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USE OF SMALL MOLECULES IN SPINAL MUSCULAR ATROPHY TYPE 3: A CASE REPORT

Carlos Molina-Castillo
Universidad La Salle México. Mexican University of Medicine
Ciudad de México - CDMX, México
https://orcid.org/0009-0000-9015-1117

María Elena Meza-Cano
Hospital Muguerza - High Specialty, Neuromuscular Neurology
Monterrey - Nuevo León, México.
https://orcid.org/0000-0003-1237-3843

María Fernández-De La Torre
Universidad La Salle México. Mexican University of Medicine
Ciudad de México - CDMX, México
https://orcid.orq/0009-0007-7553-6597

Ana Paula Solórzano-Anduiza
Universidad La Salle México. Mexican University of Medicine
Ciudad de México - CDMX, México
https://orcid.org/0000-0002-9878-4960

Roberto Loyo-González
Universidad La Salle México. Mexican University of Medicine
Ciudad de México - CDMX, México
https://orcid.org/0009-0007-3357-2071

Regina Sayún-Yoma
Universidad La Salle México. Mexican University of Medicine
Ciudad de México - CDMX, México
https://orcid.org/0009-0005-2600-1612

José Ángel Aguerrebere-Lupi
Universidad La Salle México. Mexican University of Medicine
Ciudad de México - CDMX, México

Abstract: Introduction: Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder that presents with peripheral hypotonia, atrophy, and weakness in the limbs and bulbar muscles. It is caused by the homozygous deletion of the SMN1 gene on chromosome 5q13. Prior to 2016, there was no disease-modifying treatment; Subsequently, a series of drugs were approved for which there is strong evidence regarding the presence of improvement and stabilization of motor function: Nusinersen, Risdiplam, and onasemnogene abeparvovec xioi.

Clinical case: A 24-year-old woman diagnosed with SMA at age 15 with proximal weakness of four extremities associated with atrophy and peripheral hypotonia. She is previously treated with general support measures prior to starting disease-modifying treatment: Nusinersen for 9 doses and subsequently Risdiplam. The MFM 32 motor function scales, bulbar function using the CNS BFS scale (Center of neurologic study bulbar function scale), as well as quality of life using the Qol NMD scale, are evaluated.

Results: The results, presented in linear graphs, show the evolution of the patient with and without Nusinersen treatment at 8 doses and then Risdiplam. There is a significant improvement in motor function (90-96%) post-nusinersen. Regarding the QoL NMD scale, a baseline value (29 pts), post-Nusinersen (81), treatment suspension (29 pts) and post-Risdiplam (65 pts) are recorded; demonstrating improvement with both treatments. Regarding the CNS-BFS scale (Center for Neurological Study-Bulbar function scale), a baseline start (40 pts) is recorded, improvement with 7 doses of Nusinersen with a decrease of 5 points (35 pts), a period without treatment with clinical worsening (40 pts) and a decrease after 6 months of Risdiplam (35 pts).

Conclusions: Risdiplam and Nursinersen

were effective and safe disease-modifying therapies in these patients with SMA type 3.

Keywords: SMN1 gene, spinal muscular atrophy, motor neuron disease.

INTRODUCTION

Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder, characterized by weakness in the limbs and trunk (including bulbar and respiratory muscles). It is caused by a homozygous deletion of the gene encoding survival motor neuron protein (SMN1) at the 5q13 locus, resulting in insufficient expression of survival motor neuron protein. (SMN).[1,2]

In addition to the SMN1 gene, there is a paralogous gene (SMN2), encoding the SMN protein, whose functions additionally include telomerase regeneration, transcriptional regulation, and cell trafficking. The percentage of functional protein produced by SMN2 is around 5-10%, compared to SMN1, due to a mRNA variant that prevents the production of a fully functional SMN protein. The truncated protein produced by SMN2 is usually insufficient to prevent symptoms; however, today it is possible to prevent the exclusion of exon 7 from the mRNA of the SMN2 gene. This is achieved through the action of modified antisense oligonucleotides and small molecules, which bind to specific RNA sequences of the SMN2 gene and modify the pre-mRNA splicing of the SMN2 gene, allowing for the inclusion of exon 7 and thus enhancing the expression of a complete and functional SMN protein, this is the mechanism of action of two drugs: Nusinersen and Risdiplam.[2,3]

The SMA classification is based on the age of onset of symptoms and the highest developmental milestone reached. Patients with a higher number of copies of the SMN2 gene, having higher levels of SMN protein, are carriers of a less severe phenotype, being more functional.[4] SMA type 1 is characterized by the symptomatic presentation of the disease at 6 months of age and by the inability to sit unassisted. On the other hand, type 2 SMA has the onset of symptoms between 6 and 18 months of age, accompanied by the impossibility of unassisted ambulation. Finally, SMA type 3 manifests with symptoms in patients after 18 months of age, who eventually lose the ability to walk independently; additionally, developmental milestones are progressively diminished as the disease progresses. It is worth mentioning that there is a fourth type of SMA, where the symptoms appear in adulthood and it is the type with the best prognosis.[4] Not only can the disease be classified based on the phenotype and symptoms, there is also a classification that depends on the genotype of the patient. In most patients, SMN2 copy number is predictive of the phenotype; Thus, if you have 2 copies of SMN2, you have SMA type 1; with 3 copies, SMA type 2; with 4 copies, SMA type 3 and if there are more than 4, SMA type 4 is presented.[1,4]

Previously, the treatment of this disease consisted of general measures and supportive care, adding physical rehabilitation, speech therapy, swallowing, pulmonary physiotherapy, and if necessary, mechanical ventilation. However, in 2016 the first disease-modifying therapies with antisense oligonucleotides and small molecules were introduced, causing a notable change in the natural history of the disease.[5]

The three treatments available in Mexico for this disease are nusinersen, onasemnogene abeparvovec xioi and recently the first oral medication, risdiplam. There are no comparative studies that compare the efficacy between them, however, the clinical evidence is sufficient to support their use as part of the treatment of patients with SMA.

Nusinersen is an antisense oligonucleotide

directed to promote the inclusion of exon 7 in the SMN2 gene. It is approved for pediatric and adult patients with SMA and is administered intrathecally.[6] in a dose of 12 mg (5 ml). Four loading doses must be administered, where the first 3 loading doses are given every 14 days and the fourth is given 30 days after the third. After the loading dose regimen, maintenance therapy consisting of an intrathecal injection every 4 months is started. Its use is justified by two major phase 3 double-blind randomized controlled trials; the ENDEAR and CHERISH studies. [8,12]

CLINICAL CASE

22-year-old woman who started suffering at 15 years of age with proximal weakness of four extremities; physical examination reported atrophy and hypotonia requiring help for ambulation. Relevant family history denied, no genetic history. In pathological personal history highlights lumbar disc disease, cervical syringomyelia without associated specific symptoms, insulin resistance and dyslipidemia. She currently has treatment for these diseases as well as close nutritional follow-up.

She was diagnosed with Spinal Muscular Atrophy type 3 in 2018, finding a deletion of the SMN1 gene and the presence of 4 copies of the SMN2 gene. Initially, the patient received supportive treatment with general rehabilitation measures and later, at 20 years of age, she began treatment with 8 doses of intrathecal Nusinersen. For reasons beyond our control, the patient suspended treatment for 1 year to subsequently restart treatment, this time with oral Ridisplam. The evolution with Nusineren for 8 doses, evolution in the treatment interruption period and results with Risdiplam at 6 months of treatment are shown.

Motor function is assessed using the MFM-32 scale, an assessment tool designed to measure and assess this function in patients with neuromuscular diseases, such as muscular dystrophy and spinal muscular atrophy. It consists of 32 items grouped into three domains: axial motor skills, limb motor skills, and hand functions. Each item is scored on a scale of 0 to 3 based on the patient's ability to perform a specific task, where 0 represents complete incapacity and 3 complete ability. Quality of life was assessed using the QolNMD scale, a questionnaire that assesses the quality of life in people with neuromuscular diseases by asking questions about physical, emotional, and social aspects, scored on a scale of 0 to 100. It is a useful tool to understand the impact of these diseases on the lives of patients and to assess the effect of therapeutic interventions on their quality of life. Bulbar function was evaluated using the CNS-BFS scale. Its maximum score is 105 points, it is an inversely proportional scale, that is, the lower the score, the better clinical evolution. In this case, graph IV describes a baseline start (40 points), improvement with 7 doses of Nusinersen with a decrease of 5 points (35), a period without treatment with clinical worsening (40 points) and the decrease again after 6 months. of risdiplam (35 points).

DISCUSSION

Spinal muscular atrophy, a hereditary neuromuscular disorder, manifests itself variably clinically, the severity of its presentation being directly proportional to the number of copies of the SMN2 gene. Before 2016, there were no modifying therapies for the natural history of the disease; therefore, patients received supportive care and multidisciplinary support only. Currently it is important to recognize the disease and manage to diagnose it at an early age, the appearance of new therapies that modify the natural history of the disease has allowed patients to present improvement in motor

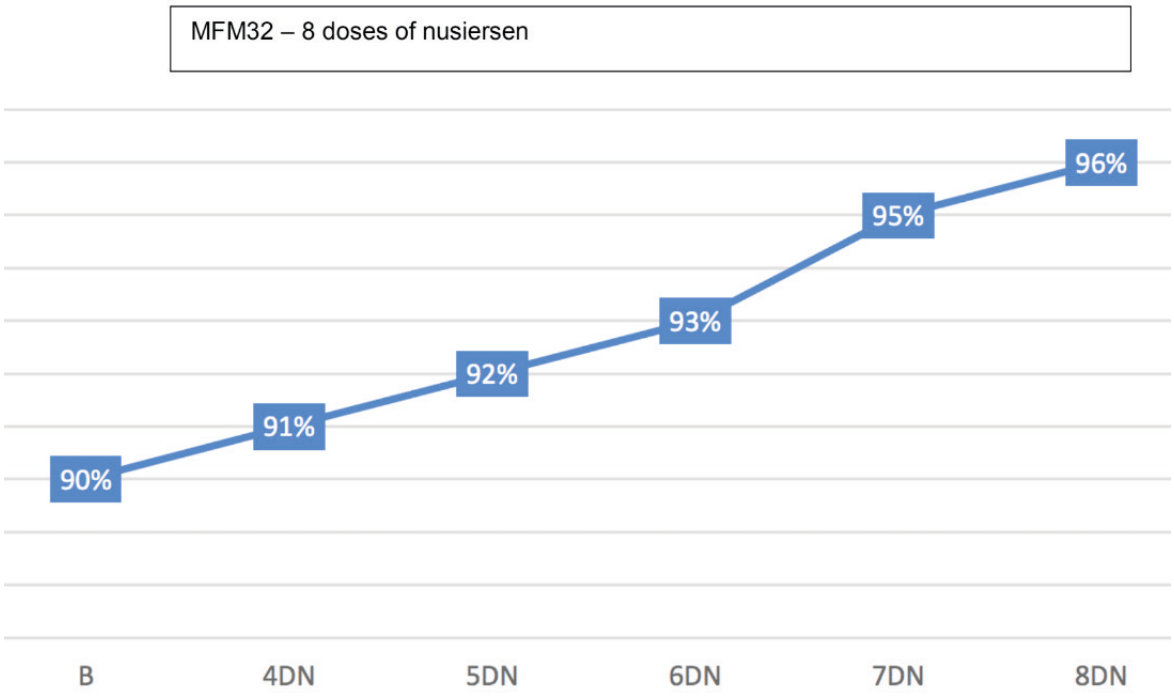

Table I. Evolution of the MFM32 scale from baseline (B) with 8 doses of Nusinersen (DN).

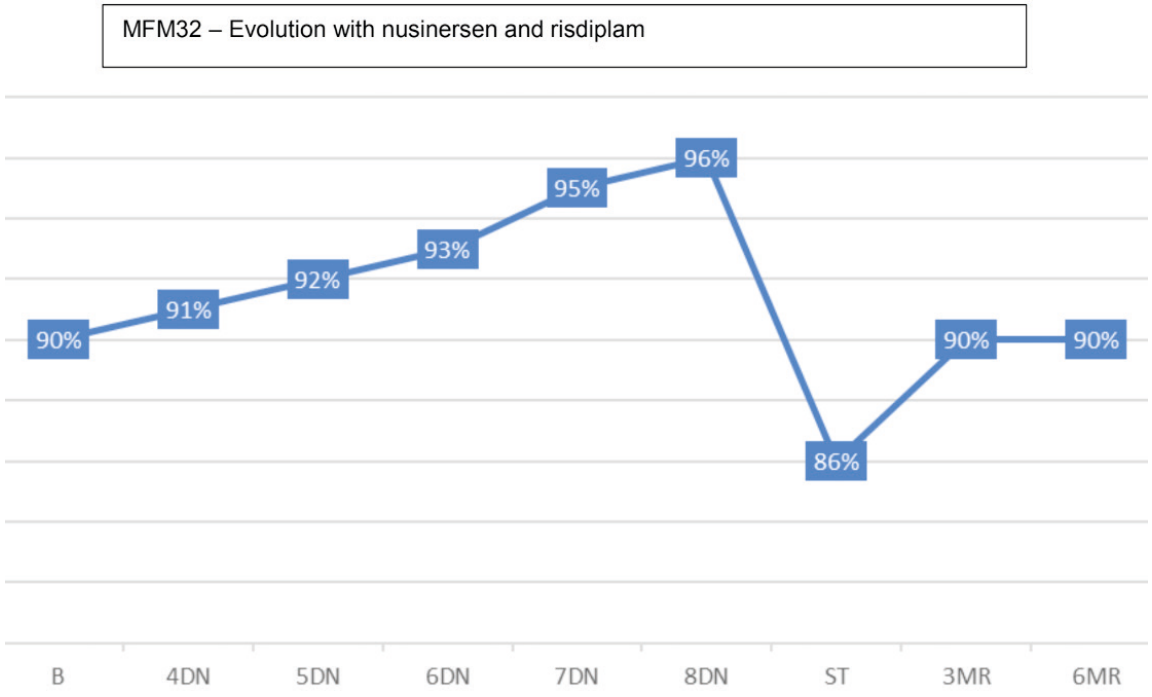

Table II. Evolution of the MFM32 scale with 8 doses of Nusinersen (DN), discontinuation of disease-modifying treatment (ST) and subsequent evolution with 3 and 6 months of treatment with Ridisplam (MR).

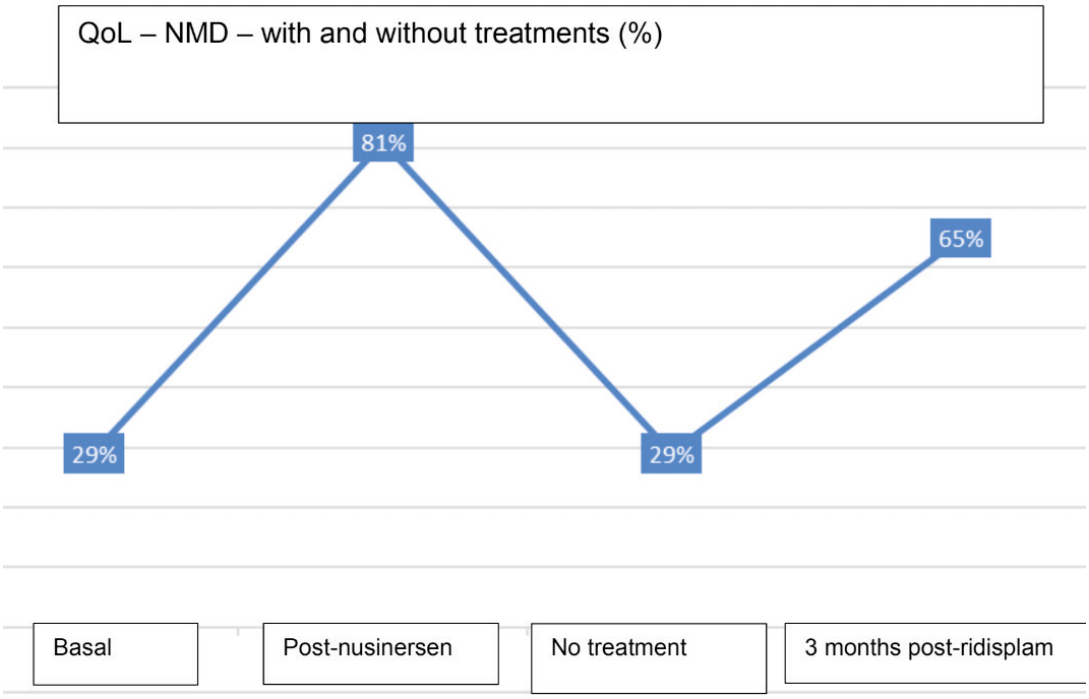

Table III. Evolution of the Qol-NMD scale with 8 doses of nusinersen, discontinuation of disease-modifying treatment, and response after 3 months in treatment with ridisplam.

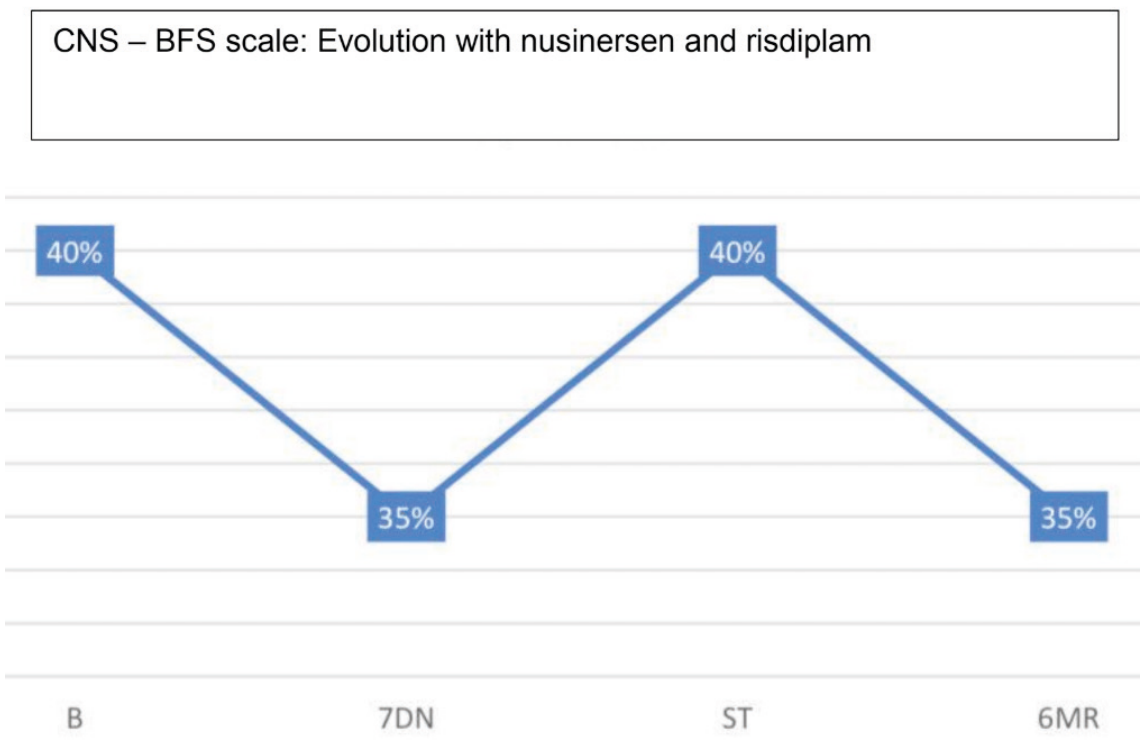

Table IV. Evolution of the CNS-BFS scale: Evolution with Nusinersen and Risdiplam

function or at least manage to stabilize it, since without treatment there will always be a decrease. of motor ability. These therapies must be started as early as possible because this way the acquisition of greater motor function will be achieved.

CONCLUSIONS

The use of therapy with antisense oligonucleotides and small molecules is recent and the information on its efficacy in Mexico is limited. The description of the results of the treatment with Nusinersen and Risdiplam in Spinal Muscular Atrophy in the Mexican population makes it possible to evaluate the clinical evidence of these treatments, allowing to transmit the experience and the subsequent possibility that it can be used in a greater number of patients in this country. In the present clinical case, with the use of disease-modifying drugs, they denote a favorable and effective result supported by the improvement in the score of motor scales and quality of life.

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