# SPINAL MUSCULAR ATROPHY: CLINICAL CHARACTERIZATION AND EVOLUTION AFTER TREATMENT WITH NEW MODIFYING THERAPIES

**Abstract**

Objectives: Conducting a retrospective analysis of the clinical characteristics and evolution of patients with spinal muscular atrophy (SMA) type 1 and 2 which were treated with the new modifying therapies.

Methods: A descriptive, cross-sectional and retrospective study was conducted with a target population of patients with a genetic diagnosis of SMA treated with nusinersen or onasemnogene abeparvovec-xioi (OAX) who were monitored by the external consultation services of pediatric pulmonology in a tertiary hospital. The data were collected from their electronic clinical records.

Results: The study describes 6 patients with ages from 14 months to 11 years, 4 of whom had a diagnosis of SMA type 1 and 2 with a diagnosis of SMA type 2. With regard to their treatment, 3 patients received nusinersen, 2 patients received OAX, and 1 patient received OAX followed by nusinersen.

The number of emergency consultations due to respiratory infections per year of treatment was 0.3/year for patients treated with OAX and 0.75/year for patients treated exclusively with nusinersen. None of the patients treated with OAX have required hospitalization for a respiratory infection to date. With regard to respiratory support, two patients had a tracheostomy, and the rest received nocturnal noninvasive mechanical ventilation as a preventive measure. Two of the patients had undergone gastrostomy. The patients treated with OAX have shown an improvement in their motor functions according to the CHOP INTEND score.

Conclusions: The description of different real-life cohorts will make it possible to homogenize the management of these patients and provide realistic expectations regarding the evolution of their condition.

# Introduction

Spinal muscular atrophy is a genetic disorder inherited in an autosomal recessive manner which causes the progressive loss of motor neurons in the central nervous system. Its underlying origin involves biallelic mutations of the SMN1 gene (survival of motor neuron 1), which can be found in the chromosomal region 5q13 (1). The SMN2 gene (survival of motor neuron 2) is an analog of SMN1 which is not expressed in exon 7.

Both genes encode the SMN protein (survival of motor neuron), but unlike SMN1, the elements generated by SMN2 present functional alterations that create an unstable SMN protein which degrades early. This causes the loss of motor neurons, mainly in the spine, with subsequent weakness and progressive muscle atrophy. In the absence of SMN1 transcription, the severity of the disease will depend on the amount of functional SMN protein generated by SMN2. A higher number of SMN2 copies means a higher amount of the resulting protein.

The approximate incidence of carriers of a genetic alteration in SMN1 ranges between 1/40 and 1/60 (2). The global incidence of the disease is 1/11000 (3), which is lower than could be expected given the frequency of carriers. This is probably explained by the fact that there are forms of this disease which are incompatible with life due to the lack of enough copies of SMN2.

The phenotypic characteristics of the disease establish the existence of 4 subtypes with a correlation between genotype and clinical symptoms. Type 1 has the earliest onset and the most severe involvement, and type 4 is the one with the mildest symptoms. SMA type 1, with two copies of SMN2, is the most common form (4) and it is characterized by early onset within the first 6 months of life and the inability to achieve the motor milestones of neural development.

From a respiratory perspective, the classical evolution of this disease used to involve the need for constant mechanical ventilation or death at a mean age of 13 months (5). Apart from the respiratory complications and the motor delay, patients often present difficulties coordinating sucking and swallowing due to bulbar involvement and they usually require enteral nutrition support between the first and fourth month since the onset of symptoms (6). Natural history studies of the disease have reported a 100% rate of need for nutrition support at 12 months of age (5).

This disorder also involves a high rate of hospitalizations, with up to 4.2 to 7.6 hospitalizations per year in patients who do not receive any specific treatment (7).

Up until the development of new therapies, the basal treatment of these patients included respiratory and nutrition support. New modifying therapies such as nusinersen, which was approved by the European Medicine Agency (EMA) in 2017; onasemnogene abeparvovec-xioi (OAX), approved in 2020 by the EMA; and risdiplam, approved by the EMA in 2021; have shown promising results regarding the acquisition of motor milestones and the decrease in morbidity and mortality (8, 9, 10). These drugs act directly on the genetic defect which is responsible for the disease (11).

Even though long-term results are yet unclear, these targeted treatments seem to slow down the development of some of the clinical characteristics of SMA, which is particularly significant when administered early after diagnosis (11).

It is important to highlight that the multisystemic involvement caused by this disease has a major impact on the quality of life of these children. Even though there are no references in the literature with specific scales to assess the quality of life of patients diagnosed with SMA, a significant impact has been observed regarding the disability-adjusted life years and the years lived with disability (12).

The Health Utilities Index Mark 3 has been used as a marker of health-related quality of life (HRQOL), and it shows an association between the type of SMA and the impact on HRQOL (13).

The studies conducted with these new treatments have shown that small changes in motor function and the decrease in disease-associated morbidity potentially has a major impact on the perceived quality of life of these patients (7). We present a cohort of 6 patients, 4 with a diagnosis of SMA type 1 and 2 with a diagnosis of SMA type 2, who were treated with the new modifying therapies. The patients presented either 2 or 3 copies of SMN2. The objective of the study is to describe the cohort and its characteristics regarding morbidity. Additionally, we compare our findings with the existing literature on other populations of patients with this same condition. The parameters included in the study are respiratory support, swallowing function, number of hospitalizations and motor function, in order to expand the existing evidence on the effect of these new therapies on SMA patients.

# Material and methods

The clinical records of all patients with a genetic diagnosis of SMA who were followed by the external services of Pediatric Pulmonology in a tertiary hospital were reviewed.

This is a cross-sectional, retrospective study. The variables analyzed include the type of mutation in SMN1 and number of copies of SMN2, specific treatment received, respiratory support, nutrition support, motor function and sleep study. Also, this study includes the number of external and emergency consultations, as well as the number of hospitalizations from the start of the treatment until December 31st, 2023.

With regard to the treatment, we specified whether they received OAX or nusinersen, and the number of doses in this last case. We also recorded the time between the onset of symptoms and the start of treatment (in days).

A difference was established regarding respiratory support between patients who did not require it and those who received noninvasive mechanical ventilation (NIMV) or invasive mechanical ventilation (IMV), and the hours of use of each therapy were registered. Patients were also divided into those who had undergone tracheostomy and those who did not.

The assessment of pulmonary function, in patients in which it was registered, was based on the parameters of the Global Lung Function Initiative 2012.

In the sleep study, the apnea-hypopnea index and the presence of desaturation during sleep were registered.

With regard to the number of emergency consultations, the frequency is expressed as the number of consultations per year of treatment. The hospitalization rate is expressed as the number of hospitalizations per year of treatment.

In the assessment of the swallowing function, the specific tests that were conducted have been registered. The assessment of the motor function is expressed based on the score of the patients in the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) (15).

This study has been approved by the Ethics Committee of the University Hospital of Salamanca on 16th of December 2024, record 2024/13, CEIm reference number E.O. 24/876. Verbally informed consent has been provided by all tutors involved. However due to the retrospective and observational nature of the study and the fact that some of the patients do not live in the same city, the study received and exemption from written informed consent by the Ethics Committee .

# Results

The cohort in our study has 6 patients, 3 boys and 3 girls. On December 31st, 2023, the ages of the patients ranged between 14 months and 11 years.

All the patients presented a homozygous deletion of SMN1 exons 7 and 8 confirmed via Sanger sequencing. Based on their clinical presentation, 4 of the patients had a diagnosis of SMA type 1, and 2 had a diagnosis of SMA type 2. All the patients with SMA type 1 presented two copies of the SMN2 gene, while in the group of patients with SMA type 2, one of them presented two copies and the other one presented three copies.

Symptoms in patients with SMA type 1 started at an age of between 15 and 92 days, while in patients with SMA type 2 it was between 303 and 414 days. The time from the onset of symptoms and the start of treatment was between 20 and 2037 days (Table 1).

With regard to the treatment, 3 patients received 5-19 doses of nusinersen (the 2 patients with SMA type 2 and 1 patient with SMA type 1), 2 patients received OAX and 1 patient who was initially treated with OAX was later referred to another hospital and was treated with nusinersen as part of the RESPOND study (16) (Table 1).

Table 1. Demographic characteristics of the patients and treatment.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Diagnosis** | | **Sex** | **Age of symptom onset1** | **Age at diagnosis1** | **Time from diagnosis to treatment1** | **Treatment** | **No. of doses of nusinersen** |
| **Patient 1** | SMA type 2 | | Female | 303 | 1065 | 2037 | Nusinersen | 15 |
| **Patient 2** | SMA type 1 | | Male | 60 | 90 | 1172 | Nusinersen | 19 |
| **Patient 3** | SMA type 2 | | Female | 414 | 434 | 77 | Nusinersen | 5 |
| **Patient 4** | SMA type 1 | | Male | 92 | 158 | 106 | OAX | 0 |
| **Patient 5** | SMA type 1 | | Male | 15 | 57 | 42 | OAX + Nusinersen | 4 |
| **Patient 6** | SMA type 1 | | Male | 37 | 46 | 20 | OAX | 0 |
|  | | 1Data expressed in days | | | | | | |

The number of emergency consultations per year of treatment due to respiratory infections was 0.3/year in patients treated with OAX and 0.75/year in patients treated with nusinersen. None of the patients treated with OAX has required hospitalization so far due to respiratory infections. Only 2 out of the 3 patients treated with nusinersen have required hospitalization, in both cases in the Pediatric Intensive Care Unit, due to the need of respiratory support with mechanical ventilation (global rate of 0.27 hospitalizations/year of treatment) (Table 2).

At the time of data collection, two of the patients had a tracheostomy and required invasive mechanical ventilation. One of them (SMA type 1) maintains constant mechanical ventilation since the fifth month of life (prior to starting treatment with nusinersen). The other patient (SMA type 2) underwent invasive mechanical ventilation in the context of exacerbation-like respiratory symptoms after receiving two doses of nusinersen, and is currently only connected to a ventilator during the nights, with spontaneous breathing during the day with a speaking valve. It was not possible to remove the tracheostomy in this patient due to velopharyngeal insufficiency and poor management of secretions requiring frequent aspirations. The rest of the patients have a proactive prescription for noninvasive mechanical ventilation at night, with different amounts of use hours depending on their tolerance (Table 2).

Table 2 Nutricional and respiratory support. Emergency department consultations.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No. of emergency consultations** | **Respiratory support** | **Oral feeding** |
| **Patient 1** | 3 | Noninvasive mechanical support | Yes |
| **Patient 2** | 4 | Invasive mechanical support | No |
| **Patient 3** | 1 | Invasive mechanical support | No |
| **Patient 4** | 0 | Noninvasive mechanical support | Yes |
| **Patient 5** | 1 | Noninvasive mechanical support | Yes |
| **Patient 6** | 0 | Noninvasive mechanical support | Yes |

Patient 1 is the only one that conducted pulmonary function tests. It was impossible to carry out the tests in the rest of the patients, either due to their age or to significant clinical involvement. The study presented a severe restrictive pattern with a forced vital capacity of 0.56 liters, which corresponds to a z-score of -6.85 according to the parameters of the Global Lung Function Initiative 2012 (14), with a decrease by 4% when the patient was on supine position. This patient also showed a significant decrease in the peak expiratory flow with a z-score of -2.74 compared to the reference values.

With regard to the sleep study, patient 5 underwent polysomnography with an apnea-hypopnea index of 1.4 per hour of study, without episodes of desaturation below 90%. The capnography could not be performed for technical reasons.

Two of the patients presented severe complications secondary to swallowing: aspiration pneumonia and frequent choking. In both cases, an endoscopic percutaneous gastroscopy was performed at 19 months of age without a videofluoroscopic study. Patient 4 started showing occasional coughing when drinking liquids and underwent a videofluoroscopic study that did not reveal alterations in the swallowing process. The rest of the patients did not present symptoms that suggested alterations in the swallowing function during the study and, at the time of data collection, no complementary tests had been conducted (Table 2).

With regard to the assessment of the motor function, patients treated with OAX undergo specific assessment via the CHOP INTEND test as part of the protocol in our center. The results were collected prior to the start of treatment, and after 1 and 4 months. The results are summarized in Table 3.

Table 3. CHOP-INTEND scores in patients treated with OAX.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **CHOP-INTEND score at diagnosis** | **CHOP-INTEND score 1st month** | **CHOP-INTEND score 4th month** |
| **Patient 4** | 19 | 31 | 40 |
| **Patient 5** | 8 | 16 | 31 |
| **Patient 6** | 7 | 16 |  |
| 1The results from the 4th month were not included because the data were collected prior to that date. | | | |

# Discussion

This study provides new real-life data on the management and support treatment of patients with SMA treated with the new modifying therapies for this disease.

Historically, the respiratory involvement represented a significant morbidity and mortality for these patients, who required respiratory support or could suffer an early death (5). It seems clear that the new modifying therapies for this condition could mean an improvement in the quality of life and prognosis of these patients, but given the low prevalence of this disease, real-life results are yet to be described.

In our population, the number of emergency consultations due to an infection per year of treatment is below the figures observed in the literature, both in patients treated with OAX (7) and with nusinersen (17).

None of the patients in our sample who received OAX required hospitalization for an infection, and in the group of patients treated with nusinersen, the hospitalization rate was 0.27/year, which is below the values of 4.2-7.6 hospitalizations per year found in the literature (7).

Even though the study period for these patients includes the post-pandemic years in which hygienic measures have been increased and there have been changes in the epidemiology of respiratory infections, the new modifying therapies could be related to the decrease in the infection-associated morbidity.

With regard to respiratory support, we have observed a decrease in the need for invasive ventilation with the new modifying therapies in our patients. As the literature shows, the use of invasive mechanical ventilation is virtually compulsory in patients who do not receive treatment and present more severe SMA phenotypes (18), whereas patients who receive treatment with OAX or nusinersen before they present symptoms do not require invasive ventilation (7, 18). In our sample, two patients required tracheostomy and invasive ventilation: patient 2, because the disease started prior to the development of modifying therapies, and patient 3, after receiving a single dose of nusinersen and in the context of a respiratory infection.

Respiratory support could not be removed in any of these patients. This could be due to the late start of the treatment for the disease, similar to what has been described in the literature.

The rest of our patients have a medical prescription for noninvasive mechanical ventilation at night, because their early administration helps to slow the progression of the restrictive pattern that is presented by these patients and to achieve better pulmonary development (11). The optimal time of use is not clearly defined. Our cohort shows variable times of use which depend mainly on the tolerance of the patient to the device.

Patient 1 presented a severe restrictive pattern in the spirometry and a marked decrease in the maximal expiratory pressure. This pattern matches the expected results, although the involvement is more severe than in other populations with SMA type 2 described in the literature (19). This may be due to the fact that our patient was older than average at the time of the study, as well as to a later start of the treatment.

The sleep study conducted on patient 5 shows apnea-hypopnea and desaturation indexes below those described in the literature (19, 20, 21), although those cohorts are very heterogeneous and do not include patients treated with OAX. Therefore, further studies are required to assess the impact of these treatments on sleep.

The literature describes that the swallowing function is affected in all patients with SMA type 1 and in over 75% of patients with SMA type 2 who have not received treatment (22). In our series, none of the patients treated with OAX presented swallowing disorders, which is remarkable when compared with other series, in which almost one third of patients with this treatment present some type of swallowing alteration (23). In the group of patients treated with nusinersen, the results are clearly poorer regarding swallowing, which could suggest that this drug has less effect than OAX.

An improvement in motor function has been observed in our patients after treatment with OAX, although this improvement seems to be more limited than what has been found in a meta-analysis of 11 published studies (24). Patients treated with nusinersen also showed a clear clinical improvement in motor function, although this was not specifically assessed in our patients with series of tests.

The main limitations in our study are the size of the sample and the heterogeneity of the patients included in it. Both aspects affect the representativity of the results and conclusions. This is a very rare disorder with a fatal prognosis, and the development of the main modifying therapies has taken place over the last few years, which means that there are patients at different stages of their disease and with different treatment patterns. This limits the comparison between patients and makes it difficult to reach conclusive results.

# Conclusions

The new modifying techniques in SMA are associated with a decrease in the need for nutrition and respiratory support, an improvement in motor function and a decrease in hospitalization rates. This contrasts with the natural evolution of the disease that is described in the literature, which represents a relief for patients and caregivers, a reduction in the healthcare burden and a potential improvement in their quality of life. Even though the results so far show a promising future, it is important to conduct close monitoring to these patients and observe their evolution over time with series of objective tests (spirometry, polysomnography, videofluoroscopy, etc.) to determine accurately the power of these new therapies. The description of different real-life cohorts will make it possible to homogenize the control, treatment and expectations of these patients for optimal management.

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