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Dose-intensive therapy (DIT) for infantile Pompe disease: A pilot study

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ABSTRACT

Background: The current standard of care for infantile-onset Pompe disease (IOPD), a severe form of acid α-glucosidase enzyme activity deficiency is: (1) detection by newborn screening, (2) early initiation of intravenous enzyme replacement therapy (ERT) using recombinant human acid alpha-glucosidase (rhGAA), with higher doses of rhGAA increasingly used to improve clinical outcomes, and (3) immune tolerization induction (ITI) using to prevent anti-rhGAA antibody formation, with methotrexate (MTX), rituximab, and IVIG used for patients who are cross-reactive immunologic material negative (CRIM-) and monotherapy with MTX used in patients who are cross-reactive immunologic material positive (CRIM+).
Objectives/methods: A pilot study evaluates a dose-intensive therapy (DIT) using high-dose ERT (40 mg/kg/week) and more frequent exposure to ERT (i.e., 3 times weekly administration) to mitigate anti-rhGAA antibody formation, as an alternative to the standard therapeutic approach for IOPD.
Results: In the first patient, DIT resulted in rapid normalization of the following: (1) bi-ventricular hypertrophy, (2) urine HEX-4, (3) CK, (4) liver transaminases. At 7 years of age, the patient continues the DIT regimen. To date, all pediatric developmental milestones have been met on time, anti-rhGAA antibodies have been negative and the patient is able to attend school and maintain normal activities of daily living.
Conclusions: Over a 7-year period, DIT for CRIM-positive IOPD was well tolerated in the first patient treated. Excellent clinical outcomes were achieved, and anti-rhGAA antibodies levels were consistently undetectable. Assessments of more patients, that includes patients with CRIM-, as well as CRIM+ IOPD, will determine if this approach consistently achieves improved clinical outcomes and immune tolerization.

1. Introduction/background

Pompe disease is a rare disease, inherited through an autosomal recessive pattern and caused by mutations of the acid α-glucosidase (*GAA*) gene localized at chromosome 17q25.2-q25.3, resulting in the absence or reduced enzyme activity of acid α-glucosidase (EC 3.2.1.20) [17,41]. Deficiency of acid α-glucosidase in Pompe disease leads to the pathologic accumulation of glycogen in the lysosomes and between the myofibrils, predominantly in the skeletal, cardiac, and smooth muscle.

1.1. Clinical management of IOPD

The current standard of care for infantile-onset Pompe disease (IOPD), a severe form of acid α-glucosidase enzyme activity deficiency is: (1) detection by newborn screening, (2) early initiation of intravenous enzyme replacement therapy (ERT) using recombinant human acid alpha-glucosidase (rhGAA), and (3) immune tolerization induction (ITI) to prevent anti-rhGAA antibody formation, with methotrexate (MTX), rituximab, and IVIG used for patients who are cross-reactive immunologic material negative (CRIM-) and monotherapy with MTX used in patients who are cross-reactive immunologic material positive (CRIM+). (Priya S. [29]; J. L. [17,32]).

The current standard dose of recombinant human alglucosidase alfa (rhGAA), is 20 mg/kg every other week intravenously (Priya S. [29]; J. L. [17,32]). Studies have shown, however, that administering higher doses of rhGAA ERT either at 40 mg/kg every other week or 40 mg/kg/

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weekly (quadruple the label dose) is associated with significant improvement in clinical outcomes (Priya S. [29]; Jesa L. [17,32]).

ITI regimen using monotherapy with methotrexate. The ITI regimens are most often used as a prophylactic approach and initiated shortly after diagnosis. ITI may also be used to address the confirmed development of anti-rhGAA antibodies after initiation of ERT [6,12,13,23]. Proteosome inhibitors are sometimes used to address high sustained antibody titers (HSAT) resistant to conventional ITI [13]).

2. Objectives

This pilot study aims to evaluate a dose-intensive therapy regimen (DIT) in IOPD, as an alternative to the standard therapeutic approach for IOPD, to accomplish the following two goals:

1. Optimizing clinical outcomes through use of high-dose rhGAA ERT (40 mg/kg/week, 4-fold the FDA approved dose).
2. Prevent/mitigate formation of anti-rhGAA antibodies through use of more frequent exposure of patient to the antigen (i.e., the total rhGAA ERT dose divided into 3 separate doses administered 3 times weekly, instead of once every other week).

3. Methods

This study took place through a research protocol that has Institutional Review Board approval and IRB approved parental consent.

3.1. Titrating rhGAA ERT to goal dose

The investigators recognize that many clinicians initiate ERT therapy in IOPD at the full goal dose and administer the infusion at a rate that follows guidelines provided by the manufacturer. With the aim to improve chances that the subject would tolerate the high-dose rhGAA ERT infusions well and mitigate the risk of infusion reactions, it was decided to start the subject at a dose lower than the goal dose and give the infusion more slowly than the FDA package insert guidelines, and then slowly titrate the dose, as tolerated by the subject, to a goal dose of 40 mg/kg/week (divided into three weekly doses) (see Table 1). The investigators chose this slow titration dosing plan as a precautionary measure, with the understanding higher doses and faster infusion rates, in general, can increase the risk for infusion reactions in some patients [47]. As an additional precautionary measure, the first ten infusions were given in the hospital with telemetry for cardiac monitoring throughout these admissions.

3.2. Dosing frequency

Dividing the overall dose into smaller, more frequent doses also provides more frequent exposure, or "prolonged exposure" of the patient to the potential antigen (i.e., rhGAA ERT), in effect mimicking a constant antigen exposure, and thereby may allow more readily for immune tolerance [48]. (Table 1).

3.3. Outcomes measured

The following biomarkers were obtained at baseline and weekly during the first 10 weeks of therapy and then once monthly thereafter through month 6, or until goal rhGAA ERT dose is reached, then every 3 months: creatinine kinase (CK), urine Hex4, Troponin I, liver transaminases, CBC, metabolic panel, anti-rhhGAA antibodies.

Neurodevelopmental testing included standard pediatric neurodevelopmental milestones. She was evaluated in the neuro-muscular clinic and had developmental assessment scores, including Gait-Stairs-Gowers-Chair) and Bruininks-Oseretsky test of motor proficiency (BOT-2) at 6.7 years of age.

Due to the nephrotic syndrome case report in a patient receiving infusions of high molecular weight proteins in the setting of potential immunogenicity (single case report in an IOPD patient and case reports in severe hemophilia B) [22,49] weekly urine protein to creatinine and albumin to creatinine ratio, were obtained as a precautionary measure. Weekly urine protein to creatinine and albumin to creatinine ratio were obtained just prior to rhGAA infusion, and post infusion,when possible, during the first 6 months of DIT, and then monthly thereafter, to monitor for protein spilling in the urine.

4. Results

To date, one subject with IOPD has participated in the DIT pilot study. The subject was a female with CRIM+ IOPD, identified through newborn screening, born at 40 weeks gestation via C-section. The pregnancy and birth history were uncomplicated, and her Apgar scores were 8 & 9 at 1 & 5 min, respectively. Her newborn screening was positive for Pompe disease day of life (DOL) # 8 days (GAA activity: 0.6 nmol/ml/h; 1 % of reference population: 4.3 and creatine/creatinine ratio: 8.5 (99 %ile of reference population: 1.1). She was evaluated the same day by a metabolic geneticist. Studies showed elevated creatine kinase (CK) of 1200 (reference: 3–225 U/L), elevated liver transaminases (aspartate aminotransferase (AST):124; reference 20–70 U/L and alanine transaminase (ALT): 59; reference:0–50 U/L) and elevated urine Hex4 at 32.3 mmol/mol creatinine (reference: </=20). Her initial EKG indicated biventricular hypertrophy. Her initial echocardiogram showed moderate right and left ventricular hypertrophy, end-diastolic ventricular septum thickness *Z*-score of +3.1 and left ventricular end-diastolic posterior wall thickness Z-score of +3.3. Initial troponin was elevated at 0.065 μg/L (ref: 0–0.045). Molecular testing through the state detected two compound heterozygous pathogenic variants in *GAA*:

1) missense mutation: c.1210G > A (p.D404N) (https://www.ncbi.nlm.nih.gov/clinvar/variation/657348/?oq=c.1210G%3EA[varname]+,+GAA&m = NM_000152.5(GAA):c.1210G%3EA%20(p.Asp404Asn; accessed 12-05-2024).

and 2) inframe deletion: c.1408_1410delAAC (https://www.ncbi.nlm.nih.gov/clinvar/variation/932895/?oq=c.1408_1410delAAC+,+

Table 1
Detailed dose escalation protocol for alglucosidase alfa (rhGAA ERT) with outlined the total weekly dose, dose frequency, duration of each dose schedule.

Dose Titration Schedule	Total Weekly Dose	Dosing Frequency	Duration of Dose Titration Step	Change from FDA approved dose (x-fold)
Initial Dose	15 mg/kg/week	15 mg/kg per infusion (once weekly)	2 weeks	1.5-fold FDA approved dose
Interim Dose	30 mg/kg/week	15 mg/kg twice weekly (Mondays and Thursdays)	6 months	3.0-fold FDA approved dose
Goal Maintenance Dose	40 mg/kg/week	13 mg/kg twice weekly (Monday and Wednesdays) + 14 mg/kg once weekly (Fridays)	Thereafter	4.0-fold FDA approved dose

All doses were rounded to nearest vial size.
Premedications:
Acetaminophen 10 mg/kg by mouth, 30–60 min prior to infusion.
Diphenhydramine 0.5 to 1 mg/kg intravenously (not to exceed 50 mg), 30–60 min prior to infusion.

GAA&m = NM_000152.5(GAA):c.1408_1410del%20(p.Asn470del; accessed 12-05-2024).

The clinical and biochemical findings along with the molecular test results confirmed the diagnosis of IOPD. CRIM testing was performed at Duke University Health System Clinical Laboratories and the subject was found to be CRIM+ on DOL# 12.

The subject's initial dose rhGAA ERT dose of 15 mg/kg/ per week (approximately 1.5-fold the FDA-approved dose) was administered on DOL# 13 with acetaminophen and diphenhydramine as pre-medications, infused intravenously over a 7-h period with escalation to 15 mg/kg twice weekly (approximately 3-fold the FDA approved dose) on week 3. The initial 10 infusions were administered in the hospital with cardiac monitoring throughout the infusion. The subject was found to have transiently elevated urine protein to creatinine ratio, post ERT infusion, after 5 doses of ERT infusions, albeit her renal function and renal ultrasound continued to be normal. She was followed by pediatric nephrology with continued urine protein monitoring, as a precautionary measure. Two weeks after initiation of rhGAA ERT, the ERT dosage was increased from 15 mg/kg twice weekly to the final goal dose of 40 mg/kg/week (4-fold the FDA-approved dose) by 6 months (Table 1). The goal dose was divided into 3 weekly doses: 14 mg/kg on Monday, 13 mg/kg on Wednesday and 13 mg/kg on Friday, each week. All doses were rounded to the nearest vial size (Table 1; Fig. 1).

Normalization of left ventricular hypertrophy was evident on echocardiogram after 2 infusions and normalization of right ventricular hypertrophy by 10 infusions. All of the subject's biomarkers normalized within 3 months of initiation of ERT and continue to be within the normal limits to date (Fig. 2; Table 2). The subject's anti-rhGAA ERT IgG and IgM antibody testing were undetectable at baseline and have consistently been undetectable to date (throughout the first 7 years of life). The subject continues to get the biomarkers (creatine kinase, liver transaminases, urine Hex4, and complete blood count) drawn every 3 months. At the time of the last visit in the neuromuscular clinic, the subject was 6 years of age and was found to continue to meet all pediatric developmental milestones at appropriate ages. Her motor examination at 6 years of age showed normal muscle bulk with mildly reduced muscle tone. Her muscle strength was 5/5 in all groups except for neck flexion, which was 4-. Her most recent GSGC (Gait-Stairs-Gowers-Chair) score, at 6 0.7 years of age, was 4, which is in the normal range. At 6.7 years of age, the BOT-2 showed her body coordination, strength, and agility in the average range. Her most recent echocardiogram from 5 years of age showed normal right and left ventricular systolic function, normal ventricular septum, and left ventricular wall end-diastolic thickness by MMODE *Z*-scores. Her ejection fraction remains normal at 60 %. Her growth and development remain appropriate for age (weight: 20.3 kg; 40th centile; z score: −0.24, height: 119 cm; 64th centile; z score: 0.38). The duration of each rhGAA ERT infusion was gradually reduced to 4.5 h during her 6 years of life and the subject continues to tolerate the infusions well. She has been receiving home infusion since approximately 1 year of age. The subject is attending mainstream school and performing well in school.

5. Discussion

This is the first study to demonstrate a dose-intensive (DIT) approach for treatment of CRIM+ IOPD, as an alternative to the current standard of care (i.e., FDA approved dosing of rhGAA ERT and ITI). It is noteworthy that the subject has been followed for 7 years while on DIT. Specifically, the subject in this study began the DIT regimen at 13 days of life and, to date, has continued this regimen for 7 years, which is the age of the subject at the time of this report. The subject has tolerated DIT very well during the 7 years of treatment, with excellent clinical management of IOPD and complete absence of anti-rhGAA antibody formation. At the time of this report, the subject is 7 years old and has met all pediatric developmental milestones on time, continues to have normal motor development, and continues to maintain Pompe disease biomarkers in normal range.

5.1. Early initiation of rh-GAA ERT

In the most severe form of Pompe disease is infantile Pompe disease (IOPD, symptoms are apparent within the first few days to first few months of life and include hypotonia, cardiomegaly, macroglossia, hepatomegaly, and progressive muscle weakness [15,21]. If untreated, the infantile form of Pompe disease will result in early death, often before 1 year of age [15,21]. Early diagnosis and treatment have been found to

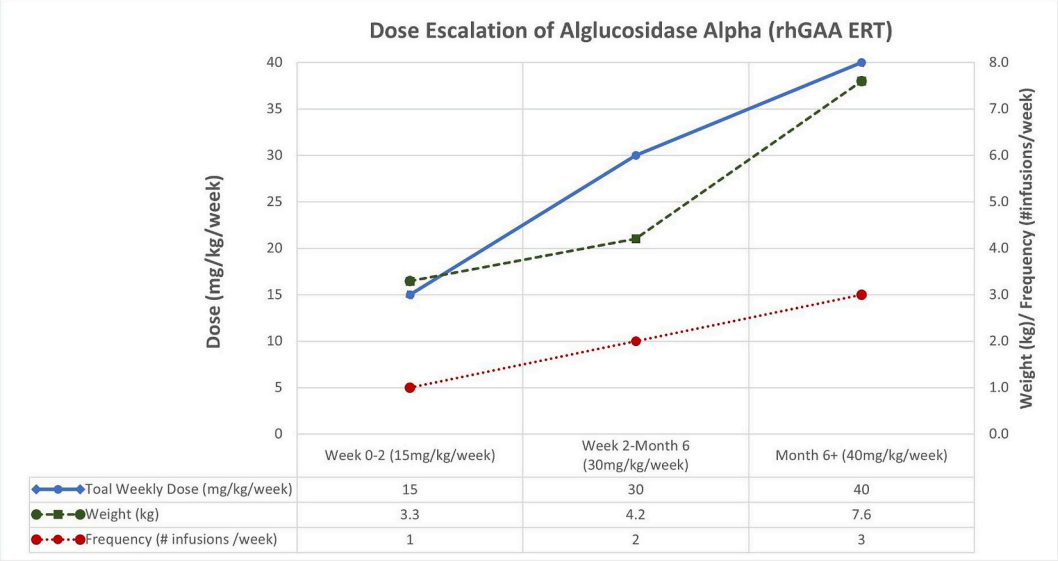

Fig. 1. Detailed dose escalation process for rhGAA ERT. X-axis: Weeks since initiating therapy. Blue line tracks dose increase (mg/kg/week) from the initial starting dose of 15 mg/kg/week administered for two weeks, 30 mg/kg/week administered for 6 months, and 40 mg/kg/week administered from 6 months onwards. Green line shows the corresponding patient weight at each dose milestone. The red line displays the frequency of infusions per week to achieve weekly total dose; 15 mg/kg week was administered as once weekly infusion, 30 mg/kg/week was administered as two infusions of 15 mg/kg on Mondays and Thursdays, 40 mg/kg/week was administered as three infusions of 13 mg/kg on Mondays and Wednesdays, 14 mg/kg on Fridays.

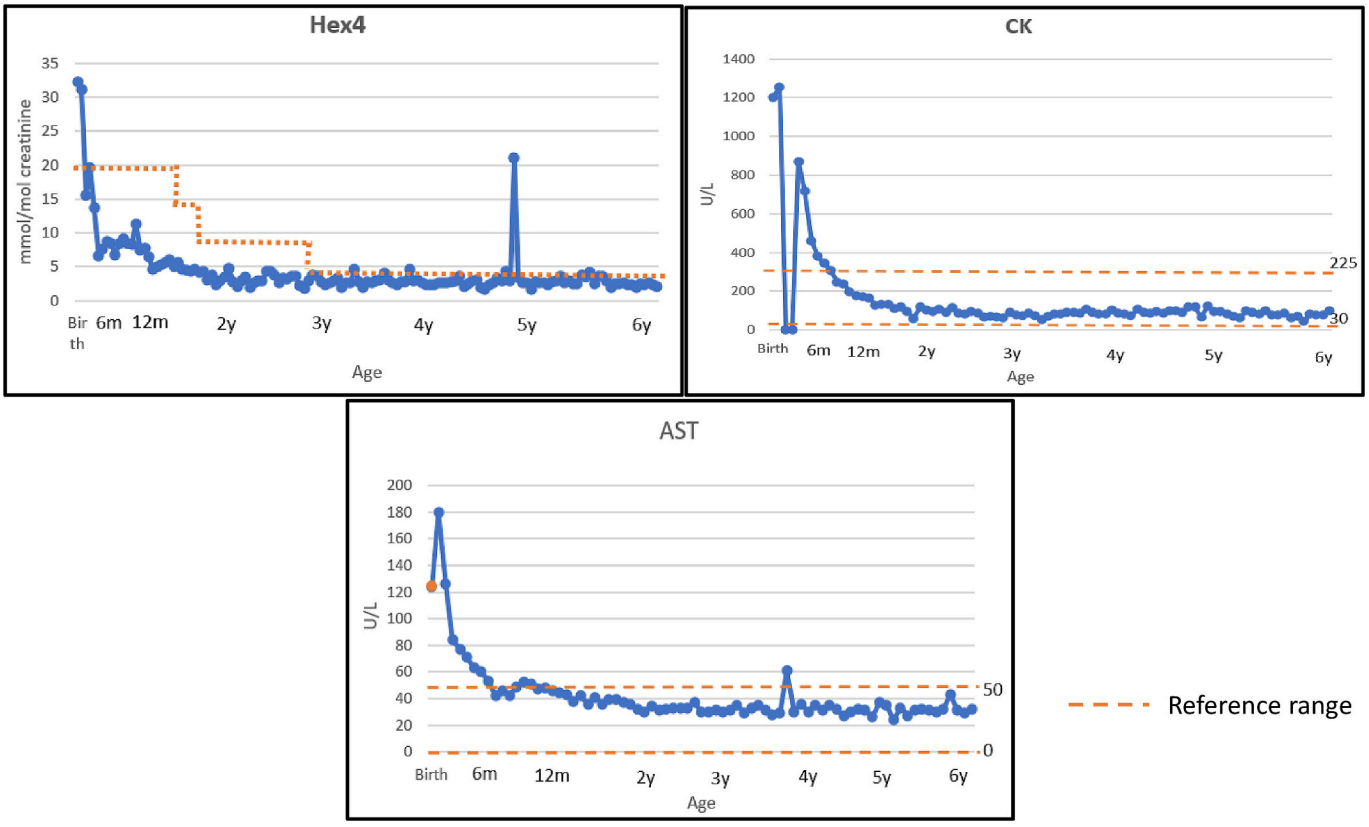

Fig. 2. Biomarker trend during ERT.
Dosing schedule for rhGAA ERT:

decrease morbidity and increase survival in children with IOPD [27,38]. Clinical improvement with early treatment initiation in respiratory function, especially ventilator-free survival, cardiomyopathy and motor function, has been well established [26,27]. As a result, Pompe disease was added to the Recommend Uniform Screening Panel (RUSP) in March 2015, and as of January 2024, 45 states screen for Pompe disease as part of their newborn screening program [39].

Nevertheless, even with early initiation, several other factors determine the effectiveness of rh-GAA ERT, including anti-rhGAA ERT antibody titers, cross-reactive immunological material (CRIM) status, the individual's pre-existing phenotype, and the rh-GAA dose (Priya S. [2,3,29]).

5.2. *Higher-dose rh-GAA ERT*

The clinical benefits and advantages of higher doses of ERT for IOPD have been well documented including significantly improved overall survival, ventilator-free survival, gross motor outcomes, and pulmonary function and a decrease in biomarker levels when compared to the standard approved dosage (Priya S. [29]; Jesa L. [17,32]).

5.3. *Immune tolerance induction therapy (ITI)*

Children with IOPD can be broadly divided into cross-reactive immunologic material negative (CRIM-) and cross-reactive immunologic material positive (CRIM+). Infants who are CRIM+ usually respond well to ERT and have lower anti-rhGAA antibody titers compared to CRIM- patients. CRIM- patients are at greater risk for mounting an immune response to rhGAA, developing sustained and higher antibody titer, and experiencing earlier seroconversion and the presence of neutralizing antibodies when compared to CRIM+ patients [31].

Anti-rhGAA antibodies can interfere with ERT efficacy by mechanisms that include reduced ERT stability, degradation of ERT in the bloodstream, anti-body mediated blockade of cellular uptake of ERT, retargeting of M6P-glycosylated ERT to macrophages, and intracellular misrouting of ERT [7,20,33,36,44,46].

Formation of anti-rhGAA antibodies can impair the efficacy of rhGAA ERT and often occurs within the first 6 months after ERT initiation but can also occur years after ERT initiation [6]. Therefore, preventing and managing anti-rhGAA antibodies to rh-GAA ERT are an ongoing important component of the clinical management of IOPD [6,28].

ITI for IOPD has demonstrated an excellent safety profile thus far and continues to be the gold standard for prevention of immunogenicity and immune tolerance induction in patients with IOPD [13,43]. The current standard of care used most often for patients with IOPD, to prevent formation of rhhGAA antibodies, uses a combination of methotrexate, rituximab, and IVIG for CRIM- IOPD patients, and a single-agent methotrexate approach for CRIM+ IOPD patients. Formation of neutralizing antibodies (Nab) can also occur and is associated with the presence of high sustained anti-rhGAA antibodies titers (>/= 12,800), which is understood to be mediated through the development of long-lived plasma cells [13,43]. Patients with Nab receiving standard ITI regimens are anticipated to experience a significant decline in NAb over an 18-month period, but may not realize full eradication of neutralizing antibodies [6,12,13,23,28]. A proteasome inhibitor, such as bortezomib, is commonly added to the ITI regimen in cases in which the development of high sustained antibody titers (HSAT) occurs. Elimination of HSAT may require more prolonged use of ITI agents and include repeated cycles of proteasome inhibitors [13]. Immune suppression due to B-cell elimination by anti-CD20 monoclonal antibody (such as rituximab) and pulmonary toxicity with methotrexate (pulmonary infiltrates, interstitial pneumonitis) are well-known side effects of these agents

Table 2
Summary of baseline laboratory and cardiac parameters prior to and through 1 year after initiating after initiation of dose-intensive ERT therapy (DIT).

Parameter	Normal Reference Range	Baseline Values (prior to initiating dose-intensive ERT therapy)	2 weeks after initiation of dose-intensive ERT therapy	1 month after initiation of dose-intensive ERT therapy	2 months after initiation of dose-intensive ERT therapy	3 months after initiation of dose-intensive ERT therapy	6 months after initiation of dose-intensive ERT therapy	9 months after initiation of dose-intensive ERT therapy	12 months after initiation of dose-intensive ERT therapy
Hex4	≤ 20 mmol/mol Cr	32.3	19.7	8.4	7.5	5.1	4.3	3.1	2.3
CK	26–192 U/L	1200	1000	460	247	162	105	117	96
ALT	0–50 U/L	59	91	62	49	38	21	24	24
AST	0–50 U/L	124	126	84	60	53	49	47	44
Anti-rhGAA ERT antibodies	Absence of anti-rhGAA ERT antibodies	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
ECHO Findings	–	Moderate left ventricular hypertrophy. End-diastolic ventricular septum thickness Z-score: +3.1. Posterior wall thickness Z-score: +3.3.	Moderate left ventricular hypertrophy. End-diastolic ventricular septum thickness Z-score: +2.9. Posterior wall thickness Z-score: +1.1.	No left ventricular hypertrophy. Normal wall thickness.	No left ventricular hypertrophy. Normal wall thickness.	–	–	–	No left ventricular hypertrophy. Normal wall thickness.

[5,19,24,42], but, importantly, have not been reported as concern in patients with IOPD. In the oncology setting, the potential toxicity of proteasome inhibitors, such as bortezomib, includes painful peripheral neuropathy, which can be irreversible in some patients [18]. Peripheral neuropathy, however, has not yet been reported as a concern with bortezomib use in the IOPD population. Cardiotoxicity, including cardiomyopathy and left ventricular dysfunction, have also been described with proteosome inhibitors [18], but not in the IOPD setting.

As described earlier in this article, immune complex deposits in the glomerular basement membrane resulting in nephrotic syndrome have been documented once in an individual with IOPD receiving high-dose ERT and who experienced persistently high anti-rhGAA antibodies [22].

5.4. Dose-intensive therapy (DIT)

In pharmacologic terms, dose intensity is defined as the amount of drug delivered per unit of time. Dose intensity can be increased in a number of ways: 1) by increasing the dose of a drug; 2) by decreasing the interval between doses (i.e., increasing the "dose density" [9] http://www.bccancer.bc.ca/pharmacy-site/Documents/Pharmacy%20FAQs/Pharmacy-FAQ-Dose-dense-vs-dose-intense.pdf; accessed 08/31024; https://www.cancer.gov/publications/dictionaries/cancer-terms/def/dose-dense-chemotherapy; accessed 08/31/24. This approach, in effect, creates a "prolonged exposure" to the antigen (Uversky et al. 2023).

A dose-intensive therapy (DIT) that involves more frequent antigen exposure, also called "prolonged exposure" to antigen, and use of higher doses of disease targeting therapy, for purposes of improved disease management and immune tolerance, has not heretofore been evaluated in IOPD, but has been broadly used in severe hemophilia. In severe hemophilia, patients are at increased risk for developing anti-drug antibodies and also stand to benefit clinically from a higher dose of disease targeted therapy in order to prevent spontaneous bleeds [4,40,45]. The dose-intensive therapy approach for hemophilia A results in the achievement of immune tolerance in 70 % of cases. The addition of intravenous immune globulin (IVIG), to this regimen is associated with an even more rapid achievement of immune tolerance and also reduced risk of transient anamnestic response (i.e., transient, rapid increase production of antibody in response to initial exposure to recombinant factor, associated with a reduced half-life of recombinant factor and delayed achievement of immune tolerance) [10,30,37,40]. Proposed mechanisms of IVIG for facilitating immune tolerance include blockage of Fc receptors on macrophages, complement absorption, enhancement of immune suppressor cells, and inhibition of lymphocyte proliferation ([1] Jan; [14,34,35]).

A dose-intensive therapy (DIT) also described in a case of a patient with Hunter syndrome [25]. A dose-intensive approach has also been described by Kim et al. [25], with reported improvement in clinical status and reduction of anti-drug antibodies through use of a dose-intensive therapy in a child diagnosed with Hunter syndrome (mucopolysaccharidosis type II) who had developed high levels of neutralizing antibodies to ERT and associated clinical decline. Dose intensity was achieved by administering twice the FDA-approved dose of ERT and also by increasing the frequency of exposure to the antigen by administering the ERT twice daily (instead of the once-weekly FDA-approved frequency)[25].

High-dose rh-GAA ERT has been shown to be well-tolerated in IOPD in previous studies. (Priya S. [29]; Jesa L. [17,32]), and was well tolerated in the first patient in this pilot study. Nephrotic syndrome has been reported in a few patients who received a dose-intensive therapies using included intravenous infusions of high-molecular weight medications. These nephrotic syndrome reports include a patient with IOPD who received ERT at 10 mg/kg for 5 days per week for 10 months and a patient with severe hemophilia B who received high dose factor IX [16,22]. In both cases the nephrotic syndrome was reversible and resolved with the discontinuation of dose -intensive therapy. The

potential for nephrotic syndrome was considered and thus monitoring urine protein was performed in this pilot study, as a precautionary measure, but no safety concerns have been observed in this regard during the subject's 7 years of DIT. Dividing the overall high dose of ERT (40 mg/kg/week) into 3 divided doses each week, was intended to mitigate risk of infusion reactions, as well as provide more prolonged exposure to the antigen to facilitate immune tolerance.

5.5. Limitations of this pilot study

Limitations of this pilot study include the following:

1) This study, to date, has enrolled only one subject, and therefore no conclusions in terms of comparative efficacy of DIT to standard of care with ERT and ITI can be made
2) The CRIM+ status of the subject in this study and her genotype that includes a missense mutation, may lower her risk of developing anti-rhGAA ERT antibodies compared to CRIM- IOPD patients. Considering this, the efficacy of the DIT therapy for IOPD in terms of clinical outcomes and mitigation of anti-rhGAA antibody formation, will be better understood if it is trialed in a larger number of IOPD patients, including patients who are CRIM-.
3) Using higher dose rhGAA ERT is more costly than using the standard FDA approved dose. The investigators were able to obtain health care insurance coverage for the DIT regimen for the subject of this study, based on the increasing number of peer-reviewed scientific medical articles showing clear and consistent evidence of improved clinical outcomes when higher doses of rhGAA ERT are used, including notable improvements in ability to ambulate and maintain ventilator-free status when a 4-fold increased dose of rhGAA ERT is used (([8,11]; P. S. [17,29]). In the United States, providing regular updates to the health care plan regarding the patient's progress while on higher dose rhGAA ERT to support the demonstration of benefits of the higher dose, is often required to maintain health care coverage for the higher dose therapy. The investigators recognize that there may be patients whose healthcare insurance does not cover a higher dose of ERT.
4) The DIT regimen involves the patient receiving rhGAA ERT 3 times weekly. The frequency of the infusions and the long duration of the infusions (initially 7 h and now weaned down to 4.5 h per infusion), represents a significant impact on patient and caregiver quality of life. Larger studies would be needed to determine if there are advantages DIT with 3 weekly doses, compared to standard bi-weekly ERT dosing and compared to standard ITI. If such advantages were identified through larger studies, then this might balance the disadvantage of more frequent infusions required with DIT. Important comparisons between these 2 therapy approaches would include ability to ambulate, maintenance of ventilator-free status, maintenance of immune tolerance to rhGAA ERT and reduced number of hospitalizations.

6. Conclusions

In summary, this case highlights the positive outcomes in a female with IOPD who received DIT, combined with early diagnosis and early initiation of therapy. Most notably, the patient achieved normal motor development at all developmental milestone time points throughout her first 7 years of life (the observation period for this study), normalized biomarkers that have been consistently maintained, and complete absence of anti-rhGAA antibody formation.

6.1. Future directions

Implementation of this regimen in additional cases will confirm the efficacy of the DIT described here. It will be important to assess the efficacy of DIT in CRIM- IOPD, as well as continue the study of DIT in CRIM+ IOPD, with the goal of validating DIT as a safe and effective alternative therapy approach for patients diagnosed with IOPD.

CRediT authorship contribution statement

Jeanine R. Jarnes: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Nishitha R. Pillai:** Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Alia Ahmed:** Writing – review & editing. **Sofia Shrestha:** Writing – review & editing, Data curation. **Molly Stark:** Writing – review & editing, Data curation. **Chester B. Whitley:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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