J Inherit Metab Dis (2010) 33:747–750
DOI 10.1007/s10545-010-9206-3

ORIGINAL ARTICLE

Treatment of infantile Pompe disease with alglucosidase alpha: the UK experience

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Received: 26 May 2010 / Revised: 2 August 2010 / Accepted: 26 August 2010 / Published online: 24 September 2010

Abstract Treatment of infantile Pompe disease with recombinant human acid α-glucosidase has shown substantial improvement in survival, and in cardiac, motor and respiratory functions. We analyzed the outcome of all patients with infantile Pompe disease treated in the United Kingdom since the availability of the enzyme, using a questionnaire-based survey circulated to all treating centres. A total of 20 infants were treated from 2000 to 2009. Median ages at diagnosis and treatment were 5.75 months (range 0.25–31 months) and 6.5 months (0.5–32 months), respectively. Median duration of treatment was 31 months (1–102 months). Overall ventilator-free survival was 35% (7/20 infants), while 35% (7/20) died at a median age of 10 months (5.75–15 months) and 30% (6/20) were alive but ventilator-dependent. Endotracheal intubation for acute deterioration carried a high risk of failure of extubation and progression to long-term ventilation (LTV), but elective general anaesthesia, in contrast, was well tolerated. Overall outcome was worse than in the pivotal clinical trials; possible causes include later diagnosis and treatment in our patients and a higher incidence of infants at the severe end of the clinical spectrum. Careful consideration must be given to all possible outcomes, including LTV, before commencing enzyme replacement therapy in newly diagnosed infants.

Communicated by: Olaf Bodamer

Competing interest: None declared.

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Introduction

Pompe disease (OMIM #232300) is a progressive neuromuscular disorder caused by the autosomal recessively inherited deficiency of the lysosmal hydrolase acid α-glucosidase (GAA). The infantile form of Pompe disease represents the severe end of the spectrum of enzyme deficiency with an estimated incidence of 1:138,000, and is characterized by progressive cardiac, respiratory and skeletal muscle weakness and early death from cardiorespiratory failure. Natural history studies suggest median ages of symptom onset at 1.6–2 months, ventilator dependency at 4.7 months and death at 6–9 months (Kishnani et al. 2006; van den Hout et al. 2003).

Enzyme replacement therapy (ERT) for Pompe disease in the form of recombinant human (rh) GAA has become available in the last few years and has resulted in improved survival and cardiac, respiratory and motor functions with treatment (Kishnani et al. 2007, 2009). The pivotal clinical trial (Kishnani et al. 2007) suggested an invasive ventilator-free survival of 88.9% at 52 weeks amongst a cohort of 18 patients with infantile Pompe disease. Although this represented a dramatic improvement on the natural history, the effectiveness of ERT (as defined by ventilator-free survival) was not sustained on longer follow-up of the same cohort,

with reported ventilator-free survival rates of 66.7% at 24 months and 49.4% at 36 months (Kishnani et al. 2009).

In England, licensed ERT for infantile Pompe disease has been available since 2006, although some patients have been on treatment for longer as part of the pivotal clinical trials. The treatment is overseen via the National Commissioning Group (NCG), an arm of the Department of Health, which plans and funds the provision of care for very rare conditions, including ERT for all lysosomal storage disorders (LSDs) (http://www.ncg.nhs.uk/). GAA therapy for infantile Pompe disease in England is prescribable via four designated centres according to nationally agreed guidelines for treatment and follow- up http://www.ncg.nhs.uk/?dl_id=77. We conducted an audit of ERT of all infantile Pompe patients treated with rhGAA in 2009 to study the outcomes in comparison with published data.

Methods

The UK NCG guidelines define infantile Pompe disease as "all patients presenting with GSD II in the first two years of life with deficiency of acid alpha-glucosidase measured in lymphocytes or skin fibroblasts" http://www.ncg.nhs.uk/?dl_id=77. This includes patients with "classic" infantile presentation with cardiomyopathy; patients presenting over the age of 2 years with hypertrophic cardiomyopathy are also treated according to these guidelines and were included in the dataset. In a small number of patients, the enzyme assay was performed on muscle.

Questionnaires were circulated to all NCG-designated centres between April and June 2009. Data were gathered on number of cases, the ages at diagnosis and treatment, current status and age, need for and age at assisted ventilation, feeding, walking, tolerance of anaesthesia and death. No cardiac data were collected.

Results

A total of 20 infants were reported to have been treated with rhGAA since 2000. Median age at diagnosis was 5.75 months (range 0.25–31 months), median age at commencement of treatment was 6.5 months (0.5–32 months), and median duration of treatment was 31 months (1—102 months).

At the time of reporting, 7 (35%) had died, 7 (35%) were alive and ventilator-free and 6 (30%) were alive but ventilator-dependent. Median age of death (n=7) was 10 months (5.75–15 months) and duration of treatment before death was 5.52 months (0.25–10 months). Thirteen out of 20 patients were alive, with a median current age of 45 months (5–108 months); this group had been treated for a median of 20 months (1–102 months). Four of the living patients were treated for <1 year and 9 were treated for >1 year. Amongst the living patients, 6 required ventilatory support; this included invasive 24-h support in 3 cases, night-time support in 2 cases, and non-invasive ventilation (BIPAP) in 1 case (Fig. 1). Tracheostomy for long-term invasive ventilation was required in 6 patients (5 living, 1 deceased at the time of reporting) at a median age of 14 months (9–36 months); duration of treatment before tracheostomy ranged from 3 to 30 months (median 14 months).

A total of 13 episodes of emergency assisted ventilation (lasting >24 h) were reported in 9 patients, indications including respiratory failure (4 episodes) cardiac failure (4), infection (4) and failure of exubation after general anaesthetic (1). Of these, 8 episodes were transient; in these cases, ventilation was required for a median of 7 days (range 2 days–2 weeks). All cases requiring ventilation for >2 weeks eventually required long-term ventilation (Fig. 1). In contrast, elective general anaesthesia was generally well tolerated. A total of 14 episodes in 10 patients were reported: 10 cases were extubated immediately after the anaesthetic, 1 patient required assisted ventilation for 3 days, and 3 previously ventilated cases were continued on ventilation afterwards.

Cardiac data were difficult to evaluate, as follow-up was not centralised and data were difficult to obtain. Furthermore, the echocardiograms were seen and interpreted by different cardiologists. For these reasons, they were not obtained.

Feeding via nasogastric tube or gastrostomy was required in 13/20 cases (65%); none of the patients who commenced assisted feeding were able to come off it after long-term ERT. Amongst 10 patients >1 year of age, 4 (40%) could walk, and 6 (60%) were unable to walk.

Patients who were diagnosed before 6 months of age had a poorer outcome than the overall cohort. Of 14 such cases, 6 (44%) had died, 4 (28%) were alive and ventilator-free and 4 (28%) were on long-term ventilation. Median duration of treatment in this group was 20.5 months (range 1.5–102 months); 3 of the 8 living patients had been treated for <1 year.

CRIM status was known in only 5 cases (25%); 3 were CRIM-positive and all these patients were alive and on long-term invasive ventilation, while both the CRIM negative cases had died. Antibody status was known in only 2 cases: both patients were positive for antibodies, alive and on long-term invasive ventilation.

Discussion

The UK experience of ERT for infantile Pompe disease does not appear to be as good as that reported in the pivotal study. We found ventilator-free survival in 7/20 cases (35%), while 7/20 cases died (35%) and 6/20 (30%) were

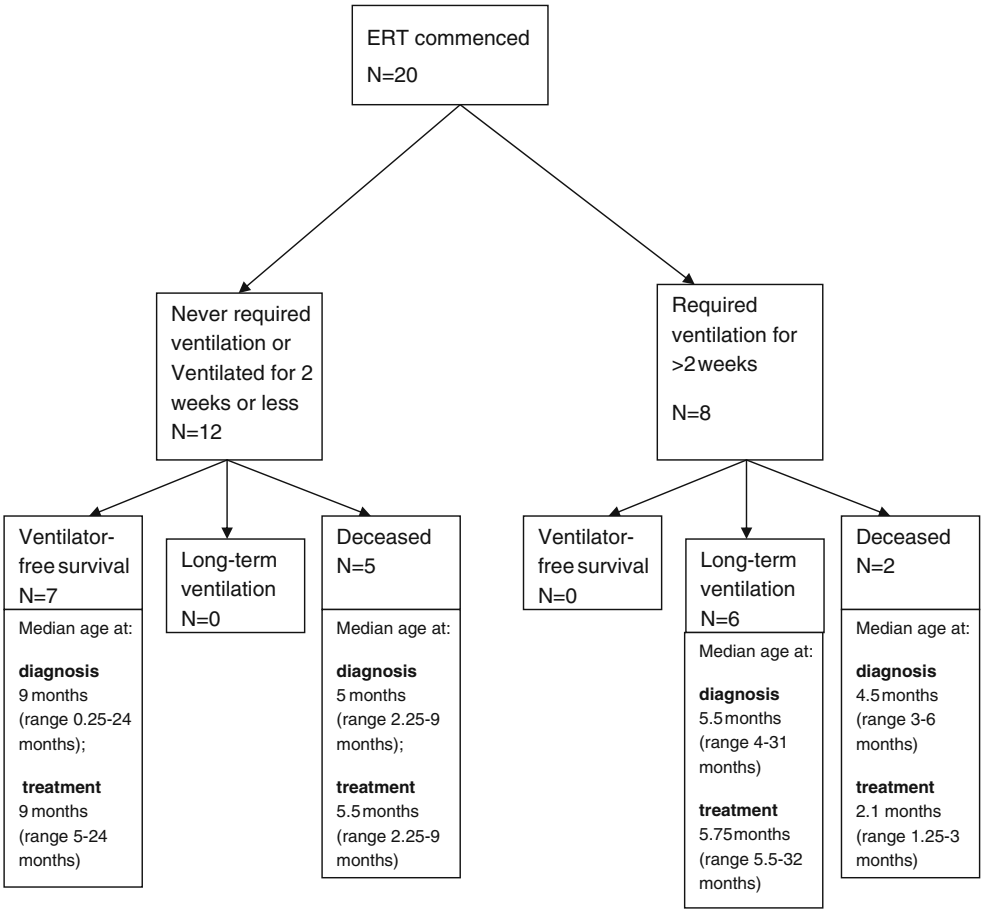

Fig. 1 Outcome of 20 infants with infantile Pompe disease patients on enzyme replacement therapy (ERT); *LTV* long-term ventilation

ventilator-dependent, an apparently worse outcome than at the end of 3 years of treatment in the pivotal study.

We identified two possible reasons for these differences. The first was age. While the eligibilty criteria and dosage schedules for treatment in the UK are very similar to those used in the pivotal trial, our cohort was characterised by older ages both at diagnosis (median age at diagnosis 5.75 vs 4.3 months in the pivotal study) and commencement of ERT (median 6.5 vs 5.3 months) and this may explain the relatively poorer outcome.

Another possible factor was the clinical severity of our patients. Paradoxically, it appears that the infants in the group with the best outcome (ventilator-free survival) were treated later than those in the groups with poorer outcome (Fig. 1). This is most likely due to a high proportion in our cohort of infants at the severe end of the clinical spectrum: 14/20 (70%) of patients presented before the age of 6 months; most of these infants presented clinically and had a less favourable overall outcome. The overriding factor determining outcome in this cohort thus appears to be the age at clinical presentation rather than the age at commencement of treatment, and may reflect a higher proportion in our population of CRIM-negative infants than in other populations. Unfortunately, CRIM testing was not available in more than a handful of cases in order to confirm this observation. Additionally, the number of older patients in our cohort was very small and included three atypical patients whose outcome possibly skewed the final results. Nevertheless, our outcome data are consistent with the findings of Nicolino et al. (2009) who reported similar findings in their cohort of patients treated with ERT.

The type and extent of cardiomyopathy can affect outcome. However, because of the limitations referred to in "Results", we were unable to evaluate its impact in our cohort. Furthermore, differentiating between the cardiac and neuromuscular components of the infantile Pompe phenotype can be very difficult. For these reasons, we have simply evaluated overall survival.

Recent data suggest that ventilator-free survival in treated patients decreases with time: 88.9% of the cohort from the pivotal study achieved this outcome after 1 year of treatment in the pivotal study, but this declined to 66.7% at 2 years and 49.4% at 3 years. These results have led to the suggestion that ERT does not improve the outcome of the most severe cases, and recent data on the poor outcome of CRIM-negative cases would appear to confirm this (Kishnani et al. 2010).

The long-term outcome of enzyme-treated patients with infantile Pompe disease is therefore highly variable. The

most desirable outcome is ventilator-free survival, and this is achievable in 35–50% of patients. However, other infants (30–35%) are unresponsive to treatment and do not survive, and more rapidly available investigations for CRIM status and genetic mutations may help to better identify this group of infants in whom ERT may not be appropriate. Around 30% of our treated cases were on long–term ventilation on follow–up. Currently, no available baseline investigations would appear to be able to predict this outcome at the time of commencement of ERT. From our data, it would appear that endotracheal intubation for acute clinical deterioration may lead to LTV in a substantial proportion of cases, especially if extubation is not possible within 2 weeks (Fig. 1). On the other hand, elective intubation for general anaesthesia does not carry the same risk.

Given the likelihood of LTV in a significant number of infants, it is essential that the possibility of long-term ventilation and all its social, financial and logistical implications be discussed fully with the parents in conjunction with a team experienced in delivering this service before commencing ERT, and also if endotracheal intubation is required for acute clinical deterioration. The current UK guidelines are being revised in accordance with these considerations.

Currently, the challenge of identifying as early as possible those infants with infantile Pompe disease who are most likely to respond to ERT remains. The lack of reliable and readily available prognostic markers makes this difficult to achieve at present. Measures such as newborn screening, readily available CRIM testing, rapid mutation analysis and the development of newer biochemical markers may help attain this goal.

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