	15.3	11.9	12.1
Platelet (k/cumm)	306	254	231	235
Lymph node index	16.8	5.1	2.5	4

Lymph node index: sum of long axis of MRI-visible lymph nodes (mm).
EM, normal (extensive) metabolizer; IM, intermediate metabolizer.

2. Materials and methods

2.1. Patients

This is 104-week open-label trial employed a combination therapy with eliglustat and ERT. Eligibility criteria were GD3 patients with p.L444P homozygous mutation, older than 6 years, had lymphadenopathy, and with stable ERT dosage over the past 6 months. The dosages of Eliglustat were 21 mg bid for body weight $<$ 25 kg and 42 mg bid for body weight $\geq$ 25 kg, and dosages were further adjusted according the genotype of *CYP2D6*. Outcome measurements included changes in plasma lyso-GL1 level, plasma chitotriosidase activity, size of lymph node, and the occurrence of adverse event (AE). Electrocardiogram (EKG) was performed regularly to monitor the occurrence of long QT syndrome. A written inform consent was obtained from the parents of each patient. This trial was approved by the Institutional Review Board (NTUH 201612250MIPB) and registered at ClinicalTrials.gov (NCT03519646).

2.2. Biomarker analysis and Measurement of lymph node size

Chitoriosidase activity was measured by a 4-Methylumbelliferone (4MU) fluoresce assay as previously report [17]. Glucosylsphingosine (lyso-GL1) was measured by LC-MSMS [18]. The long axis of each lymph node from neck to pelvis was measured from magnetic resonance imaging (MRI) images. Lymph node (LN) index for each time point was calculated by summation of all long axis measurements. A change in LN index ($\triangle$LN index (%)), comparing week 52 or 104 to baseline, was also calculated.

3. Results

3.1. Patient demographics

Four patients were enrolled into the trial. Their ages at the start of trial were 9 to 18 years, and they had lymphadenopathy with a duration of 2.5 to 7.7 years (Table 1). Their baseline Cerezyme® dosages were 60–120 U/kg every 2 weeks. Three patients (No. 1, 2, and 4) were *CYP2D6* extensive metabolizer and one (No. 3) was intermediate metabolizer, so their eliglustat doses were not altered by *CYP2D6* genotype. Pharmacokinetics study revealed that peak serum eliglustat concentration ($>$ 5 ng/mL) was achieved after the second dose and two-week maximal observed concentration (Cmax) was within the predicted therapeutic concentrations (6–14 ng/mL) [19] in all four patients (Fig. 1A). Patient No. 1 used multiple anticonvulsants at the time of enrollment, and she also took ambroxol since the 53th week (slow increase to 30 mg/kg/day in 3 months) due to worsening of seizure. She also suffered from recurrent diarrhea which resulted in her low body weight (42 kg at 18 years of age).

3.2. Improvements in endpoint measurements

Patients' median lyso-GL1 level at baseline was 80.42 ng/mL (range 46.41 to 138.29) and their median chitotriosidase activity was 1505.48 nmol/mL/h (range 622.44 to 1912.84). Patient 4 had a chitotriosidase deficiency so this biomarker cannot be used. At 104 weeks, the decrement of lyso-GL1 level was 79.8 $\pm$ 5.1% (Fig. 1B; $p = 0.025$ by Mann-Whitney test by SPSS 17.0) and the decrement of chitotriosidase was 59.6 $\pm$ 19.2% (Fig. 1C; $p = 0.2$). Three patients (patients 1, 3, and 4) completed MRI scanning at baseline and week 104, and those scans clearly demonstrated that many lymph nodes either decreased in size or disappeared during follow up (Fig. 2). LN index decreased in all of them, though the decrement was not statistically significant owing to small in case number (Fig. 1D; $p = 0.4$; Fig. 2).

3.3. Adverse events

Four SAEs were reported in patient 1 due to underlying seizure disorder. Twenty-one AEs were reported in the four patients, but these AEs were all of grade 1, transient, and recovered (Table 2). The most common AE was upper respiratory tract infection (4 patients, 9 events, 43%). The median QTc of the four patients at baseline was 422 ms (range 46.41 to 138.29), and their median maximum QTc observed during follow up was 437 ms (range 423 to 449). One episode of borderline and asymptomatic prolongation of QTc (449 ms, normal $<$450 ms), possibly related to the use of eliglustat, was reported in patient No. 2.

4. Discussion

We have reported in 2014 this cohort of GD3 patients with homozygous p.L444P mutation treated starting from early childhood [10], and until now they still don't have visceral and hematological manifestations. Among ERT-resistant symptoms, mental retardation and seizure, and probably also kyphosis, are related to central nervous system, while lymphadenopathy, pulmonary disease, and Gaucheroma are related to soft tissue infiltration of Gaucher cells [10,12]. Pulmonary involvement of GD can occur during ERT and the symptom responds variably to raising dose [12]. Lymphadenopathy can be asymptomatic as in three of our four patients, but we are not aware of any case of spontaneous regression of lymphadenopathy in GD3.

It is believed that the administrated large enzyme molecules have limited penetration to soft tissues like the lymph nodes. Recently, substrate reduction therapy (SRT) has been employed to treat storage diseases. SRT usually involves small molecules that inhibit the synthesis of

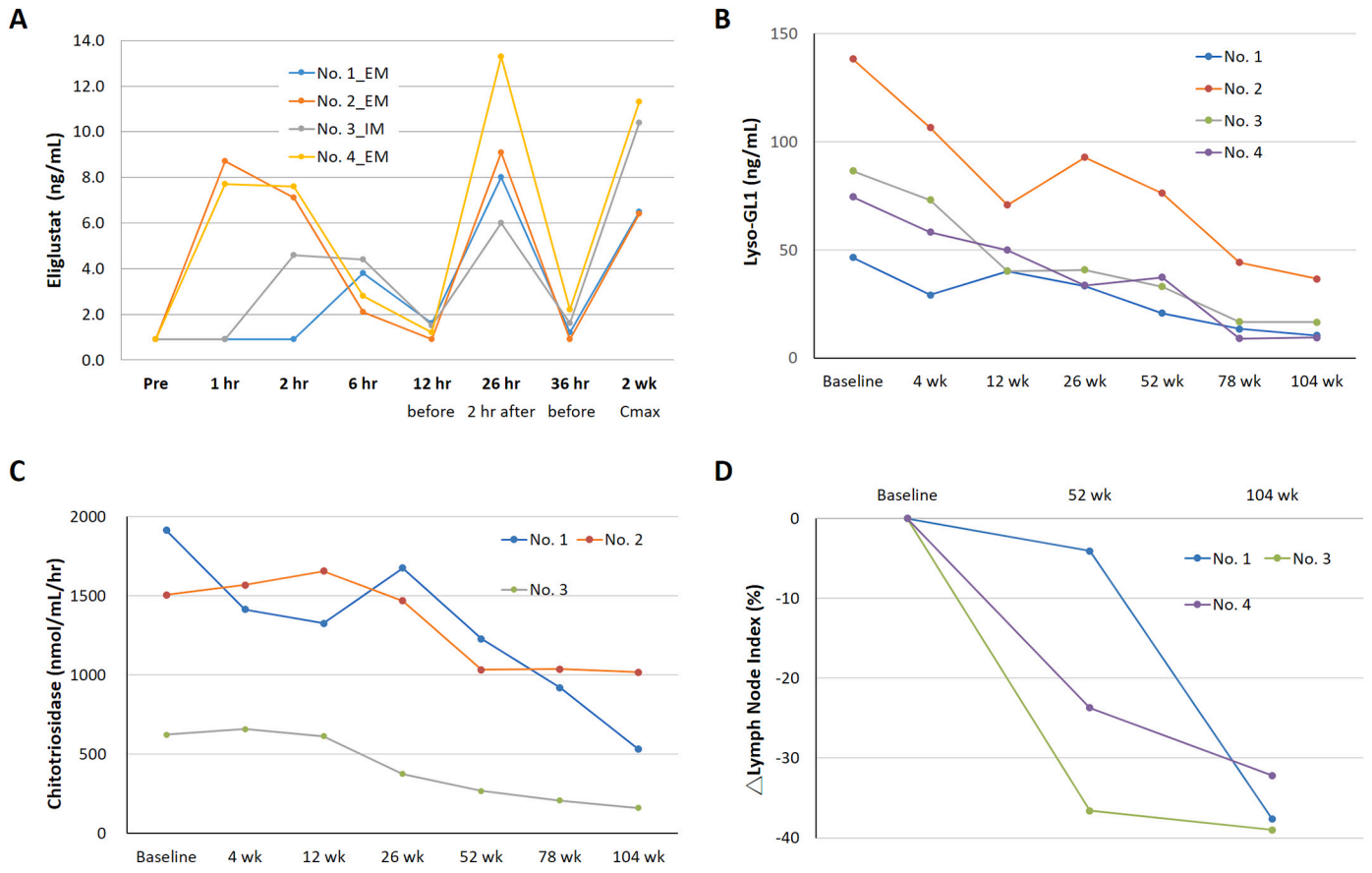

Fig. 1. Combined eliglustat and enzyme replacement therapy in 4 patients. (A) Results of pharmacokinetic study. The 12- and 36-h data were before dosing, and the 26-h data was 2 h after dosing. (B) Decrement of Lyso-GL1 levels after eliglustat therapy could be observed in all four patients. (C) Decrement of chitotriosidase activity after eliglustat therapy was observed in three patients. Patient No. 4 has chitotriosidase deficiency and was excluded from this test. (D) Decrement of lymph node index after eliglustat therapy in three patients. Patient No. 2 failed to complete the baseline MRI scanning.

substrates upstream to the metabolic block. Miglustat and eliglustat have been approved to treat GD, and migalastat can be used to treat Fabry disease [16,20,21]. Miglustat and eliglustat are both glucosylceramide synthase inhibitors, but the latter is more specific thus less likely to cause diarrhea by inhibiting disaccharidases. Eliglustat has shown good efficacy to the bone involvements in GD [15,16]. There were also case reports describing the use of SRT to combat lymphadenopathy in GD3 [22–24]. In the current report, we added another success in combined SRT and ERT treatment for lymphadenopathy in four GD3 patients, and three of them were children. There was no safety issue raised in these children. The lymph nodes regression was seen when enlarged lymph nodes were not complicated by necrosis/fibrosis highlighting need to monitor GD3 patients for LAPs before symptoms (intestinal failure) develop. To have a better result, so combination therapy can be considered.

The four patients were maintained with Cerezyme® 60–120 U/kg every 2 weeks for years, but their lyso-GL1 level and chitotriosidase activity never returned to normal. It is very encouraging that these biomarkers decreased further after the addition of eliglustat. Likely the small molecular has assessed to tissues that ERT didn't reach. Unfortunately, eliglustat dose not enter the brain so the central nervous system involvements in GD3 still don't have a treatment [25]. Ambroxol, a chaperone for GBA and is brain penetrating has been used to treat GD3 with myoclonus [26]. In patient No. 1, ambroxol also improve her seizure control. Recently, a brain-penetrating SRT, venglustat, is under clinical trial for adult patients with GD3 [27]. We hope GD3 patients will soon have a complete treatment.

5. Conclusion

The current study provides evidence for the safety and efficacy of combining eliglustat to ERT to relieve lymphadenopathy in adults and children with GD3.

Author statement

Ni-Chung Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Ni-Chung Lee and Yin-Hsiu Chien. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Ni-Chung Lee, Yin-Hsiu Chien, and Wuh-Liang Hwu. Critical revision of the manuscript for important intellectual content: Chung-Hsing Wang, Siew-Lee Wong, and Fuu-Jen Tsai. Statistical analysis: Ni-Chung Lee. Obtained funding: Ni-Chung Lee. Administrative, technical, or material support: Yin-Hsiu Chien, Chung-Hsing Wang, Siew-Lee Wong, and Fuu-Jen Tsai. Supervision: Wuh-Liang Hwu.

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Declaration of Competing Interest

Ni-Chung Lee received grant from Sanofi-Genzyme for this investigator-sponsored study.

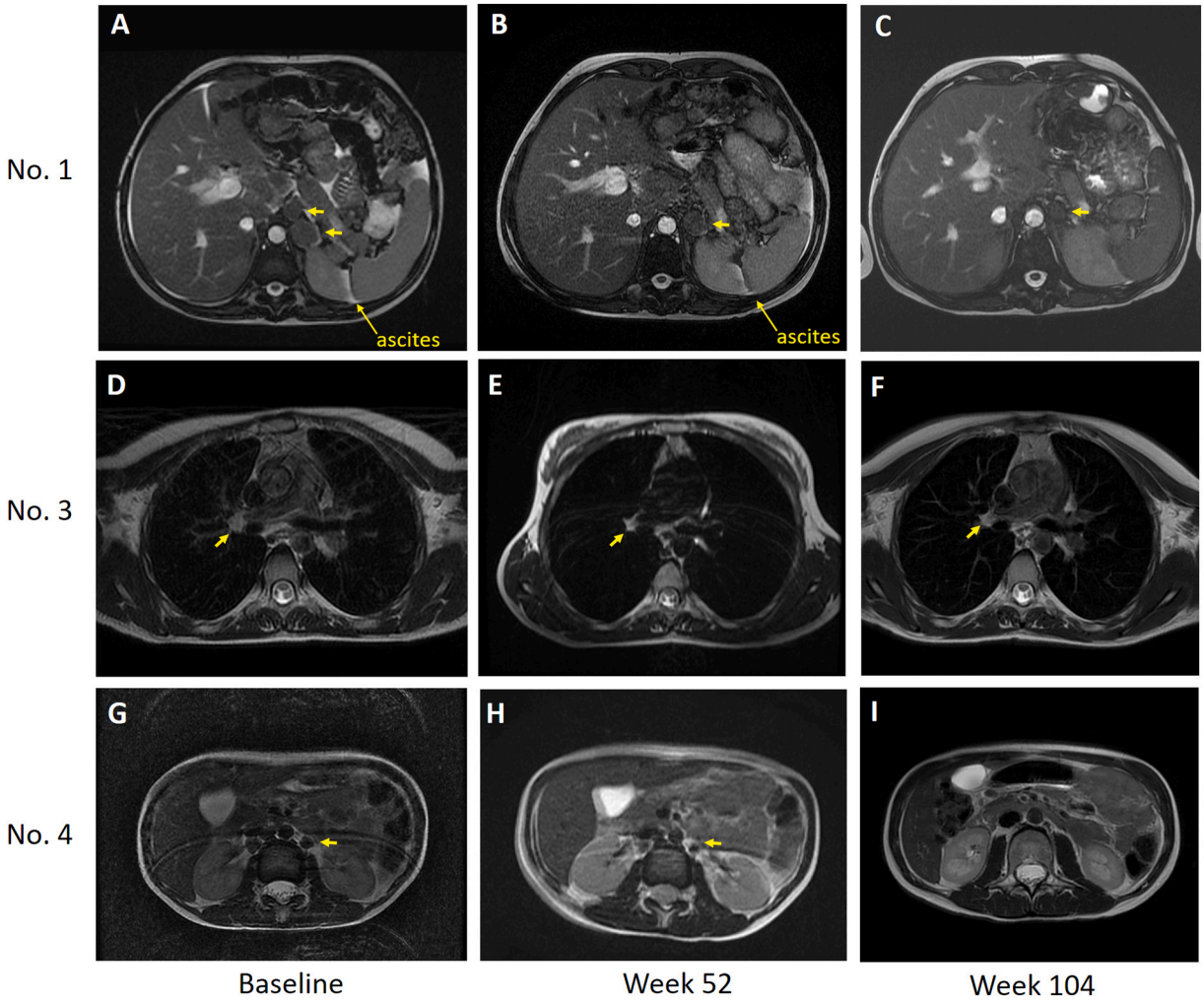

Fig. 2. Representative magnetic resonance imaging (MRI) sections for three patients at baseline, 52th week, and 104th week. In patient No. 1, the baseline scan showed two retroperitoneal lymph nodes (A, arrows), but one disappeared and the other decreased in size during follow up (B and C). A small amount of ascites was also noted during the first two MRI scans. In patient No. 2, a thoracic lymph node decreased in size during follow up (D–F, arrow). In patient No. 3, a few retroperitoneal lymph nodes were noted at the baseline scan (G), and one lymph node (arrow) decreased in size during follow up (H and I).

Table 2
Adverse events and serious adverse event reported during study period.

	Number of patients	Event count N (%)	Outcome	Relationship
Adverse events		0		
Upper respiratory tract infection	4	9 (43%)	Recovered	Not related
Myoclonic jerk-tremors	1	3 (14%)	Recovered	Not related
Fever	1	2 (10%)	Recovered	Not related
Albuminuria	1	2 (10%)	Recovered	Not related
Borderline prolonged QT*	1	1 (5%)	Recovered	Possible
Tachycardia	1	1 (5%)	Recovered	Not related
Running nose	1	1 (5%)	Recovered	Not related
Abdominal pain	1	1 (5%)	Recovered	Not related
Constipation	1	1 (5%)	Recovered	Not related
Serious adverse events		4		
Seizure	1	4 (100%)	Not recovered	Not related

* Definition of long QT is QTc > 450 ms. Patient No. 2 had one measurement of 449 ms.

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