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Pompe's disease: enzyme replacement therapy

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Abstract

The approval of Myozyme® (alglucosidase alfa; Genzyme) represented the first significant advance in therapy for Pompe's disease. Pompe's disease is the inherited deficiency of acid α-glucosidase (GAA), and hence the rationale for treatment with Myozyme®, a form of recombinant human (rh)GAA. Previously, the natural history of infantile Pompe's disease featured rapid progression of hypertrophic and dilated cardiomyopathy to death from cardiorespiratory failure by 1 year of age. The course of infantile Pompe's disease was significantly altered by enzyme replacement therapy (ERT) with rhGAA, which improved survival and ventilator-free survival, as well as reversing cardiomyopathy and improving motor development. Limitations of ERT include high dose requirements to treat the large skeletal muscle mass, suboptimal receptor-mediated uptake and complicating antibody responses to rhGAA therapy in a subset of patients. A randomized trial in late-onset Pompe's disease is under way, as an improvement in motor and pulmonary function has been reported in small trials.

Background

Therapy for lysosomal storage disorders has been possible due to the principle of cross-correction of lysosomal enzyme deficiencies. Cross-correction depends upon the mannose/mannose-6-phosphate receptor-mediated uptake of lysosomal enzymes (1). Enzyme replacement therapy (ERT) and bone marrow transplantation/stem cell transplantation were initiated based upon the principle that receptor-mediated uptake could correct the deficiency of the spectrum of tissues affected by various lysosomal storage disorders.

The first success of ERT (imiglucerase, Cerezyme®; Genzyme) in Gaucher's disease established a paradigm for later attempts in other lysosomal storage disorders (2). ERT is recommended for type I Gaucher's disease (the non-neuronopathic form), where it reliably corrects anemia, thrombocytopenia and hepatosplenomegaly. In patients with type I Gaucher's disease and skeletal involvement, ERT reduces bone marrow infiltration by Gaucher cells, restores bone growth in children, reduces the frequency of bone crises, ameliorates bone pain and increases bone mineral density. On average, bone loss takes a longer time to reverse and normal or near-normal bone mineral density can be restored after 8 or more years of treatment with imiglucerase at a dose of 60 U/kg every 2 weeks, although some patients improve even at lower doses. Bone involvement can be prevented if ERT is started at an early age prior to significant osteopenia and bone pain. In type II and III Gaucher's disease, the so-called neuronopathic forms, brain and cranial nerve involvement typically progresses despite attempts at ERT. In type III Gaucher's disease, ERT has been used successfully due to slow neurological progression and in some instances only eye involvement (3).

ERT has also been approved for mucopolysaccharidosis type I (MPS I, Hurler-Scheie syndrome) and MPS VI (Maroteaux-Lamy syndrome) (3), and more recently, ERT products were approved for Fabry's disease and Pompe's disease. ERT for Niemann-Pick type B disease is under development (3), and ERT was recently approved for MPS II/Hunter's syndrome (idursulfase, Elaprase®; Shire Human Genetic Therapies). These examples of successful ERT have amply demonstrated the robust principle of cross-correction through receptor-mediated uptake in lysosomal storage disorders.

Pathogenesis and treatment

Deficiency of acid α-glucosidase (GAA, acid maltase; EC 3.2.1.20) in Pompe's disease affects primarily the heart and smooth and skeletal muscle, and infants with Pompe's disease develop profound weakness and hypotonia. Late-onset forms of Pompe's disease feature progressive muscle weakness without significant cardiomyopathy. These patients often become wheelchair users and ventilator-dependent with disease progression. The

cause of death in Pompe's disease is usually cardiorespiratory failure, which can be precipitous. The histopathology of Pompe's disease includes marked lysosomal accumulation of glycogen in cardiac and skeletal muscle, which culminates with the leakage/rupture of lysosomes and cytoplasmic pooling of glycogen.

The utility of ERT for Pompe's disease was first demonstrated in the acid maltase-deficient Japanese quail (4), where injection of rhGAA restored the ability of affected birds to right themselves and fly. Other proof-of-principle experiments were also dependent upon cloning and characterization of the human *GAA* gene, and the efficacy of ERT for Pompe's disease was demonstrated in the *GAA* knockout (GAA-KO) mouse model by reversing glycogen accumulation and restoring GAA activity in the heart and skeletal muscle (5-8).

A defect in the trafficking of glycogen in Pompe's disease myofibers interferes with the clearance of glycogen stored in myofibers, especially type II myofibers. Defective autophagy is being increasingly recognized as an important factor in the pathogenesis of the disease. Type II myofibers were resistant to ERT due to abnormal autophagy, leading to accumulation of glycogen-laden endosomes and lysosomes in older Pompe's disease mice (9, 10). Type II myofibers held accumulated lysosomes that were alkalinized, reducing the activity of introduced hGAA; furthermore, expression of the mannose-6-phosphate receptor was relatively lower on type II myofibers, reducing the uptake of hGAA (11).

Reactions to rhGAA in immunocompetent GAA-KO mice motivated the development of tolerant Pompe's disease mice (12). Tolerant GAA-KO mice were generated by the introduction of a low-expressing liver-specific transgene that prevented immune responses against rhGAA without correcting GAA deficiency in the heart and the skeletal muscle. High-level hGAA replacement (40-100 mg/kg/dose) reduced the glycogen content of the heart and the skeletal muscle in tolerant GAA-KO mouse models (12). Patients have similarly high dose requirements, because the dose of Myozyme® is approximately 30-100-fold greater than the doses used for ERT in other lysosomal disorders (13).

Clinical studies with ERT

The prognosis of untreated infantile Pompe's disease remains dismal, and death occurred in most patients by 1 year of age in two large retrospective studies of its natural history (14, 15). The benefit of ERT in infantile Pompe's disease was demonstrated in early phase I/II and phase II clinical trials. In pilot human phase I/II studies, recombinant human acid α-glucosidase (rhGAA) purified from CHO cell cultures (n=3) (16) or transgenic rabbit milk (n=4) (17) prolonged the survival of all subjects beyond 1 year; an improvement in cardiomyopathy was also noted in all subjects. Two of 7 subjects walked independently and remained ventilator-free. The remaining 5 patients from these studies did not do well; they had residual delays in motor development or loss of motor milestones, and eventually became ventilator-dependent, and several died.

A phase II trial of transgenic rhGAA in 2 classical infant subjects demonstrated prolonged survival and improvement in cardiomyopathy during the first 10 months of follow-up (18).

Another open-label, multinational, multicenter phase II study examining the safety and efficacy of rhGAA in the treatment of infantile-onset Pompe's disease revealed an improved outcome in patients on ERT (n=8) (19). After 52 weeks of treatment, 6 of 8 patients were alive and 5 were free of invasive ventilator support. Five patients acquired new motor milestones and 3 walked independently. Four patients died after the initial study phase; median age at death or treatment withdrawal for all patients was 21.7 months, significantly later than expected for untreated patients.

In summary, various early studies of rhGAA revealed improved ventilator-free survival, cardiomyopathy, growth and motor function in patients with infantile-onset Pompe's disease in comparison to outcomes expected for patients without treatment.

The data from two pivotal clinical trials led to broad label approval of Myozyme® in 2006 for the treatment of Pompe's disease. Age upon entry and ventilator status were the primary differences between the two pivotal clinical trials (study 1 and 2, respectively). In study 1, patients were ventilator-free at study entry, while in study 2, patients were not excluded if on a ventilator. Study 1 enrolled babies less than 6 months of age and the primary endpoint was invasive ventilator-free survival *versus* survival in an untreated historical cohort; study 2 enrolled subjects 6-36 months old with a primary endpoint of survival *versus* a historical cohort (19). Secondary endpoints were identical for both studies, including changes in left ventricular mass index, growth and motor development.

Study 1 demonstrated prolonged survival, all 18 patients being alive at age 18 months and 15 of 18 (83%) showing invasive ventilator-free survival at 18 months (20). All 15 subjects with available data had reduced left ventricular mass. Growth was maintained in 15 of 18 subjects, with normal weight throughout the initial study period (1 year, or 52 weeks). Motor development continued to improve in 13 of 18 subjects, although it was delayed in some, as determined by the Alberta Infant Motor Scale (AIMS). Study 1 also compared doses of 20 and 40 mg/kg every other week, which did not significantly affect efficacy, although a greater number of adverse events was associated with the higher dose (20).

Study 2 enrolled 21 patients, aged 3 months to 3.5 years at first treatment. All patients received 20 mg/kg of Myozyme® every other week until its approval for marketing, for up to 104 weeks in some subjects. At the 52-week analysis, 16 of 21 patients were alive (Myozyme® Prescribing Information, available at http://www.myozyme.com).

Clinical trial experience in late-onset Pompe's disease has been limited to a few pilot studies. A phase I/II open-label trial was conducted in 3 later onset (ages 11, 16 and 32 years) patients (2 ventilator-dependent) with rhGAA

purified from transgenic rabbit milk (21). Initially, patients received weekly infusions of 10 mg/kg, and then the dose was increased to 20 mg/kg/week. After 3 years of treatment, their pulmonary function improved or stabilized. The youngest and least affected patient, who had been wheelchair dependent for 4 years, started to walk, suggesting that ERT could improve muscle strength, particularly when started early. The other 2 patients remained wheelchair-bound, but showed improvement in quality of life. No significant infusion reactions were reported. The authors concluded that 20 mg/kg was the minimal dose to target muscle and obtain a clinical effect, and that biweekly or weekly dosing would be necessary (21).

In another study, 5 patients with late-onset Pompe's disease between 5 and 15 years of age were treated with rhGAA at 20 mg/kg every 2 weeks. Interim data following 6 months of ERT showed a > 11% increase in predicted forced vital capacity (FVC) in 3 patients. A clinically meaningful increase in the distance walked in 6 min was also noted in 3 cases (> 37 m in all subjects) (22).

Data from an expanded-access program in advanced late-onset Pompe's disease in 18 patients (age range: 9-54 years) have also shown clinical benefit. At baseline, 17 of 18 cases had some form of ventilator use and all 18 cases were wheelchair users. Improvement in hours of ventilator use was noted in 8 of 17 cases, an improvement in muscle strength in 13 of the 18 cases and gains in weight and/or oral feeding in 7 of 18. The duration of ERT in this cohort ranged from 8.3 months to 6 years (22). More recently, it was reported that 10 of 18 patients demonstrated improvements in respiratory function. Fifteen of 16 patients self-reported positive improvements in quality of life since commencing ERT. Treatment was well tolerated, with only one report of a mild transient infusion-associated reaction during the first infusions (23).

At the present time, a randomized, double-blind, placebo-controlled study is ongoing in 90 late-onset cases with a 2:1 drug:placebo assignment. All patients have been enrolled and the study was due for completion in September 2007. In order to be included in the study, all subjects needed to be ambulatory (able to walk 40 m) and not invasively ventilated. Pulmonary and muscle strength will be assessed every 12 weeks. The primary endpoints in this study are distance walked in 6 min and FVC on a dose of 20 mg/kg every other week (24).

Safety of ERT

Infusion-associated reactions (IARs) occurred in approximately 50% of patients treated with Myozyme® in the two pivotal infantile-onset clinical studies (52-week safety data). In these studies, all IARs were assessed as mild to moderate, and there were no dropouts in the study due to IARs (Myozyme® Prescribing Information, available at http://www.myozyme.com). Some patients were pretreated with antihistamines, antipyretics and/or corticosteroids.

Experience with Myozyme® has shown that IARs occur mostly within 2 h of the infusion, and more frequently at higher infusion rates. Because of the potential for severe hypersensitivity reactions, appropriate medical support measures should be readily available, similar to precautions used when administering other foreign proteins. Patients who have experienced IARs should be treated with caution, because patients with advanced Pompe's disease may have compromised cardiac and respiratory function that could predispose them to a higher risk of severe complications from infusion reactions (Myozyme® Prescribing Information, available at http://www.myozyme.com).

Serious hypersensitivity reactions, including anaphylactic reactions, have been reported in 3% (8 of ~280 patients treated with Myozyme® in various clinical trials and expanded-access programs). Reactions included one or more of the following: bronchospasm, decreased oxygen saturation, hypotension, urticaria, periorbital edema, swollen tongue, angioneurotic edema, chest discomfort, throat tightness, tachycardia and rash. Reactions were primarily managed with a reduction in the infusion rate and/or interruption of the infusion and administration of antihistamines, corticosteroids, bronchodilators, epinephrine (in 2 patients) and/or oxygen. All 8 patients recovered without sequelae from the reactions.

One infant with Pompe's disease experienced acute cardiorespiratory failure requiring intubation and inotropic support, possibly associated with fluid overload, upon i.v. administration of Myozyme®. Babies with cardiac involvement can have severe compromise, and must be treated judiciously with input from a pediatric cardiologist and other specialists familiar with Pompe's disease. Avoiding volume overload in patients with severe cardiac compromise and slowing the infusion rate or temporarily interrupting the infusion have allowed most patients to continue therapy with Myozyme® (personal experience, Dr. Kishnani).

The majority of patients developed IgG antibodies to rhGAA, typically within 3 months of treatment. In most cases, patients either became tolerant or showed a downward trend in antibody titers over the course of ERT. Antibody responses to rhGAA could compromise the safety and efficacy of Myozyme® in some Pompe's disease patients. Animal and human studies have suggested that the development of humoral immunity against the infused enzyme presents an obstacle for successful ERT. In GAA-KO mice, the formation of anti-GAA antibodies prevented continuation of ERT beyond 3 weeks. Tolerant GAA-KO mice, however, survived long-term ERT (8). In clinical trials, Pompe's disease patients who lacked any residual GAA protein, that is patients who are cross-reacting immune material-negative (CRIM-negative), produced very high anti-hGAA antibodies and demonstrated markedly reduced efficacy from ERT (16, 19, 20). The antibody response in GAA-KO mice and in CRIM-negative Pompe's disease patients is associated with a lack of residual GAA protein expression. If GAA deficiency is caused by an underlying null mutation(s), the immune system is likely to react to rhGAA by forming antibodies. Clearly this could be an important factor in determining

the response to ERT, and further study in this area is warranted.

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References

1. Neufeld, E.F., Fratantoni, J.C. *Inborn errors of mucopolysaccharide metabolism*. Science 1970, 169(941): 141-6.

2. Beutler, E. *Lysosomal storage diseases: Natural history and ethical and economic aspects*. Mol Genet Metab 2006, 88(3): 208-15.

3. Brady, R.O. *Enzyme replacement for lysosomal diseases*. Annu Rev Med 2006, 57: 283-96.

4. Kikuchi, T., Yang, H.W., Pennybacker, M., Ichihara, N., Mizutani, M., Van Hove, J.L., Chen, Y.T. *Clinical and metabolic correction of Pompe disease by enzyme therapy in acid maltase-deficient quail*. J Clin Invest 1998, 101(4): 827-33.

5. Hoefsloot, L.H., Hoogeveen-Westerveld, M., Reuser, A.J., Oostra, B.A. *Characterization of the human lysosomal alpha-glucosidase gene*. Biochem J 1990, 272(2): 493-7.

6. Wisselaar, H.A., Kroos, M.A., Hermans, M.M., Vanbeeumen, J., Reuser, A.J. *Structural and functional changes of lysosomal acid alpha-glucosidase during intracellular transport and maturation*. J Biol Chem 1993, 268(3): 2223-31.

7. Bijvoet, A.G., Van Hirtum, H., Kroos, M.A. et al. *Human acid alpha-glucosidase from rabbit milk has therapeutic effect in mice with glycogen storage disease type II*. Hum Mol Genet 1999, 8(12): 2145-53.

8. Raben, N., Danon, M., Gilbert, A.L. et al. *Enzyme replacement therapy in the mouse model of Pompe disease*. Mol Genet Metab 2003, 80(1-2): 159-69.

9. Fukuda, T., Ewan, L., Bauer, M. et al. *Dysfunction of endocytic and autophagic pathways in a lysosomal storage disease*. Ann Neurol 2006, 59(4): 700-8.

10. Fukuda, T., Ahearn, M., Roberts, A. et al. *Autophagy and mistargeting of therapeutic enzyme in skeletal muscle in Pompe disease*. Mol Ther 2006, 14(6): 831-9.

11. Raben, N., Fukuda, T., Gilbert, A.L. et al. *Replacing acid alpha-glucosidase in Pompe disease: Recombinant and transgenic enzymes are equipotent, but neither completely clears glycogen from type II muscle fibers*. Mol Ther 2005, 11(1): 48-56.

12. Raben, N., Lu, N., Nagaraju, K. et al. *Conditional tissue-specific expression of the acid alpha-glucosidase (GAA) gene in the GAA knockout mice: Implications for therapy*. Hum Mol Genet 2001, 10(19): 2039-47.

13. Desnick, R.J. *Enzyme replacement and enhancement therapies for lysosomal diseases*. J Inher Metab Dis 2004, 27(3): 385-410.

14. Kishnani, P.S., Hwu, W.L., Mandel, H., Nicolino, M., Yong, F., Corzo, D. *A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease*. J Pediatr 2006, 148(5): 671-6.

15. Van den Hout, J.M.P., Kamphoven, J.H.J., Winkel, L.P.F. et al. *Long term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk*. Pediatrics 2004, 113(5): E448-57.

16. Amalfitano, A., Bengur, A.R., Morse, R.P. et al. *Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: Results of a phase I/II clinical trial*. Genet Med 2001, 3(2): 132-8.

17. Van Den Hout, H., Reuser, A.J., Vulto, A.G., Loonen, M.C., Cromme-Dijkhuis, A., Van Der Ploeg, A.T. *Recombinant human alpha-glucosidase from rabbit milk in Pompe patients*. Lancet 2000, 356(9227): 397-8.

18. Klinge, L., Straub, V., Neudorf, U., Voit, T. *Enzyme replacement therapy in classical infantile Pompe disease: Results of a ten-month follow-up study*. Neuropediatrics 2005, 36(1): 6-11.

19. Kishnani, P.S., Nicolino, M., Voit, T. et al. *Chinese hamster ovary cell-derived recombinant human acid alpha-glucosidase in infantile-onset Pompe disease*. J Pediatr 2006, 149(1): 89-97.

20. Kishnani, P.S., Corzo, D., Nicolino, M. et al. *Recombinant human acid α-glucosidase: Major clinical benefits in infantile-onset Pompe disease*. Neurology 2007, 68(2): 99-109.

21. Winkel, L.P.F., Van den Hout, J.M.P., Kamphoven, A.T. et al. *Enzyme replacement therapy in late-onset Pompe's disease: A three-year follow-up*. Ann Neurol 2004, 55(4): 495-502.

22. Van Der Ploeg, A.T., Marsden, D.L. *Response to treatment with Myozyme in juvenile patients with Pompe disease*. Mol Genet Metab 2007, 90: 257-8.

23. Marsden, D.L., van der Ploeg, A. *Enzyme replacement therapy in 18 older, severely affected patients with Pompe's disease*. 57th Annu Meet Am Soc Hum Genet (ASHG) (Oct 23-27, San Diego) 2007, Abst 2238.

24. *A placebo-controlled study of safety and effectiveness of Myozyme in patients with late-onset Pompe disease (NCT00158600)*. ClinicalTrials.gov Web site, November 23, 2007.