International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(CASE REPORT)

Check for updates

Combination and sequential treatments for spinal muscular atrophy: First experience with Onasemnogen abeparvovec (Zolgensma®) plus Risdiplam (Everysdi®) in a private hospital in Mexico

José Antonio Infante Cantú and Sofía Lucila Rodríguez Rivera *

Pediatric Neurologist, Tecnologico de Monterrey. Zambrano Hellion TecSalud Hospital.

International Journal of Science and Research Archive, 2025, 16(02), 863-870

Publication history: Received on 06 July 2025; revised on 10 August; accepted on 13 August 2025

Article DOI: https://doi.org/10.30574/ijsra.2025.16.2.2381

Abstract

Spinal muscular atrophy is a hereditary neuromuscular disease characterized by the degeneration of alpha motor neurons of the anterior horn of the spinal cord, leading to progressive symmetrical muscle weakness and a high risk for respiratory complications resulting in the need for some degree of ventilatory support.

Two infants are presented with hypotonic syndrome in which spinal muscular atrophy was diagnosed by a genetic study. Gene therapy with Zolgensma® with subsequent combination treatment with Risdiplam (Everysdi®) was used to evaluate the clinical improvement in motor function according to the Chop Intend Scale.

Keywords: Spinal muscular atrophy; Genetic therapy; Motor scale; Zolgensma; Survival of Motor Neuron 1 Protein

1. Introduction

Spinal muscular atrophy (SMA) is a genetic disease that causes weakness and wasting in the voluntary muscles of infants and children and, more rarely, in adults[1].

It is identified as the loss of lower motor neurons in the spinal cord and brainstem, leading to progressive symmetrical muscle weakness[2].

Specifically, it is an autosomal recessive disorder in the survival motor neuron 1 gene, SMN1, that causes a loss of specialized nerve cells, termed alpha motor neurons that control muscle movement.

The SMN protein codes for 2 genes (SMN1 y SMN2). It is vital for its role in the spliceosome assembly and biogenesis of ribonucleoproteins. A loss of the SMN protein affects the motor neuron's homeostatic environment[3]. A loss of these motor neurons prevents the sending of signals between the spinal cord and skeletal muscle, resulting in progressive proximal muscle weakness and paralysis[4].

The SMA phenotype is categorized into four grades of severity (SMA I, SMA II, SMA III, SMA IV) based on the age of onset and motor function achieved[5]. Type 1 is the most severe, where the patient is unable to sit; Type 2 is unable to walk unaided; Type 3 can achieve some walking abilities; and Type 4 is adult-onset SMA[6,7].

* Corresponding author: Sofía Lucila Rodríguez Rivera

When mutations occur in the SMN1 gene, the amount of encoded protein practically disappears, since the levels of a protein that the SMN2 gene can provide are not sufficient. The more copies of the SMN2 gene the patient has, the less severe the disease.

SMN2 copy amount largely accounts for the clinical severity between the SMA types. The higher the amount of SMN2 copy mutation (with fewer copies) the higher the probability of developing a severe phenotype.

When untreated, it will result in severe limitations to motor function, including walking incapability; high risk for respiratory complications resulting in the need for some degree of ventilatory support; as well as a high risk for orthopedic complications such as frequently painful contractures and scoliosis; and reduced life expectancy.

The 45% to 60% of cases of SMA are SMA Type 1, making it the most common form of SMA[8]. Patients with SMA Type 1 with 2 copies of SMN2 have a particularly poor prognosis. These patients usually show signs of SMA before six months of age, evident by their lack of ability to sit. Unfortunately, these infants typically do not survive past two years of age without significant mechanical ventilatory and nutritional support.

The diagnosis of SMA can be confirmed with molecular genetic testing with targeted mutation analysis[9].

Gene therapy is an experimental approach that uses imported genes to treat disorders that result from genetic mutations[10]. Gene therapies include replacing, silencing, or knocking out a mutated gene or introducing a new gene to restore additional function or protection.

Onasemnogene abeparvovec, also known as Zolgensma®, is a gene therapy that was recently approved by the US Food and Drug Administration in May 2019 as a treatment for SMA in pediatric patients under the age of two.

It consists of a single-dose, free-of-preservative, sterile, intravenous infusion of a non-replicating, self-complementary adeno-associated vector 9 (AAV9) that crosses the blood-brain barrier. The active substance in Zolgensma® contains a functional copy of the SMN1 gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB)[11].

One of the two adeno-associated vectors (AAV) inverted terminal repeats (ITRs) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. Therefore, restoring a normal SMN protein regulates cellular homeostatic pathways and, by extension, the state of the motor neuron.

Risdiplam (Evrysdi®) is the first oral drug developed to treat spinal muscular atrophy (SMA) and is approved in multiple countries worldwide. It is approved for the treatment of SMA in patients aged ≥ 2 months in the USA and the EU, with this approval further specified in the EU for the treatment of 5q-autosomal recessive SMA with a clinical diagnosis of SMA types 1, 2, or 3 or with one to four survival motor neuron 2 (SMN2) copies. As an *SMN2* pre-mRNA splicing modifier, risdiplam increases the production of full-length SMN protein, the lack of which drives the pathophysiology of SMA. In phase 2/3 clinical trials, risdiplam significantly improved motor function in infants with SMA type 1 and in patients aged 2–25 years with SMA types 2 or 3. These motor improvements were maintained with up to 2 years of treatment with risdiplam. Risdiplam was generally well tolerated, with a favourable benefit to risk balance. As an oral drug, risdiplam provides a convenient and useful treatment option across a broad range of patient ages and subtypes of SMA[12].

Chop Intend Scale (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)[13]

A 64-point motor assessment that captures neck, trunk, proximal, and distal limb strength in 14 elicited and 2 observational items are designed to evaluate muscle strength and function in infants with SMA.

Each item is graded on a scale of 0 to 4 (0 = no response, 4 = complete response).

The total score ranges from 0 to 64. Higher scores indicate improved ability.

The objective was to evaluate the efficacy in two patients with SMA who received gene therapy with onasemnogene abeparvovec (Zolgensma®) with subsequent combination treatment with Risdiplam (Everysdi®).

2. Clinical case 1

4-month-old girl, with normal pregnancy, obtained by natural childbirth, without complications. She is brought to the consultation due to hypotonia at one month of age. On neurological examination, expressive facies, with visual tracking and social smile, lingual fasciculations, hypotonia, and weakness of the 4 extremities predominantly proximal, with Daniels Scale 3/5 muscle strength, as well as areflexia, were detected. Her breathing was with thoraco-abdominal dissociation, without oxygen requirement.

Genetic testing for MLPA was requested, resulting in 0 copies of the exon 7 SMN1 gene, 1 copy of the exon 8 SMN1 gene, and 2 copies of the SMN2 gene. She was diagnosed with spinal muscular atrophy type 1 due to the onset of symptoms and genetic confirmation at four months of age.

Subsequently, anti-AAV9 antibodies were requested; they were negative with a titer <1:50. Normal liver function tests and blood counts were taken.

During her evolution, she presented respiratory infection due to rhinovirus with increased secretions, which were managed with pulmonary physiotherapy. Currently having difficulty swallowing with the use of a nasogastric tube.

The Chop Intend Scale was 37 (moderate grade) before treatment (Fig. 1).

Onasemnogene abeparvovec, also known as Zolgensma®, is applied at five months of age, in the operating room, in a sterile environment, during one hour with an infusion pump, previous and later administration of oral prednisolone.

A single dose of 1.1 x 1014 vg (viral genomes)/kg is administered as an infusion over 60 minutes. She remained hospitalized for 5 days with subsequent monitoring of liver function tests and hematic biometry, as well as vital signs under the supervision of a pediatric intensive care physician. No complications occurred.

The patient showed improvement in muscle strength with better cephalic control. The Chop Intend Scale was 45 after treatment with improvement (Fig. 2).

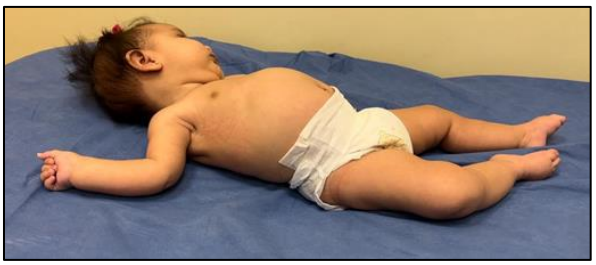

Figure 1 Before treatment

Figure 2 After treatment with Zolgensma®

Six months later, oral Risdiplam 0.20 mg/kg was started with improvement on the Chop Intend Scale to 49, achieving sitting with support (Fig. 3).

Figure 3 After treatment with Risdiplam

3. Clinical case 2

6-month-old boy, with normal pregnancy, obtained by natural childbirth, without complications. He is brought to the consultation due to neurodevelopmental delay and hypotonia at four months of age. On neurological examination, expressive facies, with visual tracking and social smile, lingual fasciculations, hypotonia, and weakness of the 4 extremities predominantly proximal, with Daniels Scale 3/5 muscle strength, as well as areflexia, were detected. His breathing was with thoraco-abdominal dissociation, without oxygen requirement.

Genetic testing for MLPA was requested, resulting in 0 copies of the exon 7 SMN1 gene, 1 copy of the exon 8 SMN1 gene, and 3 copies of the SMN2 gene. He was diagnosed with spinal muscular atrophy type 1 due to the onset of symptoms and genetic confirmation at five months of age.

Subsequently, anti-AAV9 antibodies were requested; they were negative with a titer <1:50. Normal liver function tests and blood counts were taken.

The Chop Intend Scale was 37 (moderate grade) before treatment (Fig. 4).

Onasemnogene abeparvovec, also known as Zolgensma®, is applied at six months of age, in the operating room, in a sterile environment, during one hour with an infusion pump, previous and later administration of oral prednisolone.

A single dose of 1.1 x 1014 vg (viral genomes)/kg is administered as an infusion over 60 minutes.

He remained hospitalized for 5 days with subsequent monitoring of liver function tests and hematic biometry, as well as vital signs under the supervision of a pediatric intensive care physician. No complications occurred.

The patient showed improvement in muscle strength.

The Chop Intend scale was 42 after treatment with improvement (Fig. 5).

Figure 4 Before treatment

Figure 5 After treatment with Zolgensma®

Six months later, oral Risdiplam 0.20 mg/kg was started with improvement on the Chop Intend Scale to 46, achieving sitting with support (Fig. 6).

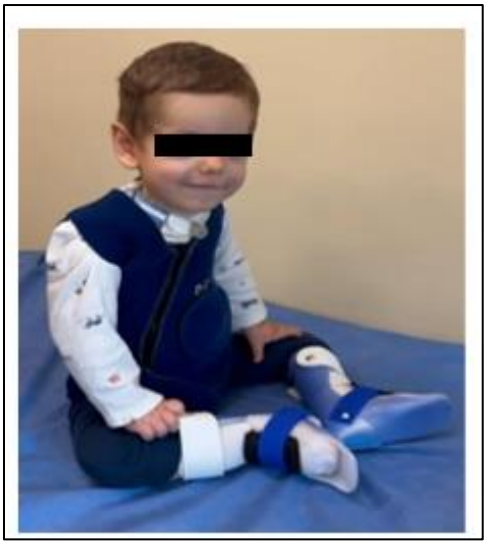

Figure 6 After treatment with Risdiplam.

4. Conclusions

SMA is a genetic disease that causes weakness and wasting in the voluntary muscles of infants and children and, more rarely, in adults.

It is an autosomal recessive disorder in the survival motor neuron 1 gene, SMN1, that causes a loss of specialized nerve cells, termed alpha motor neurons that control muscle movement.

The diagnosis of SMA can be confirmed with molecular genetic testing with targeted mutation analysis.

When untreated, it will result in severe limitations to motor function, some degree of ventilatory support, and reduced life expectancy.

Gene therapy is an experimental approach that uses imported genes to treat disorders that result from genetic mutations.

The active substance in Zolgensma® contains a functional copy of the SMN1 gene.

Risdiplam is a splicing modifier of SMN2 pre-mRNA.

The literature mentions the possibility of using combined and sequential therapies[14]. This is the first experience in a private hospital in Mexico.

The motor scale was found to differ depending on the treatment (Zolgensma® vs. Zolgensma® plus Risdiplam), with a significance level of <0.05. The Friedman test was applied.

Patients showed improvement on motor scores and did not require mechanical ventilation with combined sequential therapy of Zolgensma® plus Risdiplam.

Further studies are needed to evaluate the efficacy and safety of initial use of combined therapies.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Dabbous O, Maru B, Jansen JP, et al. Survival, motor function, and motor milestones: comparison of AVXS-101 relative to nusinersen for the treatment of infants with spinal muscular atrophy type 1. Adv Ther. 2019;36:1164–1176.

[2] Ross LF, Kwon JM. Spinal muscular atrophy: past, present, and future. Neoreviews. 2019;20:0–51.

[3] Chaytow H, Huang YT, Gillingwater TH, Faller KM. The role of survival motor neuron protein (SMN) in protein homeostasis. Cell Mol Life Sci. 2018;75:3877–3894.

[4] Chand D, Mohr F, McMillan H, et al. Hepatotoxicity following administration of onasemnogene abeparvovec (AVXS-101) for the treatment of spinal muscular atrophy. J Hepatol. 2021;74:560–566.

[5] Lowes LP, Alfano LN, Arnold WD, et al . Impact of age and motor function in a phase 1/2A study of infants with SMA type 1 receiving single-dose gene replacement therapy. Pediatr Neurol. 2019;98:39–45.

[6] Calucho M, Bernal S, Alías L, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018;28:208–215.

[7] Souza PV, Pinto WB, Ricarte A, et al. Clinical and radiological profile of patients with spinal muscular atrophy type 4. Eur J Neurol. 2021;28:609–619..

[8] Arnold WD, Kassar D, Kissel JT. Muscle Nerve. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 2015;51:157–167. [

[9] Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. Eur J Paediatr Neurol. 2020;28:38–43.

[10] Lin CW, Kalb SJ, Yeh WS. Delay in diagnosis of spinal muscular atrophy: a systematic literature review. Pediatr Neurol. 2015;53:293–300.

[11] Malone DC, Dean R, Arjunji R, et al. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. J Mark Access Health Policy. 2019;7:1601484.

[12] Paik, J. Risdiplam: A Review in Spinal Muscular Atrophy. *CNS Drugs* 36, 401–410 (2022).

[13] Glanzman, A. M., Mazzone, E., Main, M., Pelliccioni, M., Wood, J., Swoboda, K. J., … Finkel, R. S. *The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): Test development and reliability. Neuromuscular Disorders, 2010; 20(3), 155–161.*

[14] Goedeker NL, Rogers A, Fisher M, Arya K, Brandsema JF, Farah H, Farrar MA, Felker MV, Gibbons M, Hamid OA, Harmelink M, Herbert K, Kichula E, King K, Lakhotia A, Lee BH, Kuntz NL, Parsons J, Rehborg R, Veerapaniyan A, Zaidman CM. Outcomes of early-treated infants with spinal muscular atrophy: A multicenter, retrospective cohort study. Muscle Nerve. 2024 Dec;70(6):1247-1256.

Authors short biography

José Antonio Infante Cantú*1

Pediatric neurologist graduated from Instituto Nacional de Pediatria in Mexico

and from Universidad Autonoma de Nuevo Leon, Mexico.

Pediatric neurologist attached to Tecnologico de Monterrey, Zambrano Hellion Hospital, Tec Salud.

Ex-president of the Mexican Society of Pediatric Neurology, and Nuevo Leon Pediatrics College.

Coordinator of Epilepsy Clinic in Tecnologico de Monterrey, Zambrano Hellion Hospital, Tec Salud.

	An active member of the Mexican Academy of Neurology, Mexican Society of Pediatric Neurology, and Mexican Chapter of the International League against Epilepsy.
	Sofía Lucila Rodríguez Rivera*1 Pediatric neurologist graduated from La Raza National Medical Center IMSS UNAM. Pediatric neurologist attached to Tecnologico de Monterrey, Zambrano Hellion Hospital, Tec Salud, and the General Hospital of Zone No. 33 of the Mexican Social Security Institute (IMSS) Monterrey, Nuevo León. Epileptologist from the University of Murcia, Spain. Neurophysiologist from the Arturo Jauretche National University, Buenos Aires, Argentina. An active member of the Mexican Academy of Neurology, Mexican Society of Pediatric Neurology, and Mexican Chapter of the International League against Epilepsy.