Long-Term Prognosis of Patients with Infantile-Onset Pompe Disease Diagnosed by Newborn Screening and Treated since Birth

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Objective To determine the benefit of newborn screening for the long-term prognosis of patients with classic infantile-onset Pompe disease (IOPD).

Study design A cohort of patients with classic IOPD were diagnosed by newborn screening, treated with recombinant human acid α-glucosidase (rhGAA), and followed prospectively. Outcome measurements included survival, left ventricular mass, serum creatinine kinase, motor function, mental development, and systemic manifestations.

Results Ten patients who presented with left ventricular hypertrophy at diagnosis received rhGAA infusions starting at a median age of 16 days (6-34 days). All patients were cross-reactive immunologic material-positive. After a median treatment time of 63 months (range 28-90 months), all could walk independently, and none required mechanical ventilation. All patients had motor capability sufficient for participating in daily activities, but muscle weakness over the pelvic girdle appeared gradually after 2 years of age. Ptosis was present in one-half of the patients, and speech disorders were common. Anti-rhGAA antibody titers were low (median maximal titer value 1:1600, range: undetectable ~ 1:12 800).

Conclusion By studying patients treated since birth who have no significant anti-rhGAA antibody interference, this prospective study demonstrates that the efficacy of rhGAA therapy is high and consistent for the treatment of classic IOPD. This study also exposes limitations of rhGAA treatment. The etiology of the manifestations in these early-treated patients will require further study. *(J Pediatr 2015;166:985-91)*.

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Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is a lysosomal disorder in which a deficiency of acid α-glucosidase (GAA, EC 3.2.1.20) causes the intralysosomal accumulation of glycogen in all tissues, most notably in skeletal muscles.[1] Clinically, patients with Pompe disease present with a wide spectrum of symptoms, ranging from severe rapidly progressive classic infantile-onset Pompe disease (IOPD), which usually presents with hypertrophic cardiomyopathy, to slowly progressive later-onset forms with muscular weakness that can occur from early childhood to late adulthood and typically occur without cardiac manifestations. In patients with classic IOPD, symptoms start very early in life (median age of 2 months), and death occurs soon after if the patients remain untreated (median age of 8.7 months).[2,3]

Enzyme-replacement therapy (ERT) with recombinant human GAA (rhGAA)[4,5] is the only treatment available for patients with Pompe disease. In the pivotal trial of rhGAA, all patients survived to 18 months of age, and a Cox proportional hazards analysis demonstrated that rhGAA treatment reduced the risk of death or invasive ventilation by 92%.[6] The Kaplan-Meier invasive ventilation-free survival rate, however, decreased to 66.7% at age 24 months and 49.4% at age 36 months.[7] Patients with cross-reactive immunologic material (CRIM)-negative IOPD tend to develop a high titer of antibodies,[8] and CRIM-negative status predicts reduced survival and poorer clinical outcomes.[9] Nevertheless, 14 of the aforementioned 18 patients were CRIM-positive. In another

CK	Creatinine kinase
CRIM	Cross-reactive immunologic material
ERT	Enzyme-replacement therapy
GAA	Acid α-glucosidase
IOPD	Infantile-onset Pompe disease
LVMI	Left ventricular mass index
MRI	Magnetic resonance imaging
NBS	Newborn screening
PDMS-II	Peabody Developmental Motor Scale, Second Edition
Pompe-PEDI	Pediatric Evaluation of Disability Inventory specific for Pompe disease
rhGAA	Recombinant human acid α-glucosidase

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clinical trial with 21 patients treated for a median duration of 120 weeks, invasive ventilator free survival was 44%, and 19 of the 21 patients were CRIM-positive.[10] Outside of these clinical trials, the survival of IOPD patients is not clear.

Other clinical sequelae also have been observed in long-term survivors with IOPD. Survivors present with respiratory failure and an inability to walk[11] or have the ability to walk independently with residual myopathy, including generalized weakness/hypotonia, decreased endurance, persistent fatigue,[11] arrhythmia,[12] gastroesophageal reflux,[11] ptosis,[11,13] hearing loss,[11,14] hypernasal speech with a flaccid dysarthria and/or oropharyngeal dysphagia,[13,15] and abnormalities in brain myelination.[14,16] The lack of consistency in outcomes may be attributable partially to the survivors' age at the initiation of ERT, from a median age of 2.4 months[13] to 4.9 months.[11] Early initiation of ERT may result in a good histologic response[17] and thus a greater benefit to survival compared with late treatment initiation.[10,18] The benefit of early treatment initiation on other outcomes, however, is still unknown.

To achieve early diagnosis and early treatment of IOPD, we initiated a newborn screening (NBS) program for Pompe disease in 2005.[19] By 2011, 10 patients with classic IOPD were diagnosed by NBS, treated with rhGAA, and prospectively monitored at our hospital. All patients were CRIM-positive. With early treatment and little or no antibody interference, this prospective cohort study reveals the outcomes of rhGAA therapy for IOPD.

Methods

The Newborn Screening Center at the National Taiwan University Hospital initiated a NBS program for Pompe disease in 2005. The methods of screening, confirmatory process, criteria for initiating ERT, and follow-up have been described previously.[18,19] Patients with Pompe presenting left ventricular hypertrophy at newborn period were classified as having classic IOPD. Patients with confirmed left ventricular hypertrophy were treated with rhGAA (alglucosidase alfa) immediately, with a dosage of 20 mg/kg every other week. Genomic DNA from peripheral blood cells was used for mutation analysis of the *GAA* gene.[20] CRIM status was determined by western blot analysis.

Survival was compared with a Kaplan-Meier analysis between these patients with NBS, the clinically diagnosed and treated Taiwanese classic IOPD (the clinical cases), and untreated Taiwanese classical IOPD cases (the untreated cases).[18] The clinically diagnosed cases were proven to be CRIM-positive and were treated starting at age 2-6 months because of the presence of clinical symptoms such as respiratory distress or muscle weakness. The untreated cases were archived historically and were not tested for CRIM status. Survival free of ventilation support was defined as the time until invasive ventilation was required or death. Statistical significance was set at $\alpha = 0.05$ (2-tailed).

Other outcome measurements, including the left ventricular mass index (LVMI) measured using 2-dimensional echocardiography,[21] and serum creatinine kinase (CK), were assessed every 3-6 months. Motor development and function evaluation tests, including the Peabody Developmental Motor Scale, Second Edition (PDMS-II)[22] and the Pediatric Evaluation of Disability Inventory specific for Pompe disease (Pompe-PEDI),[23] were conducted every 6 months by 2 experienced therapists. The PDMS-II is a skill-based measure of gross and fine motor development for infants and children from 6 months to 6 years of age; the scores were normalized and are presented as percentiles. The Pompe-PEDI was used to assess the motor capability required for participating in daily locomotion and transfer tasks. The scores of the mobility domain of the Pompe-PEDI Functional Skills Scales, both normative standard scores (adjusted for the child's chronological age) (normal mean = 50, 1 SD = 10) and scaled scores (not adjusted for age), were analyzed in this study. Greater scores reflect a superior capability.

The contribution of other systems, including speech, hearing, vision, and cognition functions, was assessed at least once per year. Facial muscle weakness was defined as an expressionless face with a drooping open or tent-shaped mouth and the absence of the nasolabial folds.[13] Cognitive function was evaluated by the mental development index of the Bayley Scales of Infant Development-II for patients from 1 to 42 months of age and by the cognitive subsets of the Comprehensive Developmental Inventory for Infants and Toddlers[24,25] for patients older than 4 years. All measurements were tested with standardized test materials and procedures, and developmental quotients were derived according to the manuals. Brain magnetic resonance imaging (MRI) scans were performed at baseline and every 1-3 years. Anti-rhGAA IgG antibody titers were monitored every 3-6 months. This prospective observational cohort study was approved by the institutional review board of the National Taiwan University Hospital (NTUH-REC No: 200703045R).

Results

Patients Diagnosed by the NBS Program

During the study period, approximately 470 000 newborns were screened.[26] The overall incidence for Pompe disease was 1 in 17 000, and the incidence for classic IOPD was 1 in 52 000 and for other types was 1 in 25 000.[26] In this study, we included all patients with classic IOPD identified through NBS. In total, 10 newborns were identified during this period. The short-term outcomes of patients 1-5 have been reported.[18] All patients had deficient GAA activity in the lymphocytes/fibroblasts. All patients had at least one allele of the Taiwanese common *GAA* mutation c.1935C>A (p.D645E), which was always associated with the c.1726G>A (p.G576S) pseudodeficiency mutation[27]; this combined mutation is severe, and previous patients who were homozygous for this mutation all had classic IOPD. Thirteen of the 20 mutated alleles of the 10 patients had the c.1935C>A mutation (**Table**). All patients were proven to be CRIM-positive by western blot analysis (data not shown).

The 10 patients were diagnosed at a median age of 9 days (range, 0-33 days). These infants were asymptomatic at the