CASE SERIES

Nusinersen: Single-Centre Real-Life Experience in Type 1 Spinal Muscular Atrophy

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Abstract

Introduction: Nusinersen, an antisense oligonucleotide designed to treat spinal muscular atrophy, led to substantial motor milestone achievements in clinical trials. The aim of this study was to report the clinical outcome of children diagnosed with spinal muscular atrophy type 1 treated with nusinersen in a tertiary center.

Methods: Retrospective study of type 1 spinal muscular atrophy patients treated with nusinersen for more than six months. Clinical, genetic, ventilation and feeding parameters were obtained. Motor assessment included Children's Hospital of Philadelphia infant test of neuromuscular disorders.

Results: Four patients were eligible for this evaluation, with a current mean age of 33.8 months (range 25-42 months), three with two copies of survival motor neuron gene 2 and one with three copies. The mean time from first symptoms to diagnosis confirmation was three months (range 0.3-10.0 months) and from diagnosis confirmation to the beginning of treatment 1.2 months (range 0.5-1.7 months). All patients improved at least 11 points in motor score (mean change 18.5 points). Three patients achieved stable sitting and one sits with support. They are all free from continuous ventilation. The mean number of hospital admissions due to respiratory exacerbations per year variated from 0-4.2. Gastrostomy was performed in two patients and two have total oral feeding.

Discussion: We observed an improvement in motor function and ventilatory support in spinal muscular atrophy type 1 patients treated with nusinersen. Despite our small sample, our findings contribute to the increasing evidence that early diagnosis and treatment is paramount for these patients.

Keywords: Child, Preschool; Oligonucleotides/therapeutic use; Spinal Muscular Atrophies of Childhood/drug therapy; Treatment Outcome

Introduction

Spinal muscular atrophy (SMA) is the most common monogenic genetic cause of childhood mortality, with a pan-ethnic incidence of approximately 1/11,000 live births and a carrier frequency of 1/40-67 adults.[1,2] It is a severe and progressive motor neuron disease that causes the degeneration of the motor neurons in the anterior horn of the spinal cord and nuclei of the lower brainstem with progressive truncal and proximal limb weakness, and the involvement of respiratory muscles.[1] There is associated bulbar dysfunction with poor feeding and abnormal swallow function with the risk of aspiration pneumonia.[1]

Spinal muscular atrophy is an autosomal recessive disorder caused by homozygous or compound heterozygous (deletions and/or point mutations) loss of function of the survival motor neuron gene 1 (*SMN1*).[3] This gene encodes the survival motor neuron protein that is essential for the survival of the alpha motor neuron.[2] Therefore, survival motor neuron protein deficiency causes the degeneration of alpha motor fibers and neuromuscular dysfunction, thereby leading to a phenotypic spectrum classified by the age of onset and maximum motor milestone achievement. This includes a severe neonatal form (SMA type 0), extremely weak infants unable to sit unsupported (SMA type 1), non-ambulant patients able to sit independently (SMA type 2), ambulant patients with childhood-onset of motor weakness (SMA type 3), and adult onset SMA (type 4).[2] The most common subtype is SMA type 1, with children developing a progressive tetraparesis, hypoventilation,

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pulmonary aspiration, recurrent lower respiratory tract infections, dysphagia, and failure to thrive before usually succumbing to respiratory failure and death before the age of 2 years.[3]

The severity of the clinical phenotype is best related to the number and degree of function of the nearly identical survival motor neuron 2 (*SMN2*) gene copies present.[3] In *SMN2*, there is a base substitution that regulates exon 7 inclusion. These altered *SMN2* transcripts lead to the production of a truncated version of the survival motor neuron protein, resulting in reduced levels of functional full-length protein that partly rescues the phenotype.[3]

Nusinersen, included in clinical practice in December 2016, was the first therapy to be licensed for spinal muscular atrophy in Europe.[4] Nusinersen is an intrathecally-administered antisense oligonucleotide that acts by binding to exon 7 in the *SMN2* ribonucleic acid (RNA), thereby enhancing its translation into fully functional survival motor neuron protein.[2] The treatment schedule comprises four initial intrathecal injections during a two-month loading period, followed by maintenance injections every four months.[2] The early results leading to the approval of nusinersen came from the ENDEAR study, which included 122 symptomatic infants below 7 months with genetically proven spinal muscular atrophy who were not hypoxemic at study entry. This study demonstrated progress in motor milestones after 13 months of study and it included a placebo arm, but the study was terminated early because the results in the treated arm were superior to the placebo.[2]

Albeit the clinical trial experience and the widespread use of nusinersen, a longitudinal follow up in real-life setting is still scarce. The aim of our work was to report our tertiary center real-life experience SMA type 1 patients treated with nusinersen.

Methods

We performed a retrospective study of patients with a clinical and genetic diagnosis of SMA type 1 treated with nusinersen for at least six months in our center. Patients were assessed before the administration of the first dose of nusinersen, at the time of the fourth injection (63 days of treatment) and then every four months prior to the administration of the next dose. Data was collected from the clinical records of patients and the studied variables were demographic, anthropometric, clinical, ventilation, and feeding parameters. Clinical motor scores were assessed using Children's Hospital of Philadelphia infant test of neuromuscular disorders (CHOP-INTEND).[5] This scale is a validated instrument for SMA type 1 patients that measures 16 motor functions scored within four categories:

- Head and neck;
- Hands, arms, and shoulders;
- Feet, legs, and hips;
- Trunk.

Each activity is graded from 0-4, and the result is expressed in a quantitative total score ranging from 0-64.[5] The CHOP-INTEND can be applied to children from 1 to 38 months of age.[5] In addition, the presence of osteoarticular deformities was registered. Parents were informed about the data collection and they gave written informed consent. A descriptive statistical analysis was performed using Microsoft Excel® 2010.

Results

There were five genetically confirmed SMA type 1 patients treated with nusinersen for more than six months in our center. One patient died at 13 months of age, and her data was not included in the analysis, due to the lack of parental informed consent. The main clinical characteristics of patients are depicted in Table 1.

The mean time from the first symptoms to diagnosis confirmation was 3 ± 4.1 months (range 0.3-10 months) and from diagnosis confirmation to the beginning of treatment it was 1.2 ± 0.5 months (range 0.5-1.7 months) (Fig. 1). All of the patients initiated non-invasive ventilation electively. Mean current age is 33.8 ± 6.1 months (range 25-42 months) and mean follow-up time is 28.4 ± 7.2 months (minimum 19 months, maximum 40.7 months).

All of the patients improved in their CHOP-INTEND scores, with a mean change of 18.5 ± 7.4 points (range 11-30 points) (Fig. 2). Prior to treatment, three patients required continuous non-invasive ventilation and one required 14 hours of non-invasive ventilation per day. After at least six months of treatment, they all reduced the time of non-invasive ventilation and are currently on non-invasive ventilation during sleep (Fig. 2). During treatment, our patients mean number of hospital admissions due to respiratory exacerbations per year varied 0-4.2. Gastrostomy was performed in two patients during treatment and two patients have total oral feeding. Regarding weight gain, none of the patients had a global decline in the weight *z*-score or evolved to a weight *z* score < -3 (Fig. 3). Osteoarticular deformities were noted in three patients during the follow-up, namely kyphoscoliosis (Table 1). We did not report any side effects resulting from nusinersen treatment.

Patient 1 was 1.3 months old at diagnosis. He has a compound heterozygosity for the *SMN1* gene with two copies of the *SMN2* gene and at clinical presentation, he showed severe hypotonia, tongue fasciculations, and dysphagia. In this patient, we were unable to perform the first CHOP-INTEND assessment before treatment initiation, as he initiated treatment in another center at 2.3 months of age. When treatment started, he required continuous non-invasive ventilation. The first CHOP-INTEND (with a score of 41 points) was obtained three months after treatment initiation. He is currently 33 months old and a total of 12 nusinersen administrations were made. He can maintain stable sitting, touches his legs, rolls to the side, and has increased 11 points in CHOP-INTEND. The non-invasive ventilation time was reduced to 13 h/day and he had four hospital admissions due to respiratory exacerbations with no need of invasive ventilation (1.45 respiratory exacerbations per year).

Patient 2 was 2.5 months old at diagnosis and is also a compound heterozygous for the *SMN1* gene variants with two copies of the *SMN2* gene. He presented with a very typical clinical phenotype of severe hypotonia and tongue fasciculations with a baseline CHOP-INTEND score of 32 points. He began treatment at 4.2 months of age, requiring continuous non-invasive ventilation. He is currently 23 months, with a total of 10 nusinersen administrations performed. He is now able to maintain stable sitting, can roll to the side, and do the pincer grasp, and he presented an increase of 13 points in CHOP-INTEND. The non-invasive ventilation time was reduced to 14 h/day and he had eight hospital admissions due to respiratory exacerbation (4.2 respiratory exacerbations per year), two of them with intensive care unit admission with the need of invasive ventilation.

Patient 3 was 1.6 months old at diagnosis. He harbors a homozygous deletion in the *SMN1* gene, with two copies of the *SMN2* gene. At clinical presentation, he showed severe hypotonia and tongue fasciculations with a CHOP-INTEND score of 24 points. He began treatment at 2.1 months of age, requiring 14 hours of non-invasive ventilation per day. He was 15 months at the time of last evaluation, having been submitted to seven administrations of nusinersen. He achieved head control, rolls over, has stable sitting, and touches his toes with an increase of 30 points in CHOP-INTEND. The non-invasive ventilation time was reduced to 9 h/day. He had four hospital admissions due to respiratory exacerbations (3.2 respiratory exacerbations per year). This patient transitioned to gene therapy with onasemnogene abeparvovec, in a special program for

Table 1. Main characteristics of spinal muscular atrophy type 1 patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age at diagnosis	1.3 months	2.5 months	1.6 months	16 months
Genetic background	Compound heterozygosity (variant c.770_780dup, exon 6)	Compound heterozygosity (variant c.597dup, exon 4)	Homozygous deletion of exon 7 of *SMN1*	Homozygous deletion of exon 7 of *SMN1*
Number of *SMN2* copies	Two	Two	Two	Three
Clinical presentation and CHOP-INTEND	Severe hypotonia, tongue fasciculations, dysphagia 41/64*	Severe hypotonia, tongue fasciculations 32/64	Severe hypotonia, tongue fasciculations 24/64	Motor development delay, wobbles, sits only with support, multiple respiratory infections 26/64
Hours NIV/day before treatment†	24 h	24 h	14 h	24 h (since 17 months)
Age at beginning of treatment	2.3 months	4.2 months	2.1 months	17.6 months
Current age	42 months	33 months	25 months	35 months
Nusinersen doses	12	10	7	6
Clinical evolution and CHOP-INTEND	Stable sitting, touches legs, rolls to side 52/64 (+11)	Stable sitting rolls to side 45/64 (+13)	Head control, rolls over, stands with support 54/64 (+30)	Kyphosis, head control, stable sitting 45/64 (+19)
Feeding	Gastrostomy at 14 months Partial oral feeding	Gastrostomy at 15 months Total gastrostomy feeding	No gastrostomy Total oral feeding	Total oral feeding
Hours NIV/day after treatment	13 h (-9 h)	14 h (-10 h)	9 h (-5 h)	7 h (-17 h)
Osteoarticular deformities	Kyphoscoliosis	Kyphoscoliosis	-	Kyphoscoliosis
Hospital admissions	Four with continuous NIV	Eight (four with continuous NIV and two ICU admissions – need of IV)	Four with continuous NIV	None

CHOP-INTEND - Children's Hospital of Philadelphia infant test of neuromuscular disorders; ICU - intensive care unit; IV - invasive ventilation; NIV - non-invasive ventilation; SMN - survival motor neuron gene.
* Children's Hospital of Philadelphia infant test of neuromuscular disorders (CHOP-INTEND) three months after treatment initiation.
† Non-invasive ventilation started in respiratory exacerbations.

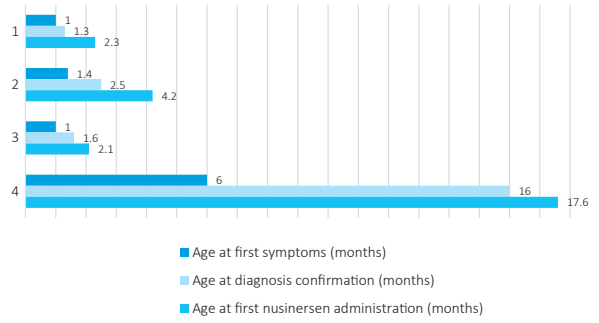
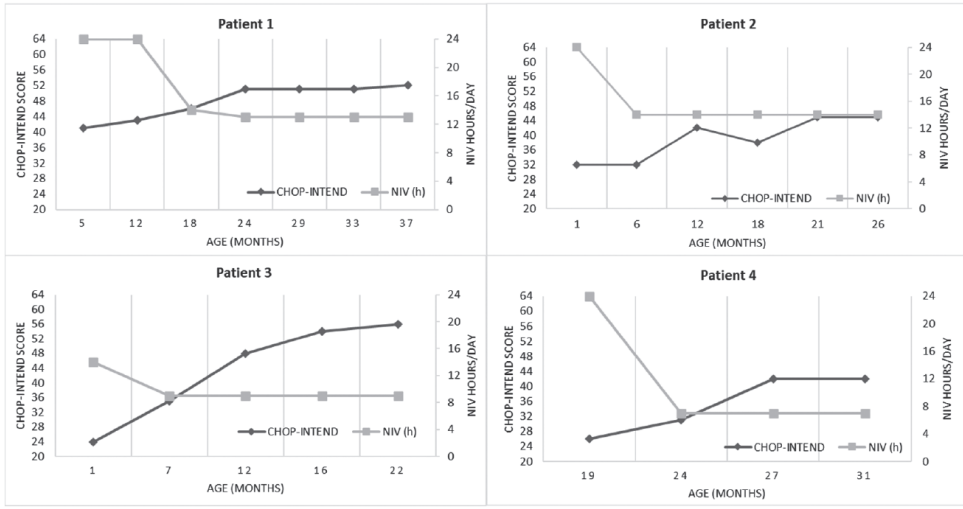


Figure 1. Ages at first symptoms, diagnostic confirmation, and first nusinersen administration.

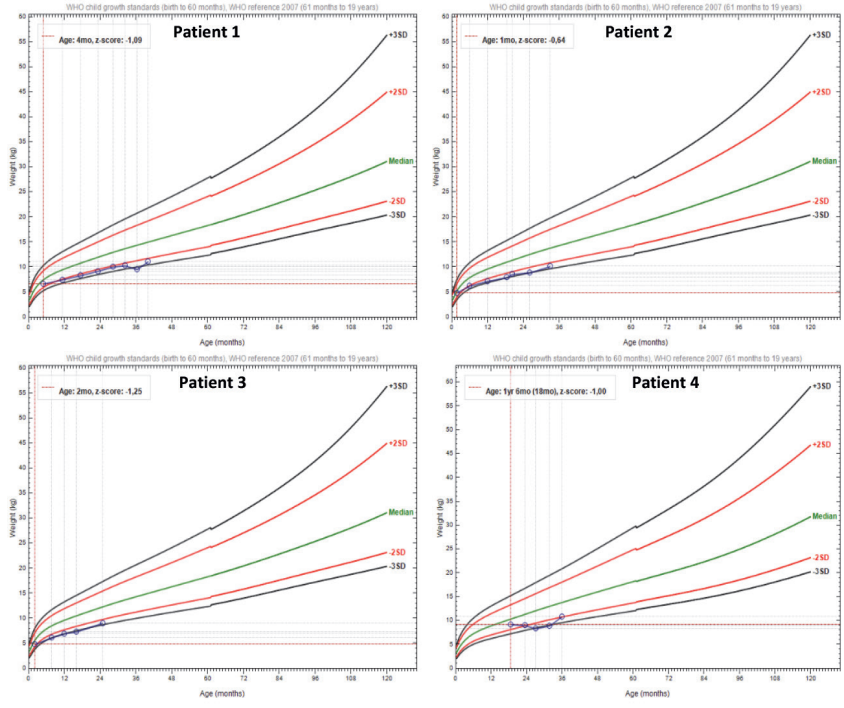
early access to the drug, after approval of the Portuguese regulatory authority at the age of 18 months.

Patient 4 was 16 months old at diagnosis and is the only one in the cohort with three *SMN2* gene copies (with a homozygous deletion of the *SMN1* gene). She presented with motor development delay, wobble of the head, seated only with support and had multiple respiratory infections. At diagnosis, CHOP-INTEND was 26 points. She began treatment at 17.6 months of age, requiring continuous non-invasive ventilation at that time. She was 26 months at her last assessment, having six



CHOP-INTEND - Children's Hospital of Philadelphia infant test of neuromuscular disorders; NIV - non-invasive ventilation.

Figure 2. Score changes in the Children's Hospital of Philadelphia infant test of neuromuscular disorders and non-invasive ventilation time reduction during nusinersen treatment.



mo - months; yr - years.

Figure 3. *Z* scores for weight for age during nusinersen treatment.

administrations of nusinersen. She currently has head control, rolls to the side, and maintains sitting, with an increase of 20 points in CHOP-INTEND. Non-invasive ventilation time was reduced to 7 h/day and she had no hospital admissions due to respiratory tract infections after nusinersen was started.

Discussion

In our four patients with SMA type 1, the age at the detection of first symptoms as well as the clinical presentation were according to those described in the literature. Although our patients were diagnosed in the very first months of life, we would like to emphasize that clinical suspicion is the key for an early diagnosis and subsequent treatment. A hypotonic infant with weakness, bulbar signs and areflexia should raise alarm for spinal muscular atrophy. The patient diagnosed at 16 months had three copies of the *SMN2* gene, leading to a less severe phenotype that probably justified her late referral and diagnosis.

According to clinical studies, an increase of at least four points in CHOP-INTEND score is considered as the cut-off for a significant response to the treatment.[6] The ENDEAR clinical trial showed a 71% responder rate after 13 months of follow-up in SMA type 1 patients.[7] The open label extension of the clinical trial confirmed an average improvement of 16.8 points on the CHOP-INTEND scale from baseline by day 1058. In the extended access programs where a much broader spectrum of SMA type 1 were treated, the responder rate was similar (42%-77%) after a six month follow-up period.[8-10] In the Italian extended access programs, the improvement was most evident in patients younger than seven months.[10] A greater change in CHOP-INTEND score from baseline in children aged less than seven months compared to older children was also found (children < 7 months: 14.4 ± 9.2, children > 7 months: 7.0 ± 6.6). In children requiring permanent ventilation support or tracheostomy, they experienced slighter improvements (CHOP-INTEND score change was 5.6 ± 7.5).[8] To our knowledge, our work is one of the few descriptions of nusinersen treatment in a real-world setting. The results of nusinersen treatment in 13 SMA type 1 patients in a real-life scenario in Hungary was described, showing an average CHOP-INTEND change of 14.9 ± 5.1 points, with a mean age at treatment initiation of 11 ± 4.4 months.[11] In our cohort, the average change in the CHOP-INTEND score (18.5 ± 7.4 points) was slightly higher than the changes observed in the open label extension of the ENDEAR trial, the younger patient group in the extended access programs, and in the Hungarian real-life experience cohort. All of our treated patients became responders by the time of the sixth injection, with an improvement in CHOP-INTEND up to 30 points.

After at least six months of treatment with nusinersen, we observed an improvement in motor function and there were substantial motor milestones achievements, in comparison with the natural history of the disease. Early initiation of treatment is vital for a therapeutic response, and, in our center, treatment was initiated nearly after diagnosis (1.2 ± 0.5 months, range 0.5-1.7 months), which could account for our slightly better results compared to the Hungarian cohort. It is known that age at treatment initiation is an important factor contributing to efficacy, but it was also previously suggested, based on the Italian extended access programs data, that treatment outcome could be influenced by the baseline motor function or the progression rate.[10]

In these patients, the respiratory muscles are frequently involved, justifying the need of non-invasive ventilation early in the course of the disease.[6] Treatment with nusinersen also resulted in a reduction of the time in ventilatory support, with all patients having non-invasive ventilation only during sleep and for time periods during the day in a respiratory exacerbation context. Respiratory insufficiency is the leading cause of death in these patients that usually need frequent hospitalizations for respiratory exacerbations. The stabilization of respiratory function to the minimum hours without the need to increase baseline ventilatory support (all symptomatic patients initiate non-invasive ventilation regardless of dyspnea in accordance with standards of care) as well as the reduction of hospital admissions due to respiratory exacerbations are remarkable signs of treatment response.[12]

Feeding difficulties are common in SMA type 1 patients and two of our four patients had a gastrostomy during treatment. These patients had a nasogastric tube at an early age due to poor sucking and swallowing and failure to thrive. This could indicate that nusinersen treatment was unable to rescue bulbar neurons and to improve poor feeding and dysphagia in these patients, but it is also possible that bulbar function was already severely compromised prior to nusinersen treatment (clinically presenting tongue fasciculations and weak cry). Two other patients can feed orally, one patient has three *SMN2* copies (and thus a possibly milder phenotype) and another patient required intermittent nasogastric tube feeding.

Children with SMA type 1 are at risk for undernutrition evolving frequently with severe nutritional

deterioration.[13] Although our patients did not achieve a normal *z* score evolution (when compared to healthy children), during the treatment course they had regular weight gain, and none became severely malnourished.

Despite the importance and results of nusinersen in our patients, these children are far from achieving near normal milestones (as seen in treated pre-symptomatic patients), as they began treatment already symptomatic, and treatment cannot rescue degenerated motor neurons.[14,15] We will probably experience further problems, as the worsening of kyphoscoliosis (which might lead to difficult intrathecal treatments), fixed joint contractures, and difficulties in oral communication (due to dysarthria). Motor scales have reached a plateau and are probably unable to capture a more accurate clinical response to treatment (like complaints of fatigue, or functional improvements, such as being able to maneuver a wheelchair). We are experiencing a longer disease duration in an increasingly more global community, which leads to different patterns of connection, not only between healthcare providers but also with parents of symptomatic patients. In addition, the arrival of new therapeutics adds additional challenges to the management of this complex condition, which witnessed a true therapeutic revolution.

As we are facing a new era of treatment of spinal muscular atrophy, and, albeit our limited experience, we would like to emphasize that early and urgent referral of suspected patients to tertiary hospitals is paramount to achieving a prompt diagnosis and to initiate treatment as early as possible.

WHAT THIS STUDY ADDS

- Nusinersen is an antisense oligonucleotide approved for the treatment of spinal muscular atrophy patients and that completely revolutionized the paradigm of clinical approach of children with this diagnosis.
- Despite our single-center small sample, our findings are promising and contribute to the increasing evidence that early diagnosis and treatment is paramount for spinal muscular atrophy type 1 patients.
- In our real-life experience, treatment with nusinersen resulted not only in an improvement in motor function, but also in a reduction of the time in ventilatory support and hospital admissions due to respiratory exacerbations.
- Clinicians will have to adjust to a more interventionist and pro-active approach in order to correspond to the changing phenotype of spinal muscular atrophy type 1 patients.

Conflicts of Interest

Joana A. Ribeiro has served as an advisory board member for Biogen®, Avexis® and Roche®. Filipe Palavra has received speaker honoraria and served as advisory board member for Biogen® and Roche®.

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Provenance and peer review

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Awards and presentations

This study was presented as an oral lecture at the European Academy of Pediatrics Congress and Master Course in 19-22 September 2019, Porto, Portugal.

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Nusinersen: Experiência Real de um Centro em Atrofia Muscular Espinhal Tipo 1

Resumo

Introdução: O oligonucleótido antissense nusinersen é utilizado no tratamento da atrofia muscular espinhal, tendo demonstrado em ensaios clínicos uma melhoria significativa nas aquisições motoras. Este estudo tem como objetivo reportar os resultados clínicos de crianças com atrofia muscular espinhal tipo 1 sob nusinersen num centro terciário.

Métodos: Estudo retrospetivo de pacientes com atrofia muscular espinhal tipo 1 sob nusinersen há pelo menos seis meses. Foram estudados parâmetros clínicos, genéticos, ventilatórios e nutricionais. A avaliação motora foi avaliada pelo teste infantil de doenças neuromusculares do Children's Hospital of Philadelphia.

Resultados: Foram incluídos quatro doentes, com idade média de 33,8 meses (25-42 meses), três com duas cópias do gene de sobrevivência do neurónio motor 2 e um com três cópias. O tempo médio desde o início da sintomatologia à confirmação diagnóstica foi de três meses (0,3-10 meses) e desde a confirmação diagnóstica até ao início do tratamento foi de 1,2 meses (0,5-1,7 meses). Todos os doentes tiveram um aumento de pelo menos 11 pontos na avaliação motora (aumento médio 18,5 pontos). Três doentes sentam-se de forma estável e um senta-se com apoio. Nenhum doente necessita de ventilação não invasiva contínua. O número médio de internamentos por intercorrências respiratórias por ano variou entre 0-4,2. Dois pacientes foram sujeitos a gastrostomia e um alimenta-se por via oral.

Discussão: Nos doentes com atrofia muscular espinhal tipo 1 sob nusinersen observou-se uma melhoria na função motora e no suporte ventilatório. Apesar desta pequena amostra, os resultados contribuem para a evidência crescente de que um diagnóstico e tratamento precoces são fulcrais.

Palavras-chave: Atrofias Musculares Espinais da Infância/tratamento farmacológico; Oligonucleotídeos/uso terapêutico; Pré-Escolar; Resultado do Tratamento