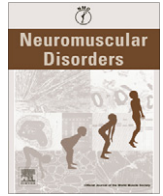




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Editorial

Where do we stand in enzyme replacement therapy in Pompe's disease?

It is now 11 years since the first pilot trial on enzyme therapy with recombinant human alpha-glucosidase in four infants with classic infantile Pompe disease [1]. In this issue of *Neuromuscular Disorders* the 3 year follow-up data are published of a study in five children with Pompe disease [2]. Earlier this year the results of a large placebo controlled study appeared in the *New England Journal*, mainly in adults [3].

This has been a slow-moving field and it is perhaps timely to take stock of where we stand in enzyme replacement therapy in Pompe disease in 2010, and what we have learned so far.

In February 1999 we started to conduct the first pilot clinical trial in four patients with classic infantile Pompe disease not knowing what to expect [1]. We had long discussions about the pro's and cons to start this first trial in infants. In fact the vast majority of patients with Pompe disease were adults. The most important considerations to choose for infants were that there were no other options for the infants and that we would have an answer soon. Without therapy patients with classic infantile Pompe disease certainly die within 1 year and motor milestones are not achieved or maintained. Further, the group is rather homogeneous. Cardiac hypertrophy is characteristic. *GAA* gene mutations are completely deleterious and alpha-glucosidase profoundly deficient. This made the endpoints clear. Survival of more than a year, achievement of motor milestones and/or reduction of cardiac hypertrophy would demonstrate efficacy of therapy.

There were also challenges. Would it be possible to turn the tides in a disease process that progresses so fast and causes such a homogeneous destruction of skeletal muscles. Further, the profound deficiency of alpha-glucosidase in classic infantile patients does not only cause storage of glycogen in muscle but leads to a generalized storage of glycogen in other tissues as well including the central nervous system, which is protected by the blood brain barrier and difficult to reach by the enzyme.

This first pilot trial provided the proof of principle that enzyme therapy had an effect in patients with Pompe disease. The provisional endpoints of the trial were met. All four patients survived until 4 years or longer. Three of these four children are still alive now in August 2010, more than 11 years later. Two of these children are completely paralytic and ventilator dependent. In retrospect, they both started therapy too late at ages of 7 and 8 months being already paralytic at that time. The other patient, who started therapy at 3 months is still able to walk at the age of eleven and goes to school, although there are some symptoms of muscle weakness.

From this initial pilot trial and larger trials published thereafter, which have led to the final registration of recombinant human alpha-glucosidase (*Myozyme*) as therapy for Pompe disease in 2006, many lessons were learned [4]. We are now of the opinion that early start of therapy is essential in infants with classic infantile

Pompe disease and that ventilation of infants should be prevented or not be started at all. This policy has improved the outcome, but still there is a lot to learn. About 50% of the infants on enzyme therapy survive without ventilation [5]. The role of antibodies, CRIM status, dosing, long term motor outcome and factors like hearing, speech development, prevention of respiratory infections, school performance are topics to be further addressed. Slowly more insight is obtained in the understanding of the disease and effects of therapy.

With infants surviving much longer than before, the clinical picture of Pompe disease is starting to change. The fact that a patient with classic infantile Pompe disease is able to walk at the age of 11 years, as do other younger patients with infantile Pompe disease receiving enzyme therapy, provides an important proof of concept that enzyme therapy may also have an effect in children of the same age with milder phenotypes and genotypes and more residual activity. In fact, patients with the most common c-32T > G (*IVS1*)/null genotype, found in 50% of the children and more than 80% of the adults, already start with 10–20% residual alpha-glucosidase in their muscles compared to none in infants. Based on their slower disease course and higher residual enzyme activity their prospects for therapy should theoretically be better than those of infants.

Endpoints in children and adults are much more difficult to choose. Survival as endpoint is not an option. The disease course in these untreated patients is variable, knowledge on the natural course of disease is still limited, but the growing numbers of natural course studies provide evidence that the disease progresses steadily in untreated patients on a group level. A large patient oriented survey performed in 255 patients (children and adults) shows that 10–15 years after the diagnosis about 50% of the untreated patients have become wheelchair bound and ventilator dependent [6]. Other studies in adults show that FVC on a group level deteriorates by 1.7–3.1% absolute percentage points per year [7,8]; in the placebo controlled trial published this year in the *New England Journal of Medicine* the decline was 2.2% in 78 months for the placebo/untreated group [3]. Studies on muscle strength and muscle function in untreated patients are very sparse. One study in 16 adults who were followed for many years showed that muscle strength tested via manual muscle testing using the MRC score deteriorates on average 1% per year on a group level. On an individual basis the disease may be stable for years or deteriorate relatively fast over a few years.

In children with Pompe disease larger studies on the natural course are even more limited than in adults. One of the difficulties is that children are subjected to growth as is their muscle mass and strength.

We found it promising though that in our study in five treated children, published in this issue of *Neuromuscular Disorders*, none

deteriorated over 3 years time [2]. FVC stabilized and showed an increase in volume comparable to normal peers or slightly better, as did muscle strength. Further some functional improvements were observed. Overall the effects were modest. Three of the five children in our study had a reduced FVC; one of them required a ventilator at night. For comparison we calculated the course of FVC in eight untreated Pompe children with an FVC < 80% at first visit. Their FVC reduced by 5% per year. The course in the untreated children was significantly different from the study group. In both groups, the study group and the reference group, children with the c-32T > G (IVS1)/null genotype and children with more severe genotypes than the c-32T > G (IVS1)/null genotype were incorporated. The findings are in line with our earlier study in two juveniles and one adult with Pompe disease followed for 8 years, which indicated that recombinant human alpha-glucosidase may stabilize or improve the disease [9].

In April 2010 the first placebo controlled study on treatment with recombinant human alpha-glucosidase in Pompe disease was published in *The New England Journal of Medicine*. Mainly adults participated in this study [3]. Both primary endpoints were met. There was a significant difference between distance walked in 6 min and change in FVC between the two groups. The difference in distance walked was 28 m in 6 min and the difference in FVC 3.4% at the end of the 78 week study period. Both effects were considered to be very modest.

In my opinion the most important achievement of this study published in *The New England Journal of Medicine* is that it showed for the first time that there is difference in effect between adults who receive placebo and those who received recombinant human alpha-glucosidase. So it provides the first evidence that treatment with recombinant alpha-glucosidase has a significant effect on a group level in adults with Pompe disease. Whether the effects are sufficient to prevent that patients need a ventilator or wheelchair in future needs further investigation. The results of the clinical trial point to the direction that enzyme therapy may stabilize the disease. For patients this could have important consequences.

Like in infants, not all child and adult patients respond equally well. There are also patients who deteriorate despite enzyme therapy [10]. There is still a lot of work to do. It is our task as clinicians and researchers to identify good and bad responders and the prognostic factors that determine the outcome. Among others role of antibodies, dosing, age, disease duration, disease severity, fibre type, effects of enzyme therapy on muscle damage and regeneration need further investigation.

Another interesting topic is the influence of muscle growth, increase of muscle mass during childhood and loss of muscle mass during late adulthood that normally occurs in healthy individuals. Pompe disease is the first muscle disease for which a therapy has become available. All what is learned from Pompe disease may be helpful in the development and understanding of therapies for other muscle diseases.

The long term effects of enzyme therapy in Pompe disease definitely need further study. In the end the clinicians with the help of their patients need to determine what is the ultimate value of the therapy. We need to have an open eye for limitations and potential improvements. Placebo controlled, randomized trials are just a first essential step to uncover what may be the tip of the iceberg. Thereafter the work really starts. In September there has been an ENMC workshop on this subject. The aim is to bring data on effects of enzyme therapy together from many countries and centres in order to get more insight in prognostic factors for and limitations of response. These concerted efforts may help in the end to develop guidelines for further therapy.

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