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Glycogen storage disease types I and II: Treatment updates

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Summary

Prior to 2006 therapy for glycogen storage diseases consisted primarily of dietary interventions, which in the case of glycogen storage disease (GSD) type II (GSD II; Pompe disease) remained essentially palliative. Despite improved survival and growth, long-term complications of GSD type I (GSD I) have not responded to dietary therapy with uncooked cornstarch or continuous gastric feeding. The recognized significant risk of renal disease and liver malignancy in GSD I has prompted efforts towards curative therapy, including organ transplantation, in those deemed at risk. Results of clinical trials in infantile Pompe disease with α -glucosidase alfa (Myozyme) showed prolonged survival reversal of cardiomyopathy, and motor gains. This resulted in broad label approval of Myozyme for Pompe disease in 2006. Furthermore, the development of experimental therapies, such as adeno-associated virus (AAV) vector-mediated gene therapy, holds promise for the availability of curative therapy in GSD I and GSD II/Pompe disease in the future.

Long-term complications of GSD Ia

Deficiency of glucose-6-phosphatase (G6Pase) underlies GSD Ia (also known as von Gierke disease; OMIM 232200), an autosomal recessive disorder of metabolism associated with life-threatening hypoglycaemia and growth retardation (Chen 2001). Infants with GSD Ia typically present with seizures and hepatomegaly at 6–8 months of age. Current therapy is focused upon the correction of biochemical abnormalities, chiefly through maintaining normoglycaemia. Dietary therapy, consisting either of continuous glucose infusion through total parenteral nutrition or of intragastric feeding, is the mainstay of patients when oral feedings are not feasible. Uncooked cornstarch (1.6–2.5 g/kg), initially every 3–4 h and eventually every 6 h, provides an alternative approach to continuous feeding (Chen et al 1984). Despite the proven

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ability to promote normal growth, if macronutrients and micronutrient are provided, dietary therapy does not prevent all the long-term complications of GSD Ia. Long-term complications include growth failure, gout, pulmonary hypertension, renal dysfunction with risk for renal failure, osteoporosis, and hepatic adenomas that can degenerate to hepatocellular carcinoma (HCC) (Chen 2001; Franco et al 2005a). Thus, GSD Ia remains a severe, multisystem disorder that results in significant morbidity and mortality. A subtype caused by a defect in the transport of glucose 6-phosphate (GSD Ib; OMIM 232200) has similar long-term complications; however, additional findings of recurrent infections and inflammatory bowel disease are caused by neutropenia in GSD Ib.

With long-term survivors the high risk for HCC in GSD Ia has become evident recently; HCC was previously thought to be a rare complication in GSD Ia (Chen 2001). Franco and colleagues reported a series of eight GSD Ia patients in whom HCC was diagnosed (Franco et al 2005a). Only two patients had positive serology for hepatitis (one for hepatitis B and one for C); no other risk factors for HCC were identified in the remaining six. The mean age at the time of HCC diagnosis was 28 years (18–45 years). All but one patient had previously documented hepatic adenomas, as seen in the majority of adult GSD Ia patients (Chen 2001). HCC has been described previously at the time of liver transplantation in GSD Ia (Lerut et al 2003). Ominously, alpha-fetoprotein (AFP) was only mildly elevated in 2 of 8 patients at the time of diagnosis of HCC (Franco et al 2005a), which confirms the need for additional biomarkers to predict individuals with GSD I at risk for HCC.

Potential of curative therapy for GSD Ia

Curative therapy for GSD Ia will require expression of G6Pase in the liver, and gene therapy could offer an alternative to liver transplantation that overcomes the obstacles of too few donor organs and a significant risk of graft rejection. The level of expression needed for successful gene therapy can be estimated, because the presence of 8% of normal G6Pase activity prevented hypoglycaemia in a patient evaluated for hepatomegaly (Keller et al 1998). Thus, 10% of normal G6Pase activity represents a therapeutic threshold for achieving efficacy in GSD Ia; however, biochemical correction throughout the GSD Ia liver might be necessary to reduce the risk for HCC.

A G6Pase knockout (G6Pase-KO) mouse model for GSD Ia was generated by Janice Chou's group at NIH, and initial gene therapy experiments have been performed in the murine model (Lei et al 1996; Zingone et al 2000). While the G6Pase-KO mice had the expected phenotype for the most part, limitations of the G6Pase knockout model included poor viability and the absence of lactic acidosis, a prominent abnormality in GSD Ia (Lei et al 1996). Only 15% of affected mice survived weaning at 21 days, despite injection with 10% glucose every 8 h (Zingone et al 2000). The mouse model has advanced the development of viral vectors for gene therapy in GSD Ia, since it is possible to generate large numbers of mice and treat them with smaller amounts of vector. Administration of a first-generation adenovirus vector encoding G6Pase improved survival markedly (Zingone et al 2000), while co-administration of the adenovirus vector and an adeno-associated virus type 2 (AAV2) vector corrected biochemical abnormalities and histopathology in the liver and kidney of neonatal G6Pase-KO mice (Sun et al 2002). Recently, a pseudotyped AAV type 1 (AAV2/1) vector prolonged survival and corrected biochemical abnormalities, including hypoglycaemia and hypercholesterolaemia, following two-weekly administrations in neonatal G6Pase-KO mice; nonetheless, histopathological abnormalities did recur in the kidney after several months (Ghosh et al 2006). An AAV2/8 vector containing the G6Pase promoter region prolonged survival to >28 weeks and partially corrected biochemical abnormalities and liver histopathology following administration at 2 weeks of age (Koeberl et al 2006). The aforementioned gene therapy experiments have not clearly established adequate preclinical data to justify a clinical trial.

The initial characterization of dogs with GSD Ia revealed that their clinical abnormalities most closely resemble severe, neonatal-onset GSD Ia in humans (Kishnani et al 2001; Perlman et al 1979). The original three Maltese puppies with GSD Ia died between 5 and 8 weeks of age with poor growth and feeding, and were found to have hepatomegaly and nephromegaly (Brix et al 1995). Evaluation of gene therapy in a canine disease model would be more predictive of success in humans than in a murine model. The canine model has low residual G6Pase activity similar to most humans with GSD Ia, and introduction of G6Pase will be less likely to stimulate an immune response (Kishnani et al 1997; Tripathy et al 1996). GSD Ia in dogs has all of the major features of GSD Ia in humans, and therefore the canine model is preferred for preclinical development of gene therapy in GSD Ia. Administration of an AAV2 vector encoding canine G6Pase corrected hypercholesterolaemia and prolonged survival, compared to untreated, affected GSD Ia dogs (Beaty et al 2002), despite the persistence of intermittent hypoglycaemia. Furthermore, preliminary data demonstrated prolonged correction of hypoglycaemia during fasting with an AAV2/8 vector in an affected dog (Fig. 1).

Hepatocyte transplantation remains a potential therapeutic intervention in GSD Ia. An initial GSD Ia patient was infused with donor hepatocytes owing to very poor response to dietary therapy (Muraca et al 2002). This case report described the near-resolution of hypoglycaemic episodes, even following the cessation of corticosteroid therapy which could elevate blood glucose independently of normal hepatocyte engraftment; however, hypoglycaemia subsequently recurred, when donor hepatocytes were apparently rejected by the patient's immune system (Muraca and Burlina 2005). Therefore, hepatocyte transplantation must undergo further development prior to widespread implementation in GSD Ia.

Pompe disease (GSD II) and acid alpha-glucosidase (GAA) deficiency

Infantile-onset Pompe disease (GSD II; OMIM 232300) is characterized by a generalized muscle weakness, hypotonia and a hypertrophic cardiomyopathy with death typically in the first year of life due to cardiorespiratory or respiratory failure (Hirschhorn and Reuser 2001; Kishnani et al 2006a).

Late-onset forms of Pompe disease (juvenile and adult forms) feature progressive weakness without significant cardiomyopathy. Patients have significant morbidity and with disease progression become wheelchair-dependent and require artificial ventilation. The cause of death in late-onset Pompe disease is usually respiratory failure, which can be precipitous. The histopathology of Pompe 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. GAA is normally widely expressed from a promoter with resemblance to a "housekeeping" gene (Hoefsloot et al 1990; Martiniuk et al 1990; Ponce et al 1999), and GAA deficiency causes lysosomal glycogen accumulation in virtually all tissues.

Early development of enzyme replacement therapy (ERT) in Pompe disease

The *in vivo* efficacy of ERT for Pompe disease was first demonstrated in the Japanese (Pompe disease) quail (Kikuchi et al 1998), and then later in the GAA knockout (GAA-KO) mouse model by reversing glycogen accumulation and restoring GAA activity in the heart and skeletal muscle (Bijvoet et al 1999; Raben et al 2003). Subsequently, pilot human phase I/II studies of recombinant human acid alpha-glucosidase GAA (rhGAA) purified from CHO cell cultures ($n = 3$) (Amalfitano et al 2001) or transgenic rabbit milk ($n = 4$) (Van Den et al 2000) prolonged all subjects' survival beyond one year; however, only four patients responded with resolved or improved cardiomyopathy. Two of seven subjects walked independently and remained ventilator-free. The remaining five patients from these pilot studies had residual delays of motor development and eventually became ventilator-dependent.

An open-label, multinational, multicentre phase II study examining safety and efficacy of rhGAA in treatment of infantile-onset Pompe disease has been reported (Kishnani et al 2006b). After 52 weeks of treatment, six of eight patients were alive and five were free of invasive ventilator support. Five patients acquired new motor milestones, and three 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, rhGAA improved ventilator-free survival, cardiomyopathy, growth, and motor function in patients with infantile-onset Pompe disease compared to outcomes expected for patients without treatment.

Pivotal trials of ERT in Pompe disease

The timeline to approval of Chinese hamster ovary (CHO) cells ERT in Pompe disease began in 1991 with initial development of CHO cells that overexpressed rhGAA (Van Hove et al 1996). A preclinical experiment in the Japanese quail model for Pompe disease provided the precedent for an initial phase I/II clinical trial (Amalfitano et al 2001; Kikuchi et al 1998). Further development of rhGAA (Myozyme) by Genzyme Corporation culminated in broad-label marketing approval in 2006 (Table 1).

The two pivotal clinical trials with Myozyme differed primarily by age at entry. Study 1 enrolled subjects less than 6 months old and the primary endpoint was invasive ventilator-free survival versus the survival in an untreated historical cohort; study 2 enrolled subjects 6–36 months old with primary endpoint survival versus a historical cohort. Secondary end-points were identical for both studies, including changes in left ventricular mass index, changes in growth, and motor development. Study 1 demonstrated prolonged survival: all 18 patients were alive at age 18 months and 15/18 (83%) showed invasive ventilator-free survival at age 18 months (Kishnani et al 2007). All 15 subjects with available data had reduced left ventricular mass. Growth was maintained in 15 of 18 subjects with normal weight throughout the study period. Motor development was advanced in 13 of 18 subjects as determined by the Alberta Infant Motor Scale (AIMS). Study 1 also compared either 20 mg/kg or 40 mg/kg every other week, which did not significantly alter efficacy; however, a greater number of adverse events were associated with the higher dose. Study 2 had slightly lower efficacy for each end-point, demonstrating the value of early treatment in infantile Pompe disease.

Ongoing clinical trials with Myozyme include the Pediatric open-label study and the Pediatric and Adult multicentre, randomized, double-blind, placebo-controlled (LOTS) study. Enrolment for this study is complete; 90 subjects of ages >8 years have been enrolled at eight sites. In order to be included in the study all subjects will be ambulatory (able to ambulate 40 m) and not invasively ventilated. (Details of inclusion criteria are available at www.clinicaltrials.gov). Pulmonary and muscle strength will be assessed every 12 weeks. The primary endpoints in this study are distance walked in 6 min and forced vital capacity (FVC). The dose will be 20 mg/kg every other week.

Data from an expanded-access program in advanced late-onset Pompe disease on 18 patients who were wheelchair users and required ventilator support at the time of start of rhGAA ERT has demonstrated reduced ventilator use in 8/17 subjects, improvement in muscle strength in 14/18, and gains in weight and/or oral feeding in 7/18. Duration of ERT in this cohort ranged from 8.3 months to 6.3 years.

Limitations of ERT for Pompe disease include a requirement for high levels of enzyme replacement and the formation of antibodies

The main limitation of ERT is a well-recognized variability of response, with heart muscle responding better than skeletal muscle. Some of the potential factors involved in this variability include the number of mannose 6-phosphate receptors in heart compared to skeletal muscle; older age at the onset of therapy; underlying pathology in terms of extent of muscle and lysosomal damage; dose as related to tissue delivery; resistance to correction by type II myofibres; and the formation of neutralizing antibodies.

Documented limitations of ERT in Pompe disease include the requirement for frequent intravenous infusions of high levels of GAA to achieve efficacy, and the possibility of humoral immunity. High-level hGAA replacement (40–100 mg/kg per dose) reduced the glycogen content of heart and skeletal muscle in tolerant GAA-KO mouse models (Bijvoet et al 1999; Raben et al 2003). The amount of rhGAA required to achieve efficacy is approximately 30- to 100-fold greater than the doses used for ERT in other lysosomal disorders (Desnick 2004). This high dose is necessary to treat the muscle mass, which comprises approximately 40% of body weight.

Animal and human studies have suggested that the development of humoral immunity against the infused enzyme presents an obstacle to successful ERT. For instance, formation of neutralizing anti-GAA antibodies and associated infusion reactions prevented continuation of ERT beyond 3 weeks in GAA-KO mice. Only by the generation of tolerant GAA-KO mice through the insertion of a low-expressing liver-specific transgene could long-term ERT be tested in a Pompe disease mouse model (Raben et al 2003). Pompe disease patients who lack any residual GAA protein are deemed cross-reacting immune material negative (CRIM-negative). CRIM-negative Pompe disease subjects produced very high anti-hGAA antibodies and demonstrated markedly reduced efficacy from ERT (Amalfitano et al 2001). In the first pilot study of ERT using CHO cell-derived rhGAA, both CRIM-negative Pompe disease subjects produced the highest titres of anti-hGAA antibodies and demonstrated markedly reduced efficacy of ERT (Amalfitano et al 2001). The similarity with regard to neutralizing antibody response in GAA-KO mice and in CRIM-negative Pompe disease patients could be linked to the 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 introduced GAA by forming antibodies.

Screening for infantile Pompe disease and monitoring the therapeutic response with a urinary biomarker (Glc₄)

A urinary biomarker for glycogen accumulation, Glc₄, has been developed as a screening test for Pompe disease (Young et al 2005); this biomarker correlated inversely with outcomes in a clinical trial of ERT (An et al 2005). Glc₄ is thought to be formed by the action of serum enzymes (α -amylases and neutral α 1–4 glucosidase) on glycogen released into circulation. Glc₄ is normally excreted by the kidneys and is present at low concentration in the urine of normal individuals. The elevation of Glc₄ in the urine of Pompe disease patients makes it useful as a biomarker for diagnosis and monitoring of the response to ERT in Pompe patients (An et al 2005; Young et al 2005). Similarly, Glc₄ is elevated in the urine of Pompe mice and is reduced by the correction of glycogen storage in striated muscle with AAV vector-mediated gene therapy (Franco et al 2005b; Sun et al 2005). The urinary biomarker for Pompe disease provides noninvasive monitoring of the response to ERT or gene therapy.

Newborn screening for Pompe disease has been developed

The need for early treatment in Pompe disease has stimulated efforts to develop newborn screening for GAA deficiency (Millington 2005). Detection of GAA deficiency in dried bloodspots has been achieved using fluorometric and MS/MS methods (Chamoles et al 2004; Li et al 2004). Recently, Pompe disease was diagnosed retrospectively by analysis of a newborn screening card with the fluorometric method (Niizawa et al 2005). While population screening will be necessary to demonstrate feasibility for either method of newborn screening, past experience predicts that Pompe disease and other lysosomal storage disorders will be amenable to detection by either of these methods (Millington 2005).

An initial trial of newborn screening for Pompe disease during 2005–2006 in Taiwan of over 70 000 newborns has detected three affected infants, two with the infantile-onset form and one with likely early juvenile-onset form. The reliable detection of Pompe disease and availability of ERT with improved response to early treatment justifies further development of newborn screening.

Gene therapy for Pompe disease relies upon the induction of immune tolerance

Intravenous administration of adenovirus (Ad) vectors encoding GAA previously demonstrated generalized correction of glycogen storage in the GAA-KO mouse model for Pompe disease (Amalfitano et al 1999; Pauly et al 2001), although glycogen gradually re-accumulated in the months following vector administration (Ding et al 2001). We previously demonstrated the secretion and uptake of constitutively expressed hGAA with AAV2/2, AAV2/6, and AAV2/8 vectors in immunodeficient, GAA-KO/SCID mice, which was not feasible in immunocompetent GAA-KO mice (Sun et al 2003, 2005). The GAA-KO/SCID mice were bred to avoid the neutralizing antibody response to hGAA introduced with an AAV or Ad vector (Ding et al 2001; Sun et al 2003). Even neonatal administration of GAA did not induce tolerance to GAA expression with an AAV2/8 vector in all GAA-KO mice (Cresawn et al 2005). When GAA-KO mice were tolerized to hGAA by neonatal administration of the recombinant enzyme, a subset of those mice did not form anti-GAA antibodies in response to administration of an AAV2/8 vector encoding hGAA (Cresawn et al 2005). Administration of an AAV2/8 vector containing a liver-specific promoter evaded the humoral response to hGAA and achieved near-total clearance of accumulated glycogen from skeletal muscle, through the induction of immune tolerance to hGAA (Franco et al 2005b). The successful development of gene therapy in GAA-KO mice indicates that curative therapy for Pompe disease may become available in the foreseeable future.

Abbreviations

AAV, adeno-associated virus
 AFP, alpha-fetoprotein
 CRIM, cross-reacting immune material negative
 ERT, enzyme replacement therapy
 G6Pase, glucose-6-phosphatase
 G6Pase-KO, G6Pase knockout
 GAA-KO, GAA knockout
 Glc₄, Glcα1-6Glcα1-4Glcα1-4Glc
 GSD I, glycogen storage disease type I
 GSD II, glycogen storage disease type II
 GSD, glycogen storage disease
 HCC, hepatocellular carcinoma

rhGAA, recombinant human acid alpha-glucosidase

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Fig. 1.

Analysis of the response to AAV vectors in GSD Ia. Blood glucose in an affected GSD Ia dog following administration of an AAV2/8 vector encoding human G6Pase at 3 and 10 days of age (1×10^{13} vector particles/kg each dose). The range for untreated, affected dogs is shown (box)

Table 1

Milestones in the development of ERT for Pompe disease

Date	Milestone
1997	Synpac obtained licensing from Duke University
1999	Phase I/II clinical trial 2000, Genzyme obtained licensing from Synpac/Duke
2001	Phase II clinical trials begins
2002	Natural history study in collaboration with Genzyme
2003	Pivotal clinical trials with Myozyme initiated
2003	Biomarker development to monitor Pompe disease
2005	Late-onset Pompe disease clinical trial begins
2006	Marketing approval for Myozyme in Europe and in USA