



Gene therapy offers new hope for children with metachromatic leukodystrophy

See [Articles](#) page 372

Metachromatic leukodystrophy (MLD) is a rare, progressive lysosomal storage disease caused by mutations in the gene encoding arylsulfatase A (ARSA), causing disease in the central and peripheral nervous systems. MLD presents in toddlers (late infantile disease) or in children (juvenile disease) with gait disturbances, loss of developmental milestones, and cognitive decline, leading to death in childhood. It is frequently not diagnosed until the later symptomatic phase when it is too late to intervene. Haematopoietic stem-cell transplantation (HSCT) from allogeneic donors has been used with mixed results. Although HSCT can slow progression of disease in the central nervous system, it does not prevent progression in the peripheral nervous system. HSCT is also associated with risks of graft-versus-host disease and treatment-related toxicity.¹⁻⁴ Additionally, small trials of intrathecal gene therapy in mice or humans did not result in improvement in symptoms of clinical disease.⁵ Thus, new therapeutic approaches are desperately needed.

In *The Lancet*, Francesca Fumagalli and colleagues⁶ report results of the first haematopoietic stem-cell gene therapy (atidarsagene autotemcel [arsa-cel]) clinical trial for young paediatric patients with early-onset MLD. The study cohort consisted of 29 patients, 16 with the late-infantile variant and 13 with the early-juvenile variant, with presymptomatic or early symptomatic disease. Patients were treated on protocol (n=20) or through expanded access (n=9) over a 7-year enrolment period. With a median follow-up of 3.2 years, three patients died, two of rapidly progressive MLD and one of a stroke of unclear cause, and 26 patients survive with encouraging results. These patients were included in the analysis of cellular and clinical outcomes, which were compared to an untreated natural history cohort of 31 patients with early-onset MLD matched by age and disease subtype. The coprimary efficacy endpoints were an improvement of more than 10% with respect to the natural history cohort in the total gross motor function measure (GMFM-88) and change from baseline of total peripheral blood mononuclear cell ARSA activity at 2 years after treatment compared with pre-treatment values. At 2 years after gene therapy, GMFM-88 scores in the gene therapy group were 66% (95% CI 48.9–82.3) higher in children with late infantile MLD ($p<0.0001$) and 42% higher (12.3–71.8) in children with early juvenile MLD ($p=0.036$) compared with the natural history, untreated cohort. Furthermore, nerve conduction velocity indexes in treated patients with late-infantile disease differed significantly in treated versus participants in the natural history cohort at years 2 ($p=0.004$) and 3 ($p=0.010$) of follow-up. This effect was not seen in early juvenile patients. Surviving patients in the gene therapy cohort also have persistent engraftment of transduced cells at 5 years, increased ARSA concentrations in peripheral blood in the late-infantile cohort, and high normal ARSA concentrations in the peripheral blood in the early-juvenile cohort at 24 months and later. ARSA concentrations in the cerebrospinal fluid was within normal range in both groups after treatment, an outcome not recorded in previous transplant studies.



Tetra Images/Getty Images

This is a well done study considering the rarity of MLD and the variability in the pace of disease progression after diagnosis. The authors showed benefit of arsa-cel gene therapy in children with presymptomatic or early symptomatic early-onset disease. Although safety and feasibility have been shown, longer follow-up will be needed to determine durability of clinical responses, especially in the peripheral nervous system, and survival of transduced cells. Other limitations include the small numbers of patients in each subgroup and the fact that the therapy is active in the earliest phases of the disease. Given that most patients with MLD are diagnosed after symptom onset, the efficacy of arsa-cel in that real-world population was not tested and is unlikely to be as good.

Arsa-cel treatment is an autologous haematopoietic stem and progenitor cell population transduced ex vivo with a lentiviral vector encoding human ARSA cDNA infused after conditioning therapy with busulfan. The strategy to deliver gene therapy through correction of engrafting haematopoietic cells was selected to produce over expression of enzyme after engraftment.^{7,8} Median engraftment was long at 28 days and likely due to the infusion of CD34⁺-selected cells after busulfan. The authors showed that myeloablative doses of busulfan conferred engraftment yet there were toxicities related to busulfan therapy in this group. Three (10%) of study participants had veno-occlusive disease or other forms of thrombotic microangiopathy despite the use of pharmacokinetics and dose adjustments during administration. Children with MLD could be at greater risk for these toxicities than those with other lysosomal storage diseases. Regardless, this risk should be reduced with use of better methods of prophylaxis against veno-occlusive disease such as defibrotide. Four patients also developed antibodies against ARSA. Although the authors did not note any interference with the efficacy of the gene therapy, it will be important to follow this occurrence for a longer period. They appropriately discuss careful monitoring and addition of immune-depleting therapies in future patients.

The results of this study, although not perfect, are very encouraging. They represent the first demonstration of arrest or slowing of progression of

both central and peripheral nervous system disease caused by MLD. Treatment of more patients with longer follow-up, probably for 10–20 years, is needed to fully understand the effect of this gene therapy on the disease. For example, is it slowing or arresting disease progression? It is also clear with arsa-cel and other gene therapy and HSCT interventions that the earlier the therapy is delivered, the more effective it is at arresting disease progression. For MLD, and other lysosomal storage diseases, early diagnosis through newborn screening will be crucial to identify babies and children at risk and before they manifest clinical symptoms of disease. The technology to screen for MLD in newborn dried blood spots is now available, and lobbying to add MLD to state newborn screening panels is definitely warranted. Arsa-cel is a very important advance for the treatment of MLD and is currently approved for marketing in the EU as Libmeldy. It should also be licensed by the Food and Drug Administration to enable treatment of MLD patients in the USA.

JK is a consultant for Neurogene, a company developing gene therapy for Krabbe disease. She is also developing a cell therapy using a microglial/macrophage cell manufactured from cord blood and under study funded by the Marcus Foundation. This technology was licensed by her institution to CryoCell International.

Joanne Kurtzberg
joanne.kurtzberg@dm.duke.edu

Marcus Center for Cellular Cures, Duke University School of Medicine, Durham, NC 27705, USA

- 1 Boucher AA, Miller W, Shanley R, et al. Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report. *Orphanet J Rare Dis* 2015; **10**: 94.
- 2 Wolf NI, Breur M, Plug B, et al. Metachromatic leukodystrophy and transplantation: remyelination, no cross-correction. *Ann Clin Transl Neurol* 2020; **7**: 169–80.
- 3 Beschle J, Döring M, Kehrer C, et al. Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy. *Mol Cell Pediatr* 2020; **7**: 12.
- 4 Vander Lugt MT, Chen X, Escobar ML, et al. Reduced-intensity single-unit unrelated cord blood transplant with optional immune boost for nonmalignant disorders. *Blood Adv* 2020; **4**: 3041–52.
- 5 Miyake N, Miyake K, Sakai A, Yamamoto M, Suzuki H, Shimada T. Treatment of adult metachromatic leukodystrophy model mice using intrathecal administration of type 9 AAV vector encoding arylsulfatase A. *Sci Rep* 2021; **11**: 20513.
- 6 Fumagalli F, Calbi V, Natali Sora MG, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet* 2022; **399**: 372–83.
- 7 Penati R, Fumagalli F, Calbi V, Bernardo ME, Aiuti A. Gene therapy for lysosomal storage disorders: recent advances for metachromatic leukodystrophy and mucopolysaccharidosis I. *J Inher Metab Dis* 2017; **40**: 543–54.
- 8 Rosenberg JB, Kaminsky SM, Aubourg P, Crystal RG, Sondhi D. Gene therapy for metachromatic leukodystrophy. *J Neurosci Res* 2016; **94**: 1169–79.