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Lenmeldy (atidarsagene autotemcel) for individuals with early metachromatic leukodystrophy (MLD): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Metachromatic leukodystrophy (MLD) is a rare autosomal recessive lysosomal storage disease characterized by deficiency of arylsulfatase A, caused by biallelic loss-of-function variants in *ARSA*. Arylsulfatase A converts sulfated glycolipids into galactocerebroside. Deficiency of this enzyme results in a progressive lysosomal buildup of toxic sulfated glycolipids in various tissues, particularly neurons, with subsequent demyelination. Clinical presentation is variable but typically divided into 1 of 3 categories based on age at disease onset: late infantile (50%-60%

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of affected individuals), juvenile (20%-40% of affected individuals), and adult-onset MLD (10%-20% of affected individuals).[1,2] Clinical manifestations typically include progressive motor dysfunction and neurocognitive decline secondary to neurodegeneration, eventually leading to loss of previously acquired skills, multiorgan system failure, or death.[3]

Management

There is currently no curative treatment for symptomatic MLD. Management is primarily centered around symptomatic care including antiepileptic, pain, spasticity, and mood regulation medications, as well as various support services and palliative care.[2] Allogeneic hematopoietic stem cell (HSC) transplantation has been used for individuals affected by juvenile or adult-onset MLD, and when performed before the onset of clinical symptoms, it may slow or halt cerebral disease progression. However, it does not affect disease progression in the peripheral nervous system, and overall outcomes are mixed.[1,4] HSC transplantation is associated with inherent risks and is not recommended for individuals with MLD who have significant neurological involvement.

Newly approved therapy

Indication and approved treatment population

Atidarsagene autotemcel (trade name: Lenmeldy) is an autologous HSC-based gene therapy approved by the FDA in 2024 (trade name: Lenmeldy) and the European Medicines Agency in 2020 (trade name: Libmeldy).[5] It is indicated for individuals with presymptomatic late infantile (PSLI; ≤30 months), presymptomatic early-juvenile (PSEJ; >30 months and <7 years), or early symptomatic early-juvenile (ESEJ; >30 months and <7 years) MLD. Atidarsagene autotemcel was approved via Priority Review and granted Rare Pediatric Disease, Orphan Drug, and Regenerative Medicine Advanced Therapy designations by the FDA.

Mechanism of action

Atidarsagene autotemcel requires autologous HSC transplantation. After HSC mobilization and apheresis, $CD34^+$ cells undergo ex vivo transduction with a lentiviral vector (LVV) (*ARSA* LVV), inserting functional copies of human *ARSA* complementary DNA into the participant's HSCs. After recipient preparation with myeloablative chemotherapy (busulfan), the transduced cells are infused into the recipient, repopulating the bone marrow and expressing functional arylsulfatase A.[6,7] Some of these progeny cells also cross the blood-brain barrier, delivering the enzyme to the central nervous system. Atidarsagene autotemcel is administered as a 1-time, single-dose intravenous infusion.[7]

Outcomes and efficacy

This intervention was evaluated in 39 children with MLD across 2 single-arm, open-label clinical trials and a European Union expanded access program.[8] Efficacy was assessed by evaluating both motor (Gross Motor Function Classification MLD scale) and neurocognitive function, with a primary endpoint of severe motor impairment-free survival. Follow-up evaluations were performed for up to 12 years after intervention (median 6.8 years).[7]

Compared with an external untreated natural history cohort (49 children), PSLI MLD participants showed significantly extended survival and motor function: 100% (17 total) had preserved neurodevelopmental skills at 5 years vs 0% untreated; most participants retained independent ambulation past 5 years of age; all PSLI MLD participants were alive by 6 years of age vs 58% of untreated (14/24); severe cognitive impairment was not observed in almost any PSLI MLD participants.[7,9]

Among 7 participants with PSEJ MLD, 1 died from cerebral infarction. Three retained normal gait up to 12 years of age; 2 untreated matched siblings lost all motor function by 6 years of age. Two participants retained stable normal cognitive function at 11 years of age.[7]

From the 10 participants with ESEJ MLD, 2 died from MLD progression. One had severe disease progression, whereas 6 of the remaining 7 participants retained normal cognitive function. However, 5 were no longer able to walk without support.[7] Twenty-eight participants with MLD (PSLI, PSEJ, and ESEJ) had preexisting gallbladder disease before intervention, 14 of whom (50%) demonstrated persistent MLD gallbladder disease after intervention. Five participants developed MLD gallbladder disease after intervention.[9,10]

Adverse effects and toxicity

Most common (>10%) adverse effects occurred within 1 year of intervention and were related to myeloablative conditioning: febrile neutropenia, stomatitis, respiratory tract infections, rash, device-related infections, other viral infections, gastroenteritis, and hepatomegaly.[11] Laboratory abnormalities, such as elevated D-dimer, neutropenia, and/or transaminitis, were also observed (~10%).[7] One participant died from a cerebral infarction secondary to a thrombotic event approximately 1 year after intervention.[7] Another participant experienced encephalitis 1 month after intervention. Three participants developed veno-occlusive disease, and 4 experienced delayed platelet engraftment.[7] Neutrophil engraftment failure, insertional oncogenesis (LVV-mediated), and hypersensitivity reactions were not observed in clinical trials. Participants receiving atidarsagene autotemcel should be monitored for hematologic malignancies given the overall risk of insertional oncogenesis, including a complete blood count with differential annually and integration site analysis as warranted, for at least 15 years.[7] There are no clinical data regarding the use of atidarsagene autotemcel in pregnant persons or its effects on lactation or fertility.[7]

Additional considerations

Other clinical trials for MLD are ongoing, including a phase-1/2 trial of intracerebral administration of an adeno-associated virus (AAV) vector containing *ARSA* complementary DNA (AAVrh.10cuARSA),[12] a phase-2 trial of intrathecal enzyme replacement therapy (SHP611),[13] and a phase-3 trial to evaluate the efficacy of cryopreserved atidarsagene autotemcel.[14]

Conflict of Interest

All workgroup members receive a 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: Sandhya Kharbanda is a principal investigator for an unrelated clinical trial sponsored by Orchard Therapeutics. All other authors declare no additional conflicts of interest.

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