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ACMG THERAPEUTICS BULLETIN

Elivaldogene autotemcel approved for treatment of cerebral adrenoleukodystrophy (CALD) in males: A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Adrenoleukodystrophy (X-ALD) is an X-linked disorder caused by pathogenic variants in *ABCD1*. *ABCD1* encodes a transporter required for 26-carbon fatty acids to cross peroxisome membranes for beta-oxidation or sphingolipid synthesis. In X-ALD, very-long-chain fatty acids (VLCFA) accumulate throughout the body, in particular, the brain, spinal cord, and adrenal glands. VLCFA accumulation disrupts the blood-brain barrier, and focal leukocytes infiltrate the white matter. Affected males may present with cerebral adrenoleukodystrophy (CALD), adrenomyeloneuropathy (AMN), and/or primary adrenocortical insufficiency.

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Heterozygous females are not at risk for CALD but may present with AMN and primary adrenal insufficiency in adulthood.[1] CALD is characterized by rapidly progressive, irreversible neurocognitive degeneration, resulting in early death. To screen for this lethal disease manifestation, the US Recommended Uniform Screening Panel added X-ALD in 2015, and many states are currently screening for this condition.[2]

Management and Treatment

Consensus-based management guidelines published in 2022 include recommendations for age-related interval of brain magnetic resonance imaging (MRI) monitoring of affected males to detect early signs of CALD before clinical symptoms, as well as laboratory monitoring for adrenal insufficiency. Multidisciplinary care encompassing genetics, neurology, and endocrinology is necessary for disease management. These guidelines include considerations for all patients, in terms of long-term care and counseling for pediatric patients identified by newborn screening.[3]

There are currently no other Food and Drug Administration–approved (FDA) specific treatments for X-ALD. The standard treatment for CALD has been allogeneic hematopoietic stem cell (HSC) transplant early in the course of cerebral disease, aiming to halt the progression of demyelination in the central nervous system. Adrenal insufficiency is treated with standard steroid replacement therapy.[4] There is no specific treatment for AMN.

Newly Approved Therapy

Indication and approved treatment population

Elivaldogene autotemcel (trade name: SKYSONA) is a Lenti-D lentiviral vector-based gene therapy. Elivaldogene has been FDA approved for males, aged 4 to 17 years old, with evidence of early and active cerebral ALD. Ideal patients are asymptomatic or mildly affected (neurologic function score, NFS $\leq$1) with Loes scores of 0.5 to 9 and evidence of gadolinium enhancement on brain MRI. FDA approval was obtained via accelerated approval.[5]

Mechanism of action

Elivaldogene therapy begins with mobilization and apheresis of the patient's peripheral blood autologous CD34+ HSCs. These cells are transduced with lentiviral vector containing ABCD1-cDNA for functional human ALD protein (Lenti-D LVV). Efficacy of the transduction is verified by polymerase chain reaction assays quantifying DNA insertions (vector copy number), ability of the stem cells to form hematopoietic cell colonies, and ALD protein expression by flow cytometry reflecting the success of the genetic modification. Once the manufactured process is verified, the engineered CD34+ cells are reintroduced back to the patient following full myeloablative and lymphodepleting chemotherapy conditioning to ensure engraftment. The transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including monocytes capable of producing functional ALD protein. ALD protein can then participate in local degradation of VLCFAs preventing further inflammation and demyelination.[5]

Outcomes and efficacy

Cartier et al demonstrated that autologous transplant of lentiviral vector engineered CD34+ cells led to functional production of ALD protein in 2 patients with progressive CALD.[6] Radiographically, cerebral demyelination arrested 14 to 16 months post therapy, and clinically, the 2 patients remained stable. These results led to the STARBEAM trial (ALD-102) enrollment of males with early active ALD treated with elivaldogene. Eichler et al reported the interim results of 17 boys who received elivaldogene, demonstrating that most patients (n = 15) remained alive and free of major functional disabilities with stabilized lesions on brain MRI.[7] Twelve patients maintained a CALD-specific NFS of 0 during the follow-up period between 18 to 36 months.[7] The stabilized Loes scores suggest limited disease progression after treatment. Safety and efficacy of elivaldogene was assessed by 2 open-label clinical trials (ALD-102 and ALD-104) with total enrollment of 67 males with early active ALD, demonstrating 90% overall survival 2 years post therapy.[5] Slower progression to major functional disability or death from time of symptom onset (first NFS $\geq$1) was seen for patients treated with elivaldogene compared with the known natural history rates of lesion progression among untreated boys.[5]

Adverse effects and toxicity

Hematological malignancy developed in 3 study participants and is a boxed warning on the package insert. Malignancies demonstrated integration into the *MECOM* proto-oncogene between 14 months and 7.5 years after elivaldogene treatment. The most common adverse reactions include mucositis, nausea, vomiting, diarrhea, decreased appetite, febrile neutropenia, alopecia, and seizures. Laboratory abnormalities include leukopenia, lymphopenia, neutropenia, anemia, and hypokalemia.[5]

Additional Considerations

Numerous clinical trials for X-ALD are in process or being planned around the world. Clinical trials of elivaldogene are continuing to monitor treated patients for long-term outcomes. A phase 1/2 study is in progress with an AAV9 vector using an in vivo gene therapy strategy.[8] Another study is evaluating intrathecal administration of oligodendrocyte-like cells,

derived from an unrelated umbilical cord transplantation, to expedite delivery of donor cells to the central nervous system during the engraftment period post transplantation.[9] Two other studies are exploring modifications to stem cell transplantation protocols to improve engraftment efficiency and reduce mortality (NCT03513328, NCT04528706). A phase 1b, multicenter, randomized, anonymized, placebo-controlled study to treat AMN symptoms in males is in progress (NCT04973657). Another study is recruiting females with X-ALD and restless leg syndrome for response to pramipexole (NCT05003648). Several registries are recruiting patients to expand natural history data and disease progression of ALD (NCT03789721, NCT05008874, and NCT05939232).

Elivaldogene was granted orphan drug, rare pediatric disease, and breakthrough therapy designations by the FDA. It received priority review and rare pediatric priority review voucher upon approval.

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Conflict of Interest

The authors declare no conflicts of interest.

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