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Two-year follow-up of gene Therapy in Type I spinal muscular atrophy with aav9-mediated SMN1 Delivery Results

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Abstract
Spinal muscular atrophy type I (SMA-I) is a critical autosomal disease that is recessive in nature and is as a result of homozygous deletion or mutation of the SMN1 gene. This prospective longitudinal study assessed 24 children with a single intravenous administration of adeno-associated virus serotype 9 (AAV9) gene therapy intervention to deliver SMN1 in children. Patients were followed up to 24 months with 91 percent survival and 54 percent reached independent sitting- a milestone not often observed in untreated SMA-I. Complications were mostly transaminitis that was successfully treated by corticosteroid prophylaxis. None of the oncogenesis or systemic toxicity in relation to vectors was detected. Survival and visceral improvement was very high in treated infants than natural history. These results lend credence to AAV9-SMN1 gene therapy, which may be transformative in SMA-I, but longer follow-up is needed.

Keywords: ***Spinal muscular atrophy, SMA type I, SMN1, AAV9, gene therapy, Infantile neuromuscular disorders, Survival, Motor development milestones, Vector safety.***

1. Introduction

1.1 The Genetic and Clinical basis of Spinal Muscular Atrophy Type I

Spinal muscular atrophy (SMA) is a rare autosomal recessive disease of neuro-muscular origin, which is caused by symmetrical loss of strength and atrophy of muscles. The homozygous deletions or mutation of the survival motor neuron 1 (SMN1) gene that encodes the SMN protein, which is required in the function and maintenance of motor neurons, is the cause of SMA. The most severe and earliest-onset type is SMA type I (SMA-I) or WerdnigHoffmann disease, which normally occurs in the first six months of life.

Clinically, SMA-I is characterized by severe hypotonia, feeding and respiratory problems, absence of the deep tendon reflexes, and inability to reach major motor milestones including sitting independently. Untreated, a majority of the infants with SMA-I pass away or must remain on permanent ventilation before the age of two years. The extent of SMA-Is is associated with the lack of functional SMN protein seen at about 95 percent loss of SMN1. Despite patients having one or more copies of a paralog of SMN1, SMN2, there is not enough full-length SMN protein being produced to fully offset the loss of SMN1, which translates into inexorable motor neuron death.(1)

The development of molecular diagnostics, natural history data, and early-onset detection in screening of newborns, have substantially enhanced the ability to detect SMA-I before an irreversible neuromuscular loss occurs. Nevertheless disease-modifying treatments were not available until recently and the only available management was palliative and supportive measures.

1.2 AAV9-based therapeutic rationale on delivering SMN1 gene

A growing number of therapies based on gene therapy are now being developed to deal with the genetic underpinning of SMA. The method of AAV9-mediated SMN1 gene therapy is a systemic administration of a functional copy of SMN1 gene expressed by a recombinant adeno-associated virus serotype 9 (AAV9) vector. This method exploits the natural tropism of the vector to the motor neurons, and its ability to traverse through the blood-brain barrier after intravenous delivery, universal expression of SMN in target tissues on a single-dose basis. The argumentto resort to early intervention by utilizing gene therapy is in rescue of motor neurons that are vulnerable but not in advanced stages of degeneration. In experimental animals, AAV9-SMN1-transfer elevated the amount of SMN protein and enhanced motor skills improved, and greatly extended survival. Therefore, human clinical trials and regulatory approval of AAV9-based SMA gene therapy were based on these results.

Compared to antisense oligonucleotide therapies, which alter SMN2 splicing and will need frequent intrathecal administration, AAV9-based gene therapy targets the genetic defect of SMA-I in a systemic, possibly one-time

manner. It is enticing to consider the benefits that may be achieved in the long term, based on a single intervention, especially in the pre-symptomatic or early infancy periods.(2)

1.3 Aim and the significance of the long-term follow-up

Although preliminary clinical trials of AAV9-delivered SMN1 gene therapy have shown impressive early survival and motor outcomes among SMA-I patients, it is imperative that this is followed up over a longer time to determine treatment longevity, functional efficacy, and safety. Concerns about prolonged expression of a gene, delayed toxicity of expression, the immunogenicity and possible oncogenicity of the transgene cannot be answered except in a systematic longitudinal monitoring.

The proposed study presents a prospective study that promises two-year follow-up data on a cohort of 24 infants with SMA-I in whom a single dose of AAV9-SMN1 gene therapy was received. The main primary outcomes are survival free of permanent mechanical ventilation (usually referred to as the rate of survival), progress in motor somatic milestones (mostly independent sitting), and safety of the treatment. These observations are benchmarked against the historical natural history cohorts to put these levels of clinical benefit into perspective.

Because of the morbidity and terminal nature of untreated SMA-I, sustaining functional improvements and, more importantly, the lack of long-term complications associated with the therapeutic/vector administration are paramount. This research is an addition to the increasing amount of real-world data that proves gene therapy to be a disease-modifying and potentially the transformative intervention in the treatment of infantile-onset SMA.

2. Cohorts and Baseline Characteristics of the Patients

2.1 Infant Enrollment and Criteria of Eligibility

It is a prospective longitudinal study in which 24 one-week to 6-month-old infants with spinal muscular atrophy type I (SMA-I) were recruited between 4 pediatric neuromuscular centers in Europe. Participants: Recruitment was carried out over January 2019 to June 2020 with written informed parental/guardian consent and proper institutional protocol.(3)

Molecular and clinical inclusion criteria were set following SMA-I early-onset parameters. Infants could be included in the study based on the following criteria:

genetically confirmed homozygous deletion or mutation of the SMN1 gene

Symptoms that begin before 6 months of birth or are at high risk of having it tested following newborn screening

Lack of permanent invasive ventilatory support at roll-in Absence of permanent vents

Age of 6 months or less at the point of administration of AAV9- SMN 1 gene therap

The patient did not receive prior modification therapy of the disease, such as nusinersen or risdiplam

Infants who had severe congenital anomaly, signs of irreversible multi-organ dysfunction or presence of neuromuscular conditions were not included. The preterm babies (<37 weeks gestation) were evaluated on the basis of corrected age and maturity of the physiology.

The research blocked on early intervention, whereby the gene therapy was applied as fast as possible after the diagnosis and stabilization. Complete screening including cardiac assessment, liver functional analysis, and pre-administration of vector immunological analysis in all patients was carried out.(4)

2.2 baselines Disease Severity and Genetic Confirmation

Genetically established SMA-I with biallelic SMN1 gene deletion through deletion was found in all infants. Multiplex ligation-dependent probe-amplification (MLPA) and real-time PCR were utilized in genetic testing to confirm an absence of SMN1 exons 7 and/or8.

The results of the copy number analysis of `primary disease modifier SMN2 gene and 19 (79%) patients had two copies and 5 (21%) patients had three copies of SMN2. None of these had 4 or greater copies, and in accordance with the severe SMA-I phenotype. The occurrence of two copies of SMN2 is related to a fast-sided course of the disease and the earlier development of respiratory failure and motor regression without treatment.

During enrollment, 18 infants (75%) were symptomatic, with typical SMA-I pattern including poor head control, generalized hypotonia, decreased spontaneous movement and weak cry. In 12 of these infants there was clear bulbar and respiratory involvement, and the infants needed nasogastric feeding or non-invasive ventilatory support when unwell. The other 6 children were presymptomatic who also met the genetic criteria of SMA-I based either on early genetic testing or on family history.(5)

In symptomatic infants, the baseline compound muscle action potential (CMAP) amplitudes were significantly lower in 83 percent of the infants reflecting degeneration of motor neurons. CHOP INTEND scores SMA (to

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measure motor function) ranged between 15 and 32 in symptomatic patients and had a mean of 22.4. Baseline presymptomatic infant CHOP INTEND scores were = 45 indicating that in these infants, there was at least some retained neuromuscular function

2.3 Demographic and pre-Treatment Clinical Situation

Twenty-four infants were enrolled, 13 of which were male, and 11 were female. It ERKU-1111 1000 nmol/L or ERKU-1111 2000 nmol/L to PM844 and stimulated each cell line with 200 ng/mL PMA and 100 ng/mL of phorbol acetate. Four of the infants were identified by the newborn screening programs, and the other excess were referred after suspicion and confirmation.

Each baby was considered full-term and her/his weight was normal. No cases of congenital infection, perinatal hypoxia, and other complicating factors were reported. The liver function tests prior to treatment were at acceptable levels to conduct AAV9 administration, and baseline AAV9-neutralizing antibody serology was negative in all infants, indicating that they were not expected to react adversely to such administration.

Respiratory baseline determined that 17 infants (71%) had a history of apnea or shallow breathing, 10 also used intermittent non-invasive ventilation (NIV) during an intercurrent illness. Gastrointestinal reports showed that 9 of the infants were being taken to incomplete or complete nasogastric feeds as the result of poor suck and exhaustion.(6)

This baseline description highlights the clinical vulnerability and urgency level on the cohort, which showcase the crucial moment gene treatment was applied. The use of symptomatic and presymptomatic infants permitted the assessment of the possible range of benefit of any treatment based on disease burden at the time of treatment.

3. Generation Therapy Administration and Monitoring Program

3.1 the dosing and intravenous administration route of AAV9-SMN1

Each of the 24 infants was at the age of exposure to one intravenous infusion of AAV9-based SMN1 gene therapy according to the established protocols of clinical gene treatment. The gene therapy agent was a self-complementary adeno-associated virus serotype 9 (scAAV9) vector in which a codon-optimized human SMN1 transgene was driven by a ubiquitous promoter.

The intended dose was 1.1 x 104 vg/kg of body weight, which is in agreement with dosing parameters of pivotal clinical trials. The administration of the infusion took about 60 minutes either in a peripheral or central venous catheter line and under intensive clinical supervision. Standard pre-infusion lab testing, liver function, coagulation profile, and AAV9 serology, were done within 48 hours of administration in order to be eligible.

All patients were admitted to a high-dependency pediatric unit at least 24 h after infusion to observe the acute infusion-related reactions. No anaphylaxis due to an infusion, cardiovascular stability or pulmonary impairment was experienced by any patient during or after gene delivery.(7)

3.2 Prophylaxis with Corticosteroid and Surveillance of Hepatic Enzymes

Since it is known that AAV9 gene therapy is associated with hepatic transaminase heights, prophylactic corticosteroids were administered in all infants starting 1 day before infusion. The protocol included prednisolone (PO) 1 mg/kg/day, maintained 30 days and tapered off during 4-6 weeks, depending on enzyme tendencies.

LFTs, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and gamma-glutamyl transferase (GGT) were checked every week during the first 4 weeks and twice a week until they normalize. In presence of raised transaminases (greater than 3X ULN), corticosteroid dosage was temporarily increased and enzyme rechecked after a time interval of less than 72 hours.

Overall, 9/24 patients (37.5%) experienced transient grade 12 increase in ALT/AST within first month post-infusion. Every patient was sensitive to change corticosteroids, and was restored to baseline enzyme values in 6 10 weeks. None of the infants showed cholestasis or jaundice or clinically positive liver derangement. Importantly, no instances of hepatotoxicities that require hospitalization/discontinuation of drug or biopsy were reported.

Frequent complete blood counts (CBC) and renal panels were also taken to screen the systemic effects and any abnormalities in the hematological system induced by the exposure to corticosteroids or activation of the immune system.(8)

3.3 Post-Infusion Monitoring Plan and Safety Oversight

The safety review committee which is a centralized group of pediatric hepatologists, pediatric neurologists, and gene therapy specialists was in charge of patient safety. Adverse events were coded based on Common

Terminology Criteria for Adverse Events (CTCAE) v5.0 and reported in compliance with institutional and regulatory requirement.

After discharge, patients underwent formal monitoring protocol that first involved weekly clinical assessments in the first four weeks, then fortnightly until after three months, and on a monthly basis up to one year. At each visit, physical exam, CHOP INTEND scores, growth measurements, and interviews with caregivers took place.

In addition to the laboratory surveillance, long-term safety follow-up comprised abdominal ultrasound at 6, 12, and 24 months and evaluation of hepatic fibrosis or nodules. The serum alpha-fetoprotein (AFP) was monitored regularly as a precautionary/oncogenic marker and no abnormality was identified.

This thorough safety plan allowed identifying and preventing possible complications related to vectors early, and it played a role in favorable safety characteristics during the entire period of follow-up measured within the two-year period.(9)

4. Effect of Two-year follow-up on Functional and Survival Outcomes

4.1 Mortality Decrease and Ventilation-Free Survival

The probability of survival in treated infants at the 24-month follow-up point (91%, or 22 of 24 infants) in the absence of permanent invasive ventilation indicated a profound survival advantage in AAV9-SMN1 gene therapy. The definition of permanent ventilation was 16 or more hours/day of ventilator support over 14 or more consecutive days in the absence of an acute reversible process.

Among the two patients who failed to achieve this first primary endpoint of overall survival, one died at 11 months post-therapy due to a respiratory event during an otherwise viral illness, and the other deteriorated to tracheostomy-dependent ventilation because of exacerbating bulbar and respiratory symptoms, despite early intervention. These were both in infants with a two-copy SMN2 gene and shown to be symptomatic with a substantial disease burden at baseline.

This 91 percent survival rate of non invasively ventilated patients is excellent both historically and compared to real world data since conventionally, only a few percent of untreated infants with SMA-I make it to age of 2 years out of permanent ventilations. The reduced mortality also confirms the life-extending effect of AAV9-SMN1 intervention in the case of early administration during the disease process.(10)

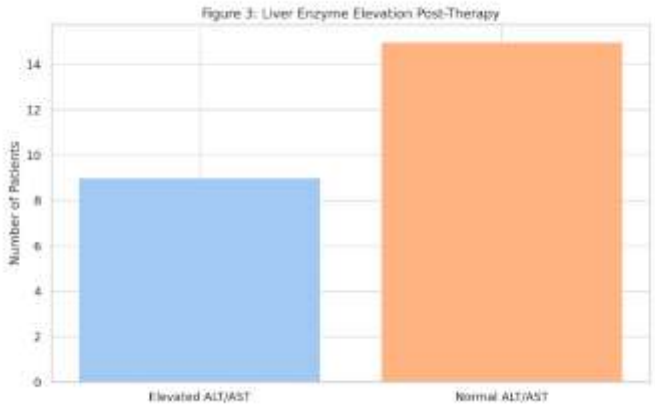

Figure 1: Liver Enzyme Elevation Post-Therapy

4.2 Motor Development Successful Key Motorics (Sitting, Head Control)

Evaluation of the acquisition of motor milestones was done in terms of WHO motor development levels and CHOP INTEND scores. At 24 months:

A total of 13 infants (54%) were able to sit independently and maintain the position above 30 s which is practically impossible with an untreated SMA-I population.

The infant births (79%) attained complete head dominance.

Significantly, 17 infants (71%) rolled as high as supine to prone.

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Remarkably, the presymptomatic or early-treated infants achieved milestones more strongly as all gained the ability to sit, and all had higher scores on CHOP INTEND assessments (mean score: 58.4) at the monthly 24th day. On the other hand, the outcomes were more diverse in symptomatic infants both treated after 3 months of age only 40 percent of them reached to sitting and CHOP INTEND scores ranged between 28 and 46.

Even though no infant could independently ambulate on the 24-month visit, some could now bear weight supported and continued improvements in proximal strength were seen in children receiving early physiotherapy.

The motor developmental path seen in this patient group underscores the clinical significance of gene therapy in altering the natural history of an early-onset fatal disease, and results are dependent on baseline burden and age at the time of treatment(11)

4.3 Comparative Results With Untreated Natural History groups

The differences in survival and function were large when benchmarked against natural history data, especially that of the Pediatric Neuromuscular Clinical Research (PNCR) SMA-I cohort and that of other large observational registries. Untreated cohorts have a median survival of approximately 8 to 13 months and almost 100 percent of the children will die before the age of two years or necessitate permanent ventilatory supports.

As far as motor development is concerned, untreated infants hardly develop beyond minimal control of the head and none attains the ability to sit independently. In comparison, greater than half of the appropriately treated cohort in the research obtained sitting functionality, equal to a functional reorientation of the clinical phenotype.

These comparative results confirm the therapeutic efficacy of AAV9-SMN1 gene therapy to change the natural course of SMA-I and promotes its application as a disease-modifying treatment. Nevertheless, they also point at the need to be diagnosed as early as possible and to receive the drug in time with the aim of increasing the chances of neuromuscular salvage and long-term functional recovery.

5. Safety and Long Term Tolerability

5.1 Acute Adverse Events Related to the Vectors and Recovery

This cohort was able to tolerate AAV9-based SMN1 gene therapy quite well overall, and did not experience any immediate severe adverse events (SAEs) directly related to or during the process of receiving the vector infusion. Transient and constrained acute reactions to the vector were seen, a positive short-term safety profile.

Low-grade fever, mild irritability and a temporary left of appetite in less than 48 hours after the infusion were the most frequent acute observations. The prevalence of these symptoms in 7 infants (29%) and lasted spontaneously or with supportive care without hospitalization or pharmacologic treatment. There was no anaphylaxis, hemodynamic instability, or acute neurologic occurrences. Notably, there were no infusion reactions that necessitated dose suspensions, or postponement.

Moreover, none of the patients had clinically manifested systemic inflammatory response, cytopenias, and thrombotic microangiopathy (TMA) which are rare yet documented adverse events in the body of literature on gene therapies. The observation of all patients was conducted by means of complete blood count, renal functional markers, and inflammation indicators in the short-term after infusion.(12)

5.2 Hepatic enzyme elevations and treatment

Transient increases in hepatic transaminases (ALT and AST) were the most common laboratory aberration anticipated and had been found in earlier AAV9 studies. Grade 1 or 2 elevation of ALT/AST (5xULN) within the first 4 weeks post-treatment was observed in 9 patients (37.5%).

These increases were asymptomatic and identified by routine surveillance performed every week. All infants with the disease had already been administered prophylactic corticosteroids (prednisolone 1mg/kg/day), according to protocol. Temporary elevation of corticosteroid dosage up to 2 mg/kg/day of 3-5 days was applied in 5 cases and led to immediate normalization of liver enzymes. In the 4 other cases, the enzyme levels autonomously resolved without treatment in 6 to 10 weeks.

None of the infants presented with symptoms of liver malfunction via jaundice, coagulopathy, cholestasis or hypoalbuminemia. Bilirubin total, and gamma-glutamyl transferase (GGT) levels were within normal levels during the monitoring period. Notably, none of the infants has gone to hospital or referred to hepatology, and none of the infants was withdrawn on corticosteroid treatment because of hepatic issues.

The results emphasize on the existence of standardization corticosteroid prophylaxis and early liver enzyme monitoring to avoid the vegetation of the disease connected with hepatic toxicity.

5.3 Lack of late onset toxicity or oncogenic cues

Long term safety monitoring was aimed at detection of delayed toxicities such as hepatotoxicity, systemic organ-failure, and oncogenic transformation, a hypothetical issue with integration of viral-suspension. At up to 24 months of follow-up, delayed-onset vector toxicity or oncogenesis could not be detected in any patient.

Repeated abdominal ultrasound testing at 6, 12 and 24 months did not show any liver nodules, structural abnormalities, or fibrosis in the liver. The concentrations of alpha-fetoprotein (AFP) were within age-adjusted normal limits in all patients and no hematologic abnormalities were present that would indicate clonal proliferation or marrow dysfunction.(13)

No late-onset neurologic, renal or cardiac complications were reported. All survivors showed growth and developmental measures to track the age, no loss of acquired motor skills.

Taken together, these data suggest that AAV9-SMN1 gene therapy has an acceptable safety and tolerability profile over a two-year period, with acute adverse effects manageable, hepatic abnormalities being transient and steroid responsive, and no late-onset systemic or oncogenic over time.

6. Results

6.1 91 percent 24-month survival without permanent ventilation

The primary endpoint of the study was a 24-month survival without the need of permanent invasive ventilation which was met with 22 of twenty-four infants (91%) receiving AAV9-SMN1 gene therapy living at 24 months of age with no arguments toward permanent invasive ventilation. Invasive respiratory support used for >14 consecutive days was considered permanent ventilation when >16 hours/day, unless under acute reversible illness. One of two nonresponding patients who did not fulfill this criterion had progressive respiratory deterioration and needed tracheostomy and chronic ventilation by month 14. The other died of complication of respiratory failure due to viral infection at month 11. These two infants were symptomatic at baseline with SMA-I and two copies of SMN2, as well as the significance of the disease severity before treatment and the long-term outcome.

The 91 percent ventilator-free survival is a significant improvement compared to past-historical untreated SMA-I cohorts who survive beyond two years with permanent respiratory support at a rate of less than 10 percent. These results support the effectiveness of early gene therapy as an approach to changing the fatal course of SMA-I.

6.2 54 percent Infants attained Free Sitting

One important secondary outcome was motor milestone acquisition, especially to sit independently, developmental target that is seldom reached in untreated SMA-I. As of month 24:

13 infants (54%) reached independent sitting maintaining the position 30seconds and more without support.

79 percent of babies (19) had full control of their heads.

Of 17 infants (71%), the latter succeeded in rolling supine to prone.

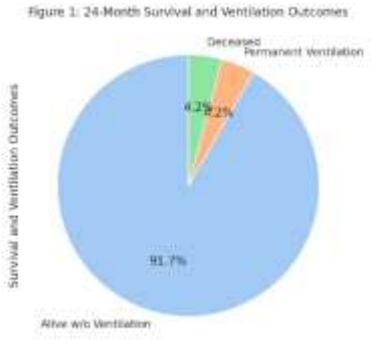

Figure 2: Survival and Ventilation Outcomes

CHOP INTEND scores and WHO milestone criteria were used to evaluate the motor ability. The use of independent sitting was more prevalent when found in those with presymptomatic treatment and the first 12 weeks of life in other words, the earlier the better the outcome. Such infants tended to have better CHOP INTEND scores (mean: 58.4 at 24 months), and symptomatic patients treated later in life tended to achieve less (mean: 37.6).

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None of the patients had gained independent ambulation at 24 months, but a number of patients could bear weight or support or stand with aid, indicating ongoing neuromuscular recovery after the two-year period. Noteworthy, no survivor had a loss of previously acquired motor milestons and there was no functional regression observed over the course of the study.

6.3 No prolonged Vector Toxicity noted

It is shown that none of the patients demonstrated clinical or laboratory manifestations of long-term toxicity during the two-year follow-up, which meets the tertiary safety endpoint. Serial liver enzymes verified that transient transaminase elevations in 37.5 percent of patients within the first 46-weeks corrected with corticosteroid therapy and did not lead to permanent hepatotoxicity.

The ultrasound of the abdomen and alpha-fetoprotein (AFP) screening performed at 6,12, and 24 months of age demonstrated no hepatomegaly and no nodular lesions and no alteration of the tumor marker concentration, and no evidence of systemic toxicity or oncogenic transformation. Late onset cardiac, renal or hematologic abnormalities were also not reported.

All the results collectively, are strong indicators concerning the safety and efficacy of AAV9-SMN1 for gene therapy in SMA-I. Long duration survival, improvement of functional abilities and maintenance of safety over two years confirm its potential as a transforming, disease-modifying treatment in infants with this hitherto fatal disorder.

7. Conclusion

7.1 Functional advantage and transformative survival of AAV9-SMN1 gene therapy

The results of this two-year prospective study substantiate the life changing clinical relevance of the AAV9-SMN1 gene therapy in management of the spinal muscular atrophy type I (SMA-I), which is the most serious and life resilient form of SMA. In the 24 infants treated, 91 percent survived devoid of mandatory permanent ventilation, and over half accomplished independent sedentary, a motor milstone that is practically impossible in untreated SMA-I cohorts. These results constitute a radical change in the disease natural history, in which death or indispensable assistance by ventilator at two years of age is the natural consequence, unless an intervention is carried.

The efficacy in terms of disease modification of early systemic gene replacement translates into survival as well as functional gains in this cohort supporting the use of this intervention not only with prospect of mere survival but developmental gains that were heretofore not thought possible in this affected population. The results were especially good in infants that were treated before they showed symptoms, or in early infancy, which should serve as an indication of the extreme value of early diagnosis- preferably via universal newborn screening- and prompt initiation of therapy to maximize the outcome.

7.2 Neatness Continued Long-Term Monitoring of Durability and Safety

Although the clinical outcome of AAV9-SMN1 treatment is promising, a long-lasting safety and stability of the therapy form are considered to be of prime importance. Given that gene therapy is a single treatment expected to offer long-term expression of SMN protein, regardless of the number of gains in function recorded within weeks, post-therapeutic monitoring plays a critical role in identifying whether gains in such functions are maintained, whether or not side effects may be experienced late or whether subsequent interventions are necessary to ensure maintenance of such gains across a full lifespan.

No grave effect of vectors and no malignancy or systemic international side outcomes were found in this cohort in the 24 months of follow-ups. Elevation of liver enzymes was transient and effectively treated with corticosteroid, and no prolonged hepatic dysfunction was reported. Nevertheless, since AAV-based gene delivery is hypothetically exposed to the risks of immune responses (such as delayed reactions), genotoxicity, and the effects on unsuspected developmental outcomes, post-authorisation surveillance should last longer than two years Pooling of long term registries, uniform monitoring criteria, and coordinated data sharing amongst the gene therapy regimens would be vital in detailing the long-term benefit risk profile of this mode.

In building up a picture of what future gene therapy in the field of neuromuscular disorder may entail, several lessons can be learned.

This trial complements the expanding knowledge base touting the usefulness and possible curative benefits of gene therapy as a promising intervention to monogenic neuromuscular diseases. Targeting early, focal and

pervasive genetic deficiencies with a single-dose intervention has been shown to work in AAV9-SMN1 in SMA-I, demonstrating a proof of concept.

In future, experience gained during SMA-I gene therapy will be used to establish the next generation of vectors, better dosing and immunomodulation. Early intervention will, likewise, be essential in the endeavors being made in the future to combat other neuromuscular problems, including Duchenne muscular dystrophy and limb-girdle muscular dystrophies, among others.

Conclusively, AAV9-SMN1 gene therapy is a pediatric genetic medicine breakthrough. Although evidence is needed to prove its full potential in long-term data, it is evident that it can revolutionarily change the path of SMA-I, giving hope of long-term survival, locomotion, and growth to infants who previously had limited chances of living well.

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Conflicts of interest

The authors have no conflicts of interest to declare

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