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Enzyme replacement therapy for children with acid sphingomyelinase deficiency in the real world: A single center experience in Taiwan

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ABSTRACT

Background: Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disease with multi-systemic involvement, with no disease-modifying treatment available. Olipudase alfa is an investigational enzyme product developed to replace the deficient acid sphingomyelinase in ASMD patients. Several clinical trials have reported promising safety and efficacy results in adult and pediatric patients. However, no data have been reported outside of the clinical trial setting yet. This study aimed to evaluate major outcomes in pediatric chronic ASMD patients receiving olipudase alfa in the real-world setting.

Materials and methods: Two children with type A/B (chronic neuropathic) ASMD have received olipudase alfa treatment since May 2021. Clinical parameters, including height, weight, complete blood count, liver function tests, lipid profiles, biomarkers, abdominal ultrasonography with shear wave elastography, chest computed tomography, nerve conduction studies, neurodevelopmental evaluations, and six-minute walk tests, were checked at baseline and every three to six months in the first year of enzyme replacement therapy (ERT) to assess its efficacy and safety.

Results: The two patients in our study started olipudase alfa treatment at the age of 5 years and 8 months and 2 years and 6 months. During the first year of treatment, both patients saw a reduction in their hepatic and splenic volumes as well as liver stiffness. Height z-score, weight z-score, lipid profiles, biomarker levels, interstitial lung disease scores, and bone mineral densities also improved over time. The six-minute walk test showed a gradual increase in walking distance in both patients. There were no obvious improvements or deterioration in neurocognitive function and peripheral nerve conduction velocities after treatment. No severe infusion-associated reactions were noted during the first year of treatment. One patient had two episodes of transient but significantly elevated liver enzymes during the dose-escalation phase. The patient was asymptomatic, and the impaired liver function resolved spontaneously within two weeks.

Conclusion: Our results provide real-world experience that olipudase alfa is safe and effective in improving major systemic clinical outcomes for pediatric chronic ASMD patients. Monitoring of liver stiffness by shear wave elastography is a noninvasive procedure that can monitor treatment efficacy during ERT.

1. Introduction

Acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick disease type A, A/B, and B, is a rare lysosomal storage disease caused by bi-allelic mutations in the *SMPD1* gene, which encodes for acid-sphingomyelinase (ASM), an enzyme responsible for the breakdown of sphingomyelin. The resulting decreased enzyme activity leads to an accumulation of sphingomyelin in multiple major organs. The typical presentation in children includes hepatosplenomegaly, interstitial lung disease, cytopenia, dyslipidemia, and growth failure with or without neurological deficits. There is a broad spectrum of clinical severity, ranging from the most rapidly-progressing

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neurodegenerative infantile neurovisceral ASMD (Niemann-Pick disease type A) to chronic neurovisceral ASMD (Niemann-Pick disease type A/B) and chronic visceral ASMD (Niemann-Pick disease type B) without neurologic involvement [1,2]. While children with infantile neurovisceral ASMD have a uniform disease course with early, typically before age 1 year, and rapidly-progressing neurodegeneration, children with chronic neurovisceral ASMD present slower but variable onsets and degrees of neurological involvement [1]. It may be difficult to differentiate the more severe end of chronic neurovisceral cases from infantile neurovisceral cases at initial evaluations since they both present apparent developmental delays in early childhood. Nevertheless, several previous mutational analyses have provided important genotype-phenotype correlations regarding the type of ASMD. For example, the presence of *SMPD1* mutations of R496L, L302P, and P330fs*52 predicts a infantile neurovisceral phenotype in the Ashkenazi Jewish community [3].

The estimated incidence of ASMD is around 0.4 to 0.6 per 100,000 births worldwide [4]. However, the exact prevalence and incidence of ASMD is still unknown and may be underestimated. In spite of its rarity, ASMD causes tremendous physiological and psychological burden for patients and their caregivers. In the past, because there has been no available disease-modifying treatment, the management of ASMD has generally been restricted to symptom relief and supportive care [3,5]. The human recombinant enzyme, olipudase alfa, was designed to replace the deficient ASM in ASMD patients. To date, three ongoing clinical trials investigating the safety and efficacy of olipudase alfa have demonstrated promising short- and long-term results, both in adults and pediatric patients [6–8]. However, there is little published information outside of the clinical trial setting. Here, we present two unrelated pediatric ASMD cases, both diagnosed in a medical center in southern Taiwan and receiving olipudase alfa as compassionate therapy since May 2021. The real-world treatment experience and the one-year results after ERT are presented. Conducting a clinical trial for a rare disease like ASMD can be challenging due to the small numbers of patients eligible to participate. The results generated from such a small trial do not provide as much evidence as a larger trial would [9]. In these cases, real-world data provide supportive evidence for appropriate use. Real-world data has also been used to support regulatory decisions for certain rare diseases [10]. In our study, the data, including the timing of collection, for outcome measures were generally in concordance with the protocols provided in clinical trials. However, in this real-world setting, we pursued a more practical way to measure outcomes that does not expose the patient to radiation, is non-invasive, and does not come with the risks of anesthesia, so the families are more willing to receive regular long-term monitoring.

2. Materials and methods

2.1. Patients and enzyme replacement therapy

Two unrelated pediatric patients were diagnosed with ASMD at National Cheng-Kung University Hospital in 2018 and 2020. The patients characteristics are listed in Table 1. Patient 1 (P1) was diagnosed with ASMD at the age of 3 years and 2 months and patient 2 (P2) at 1 year and 11 months. Both patients had chronic neurovisceral ASMD (type A/B), based on their clinical course and genotype information, and were therefore eligible for ERT. In both patients, bi-weekly enzyme administration of olipudase alfa as compassionate use has been given since May 2021, when P1 was 5 years and 8 months old and P2 was 2 years and 6 months old. Olipudase alfa was initiated at 0.03 mg/kg and titrated to 3 mg/kg. Based on the high incidence of mild infusion-related reactions (IAR) in the pediatric cohort in one clinical trial, both patients were premedicated with intravenous antihistamines and steroids. The clinical trial reported 102 treatment-related IARs in 20 pediatric patients during the first year of treatment, but 88% (90/102) were mild [6]. Since olipudase alfa can be associated with transient elevation of liver enzymes during dose escalation, liver function tests, including Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total bilirubin, and direct bilirubin, were taken before and 48 hours after injection in this phase [6]. Treatment-related adverse events (AEs), including IAR, such as hypersensitivity or acute phase reactions, and impaired liver function were recorded and classified as mild, moderate, and severe according to the administration protocol of olipudase alfa. A dose de-escalation or discontinuation was considered if moderate or severe AE occurred. Since anti-drug antibodies IgG and IgE have been associated with IAR, [6] they were checked every three months as well as when severe IAR developed. This study was approved by the Ethics Committee of National Cheng-Kung University Hospital (approval number: B-ER-111-182). Informed consents were obtained from the legal guardians of the patients.

2.2. Clinical and laboratory assessments

Every 12 weeks, height and weight z-scores were recorded based on Taiwanese growth standards [11]. Blood samples were drawn for complete blood count (CBC), liver function tests, lipid profiles, and biomarkers. Lyso-sphingomyelin (Lyso-SM), a de-acylated form of sphingomyelin, was used as a biomarker to track disease burden [12]. Both patients were too young to cooperate with pulmonary function testing, so a six-minute walk test (6MWT) was performed as an alternative to evaluate the patients' general functional status. Both patients received nerve conduction velocity (NCV) tests to evaluate the presence and degree of peripheral neuropathy. Neurocognitive function was

Table 1
ASMD patient characteristics.

	Gender	Ethnicity	Age at symptoms onset	Age at diagnosis	Age at treatment start	*SMPD1* variant	Clinical manifestations
P1	Male	Taiwanese	<3y	3y2m	5y8m	c.1486 + 5G > C(pat) c.1497_1498delGTinsAC (Y500H) (mat)	Hepatosplenomegaly Mildly elevated liver function Growth failure Interstitial lung disease Bilateral cherry-red spots Developmental delay
P2	Male	Taiwanese	<1y	1y11m	2y6m	c.1486 + 5G > C(pat) c.1498 T > C, p.Tyr500His(Y500H) (mat)	Hepatosplenomegaly Mildly elevated liver function Growth failure Interstitial lung disease Repeated bronchopneumonia episodes Bilateral cherry-red spots Developmental delay

mat: maternal; pat: paternal.

assessed by Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV) for P1 and Bayley-III for P2.

2.3. Imaging assessment

Liver and spleen volumes were estimated using abdominal ultrasonography performed by a single experienced pediatric gastrointestinal specialist. The estimated liver volume was calculated using an equation developed by Jessie Childs in 2016 [13,14]. Three simple linear ultrasound measurements were recorded: the diameter of the right lobe of the liver from dome to tip (A), the maximum anterior to posterior diameter of the right lobe of the liver (B), and the maximum anterior to posterior diameter of the left lobe of the liver (C). They were then fit into the following equation: Liver volume (cc) = 343.71 + (0.84 X ABC), where the three measurements are expressed in centimeter (cm). The estimated spleen volume (cc) was calculated using the standard prolate ellipsoid formula: length (cm) × width (cm) × depth (cm) × 0.523, which is frequently used for estimating the volume of many irregularly shaped organs [15]. Multiples of normal (MN) of the normal liver and spleen volume were calculated, assuming liver and spleen volumes account for 2.5% and 0.2% of body weight (kg), respectively [6]. We further assessed the degree of liver stiffness. 2D-shear wave ultrasound elastography (2D-SWE) was performed for each patient (Toshiba Aplio 500, Toshiba Medical Systems Corporation, Tochigi, Japan) to measure shear wave speed in the liver and converted to elasticity, as expressed in kilopascals (kPa). The cutoff values for stiffness ranged between 4.1386 kPa and 4.88 kPa in the pediatric groups [16–18].

Chest high-resolution computed tomography (HRCT) performed before and after treatment was interpreted and visually scored by a single pediatric radiologist with 6 years of experience. The scoring was based on a 4-point scale, according to the presence of thickened interlobular septa and intralobular lines area, ground glass opacity, and the involvement area: 0 = no interstitial disease; 1 = 1–25% lung volume affected; 2 = 26–50%; 3 = 51–100% [19]. Bone mineral density was measured using dual energy X-ray absorptiometry (DXA), and an age-matched Z score was determined from the images of the lumbar spine (L1-L4) at baseline and 1 year after treatment [20].

3. Results

3.1. Safety and adverse events

The dosage was successfully titrated to 3 mg/kg in both patients. No severe infusion-related allergic reactions (IAR) that resulted in dose adjustment were noted in either patient. P1 developed low-titer IgG antidrug antibodies to olipudase alfa (Titer: 50) at week 40. He did not exhibit any discomfort indicating IAR during infusion and the antibodies resolved spontaneously afterwards. However, two episodes of significant AST and ALT elevation (AST: 439 U/L and 344 U/L, reference range: 10–50 U/L; ALT: 454 U/L and 253 U/L, reference range: ≤50 U/L) were noted in P2 at a dosage of 0.6 mg/kg and 2 mg/kg, respectively. P2 remained asymptomatic, and the liver enzymes returned to levels within normal limits spontaneously before the next injection. We responded to the events with a transient dose de-escalation for the following injection. P2 resumed dose titration successfully after the episodes. Also, P1 had one episode of asymptomatic AST and ALT elevation (AST: 140 U/L; ALT: 55 U/L) at a dosage of 2 mg/kg. The same dose was repeated once at the next infusion, followed by a dose titration without further incident.

3.2. Tracking spleen/liver volume and liver stiffness

Both patients had significant hepatosplenomegaly at baseline. The estimated liver volume and spleen volume, though still increased, reduced after ERT, as shown in Fig. 1. Both patients had elevated liver stiffness values at baseline. The value decreased from 27.3 kPa (baseline) to 7.8 kPa (1 year after treatment) in P1 and 8.8 kPa (baseline) to 6.6 kPa (1 year after treatment) in P2 (Fig. 2). As for liver function tests, P1 had mildly elevated AST but normal ALT at baseline (AST: 72 U/L, reference range: 10–50 U/L; ALT: 43 U/L, reference range: ≤50 U/L), and the AST level normalized after treatment. P2 had mildly elevated AST and normal ALT at baseline (AST: 64 U/L, reference range: 10–50 U/L; ALT: 35 U/L, reference range: ≤50 U/L), and the AST level remained slightly elevated (41–60 U/L) after treatment. Both patients had ALT levels within the reference range at baseline and after one year of treatment. Episodes of transient AST/ALT elevation after infusion during the dose escalation period were excluded.

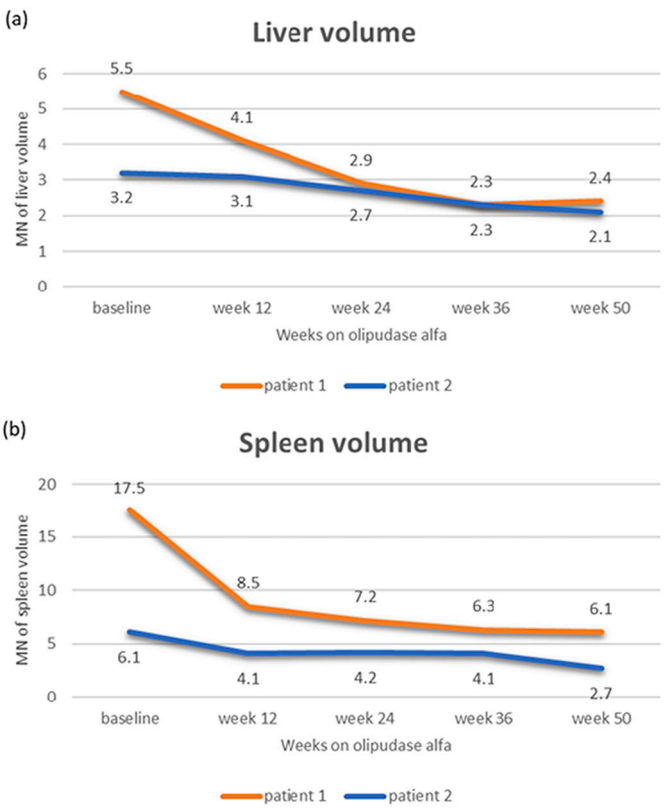

Fig. 1. The change in hepatic volumes (a) and splenic volumes (b), expressed in multiples of normal (MN), from baseline to week 12, week 24, week 36, and week 50 on olipudase alfa treatment. Both patients showed improvement of hepatosplenomegaly.

3.3. Lipid profiles

Both patients had dyslipidemia, including decreased high-density lipoprotein cholesterol (HDL-c) and elevated triglycerides (TG), total cholesterol, and low-density lipoprotein cholesterol (LDL-c) at baseline. After treatment, the levels of TG, cholesterol, LDL-c gradually declined and were within normal limits at week 50. HDL was increasing but still below the lower limit of normal at week 50. (Fig. 3).

3.4. Biomarkers

Lyso-SM was significantly elevated in both patients at baseline but dramatically declined after treatment, especially in the first 6 months, and then remained slightly elevated above the upper normal range (Fig. 4).

3.5. Lung disease and exercise tolerance

Both patients had significant interstitial lung disease at baseline.

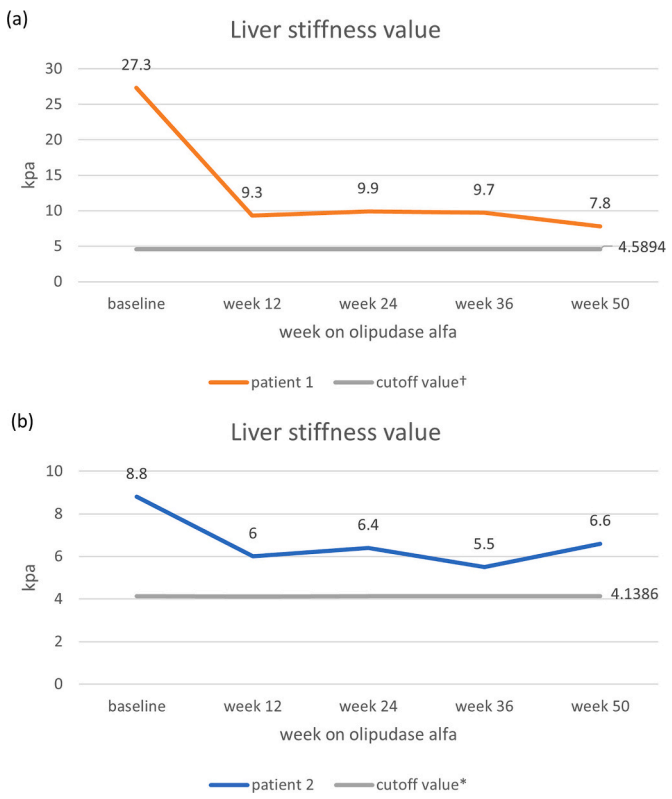

Fig. 2. Both patients had significantly elevated liver stiffness values at baseline but improved after treatment in P1(a) and P2 (b).
†liver stiffness cutoff value in children aged 6–8 years [16].
*liver stiffness cutoff value in children aged 3–5 years [16].

However, none of them needed supplemental oxygen before treatment. The interstitial lung disease score (ILD score) decreased from 3 to 0.625 in P1 and 2.5 to 1.375 in P2 after one year of treatment. The lung images at the level of the higher hemidiaphragm are shown in Fig. 5 and Fig. 6, which shows an improvement in ground glass patterns in the bilateral lung fields for both patients. Both patients were unable to do 6MWT at baseline. P1 was physically weak because he suffered from gastrointestinal illness caused by severe abdominal distension at baseline. P2 had developmental delay and was too young to cooperate with the test. However, 6-minute walking distance gradually increased from 42.6 meters to 63.8 meters to 74.5 meters at weeks 12, 24, and 50 for P1. P2 also had improvements in 6-min walking distance after treatment, from 106 meters to 191 meters at weeks 12 and 50.

3.6. Skeletal disease

Both patients had no history of pathological fracture. The age-matched z-score of bone mineral density for P1 increased from −2.3 to −1.6. P2 did not complete the procedure due to his young age.

3.7. Growth pattern

Compared to age- and sex-matched general population based on Taiwanese growth standards, both patients suffered from significant failure to thrive at baseline (P1: height z-score −3.28, weight z-score −1.72; P2: height z-score −3.4, weight z score −1.76). After treatment, P1 had a height z-score gain of 0.52 and P2 of 0.9. P1 had a weight z-score gain of 0.7 and P2 of 0.46 (Fig. 7). At 50th week after treatment, the weights of both patients were above the 3rd percentile line even though their heights were still below the 3rd percentile line. In general, the growth pattern for both patients were improving.

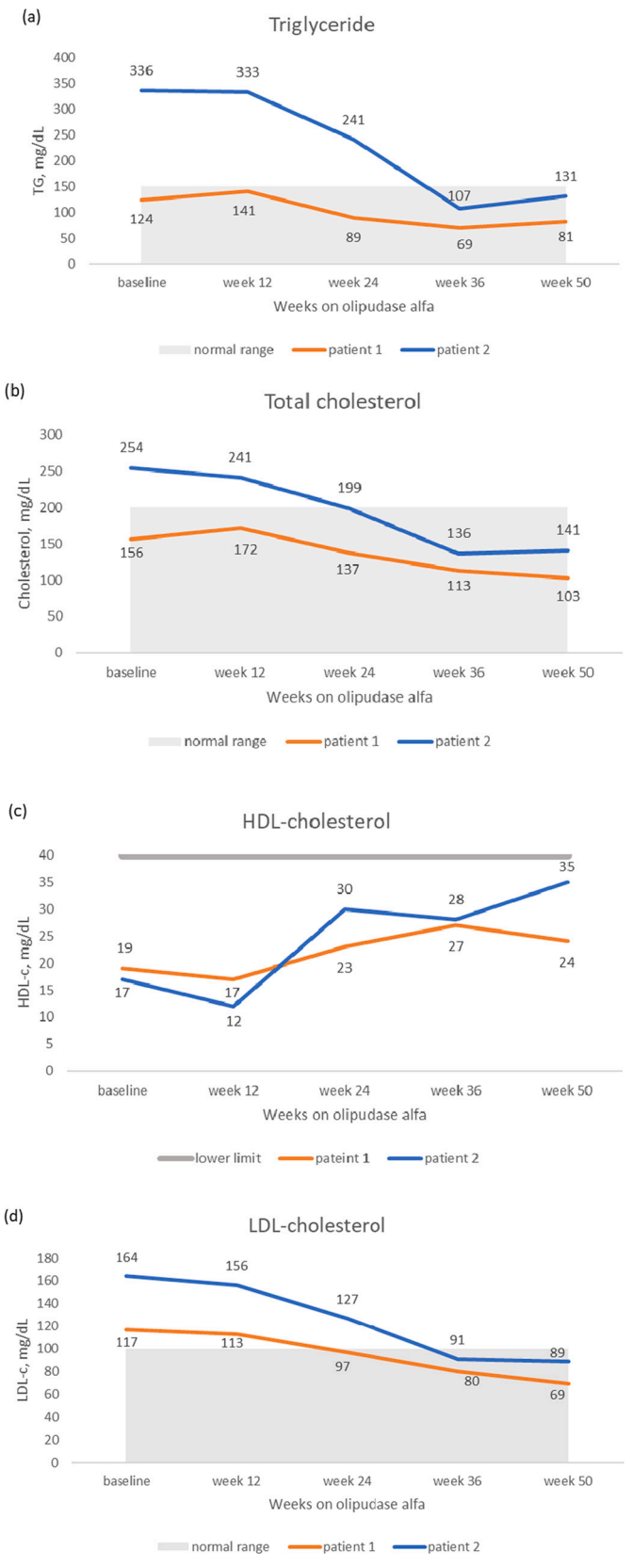

Fig. 3. Change in TG (a), total cholesterol (b), HDL-c (c) and LDL-c (d) from baseline to week 12, week 24, week 36 and week 50 on olipudase alfa treatment. Both patients showed improvement of dyslipidemia. HLD-c: high-density lipoprotein cholesterol; TG: triglyceride; LDL-c: Low-density lipoprotein cholesterol.

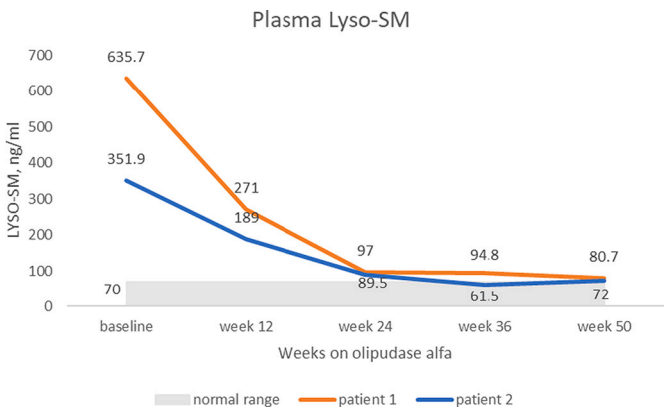

Fig. 4. Lyso-SM levels from baseline to week 12, week 24, week 36, and week 50 on olipudase alfa treatment. In both patients, levels decreased over time. Lyso-SM: lyso-sphingomyelin.

3.8. Peripheral neuropathy and neurocognitive function

Both patients had developmental delays and peripheral neuropathy at baseline. P1 started rolling over when he was 5 to 6 months old and sitting when he was 7 to 8 months. He could walk independently when he was 1 year and 3 months old but the gait remained unsteady. P2 started rolling over at the age of 7 months and crawling at the age of 11 months. By the time he was diagnosed at the age of 1 year and 11 months old, he could walk only with assistance. Besides, the neurological examinations revealed that both patients had decreased deep-tendon reflexes (DTRs). The full-scale IQ scores, measured using the WPPSI-IV, were 56 at baseline and 50 at week 50 in P1. P2 had Bayley III cognitive, language, and motor scores of 65, 71, 58 at baseline and 60, 59, 52 at week 50. Both patients had no noticeable improvement after treatment. Both patients had a decrease in sensory and motor nerve conduction velocities at baseline. The conduction velocities showed no obvious improvement or deterioration after treatment (results shown in Supplentary Table 1).

3.9. Platelet count

P1 had mild thrombocytopenia (147,000/μL) at baseline. After treatment, platelet count improved and remained at low-normal value (150,000/μL – 200,000/μL). P2 had normal platelet counts at baseline and after 1 year of treatment.

4. Discussion

Prior to the development of olipudase alfa enzyme replacement therapy there was no disease-modifying treatment available for ASMD patients. Hematopoietic stem cell transplantation (HSCT) has been

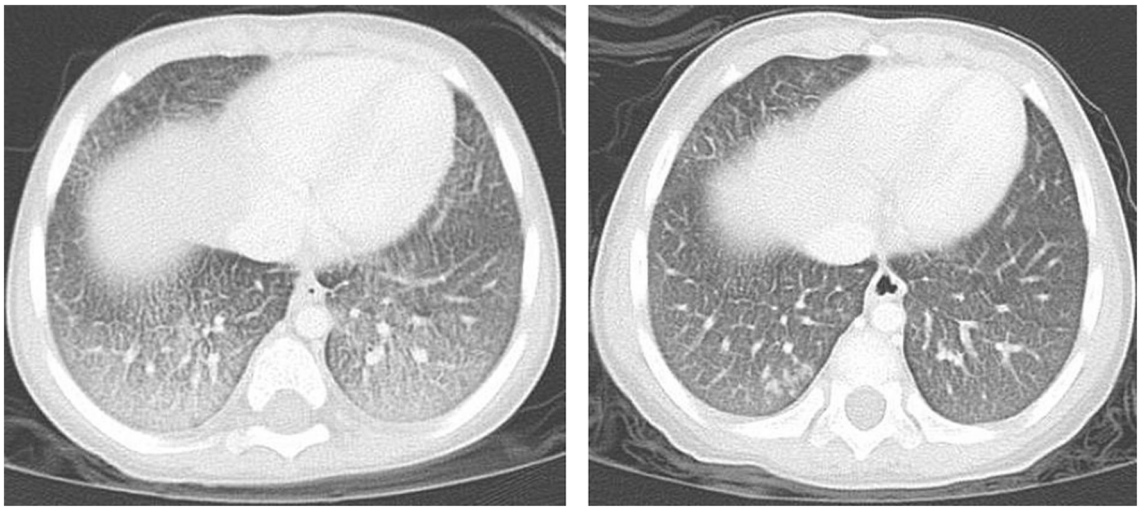

Fig. 5. Chest CT image of P1 before and after treatment shows decreased ground glass opacities in the bilateral lung fields. Left: baseline; Right: 1 year after ERT.

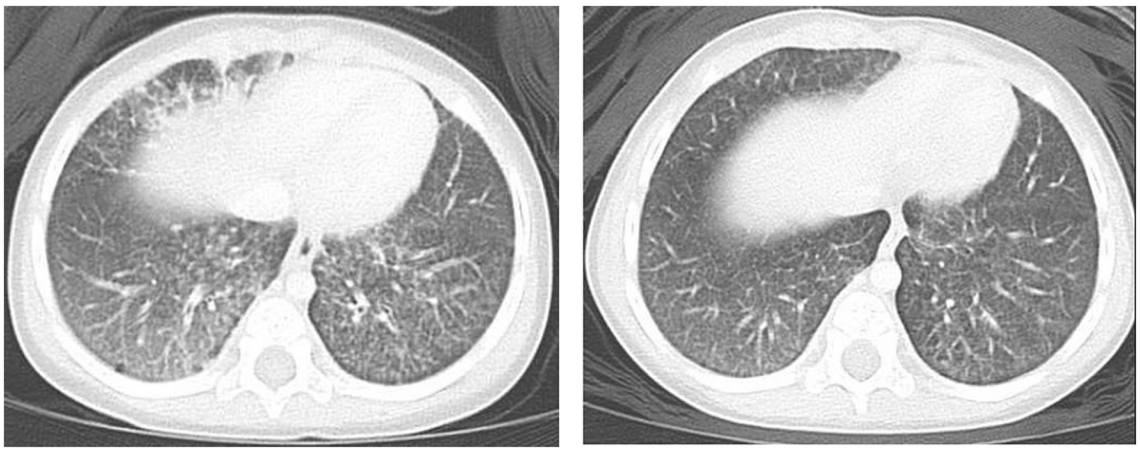

Fig. 6. Chest CT image of P2 before and after treatment shows decreased ground glass opacities in the bilateral lung fields. Left: baseline; Right: 1 year after ERT.

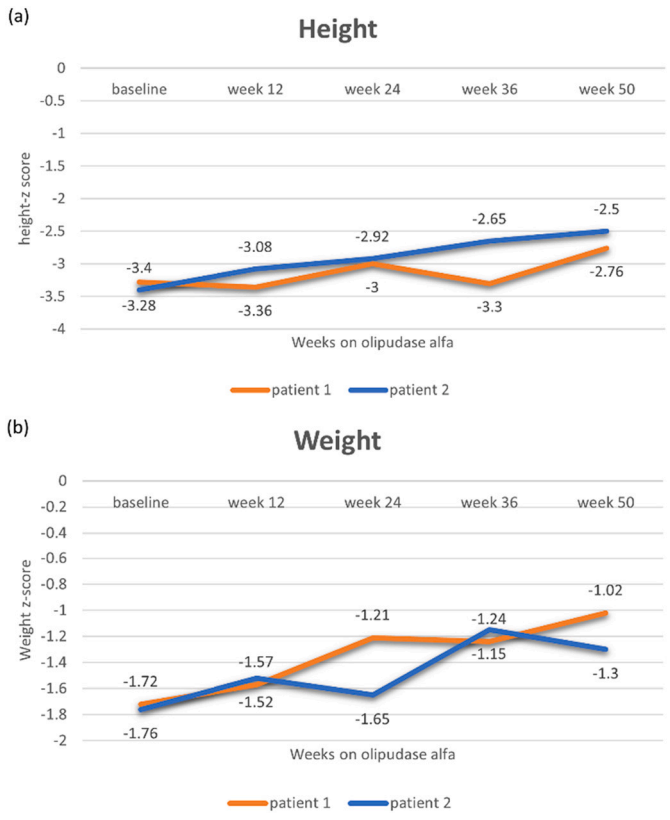

Fig. 7. The change in height z-score (a) and weight z-score (b) from baseline to week 12, week 24, week 36 and week 50 on olipudase alfa. Both patients showed improvements in growth after treatment.

shown to correct dyslipidemia, cytopenia, pulmonary infiltration, and hepatosplenomegaly in ASMD patients, but the neurological benefits are still unclear [21]. In addition, the complications of the procedure and the difficulty finding a human leukocyte antigen (HLA)-matched donor have prevented HSCT from becoming standard of care [22–24]. The investigational human recombinant enzyme, olipudase alfa, has given hope for ASMD patients, especially those suffering from the chronic visceral and chronic neurovisceral types, who survive longer and suffer from the illness longer than those with the infantile neurovisceral type. The two cases in our study were classified as chronic neurovisceral type ASMD. They had early neurological involvements but no rapid neurodegeneration was noted later on. Besides, both of them did not harbor alleles known to predict infantile neurovisceral phenotype. Instead, each of them carried a Y500H allele, which was previously reported to be present in chronic visceral and chronic neurovisceral patients in a Chinese cohort of ASMD cases [25]. According to their genotypes and clinical conditions, they were diagnosed chronic neurovisceral ASMD and were eligible for ERT treatment. However, it has to be mentioned that the decision to treat with ERT or not for an ASMD patient with early neurological involvement may be difficult to make because, in the early childhood, it's not easy to differentiate chronic neurovisceral ASMD and infantile neurovisceral ASMD, who are not indicated for ERT. Therefore, when it comes to the decision to treat or not for such cases, exclusion of those with known genotypes predicting infantile neurovisceral ASMD should be considered. Besides, treating physicians should keep monitoring the disease courses, re-evaluating the possibility of infantile neurovisceral type ASMD if the patients' condition are still deteriorating after ERT. A policy of stopping treatment for these deteriorating cases may be existing and somewhat different in each country.

While cases with infantile neurovisceral type were not treated with ERT because of the expected rapid course of neurodegeneration, promising short- and long-term results of major clinical outcomes in chronic ASMD have been reported by three landmark clinical trials, two of which enrolled adult patients, and one of which enrolled pediatric patients [6,7,26]. ASCEND-PED was a phase 1/2, international, multicenter, non-randomized trial to evaluate the safety and efficacy of olipudase alfa in patients younger than 18 years of age with ASMD. Twenty patients, including adolescents, children, and young infants, were included. One-year results indicate good tolerability of the drug and clinically meaningful improvements. Two-year results showing continuing benefits from the first to second years for children has been reported as well [27]. However, no data outside of clinical trials have been reported yet. We believe our study was the first to share the real-world experience of olipudase alfa in ASMD patients. Our results mirror those found in the ASCEND-PEDS trial. Both of our patients tolerated the therapy well without severe IAR. Major clinical outcomes for pediatric patients included improvements in weight and height, enlarged hepatic and splenic volumes, improved dyslipidemia, reduced interstitial lung disease and osteopenia. As expected, neurocognitive function did not improve, since olipudase alfa does not cross the blood-brain-barrier.

In addition to this, we evaluated several other clinical parameters [28]. First, the degree of liver stiffness was measured using swear-wave elastography, which is a non-invasive tool for assessing liver stiffness without taking the procedural risk of liver biopsy. It has been shown to be an accurate and reproducible technique to assess liver fibrosis in pediatric patients with nonalcoholic fatty liver disease and was recommended in diseases presenting with significant hepatic steatosis, such as lysosomal acid lipase deficiency [29,30]. It has also been studied for assessing liver stiffness in Gaucher disease (GD), another type of sphingolipidosis, and the results have suggested ERT had a beneficial effect on liver fibrosis [31,32]. Nascimbeni et al. found that liver stiffness values were correlated with disease severity in GD patients. Furthermore, the length of ERT was significantly lower in GD patients with significant liver fibrosis and was inversely correlated with liver disease [32]. Similar to Gaucher disease, ASMD patients carry a long-term risk of liver fibrosis, which further results in portal hypertension and hepatocellular carcinoma [33]. However, conventional liver function tests, such as AST or ALT, might remain normal even though extensive fibrosis can be seen on liver histology [34]. We found that both of our patients had elevated liver stiffness values despite the fact their liver function tests were normal or only slightly elevated before treatment. A reduction in liver stiffness was noted after one year of ERT therapy. Our results suggest that, similar to GD, ERT might alleviate liver stiffness in ASMD patients. Longer follow-up and more cases are needed to validate this assumption.

Second, we performed a nerve conduction study (NCS) to evaluate the presence and degree of peripheral neuropathy. Previous studies showed sphingomyelin accumulation also occurs in peripheral Schwann cells, and ASMD patients may present with chronic demyelinating neuropathy [35,36]. However, the presence of peripheral neuropathy and the treatment effect of ERT on peripheral neuropathy are less often discussed, probably because peripheral neuropathy is less severe than central nervous system deterioration [37,38]. The neurological examinations performed by our experienced pediatric neurologist found both patients had decreased deep tendon reflexes and were relatively hypotonic before treatment. Their baseline NCS also showed decreased sensory and motor nerve conduction velocities, indicating chronic sensorimotor demyelinating neuropathy. However, there were neither noticeable improvements nor deterioration in nerve conduction velocities in our patients after ERT for 1 year. The exact mechanism of how ASMD results in peripheral neuropathy and how ASMD patients with peripheral neuropathy would benefit from ERT is still unknown, due to the short-term evaluation in our study. Longer follow-up is needed to improve this understanding.

Third, we arranged 6MWT for exercise tolerance assessment. 6MWT has long been an easy and comprehensive tool to evaluate the general functional capacity of patients with chronic pulmonary, cardiac, or

neuromuscular disease [39]. It is widely used in patients with Pompe disease and mucopolysaccharidosis (MPS) as a useful clinical endpoint of ERT treatment response [40–42]. It has also been investigated in a few patients with ASMD. Hollak et al. found that ASMD patients had worse performance than healthy subjects and seemed to deteriorate over time without treatment [43]. In our study, both ASMD patients showed a gradual increase in walking distance after ERT. The exact correlation between 6MWT and the severity of pulmonary disease in ASMD needs further research. Furthermore, the younger patients who fail to cooperate with lung function tests may also be unwilling to cooperate with 6MWT. The test results are prone to interference with other environmental factors and need to be interpreted with caution. However, in the clinical setting, 6MWT still serves as an easy and practical tool to monitor ERT treatment response and global/multiorgan status of ASMD patients.

There were several limitations of this study. First, we did not perform abdominal CT or magnetic resonance imaging, the gold standard, to evaluate liver volume, because the parents were very concerned about the risk of sedation for the procedure. Instead, abdominal ultrasound, carried out by a single experienced pediatric GI specialist, was arranged together with a consistent equation for serial and frequent volume estimation. Although its accuracy for determining the actual liver volume has not been validated, it holds value for tracking the response to treatment over time and is more practical in the real-world setting. Furthermore, ultrasound is more advantageous because it is more accessible, radiation-free, low cost, time-saving, and free of anesthesia risk. Second, we did not perform lung function testing since our patients could not cooperate with the procedure. Previous research showed imaging studies were not sufficient in the evaluation of pulmonary disease in chronic ASMD [19], and so it is better to interpret imaging studies in conjunction with functional testing. However, we used the 6MWT, which provides prognostic information for chronic pulmonary or cardiac diseases, such as idiopathic pulmonary fibrosis or Pompe disease [42,44]. For this reason, we are confident it also provided information about ERT treatment response in ASMD patients. Based on our 6MWT results, we believe ERT brought general benefits, including lung function, to our patients. Finally, we had a small sample size that limited the statistical power to show the significance of our results since ASMD is a ultra-rare genetic disease. However, the trends in improvement are evident and the results were compatible with the clinical trial results. Our patients still receive ERT regularly at our hospital currently. The outcome measures in our study kept gradually improving and stable. We plan to have a longer-term follow up period of at least 5 years since the results from clinical trials have provided evidence for continuing benefits of ERT in chronic ASMD patients. The laboratory, anthropometric data and abdominal ultrasonography would be checked every three to six months while chest CT and the neurological exams would be assessed at least every one to two years.

5. Conclusion

Enzyme replacement therapy with Olipudase-alfa is safe and effective in pediatric ASMD patients. The treatment improved hepatosplenomegaly, bone mineral density, pulmonary infiltration, dyslipidemia, and the growth patterns of the affected children. Lyso-SM, the primary biomarker for disease burden, decreased with time during treatment. Liver stiffness value and 6-minute walking distance (6MWT) improved as well. Both are considered candidate biomarkers for pediatric ASMD patients but require further validation. Our results, which mirror the results of previously published data, suggest general benefits in major clinical outcomes for ASMD pediatric patients. Further investigation and follow up are needed to monitor central and peripheral neurological involvement.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of National Cheng-Kung University Hospital (approval number: B-ER-111-182). Informed consents were obtained from the legal guardians of the patients.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

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Authors' contributions

Yen-Yin Chou was responsible for the study conception and design. Chiao-Yu Yang and Yao-Jong Yang performed the abdominal ultrasonography. Bow Wang interpreted chest computed tomography images. Wen-Hou Yu performed the neurological exams. All authors participated in the data collection and interpretation. Yu-Wen Pan was responsible for manuscript writing. Meng-Che Tsai and Yen-Yin Chou critically reviewed and revised the manuscript. All authors have read and approved the final version of manuscript.

Declaration of Competing Interest

The authors declared no conflicts of interests relevant to this article.

Data availability

Data will be made available on request.

Acknowledgement

Sanofi/Genzyme sponsored the olipudase alfa for compassionate use. The study sponsor did not participate in study design, data analysis, manuscript writing, or the decision to submit the manuscript for publication, but did have the opportunity to review the final manuscript for accuracy and to make non-binding suggestions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2023.100957.

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