Variable Response to Enzyme Replacement Therapy in Two Chinese Children with Infantile-onset Pompe Disease in Hong Kong

GWK Poon, AMK Kwok, PT Cheung, TC Yung, YK Ng, NS Tsoi, KY Wong, LCK Low

Abstract

Pompe disease, a rare autosomal recessive disorder caused by a deficiency of acid alpha-glucosidase, results in lysosomal accumulation of glycogen in multiple tissues, primarily affecting muscles. Infantile-onset Pompe disease is characterised by generalised muscle weakness, hypotonia and lethal cardiomyopathy, resulting in death within the first year of life. The advent of enzyme replacement therapy has changed the natural history of the disease. We report our experience of the use of recombinant human acid alpha-glucosidase in the treatment of two Chinese patients with infantile-onset Pompe disease in Hong Kong.

Key words: Chinese; Enzyme replacement; Pompe disease

Introduction

Pompe disease, also known as glycogen storage disease type II, is a rare autosomal recessively inherited metabolic disorder caused by a deficiency of acid alpha-glucosidase (GAA), resulting in lysosomal glycogen accumulation in multiple tissues, primarily affecting muscles. The disease spectrum has a range of signs and symptoms. The severity varies by age of onset, organ involvement including the degree and severity of muscular involvement, and rate of progression. It is broadly classified into the infantile-onset and late-onset forms. Infantile-onset Pompe disease, which is characterised by progressive cardiomyopathy, respiratory and skeletal muscle weakness, usually results in death within the first year of life,1,2 whilst the milder late-onset form is associated with muscular and respiratory insufficiency later in childhood, or even adult life, causing significant morbidity. Recent studies of recombinant human acid alpha-glucosidase (rhGAA) used in the treatment of patients with infantile-onset Pompe disease showed encouraging results.3-5 rhGAA is well tolerated and significantly improved survival. It is capable of improving cardiac function and varying degrees of skeletal muscle function. We started to use rhGAA since 2006 and here we report our experience with rhGAA in two Chinese patients with infantile-onset Pompe disease.

Case Reports

Patient A

Patient A was the second child of the family born to healthy non-consanguineous Chinese parents. The elder sibling was a healthy five-year-old girl. She was born full term by normal spontaneous delivery with a birth weight of 3.06 kg. The antenatal course was uneventful. She was hospitalised at two months of age for rotavirus gastroenteritis and was incidentally found to have mildly
deranged liver transaminases. She had regular follow-up in a district general hospital until she presented at five months of age with shortness of breath. Her mother reported that the child had been feeding poorly since early infancy and upon presentation at five months, she was found to be in heart failure with significant motor delay. She was floppy at the time with poor head control and could not reach out or show voluntary grasp. Soon after admission, she required mechanical ventilation and inotropic support in the intensive care unit. Electrocardiogram showed huge QRS complexes with left ventricular strain pattern (Figure 1) and echocardiogram showed severely dilated left ventricle with poor left ventricular contractility; the left ventricular shortening fraction (LVSF) was only 8% and the left ventricular ejection fraction (LVEF) was 24%. Initial work-up for cardiomyopathy was inconclusive. Transcatheter endomyocardial biopsy showed features of Pompe disease with diffuse vacuolation of myocytes, abundant intracellular glycogen, mostly confined to lysosomal bodies, and normal-looking mitochondria. Urine glucose tetrasaccharide level was markedly elevated. She was confirmed to have Pompe disease at six months of age by low acid alpha-glucosidase enzyme activity in dried blood spot, whole blood mononuclear cells and cultured skin fibroblasts using methods previously described (Table 1).

With maximum anti-failure treatment, she could be weaned off inotropic support but remained ventilator-dependent before the start of enzyme replacement therapy (ERT). She was started on ERT with bi-weekly intravenous Myozyme infusion (Genzyme Corporation, Framingham, MA, USA) at 20 mg/kg/dose since seven months of age in June 2006. Brief periods of junctional bradycardia were noted when she was given the first two doses of Myozyme infusions but settled spontaneously on both occasions. Her

![Figure 1](ECG Patient A before ERT)
cardiac enzymes were elevated and ECG showed patterns suggestive of transient myocardial ischaemia. Serial follow-up echocardiogram showed a small reduction of her left ventricular mass, which dropped from 327 gram/m² before ERT to 206 gram/m² after four months of ERT (Table 2), and there was a reduction of cardiomegaly on chest radiographs whilst on treatment (Figure 2). However, clinically there was no significant improvement in her left ventricular function. She remained ventilator-dependent and tracheostomy was required at ten months of age. Her cardiac function remained marginal and she required intermittent inotropic support for episodes of decompensation. Her condition deteriorated dramatically after an episode of pneumonia at thirteen months of age (six months after

<table>
<thead>
<tr>
<th>Cardiac indices</th>
<th>Before treatment</th>
<th>After 1st dose</th>
<th>Pre-2nd dose</th>
<th>After 2 months of ERT</th>
<th>After 4 months of ERT</th>
<th>After 6 months of ERT but during acute pneumonia</th>
<th>After 9 months of ERT</th>
<th>After 12 months of ERT</th>
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</thead>
<tbody>
<tr>
<td>LVSF (%)</td>
<td>12.3</td>
<td>5.36</td>
<td>10.3</td>
<td>9.7</td>
<td>12</td>
<td>10.4</td>
<td>15.7</td>
<td>13</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25.3</td>
<td>14.2</td>
<td>18.0</td>
<td>19.8</td>
<td>28</td>
<td>9.8</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>327</td>
<td>–</td>
<td>321</td>
<td>309</td>
<td>206</td>
<td>241</td>
<td>–</td>
<td>309</td>
</tr>
</tbody>
</table>

Table 1 GAA activity assays of our two patients with infantile-onset Pompe disease

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Dried blood spot (µmol/L/hr)</td>
<td>0.20</td>
<td>0.21</td>
<td>12.22±5.88</td>
</tr>
<tr>
<td>Whole blood mononuclear cells (nmol/mg protein/hr)</td>
<td>0.68</td>
<td>0.42</td>
<td>25.30±3.94</td>
</tr>
<tr>
<td>Cultured skin fibroblasts (nmol/mg protein/hr)</td>
<td>0.18</td>
<td>–</td>
<td>106.29±60.46</td>
</tr>
</tbody>
</table>

Table 2 Cardiac indices of Patient A after treatment with enzyme replacement therapy

Figure 2 Chest radiographs of Patient A before and after 26 weeks of ERT.
commencement of ERT), complicated by acute renal failure. Despite gradual improvement in her renal function, her cardiopulmonary function continued to go a downhill course thereafter but her parents opted for continuation of treatment. Despite optimising the inotropic support, intravenous diuretics and slowing of the infusion rate of ERT, she had worsening of heart failure with tachycardia, drop in blood pressure and turning cold and clammy whenever she was given Myozyme infusion.

The clinical deterioration observed could also be ascribed to the presence of anti-rhGAA antibodies which was detected five months after commencement of ERT. Levels of IgG antibodies against rhGAA, measured with the use of an enzyme-linked immunosorbent assay, increased rapidly, reaching a peak antibody titre of 1:204800 fifteen months after commencement of ERT (Table 3). The rising titres of anti-rhGAA antibodies were negative for IgE subclass. No circulating immune complex was detected by the Quidel CIC-C1q binding assay and the Raji cell replacement assay in all the specimens sent since commencement of ERT and there was no inhibition of enzyme activity in vitro by inhibitory antibody assay (Table 3). However, Patient A had a single positive test for inhibition of enzyme uptake by human fibroblast cells in vitro (with a titre of 20 by inhibitory antibody flow cytometry assay) after eleven months of ERT and the anti-rhGAA antibody titre at the time was 1:102400. The latter test was repeated and was found negative in subsequent assessments after stopping the ERT, even though the anti-rhGAA antibody titre continued to rise to 1:204800 (Table 3). In view of the very high anti-rhGAA antibody titre and the poor clinical response to ERT, she was tested for cross-reactive immunologic material (CRIM) and was unexpectedly found to be CRIM-positive.

Psychomotor development was assessed at regular intervals using the Alberta Infant Motor Scale (AIMS) and muscle charting of voluntary muscle power. She had no apparent motor gain despite ERT and her skeletal muscle weakness remained severe.

Taking into consideration the deterioration in her cardiopulmonary status despite ERT, rhGAA was discontinued after thirteen months of treatment. Inotropic support was gradually weaned off six months after stopping ERT. She remained ventilator-dependent throughout her stay in the intensive care unit. She finally died of intractable heart failure at thirty-three months of age, thirteen months after stopping ERT.

**Patient B**

Patient B presented with marked hypotonia, muscle weakness, cardiomegaly, and hepatomegaly soon after birth. She had no symptoms of heart failure. She was the only child of a non-consanguineous Chinese couple, with no significant family history of note. Her antenatal course was uneventful. She was delivered by lower segment Caesarean section at term with a birth weight of 2.95 kg. Initial investigations at two weeks of life showed elevated muscle enzymes - [aspartate aminotransferase (AST) 124 U/L (normal: 15-60 U/L), lactate dehydrogenase (LDH) 1497 U/L (normal: 470-920 U/L), creatine kinase (CK) 1089 U/L (normal: 60-365 U/L) and its isoenzyme CK-MB was also elevated to 33 U/L (normal: <16 U/L)]. Chest radiograph showed increased cardiothoracic ratio of 0.61. Electrocardiogram (ECG) showed huge QRS voltage compatible with biventricular enlargement (Figure 3). There were also changes suggestive of Wolff-Parkinson-White syndrome with shortened PR intervals and delta waves on the ECG, but the changes were transient and her ECG became normal before treatment. Echocardiogram showed features of hypertrophic cardiomyopathy with thickened interventricular septum and left ventricular posterior wall; the left ventricular mass index (LVMI) was 116.4 gram/m²

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Investigation results of high anti-rhGAA antibody titre in Patient A</th>
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<tr>
<td></td>
<td>Duration of ERT</td>
</tr>
<tr>
<td>Nov 2006</td>
<td>5 months</td>
</tr>
<tr>
<td>Feb 2007</td>
<td>8 months</td>
</tr>
<tr>
<td>May 2007</td>
<td>11 months</td>
</tr>
<tr>
<td>Aug 2007</td>
<td>1 month after stopping ERT</td>
</tr>
<tr>
<td>Sep 2007</td>
<td>2 months after stopping ERT</td>
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(normal <84.2 gram/m²). There was no ventricular outflow tract obstruction and the left ventricular contractility was satisfactory. Workup for the hypotonia and cardiomyopathy including cranial ultrasonography, liver and renal function tests, blood glucose, ammonia, lactate, amino acid pattern, acylcarnitine profile, and urine organic acid profile were all normal. The acid alpha-glucosidase enzyme activity was only 0.2 μmol/L/hr in dried blood spot (normal: 12.22±5.88 μmol/L/hr) and 0.42 nmol/mg protein/hr in mononuclear cells (normal: 25.30±3.94 nmol/mg protein/hr), and she was confirmed to have Pompe disease (Table 1).

She began to receive bi-weekly intravenous rhGAA (Myozyme) infusion at 20 mg/kg/dose after confirmation of diagnosis at two months of age. At the time of this report,

![Figure 3](image_url)

Figure 3  ECG of Patient B before and after two years of ERT, (a) before treatment; (b) two years after treatment.
she had been on ERT for more than two years. She had maintained normal cardiac function and was making steady progress in her motor function. She had an episode of supraventricular tachycardia one week after the first dose of Myozyme infusion; otherwise she tolerated the ERT well and did not develop other significant allergic or adverse reactions. The incident was reported to the independent Data and Safety Monitoring Board (DSMB) and it was concluded that there was no safety concern regarding the use of Myozyme. The association of WPW and Pompe disease has been well described previously.7,9 The mechanism of accelerated atrioventricular conduction in Pompe disease may be related to the insulator effect of glycogen accumulation in conduction tissue causing interference.7,9 She was put on propranolol for a year and there was no recurrence of supraventricular tachycardia since she came off the drug. Both the cardiomegaly and hepatomegaly resolved soon after treatment, and serial echocardiographic assessments showed reduced myocardial hypertrophy after six months of treatment (Figure 4). The left ventricular function remained satisfactory. She developed a low level of antibody against rhGAA within three months of treatment, and the antibody titre remained at a very low level over the next two years. She had some feeding difficulty due to oropharyngeal incoordination in the early infancy. After intensive oromotor training, she could tolerate solid food and thickened fluid orally without any aspiration. She had no history of aspiration pneumonia and had been thriving well, with her height and weight growing along the 90th and 50th centiles respectively. She received intensive physiotherapy and occupational therapy after the diagnosis. Functional measures of the motor system, using AIMS at 0-18 months of age showed that she had made steady progress in her gross motor function from 5 to 18 months of age (Figure 5). Assessment at two years of age using Peabody Developmental Motor Scale (PDMS2) showed that she was at the third centile for gross motor function. She was able to walk independently at the age of seventeen months, and was able to walk up and downstairs with hands held by two years of age. Her muscle enzyme levels dropped during the first year of the treatment, but then rose again significantly after one year of age and this coincided with her increasing ambulation (Figure 6). Meanwhile, her CK-MB remained static and there was no clinical evidence of rhabdomyolysis. She remained hypotonic with a myopathic facies and tented upper lip. She achieved the 50th centile for fine motor function at two years of age, as revealed by PDMS2. She could scribble freely with a pencil and pick up small objects using pincer grasp. She could feed herself with a spoon and drink from a cup. She understood verbal commands and spoke meaningful single words. Developmental assessment at twenty-three months of age, using the Griffith Mental Developmental Scale, showed that her fine motor skills were appropriate for her age, whilst her gross motor skills and language development were lagging behind by 9-10 months. Patient B has just celebrated her second birthday a few months ago and we have been treating her with Myozyme for just over 25 months.

**Discussion**

The natural course of infantile-onset Pompe disease has been well studied by van den Hout et al and The Infantile-Onset Pompe Disease Natural History Study Group.1,2 Retrospective studies showed that patients with infantile-onset Pompe disease classically had their first symptoms at a median age of 1.6-2.0 months and were often diagnosed at a median age of 4.5-5.3 months, presenting with cardiomegaly, hypotonia, cardiomyopathy, respiratory distress, muscle weakness, feeding difficulties and failure to thrive. Death occurred at a median age of 6.0-8.7 months.1,2 Recent studies in patients with infantile-onset Pompe disease treated with rhGAA

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**Figure 4** Changes in left ventricular mass index of Patient B with ERT.
showed that prolonged survival, reversal of cardiomyopathy and motor gains could be achieved.\textsuperscript{3,4,5} Further development of rhGAA, in the form of Myozyme, culminated in broad-label marketing approval by the European Union and the US Food and Drug Administration as therapy for Pompe disease in 2006. Myozyme was generally well-tolerated. Adverse events on Myozyme were mostly mild to moderate and were mainly infusion-associated reactions that occurred during or within two hours after the infusion.\textsuperscript{10} No death has occurred relating to Myozyme infusion.\textsuperscript{10} The main limitations of ERT in Pompe disease include the requirement of frequent intravenous infusions of rhGAA every fortnightly to achieve efficacy, the possibility of humoral immunity, and variable response.\textsuperscript{11} Potential factors involved in this variability of response to treatment include the age at initiation of ERT, the extent of lysosomal and muscle damage at the start of ERT, the dose of ERT as related to tissue delivery and the formation of neutralising antibodies.\textsuperscript{11} The lower number of mannose-6-phosphate receptors in skeletal muscle in comparison with that in the heart accounts for the better response observed in heart muscle than in skeletal muscle following treatment with Myozyme. rhGAA can clear glycogen efficiently from cardiac muscles. Slow-twitch type I myofibres that have a high concentration of mitochondria and use oxidative metabolism as the chief energy source, also respond well to ERT.\textsuperscript{12} In contrast, the fast-twitch glycolytic type II myofibres of skeletal muscles are much more resistant to therapy. It has been shown that type IIA myofibres do respond to therapy in a single study of one patient with infantile-onset Pompe disease.\textsuperscript{13} More studies are needed to evaluate the response of different muscle fibre types to ERT. The resistance of type II myofibres to therapy may be explained by the low abundance of proteins involved in endocytosis and trafficking of lysosomal enzymes combined with increased autophagy in type II myofibres.\textsuperscript{12,14,15} Recent studies suggested that clearing or preventing autophagic buildup seemed to be a necessary target of Pompe disease therapy.\textsuperscript{15,16}

Patient A presented to our hospital only one month after the broad-label approval of rhGAA in the treatment of Pompe disease by US Food and Drug Administration. She was in a poor clinical state upon presentation at five months of age with severe heart failure, requiring mechanical ventilation and inotropic support soon after admission. There was little published literature on the use of rhGAA in Pompe disease at the time but given the available information, we decided to treat her with ERT. To our knowledge, Patient A was the first Pompe patient to be treated by ERT in Hong Kong. It is worth noting that even though she could be weaned off inotropes, she remained
ventilator-dependent before the start of treatment. Despite ERT, there was no significant clinical improvement in her cardiac status. Her condition further deteriorated after an episode of pneumonia, complicated by acute renal failure. It also coincided with the detection of IgG antibodies to rhGAA, which is thought to reduce the effectiveness of the ERT. In clinical trials, 89% of thirty-nine paediatric patients (age range, 1 month to 3.5 years) treated with rhGAA were positive for IgG antibodies to GAA and most developed antibodies within the first three months of therapy. Occurrence of inhibitory activity of antibodies by in vitro testing was rare, as in Patient A, but the very high antibody titre was of concern. Some patients with Pompe disease have a small amount of natural but inactive GAA enzyme called cross-reacting immunologic material (CRIM) that is recognised by anti-GAA antibodies. Those who lack any residual GAA protein are deemed CRIM-negative. About 40% of patients with infantile-onset Pompe disease are CRIM-negative and they produce very high IgG antibodies to rhGAA and demonstrate markedly reduced efficacy from ERT.17 Although Patient A was CRIM-positive, her outcome was expected to be poor as she was already severely affected and had limited residual functional status before the start of ERT.

In contrast, Patient B was diagnosed at one month of age and was started on ERT since the age of two months. Compared to the historical untreated patients with infantile-onset Pompe disease and those treated late as in Patient A, Patient B has made significant progress and is now enjoying relatively good quality of life despite delay in gross motor and language development. This echoes the findings of the pivotal clinical study that demonstrated the safety and efficacy of rhGAA in the treatment of infantile-onset Pompe disease. In the study which enrolled eighteen patients with infantile-onset Pompe disease aged six months or younger who were ventilator-free at the start of enzyme replacement therapy, fifteen out of eighteen infants (83%) treated with Myozyme were both alive and free of invasive ventilatory support at eighteen months of age.5 This is in contrast to the report on the natural history of the condition by van den Hout et al, where only 2 of 133 infants (1.5%) with infantile-onset Pompe disease were alive at eighteen months of age. The pivotal study by Kishnani et al also showed that fifteen patients had reduced left ventricular mass, and growth was maintained in fifteen of the eighteen patients throughout the study period.5 Motor development was advanced in thirteen of the eighteen patients as determined by the AIMS. Seventeen patients were evaluated with the Bayley Scales of Infant Development, Second Edition (BSID-II) and nine patients (53%) had mental development index (MDI) scores within the normal limits (MDI scores 85 to 115), whilst four patients (23.5%) had mildly delayed performance (MDI scores 70 to 84) and four others (23.5%) with significantly delayed performance (MDI scores ≤69).5

ERT for infantile-onset Pompe disease has converted a rapidly fatal disease to one that is compatible with prolonged survival. Studies reporting on the successful treatment of Pompe disease raise many ethical questions. This is well summarised in the editorial by Wagner, “these questions include whether the treatment will be converting a lethal disorder to a chronic severe disorder, what the quality of life will be for the individual and family, how end of life discussions will now be made, and possibly, whether adequate resources exist in our society for this intervention."18 ERT is extremely costly and the treatment response could be variable. Patient B is now approaching 12.5 kg; the cost of Myozyme comes to around HK$ 55,000 per month but there will be additional cost as she gets heavier on follow-up. Funding of such expensive treatment is always a problem in any healthcare system. Currently there is no legislation on the use of orphan drugs in Hong Kong. Obtaining sustainable funding for orphan drugs remains a challenge in the management of rare inherited metabolic diseases. Patient A was supported by a special fund of the Government of the Hong Kong Special Administrative Region (HKSAR) for dependents of civil servants. Patient B was initially supported by a charitable fund established by the news media and subsequently by a special fund from the Government of the HKSAR.

In conclusion, early treatment of ERT in selected patients with infantile-onset Pompe disease can change the natural history of the disease and physicians should have a high index of suspicion of this rare form of inherited metabolic disorder. We support the finding of Kishnani et al that initiation of ERT prior to six months of age show great promise to reduce the mortality and disability associated with infantile-onset Pompe disease.5 However, the cost to quality of life ratio will be extremely high for ERT in Pompe disease. Patient selection for this expensive treatment and the source of funding for subsequent patients with this disorder will need to be critically reviewed in Hong Kong.

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References