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Velmanase alfa approved for treatment of non-central nervous system manifestations of alpha-mannosidosis: A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Alpha-mannosidosis is an autosomal recessive lysosomal disorder caused by pathogenic variants in *MAN2B1*, which leads to deficient or absent acid alpha-mannosidase enzyme activity. Alpha-mannosidase hydrolyzes terminal residues of alpha-D-mannosides during glycoprotein degradation. Deficient enzyme activity results in the accumulation of oligosaccharides or glycopeptides in lysosomes, thus impairing lysosomal function and harming cellular functions, such as autophagy, exocytosis, and

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calcium and pH regulation.[1] Affected individuals may present with a spectrum of symptoms, including hearing loss, progressive myopathy, coarse facial features, skeletal abnormalities, and immune deficiency. Central nervous system traits include intellectual disability and cerebellar ataxia. Alpha-mannosidosis may be categorized into 3 subtypes—mild, moderate, and severe forms; however, the clinical manifestations fall along a continuum of disease severity. Except for the severe early lethal form, progression can be insidious with some individuals living into the sixth decade of life.[2]

Management and treatment

No management guidelines have been published for alpha-mannosidosis. Surveillance may include skeletal assessments to include pain and range of motion, audiometry and otolaryngology screening to evaluate for hearing loss and ear infections, neuropsychological testing, ophthalmologic exams, and regular multi-systemic monitoring by a physician. Signs and symptoms are treated per standard of care.[2] Before 2023, there were no US Food and Drug Administration (FDA)-approved therapies for alpha-mannosidosis. Bone marrow transplantation has been utilized with variable improvement in neurocognitive function and stabilization in several clinical parameters. However, transplant also carries a high risk of complications or even death.[3,4]

Newly approved therapy

Indication and approved treatment population

Velmanase alfa-tycv (trade name: LAMZEDE) is an enzyme replacement therapy approved by the FDA for treatment of non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients. Velmanase alfa received orphan drug designation and FDA approval was obtained via the regular (non-accelerated) approval pathway. It was approved by the European Medicines Agency in 2018.

Mechanism of action

Velmanase alfa is a recombinant human alpha-mannosidase protein with conjugated mannose-6-phosphate (M6P) residues (0.4-0.8 mol M6P/mol enzyme) that is internalized via binding to the M6P receptor on the cell surface and transported into lysosomes where it catalyzes the degradation of mannose-containing oligosaccharides. It is administered as an intravenous infusion once weekly.[5]

Outcomes and efficacy

Velmanase alfa was evaluated in a phase III multicenter, double anonymized, randomized, placebo-controlled trial of 25 individuals ages 5 to 35 years with the co-primary endpoints of change in serum oligosaccharides (S-oligo) and the 3-minute stair-climb test (3MSCT). After 52 weeks, the treatment group demonstrated a statistically significant improvement in S-oligo clearance. No statistically significant changes in motor or pulmonary function were detected, although there were trends toward improved 3MSCT, 6 minute walk test (6MWT), and forced vital capacity (FVC) (% predicted), particularly in the pediatric cohort.[6] Integrated data of 33 individuals from the phase I/II and III trials and rhLAMAN-07 (NCT01908712), rhLAMAN-09 (NCT01908725), and rhLAMAN-10 (NCT02478840) studies demonstrated statistically significant improvements in S-oligo clearance, 3MSCT, 6MWT, and FVC after a mean treatment exposure of 29.3 months.[7] Improvements in S-oligo clearance, hearing, serum immunoglobulin levels, and/or quality of life were seen in a phase II study with 5 children under 6 years of age.[8]

Adverse effects and toxicity

Velmanase alfa carries a boxed warning of hypersensitivity reactions including anaphylaxis. Hypersensitivity reactions were reported in 36% of adults and 58% of pediatric participants. The most common symptoms included nasopharyngitis, pyrexia, headache, and arthralgia. One individual was withdrawn from the clinical trial because of repeated infusion-associated reactions and resumed treatment after 89 weeks. Major visceral malformations were observed when velmanase alfa was administered to pregnant animals.[5] There are no human data on velmanase alfa use in pregnant people.

Additional considerations

At the time of this writing, there are ongoing clinical trials for the neurologic symptoms of alpha-mannosidosis, including augmented stem cell transplantation (NCT02254863),[9] in which umbilical cord blood-derived oligodendrocyte-like cells are administered intrathecally to individuals with metabolic disorders undergoing standard treatment with umbilical cord blood transplantation. Likewise, NCT02171104[10] is evaluating busulfan- and fludarabine-based conditioning regimens to try and improve the engraftment of donor hematopoietic stem cell transplant. Preclinical animal studies investigating molecular chaperones[11] or gene therapy[12] for alpha-mannosidosis have also been published.

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Conflict of Interest

V. Reid Sutton has consulted with Chiesi to develop educational materials for alpha-mannosidosis. All other authors declare no conflicts of interest.

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