Editorial

ANNALS OF MEDICINE & SURGERY

OPEN

'Lenmeldy (OTL-200) in MLD: FDA's validation of advanced therapy'

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Introduction

Metachromatic leukodystrophy (MLD) is a rare disease studied within lysosomal storage disorders. It is inherited in an autosomal recessive manner primarily due to mutations in the ARSA gene, which lead to a deficiency of the arylsulfatase A lysosomal enzyme[1,2]. This deficiency causes sulfatides to accumulate as metachromatic granules in nervous system cells, damaging the myelin sheath and resulting in demyelination[1]. Symptoms include motor impairment, ataxia, optic atrophy, spasms, and cognitive impairment[1,2]. Sulfatides also accumulate in internal organ cells like the gallbladder, increasing the risk of malignant tumors[1]. Additionally, they alter the morphology of the endoplasmic reticulum (ER) and mitochondria in Schwann cells[3].

Mutations in the PSAP gene can also cause MLD by affecting the sphingolipid activator protein SapB, leading to similar sulfatide accumulation and thus demyelination[4]. However, for the purpose of this article, we will focus on the ARSA gene, as it is the main target of Lenmeldy. MLD is primarily diagnosed through genetic sequencing to detect mutations, along with clinical symptoms like progressive neurologic dysfunction, brain MRI showing leukodystrophy, and biochemical tests measuring ARSA enzyme activity[1]. Nonstandard methods include quantifying sulfatides in plasma and urine and assessing peripheral nerve size, which can help in both diagnosis and prognosis[5].

Despite its rarity (1 in 40 000–160 000), MLD is a significant global leukodystrophy without authorized treatments, leaving supportive care as the only management option[1].

However, a breakthrough occurred with FDA approval of Lenmeldy gene therapy on 18 March 2024[6]. This gene therapy promises improved quality of life and potential outcomes for MLD patients, marking a pivotal advancement in the landscape of neurological diseases. This article explores the FDA's approval of Lenmeldy gene therapy and its implications for the future of MLD treatment.

Overview of Lenmeldy

Lenmeldy, also known as OTL-200[7], is a single-use, genetically engineered infusion therapy designed to halt the progression of metachromatic leukodystrophy (MLD). This therapy involves harvesting CD34+ hematopoietic stem cells (HSCs) from the patient's bone marrow or peripheral blood, which have the potential to develop into white blood cells. These cells are then transduced with a lentiviral vector carrying the ARSA gene, enabling them to produce the ARSA enzyme that is deficient in individuals with MLD[8]. After the patient undergoes a myeloablative conditioning regimen with Busulfan to facilitate engraftment[9], the modified CD34+ cells are infused back into the patient intravenously. These cells travel through the bloodstream to the bone marrow, where they engraft, proliferate, and differentiate into leukocytes that secrete functional ARSA enzymes. This enzyme helps degrade sulfatides in surrounding cells, thereby mitigating the symptoms of MLD[9].

Conventional pharmacokinetics do not apply to Lenmeldy because the modified cells persist and actively function within the patient's body to halt the progression of MLD[9]. Unlike traditional medications that require elimination from the body, Lenmeldy does not need to be removed. Biodistribution studies have shown that Lenmeldy is distributed to hematopoietic tissues and disease target organs, particularly the brain[9].

The effectiveness of Lenmeldy was evaluated through clinical studies and an expanded access program focusing on survival without severe motor disability as the primary measure. Treated children showed increased survival rates and improvements in language, cognitive abilities, and motor function[6]. The safety profile was deemed manageable and aligned with the disease and treatment process, with ongoing long-term safety monitoring postmarketing.

Efficacy and safety profile

Atidarsagene autotemcel (arsa-cel, OTL-200, marketed as Libmeldy or Lenmeldy) is an autologous hematopoietic stem cell-based gene therapy recently approved for metachromatic leukodystrophy[6].

The efficacy of Lenmeldy or arsa-cel for early-onset MLD was assessed in a clinical trial in patients with presymptomatic late-infantile MLD, where the symptoms appeared before 30 months of age, and presymptomatic early juvenile MLD, that is, when symptoms appear between 30 months and 6 years[10]. An

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:6376–6380

Received 8 July 2024; Accepted 10 September 2024

Published online 17 September 2024

http://dx.doi.org/10.1097/MS9.0000000000002580

integrated analysis was conducted using data from a prospective, nonrandomized, phase 1/2 clinical study, combined with expanded-access frameworks. This analysis included 29 pediatric patients with early-onset MLD treated with arsa-cel, compared to a natural history cohort of 31 untreated patients. Presymptomatic or early symptomatic MLD is characterized by symptoms for less than 6 months with an IQ of 70 or more and the ability of the patient to walk independently for at least 10 steps[11]. The primary efficacious outcomes included a 10% improvement in gross motor function over 2 years, assessed by using the proper gross motor function measure (GMFM), a change in the activity of the arylsulfatase-A (ARSA) enzyme in the total peripheral blood mononuclear cell when compared to baseline after 2 years, and an improvement in ARSA activity in the CSF, which was initially undetectable but became estimable 3 months post-treatment and reached normal levels by 6–12 months. Most treated patients maintained an impairment-free survival, that is, they were able to preserve and sustain gross motor functions at or below level 4 of classification. MRI total scores showed reduced white matter involvement, and an improvement in nerve function was observed[10].

Adverse effects included anti-ARSA antibody formation in five cases, which resolved spontaneously or with rituximab therapy, busulfan-associated veno-occlusive disease, and thrombotic microangiopathy[10]. Two patients experienced metabolic acidosis, and two had gallbladder polyps, both related to the underlying disease. No malignant transformations were observed. The study[10] revealed three deaths, all unrelated to the treatment, attributed to rapid disease progression and/or ischemic stroke. The most common adverse effects related to busulfan conditioning included febrile neutropenia, gait disturbance, and stomatitis[10].

Table 1 summarizes the clinical trial evaluating the efficacy and safety of Lenmeldy (arsa-cel) in patients with early-onset metachromatic leukodystrophy (MLD).

In conclusion, Lenmeldy offers a promising treatment option for metachromatic leukodystrophy, enhancing patient care and disease prognosis.

Current studies on Lenmeldy

Retrospective cohort studies and clinical cases highlight the long-term efficacy and safety of Lenmeldy, a gene therapy for metachromatic leukodystrophy (MLD).

Atidarsagene autotemcel's efficacy and safety were demonstrated in a real-world study[12] at Royal Manchester Children's Hospital, where 17 patients were reviewed. Four met the eligibility criteria and showed successful treatment outcomes. Common adverse effects were related to busulfan conditioning, with no serious treatment-related complications observed. This study highlights the importance of early diagnosis and treatment for optimal results[12]. Atidarsagene autotemcel has demonstrated significant benefits in children with early-onset MLD by preserving cognitive and motor function and slowing disease progression, underscoring the potential for improved outcomes with timely intervention.

Patients who underwent hematopoietic stem cell transplantation (HSCT) after symptom onset experienced significant psychomotor decline compared to untreated individuals. However, HSCT has shown benefits in adult MLD patients, including slowed disease progression and stabilized neurological and cognitive function based on EEG and MRI results, even after symptom onset[5]. In early-onset MLD cases treated with HSCT before or soon after symptom onset, Lenmeldy helps stabilize the disease and reduce loss of motor and cognitive skills[1]. A case–control study showed that it treats neuroinflammation and facilitates remyelination in the central nervous system, although its effect on peripheral neuropathy remains unknown[13].

Cord blood cell transplantation (CBCT) is a viable alternative to hematopoietic stem cell transplantation (HSCT) for early infantile and juvenile metachromatic leukodystrophy (MLD). A longitudinal study[14] and a case series with a literature review[15] concluded that CBCT maintains cognitive function and delays neurodegeneration, though it can induce peripheral neuropathy as a side effect. Clinical trials of MGTA-456, a drug that enhances microglial engraftment post-CBCT, may further improve outcomes[1]. Mesenchymal stem cell (MSC) therapy also shows promise; a case report[16] demonstrated that MSC infusion improves nerve conduction velocity and neurological stability, especially when combined with HSCT in adult MLD patients[1].

Table 2 provides a summary of the research related to OTL-200.

In summary, Lenmeldy's efficacy and safety, alongside therapies like MSC and CBCT, promise advancements in MLD treatment. Future research should refine protocols, enhance immunomodulation, and explore innovative therapies.

Table 1

Summary of the clinical trial evaluating the efficacy and safety of Lenmeldy (OTL-200) in patients with early-onset metachromatic leukodystrophy (MLD)

Aspect	Details
Therapy	Atidarsagene autotemcel
Trial name	Lentiviral hematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomized, open-label, phase 1/2 trial and expanded access
Method	Integrated analysis of a prospective, non-randomized, phase 1/2 clinical study and expanded-access frameworks. 29 pediatric patients with early-onset MLD treated with arsa-cel and compared to a natural history cohort of 31 untreated patients
Patient population	Pre-symptomatic or early symptomatic early-onset MLD with biochemical and molecular confirmation of diagnosis
Follow-up	Median follow-up of 3.16 years (range 0.64–7.51 years)
Efficacy outcomes	1. 10% improvement in gross motor function over 2 years 2. Increased ARSA enzyme activity in blood compared to baseline 3. Reduced white matter involvement on MRI 4. Improved nerve function
Adverse effects and safety	1. Anti-ARSA antibody formation (resolved spontaneously or with rituximab) 2. Busulfan-associated Veno-occlusive disease 3. Thrombotic microangiopathy 4. Metabolic acidosis 5. Gallbladder polyps 6. Febrile neutropenia 7. Gait disturbance 8. Stomatitis 9. No malignant transformations observed 10. Two deaths due to disease progression and one due to a sudden event deemed unlikely to be related to treatment

Table 2

Summary of research related to OTL-200 (atidarsagene autotemcel)

Study name	Study type	Treatment used	Patient population	Outcomes	Adverse effects	Comments
Real-world study at Royal Manchester Children's Hospital	Retrospective cohort study	Atidarsagene autotemcel	Seventeen patients with MLD; four met eligibility	Preservation of cognitive and motor functions; slowed disease progression	Common: related to busulfan conditioning. No other serious complications	Highlights the importance of early diagnosis and treatment for optimal results
Long-term outcome of allogeneic hematopoietic stem cell transplantation in patients with juvenile metachromatic leukodystrophy compared with nontransplanted control patients	Case–control study	Hematopoietic stem cell transplantation (HSCT)	Early-onset MLD; treated pre/postsymptom onset	Stabilization of disease; reduced loss of motor and cognitive skills; slowed progression in adults	Potential psychomotor decline if administered postsymptom onset	Demonstrates efficacy in stabilizing MLD in early-onset cases; benefits noted in adults with late intervention
Neurodevelopmental outcomes of umbilical cord blood transplantation in metachromatic leukodystrophy	Longitudinal study	Cord blood cell transplantation (CBCT)	Twenty patients: six with late-infantile onset, 14 with juvenile onset	Maintains cognitive function; delays neurodegeneration	Induces peripheral neuropathy and mild deterioration in motor skills	Serves as an alternative to HSCT; additional adverse effects to be managed
Outcome of early juvenile onset MLD after unrelated cord blood transplantation: a case series and review	Case series and review	Cord blood cell transplantation (CBCT)	Three asymptomatic children (aged 2 years 4 months, 2 years 8 months, 5 years 5 months) + two untreated symptomatic siblings	Significant slowing of disease progression in treated patients; stable parameters observed	Induces peripheral neuropathy and mild intellectual impairment	UCBT significantly alters the natural history of early juvenile onset MLD; benefits noted in comparison to untreated siblings
Reduced intensity conditioning HSCT with mesenchymal stromal cells infusion for the treatment of MLD: a case report	Case report	Mesenchymal stem cell therapy (MSC)	23-year-old adult female with MLD	Improved nerve conduction velocity; neurological stability when combined with HSCT	No side effects reported	Shows promise, particularly when combined with HSCT

Future implications

Lenmeldy treatment is specifically approved for individuals with selective MLD subtypes, including asymptomatic late infantile or early juvenile disease, who maintain independent walking ability and show no decline in cognitive ability. Patients not meeting these criteria are ineligible, reducing the potential beneficiary pool.

Metachromatic leukodystrophy (MLD) can be detected in newborns with almost 100% test specificity[17]. Through this kind of screening, afflicted children can be identified early, improving diagnostic accuracy while also exposing a wider range of disease phenotypes[17]. Among them is a rise in the frequency of milder types, which emphasizes how important early screening is for enabling prompt therapies that lead to better patient outcomes[17]. However, without a national newborn screening (NBS) program for MLD, many patients are diagnosed late in the disease course, making them ineligible for treatment. A recent survey of MLD caregivers in the UK provides strong support for the necessity of such NBS programs[18].

There is a scarcity of Qualified Treatment Centers (QTC) with expertise in LD management and HSC transplantation, which can further delay access to treatment for eligible patients. Royal Manchester Children's Hospital (RMCH) stands as the sole QTO for arsa csel in the United Kingdom. The prolonged approval process for screening programs, such as adding MLD to the UK newborn blood spot program, leads to the deterioration and premature death of affected children. This situation places a significant financial and psychological burden on the entire family[12]. Diagnostic delays result in patients being diagnosed at advanced stages, where treatment options like Lenmeldy are less effective. Providing education and training to healthcare professionals about MLD symptoms, diagnostic criteria, and treatment options can help improve early recognition and referral of MLD patients to specialized centers for evaluation and potential treatment[19].

Fast-tracking the approval and implementation of a national NBS program for MLD can enable early diagnosis and timely treatment with Lenmeldy before symptom onset. Increasing the number of QTCs equipped to administer Lenmeldy and provide comprehensive care for MLD patients can reduce waiting times and improve access to treatment for eligible patients.

Conclusion

In conclusion, Lenmeldy represents a pivotal advancement in treating metachromatic leukodystrophy (MLD), demonstrating efficacy in preserving cognitive and motor function while slowing disease progression. However, challenges persist, particularly regarding accessibility in regions with limited resources for gene therapy and disparities in access to diagnostic testing. Addressing these disparities requires concerted efforts to expand treatment centers and implement comprehensive screening programs. Moving forward, more research and infrastructure development in the healthcare sector are crucial to refine protocols, enhance accessibility, and explore additional therapeutic options to further improve outcomes for all MLD patients.

Ethical approval

As this is an editorial article without the involvement of patients, no ethics approval was necessary.

Consent

As this is an editorial article without the involvement of patients, ethical considerations regarding patient consent and privacy do not apply.

Source of funding

Not applicable.

Author contribution

A.A.Q.: conceptualization, writing and reviewing, and drafting the manuscript; B.S., A.S.A., A.H.S., and H.T.: writing; M.F.T. and M.H.J.: reviewing.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

As this is an editorial article without the involvement of human subjects, do not apply.

Guarantor

All the authors certify to be the guarantor.

Data availability statement

No data was used for the research described in the article.

Provenance and peer review

Not applicable.

Acknowledgements

Not applicable.

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