White paper

Improved outcomes for children with MLD following gene therapy: findings from a parent survey

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Executive summary

Background: Metachromatic leukodystrophy (MLD) is an ultra-rare inherited disease in which deficiencies in arylsulfatase A (ARSA) result in the accumulation of sulfatides and demyelination, leading to progressive loss of motor and cognitive skills and premature death. The gene therapy atidarsagene autotemcel (OTL-200; Libmeldy®; Orchard Therapeutics) is designed to correct the deficiency in the ARSA gene and is approved in the EU, UK, Iceland, Liechtenstein and Norway for the treatment of children with: i) pre-symptomatic late-infantile (LI) MLD; ii) early juvenile (EJ) MLD without clinical manifestations and iii) early clinical manifestations of EJ MLD. It has Regenerative Medicine Advanced Therapy status in the USA.

Atidarsagene autotemcel has been evaluated in a phase 1/2 open-label study (n=20) and accelerated access programmes (n=9) and the findings compared with an age-matched natural history cohort (n=31). At 2 years after treatment, children with pre-symptomatic or early MLD showed either normal motor and cognitive development, or the progression was halted or slowed.

MLD has a marked impact on the health-related quality of life (HRQL) of patients and carers/families. The current study of parents of children who have received atidarsagene autotemcel for MLD explored their experience of the treatment, focusing on disease stability and burden.

Method: The study consisted of a specially designed survey to collect demographic data and aspects of disease burden and carer burden, based on multiple choice, dichotomous and free-text answers.

Results: Responses were received from 13 parents of 13 children who had received gene therapy for MLD. Seven children with LI MLD had been treated 4–12 years prior (mean ± SD 6.8 ± 2.3 years), at a median age of 1.1 years (range 0.6–1.1) (13 [7–13] months). One child had pre-symptomatic EJ MLD and five had early symptomatic EJ MLD and had been treated 7–8 years prior (7.1 ± 0.6 years), at a mean age of 7 years (range 4–12).

- None of the seven children with LI MLD had visible symptoms before treatment and four showed no symptom progression during or after treatment and none showing progression once treatment was established. At the time of the survey, three had age-normal mobility, and six could move independently with no aid or support. All seven were in full-time mainstream school without additional support and were considered by their parents to be working towards their expected cognitive level. Only two had any problems with understanding and speech. Children took part in a full range of physical and non-physical activities without difficulty. All seven were independent in self-care. None had pain or discomfort or any symptoms.
- The five children with early symptomatic EJ MLD had mobility impairments before treatment. Some had symptom progression during or after treatment, but symptoms stabilised in most. Most of the children with symptomatic EJ MLD had some locomotion at the time of the survey, with two able to move independently with no aid or support. Three children were in full-time mainstream school without support, with all working at their expected levels, and did not have problems with understanding or speech. Two children could participate fully in physical and non-physical activities, and the other four with some support. Four children could manage self-care independently with little or no help. Three children experienced some pain and discomfort, but this was not severe. All except one child had few other symptoms, and none severe.
- Six parents of children with LI MLD reported no limitations in their daily lives because of their treated child, and no physical or mental health problems. Four of five parents with EJ MLD reported some limitations, but few reported mental or physical health problems.
- All nine parents who had a treated and non-treated child with MLD perceived that their treated child had good quality of life compared with the non-treated child. Parents personal statements included stark contrasts between the happy active lives of treated children and the inexorable decline of untreated children with MLD and described benefits of treatment for the whole family and hopes for the future.

Conclusions: This survey describes positive effects of gene therapy across all aspects of children's lives beyond clinical measures, including education, physical and non-physical activities, self-care and quality of life.

- Whilst MLD has been reported to have a marked effect on the quality of life of carers and families, the surveyed parents of children with LI MLD reported little burden following gene therapy, even several years later, consistent with the broad benefits reported in their children.
- Parents reported children with EJ MLD were at their expected cognitive levels or still improving in understanding and speech and, although they had some limitations, all children were able to participate in regular physical and/or non-physical activities.

1 Overview

Metachromatic leukodystrophy (MLD) is a lysosomal storage disease in which deficiency in the enzyme arylsulfatase A (ARSA) results in the accumulation of sulfatides in neural and visceral tissues and myelin degeneration in the central and peripheral nervous systems [1, 2]. ARSA deficiency is due to autosomal recessive biallelic mutations in the *ARSA* gene [3]. MLD is an ultra-rare condition, with an estimated worldwide prevalence of 0.1–0.9 per 100,000 [4].

Children with MLD develop normally initially but sulfatide accumulation and demyelination lead to the progressive loss of acquired speech, cognitive and motor skills and may become unable to swallow safely [5]. Most lose their motor and cognitive function within 3 years of disease onset and become bedridden with severe cognitive impairment and completely dependent on parents and caregivers [6]. Premature death is likely without treatment [3].

MLD is classified by four main clinical phenotypes based on the age of symptom onset [6] (Table 1). Late infantile (LI) MLD is the most common variant, with symptom onset at ≤30 months of age, and accounting for 40–60% of cases in European studies [7]. Generally, earlier age at symptom onset is associated with more rapidly progressive disease and shorter life expectancy. A retrospective systematic review of MLD cases since 1921 reported 5- and 10-year survival rates after symptom onset of 70% and 44%, respectively, for juvenile MLD (mean age 10 years at diagnosis) but 25% and 0%, respectively, for infantile MLD, although 5-year survival rates have improved since 1990 compared with before 1970 to 52% for infantile and 100% for juvenile) (Table 1) [8].

Table 1 Clinical phenotypes of MLD

Phenotype	Frequency [7]	Age at symptom onset [6]	Characteristics [6]	Survival probability [8][a]
Late infantile (LI)	40–60%	≤30 months	No residual ARSA activity Most aggressive form Highly predictable relentlessly progressive loss of motor and cognitive function and early death	Mean age at death, 4.2 years 5-year survival after onset, 25% 10-year survival, 0%
Early juvenile	20–35%	30 months to 6 years	Slower, more protracted initial disease progression than in LI, but symptoms progress rapidly once they appear and disease progression is similarly rapid once the ability to walk independently is lost	Mean age at death, 17.4 years 5-year survival after onset, 70% 10-year survival, 44%
Late juvenile		6–17 years	Cognitive and behavioural symptoms precede deterioration in motor function Slower and more prolonged disease course than with earlier onset forms	
Adult	15–25%	≥17 years		Mean age at death, 43.1 years 5-year survival after onset, 87% 10-year survival, 70%

[a]Based on systematic literature review, 1920–2006; 142 studies; 303 cases (98 late infantile; 78 juvenile; 127 adult). 5-year survival rate was significantly better after 1990 than before 1970 (late infantile, 52% vs 14%; juvenile: 100% vs 46%: adult, 95% vs 67%)

Atidarsagene autotemcel (OTL-200; Libmeldy®; Orchard Therapeutics) is a gene therapy that corrects the *ARSA* deficiency in MLD [9]. In this treatment, CD34+ haematopoietic stem and progenitor cells (HSPCs) are harvested from the patient's bone marrow or peripheral blood. The cells are transduced with *ARSA* lentiviral vector, which inserts one or more copies of the human *ARSA* cDNA directly into the genome, rendering the genetically modified cells capable of producing functional ARSA [9]. The patient undergoes myeloablative treatment with busulfan, after which the genetically modified HSPCs are infused; they engraft and repopulate the haematopoietic compartment and cross the blood–brain barrier and engraft in the central nervous system [9]. The cells produce supraphysiological levels of ARSA, which is taken up by surrounding cells, breaking down the build-up of harmful sulfatides[10]. Engraftment and reconstitution of ARSA activity in peripheral blood cells and cerebrospinal fluid takes 3–12 months following gene therapy [9]. However, the beneficial effect is expected to persist for the patient's lifetime given the self-renewing properties of gene-corrected HSPCs [6].

Atidarsagene autotemcel is approved in the European Union, UK, Iceland, Liechtenstein and Norway, and is designated as a Regenerative Medicine Advanced Therapy in the USA, allowing accelerated approval [11]. It is licensed for the treatment of children with: i) pre-symptomatic late-infantile MLD; ii) early juvenile (EJ) MLD without clinical manifestations; iii) early clinical manifestations of EJ MLD (i.e. able to walk independently and before the onset of cognitive decline) [9]. An early diagnosis is crucial to be able to administer the therapy early in life, before rapid deterioration occurs [12].

Atidarsagene autotemcel has been evaluated in a phase 1/2 open-label non-randomised study (n=20) and the findings combined with those from expanded access programmes (n=9) [10]. Sixteen children had pre-symptomatic LI MLD (one of whom became symptomatic between enrolment and treatment) and 13 had EJ MLD (eight with early symptoms). All patients showed durable and stable peripheral and multi-lineage engraftment of gene-corrected cells 1 month after treatment, and ARSA activity was restored to the normal range in the haematopoietic and central nervous systems within 3 months and remained stable[10].

The clinical effects of gene therapy were evaluated by comparison with an age-matched natural history cohort within the same disease subtypes (19 with LI MLD; 12 with EJ MLD), with follow-up for up to 8 years to date[10]. Patients with pre-symptomatic LI or EJ and early-stage EJ treated with atidarsagene autotemcel showed either normal motor development at 2 years after treatment, or stabilisation or delayed progression of motor dysfunction, as measured by the Gross Motor Function Measure (GMFM) total score (an assessment of gross motor activities in five domains: lying and rolling, sitting, crawling and kneeling, standing, and walking, running and jumping and the Gross Motor Function Classification for MLD (GMFC-MLD; a standardized assessment of clinically relevant stages from normal [Level 0] to loss of all gross motor function [level 6], for use from age 18 months [13], described in the footnote of Figure 2). Most patients also showed normal acquisition of cognitive skills. Treatment benefits were particularly apparent in patients who were pre-symptomatic before treatment. Furthermore, brain MRI suggested that the progressive demyelination and atrophy that characterize MLD were delayed if not stabilised or prevented. Twenty-six patients (90%) were alive at a median follow-up of 3.2 years (range 0.64–7.51) [10].

Health-related quality of life (HRQL) is an important outcome in rare diseases because of their often chronic nature and lack of effective treatment options [14]. Rare diseases also have a marked impact on the daily life and long-term wellbeing of families, who often provide substantial informal care [15]. MLD has been reported to have a substantial impact on HRQL of patients and on the emotional, social and psychological wellbeing of carers (largely parents) and the extended family [5, 16-18]. Here we report the findings of a survey conducted with families of children with LI or EJ MLD

following gene therapy, to understand their experience of the disease and treatment, focusing on disease stability and burden.

2 Method

The study was carried out by the ArchAngel MLD Trust and UK MPS Society on behalf of three UK organisations supporting MLD patients: the UK MPS Society, MLD Support UK and ArchAngel MLD Trust.

2.1 Survey

The study consisted of a specifically designed survey to collect demographic data and explore: disease burden, mobility (GMFC-MLD score), self-care, cognitive skills, pain, medical symptoms, hospital appointments, schooling, activities and carer burden. Questions were multiple choice or required dichotomous or free-text answers. Respondents also had the opportunity to provide personal statements.

2.2 Study population

The questionnaire was emailed by ArchAngel MLD Trust to 13 English-speaking individuals from seven countries (Canada, France, Italy, Republic of Ireland, Sweden, UK, USA) who were parents/caregivers of patients who had a confirmed diagnosis of LI or EJ MLD (pre-symptomatic or early symptomatic) and who had received gene therapy. Respondents had to be at least 18 years of age and able to provide informed consent.

Background information was provided about the aims of the survey and data anonymity, and requested informed consent to participate electronically. Respondents could withdraw from the study at any time, without giving a reason. ArchAngel MLD Trust received the survey responses electronically and shared the de-identified surveys with MPS Society for analysis. ArchAngel MLD Trust followed-up with patients to collect missing responses.

The study took place between July and August 2021.

3 Results

Responses were received from all participants who were invited to take part in the study: 13 parents of 13 children with MLD who had received gene therapy.

3.1 Participant characteristics

Seven of the treated patients had LI MLD, one had pre-symptomatic EJ MLD and five had early symptomatic EJ MLD. Nine families also had an older child with MLD who had not received gene therapy (7 with a treated child with LI; 2 with a treated child with EJ). Two of the children with LI MLD were brothers.

Children with LI MLD had received gene therapy 4–12 years prior (mean ± SD 6.8 ± 2.3 years), at a median age of 1.1 years (range 0.6–1.1) (13 [7–13] months). Children with EJ MLD had received gene therapy 7–8 years prior (7.1 ± 0.6 years), at a mean age of 7 years (range 4–12) (Table 2).

Table 2 Characteristics of children with MLD

		Late infantile (n=7)	Early juvenile (n=6)
Male/female, n		5/2	3/3
Age at time of survey, years	Median (range)	6.0 (4.4–11.5)	14.1 (10.7–18.5)
	Mean ±SD	6.8±2.3	14.4±2.7
Age at diagnosis, years	Median	0.8 (0.1–1.0)	6.4 (3.6–11.0)
	Mean ±SD	0.6±0.4	6.4±2.6
Age when treated, years	Median (range)	1.1 (0.6–1.1)	7.2 (4.1–11.8)
	Mean ±SD	0.9 ± 0.2	7.2 ± 2.6
Time since treatment	Median (range)	5.4 (3.3–10.4)	7.0 (6.6–8.1)
	Mean ±SD	5.8±2.3	7.1±0.6

3.2 Treatment effect

Parents reported the treatment effect to be established at a median of 6 months after treatment (range 6–21) in children with LI MLD (n=5) and at 3 (3–24) months in children with EJ MLD (n=3) (Table 3). However, some children showed a much longer time to treatment effect.

Table 3 Reported time (in months) from treatment administration to established treatment effect

	Late Infantile (n=5)	Early Juvenile (n=3)
Median	6	3
Mean ±SD	9.6±7.2	9.6±12
Range	6–21.6	3–24

3.2.1 Disease stability

None of the seven children with LI MLD had visible symptoms before treatment and four showed no symptom progression during or after treatment. Likewise, the single child with pre-symptomatic EJ MLD did not have symptoms at any time from treatment administration onwards (Figure 1).

Three children with LI MLD showed progression of neurological symptoms after the start of treatment (mild peripheral neuropathy and slight change in white matter) but these symptoms stabilised once the treatment effect was established, with no further progression (Figure 1).

The five children with early symptomatic EJ MLD largely had symptoms related to mobility before treatment (e.g. balance issues, falling/tripping, abnormal gait; n=5), followed by tremors (n=3). Two children did not experience symptom progression during treatment (i.e. between gene therapy and the treatment effect becoming established), but one had a decline in walking after the treatment effect had become established, and one developed a slight turning of feet and muscle tightness. The other three children with symptomatic EJ MLD experienced progression of symptoms during treatment but in two children the symptoms stabilised once the treatment effect was established, with no further progression. Symptoms did not stabilise in one child, and they experienced progression in all aspects of general living after the treatment effect was established (Figure 1).

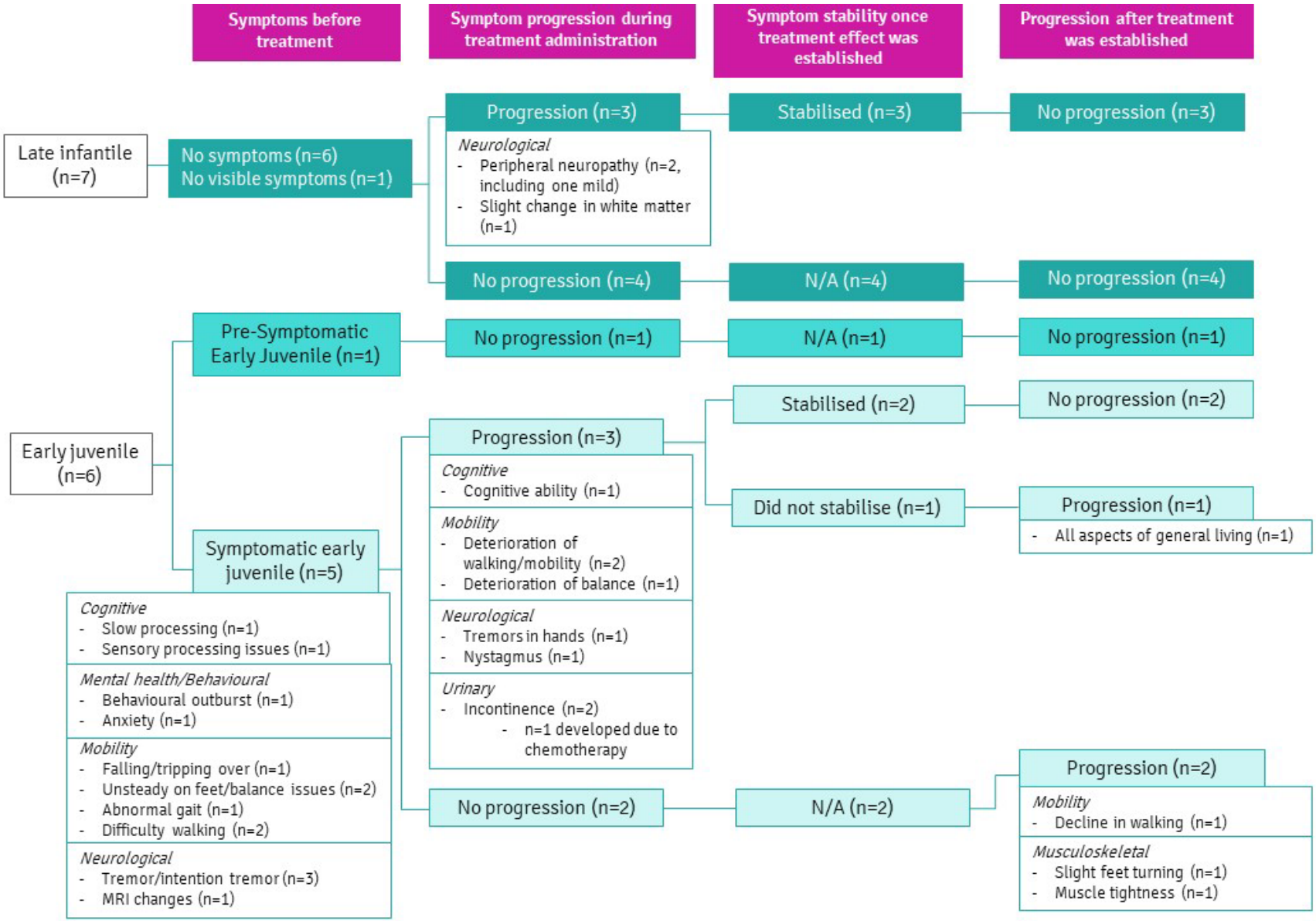

Figure 1 Disease stability: symptom presence and progression

3.2.2 Mobility – current GMFC-MLD score

Twelve parents knew their child's current score (one score missing for a child with LI MLD); 11 of these children had a score of 0–2, indicating some degree of locomotion, and one child with EJ MLD had a score of 4 indicating impaired locomotion or posture (Figure 2).

GMFC-MLD scores were available for six LI MLD children. All six children had GMFC-MLD scores in the range 0–2. Parents of three children reported a current score of 0, indicating age-normal mobility, with two parents also stating that their child "has always maintained their curve with age progression and no declines" and "GMFC has always been normal with no regression" (Figure 2a).

Parents were also asked to choose the statement that best described their child's mobility now. From seven LI MLD children, six were considered independent at walking and did not need aids or support. The child with GMFC-MLD score of 2 was considered independent but requiring support or aids (Figure 2b).

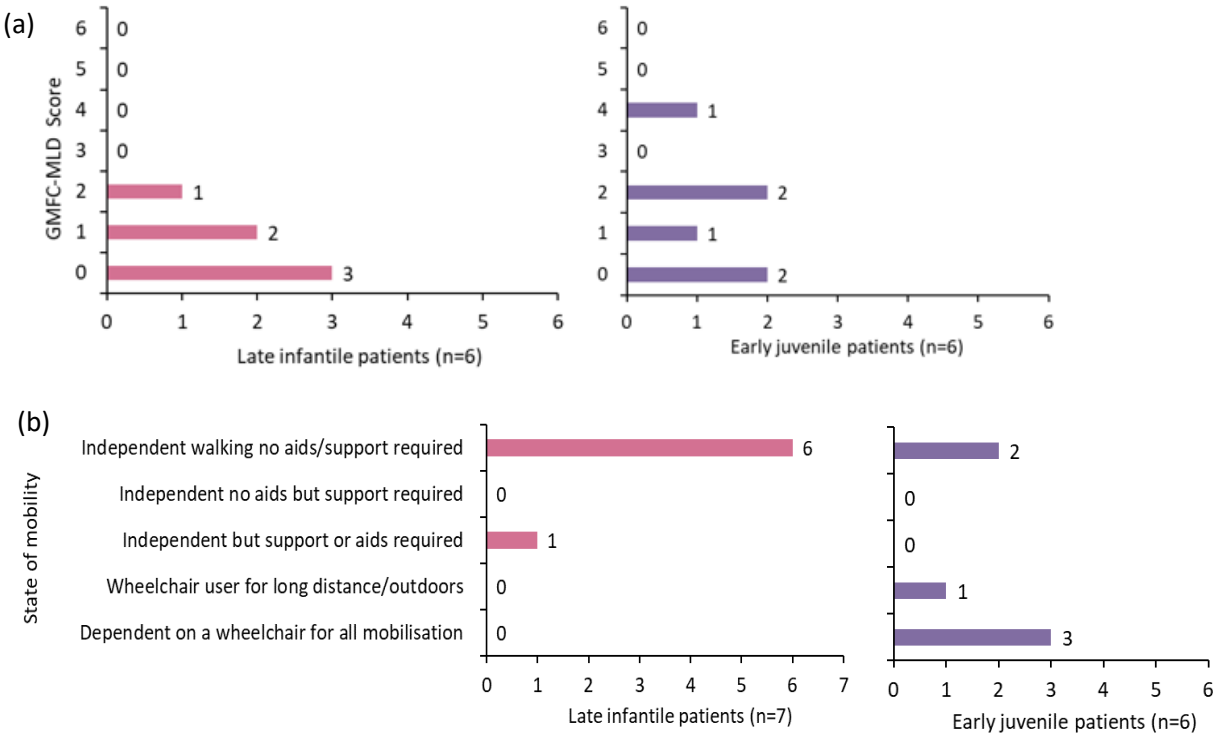

Figure 2 Mobility based on (a) parent-reported current Gross Motor Function Classification for MLD (GMFC-MLD) score and (b) description of mobility state

GMFC-MLD Level 0 = Walking without support with quality of performance normal for age; Level 1 = Walking without support but with reduced quality of performance (i.e. instability when standing or walking); Level 2 = Walking with support. Walking without support not possible (fewer than 5 steps); Level 3 = Sitting without support and locomotion such as crawling or rolling. Walking with or without support not possible; Level 4 = Sitting without support but no locomotion or sitting without support not possible, but locomotion such as crawling or rolling; Level 5 = No locomotion or sitting without support, but head control is possible; Level 6 = Loss of any locomotion as well as loss of any head and trunk control [19].

Among the parents of children with EJ MLD (including one child with pre-symptomatic disease), two reported a score of 0 and three reported a score of 1 or 2. One parent reporting a GMFC-MLD score of 2 explained that the score had fluctuated because of problems with feet, tremors and some muscle weakness; the child was wheelchair dependent for all mobilisation. One child with EJ MLD had a reported GMFC-MLD score of 4, 6.6 years after treatment; their parent explained that symptoms had not progressed since the treatment effect was established but the score had increased because the child had developed hip sub-luxation as a secondary complication of wheelchair use and inadequate postural support.

Overall, three children with EJ MLD children were wheelchair-dependent for all mobilisation and one used a wheelchair for long-distances and when outdoors. Two were independent with no need for aids or support (Figure 2b).

3.2.3 Education

All seven children with LI MLD attended mainstream school full-time and did not require additional support. Three of the six children with EJ MLD were also in full-time mainstream school. One (with pre-symptomatic EJ MLD) did not require additional support and two were provided with a learning support assistant to help with learning needs. Two children with EJ MLD were in full-time special education and/or received provision for physical disability and additional support for 4 or more hours per day, such as a personalised curriculum to accommodate slow processing, support with learning and understanding, and support with physical tasks and self-care. One child with EJ MLD attended both a mainstream school and special educational needs provision part-time for physiotherapy, and received support in the form of audio instructions, a timetabled weekly structure and extra time to complete tasks.

3.2.4 Cognitive function

Intelligence quotient score were reported for one patient with LI MLD (106) and four with EJ MLD (median 96.5; mean 95.5±13.8; range 80–109).

All seven children with LI MLD were considered by their parents/carers to be working towards or at their expected cognitive level at the time of the survey. Among the six children with EJ MLD, three were working towards or at expected levels. Two of the three who were not working towards or at expected cognitive levels for their age were still improving in understanding and speech.

3.2.5 Understanding and speech

Five of the seven children with LI MLD children were reported to have no problems with understanding at the time of the survey and two had some problems (Figure 3). Among the six children with EJ MLD, four had no problems, one had some problems and one had significant problems. None of the seven children with LI MLD had speech problems. Among the six children with EJ MLD, three had no problems with speech, two had some problems and one had significant problems.

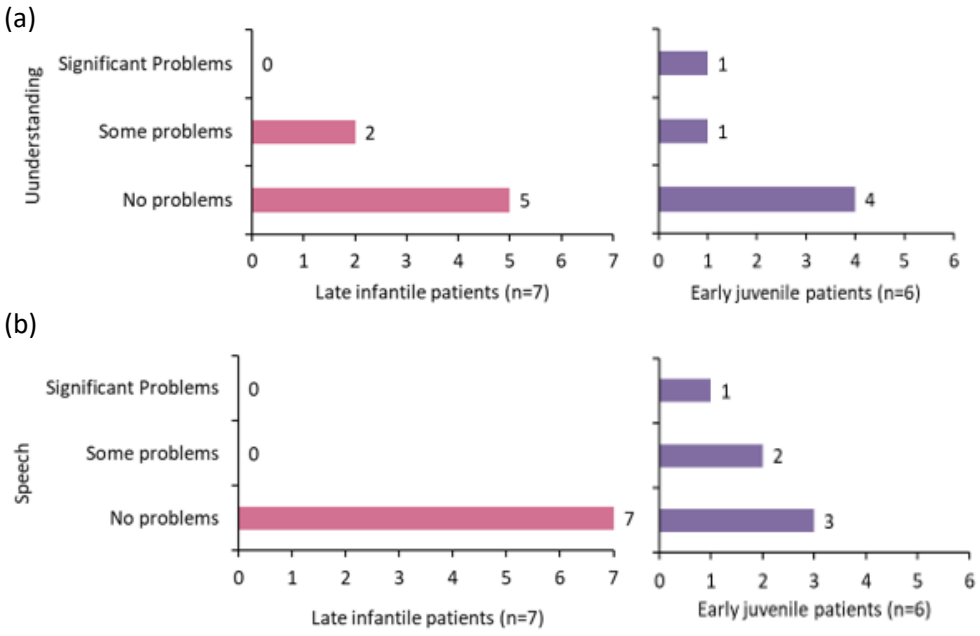

Figure 3

Parent-reported problems with (a) understanding and (b) speech

3.2.6 Activities

Parents reported that, once the treatment effect was established, all the children with LI MLD were able to participate in a broad range of physical activities and non-physical activities without difficulty (Table 4). Among the six children with EJ MLD, two could participate in activities without difficulty and four had some difficulties.

Table 4 Activities that children could participate in since the treatment effect was established (numbers in parentheses are the number of children reported to undertake the activity)

	Late Infantile (n=7)	**Early Juvenile (n=6)**
Physical activities	**No problems with (n=7):** • Horse riding (2) • Swimming (4) • Football (2) • Dancing (2) • Basketball (2) • Sailing (1)	**No problems with (n=2):** • Horse riding (1) • Swimming (1) • Biking (1) • Cubs/scouts (1) • Activity week (rock climbing, canoeing, karate, orienteering) (1) **Some problems with (n=4):** • Swimming (3) • Wrestling (1) • Daily use of walking machine (1) • Gardening (1) • Different sports once a week at school (1)
Non-physical activities	**No problems with (n=7):** • Computer coding club (1)	**No problems with (n=2):** • Blanket making (1)

	• Computer-based design/editing (1) • Roblox (online game platform and game creation system) (2) • Listening to music (1) • Watching football (1) • Building cars with building blocks (1) • Internet research (1)	• Young carer club (1) **Some problems with (n=4):** • Arts & crafts (1) • Baking/cooking club (3) • Singing (1) • Computers (1)
Parents were asked "What activities does your child participate in (for example sports, swimming, dancing, martial arts, football, arts & crafts, baking)		

3.2.7 Self-care

Parents were asked whether their child were independent with self-care (e.g. washing and dressing) or required support All seven children with LI MLD were independent in these activities at the time of the survey. Among the six children with EJ MLD, two were independent, two required minimal help (to get in and out of the shower) and two required full assistance with all aspects of personal self-care and hygiene (e.g. due to poor motor control).

3.2.8 Pain and discomfort

Parents were asked whether their child had any pain or discomfort. None of the seven children with LI MLD were reported to have pain or discomfort at the time of the survey. Among the six children with EJ MLD, three had no pain or discomfort whereas three some pain or discomfort. None of the children with either MLD phenotype were reported to experience a lot of pain or discomfort (Figure 4).

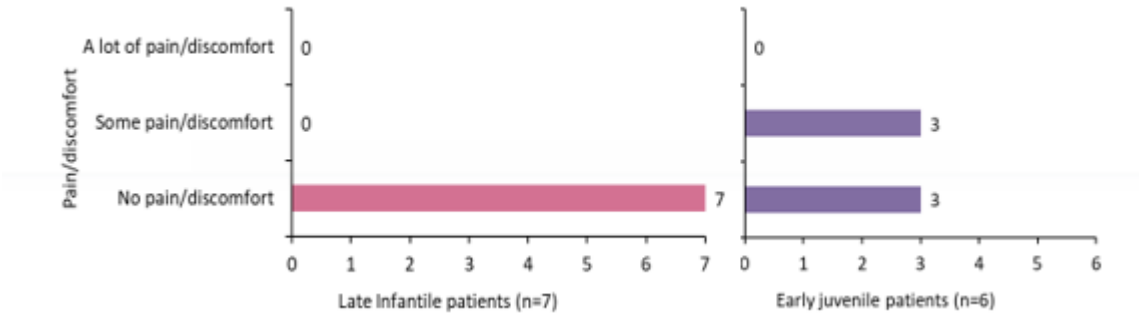

Figure 4 Parent-reported pain and discomfort

3.2.9 Medical symptoms

Respondents were asked which symptoms their children experienced from a list; multiple responses could be given.

None of the seven children with LI MLD were reported to experience any of the symptoms at the time of the survey. Among the six children with EJ MLD, three had none of the listed symptoms, one had behavioural issues, one had a partial hip dislocation due to poor equipment, and two each had visual problems, constipation, or incontinence due to chemotherapy (Figure 5). Four of these symptoms were reported for the same patient, who was the only patient to require specific medication. There were no reports of gastrointestinal problems related to feeding or nutrition, seizures, hearing problems, scoliosis or recurrent respiratory infections.

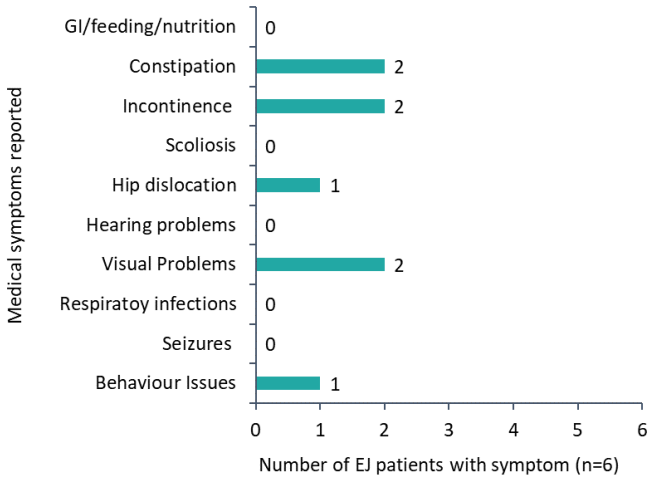

Figure 5 Medical symptoms reported by parents

3.2.10 Hospital visits

Once the treatment effect had become established, three patients visited hospital for MLD-related reasons other than clinical trial visits or routine clinical appointments. One patient with LI MLD attended for physiotherapy and equipment; one with EJ MLD visited twice for foot surgery, and one with EJ MLD attended for unspecified health issues. None of the children required emergency hospital admissions in the last 12 months as a direct consequence of MLD.

3.3 Quality of life

All nine parents who had a treated and non-treated child with MLD perceived that their treated child had good quality of life compared with the non-treated child.

3.4 Carer burden

Five of the seven parents of treated children with LI MLD reported that they had no limitations in participating in everyday life and activities; one parent who reported limitations said that this was not because of the treated child. By contrast, four of five parents of children with EJ MLD (including the child with pre-symptomatic EJ MLD) stated they had limitations in participating in everyday life and activities, which two parents attributed to the treated child (one parent did not answer the question).

Five of the seven parents of children with LI MLD had no mental or physical health problems whereas two reported moderate problems (Figure 6). One attributed their mental health problems to “Seeing my eldest daughter suffer and die at the hands on MLD when if it had been diagnosed at birth, she would still be with us”; the same parent described physical problems of “Back, shoulder and neck problems from lifting my untreated child awkwardly as it was the least painful way for her to be moved. Also, from sleeping slumped over the sides of hospital beds too many times”.

Five of the six parents of children treated for EJ MLD reported no mental health problems and one reported moderate problems. Four had no physical health problems whereas two had moderate problems. None of the problems were considered severe.

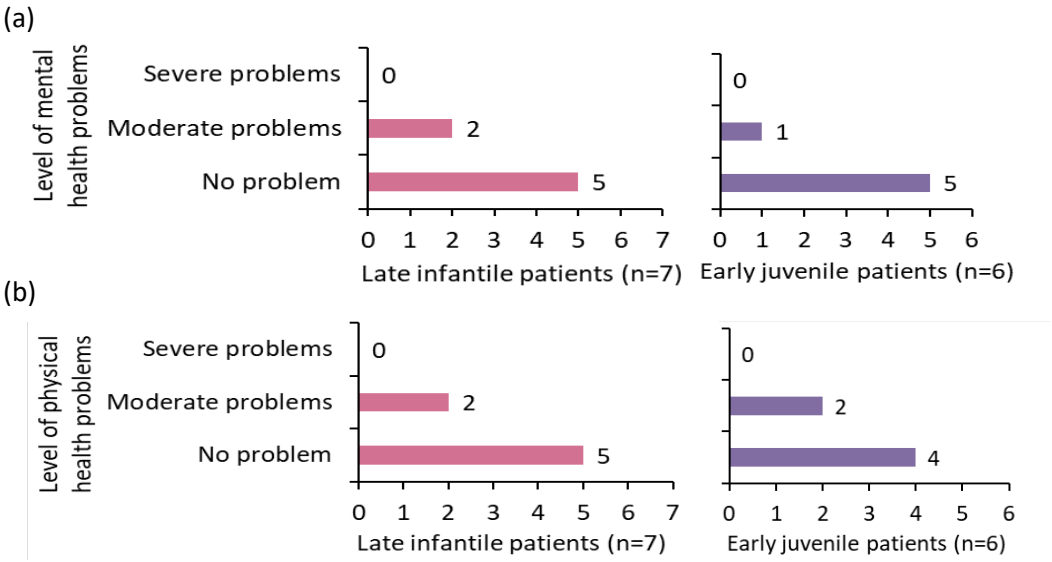

Figure 6 (a) Mental and (b) physical health problems reported by carers/parents

3.5 Personal statements about treatment

Parents were asked what hope or aspirations the treatment had given them, and to write one powerful statement advocating gene therapy. The answers to these two questions had common themes. Parents described stark contrasts between the rapid disease progression – and death – of an untreated child compared with the hope of a normal life for their treated child. Parents described treated children as enjoying life. Parents also described more freedom for the family, more time for parents to pursue career goals and improved social life. A child who continued to use a wheelchair was still considered able to live a normal life without suffering.

Parents described the treatment as life-saving – for both their child and for other family members – and talked about hopes for the future. One parent described their child as normal and healthy; “he doesn’t even know he has MLD and is unaware of any difference between himself and his peers”. One mother described being able to be “100% mum. Not 20% nurse 20% admin, 20% voice for my child to get what they need, 10% dietician, 10% physio, 10% OT, 5% counsellor to the rest of the family and what little is left as mum”.

Parents expressed distress at the thought of not having access to treatment for any future children and felt strongly that other children should have access to the therapy: “The approval of this therapy […] can eradicate this cruel disease and I beg you for the sake of the children like my son [name] who have yet to be born not to deny them a chance at life as is their human right and our responsibility as adults in society”.

Children who had received gene therapy talked about playing with siblings, doing well at school, being happy and having plans for the future.

Table 5 Parents' quotes illustrating the hope or aspirations the treatment had given them, and powerful statements advocating the treatment

Age when treated	Time since treatment	Illustrative quotes
7 mos	5 yrs, 4 mos	*"To lead a normal life where my child and us as a family are not limited to staying within our home or only a short distance from home. They can experience and learn the world around them by travelling and learning. (parent of two treated children with MLD)".*
9 mos	5 yrs, 3 mos	
1 yr, 1 mo	4 yrs, 3 mos	*"Many children diagnosed at a similar stage of disease development but who did not receive treatment are now either extremely ill and totally incapacitated or have long since passed away. Our child may use a wheelchair and require help with aspects of life, however there is no suffering and in our minds, there is no comparison to the untreated children and we are beyond grateful for this opportunity.*
1 yr, 1 mo	4 yrs, 3 mos	*"Both my boys were diagnosed in the same week in [year] with a terminal illness. One was untreated and he died aged 6 in [date]. Our younger son has been saved by this therapy, and this therapy has saved our family from a total disaster".*
1 yr, 1 mo	4 yrs, 3 mos	*"We have seen the difference between treated and untreated play out in front of our eyes over the last 4 yrs. The contrast is black and white to us […] MLD is amongst the cruellest of any disease in the suffering it inflicts on its victims. Our oldest boy was fine up to the age of 2, lost all his physical abilities by the age of 3 and slowly faded over the next 3 years through excruciating symptoms until his body just gave up. His life was an agony".* *"I really feel that it is impossible for those who have not witnessed it to appreciate the difference this therapy makes and the consequences of not administering it when needed".*
1 yr, 1 mo	4 yrs, 3 mos	*"Our treated boy walks the 1.3 km route to school with me everyday past his brother's grave […] he leaves different toys and treats for his brother […] and walks on to school oblivious to the fact that if it wasn't for his brother he would be the one buried there".*
1 yr, 1 mo	3 yrs, 3 mos	*"A normal life for our child […] he is not condemned like his brother.*
4 yrs, 1 mo	7 yrs, 3 mos	*"The difference between untreated and treated children is Night and Day. Children whose minds and bodies are utterly ravaged versus children who are fully participating in life, with no signs of disease".*
4 yrs, 1 mo	7 yrs, 3 mos	*"Happy, engaged and enjoys life immensely".*
7 yrs	6 yrs, 7 mos	*"For a pre symptomatic child, the treatment is outstanding. For a child with symptoms, the disease can accelerate so fast that the child loses physical and cognitive ability so quickly".*

4 Discussion

Gene therapy with atidarsagene autotemcel, which corrects the ARSA deficiency in MLD, has been shown to provide sustained clinical benefit in children with MLD, restoring motor and cognitive function and extending survival [10]. In the current survey, parents considered the treatment effect to be established at a median of 6 months for children with LI MLD and 3 months in children with EJ MLD, which is consistent with 3–12 months for engraftment and reconstitution of ARSA activity in

peripheral blood cells and cerebrospinal fluid following gene therapy [10]. For some children in this survey, the effect took up to 2 years, however. All children had received treatment at least 3 years prior, and some up to 10 years prior (Table 2). The surveyed parents reported disease stabilization across multiple domains beyond mobility and cognition: self-care, understanding and speech, pain and discomfort, education and activities. Parents reported few medical symptoms or hospital visits, whereas an international survey of carers of children with MLD (34 families) reported a mean of four inpatient and 30 outpatient hospital visits in the previous 12 months [20]. Parents described their treated children as participating fully in life and daily activities (Table 5).

Adults and children with rare diseases have significantly worse HRQL in all domains compared with population norms [21]. Children with LI or juvenile MLD have been reported to have HRQL significantly below the population average (32.7 vs 77.8 measuring using the well-validated Paediatric Quality of Life [PedsQL] questionnaire) [16]. HRQL of children before treatment was not available, so it has not been compared before and after gene therapy; however, all children with LI MLD and all but one with EJ MLD in the current survey were considered to have good HRQL by their parents. Furthermore, the wide-ranging improvements in motor and cognitive skills and ability to participate fully in daily life described in this survey can be expected to be associated with improved HRQL. For example, all but one child was in mainstream education, either full- or part-time – in contrast to the survey of 34 carers of untreated children, which reported that 25% of children were not attending school or receiving home schooling [16]. Children who had received gene therapy for MLD were able to take part in a full range of physical and non-physical activities, largely unassisted, including children whose symptoms had progressed. Together, these findings indicate that children are still able to participate fully in life 4–12 years after treatment – in stark contrast to the prospect of being bedridden within 3 years of diagnosis without treatment [13]. In their personal statements, parents described their children's enjoyment of normal life and having hopes and aspirations for their children as adults. All nine parents who had an older child with untreated MLD perceived that the treated child had good HRQL compared with the non-treated child. Some parents described stark contrasts between treated and untreated children as "night and day" and "black and white". One contrasted a child whose mind and body was "utterly ravaged" by the disease with their treated sibling who was fully participating in life with no signs of disease (Table 5).

Rare diseases have a marked impact on families, who often provide substantial informal care. A 2018 US survey of 1400 caregivers suggested that rare diseases have a broad and lasting impact on caregivers [15]. Rare and progressive childhood neurological conditions have also reported to have a significant impact on families and carers, in terms of providing care, potentially compromising ability to work and socialize, and living with the uncertainties around diagnosis and disease progression [5, 17, 20, 22]. Ammann-Schnell et al. described a substantial burden of MLD on parents and families (27 families; 30 children with MLD in Germany). Parents of children with MLD had significantly lower HRQL than parents of healthy children ($P < 0.001$; measured using the PedsQL Family Impact module) and mothers showed significantly poorer HRQL than fathers and were more dissatisfied with their professional development as a result of their child's disease. More severe disease had a greater impact on family functioning. Parents reported effects on healthy siblings in terms of behaviour and having to take on caring roles and family responsibilities. Likewise in the international survey of 34 families with a child with untreated MLD reported stress on familial relationships and negative effects on spousal relationships, work and career progression and mental health [20]. By contrast, most of the parents in our study reported that their treated child with MLD did not limit their daily lives or physical and mental wellbeing. This is consistent with the broad-ranging benefits

of gene therapy on daily life, as well as clinical benefits, in their children. Parents of children with LI MLD reported no limitations. Children with EJ MLD, unless pre-symptomatic, are likely to have some impairments in daily life, which in turn might be expected to limit their carers' activities. However, only two carers attributed limitations to their treated child with MLD, and any physical or mental problems were mostly mild. Thus, gene therapy has beneficial effects throughout the family. It should be borne in mind that nine of the 13 parents surveyed also had an older child with MLD, which may complicate the exploration of limitations due to one of the two children.

Studies in rare diseases are challenging because of small patient numbers and thus the findings should be interpreted with caution. There may have been selection bias, in that parents of successfully treated may have been more likely to respond to the survey. Whilst it might have been preferable to survey parents before and after treatment, the descriptions of treated children provided in this survey – and the graphic contrasts with untreated children – give a valuable insight into the beneficial impact of gene therapy on daily life for children and their families, in some cases up to 10 years later. The current study provides supporting evidence for the benefits of gene therapy beyond clinical effects.

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