Genetics in Medicine (2025) 27, 101373

ELSEVIER

Genetics in Medicine
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine

ARTICLE

Efficacy of transitioning from alglucosidase alfa to avalglucosidase alfa in infantile-onset Pompe disease: A single-center cohort analysis

Yin-Hsuan Chien[1,2], Hui-An Chen[1,3,4], Rai-Hseng Hsu[1,3,4], Chien-Hua Yeh[3], Ching-Ya Fang[3], Ni-Chung Lee[1,3,4], Wuh-Liang Hwu[1,3,4,5], Yin-Hsiu Chien[1,3,4,*]

ARTICLE INFO

Article history:
Received 10 May 2024
Received in revised form
30 January 2025
Accepted 31 January 2025
Available online 7 February 2025

Keywords:
Biomarker
Cipaglucosidase alfa
Efficacy
Enzyme replacement therapy
Pompe disease

ABSTRACT

Purpose: Although alglucosidase alfa (AGL) is the standard treatment for Pompe disease, its efficacy is limited, partially because of its low mannose-6-phosphate content. Avalglucosidase alfa (AVA), a glycoengineered recombinant human acid α-glucosidase, has shown improved receptor-mediated uptake compared with AGL. Herein, we report the long-term efficacy and safety of AVA in patients with infantile-onset Pompe disease (IOPD) previously treated with AGL.

Methods: This retrospective cohort study included 9 patients with IOPD who transitioned from AGL to AVA; these patients were diagnosed and treated after being detected with IOPD via newborn screening. We analyzed the clinical status, biomarker levels (serum creatine kinase and urine glucose tetrasaccharide), and functional assessments before and after AVA treatment of these patients. Statistical analyses were performed using the Wilcoxon matched-pair signed-rank test.

Results: Due to inadequate responses, all 9 patients received AGL at dosages exceeding the label recommendations, including one who also had tried cipaglucosidase alfa plus miglustat before transitioning to AVA. After transitioning to AVA at a dosage of 40 mg/kg every other week for a median duration of 4.9 years, the patients experienced significant reductions in biomarker levels (serum creatine kinase levels decreased by 63% and urine glucose tetrasaccharide levels decreased by 69%). Functional assessments, including pulmonary function and 6-minute walk tests, showed improvement in young patients but remained stable in older patients. Safety analyses revealed manageable infusion-associated reactions. Immune modulation therapy for antidrug antibodies was administered to 1 IOPD patient.

Conclusion: The transition from a high dose of AGL to AVA demonstrated sustained improvements in biomarker levels and motor function in patients with IOPD. Early initiation of AVA is crucial for patients with IOPD.

© 2025 The Authors. Published by Elsevier Inc. on behalf of American College of Medical Genetics and Genomics. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The Article Publishing Charge (APC) for this article was paid by Yin-Hsiu Chien.

*Correspondence and requests for materials should be addressed to Yin-Hsiu Chien, Department of Medical Genetics, National Taiwan University Hospital, 8 Chung-Shan South Road, Taipei 10041, Taiwan. *Email address:* chienyh@ntu.edu.tw

Affiliations are at the end of the document.

doi: https://doi.org/10.1016/j.gim.2025.101373

1098-3600/© 2025 The Authors. Published by Elsevier Inc. on behalf of American College of Medical Genetics and Genomics. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Pompe disease, also known as type II glycogen storage disease, is a rare autosomal recessive neuromuscular disorder attributed to variants in the acid α-glucosidase (*GAA*(HGNC:4065)) gene. Deficiency of lysosomal GAA, an enzyme crucial for lysosomal glycogen breakdown, results in severe cardiac and skeletal myopathies owing to progressive glycogen accumulation.[1] Alglucosidase alfa (AGL), an enzyme replacement therapy (ERT) that utilizes recombinant human GAA (rhGAA), was approved for the treatment of Pompe disease in 2006. However, the efficacy of AGL is limited, particularly in patients with infantile-onset Pompe disease (IOPD).[2] Inadequate drug targeting of skeletal muscles may be primarily caused by the low mannose-6-phosphate (M6P) content in AGL.[3,4] Recently, avalglucosidase alfa (AVA), a glycoengineered rhGAA with increased bis-M6P (bis-M6P) levels to enhance receptor-mediated uptake,[5,6] has been approved for the treatment of Pompe disease; however, the specifics of this approval vary across different regions of the world. This approval was primarily grounded in the pivotal randomized phase 3 studies EFC14028 (COMET)[7,8] for patients with naive late-onset Pompe disease (LOPD) and the phase-2 study ACT14132 (Mini-COMET)[9] for patients with IOPD previously treated with AGL for more than 6 months. The study of treatment-naive patients with IOPD (Baby-COMET) at the time of manuscript preparation is still ongoing. Additionally, cipaglucosidase alfa (cipa) plus miglustat (mig) have been approved for treating adult patients with LOPD.[10-12]

The treatment of patients with IOPD is more challenging because these patients[13] have lower residual GAA activity and more severe phenotypes than patients with LOPD.[14] Moreover, IOPD exhibits a large variability in both clinical manifestations and responses to ERT. Previous studies have suggested that higher doses of AGL, instead of the labeled dose of 20 mg/kg every other week (eow), are necessary for better clinical outcomes in IOPD.[15,16] The mini-COMET study explored 2 dosages of 20 and 40 mg/kg/eow and demonstrated better motor function in the 40 mg/kg/eow than in the other group.[9] Consequently, the proposed AVA dosage for IOPD is 40 mg/kg/eow, which is higher than that for LOPD (20 mg/kg/eow).[9]

Given the limited evidence available, particularly regarding the efficacy of AVA in patients with IOPD in a real-world setting, this study aimed to add to the existing knowledge by analyzing the transition from AGL to AVA in a cohort of patients with IOPD predominantly identified and treated through newborn screening (NBS). By evaluating clinical outcomes, biomarker responses, and safety profiles, this analysis sought to provide insights into the effectiveness of this therapeutic transition in improving patient outcomes.

Materials and Methods

Study design

We retrospectively analyzed 9 patients with IOPD who were diagnosed and treated after being detected with the disease via NBS. All patients presented with Pompe disease-related symptoms/biochemical abnormalities from infancy. An additional patient (patient 10), who was treated with an alternative rhGAA, was also analyzed. He presented with hypotonia and muscle weakness at birth but declined Pompe disease NBS. A delay in motor milestones without cardiomegaly led to a clinical diagnosis of Pompe disease at 2.8 years of age, with ERT initiation occurring at 3.2 years of age. Therefore, he was classified as having childhood-onset Pompe disease. All patients switched to AVA for >1 year by December 31, 2023.

Data collection

Baseline data collected before and after switching to AVA included *GAA* genotype, age at symptom onset, ERT initiation and switch, ERT doses and duration, ventilatory and ambulatory status, feeding, and motor functions. Assessments were performed at baseline and at least every 3 months after switching to AVA. Biochemical data included creatine kinase (CK), urine glucose tetrasaccharide (urine Glc4 or uGlc4), and antidrug antibody (ADA) levels. Those variants of *GAA* genes were identified through Sanger sequencing. Variants were annotated using the transcript NM_000152.5. The genomic coordinates were determined based on the GRCh38 reference genome and the genomic reference sequence NC_000017.11. Urine Glc4 concentrations were determined using ultrahigh-performance liquid chromatography-tandem mass spectrometry analysis in our laboratory, as previously described.[15] Motor function was evaluated by experienced physical therapists in an age-specific manner, using E domain of gross motor function measure (GMFM-88-E), 6-minute walk test (6 MWT), and quick motor function test (QMFT). Respiratory function was measured using forced vital capacity (FVC) in the sitting and supine positions in patients aged >5 years. Safety tests, including ADA titers and complement activation, were performed by the Laboratory Corporation of America (LabCorp).

Data analysis

Descriptive statistics were used to summarize the patient characteristics and outcomes. The Wilcoxon matched-pairs signed-rank test was used to compare changes before and after switching to AVA. The Institutional Review Board of the National Taiwan University Hospital (NTUH-IRB; No. 202109154RIND; 200703045R) approved the study

protocol, and all patients provided written informed consent before enrolling in the study.

Results

Patient demographics

A total of 9 patients with IOPD, comprising 5 males and 4 females, underwent AGL treatment for durations ranging from 2.7 to 12.1 years; their demographics are outlined in Table 1. All patients were identified through our Pompe disease NBS program, leading to the early initiation of ERT at a median age of 14 days (6-33). Patients 1 to 7 were started at 20 mg/kg/eow, whereas patients 8 and 9 were started at 40 mg/kg/eow because of changes in the local dosing policy. The response to AGL in patients 1 to 9 has been previously described.[15] Additionally, immunomodulation therapy for patients 8 and 9 has been partially presented separately.[17] None of these 9 patients received preventive immune modulation therapy, including transient methotrexate, before having their first AGL. Patients 1 to 5 had participated in mini-COMET,[9] consequently experiencing a longer exposure to AVA than the other patients.

At the time of transition, 6 patients received double (1 of them receiving 2.5 times) the labeled dose of AGL, whereas the remaining 3 received 4 times the labeled dose. Their median lifelong AGL dose was 1.77-fold of the labeled dose at 20 mg/kg/eow (range 1.52-2.76-fold). Patients 1 to 4 were switched because of clinical decline, and patient 5 was switched because of a suboptimal treatment response, in accordance with the mini-COMET inclusion criteria. Patients 6 and 7 were switched because of clinical deterioration, whereas patients 8 and 9 were switched because of an inadequate treatment response supported by high levels of biomarkers. At the time of transition, 3 patients were classified as the expanded and revised Gross Motor Function Classification System (GMFCS-E&R) level 1 (normal), 3 as level 2, 2 as level 3, and 1 as level 4.

Efficacy

Patients 1 and 2 started AVA at 20 mg/kg/eow, and the dosage was escalated according to the mini-COMET's instructions to 40 mg/kg/eow at the ages of 11.8 and 11.3 years, respectively. All the other patients were administered AVA at a dosage of 40 mg/kg/eow. At the data cutoff on December 31, 2023, the 9 patients had a median exposure to AVA of 4.9 years (range, 1.5-6.1). After the transition, CK levels decreased in all patients from a baseline median level of 1118 IU/L (range, 684-1571) to the latest median level of 427 IU/L (range, 190-521; $P < .0001$), reflecting a 63% reduction (range, 41%-84%) (Figure 1A). uGlc4 levels also decreased in all patients from a baseline median level of 35.56 mmol/mol Cre (range, 116.24-86.45) to a latest median level of 11.04 mmol/mol Cre (range, 5.01-27.01; $P = .0038$), exhibiting a 69% reduction (range, 30%-90%) (Figure 1B).

At the time of data collection, none of the 9 patients required full-time or invasive ventilator support and tube feeding. Patients 3 and 6 used BiPAP for night-time hypoventilation. Pulmonary function was assessed using FVC and expressed as a percentage of prediction, which either improved or remained stable after transitioning to AVA (P for sitting and supine FVC = .7954 and .700, respectively). Patients 8 and 9 were too young at the time of transition for FVC testing; therefore, patient 8 did not have a baseline, and patient 9 had a baseline only at 2 months after transition (Table 1).

Four patients completed both the baseline and transition 6 MWT, and their performance did not change significantly. In all 9 patients, the median GMFM-88-E domain scores were 63.89% (range, 0-91.67) at baseline and 36.11% (range, 0-88.89) at the latest assessment, with a P value of .1163. The median QMFT scores of the patients were 31.5 (range, 10-46) at baseline and 21.5 (range, 11-51) at the latest assessment, with a P value of 0.183. Changes in the 16 QMFT items from baseline were further analyzed. Three patients demonstrated improvement of ≥2 points (4 points are full) in squatting (2 patients), hip and knee flexion (1 patient), and jumping (1 patient). Seven patients demonstrated an improvement of 1 point in raising the torso (2 patients), neck flexion (2 patients), hip and knee flexion (3 patients), extension of the legs (1 patient), extension of the arms (1 patient), squatting (1 patient), picking up an object (1 patient), walking 10 m (1 patient), and walking up steps (1 patient). Most of the improvements appeared within 1 year of the transition. Eight of the 9 patients remained at the same GMFCS-E&R level after the transition, and only patient 2 deteriorated from level 2 to 3. Among the 3 patients classified as level 1 at baseline, 2 were transitioned before 5 years of age and showed improvement in GMFM-88-E.

The longitudinal follow-up data for each patient are shown in Figure 2. Patient 1 showed an equivocal response in biomarker levels, such as CK and uGlc4, while on AVA at a dosage of 20 mg/kg/eow. However, a clear improvement was observed when the dosage was increased to 40 mg/kg/eow. Patient 5 transitioned to AVA at a dosage of 40 mg/kg/eow at the age of 8 years, maintaining good motor function at GMFCS-E&R level 1. After 4.9 years of AVA treatment, her motor function remained stable at GMFCS-E&R level 1. Patient 6, who switched from AGL to AVA at the highest dose of 40 mg/kg/week at the age of 9.9 years, experienced a further decrease in biomarker levels; however, her motor function continued to decline.

Safety consideration

All patients received antihistamines as premedication for AVA; however, none received premedication during their last dose of AGL, and none experienced infusion-associated reactions (IARs) while on AGL. We followed an escalating

Table 1 Efficacy of AGL and avaglucosidase AVA in 10 children with Pompe disease

No	Sex	*GAA* Variant–2[a]	ACMG/AMP Classification	Age at 1st AGL	Dose of Last AGL	Lifelong AGL Dose Fold (X)	Age at 1st AVA (y)[d]	AVA Exposure (y)	Current Age (y)	Current Motor Status	Conditions at Transition to AVA				Conditions at Last Assessment				Current ADA Titers	ID
											FVC	MWT	GM	QMFT	FVC	MWT	GM	QMFT		
1	M	c.784G>A p.(Glu262Lys) g.80107648G>A	Pathogenic (PM1, PM2, PM3, PP2, PP3, PP4)	17 d	20 qw	1.62	10.8 (11.8)	6.1	16.9	Difficult in climbing	65/56	300.0	65.28	30	64/48	255.0	55.56	29	Neg	6
2	M	c.1062C>G[b] p.(Tyr354Ter)[b] g.80108396C>G[b]	Pathogenic (PM2, PM3, PVS1)	12 d	20 qw	1.52	10.3 (11.3)	5.8	16.1	Difficult in independent walking	32/17	344.0	55.56	33	29/17	-	9.72	13	Neg	8
3	M	c.2841dup p.(Leu948SerfsTer70) g.80119313dup	Pathogenic (PM3 PM2 PVS1)	29 d	40 eow	1.59	11.9	5.7	17.6	Wheel-chair dependent	26/17	-	0	10	15/15	-	0	11	Neg	4
4	M	c.1935C>A[c] p.(Asp645Glu)[c] g.80112922C>A[c]	Pathogenic (PM1, PM2, PM3, PM5, PP2, PP3, PP4, PS3)	14 d	20 qw	1.65	7.2	5.6	12.8	Independent walker	50/42	315.8	63.89	37	38/30	392.5	36.11	26	Neg	10
5	F	c.1935C>A[c] p.(Asp645Glu)[c] g.80112922C>A[c]	Pathogenic (PM1, PM2, PM3, PM5, PP2, PP3, PP4, PS3)	6 d	25 qw	1.77	8.0	4.9	12.9	Independent walker	52/43	397.6	91.67	46	71/57	390.0	87.5	48	200	17
6	F	c.1199_1210del p.(Val400_Asn403del) g.80108701_80108712del	Likely Pathogenic (PM2, PM3, PM4)	16 d	40 qw	2.19	9.9	2.5	12.4	Difficult in independent walking	16/18	-	38.89	19	17/13	-	16.67	11	Neg	11
7	F	c.1199_1210del p.(Val400_Asn403del) g.80108701_80108712del	Likely Pathogenic (PM2, PM3, PM4)	14 d	40 qw	2.04	12.1	2.6	14.7	Difficult in independent walking	48/-	-	34.72	19	23/25	-	16.67	17	Neg	9
8	M	c.1935C>A[c] p.(Asp645Glu)[c] g.80112922C>A[c]	Pathogenic (PM1, PM2, PM3, PM5, PP2, PP3, PP4, PS3)	33 d	40 eow	1.93	2.8	2.5	5.3	Independent walker	-	-	73.61	-	56/70	-	88.89	-	12, 800	27, B4
9	F	c.2024_2026del p.(Asn675del) g.80113011_80113013del	Pathogenic (PM1, PM2, PM3, PM4, PS3)	8 d	40 qw	2.76	4.7	1.5	6.2	Independent walker	67/50[e]	300.0	72.22	43	68/69	343.0	87.5	51	1600	26, B2
10	M	c.1781G>A p.(Arg594His) g.80112604G>A	Likely Pathogenic (PM1, PM2, PM3, PM5, PP2, PP3, PP4, PS3)	38 m	20 qw	1.00	14.7	1.1	15.8	Difficult in independent walking	58/45	186.0	15.28	25	54/48	157.4	8.33	18	12, 800	A2

-, not tested; *ACMG*, the American College of Medical Genetics and Genomics; *ADA*, antidrug antibody; *AGL*, alglucosidase alfa, dose expressed as mg/kg; *AMP*, the Association for Molecular Pathology; *AVA*, avalglucosidase alfa; *eow*, every other week; *F*, female; *FVC*, forced vital capacity, expressed as a percentage of the prediction of the sitting/supine position; *GM*, E domain of gross motor function measure-88, expressed as scores in percentage; *ID*, previous patient No, as revealed in our previous publications[15,17]; *M*, male; *MWT*, 6-minute walk test, expressed as meters; *Neg*, negative; *QMFT*, quick motor function test; *qw*, every week.

[a]All patients had 1 allele as c.[1935C>A;1726G>A] g.[80112922C>A;80112072G>A] p.[(Asp645Glu; Gly576Ser)] in the *GAA* gene, annotated using the transcript NM_000152.5. The genomic coordinates were determined based on the GRCh38 reference genome and the genomic reference sequence NC_000017.11.

[b]The allele is present in cis with c.1286A>G p.(Gln429Arg) g.80108788A>G.

[c]These alleles are present in cis with c.1726G>A p.(Gly576Ser) g.80112072G>A.

[d]Patients 1 and 2 were initially on AVA 20 mg/kg/eow, and the dosage was increased to 40 mg/kg/eow at ages 11.8 and 11.3 years, respectively.

[e]Two months after transition.

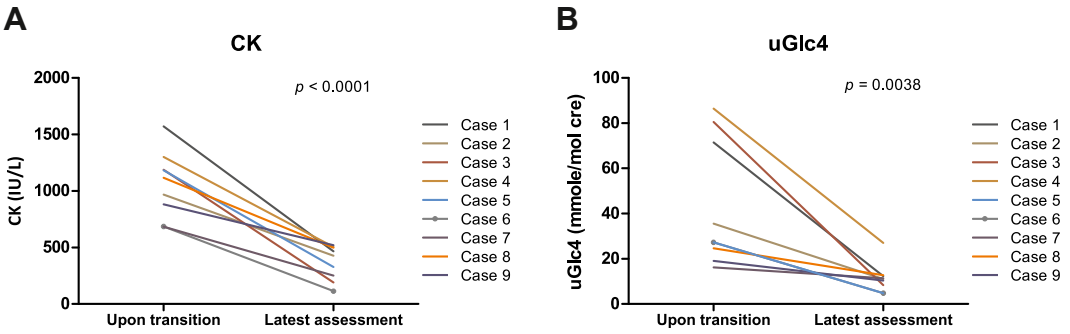

Figure 1 Decrease in biomarker levels upon transitioning from alglucosidase alfa to avalglucosidase alfa. A. CK levels during transition and at the latest assessment. The levels decreased in all patients. B. uGlc4 levels during transition and at the latest assessment. The levels decreased in all patients. CK, creatine kinase; uGlc4, urine glucose tetrasaccharide.

infusion rate protocol according to the AVA pharmacy manual. Patient 3 developed recurrent urticaria during infusions, requiring the addition of corticosteroids in the premedication 1 day before each infusion. Although his urticaria initially improved, it recurred 22 months after starting the AVA. Despite negative ADA results, complement activation was observed. To address his IARs, we extended his infusion time from 5 to 9 hours, split the dosage to 20 mg/kg/week for 3 months, administered antihistamines throughout the infusion for 4 years, included corticosteroids in the premedication 2 days before infusion for 4 years, and used Montelukast Sodium to stabilize mast cells for 20 months. No IARs occurred 6 months after the implementation of these management strategies. Currently, he continues premedication with corticosteroids and antihistamines, 1 dose each just before receiving 40 mg/kg/eow of AVA for a 6.5-hour infusion each time. Two other patients (patients 2 and 4) experienced mild skin reactions on several occasions, which were managed with corticosteroid and antihistamine premedication for several months before transitioning to antihistamines only. There were no IgG ADAs in these 2 cases, although IgE ADAs were not measured.

Patients 6 and 7 received very high AGL doses. Patient 6 was on AGL 40 mg/kg/week for 1.5 years and experienced persistent microalbuminuria (albumin/creatinine dipstick: 80 mg/g, normal <30) and proteinuria (protein dipstick: 100 mg/dL). Patient 7 received AGL 40 mg/kg/week for 1 year and had microalbuminuria (dipstick: 80 mg/g) on 2 occasions. Although no biopsy was performed, routine nephrology workups revealed no specific etiologies. After transitioning to AVA, the 2 patients no longer experienced proteinuria or microalbuminuria. Serum CK and uGlc4 levels normalized. They both reported improvements in muscle power, endurance, facial expression, and increased engagement in daily activities 6 months after AVA.

Persistence of ADA to rhGAA

Patient 8 exhibited sustained high titers of ADA to AGL (titers up to 12,800-51,200) and an inadequate treatment response.[17] After successfully undergoing immune modulation therapy to eliminate ADA in AGL, Patient 8 transitioned to AVA and experienced a resurgence of ADA, with titers ranging from 3200 to 12,800 15 months after AVA exposure. Consequently, another round of immune modulation therapy is ongoing for patient 8. Patients 1 to 7 had low or negative ADA titers (Table 1).

Experience with an alternative rhGAA

Patient 9, after immune modulation therapy, was switched from AGL 40 mg/kg/week to cipa/mig 20 mg/kg/eow because of an inadequate treatment response at ages of 3 years (Figure 3). Because the patient reported frequent falls and reduced physical activity after switching, the infusion frequency was increased from eow to weekly, starting from week 13. However, fluctuations in physical activity, which were particularly noticeable 1 day before the next infusion, still occurred. Consequently, the cipa dosage, as guided by the pharmacokinetic results and modeling predictions, was increased to 25 mg/kg/week and eventually to 30 mg/kg/week starting from 8 months on cipa/mig. This led to physician-reported improvements in muscle strength and reduced ptosis. Furthermore, as shown in Figure 3, the GMFM-88-E domain score increased from 59.7% to 72.22% between the initial and final assessments, along with the target dose of cipa/mig. After 1.7 years on cipa/mig, owing to persistently high serum CK and uGlc4 levels, the patient was switched to AVA at a dose of 40 mg/kg/eow at the age of 4.7 years, and gross motor function further improved. The patient's cardiac condition remained stable throughout the study period.

Patient 10 was previously described as having high ADA levels, inadequate treatment response, and immune modulation therapy.[17] After successfully undergoing immune modulation therapy to eliminate ADA to AGL, he transitioned to cipa/mig 20 mg/kg/eow and reported an improvement in standing up and endurance after switching from AGL to cipa/mig. Despite a baseline 6 MWT of only 123 meters, his muscle power and function increased, particularly in the upper limbs. Additionally, increased

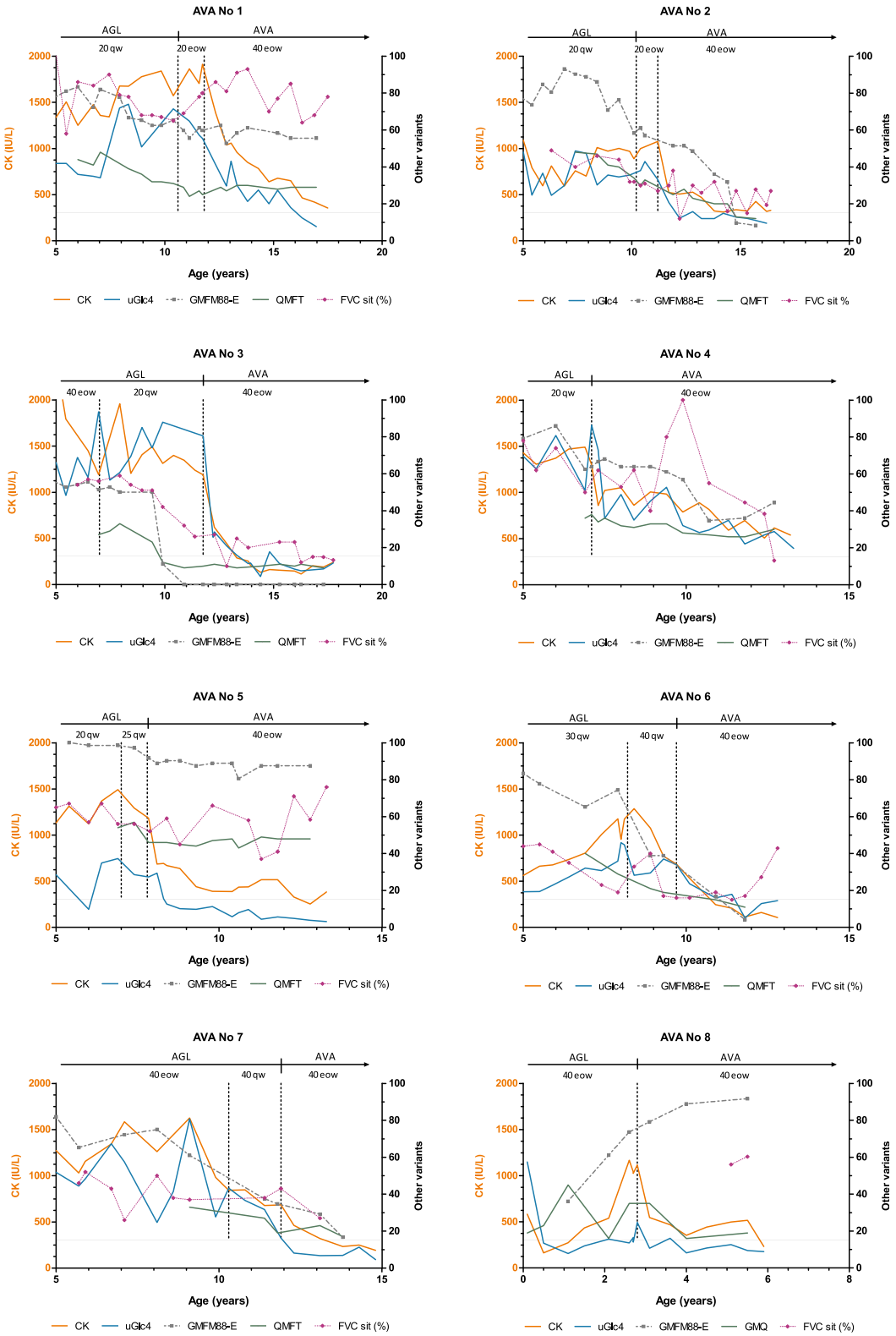

Figure 2 Longitudinal follow up of 8 patients transitioning from AGL to AVA in this study. The *x*-axis represents age in years. Serum creatine kinase levels are plotted against the left *y*-axis, whereas other markers (uGlc4 level, GMFM-88-E score as a percentage, quick motor function test score, and forced vital capacity in the sitting position as a percentage) are plotted against the right *y*-axis. uGlc4 is denoted as mmol/mol Cre. AGL, alglucosidase alfa, dose expressed as mg/kg; AVA, avalglucosidase alfa; Cre, creatine; eow, every other week; FVC, forced vital capacity; GMFM-88-E, E domain of gross motor function measure-88; QMFT, quick motor function test; qw, every week; uGlc4, urine glucose tetrasaccharide.

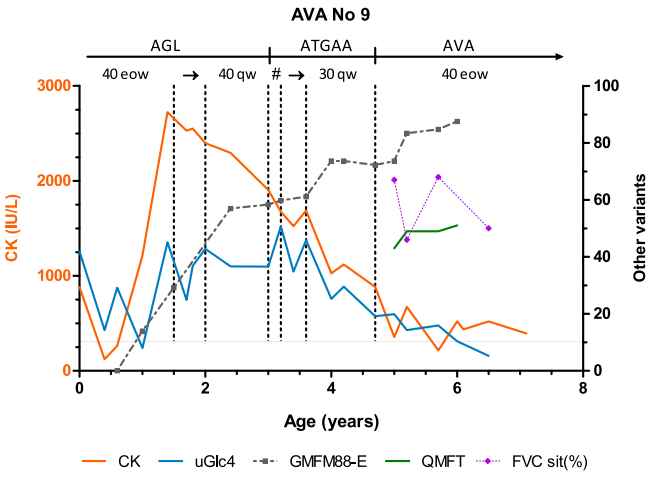

Figure 3 Changes in serum CK and uGlc4 levels and gross motor functions during different enzyme replacement therapies in patient 9. The patient initially received AGL at a dosage of 40 mg/kg/week, followed by a transition to cipa/mig up to 30 mg/kg/week for a duration of 1.7 years, and subsequently switched to AVA at a dosage of 40 mg/kg/eow. The *x*-axis represents the age in years. Serum CK levels are depicted against the left *y*-axis, whereas other markers (uGlc4 level, E domain of gross motor function measure-88 [GMFM-88-E] score as a percentage, quick motor function test [QMFT] score and forced vital capacity [FVC] in the sitting position FVC as a percentile) are plotted against the right *y*-axis. uGlc4 is denoted as mmol/mol Cre. This figure illustrates the biochemical and functional improvements in the patient after transitioning to AVA. AGL, alglucosidase alfa, dose expressed as mg/kg; ATGAA, cipaglucosidase alfa (cipa) plus miglustat (mig); AVA, avalglucosidase alfa; #: ATGAA at 20 mg/kg/eow; CK, creatine kinase; Cre, creatine; eow, every other week; qw, every week; uGlc4, urine glucose tetrasaccharide.

engagement in outdoor activities, such as cycling, has been reported. After receiving cipa/mig for 6.5 years, he decided to switch to AVA on the market at a dosage of 40 mg/kg/eow at the age of 14.7, aiming for further improvement with a new ERT. His CK level decreased by 45% (from 1471 to 813 IU/L) after switching to cipa/mig. There was no change in the uGlc4 levels. After switching from cipa/mig to AVA for 1.1 years, he exhibited a further 28% decrease in CK levels but no change in uGlc4 levels. After the transition to AVA, the patient experienced a resurgence of ADA, with titers ranging from 12,800 to 51,200, 5 months after AVA exposure. Consequently, another round of immune modulation therapy was administered to patient 10. Neither patient reported side effects to cipa/mig.

Discussion

This study provides insights for up to 6.5 years of experience with AVA in a cohort of patients with IOPD who were treated with AGL shortly after birth. Our findings revealed sustained improvements in biomarker levels and improvements or maintenance of clinical function by AVA over this extended period, even in patients who received a high AGL dosage of 40 mg/kg/week before switching to AVA 40/mg/eow. Additionally, we highlight the challenges and complexities associated with managing IOPD and optimizing treatment strategies.

In this study, AVA demonstrated superior efficacy compared with AGL in reducing the levels of Pompe disease-related biomarker levels. This finding aligns with the finding from the COMET study, a trial aimed at understanding the response of patients with LOPD treated with AVA. In patients with IOPD, given the severe nature of IOPD, despite initially prescribing the recommended AGL dosage of 20 mg/kg/eow in 81% of patients, over half (51.8%) ultimately required higher dosages, with some individuals receiving up to 4-fold of the labeled dosage (40 mg/kg/week).[16] However, a higher dose of AGL, especially in patients with ADA, may lead to risks such as proteinuria or trigger a stronger immune reaction. In our study, AVA at 40 mg/kg/eow led to a rapid and sustained decrease in serum CK and uGlc4 levels, even in patients treated with AGL at 40 mg/kg/week, indicating better elimination of accumulated glycogen, in line with the enhanced uptake efficacy associated with this new generation of rhGAA.

Cellular uptake is a critical step for ERT with rhGAA, primarily mediated by the cation-independent M6P receptor.[18,19] Given the low M6P receptor expression in skeletal muscles,[20] which accumulate high levels of glycogen, it is vital for rhGAA to have sufficient M6P, preferably bis-M6P, to ensure high-affinity uptake through the M6P receptor.[18] However, the M6P content in AGL varies between batches, ranging from 0.7 to 1.2 mol of M6P/mol of rhGAA,[6,21,22] resulting in only up to 27% of AGL binding to an M6P-containing column.[2] Additionally, the proportion of bis-M6P in AGL is only 1% or less.[3] The loss of therapeutic efficacy is only partially compensated by increasing the dose. AVA has been enhanced by chemically conjugating the 7 N-linked glycosylation sites on GAA, yielding approximately a 70-fold increase in bis-M6P and a 15-fold increase in total M6P content compared with AGL.[23] Initial preclinical studies with AVA demonstrated improved delivery to muscles, enhanced clearance of muscle glycogen, and improved motor function of Pompe mice.[4-6] Although factors such as decreased M6P receptor density in aged cells,[2] defective autophagy,[24] and altered lysosomal processing of exogenous enzyme[1] may compromise the treatment effect of AVA in patients, our results demonstrate the excellent efficacy of AVA in patients with severe Pompe disease.

Our study also highlights the heterogeneity in treatment response among patients with IOPD, as evidenced by the varied outcomes observed after the switch to different ERTs. Clinical improvements, objectively assessed using the QMFT and GMFM-88-E, were obvious in young patients and patients with good baseline motor function. For the other patients, there were still some positive responses in variable motor functions, such as squatting and hip and knee flexion, followed by raising the torso and neck flexion. Although a decrease in serum CK levels indicates less

muscle damage, a direct link between biomarker levels and clinical outcomes has not yet been established. We hypothesized that an earlier initiation of AVA may be associated with a better treatment response to biomarkers and better outcomes. For instance, uGlc4 levels normalized more quickly in patient 5 compared with patient 6, who experienced a continued decline in GMFM-88-E domain scores and FVC, ultimately necessitating the use of a 4-legged walker by the end of the study. Therefore, early initiation of AVA is crucial both in naive patients and when switching therapies. The ongoing Baby-COMET trial (NCT04910776) in treatment-naive patients with IOPD should offer further insights into the prevention of muscle damage in patients with IOPD. Efforts to further optimize rhGAA processing[25] and uptake[26] are also underway.

ADA in patients treated with either AGL or AVA may still be challenging, as demonstrated in our patients. Although we modulated the immune response to the original AGL, the introduction of AVA led to high ADA titers, possibly because of cross-reactive memory or other factors that led to an escape from immune tolerance. Continuous postswitch monitoring of ADA status is essential for patients transitioning from AGL to ACA. Additionally, ongoing immune modulation therapy may be necessary even after the transition.

The consecutive use of 2 different generations of rhGAAs in our 2 patients, 9 and 10, accentuated the heterogeneity of Pompe disease, especially in terms of treatment response. Despite both patients displaying symptoms from infancy, the individual lacking cardiomyopathy at birth (patient 10) responded well in motor function to the planned dosage of cipa at 20 mg/kg/eow, whereas the other patient required a higher dose of 30 mg/kg/week to address the muscular aspects. Notably, the biomarker responses after transitioning to cipa/mig varied between patients. Large-scale clinical trials are imperative to further elucidate these observations and aid the decision-making process regarding diverse formulations of ERT.

Despite its strengths, this study has a few limitations. The retrospective nature of the analysis and small sample size limit the generalizability of our findings. Furthermore, the lack of a control group makes it challenging to draw definitive conclusions regarding the comparative efficacy and safety of AVA and alternative therapeutic approaches. Additionally, we did not evaluate other domains of Pompe disease manifestations such as ptosis, hearing, white matter changes, or cognitive function. Further studies are necessary to underscore personalized and tailored treatment approaches that consider individual patient characteristics and disease severity.

Summary

Thus, this patient cohort underscores the superiority of AVA over AGL in reducing biomarker levels, with potential positive effects on motor outcomes. However, both drugs cause ADA-related adverse events, and cross-reactions are likely to occur. This study emphasizes the critical importance of early treatment initiation for IOPD with AVA; however, the complete eradication of motor symptoms through immediate post-NBS initiation remains uncertain. Further research and long-term large-scale monitoring are needed to elucidate the comparative efficacy, safety, and optimal timing of AVA treatment initiation in patients with IOPD.

Data Availability

The data collected for the study, including individual participant data and a data dictionary defining each field in the data set, will be made available to others upon request.

Acknowledgments

The authors extend their gratitude to Sanofi for providing expanded access to avaglucosidase alfa and Amicus Therapeutics for cipaglucosidase alfa/miglustat for the patients. Additionally, the authors express their profound thanks to all patients and their families for their invaluable participation and consent to participate in this observational study.

Funding

Sanofi/Genzyme partially sponsored this observational study (SGZ-2022-13798). The study sponsor was not involved in the (1) design of the study; (2) collection, analysis, and interpretation of data; (3) writing of the report; and (4) decision to submit the manuscript for publication. Yin-Hsuan Chien wrote the first draft of the manuscript. None of the authors received an honorarium, grant, or other form of payment to produce this manuscript.

Author Contributions

Conceptualization: Yin-Hsiu Chien; Data Curation: Yin-Hsuan Chien, C.H.Y., C.Y.F.; Formal Analysis: Yin-Hsiu Chien; Investigation: H.A.C., R.H.H., N.C.L., Yin-Hsiu Chien; Supervision: Yin-Hsiu Chien, W.L.H.; Resources: Yin-Hsiu Chien; Visualization: Yin-Hsuan Chien, H.A.C.; Writing-original draft: Yin-Hsuan Chien; Writing-review and editing: Yin-Hsiu Chien, W.L.H.

Ethics Declaration

This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice. The study protocol was reviewed and approved by the National

Taiwan University Hospital Institutional Review Board (NTUH-IRB; Nos. 202109154RIND and 200703045R). Written informed consent was obtained from the individuals or their legal guardians before any study-related procedures.

Conflict of Interest

Yin-Hsiu Chien has served on advisory boards for Amicus Therapeutics and Sanofi Genzyme, undertaken contracted research for Sanofi Genzyme, and received honoraria, consulting fees, and travel expenses from Sanofi Genzyme. Wuh-Liang Hwu has served on advisory boards for Sanofi Genzyme, and received honoraria, consulting fees, and travel expenses from Sanofi Genzyme. Ni-Chung Lee has served on registry advisory boards for Sanofi Genzyme and received honoraria and travel expenses from them. All other authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Openai.com/ChatGPT3.5 to improve the language. After using this tool/service, the authors reviewed and edited the content as required and take full responsibility of the manuscript content.

Affiliations

[1]Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Pediatrics, Taipei City Hospital, Zhong-Xing Branch, Taipei, Taiwan; [3]Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan; [4]Department of Pediatrics, National Taiwan University College of Medicine, Taipei, Taiwan; [5]Center for Precision Medicine, China Medical University Hospital, Taichung, Taiwan

References

1. Meena NK, Raben N. Pompe disease: new developments in an old lysosomal storage disorder. *Biomolecules*. 2020;10(9):1339. http://doi.org/10.3390/biom10091339
2. Do HV, Khanna R, Gotschall R. Challenges in treating Pompe disease: an industry perspective. *Ann Transl Med*. 2019;7(13):291. http://doi.org/10.21037/atm.2019.04.15
3. Park H, Kim J, Lee YK, et al. Four unreported types of glycans containing mannose-6-phosphate are heterogeneously attached at three sites (including newly found Asn 233) to recombinant human acid alpha-glucosidase that is the only approved treatment for Pompe disease. *Biochem Biophys Res Commun*. 2018;495(4):2418-2424. http://doi.org/10.1016/j.bbrc.2017.12.101
4. Zhu Y, Li X, Kyazike J, et al. Conjugation of mannose 6-phosphate-containing oligosaccharides to acid α-glucosidase improves the clearance of glycogen in Pompe mice. *J Biol Chem*. 2004;279(48):50336-50341. http://doi.org/10.1074/jbc.M409676200
5. Zhu Y, Jiang JL, Gumlaw NK, et al. Glycoengineered acid alpha-glucosidase with improved efficacy at correcting the metabolic aberrations and motor function deficits in a mouse model of Pompe disease. *Mol Ther*. 2009;17(6):954-963. http://doi.org/10.1038/mt.2009.37
6. Zhu Y, Li X, McVie-Wylie A, et al. Carbohydrate-remodelled acid alpha-glucosidase with higher affinity for the cation-independent mannose 6-phosphate receptor demonstrates improved delivery to muscles of Pompe mice. *Biochem J*. 2005;389(3):619-628. http://doi.org/10.1042/BJ20050364
7. Kishnani PS, Diaz-Manera J, Toscano A, et al. Efficacy and safety of avalglucosidase Alfa in patients with late-onset Pompe disease after 97 weeks: a phase 3 randomized clinical trial. *JAMA Neurol*. 2023;80(6):558-567. http://doi.org/10.1001/jamaneurol.2023.0552
8. Diaz-Manera J, Kishnani PS, Kushlaf H, et al. Safety and efficacy of avalglucosidase alfa versus alglucosidase alfa in patients with late-onset Pompe disease (COMET): a phase 3, randomised, multicentre trial. *Lancet Neurol*. 2021;20(12):1012-1026. http://doi.org/10.1016/S1474-4422(21)00241-6
9. Kishnani PS, Kronn D, Brassier A, et al. Safety and efficacy of avalglucosidase alfa in individuals with infantile-onset Pompe disease enrolled in the phase 2, open-label Mini-COMET study: the 6-month primary analysis report. *Genet Med*. 2023;25(2):100328. http://doi.org/10.1016/j.gim.2022.10.010
10. Blair HA. Cipaglucosidase Alfa: first approval. *Drugs*. 2023;83(8):739-745. http://doi.org/10.1007/s40265-023-01886-5
11. Byrne BJ, Schoser B, Kishnani PS, et al. Long-term safety and efficacy of cipaglucosidase alfa plus miglustat in individuals living with Pompe disease: an open-label phase I/II study (ATB200-02). *J Neurol*. 2024;271(4):1787-1801. http://doi.org/10.1007/s00415-023-12096-0
12. Schoser B, Roberts M, Byrne BJ, et al. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial. *Lancet Neurol*. 2021;20(12):1027-1037. http://doi.org/10.1016/S1474-4422(21)00331-8
13. van Capelle CI, van der Meijden JC, van den Hout JM, et al. Childhood Pompe disease: clinical spectrum and genotype in 31 patients. *Orphanet J Rare Dis*. 2016;11(1):65. http://doi.org/10.1186/s13023-016-0442-y
14. Taverna S, Cammarata G, Colomba P, et al. Pompe disease: pathogenesis, molecular genetics and diagnosis. *Aging (Albany NY)*. 2020;12(15):15856-15874. http://doi.org/10.18632/aging.103794
15. Chien YH, Tsai WH, Chang CL, et al. Earlier and higher dosing of alglucosidase alfa improve outcomes in patients with infantile-onset Pompe disease: evidence from real-world experiences. *Mol Genet Metab Rep*. 2020;23:100591. http://doi.org/10.1016/j.ymgmr.2020.100591
16. Kishnani PS, Kronn D, Suwazono S, et al. Higher dose alglucosidase alfa is associated with improved overall survival in infantile-onset Pompe disease (IOPD): data from the Pompe Registry. *Orphanet J Rare Dis*. 2023;18(1):381. http://doi.org/10.1186/s13023-023-02981-2
17. Chen HA, Hsu RH, Fang CY, et al. Optimizing treatment outcomes: immune tolerance induction in Pompe disease patients undergoing enzyme replacement therapy. *Front Immunol*. 2024;15:1336599. http://doi.org/10.3389/fimmu.2024.1336599
18. Tong PY, Gregory W, Kornfeld S. Ligand interactions of the cation-independent mannose 6-phosphate receptor. The stoichiometry of mannose 6-phosphate binding. *J Biol Chem*. 1989;264(14):7962-7969. http://doi.org/10.1016/S0021-9258(18)83136-2
19. Reuser AJ, Kroos MA, Ponne NJ, et al. Uptake and stability of human and bovine acid alpha-glucosidase in cultured fibroblasts and skeletal muscle cells from glycogenosis type II patients. *Exp Cell Res*. 1984;155(1):178-189. http://doi.org/10.1016/0014-4827(84)90779-1
20. Kohler L, Puertollano R, Raben N. Pompe disease: from basic science to therapy. *Neurotherapeutics*. 2018;15(4):928-942. http://doi.org/10.1007/s13311-018-0655-y

21. Togawa T, Takada M, Aizawa Y, Tsukimura T, Chiba Y, Sakuraba H. Comparative study on mannose 6-phosphate residue contents of recombinant lysosomal enzymes. *Mol Genet Metab*. 2014;111(3):369-373. http://doi.org/10.1016/j.ymgme.2013.12.296
22. McVie-Wylie AJ, Lee KL, Qiu H, et al. Biochemical and pharmacological characterization of different recombinant acid alpha-glucosidase preparations evaluated for the treatment of Pompe disease. *Mol Genet Metab*. 2008;94(4):448-455. http://doi.org/10.1016/j.ymgme.2008.04.009
23. Kishnani PS, Chien YH, Berger KI, Thibault N, Sparks S. Clinical insight meets scientific innovation to develop a next generation ERT for Pompe disease. *Mol Genet Metab*. 2024;143(1-2):108559. http://doi.org/10.1016/j.ymgme.2024.108559
24. Raben N, Wong A, Ralston E, Myerowitz R. Autophagy and mitochondria in Pompe disease: nothing is so new as what has long been forgotten. *Am J Med Genet C Semin Med Genet*. 2012;160C(1):13-21. http://doi.org/10.1002/ajmg.c.31317
25. Selvan N, Mehta N, Venkateswaran S, et al. Endolysosomal N-glycan processing is critical to attain the most active form of the enzyme acid alpha-glucosidase. *J Biol Chem*. 2021;296:100769. http://doi.org/10.1016/j.jbc.2021.100769
26. Liu L, Lee WS, Doray B, Kornfeld S. Engineering of GlcNAc-1-Phosphotransferase for production of highly phosphorylated lysosomal enzymes for enzyme replacement therapy. *Mol Ther Methods Clin Dev*. 2017;5:59-65. http://doi.org/10.1016/j.omtm.2017.03.006