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Case Report

Optimizing clinical outcomes: The journey of twins with CRIM-negative infantile-onset Pompe disease on high-dose enzyme replacement therapy and immunomodulation

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ABSTRACT

Infantile-onset Pompe disease (IOPD) is caused by a deficiency in the enzyme acid alpha-glucosidase (GAA). It is characterized by severe and progressive hypertrophic cardiomyopathy and muscle weakness with death in the first 2 years of life if left untreated. Enzyme replacement therapy (ERT) with alglucosidase-alfa is lifesaving, but its effectiveness is influenced by the patient's cross-reactive immunologic material (CRIM) status, dose of ERT, and the development of high antibody titers, which can reduce the therapy's efficacy. The inability of CRIM-negative IOPD patients to produce native GAA exposes them to a high risk of development of anti-rhGAA IgG antibody titers, leading to treatment failure. We present the case of CRIM-negative dizygotic twins treated with high-dose alglucosidase-alfa (40 mg/kg/week), initiated at 28 days (Twin A) and 44 days (Twin B). Both twins received immune tolerance induction (ITI) with rituximab, methotrexate, and IVIG to mitigate antibody response. Initial evaluations revealed elevated left ventricular mass index (LVMI) and elevated biomarkers (urine glucose tetrasaccharide (Glc_4), creatine kinase (CK), and aspartate aminotransferase (AST)) in both twins. Following treatment, cardiac function and biomarkers normalized within several months, with a slight delay in Twin B compared to Twin A, likely attributed to the later initiation of ERT. Both twins safely tolerated ITI, achieving immune tolerance with low antibody titers. At 28 months, the twins transitioned to avalglucosidase-alfa (40 mg/kg every other week (EOW)), which was well tolerated without an increase in antibody titers. At 39 months, both twins exhibited normal cardiac function, LVMI, and biomarkers. Motor skills continued to improve, though some kinematic concerns persisted. These cases underscore the importance of early, high-dose ERT combined with ITI in managing CRIM-negative IOPD. While transitioning to avalglucosidase-alfa at 40 mg/kg/EOW was beneficial and well-tolerated in our patients, further studies are needed to confirm its long-term efficacy compared to the high-dose weekly 40 mg/kg alglucosidase-alfa.

1. Introduction

Pompe disease, also known as glycogen storage disease type II (OMIM #232300) [1], is an autosomal recessive disorder resulting from a deficiency in the lysosomal enzyme acid alpha-glucosidase (GAA) [1,2], leading to the accumulation of glycogen in skeletal, cardiac, and smooth muscles [2]. Infantile-onset Pompe disease (IOPD) is at the most severe end of the disease spectrum, characterized by cardiomyopathy,

Abbreviations: CRIM, cross-reactive immunologic material; ITI, immune tolerance induction; LV, Left ventricle; LVMI, Left ventricular mass index; urine Glc_4, urine glucose tetrasaccharide; CK, creatine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IOPD, Infantile-onset Pompe disease; ERT, enzyme replacement therapy; GAA, acid alpha-glucosidase; rhGAA, recombinant human acid α-glucosidase; HSAT, high and sustained anti-rhGAA IgG antibody titers; IVIG, intravenous immunoglobulin; NBS, newborn screening; GMFM-88, Gross Motor Function Measure-88; PDMS-2, Peabody Developmental Motor Scales – 2nd Edition; LAC, lymphocyte absolute count; EF, ejection fraction.

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failure to thrive, hypotonia, and respiratory insufficiency. Without treatment, most infants do not survive beyond the first one to two years of life due to cardiorespiratory failure [1].

In 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (rhGAA; alglucosidase alfa) was approved by the Food and Drug Administration (FDA), improving survival, cardiac and motor outcomes [3]. However, patient outcomes on ERT remained variable due to factors including cross-reactive immunologic material (CRIM) status, anti-rhGAA immunoglobulin G (IgG) antibody titers, age of ERT initiation, ERT dose, and extent of disease progression at diagnosis [4–8]. The inability of CRIM-negative IOPD patients to produce native GAA exposes them to a high risk of immunological challenges, including the development of high and sustained anti-rhGAA IgG antibody titers (HSAT; antibody titers ≥12,800) [5,9]. The development of HSAT significantly impairs the efficacy of ERT due to the neutralizing response of the antibodies on either enzyme uptake into cells or the catalytic activity of the enzyme, translating into treatment failure [6,10]. Immune tolerance induction (ITI) to prevent and mitigate an immune response is now a standard of care, especially in CRIM-negative IOPD [11]. A short course of rituximab, methotrexate, and intravenous immunoglobulin (IVIG) for ERT-naïve patients has successfully induced immune tolerance with significant improvement in survival and clinical outcomes [12,13].

Age and stage of the disease at treatment initiation also significantly impact treatment outcomes [14]. Patients with pronounced cardiomyopathy, significant motor delay, and requiring ventilatory support at baseline tend to have a suboptimal response to ERT compared to patients diagnosed and treated in the earlier stage of the disease [3]. Among a Taiwanese cohort of CRIM-positive IOPD patients diagnosed by newborn screening (NBS), ERT initiation within the first month of life led to improved long-term outcomes including independent walking and ventilator-free survival [15]. Although the data demonstrated significant benefits of early treatment, the study did not include the most severe phenotype, CRIM-negative IOPD. Li et al. investigated the benefits of early ERT concomitant with ITI (rituximab, methotrexate, and IVIG) in CRIM-negative IOPD patients and compared the outcomes with CRIM-negative patients treated beyond 4 weeks of age [14]. Twenty CRIM-negative IOPD patients were grouped based on age at ERT initiation: early (ETG, before 4 weeks of age), intermediate (ITG), and late treatment groups (LTG) [14]. Median ages were 2.1 weeks for ETG, 7.6 weeks for ITG, and 17.9 weeks for LTG [14]. Early treated patients showed improved clinical outcomes, biomarkers and survival without respiratory or feeding assistance compared to patients treated at greater than 4 weeks of age [14].

Alglucosidase-alfa at doses of 40 mg/kg/week have been shown to further improve clinical outcomes and biomarkers such as aspartate aminotransferase (AST), creatine kinase (CK), and urine glucose tetrasaccharide (Glc_4) [15–18]. The twins described in this study were started on this ERT dose based on these findings. Next-generation therapies with improved targeting of skeletal muscles have been another advancement in the field [19,20]. Avalglucosidase-alfa and Cipaglucosidase-alfa are next-generation recombinant human GAA (rhGAA) ERT designed for enhanced targeting of mannose-6-phosphate (M6P) receptor-mediated uptake [21,22]. Avalglucosidase-alfa given at 20 mg/kg EOW and 40 mg/kg/EOW has demonstrated a positive impact on motor and cardiac function in 22 patients with IOPD with a suboptimal response or plateau on alglucosidase-alfa. One of them switched from a dose of 40 mg/kg/week of alglucosidase-alfa to 40 mg/kg/EOW of avalglucosidase-alfa demonstrating further improvement in clinical outcomes [23].

The study details the clinical journey and outcomes of dizygotic twins with CRIM-negative IOPD, who were initiated on high-dose alglucosidase-alfa at 40 mg/kg/week along with ITI at 28 and 44 days of age, respectively. As twins with the same pathogenic variants diagnosed and treated early, their case uniquely highlights the impact of early treatment on the most severe Pompe disease phenotype, emphasizing the importance of NBS. It also allows assessment of how even a few days delay in treatment can affect disease progression and ERT response. Earlier treatment initiation manifested in earlier normalization of cardiomyopathy and biomarkers in Twin A compared to Twin B. Both twins transitioned to avalglucosidase-alfa at 28 months and currently demonstrate normal cardiac function, stable biomarker levels, and steadily improving motor function, walking and running at 3 years old.

2. Methods

A retrospective chart review of a set of dizygotic twins born to non-consanguineous parents of African-Jamaican descent at 38 weeks and 3/7 days of gestation was conducted. Clinical data including *GAA* pathogenic variants, age, and doses of ERT + ITI treatment, overall and invasive ventilator–free survival, left ventricular mass index (LVMI), feeding status, motor status, CK, urine Glc_4, and anti-rhGAA IgG antibodies were extracted from medical records. The upper limit of normal (ULN) urine Glc_4 were determined according to age, as previously published [24]. Motor status was described based on chart review and physical therapy assessments done at Duke University Medical Center which included Gross Motor Function Measure-88 (GMFM-88) [25], Peabody Developmental Motor Scales – 2nd Edition (PDMS-2) [26], and kinematic and postural assessment performed at 23, 32 and 41 months of age. Anti-rhGAA IgG antibody titers were determined by LabCorp as previously described [27]. LVMI was manually calculated based on Doppler echocardiography reports. Clinical outcomes were compared to CRIM-negative IOPD patients treated before or at age 1 month with ERT initiated at less than 40 mg/kg/week and ITI [14].

3. Report

We discuss the case of a set of male (Twin A) and female (Twin B) 3-year-old CRIM-negative IOPD twins, homozygous for a nonsense mutation (c.2560C > T; p.Arg854*) in exon 18 of *GAA* [28]. CRIM-negative status was predicted based on the variants detected [28].

3.1. Twin A

Twin A presented with poor feeding and axial hypotonia shortly after birth. An echocardiogram at age 4 days revealed moderate left ventricular (LV) hypertrophy and LV septal and posterior wall measurement with *Z*-scores >2.0. At age 1-week, high LVMI (99.4 g/m^2), CK (1648 U/L), AST (111 U/L), and urine Glc_4 (23.7 mmol/mol creatinine (Cn)) (Fig. 1) raised suspicion for IOPD. At age 3 weeks, a diagnosis of CRIM-negative IOPD was confirmed by detection of low GAA enzyme activity (2.10 pmol/punch/h, normal level > 3.88 pmol/punch/h) and genetic testing.

At age 28 days, alglucosidase-alfa was initiated via port-a-catheter without premedication at 40 mg/kg weekly alongside an ITI regimen as previously published [12]. LVMI had increased to 114.94 g/m^2 (Fig. 1D). By age 2 months, LVMI had normalized to 54.9 g/m^2 (Fig. 1D). A G-tube was inserted due to poor feeding, dislodging around 11 months with no need for replacement due to adequate oral feeding. With ERT initiation, normalization of CK and AST occurred by age 3 months (Fig. 1A and B). Urine Glc_4 levels normalized at 1.75 months (Fig. 1C). Patient continues to maintain normal LVMI, urine Glc_4 and AST levels throughout the follow-up period (Fig. 1B, C, D). Transient CK elevations between 8 and 14 months (range: 210–311) and between 26 and 38 months (range: 208–255 U/L) (ULN CK <200 U/L) were detected (Fig. 1A).

At age 5 months, a complete B cell recovery was observed (measured as normalization of CD19%), in the setting of negative anti-rhGAA antibody titers. The patient is up to date on age-appropriate vaccination and antibody titers for the respective vaccinations were ordered.

Developmentally, according to the chart, twin A showed slight head

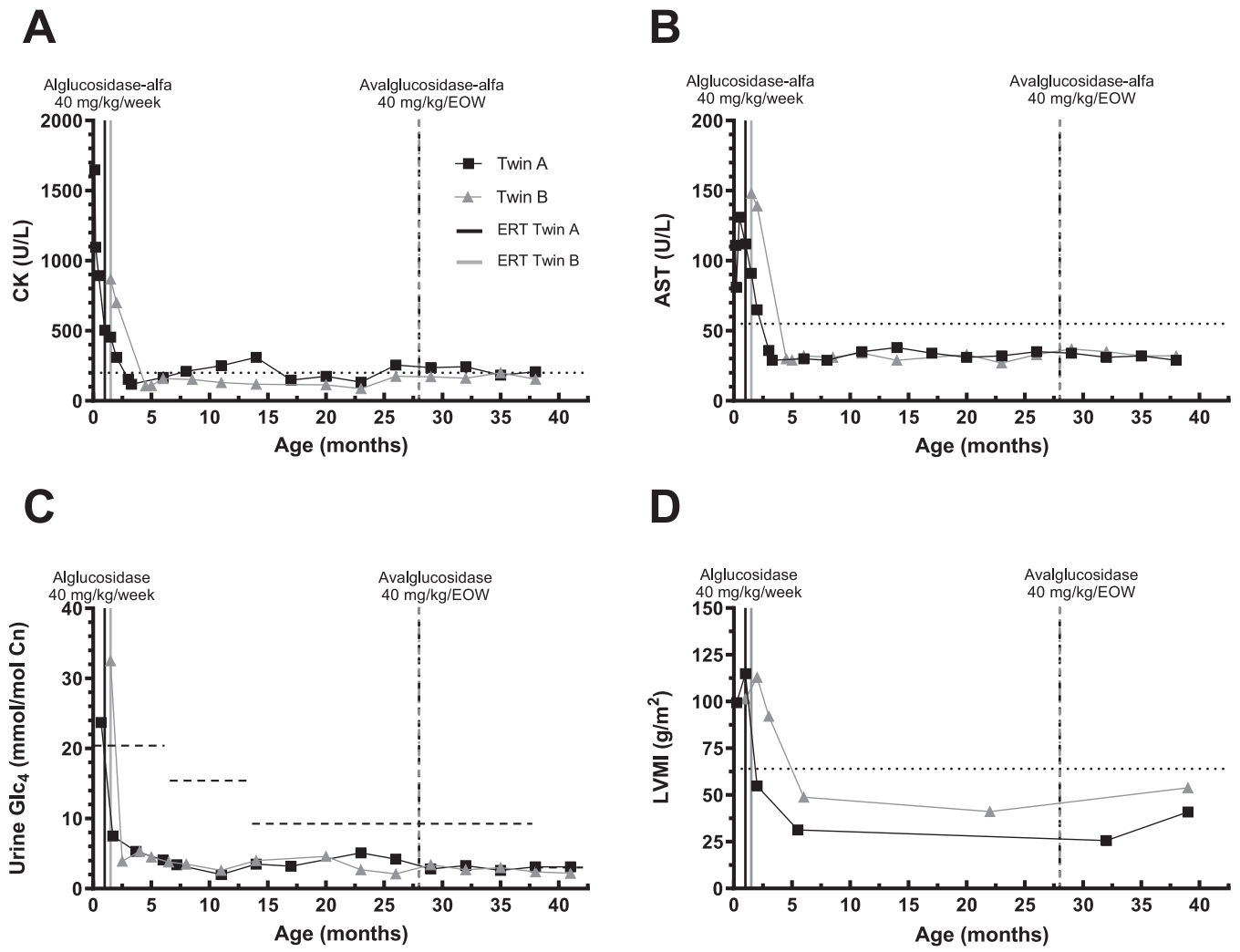

Fig. 1. Comparison of twin A and B biomarker and LVMI trends.

lag when pulled to sit at 4 months of age; but by 6 months of age could roll both ways and was able to maintain proper sitting if placed, get into sitting independently at 7 months of age, take his first steps at 9 months and walked across the room without falling at 15 months. Hearing was evaluated at age 17 months with no abnormal findings detected. At 21 months, his local team reported that he was able to squat, and walk upstairs holding 1 railing, but showed genu recurvatum (knee hyper-extension) and foot slap on the right when walking.

Upon evaluation at Duke at 23 months of age, he showed continued progress on motor milestones, walking independently with a flat foot gait, ascending and descending stairs using a railing with a step-to pattern, and moving between squatting and standing without hand support. He was not yet running, jumping nor hopping, and was not achieving standing through ½ kneeling. GMFM Dimensions D, E, D&E percents and PDMS-2 Standing and Locomotion Subscales are reported at 23, 32 and 41 months (Fig. 2 and Table 1) . Mild terminal head lag was noted when pulled to sit from supine, as were other kinematic features common in children with Pompe disease, including occasional posture of lower extremity flexion, abduction, and external rotation in sitting, slight rounding of the back and a posterior pelvic tilt, with mild iliotibial band tightness. Reflexes were 2+ bilaterally and Gower's sign was negative.

At 28 months, he transitioned to avalglucosidase-alfa administered at a dose of 40 mg/kg EOW, which was safely tolerated. After the transition to avalglucosidase-alfa, mother reported further improvement in strength and motor skills, with engagement in activities such as jumping, running, and navigating stairs, both with and without a railing for support.

When evaluated at Duke at 32 months, his gross motor skills showed significant improvement, functioning in the average range for age on the PDMS-2 (Fig. 2 and Table 1). He demonstrated the ability to run, achieve standing through ½ kneeling without hand support, stand on one foot long enough to step over an object at knee height, jump up 2 in., jump forward 5 in., and ascend and descend stairs without a railing using a step-to pattern. Kinematic features characteristic of Pompe disease in children persisted, including lumbar lordosis while standing, scapular winging, occasional hyperextension of knees (genu recurvatum), a tendency to maintain hip and knee flexion, genu valgus at the knees, flat foot gait, and a moderate, consistent head lag when pulled into a sitting position.

At 36 months, vision screening was negative for any refractory errors or other abnormal findings.

At 39 months, twin A was reported to be active and keeping up with his peers easily. His stature was in the 6th percentile for age, weight in the 11th percentile, and BMI in the 41st percentile. Patient anti-rhGAA antibody titers were consistently monitored post-ERT initiation and remained negative up to the latest assessment at 39 months.

When evaluated at Duke at 41 months, Twin A was continuing to show gains in gross motor skills, with steadily improving score on GMFM Dimension E (Walking, Running, and Jumping) and with improved raw score on the Locomotion Subscale of the PDMS-2 reflecting continued acquisition of motor skills (Fig. 2 and Table 1). However, he showed a

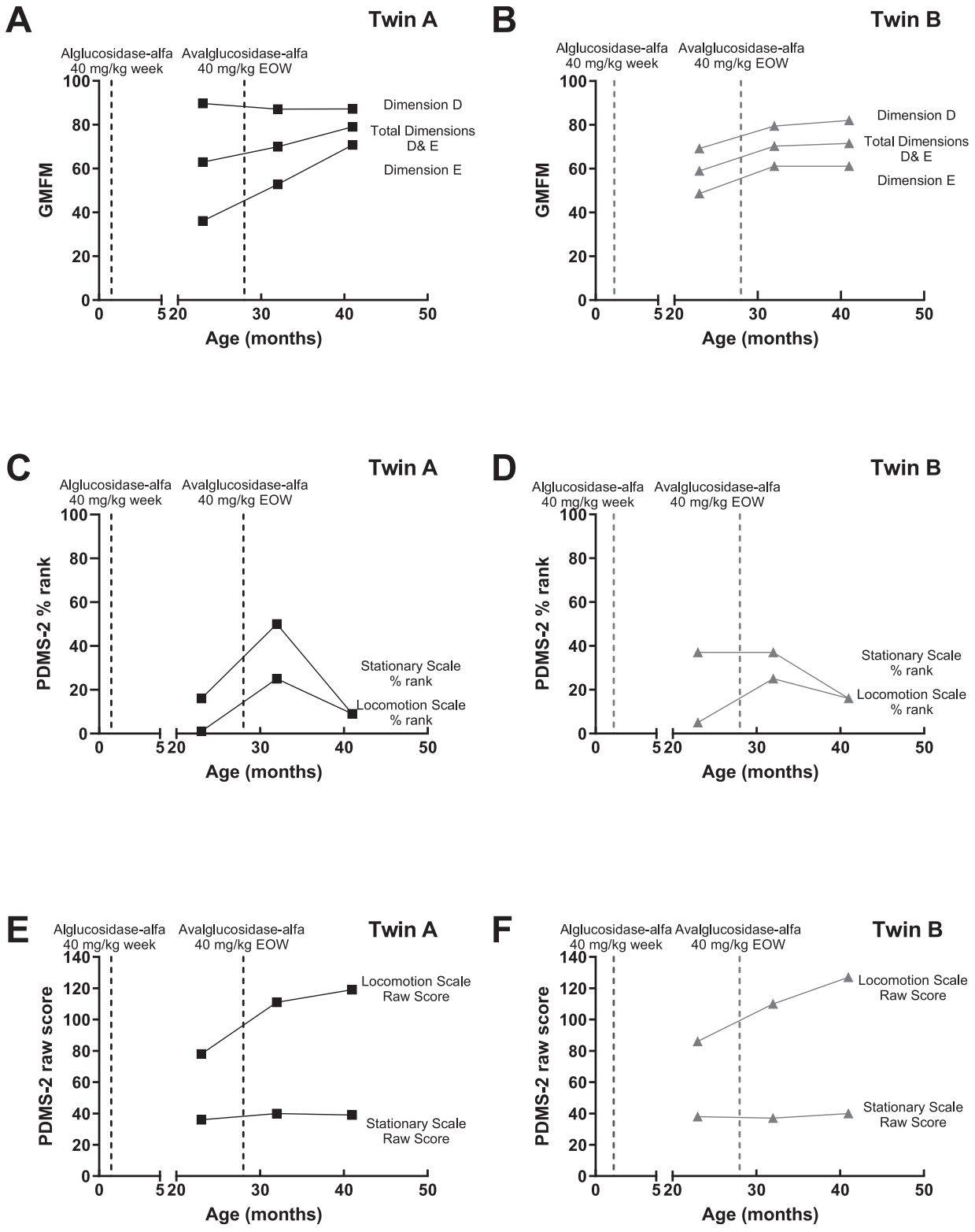

Fig. 2. Summary of GMFM-88 (%) & PDMS-2 (% & raw score) progression in Twin A & B.

slower rate of motor gains compared to age level peers and scored in the below average range on Stationary and Locomotion Subscales of the PDMS-2 (Fig. 2 and Table 1). He continued to demonstrate postural deviations suggestive of decreased core and proximal strength including lumbar lordosis and an anterior pelvic tilt in standing; scapular winging; occasional hyperextension of knees alternating with a tendency to remain in hip and knee flexion. He also presents with genu valgus at the knees which increases dynamically and during motorically challenging tasks; and demonstrates a flat foot gait without heel strike in addition to a moderate and consistent head lag with pull to sit.

Table 1
Physical therapy assessment scores.

	Twin A	Twin B
GMFM 23 months	Dimension D (Standing): 89.74 % Dimension E (Walking, Running, Jumping): 36.11 % Totals of Dimensions D & E: 62.93 %	Dimension D: 69.23 % Dimension E: 48.61 % Totals of Dimensions D & E: 58.92 %
GMFM 32 months	Dimension D: 87.18 % Dimension E: 52.78 % Total of Dimensions D and E: 69.98 %	Dimension D: 79.49 % Dimension E: 61.11 % Total of Dimensions D & E: 70.3 %
GMFM 41 months	Dimension D: 87.18 % Dimension E: 70.83 % Total of Dimensions D and E: 79.01 %	Dimension D: 82.05 % Dimension E: 61.11 % Total of Dimensions D & E: 71.58 %
PDMS-2 23 months	Stationary subscale raw score: 36 Stationary subscale standard score: 7 (below average) Stationary subscale percentile rank: 16 Locomotion subscale raw score: 78 Locomotion subscale standard score: 3 (very poor) Locomotion subscale percentile rank: 1	Stationary subscale raw score: 38 Stationary subscale standard score: 9 (average) Stationary subset percentile rank: 37 Locomotion subscale raw score: 86 Locomotion subscale standard score: 5 (poor) Locomotion subscale percentile rank: 5
PDMS-2 32 months	Stationary subscale raw score: 40 Stationary subscale standard score: 10 (average) Stationary subscale percentile rank: 50 Locomotion subscale raw score: 111 Locomotion subscale standard score: 8 (average) Locomotion subscale percentile rank: 25	Stationary subscale raw score: 37 Stationary subscale standard score: 9 (average) Stationary subscale percentile rank: 37 Locomotion subscale raw score: 110 Locomotion subscale standard score: 8 (average) Locomotion subscale percentile rank: 25
PDMS-2 41 months	Stationary subscale raw score: 39 Stationary subscale standard score: 6 (below average) Stationary subscale percentile rank: 9 Locomotion subscale raw score: 119 Locomotion subscale standard score: 6 (below average) Locomotion subscale percentile rank 9	Stationary subscale raw score: 40 Stationary subscale standard score: 7 (below average) Stationary subscale percentile rank: 16 Locomotion subscale raw score: 127 Locomotion subscale standard score: 7 (below average) Locomotion subscale percentile rank: 16

3.2. Twin B

CRIM-negative IOPD was suspected in Twin B following her twin brother's diagnosis and confirmed by genetic testing at 24 days. At 1 month, echocardiography showed moderate left ventricle dilation, left ventricular hypertrophy (LVMI = 101.4 g/m^2) (Fig. 1D), and reduced systolic function. At 1.5 months, she began ERT alglucosidase-alfa at 40 mg/kg weekly via port-a-catheter with ITI.

Elevated CK (868 U/L) and AST levels (148 U/L) at 1.5 months normalized to CK (106 U/L) and AST (30 U/L) at 4.5 months (Fig. 1A and B). A substantial decrease in urine Glc_4 levels (32.5 mmol/mol Cn) from 1.5 months of age also occurred with normalization of urine Glc_4 (3.9 mmol/mol Cn) by age 2.5 months (Fig. 1C). LVMI was elevated (112.88 g/m^2) at 2 months, decreased to 92.13 g/m^2 at 3 months and normalized (48.8 g/m^2) by the age of 6 months (Fig. 1D). Normal biomarker and LVMI trends persisted until the last assessment at 38 months for CK (154 U/L), AST (32 U/L), and at 41 months for urine Glc_4 (2.4 mmol/mol Cn) (Fig. 1A, B and C).

At age 5 months, a complete B cell recovery was observed (measured as normalization of CD19%), in the setting of negative anti-rhGAA antibody titers. The patient was up to date on age-appropriate vaccination and antibody titers for the respective vaccinations were ordered.

Developmentally, at 15 months, she exhibited normal reflexes bilaterally, negative Gower's sign and mild iliotibial band tightness. Motor milestones, including standing and walking independently, were achieved by 13–15 months, with continued progress at 23 months (Fig. 2 and Table 1). Hearing was evaluated at age 17 months with no abnormal findings detected.

Upon evaluation at Duke at 23 months of age, she was reported to be making consistent progress in motor milestones, walking independently and independent in transitions between positions, achieving standing from sitting without hand support, and achieving standing from squatting or through ½ kneeling with 1 handed support on her knee, and able to ascend and descend stairs using a step-to pattern, holding 1 railing when ascending and 2 railings when descending. She was not able to jump or hop and had difficulty balancing on 1 ft, walking with a flat foot gait without heel strike and with intermittent toe-walking. GMFM Dimensions D, E, D&E percents and PDMS-2 Standing and Locomotion Subscales are reported at 23, 32 and 41 months (Fig. 2 and Table 1). Kinematic features common in children with Pompe disease were present, including scapular winging, rib flaring, occasional hyperextension of knees alternating with a tendency to remain in hip and knee flexion. Genu valgus, subtalar pronation with midfoot push-off were also present.

At 28 months, she transitioned to avalglucosidase alfa at a dose of 40 mg/kg EOW which was safely tolerated. After transition, mother reported further improvement in strength and motor skills, engaging in activities such as jumping, running, and navigating stairs, both with and without using a railing for support.

At 32 months, she showed continued gains in gross motor function, functioning in the average range for age on the PDMS-2 (Fig. 2 and Table 1), walking independently and achieving standing by pushing up on 2 hands on the floor without a hand on a knee. She was also able to maintain single limb stance while stepping over an object at knee level, with emerging jumping. However, she was not yet running and was not showing heel strike. PT assessment continued to document kinematic features characteristic of Pompe disease in children including scapular winging, lower rib flaring, a posterior pelvic tilt and rounded back in sitting. A wide base of support in sitting and standing, subtalar pronation in standing with occasional hyperextension of knees alternating with a tendency to remain in hip and knee flexion, and genu valgus at the knees were also documented.

At 36 months, vision screening was negative for any refractory errors or other abnormal findings.

At 39 months, twin B remained active, meeting developmental milestones on time and keeping up with her peers easily. Her stature was in the 67th percentile for age, weight in the 59th percentile and BMI in the 49th percentile. Anti-rhGAA antibody titers were consistently monitored post-ERT initiation indicating successful immune tolerance (range: 0–1600) up to the latest assessment at 39 months.

At 41 months, PT assessment at Duke demonstrated continued improvements in her gross motor skills. She was able to ascend stairs without railing support using a step-to pattern and was able to descend stairs holding 1 railing with a step-to pattern. She demonstrated

emerging running but was still lacking heel strike during gait. Although she was continuing to gain motor skills, as evidenced by steadily increasing score on GMFM Dimension D (Standing) and increasing raw scores on the PDMS-2, she showed a slower rate of motor gains compared to age level peers and scored in the below average range on Stationary and Locomotion Subscales of the PDMS-2 (Fig. 2 and Table 1). Kinematic features characteristic of Pompe disease in children persisted, including scapular winging and rib flaring, subtalar pronation with midfoot push off, occasional hyperextension of knees alternating with a tendency to remain in hip and knee flexion. Genu valgus at the knees was also documented.

4. Discussion

This report highlights a positive outcome in a set of dizygotic twins with CRIM-negative IOPD initiated early on high-dose alglucosidase-alfa (40 mg/kg/week) with concomitant ITI, transitioning to avalglucosidase-alfa (40 mg/kg/EOW).

By 32 months, the twins demonstrated normal LVMI, cardiac function, and stable biomarkers, along with steadily improving motor skills in GMFM Dimensions D (Standing) and E (Walking, Running, and Jumping) percents and PDMS-2 percentile scores on Stationary and Locomotion Subscales indicated gross motor skills within the average range for age. However, more recent assessment at 41 months revealed decreased percentile scores on PDMS-2 relative to age-level peers, despite gained skills because they were not gaining skills as quickly as age level peers in more challenging tasks such as unilateral standing, hopping, and jumping, primarily due to residual kinematic challenges such as anterior pelvic tilt and subtalar pronation. To enhance alignment and stability, inframalleolar orthoses were recommended.

On the GMFM, which assesses actual improvement not compared to age level peers, Twin A outperformed Twin B at the most recent assessment at 41 months with a 7.43 % higher GMFM D&E total score, 5.13 % higher Dimension D, and 9.72 % higher Dimension E scores, surpassing the minimal clinically important difference (MCID) of large effect size [29]. Delays in motor milestones and time to normalization of biomarkers were observed in Twin B, likely due to a 16-day delay in treatment initiation [15]. For instance, Twin A took his first steps at 9 months and Twin B at 13 months. Twin A could descend stairs without using a railing at 32 months and Twin B still needed to use a railing at 41 months. Tasks requiring attention and following directions, such as walking between lines or maintaining hands on hips during balance tasks, were sometimes more challenging for Twin A, resulting in lower gains in specific scores requiring attention and following directions though steady motor progress occurred in both twins. Despite their progress, the twins continue to display postural and kinematic deviations, indicating decreased core and proximal strength. These cases underscore the importance of pediatric physical therapists experienced in neuromuscular disorders for managing IOPD.

To the best of our knowledge, none of the reported cases of CRIM-negative IOPD were started early on high-dose ERT of 40 mg/kg/week [4,12,14,29–32]. A study on 5 CRIM-negative IOPD patients treated early (median age 2.1 weeks) with a lifelong average dose of ERT of 1.57 (1.04–2.01) x standard dose showed stable biomarker trends and improved survival without needing respiratory or feeding support [14]. However, these patients had delayed normalization of biomarkers compared to the twins treated with 40 mg/kg/week [33,34]. This confirms what was previously demonstrated that a delay by even a few days in ERT initiation can significantly impact long-term IOPD outcomes. Recently, in-utero ERT has resulted in promising outcomes in a fetus with CRIM-negative IOPD, with the patient having normal cardiac parameters, age-appropriate motor function, and developmental milestones postnatally [35].

Avalglucosidase alfa and cipaglucosidase-alfa are a next-generation recombinant human GAA (rhGAA) ERT designed for enhanced targeting of mannose-6-phosphate (M6P) receptor-mediated uptake [21,22]. The mini-COMET trial supports the positive clinical impact on motor and cardiac function with the use of avalglucosidase-alfa in patients with IOPD who had a suboptimal response or plateau on alglucosidase-alfa. Benefits were even noted in patients who switched from alglucosidase-alfa doses of 40 mg/kg/week to avalglucosidase-alfa administered at a dose of 40 mg/kg EOW in an outpatient setting, with no increased safety risk seen [23]. In the case of our patients, this transition resulted in continued benefits.

The data presented herein further validates the value of early diagnosis and early treatment in improving the clinical outcomes of patients with IOPD. Furthermore, these cases demonstrate that the outcomes in early treated patients can be further enhanced by implementing a higher dose of ERT from the outset. It is yet to be seen if the approach of early treatment combined with higher dose of therapeutic protein can resolve the residual impairments that are seen in long-term survivors of IOPD. The role of PT remains critical as it helps recognize and target subtle residual deficits that can persist despite the significant positive impact of early treatment. It also enables the tracking of movement components, function, and musculoskeletal status over time. This facilitates the optimization of early ERT benefits through appropriate exercises that promote optimal muscle activity and selective strengthening, supporting proper alignment, motor development, and function. Initiating treatment as early as possible, even in utero, could potentially address these issues more effectively. A longer follow-up duration is needed for additional assessment of clinical outcomes. Further studies assessing long-term outcomes in a larger cohort of IOPD patients who are treated right after birth on higher dose of ERT are needed to understand the degree of improvement.

Ethics statement

The privacy rights of human subjects have been observed. Mother signed a medical record release form to use the twins' data for a research case study.

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CRediT authorship contribution statement

Angie H. Fares: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Ankit K. Desai:** Writing – review & editing, Visualization, Formal analysis. **Laura E. Case:** Writing – review & editing, Visualization, Investigation, Formal analysis. **Cassie Sharon:** Investigation. **Amy Klinepeter:** Investigation. **Amelia Kirby:** Investigation. **Matthew T. Lisi:** Investigation. **Rebecca L. Koch:** Writing – review & editing, Visualization, Conceptualization. **Priya S. Kishnani:** Writing – review &

editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

Priya S. Kishnani reports a relationship with Sanofi Genzyme that includes: board membership, consulting or advisory, and funding grants. Priya S. Kishnani reports a relationship with Amicus Therapeutics Inc. Research & Gene Therapy Center of Excellence that includes: board membership, consulting or advisory, and funding grants. Priya S. Kishnani reports a relationship with Maze Therapeutics Inc. that includes: consulting or advisory and equity or stocks. Priya S. Kishnani reports a relationship with Asklepios BioPharmaceutical Inc. that includes: consulting or advisory and equity or stocks. Priya S. Kishnani reports a relationship with Babies that includes: board membership. Ankit K. Desai reports a relationship with Sanofi Genzyme that includes: funding grants. Ankit K. Desai reports a relationship with Lysosomal Storage Network that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

all the relevant data is already included

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