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Cipaglucosidase alfa and miglustat for treatment of late-onset Pompe disease (LOPD): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

Pompe disease is an autosomal recessive lysosomal disease caused by biallelic pathogenic variants in *GAA*, resulting in a deficient or absent acid alpha-glucosidase (GAA) enzyme that normally hydrolyzes intralysosomal glycogen into glucose. Deficiency of GAA leads to an accumulation of glycogen within lysosomes throughout the body, particularly in cardiac and skeletal muscles, resulting in cellular damage.[1] Infantile-onset Pompe disease (IOPD) is characterized by hypertrophic cardiomyopathy, hypotonia, and respiratory insufficiency that rapidly progresses to death if

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left untreated. Late-onset Pompe disease (LOPD) can present from infancy to adulthood and is characterized by progressive proximal muscle weakness and respiratory dysfunction, typically without cardiomyopathy. Although LOPD affects multiple organ systems, the most severe complications arise from progressive respiratory muscle weakness, which can result in ventilatory dependence and early mortality.[2] Pompe disease is included on the Recommended Uniform Screening Panel and is therefore on the newborn screen (NBS) in most states in the United States.[3]

Management and treatment

Consensus management guidelines for IOPD,[4] LOPD,[5] and Pompe disease identified through newborn screen[6] have been published. This involves a multidisciplinary approach encompassing genetics, pulmonology, cardiology, gastroenterology, physical/occupational therapy, and neurology subspecialist care.

The timing of symptom onset and rate of progression of LOPD is highly variable across affected individuals, making the decision of when to start treatment challenging. With LOPD increasingly identified through newborn screening, the use of standardized assessments to monitor symptom onset and progression has been suggested to support disease management.[6]

In both IOPD and LOPD, early diagnosis and treatment lead to improved clinical outcomes. Before cipaglucosidase alfa and miglustat, there were 2 FDA-approved treatments for Pompe disease, namely, alglucosidase alfa since 2010 and avalglucosidase alfa since 2021, which are both recombinant human GAA (rhGAA) enzyme replacement therapies. Alglucosidase alfa is indicated for all patients with Pompe disease, whereas avalglucosidase alfa is a modified enzyme replacement therapy (ERT) indicated for the treatment of patients one year of age and older with LOPD. Although clinical benefits have been attained in patients with Pompe disease treated with alglucosidase alfa and avalglucosidase alfa, the declining efficacy and continued symptom progression for some patients over the long-term highlight the need for more efficacious therapies.[7-9]

Newly approved therapy

Indication and approved treatment population

Cipaglucosidase alfa (trade name: POMBILITI) and miglustat (trade name: OPFOLDA) is an ERT and enzyme stabilizer, respectively, approved as combination therapy by the FDA for the treatment of LOPD in adult patients not improving on other ERTs.[10,11] Cipaglucosidase alfa and miglustat received an orphan drug designation and FDA approval was obtained via the regular (non-accelerated) approval pathway.

Mechanism of action

Cipaglucosidase alfa and miglustat is a 2-component therapy. Cipaglucosidase alfa is a rhGAA replacement enzyme containing high levels of mannose-6-phosphate receptors (bis-M6P) for intake into muscle cells and transport into the lysosomes. Once inside the cell, cipaglucosidase alfa breaks down accumulated glycogen. Unlike avalglucosidase alfa, which conjugates synthetic bis-M6P to rhGAA N-glycans in Chinese hamster ovarian cells, cipaglucosidase alfa is produced from Chinese hamster ovarian cell lines selected for rhGAA N-glycan profiles with a stronger affinity for receptor binding, improved catalytic efficiency, and greater glycogen clearance in participants with LOPD.[10,12]

Miglustat, an iminosugar that mimics the terminal glucose of glycogen, addresses the challenge of rapid rhGAA inactivation in blood and interstitial space after intravenous infusion by binding to cipaglucosidase alfa's active site and stabilizing the enzyme during circulation when coadministered.[11,12]

Cipaglucosidase alfa is administered intravenously every other week, whereas miglustat is administered by oral capsules taken every other week, 1 hour before the start of cipaglucosidase alfa infusion.[10,11]

Outcomes and efficacy

Cipaglucosidase alfa and miglustat were evaluated in the PROPEL phase 3 multicenter, double anonymized, randomized trial (NCT03729362), which evaluated cipaglucosidase alfa plus miglustat vs alglucosidase alfa plus placebo in 123 adults with LOPD who had either been receiving alglucosidase alfa for at least 2 years or were treatment naive. The study did not achieve statistical superiority for the primary endpoint of improved 6-minute walk distance at 52 weeks from baseline.[13,14] However, the study did show clinically meaningful but not statistically significant improvement in a secondary endpoint of sitting forced vital capacity (FVC) for cipaglucosidase alfa plus miglustat relative to alglucosidase alfa plus placebo. At week 52 compared with baseline, cipaglucosidase alfa plus miglustat was also associated with numerically favorable but not statistically significant secondary endpoints of change in the lower manual muscle test score, Patient-Reported Outcomes Measurement Information System physical function and fatigue scores and the Gait, Stairs, Gower's maneuver, and Chair total score. There was a statistically significant reduction in creatine kinase levels and Hex4 levels at week 52 with cipaglucosidase alfa plus miglustat compared with alglucosidase alfa plus placebo in both the overall population and the ERT-experienced cohort.

In the open-label extension of the PROPEL trial (NCT04138277), long-term treatment with cipaglucosidase alfa plus miglustat in 118 participants with LOPD demonstrated sustained effects for up to 104 weeks.[13,15] Participants who continued to receive cipaglucosidase alfa plus miglustat ($n = 81$) maintained improvements in 6-minute walk distance, whereas those switching from alglucosidase alfa plus placebo to cipaglucosidase alfa plus miglustat ($n = 37$) showed stabilization but no statistically significant improvement. Cipaglucosidase alfa plus miglustat also

stabilized sitting FVC in both ERT-experienced and ERT-naive participants in the open-label extension, after an initial decline in sitting FVC for ERT-experienced participants who received alglucosidase alfa plus placebo and in ERT-naive participants in both treatment groups in the PROPEL study.

Adverse effects and toxicity

Cipaglucosidase alfa carries a boxed warning for hypersensitivity reactions, including anaphylaxis. In the pooled safety analysis from 3 clinical trials, 41 of 151 (27%) of cipaglucosidase alfa-treated participants experienced hypersensitivity reactions, including 4 of 151 (3%) of participants who reported severe hypersensitivity reactions and 4 of 151 (3%) additional participants who experienced anaphylaxis. Three of the 4 (3/151; 2%) participants experiencing anaphylaxis discontinued the trial. Symptoms of severe hypersensitivity reactions included urticaria, pruritus, and flushing.[10]

Infusion-associated reactions (IARs) are also in the boxed warning. IARs were reported in 32% of cipaglucosidase alfa-treated participants in clinical trials. In these trials, 3% of cipaglucosidase alfa-treated participants reported 11 severe IARs, including symptoms of pharyngeal edema, anaphylactic reaction, urticaria, pruritus, chills, dyspnea, and flushing. The majority of IARs were assessed as mild to moderate. IARs that led to treatment discontinuation were urticaria, anaphylactic reaction, chills, and hypotension.

The risk of acute cardiorespiratory failure in susceptible patients is the last boxed warning. Patients that are susceptible to fluid volume overload or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of a serious exacerbation of their cardiac or respiratory status during the cipaglucosidase alfa infusion.

Miglustat does not have any boxed warnings.

Cipaglucosidase alfa, in combination with miglustat, is contraindicated in pregnancy because of the potential embryo-fetal harm based on increased cardiovascular malformations in rabbit offspring when administered during pregnancy. The pregnancy status of individuals of reproductive potential should be determined before initiating treatment. Miglustat carries a US FDA category C rating.

Additional considerations

At the time of this writing, there are ongoing clinical trials for LOPD including investigational gene therapy products (NCT06391736, NCT06178432) and substrate reduction therapy (completed, NCT05249621). There are also studies about the antidrug antibody levels and biomarkers in blood among individuals with LOPD (NCT06150820), muscle training in LOPD (NCT05431127), nutritional therapy in LOPD (NCT06130228), and others.

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Conflict of Interest

Elizabeth K. Baker, Jennifer L. Cohen, and Irene J. Chang receive salary for providing clinical services that may be relevant to the content of this document in either the laboratory or patient care setting at their listed affiliations. The following workgroup members have additional conflicts of interest: Irene J. Chang is a principal investigator for an unrelated clinical trial sponsored by Sanofi Genzyme. Jennifer L. Cohen served as a consultant for Bayer HealthCare Pharmaceuticals and served as an advisor for a Sanofi Genzyme advisory board. All other authors declare no additional conflicts of interest.

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