Very Early Treatment for Infantile-Onset Pompe Disease Contributes to Better Outcomes

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Objective To evaluate whether very early treatment in our patients would result in better clinical outcomes and to compare these data with other infantile-onset Pompe disease (IOPD) cohort studies.

Methods In this nationwide program, 669 797 newborns were screened for Pompe disease. We diagnosed IOPD in 14 of these newborns, and all were treated and followed in our hospital.

Results After 2010, the mean age at first enzyme-replacement therapy (ERT) was 11.92 days. Our patients had better biological, physical, and developmental outcomes and lower anti-rh acid α-glucosidase antibodies after 2 years of treatment, even compared with one group that began ERT just 10 days later than our cohort. No patient had a hearing disorder or abnormal vision. The mean age for independent walking was 11.6 $\pm$ 1.3 months, the same age as normal children.

Conclusions ERT for patients with IOPD should be initiated as early as possible before irreversible damage occurs. Our results indicate that early identification of patients with IOPD allows for the very early initiation of ERT. Starting ERT even a few days earlier may lead to better patient outcomes. *(J Pediatr 2016;169:174-80)*.

Pompe disease is an autosomal-recessive lysosomal storage disorder characterized by the deficiency of acid α-glucosidase (GAA),[1,2] which leads to the progressive accumulation of glycogen in numerous types of cells and tissues.[3,4] A broad spectrum of clinical phenotypes is observed, ranging from the severe, rapidly progressive infantile-onset Pompe disease (IOPD) characterized by cardiac involvement to the attenuated, late-onset Pompe disease.[5-7] Early enzyme-replacement therapy (ERT) with recombinant human alglucosidase alpha (Myozyme; Genzyme, Boston, Massachusetts) can prolong survival and improve the long-term outcome of patients with IOPD.[6,8,9] Nevertheless, it remains unknown whether therapeutic outcomes differ between very early (10 days of age) and early (1 month of age) IOPD treatment.

Newborn screening is the only way to initiate the early diagnosis and treatment of Pompe disease.[8,9] However, even when the newborn screening is used, the earliest mean age at the start of ERT is about 21 days.[10] The Taipei Veterans General Hospital (TVGH) began Pompe newborn screening in 2008, testing approximately two-thirds of the newborn population in Taiwan.[4,6,8] By 2010, we had established an effective newborn screening program with rapid diagnostic strategies,[4] and almost all of the infants with suspected IOPD could be diagnosed correctly within 2 hours and receive ERT within 4 hours of admission. With such an effective system, most of our patients with IOPD started their ERT at about 11 days of age. In this 6-year cohort study, we report the prognosis of 14 patients with IOPD who received very early ERT and compare these results with those of similar cohorts. Furthermore, we compare the outcomes of 5 patients with IOPD who have identical GAA gene mutations to disclose possible differences between few days earlier treatment.

Methods

Pompe disease screening was added to the newborn screening system in Taiwan in 2008. In this nationwide program, 669 797 newborns were screened for Pompe

AST	Aspartate aminotransferase
Bayley-III	Bayley Scale of Infant and Toddler Development, Third Edition
CK	Creatine kinase
CRIM	Cross-reactive immunologic
ERT	Enzyme-replacement therapy
GAA	Acid α-glucosidase
IOPD	Infantile-onset Pompe disease
LDH	Lactate dehydrogenase
LVMI	Left ventricular mass index
PDMS-II	Peabody Development Motor Scale, Second Edition
TVGH	Taipei Veterans General Hospital

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disease between January 1, 2008, and January 31, 2014. Dried blood spot screening was conducted at the Taipei Institute of Pathology and Chinese Foundation of Health newborn screening centers with the use of a fluorescence (4-methylumbelliferone) assay; this test was changed to the tandem mass spectrometry method after 2010. Infants with GAA activity ≤0.50 mmol/L/h (normal activity >2.0 mmol/L/h) were referred immediately to the TVGH for diagnostic confirmation. The study population included all infants with IOPD who were referred to the TVGH between January 2008 and January 2014. The study protocol was approved by the Institutional Review Board of the TVGH.

Physical examinations, blood tests, and echocardiography were performed within 2 hours upon referral of infants. Blood samples were assessed for creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and lymphocyte GAA enzymatic activity. After 2010, all transferred newborns were started on ERT within 4 hours of admission if they had the following manifestations: (1) general weakness; (2) extremely low initial GAA activity (<0.50 mmol/L/h); (3) elevated CK (>250 U/L); and (4) elevated left ventricular mass index (LVMI; >80 g/m^2). Quadriceps muscle biopsies and GAA gene sequencing were performed after parental informed consent was obtained.

All confirmed patients with IOPD underwent regular ERT and physical therapy every 2 weeks thereafter. Echocardiography was performed monthly for 6 months and then once every 3-6 months. Blood tests for CK, LDH, and AST were performed monthly for 6 months and then once every 3 months. The level of anti-rh GAA antibodies titer to ERT was determined before ERT and 1 and 2 years after ERT. Developmental surveys were conducted with the Bayley Scale of Infant and Toddler Development, Third Edition (Bayley-III), and the Peabody Development Motor Scale, Second Edition (PDMS-II).[11]

Statistical Analyses

Data are presented as the median with range and mean ± IQR. Statistical tests were performed by the

Table I. Patient characteristics of 14 patients with IOPD

Patient no.	Sex	GA, wk, BBW, kg	Age at referral, d	Age at first ERT, d	End-of-study age, mo	End-of-study BH, cm (percentile)	End-of-study BW, kg (percentile)	GAA mutation
1	F	38, 3.1	51	79	64	110 (15-50)	18.3 (15-50)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
2	F	37, 3.2	18	18	61	108 (15-50)	18 (3-15)	c.1411_1414del, (E471fsX5), heterozygous c.872 T→C, (p.L291P) heterozygous
3	M	38, 3.5	15	15	49	100.5 (15)	15.8 (15-50)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
4	M	39, 3.3	9	9	48	100 (15-50)	17.5 (50-85)	c.1935 C→A, (p.D645E), heterozygous c.2303 C→T, (p.P768L), heterozygous
5	M	38, 3.1	12	12	39	97 (15-50)	17 (50-85)	c.1396 G→T, (p.V466F), heterozygous c.1935 C→A, (pD645E), heterozygous
6	F	39, 3.0	9	9	37	95 (15-50)	15 (50-85)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
7	F	39, 3.1	8	23	26	88 (50)	12.6 (50)	c.2238 G→C, (p.W746C), heterozygous c.2237 G→A, (p.W746X), heterozygous c.1726 G→A, (p.G576S), heterozygous
8	F	34, 2.2	12	12	25	85 (15-50)	12 (50)	c.1935 C→A, (pD645E), heterozygous IVS7+2 T→C, heterozygous c.1726 G→A, (p.G576S), heterozygous
9	M	39, 3.7	7	7	24	86 (15-50)	11.9 (15-50)	IVS7+2 T→C, heterozygous c.1935 C→A, (p.D645E), heterozygous c.1726 G→A, (p.G576S), heterozygous
10	M	39, 2.9	13	13	24	85 (15-50)	12.0 (15-50)	c.1082 C→T, (p.P361L), heterozygous c.1935 C→A, (p.D645E), heterozygous c.1726 G→A, (p.G576S), heterozygous
11	F	39, 2.9	10	10	20	91 (97)	11 (50)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
12	F	41, 2.6	6	6	15	78 (15-50)	8.5 (3-15)	c.1935 C→A, (p.D645E), homozygous c.1726 G→A, (p.G576S), homozygous
13	F	36 ± 5, 3.3	8	8	14	80 (85)	12.15 (97)	c.1411_1414del, (E471fsX5), heterozygous c.1935 C→A, (pD645E), heterozygous c.1726 G→A, (p.G576S), heterozygous
14	M	39 ± 5, 2.49	13	13	13	75 (3-15)	9 (15)	c.1726 G→A, (p.G576S), heterozygous c.1935C→A, (pD645E), heterozygous c.2274insC, (p.G759fs), heterozygous
Mean		38.3 ± 1.5, 3.02 ± 0.38	3.02 ± 0.38	11.92 ± 4.53*	32.7 ± 16.4	38.8 ± 23.1th (percentile)	43.5 ± 24.4th (percentile)	-

BBW, birth BW; *BH*, body height; *BW*, body weight; *F*, female; *GA*, gestational age; *M*, male.
*Excludes patient 1 (diagnosed before 2010).

Wilcoxon rank sum test and Kruskal-Wallis test. Differences between our and other studies were compared with oneway ANOVA or 2-sample *t*-test. Analysis of longitudinal data by linear regression of the mean value vs the outcome for biochemical variables yielded a Pearson product-moment correlation coefficient. All statistical analyses were 2-sided, with $P < .05$ considered to be statistically significant. All statistical analyses were performed with SPSS 15.0 statistics software (SPSS Inc, Chicago, Illinois) and SigmaStat 3.1 (Jandel Scientific, San Rafael, California).

Results

During the period between January 2008 and January 2014, we screened 669 797 newborns. Of these, 47 were referred directly to our hospital after the first dried blood spot screening because of GAA values lower than the cutoff value (<0.50 mmol/L/h), and 14 were diagnosed with IOPD. Patient 1 was diagnosed in 2009, before the establishment of the rapid diagnostic strategies in 2010. This patient was referred to us at 51 days of age and received ERT at 79 days of age after confirmation by muscle biopsy, lymphocyte GAA enzyme assay, and GAA gene sequencing. The remaining 13 patients with IOPD were diagnosed after the establishment of the rapid diagnostic strategies. Of these, only one (patient 7) did not have the LVMI >80 g/m^2 at the initial diagnosis. The patient received her first ERT at 23 days of age after identification of the *GAA* gene mutations c.2238 G>C (p.W746C) and c. 2237 G>A (p.W746X). The remaining 12 infants diagnosed with IOPD met the rapid diagnostic strategies and received their first ERT within 4 hours of admission at a mean age of 11.56 ± 3.4 days.

The demographic characteristics of the 14 patients with IOPD included in this study are presented in Table I. After 2010, the mean age at initial ERT was 11.92 days (range, 6-23 days). The prognostic factors for 13 patients with IOPD diagnosed after 2010 and patient 1 who was diagnosed before 2010 are presented separately in Table II. For the 13 patients with IOPD (patient 2 to patient 14), the median pre-ERT LVMI was 116.3 g/m^2 (range, 61-192 g/m^2; normal range, <65 g/m^2). Left ventricular hypertrophy improved quickly after 3-4 months of ERT, then resolved and remained stable in all 13 patients after 6 months. The mean end-of-study LVMI was 53.9 g/m^2 (Table II). Normal cognitive function (105.0 ± 12.0, Bayley-III scale) and normal motor function (96.0 ± 13.4, PDMS-II) were observed in the 13 patients with IOPD (patient 2 to patient 14) as well 1 year after ERT. These results are better than those presented in previously published IOPD studies.[10,12-15]

Patient 1, who received ERT at 79 days of age, had slower improvement of left ventricular hypertrophy (LVMI 80 g/m^2 6 months after ERT) and poorer motor function scale (PDMS-II score of 58 1 year after ERT). Coincidentally, 5 of the 14 patients with IOPD (patients 1, 3, 6, 11, and 12, treated at 79, 15, 9, 10, and 6 days of age, respectively) had identical GAA gene mutations (c.1935 C>A; c.1726 G>A, homozygous). Among them, we found that starting ERT even a few days earlier was associated with better biochemical responses and developmental outcomes (Figure 1). Analysis of longitudinal data for biochemical variables yielded a Pearson product-moment correlation coefficient for CK, LDH, and AST 1 year after ERT of 0.86, 0.83, and 0.80, respectively. The same tendencies were observed when the Bayley-III and PDMS-II scales were used.

All 14 patients with IOPD were cross-reactive immunologic (CRIM)-positive and had no anti-rh GAA antibodies before treatment. In the 13 patients with IOPD who were diagnosed after 2010, 11 patients developed detectable anti-rh GAA antibodies after 1 year of ERT. The peak anti-rh GAA IgG antibody titer in the 13 patients was 1376.9 ± 1920.3 (range, 0-6400). After 2 years of ERT, only 10 patients had detectable anti-rh GAA antibodies. Nine of the 10 patients had decreased IgG antibody titers compared

Table II. Outcomes of the patients with IOPD

Patient no.	LVMI at baseline/ 6 mo after ERT, g/m^2	Age of independent walking, mo	Hearing disorder	Ptosis	Vision disorder	Cognitive function test (Bayley-III)	Motor function (PDMS-II)	IgG antibody titer maximum/2 y after ERT
2	82/42	11.5	N	–	N	120	112	UD/UD
3	154/61	13	N	+	N	95	82	100/100
4	110/40	13	N	–	N	115	107	200/100
5	105/60	13	N	–	N	95	100	100/UD
6	192/47	12	N	–	N	105	88	400/200
7	61/44	10	N	–	N	110	110	800
8	140/42	11	N	–	N	120	115	UD
9	112/50	10	N	–	N	90	76	100
10	112/64	13	N	–	N	95	91	200
11	125/40	12	N	–	N	125	107	3200/1600
12	88/67	13	N	–	N	100	79	6400/3200
13	131/54	12	N	–	N	90	85	3200/800
14	101/90	12	N	–	N	–	–	3200/1600
Mean*	116.3 ± 32.2/53.9 ± 13.8	11.9 ± 1.0	–	–	–	105.0 ± 12.07	96.0 ± 13.4	1376.9 ± 1920.3/584 ± 945.3

N, normal; *titer*, anti-rhGAA IgG antibody titer; *UD*, undetectable.
*Excludes patient 1.

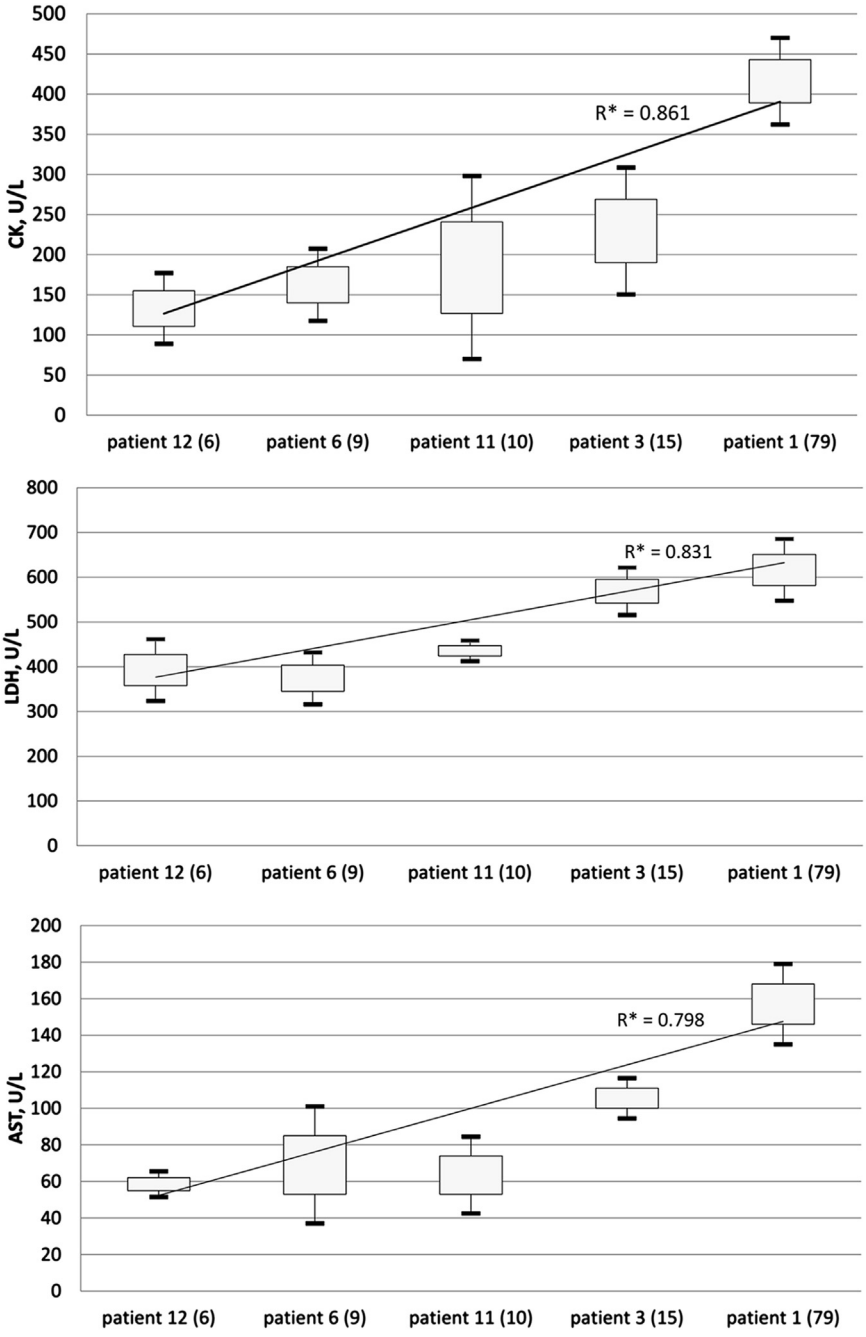

Figure 1. The regression lines present the Pearson product-moment correlation coefficient for the data of CK, LDH, AST, Bayley-III, and PDMS-II scales 1 year after ERT for patients 1, 3, 6, 11, and 12, who having identical mutations, treated at 79, 15, 9, 10, and 6 days of age, respectively. *(Continues)*

with the data after 1 year of treatment. The median titer after 2 years of ERT was 584 ± 945.3 (range, 0-1:3200) (**Figure 2**; available at www.jpeds.com). These results demonstrated a downward trend over time in anti-rh GAA IgG antibody titers. Overall, our patients had very low anti-rh GAA IgG titer compared with that of other reported patients with IOPD who are CRIM-positive.[10,12-15]

Changes of the 13 patients who were diagnosed after 2010 in CK, LDH, and AST over time also were observed. CK, LDH, and AST decreased rapidly over the first 6 months after ERT initiation, with a gradual increase seen thereafter. The median pre-ERT serum CK level was 540.2 ± 180 U/L (109-2406 U/L), which decreased to 132.6 ± 42.8 after 6 months and then increased to 218.7 ± 122.9 after 1 year of treatment, and to 373.9 ± 309.9 after 2 years of treatment. The same trend was seen for LDH (544.6 ± 95.1, 354.3 ± 37.7, and 483.0 ± 140.2) and AST (113.4 ± 32.2, 51.5 ± 13.5, 76.2 ± 34.5), respectively.

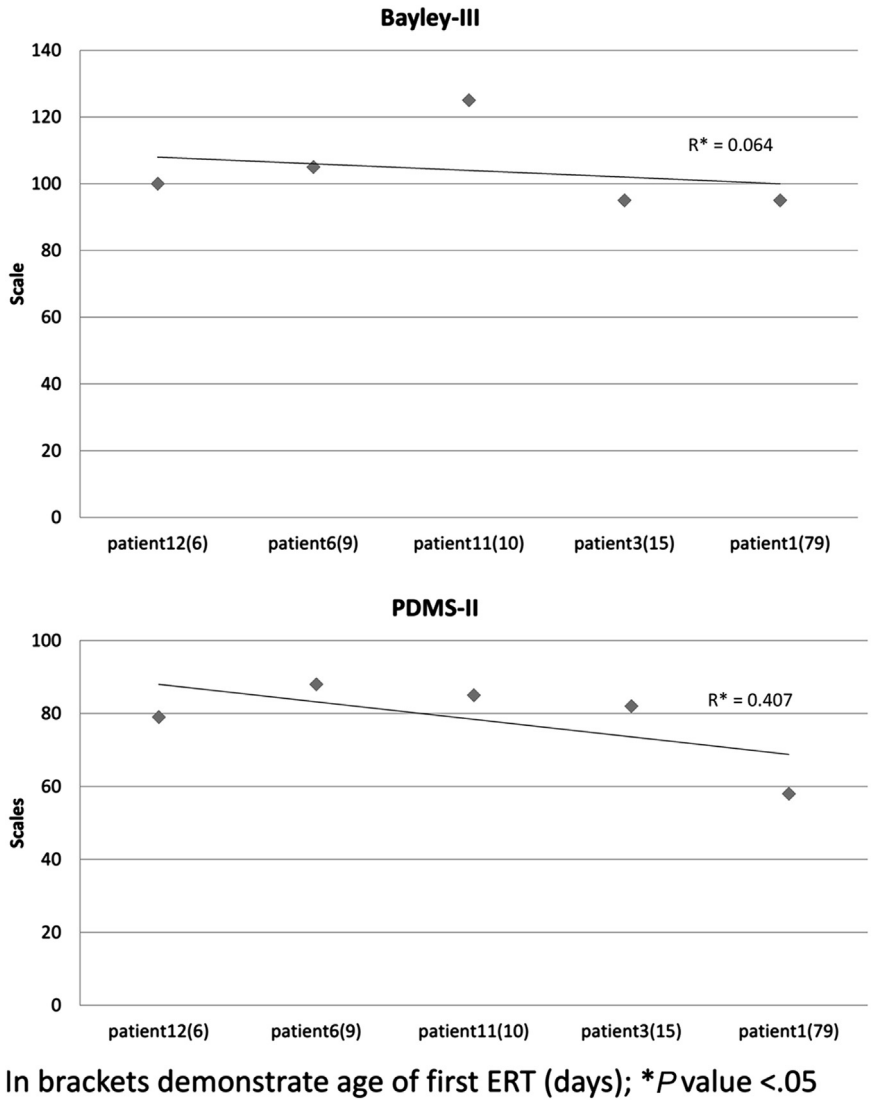

Figure 1. Continued.

We compared the prognostic variables collected after 2010 with those of other studies of CRIM-positive IOPD,[10,12-15] with particular attention to the study of Chien et al,[10] which was based on the same population from different areas of Taiwan. The cohort reported by Chen et al had the same mutation hot spots of Taiwanese population (c.1935 C>A) but

Table III. Comparison of patient outcomes between studies of IOPD

Study group	Patient no.	Age of ERT initiation, d	Treatment duration, y	CRIM status	IgG antibody titer, mean (range)	Age of independent walking, mo	Cognitive Score: Bayley-III	CK after 2 y of ERT, U/L, median (range)
Our study* (after 2010)	13	11.9 (6-23)	2.67 (1.1-5.3)	+	584 (0-3200)	11.9 ± 1.0	105.0 ± 12.07	227 (138-1082)
Taiwan, Chien et al[10]	10	21.6 (6-34)†	5.3 (2.3-7.6)	+	1230 (0-6400) (P = .08)	15.15 ± 2.93†	82 ± 9.42†	1032† (492-1700)
US, Banugaria et al[15]	25	198 (57-450)†	4.3	+	200-51 200 (no raw data)	–	–	–
US, Spiridigliozzi et al[12]	15	125.5 (13-181)†	–	12(+):3(–)	–	–	88.5 ± 14.3†	–
The Netherlands, van Gelder et al[14]	11	93.2 (105-120)†	5.6 (0.3-13.7)	+	31 250 (1250-156 250)†	–	–	–
Europe, Ebbink et al[13]	10	85.7 (3-249)†	5.6 (0.8-10.6)	–	–	16.57 ± 1.59†	81 ± 23.4†	–

–, no data.
*Excludes patient 1.
†P < .05.

began to receive ERT about 10 days later than our cohort (mean ages at ERT initiation, 11 vs 21 days). The data presented in **Table III**[10,12-15] show that earlier ERT initiation was associated with better outcomes in CK level after 2 years of ERT, IgG antibody titers, and developmental scales. There were also significant differences in IgG antibody titers (for the studies of Chien et al,[10] $P = .08$; van Gelder et al,[14] $P < .05$) and developmental surveys ($P < .05$) between the other groups. Moreover, all of our patients survived, and the survival without mechanical ventilation and walking devices was 100%.

Discussion

Because the damage in IOPD progresses very rapidly, we believe ERT should be started as early as possible. Residual clinical sequelae have been observed in long-term survivors of IOPD.[16-18] Such patients present with respiratory distress and residual myopathy, including generalized weakness/hypotonia, ptosis, hearing loss, hypernasal speech with flaccid dysarthria, and/or oropharyngeal hypotonia.[19-24] Whether the severity of sequelae differs by the age of ERT initiation in terms of just a few days difference has not been assessed. Although many studies have reported that earlier administration ERT is associated with better outcomes, no large-scale studies have demonstrated that, among newborns receiving very early treatment, initiation of treatment a few days earlier might result in further better outcomes.

Among our patients treated very early, better outcomes might have been achieved with even a few days of earlier treatment, as indicated by the analysis of 5 patients with identical GAA gene mutations treated at 6, 9, 10, 15, and 79 days of age, respectively. We find that the earlier the initiation of ERT, the better the response in CK, LDH, and AST levels and the performance on Bayley-III and PDMS-II tests after 1 year of treatment. High CK, LDH, and AST levels usually suggest persistent muscle damage and may relate to a poorer long-term prognosis.

ERT has been proven to account for most of the improvements in IOPD survival.[4,10,20-24] However, patients may have a poorer clinical response to ERT secondary to greater sustained IgG antibody titers.[25-28] Some reports demonstrate that patients who are CRIM-positive also can develop antibodies, normally with a more attenuated response that slowly regresses after a plateau at modest titers.[10,27,28] By contrast, some patients who are CRIM-positive will develop high IgG antibody titers that persist for a long time,[10,14,15,27,28] yet the reasons for these differences in IgG antibody titers between patients who are CRIM-positive remain unknown.[10,14,15,27,28] In our cohort, all patients are CRIM-positive and have very low IgG antibody titers compared with those of other previously reported patient cohorts with CRIM-positive IOPD.[10,14,15] After receiving ERT for 2 years, only 10 of 14 patients in this study have detectable anti-rh GAA antibodies (mean, 1:600).

The age at ERT initiation might influence the immune response in patients who are CRIM-positive because of the immaturity of the neonatal immune system[29,30]; therefore, very early administration of ERT might induce better tolerance.[29,30] Alternatively, the benefit of earlier ERT can be explained by the "danger model" that suggests the immune system needs alarm signals from injured tissues to be activated; hence, earlier treatment decreases the amount of tissue damage.[31] Many studies have shown that high IgG antibody titers to ERT are associated with poorer outcomes in patients with CRIM-positive and CRIM-negative IOPD.[14,15] Our patients have very low IgG antibody levels after 2 years of treatment, which indicate that earlier administration of ERT is associated with lower IgG antibody titers and possibly accounts for the patients' better outcomes.

Combining the results of the 2 Taiwanese-based newborn screening studies[10] and data from the analysis of our 5 patients with IOPD with identical mutations, we propose that starting ERT just a few days earlier can influence the long-term outcomes of patients with IOPD.

Our study has some limitations that warrant mention. Although our results generally are favorable, the length of follow-up and the number of patients are limited. Longer follow-up is essential to investigate sustainable outcomes in adults. For patients with IOPD, ERT should be initiated as early as possible before irreversible damage occurs. Our results indicate that an effective newborn screening program combined with rapid diagnostic strategies and initiation of treatment facilitates very early IOPD diagnosis. ■

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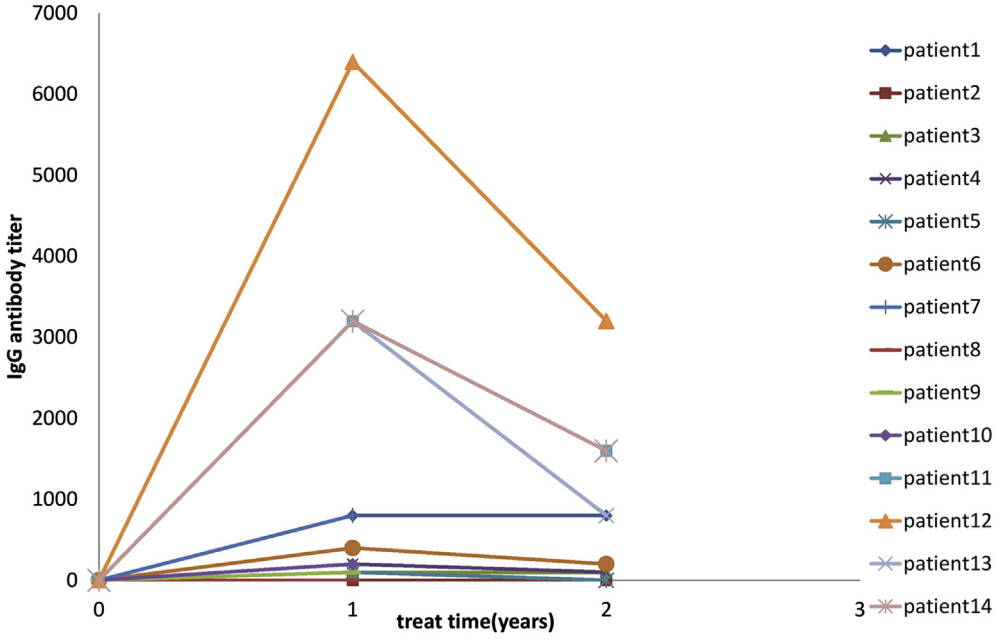

Figure 2. GAA antibodies before and 1 and 2 years after ERT.