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Olipudase Alfa for Acid Sphingomyelinase Deficiency

By: Gabriella Lorusso, Pharm.D.

Background: Acid sphingomyelinase deficiency (ASMD), formerly known as Niemann-Pick disease, is a lysosomal storage disorder resulting from reduced activity of the acid sphingomyelinase (ASM) enzyme.¹ This enzyme is responsible for the breakdown of sphingomyelin to ceramide and phosphocholine. Decreased ASM activity leads to intra-lysosomal accumulation of sphingomyelin, cholesterol, and other cell membrane lipids in various tissues (e.g., spleen, lung, bone marrow, lymph nodes) which can cause multi-organ dysfunction. This rare, inherited, disease has a prevalence of 0.4 to 0.6 in 100,000 births. There are three different types of ASMD. Type A occurs in early infancy and is the most severe, rapidly progressing form characterized by multi-organ involvement including neurological manifestations.^{2,3} Type A/B occurs in infancy to childhood

and is similar to Type A, but may have a slower progression. Type B, the most common and least severe form of ASMD, can occur from childhood to adulthood and has minimal neurological manifestations. Olipudase alfa-rpcp (Xenpozyme™; Sanofi-Genzyme) was developed as a specific enzyme replacement therapy to help prevent ASMD-associated lipid accumulation and end-organ damage.² It was approved by the Food and Drug Administration in August 2022 for the treatment of non-central nervous system (CNS) manifestations of ASMD in adult and pediatric patients.

Mechanism of Action: Olipudase alfa is a recombinant sphingomyelin-specific enzyme replacement therapy that acts as an exogenous source of ASM. Olipudase alfa does not cross the

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Betibeglogene Autotemcel for Beta-thalassemia

By: Trate DeVolld, Pharm.D.

Background: Beta (β)-thalassemia is a hereditary blood disorder caused by one or more mutations in the β -globin gene.¹ This leads to the absence (β^0) or reduction (β^+) of beta-globin chain production required for hemoglobin (Hb) synthesis and leads to severe anemia. This disease may be classified as major, intermedia, or minor. Beta-thalassemia major is the most severe form and occurs in homozygous (β^0/β^0 , β^+/β^0) or compound heterozygous (β^+/β^+) individuals. This disease state usually occurs between 6 months and 2 years of

age and causes symptoms of severe anemia (e.g., fatigue, cachexia, and heart failure). It is most common in Mediterranean countries where carrier rates are as high as 18%. However, the prevalence of β -thalassemia has increased in the United States approximately by 7.5% over the last 50 years.² Management is currently limited to supportive care and typically includes recurrent blood or blood product transfusions, splenectomy, bone marrow or stem cell transplants, and induction of fetal Hb.¹

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blood-brain barrier or modulate CNS manifestations of ASMD.

Clinical Trials: The ASCEND trial was a phase 2/3 double-blind, placebo-controlled 52-week study that evaluated the safety and efficacy of olipudase alfa for non-CNS ASMD in adults.⁵ The study occurred between December 18, 2015 and October 17, 2019. Adult patients (N=36) with confirmed ASMD, a diffusing capacity of the lung for carbon monoxide (DL_{CO}) ≤ 70% of predicted normal, a spleen volume ≥ 6 multiples of normal, and a splenomegaly-related score ≥ 5 were included. Participants were randomized 1:1 to receive olipudase alfa or placebo and started on olipudase alfa 0.1 mg/kg with titrations every 2 weeks to the target maintenance dose of 3 mg/kg. Doses could be adjusted based on tolerability and pre-specified dose-limiting toxicities. The two independent primary efficacy endpoints were the percentage change in baseline to week 52 in percent predicted DL_{CO} and spleen volume. These endpoints were chosen based on their association with reduced quality of life in ASMD patients. In ASMD, reduced DL_{CO} correlates with symptom severity and splenomegaly has been linked to increased mortality.⁶ Secondary endpoints included liver volume, platelet counts, and patient-reported outcomes (PROs).⁵ The least squares (LS) mean percentage change from baseline to week 52 for the percent predicted DL_{CO} was significantly greater in the olipudase alfa group than the placebo group (22% vs 3%, respectively, difference=19.1, P=0.0004). The LS mean percentage change from baseline to week 52 in spleen volume was significantly greater in the olipudase alfa group than the placebo group (39% decrease vs 0.5% increase, respectively, difference= -39.9%, P<0.0001). Changes in liver volume and platelet count also favored olipudase alfa. For PROs, changes from baseline were not different between the two groups. All patients experienced at least one adverse event mostly classified as mild and none led to treatment discontinuation. Infusion-associated reactions were more common in the olipudase alfa group than the placebo group (44% vs 27%, respectively). The authors concluded that olipudase alfa was well tolerated and associated with significant clinical improvements in patients with ASMD. The ASCEND-PEDS trial was a phase 1/2 international, multicenter, open-label trial that assessed the safety and tolerability of olipudase alfa therapy through 64 weeks in pediatric patients.⁷ The study occurred from May 1, 2015 to December 9, 2019. Pediatric patients ages 1-17 years old with confirmed ASMD (N=20) were eligible. Olipudase alfa was administered every 2 weeks starting at 0.03 mg/kg until reaching 3 mg/kg (the target maintenance dose). Patients were monitored for 24 hours post-infusion, and doses could be adjusted based on pre-specified dose-limiting toxicities. All patients experienced at least one adverse event, with the majority classified as mild (88%). The most common adverse events were pyrexia (75%), cough (70%), vomiting (60%), nasopharyngitis (55%), and diarrhea (55%).

Five patients experienced at least one serious adverse reaction, including one anaphylactic reaction in a 17-month-old patient. There were no clinically significant abnormalities in laboratory values or vital signs. Exploratory efficacy outcomes including liver and spleen volume, liver function tests, plasma lipid levels, platelet counts, and growth were also assessed and demonstrated improvement with olipudase alfa. The authors concluded that olipudase alfa was well tolerated and associated with potentially meaningful clinical outcomes in the pediatric population.

Dosing and Administration: Olipudase alfa is administered as an intravenous infusion every 2 weeks.⁴ The recommended starting dose for adult patients is 0.1 mg/kg and 0.03 mg/kg for pediatric patients. The dose of olipudase alfa is increased every 2 weeks to reach a target maintenance dose of 3 mg/kg in adult and pediatric patients.

Cost and Availability: Olipudase alfa is available as a 20 mg single-dose vial for reconstitution (NDC 58468-0050-1).⁴ The average wholesale price per vial is \$8,570.40.⁸ The annualized maintenance therapy cost for a 25-kilogram pediatric patient is approximately \$835,000.

Formulary Status: Olipudase alfa was recently approved for addition to the CCHS Pediatric Formulary, restricted to the Department of Hematology and Oncology for outpatient use.

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Recurrent blood transfusions often produce iron overload leading to serious hepatic, endocrine, and vascular complications associated with over 70% of deaths in patients with β -thalassemia major. In August 2022, betibeglogene autotemcel (Zynteglo®; BlueBird Bio, Inc.) became the first cell-based gene therapy approved by the Food and Drug Administration for the treatment of adult and pediatric patients with β -thalassemia who require regular red blood cell (RBC) transfusions.³

Mechanism of Action: Betibeglogene autotemcel (beti-cel) is an autologous gene therapy that utilizes the transduction of CD34+ cells with BB305 lentiviral vector to add functional copies of a modified β -globin gene into the patient's hematopoietic stem cells.³ After administration of this therapy, transduced CD34+ cells engraft in the bone marrow and differentiate to produce red blood cells (RBCs) containing a modified β -globin protein (β^{A-T87Q} -globin) which combines with α -globin to produce functional adult Hb. Betibeglogene autotemcel has the potential to restore HbA and total Hb to normal levels and eliminate dependence on regular RBC transfusions.

Clinical Trials: The efficacy of beti-cel was assessed in two phase 3 open-label, single-arm, 24-month multicenter trials (Study 1 and 2) in 41 patients 4 to 34 years old who regularly received transfusions for β -thalassemia.^{3,4} Study 1 enrolled patients with a non- β^0/β^0 genotype and Study 2 enrolled patients with any genotype of β -thalassemia. To participate in these phase 3 trials, patients had to receive at least 100 mL/kg/year of packed red blood cells (pRBCs) or eight or more pRBC transfusions per year in the 2 years before enrollment. Patients with severe cardiac iron buildup or advanced liver disease were excluded. All patients received granulocyte-colony stimulating factor (G-CSF) and plerixafor for mobilization and apheresis for cell collection as part of beti-cel preparation. Myeloablative conditioning with busulfan was done before beti-cel administration. Study 1 (N=23) and Study 2 (N=18) had a primary endpoint of transfusion independence (TI). Transfusion independence was defined as maintaining a weighted average Hb ≥ 9 g/dL beginning 60 days after the last transfusion without receiving any pRBC transfusions for a continuous period of ≥ 12 months. Twenty of twenty-two (91%) of patients in Study 1 and 12/14 (86%) of patients in Study 2 met the primary endpoint of TI. All 32 patients maintained TI throughout the duration of both studies. The median weighted average Hb of those with TI in Study 1 and Study 2 was 11.8 g/dL and 10.2 g/dL, respectively. These patients exhibited durable normal or close-to-normal total Hb levels, with a median total Hb of 11.4 g/dL at the last follow-up appointment. Based on results from Study 1, the authors concluded that for most patients with a non- β^0/β^0 genotype, transfusion-dependent β -thalassemia, a one-time beti-cell infusion effectively achieved TI with near normal Hb levels.⁴

Safety: The most commonly reported serious reactions in the clinical trials were thrombocytopenia (100%), neutropenia (100%), leukopenia (100%), anemia (95%), lymphopenia (61%), stomatitis (63%), febrile neutropenia (51%), and liver veno-occlusive disease (7%).³ This adverse effect profile was mostly attributed to myeloablation induced by busulfan. By the last follow-up, no cases of oncogenesis, graft-versus-host disease, graft failure, or rejection were observed and no deaths were reported.

Dosing and Administration: Betibeglogene autotemcel is provided as a single-dose intravenous infusion containing a suspension of CD34+ cells in up to four infusion bags which contain 2 to 20 million cells/mL suspended in a cryopreservation solution.³ The minimum recommended dose of beti-cel is 5 million CD34+ cells/kg. Before cell collection through apheresis, patients must undergo mobilization with G-CSF and plerixafor. To meet the target dose of CD4+ cells, at least 12 million CD4+ cells/kg should be collected with a backup collection in case cell rescue is required. After the frozen beti-cel dose is delivered from BlueBird Bio, patients undergo myeloablative conditioning with busulfan over 4 days. Following myeloablation and a 48-hour washout period, beti-cel is infused within 4 hours of being thawed over less than 30 minutes. No premedications are required.

Cost and Availability: Betibeglogene autotemcel (Zynteglo®) (NDC 73554-3111-1) is available as a single-dose infusion and is only administered at qualified treatment centers.^{3,5} The predicted cost of the gene therapy alone is \$2.8 million.⁵

Formulary Status: Betibeglogene autotemcel is on CCHS Pediatric Formulary, restricted to Staff Physicians in Pediatric Bone Marrow Transplant with the following restriction criteria:

1. Use only in pediatric patients with β -thalassemia who require regular RBC transfusions
2. Authorization or covered approval must be obtained from the patient's insurance company in conjunction with the manufacturer

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