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Human Acid α-Glucosidase

Treatment of Pompe's Disease

rh-α-Glucosidase
rhGAA
Myozyme™
Pompase™

Recombinant human acid α-glucosidase (acid maltase)

EN: 273920

Abstract

Pompe's disease or glycogen storage disease type II is an inherited progressive skeletal muscle disorder caused by deficiency of the lysosomal enzyme α-glucosidase. The most severe form of the disease affects infants and results in feeding difficulties, respiratory and cardiac problems and motor delay. A late-onset form of the disease also exists, which is less severe. Enzyme replacement therapy has recently been investigated in pilot studies using a recombinant human α-glucosidase from rabbit milk. Initially, normalization of α-glucosidase activity and degradation of lysosomal glycogen in heart, skeletal and smooth muscle were observed in mouse models of the disease, indicating the potential for enzyme therapy. Subsequent pilot studies in patients with both the infantile and juvenile forms of the disease have shown promising results, particularly in those patients whose treatment is initiated early in the development of the disease. Patients showed an improvement in cardiac function. Improvements in biochemical function and tissue morphology correlated with an improvement in the clinical condition of patients, with motor function significantly improved in a number of the patients. The recombinant enzyme was generally well tolerated, with infusion reactions being the most commonly reported adverse effects.

Introduction

Pompe's disease or glycogen storage disease type II is an inherited progressive skeletal muscle disorder. It is a rare disease, affecting 5,000 to 10,000 people worldwide. The characteristic lysosomal glycogen accumulation is caused by deficiency of the lysosomal enzyme α-glucosidase. The most serious form of the disease is seen in babies with the infantile form of the disease. It commonly presents in the first few months after birth with respiratory and feeding difficulties and muscle weakness. Developmental milestones such as rolling over, sitting and standing are not achieved. Increased heart size due to hypertrophic cardiomyopathy is characteristic. Most infants with the disease die of cardiorespiratory failure within the first year of life.

A late-onset form of the disease also exists, which is less severe. It may occur at any age and results in a progressive dysfunction of skeletal muscles. The heart is generally not involved. Patients eventually become wheelchair bound and depend on artificial respiration. Respiratory failure is the main cause of death. The age of death usually depends on the rate of progression of the disease and degree of involvement of respiratory muscles.

In both forms of the disease, there is generally good correlation between the severity of the disease and the level of residual enzyme activity; α-glucosidase activity is virtually absent in severe infantile cases, but residual activities up to 20% of normal are seen in late-onset cases. There had been no potential treatment for the disease until the development of enzyme therapy in the 1960s. Early attempts to develop treatment failed but the recent production of recombinant human α-glucosidase from rabbit milk has resulted in promising advances in the treatment of Pompe's disease. Developments in DNA technology have enabled large-scale production of the recombinant enzyme and phase II trials are now in progress.

Pharmacological Actions

Recombinant human α-glucosidase has been produced on an industrial scale in the milk of transgenic rabbits. Transgenic rabbits of the selected strain produced up to 8 g of the enzyme per liter of milk and the purified

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enzyme was comparable to the α-glucosidase precursor secreted in human urine. The therapeutic effectiveness of the purified recombinant human α-glucosidase was assessed in α-glucosidase deficient knockout mice. Following a single i.v. dose of the enzyme, normalization of α-glucosidase activity occurred in all tissues except the brain. Weekly enzyme infusions or placebo were then administered over a period of 6 months. The enzyme-treated mice showed degradation of lysosomal glycogen in heart, skeletal and smooth muscle. The tissue morphology also improved substantially despite the advanced state of disease at the start of treatment (1).

Clinical Studies

In the first clinical study in infants with Pompe's disease, 4 patients received recombinant human α-glucosidase from transgenic rabbit milk. The study was conducted as a single-center, open-label pilot study. Four patients, less than 10 months old, with the most severe infantile form of the disease were recruited. Patients had hypertrophic cardiomyopathy and severe α-glucosidase deficiency. Diagnosis was confirmed by evidence of lysosomal glycogen storage in muscle biopsy. All the patients had presented with symptoms before 3 months of age and the diagnosis was confirmed before 6 months of age. Patients received 15 or 20 mg/kg of recombinant human α-glucosidase weekly for 12 weeks, then 40 mg/kg weekly for a further 24 weeks. Muscle biopsies were scheduled at baseline and at 12-week intervals. Neuromotor and mental development were assessed at regular intervals. After 24 weeks, all patients had acquired normal α-glucosidase activities from a baseline of 1-2% of the normal value. Tissue morphology showed a significant reduction in storage of lysosomal glycogen 12 weeks after the dosage increase, although the total tissue glycogen content had not changed significantly. Biochemical and tissue changes correlated with an im-provement in the clinical condition of all the patients. Motor improvement was observed in all patients, with the best effect observed in the 2 patients enrolled at the youngest age (2.5 and 3 months). One of these patients reached developmental milestones and at 12 months was able to crawl and to stand with the support of one arm. There was a significant reduction in left ventricular mass index in all patients. The recombinant enzyme was generally well tolerated. Infusion reactions in all 4 patients were observed, but were managed by adapting the infusion rate. There were no changes in blood pressure (2, 3). The 4 patients included in this study continued to receive recombinant human α-glucosidase and remained alive at 3 years of age (4).

At the same study center, 3 patients with juvenile Pompe's disease were also treated with weekly infusions of the recombinant enzyme (10 increasing to 20 mg/kg). The patients were 12, 16 and 32 years of age on entry and were all wheelchair bound. After 1.5-2 years of treatment, pulmonary function had stabilized or improved and α-glucosidase activity in muscle had increased. The youngest patient started to walk after 4 years of wheelchair dependency (4).

In a further phase II study, 8 infants received 10 mg/kg of recombinant human α-glucosidase weekly. All the patients had left ventricular hypertrophy and less than 1% α-glucosidase activity. Echocardiograms and electrocardiograms were performed at baseline and after 4, 8, 12 and 24 weeks. Preliminary data in 5 patients indicated that administration of the enzyme resulted in a rapid cardiac response, with a marked decrease in left ventricular mass, improved systolic function and resolution of outflow tract obstruction (5).

A phase II clinical study (1702) evaluating recombinant human α-glucosidase (Myozyme™) was initiated in March, 2003 will enroll up to 16 children between the ages of 6 months and 3 years at centers in the U.S. and Europe. A second study (1602) is also under way and will include up to 16 infants under the age of 6 months at the time of their first infusion. The efficacy of Myozyme™ will be assessed by patient survival, respiratory function, cardiac status and motor development. Safety is also being evaluated. Enrollment in both studies is expected to be completed during 2003. The development program for Myozyme™ has been granted fast track status by the FDA (6, 7).

Conclusions

Pilot studies in patients with both the infantile and juvenile forms of Pompe's disease have shown promising results in the treatment of this disease. In all studies, improvement in cardiac function has been observed. Signifiicant improvement in motor function has also been seen, particularly in patients whose treatment was initiated early in the progression of their disease. However, the number of patients treated in each study was small and confirmatory phase II studies are required to further assess the efficacy and safety of this therapy. In addition, long-term follow-up of patients receiving continuous treatment will be necessary to evaluate the prospects of enzyme therapy for Pompe's disease.

Source

Genzyme Corp. (US); licensed from Pharming BV (NL).

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