Eliglustat Combination Therapy For Enzyme Replacement Therapy Resistant Soft Tissue Involvement In Pediatric Gaucher Disease

Ni-Chung Lee, MD, PhD; Yin-Hsiu Chien, MD, PhD; Chung-Hsing Wang, MD; Siew-Lee Wong, MD; Steven Shinn-Forng Peng, MD; Fuu-Jen Tsai, MD, PhD; Wuh-Liang Hwu, MD, PhD

1Department of Medical Genetics and Pediatrics, National Taiwan University Hospital, Taipei, Taiwan
2Division of Genetics and Metabolism, Children's Hospital of China Medical University, Taichung, Taiwan; School of Medicine, China Medical University, Taichung, Taiwan
3Department of Pediatrics, Ditramson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan
4Department of Radiology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
5Department of Medical Genetics, Children's Hospital, China Medical University, Taichung, Taiwan; School of Chinese Medicine, China Medical University, Taichung, Taiwan

Abstract

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

Introduction

Enzyme replacement therapy (ERT) is a standard treatment for Gaucher disease (GD). However, GD type 3 (GD3) patients treated with ERT still suffer from complications including lymphadenopathies (LAPs).1 In our previous study, LAPs, some associated with protein-losing enteropathy, occurred in 70% of GD3 patients with GBA p.L444P homozygous mutation who underwent stable enzyme replacement therapy (ERT).1 In 2014, Eliglustat, a substrate reduction therapy (SRT), was approved for treatment of adult GD type 1 (GD1) patients. Eliglustat, a small molecules substrate inhibitor, shows noninferior efficacy than ERT in hematological and visceral parameters.2 Eliglustat also demonstrates good efficacy to improve bone mineral density and stabilize bone disease.3,4 It is likely that small molecules penetrate into soft tissues better than the large molecule enzymes.5 In this study, we want to explore if Eliglustat can help GD3 children with ERT-resistant LAPs.

Methods

This is a 104-week open-label trial employing combination therapy with Eliglustat and ERT. Eligibility criteria were GD3 patients with p.L444P homozygous mutation, older than 6 years, who had developed LAPs, and with no change in 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 ≥ 25 kg, however, the dosages could be further adjusted according the genotype of CYP2D6. A pharmacokinetic study was done for each patient at the beginning of the trial. The dosage of ERT could not be changed during the trial period. Outcome measurements including changes in plasma lyso-GL1 level, plasma chitotriosidase activity, size of lymph nodes, and the occurrence of adverse events (AEs). A written inform consent was obtained from patients’ parents. This trial has been approved by the Institutional Review Board (NTUH 201612250MIPB) and registered at ClinicalTrials.gov (NCT03519646).
Results

Four patients were enrolled into the trial. Their ages at the start of trial were 9-18 years, and they had LAPs for 2.5-7.7 years (Table 1). Patient 1 used multiple anticonvulsants (Zolpidem, Clonazepam, Levetiracetam, Valproid acid, Lorazepam, and Diazepam) at time of enrollment, and also took Ambroxol since the 52th week. The other three patients didn’t use other medication. Their baseline ERT dosage was 60-120U/kg every 2 weeks. Three patients (No. 1, 2, and 4) were CYP2D6 extensive metabolizer and Patient 3 was intermediate metabolizer, so their Eliglustat doses were not changed by genotype. Pharmacogenetics study revealed that peak serum eliglustat concentration > 5 ng/mL was achieved after the second dose (Fig. 1A). At 104 weeks, the decrement of lyso-GL1 was 79.8±5.1 % (Fig. 1B; p = 0.025 by Mann-Whitney test) and the decrement of chitotriosidase was 59.6±19.2 % (Fig. 1C; p = 0.2). All 3 patients who completed MRI scanning (patients 1, 3, and 4) showed a decrease in lymph node index (sum of long axis of MRI-visible lymph nodes from neck to pelvis in mm), but the decrement was not statistically significant owing to small in case number (Fig. 1D; p=0.4).

Table 1. Demographic information of patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at diagnosis</th>
<th>Age at ERT start</th>
<th>Eliglustat concentration</th>
<th>CYP2D6 genotype</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>14</td>
<td>20</td>
<td>1.46±0.144</td>
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<tr>
<td>2</td>
<td>M</td>
<td>10</td>
<td>37</td>
<td>1.46±0.144</td>
<td>1A/1A/1A/1A/1A</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>14</td>
<td>116</td>
<td>1.46±0.144</td>
<td>1A/1A/1A/1A/1A</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>14</td>
<td>116</td>
<td>1.46±0.144</td>
<td>1A/1A/1A/1A/1A</td>
</tr>
</tbody>
</table>

Figure 1. Combined Eliglustat and enzyme replacement therapy in 4 patients. (A) Results of pharmacokinetic study. Arrows indicate the time of Eliglustat administration. (B) Decrease of Lyso-GL1 levels after Eliglustat therapy. (C) Decrease of chitotriosidase activity after Eliglustat therapy. Patient 4 has chitotriosidase deficiency and was excluded from this test. (D) Decrease of lymph node index after Eliglustat therapy. Patient 2 was not cooperative at the baseline MRI scanning.

Four SAEs were encountered in patient 1 due to underlying seizure disorder. A total of 21 AEs (all grade 1, transient, and recovered) were recorded in the four patients, including nine episodes of upper respiratory tract infection in four patients, and three episodes of myoclonic jerk, two episodes of fever, two episodes of microalbuminuria, and one episode of borderline QTc (449 ms, normal < 450 ms), tachycardia, running nose, abdominal pain, and constipation in one each patient. Only the prolonged QTc is possibly related to the use of Eliglustat.

Conclusion

The current study demonstrates no safety concerns were identified of combined Eliglustat and ERT treatment in four GD3 patients. These patients underwent stable ERT since early childhood, but still suffered from symptoms including kyphosis and LAPs. Our results are encouraging that not only patients’ LAPs improved, their biomarkers including lyso-GL1 and chitotriosidase also decreased. GD3 is a severe form of GD that before the era of ERT, patients usually die of visceral diseases early in life. After starting ERT from early childhood, patients with a mild form of GD3, represented by homologous L444P mutation (or GD3B), can grow up without significant visceromegaly or bone crisis. Nevertheless, their biomarkers never return to normal after ERT, not like treated GD1 patients. The current study provides a rationale to further study Eliglustat in children of GD3. Currently, Eliglustat is only approved for the treatment of adult patients with GD1. Further study will be needed to elucidate the role of Eliglustat in children and combinatorial therapy with ERT.

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