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Survival without Permanent Respiratory Support in a Patient with SMA Type 1 Treated with Nusinersen

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ABSTRACT

Spinal muscular atrophy (SMA) is a rare, but severe disease, which is characterized by progressive muscular weakness resulting in permanent assisted ventilation before the age of 2. Supportive care used to be the only available treatment. However, relevant progress has been achieved with the approval of nusinersen (an antisense oligonucleotide modulating SMN2 splicing), which changed the disease outcome for many patients. Thus, management of SMA patients requires a multidisciplinary approach with pharmacological and non-pharmacological treatments to provide the necessary supportive care for symptom management, nutritional support and active rehabilitation to optimize muscle function. In this paper we aimed to report the first patient with type 1 SMA in the Latin America region that was able to get off the ventilator without a tracheostomy after an early treatment with nusinersen, continuing to date stable and with no need of ventilatory support.

Introduction

Spinal muscular atrophy (SMA) is a rare, but severe disease, caused by autosomal recessive mutations of the survival motor neuron 1 (SMN1) gene and is characterized by progressive muscular weakness due to loss of the anterior horn motoneurons in the spinal cord and the brain stem nuclei[1]. The SMA (also known as Werdnig-Hoffman Disease) incidence has been described in up to 1 in 11.000 live births [1-2]. Based on age at onset and maximum motor function achieved, the clinical phenotypes are classified as follows: i) very weak infants unable to sit unsupported (type 1); ii) non-ambulant patients, able to sit independently (type 2); iii) up to ambulant patients with childhood (type 3) and iv) adult onset SMA (type 4)[2-3]. In the last decade there has been increasing evidence of improvements in the natural history of all the SMA types[4-6]. It was due to the development of specific treatment and an increase of survival as a consequence of a more proactive approach (i.e: introduction of non-invasive ventilation, enteral feedings, among others)[3]. Thus, relevant progress has been achieved, which changed the disease outcome for many patients. Nusinersen (Spinraza®) was the first drug approved for the treatment of SMA[7-8]. Investigation into other SMA therapies has continued, and a gene replacement therapy was approved by FDA in 2018. This gene therapy is known as AVXS-101 (Onasemnogene Abeparvovec, Zolgensma®)[9]. On the other hand, respiratory impairment is the leading cause of morbidity and mortality in SMA type 1 patients[1-3]. Chest muscle weakness,

abnormal chest wall shape and underdeveloped lungs have been reported as the main progressive respiratory complications, as the diaphragm function is relatively spared. Ineffective cough results in secretion clearance alterations and recurrent respiratory infections[1-3]. SMA patients can also develop sleep disordered breathing and nocturnal hypoventilation[2].

We aimed to report the first patient with type 1 SMA in the region that was able to get off the ventilator without a tracheostomy after an early treatment with nusinersen, continuing to date (at the time of writing this paper) stable and with no need of ventilatory support.

Case Report

We present a 17-month-old female, with diagnosis of type 1 SMA under treatment with nusinersen, starting at 3 months of age and with a total of 6 doses received, according to protocol. Although the videofluoroscopy swallowing study did not show aspiration nor microaspiration, she has been receiving feeding with a nasogastric tube since she was 13 months of age due to an alteration in the first stage of swallowing and poor weight progression. Since her discharge, she has been indicated non-invasive mechanical ventilation (NIMV) with positive nocturnal pressure during sleep, but with regular to null compliance. In June 2020, at 17 months of age, she was admitted at the pediatric intensive care unit due to acute hypoxemic respiratory failure. Her respiratory exam showed: respiratory rate 66 breaths per minute, paradoxical respiration, heart rate of 185 beats per minute, 38 degrees Celsius of body temperature and 85% of blood oxygen saturation. Auscultation revealed bilateral hypoventilation and thick bilateral rales. Manual cough assistance with assistance of the inspiratory time with a self-inflating bag and of the expiratory phase with abdominal compression was initiated. Excessive fluid mucous secretions were aspirated through the nasal and oropharyngeal routes. At the same time, NIMV in PC-NIV mode was administered with the following parameters: peak inspiratory pressure (PIP) of 19 cmH2O, positive pressure at the end of expiration (PEEP) of 7 cmH2O, respiratory rate of 30 cycles per minute, inspiratory time (Ti) of 0.6 seconds, fraction of inspired oxygen (FiO2) of 0.21. This treatment was well tolerated initially and she showed recovering of the saturation of blood oxygen to 95%, respiratory rate of 40 breaths per minute, although persistence of tachycardia with a heart rate of 180 beats per minute was noted. Respiratory samples were taken: PCR for SARS-CoV-2, VSNF and PCR for adenovirus, all their results being negative. After 4 hours of treatment, she evolved into a more severe respiratory failure, for which she required orotracheal intubation with a number 4 tube and invasive pressure-controlled mechanical ventilation. At that moment, the set parameters were: PIP 27 cmH2O, PEEP 7 cmH20, respiratory rate 25 per minute, inspiratory time 0.6 seconds, FiO2 of 0.6. The patient showed a good response, achieving saturation of blood oxygen of 99%, HR 120 beats/min, respiratory rate of 25 for minute. Tracheal aspirate sample was taken, and it yielded negative results.

The patient was handled according to the recommendations from the IMV disconnection protocol, proposed by Bach et al.[10-11], and the guidelines for the acute treatment of patients with SMA[3, 12]. However, some adaptations were made according to our center´s equipment. Cough assistance was performed manually with a lung volume recruitment bag. Assisted inspiration was carried out with a single breath inspiration, followed by abdominal compression to increase expiratory airflow along with increased inspiratory capacity. After cough assistance maneuvers, abundant secretions were aspirated through the orotracheal tube. The session was terminated when the patient showed a good response based on her bilateral vesicular murmur and no added sounds. She received 8 sessions per day along with both nasal and oropharynx aspiration. Three days after admission, periods of PSV were started, with PS of 10cmH2O, PEEP of 7 cmH2O and FiO2 of 0.21 with good tolerance: respiratory rate of 30 per minute, exhaled tidal volume of 80 ml, blood oxygen saturation of 98 %. The weaning of AVM was progressed daily, prolonging the periods of PSV. On the eighth day, with fulfillment of the extubating criteria (afebrile, awake without sedation, aspiration every 3 hours, not requiring aspiration through the nose, or oxygen), she was electively extubated and switched to preventive NIMV with home equipment: Astral 150-ResMed in PC mode with the following parameters: PIP 12cmH2O, PEEP 6 cmH2O, Respiratory rate 20 per minute, FiO2 0.21. The patient's nasal interface Wisp pediatric Philips Respironics was used, in addition to abdominal girdle and flat dorsal decubitus. On the tenth day from admission, weaning from non-invasive ventilation with good tolerance for short periods was started. Finally, on the fifteenth day, it was possible to wean her from daytime non-invasive ventilation. The patient was discharged with non-invasive nocturnal ventilation during sleep and spontaneous ventilation with ambient FIO2 during the day.

Discussion

Based on data from the pivotal clinical trial, nusinersen should be indicated in patients who are not fully dependent on a mechanical ventilator[7-8]. Many studies have shown the

effect of nusinersen on motor function or survival rate in SMA type 1 patients[13-14]. On the other hand, one recently published study evaluated the effect of nusinersen on SMA type 1 patients who were already on mechanical ventilation[15]. Patients who were already ventilated at treatment initiation were clinically stable, and they maintained a similar level and type of ventilatory support as that at the time of treatment initiation[15]. However, there was no improvement in respiratory insufficiency or reduction in the need for assisted ventilation among any of the children. This study group consisted of patients with a median age at enrollment of 13.5 months (range 1-184), which is significantly older than the population in the ENDEAR trial[13] (i.e., mean 163 days, range 52-242), and therefore reflects a more advanced disease course at the time of treatment initiation. A previous nusinersen RCT suggested that early initiation of treatment may maximize its efficacy[13]. Therefore, even though this real-world finding suggest that respiratory improvement is unlikely among nusinersen-treated patients with SMA1, it is possible that greater stability of the respiratory condition may be achieved among younger patients whose treatment is initiated at an earlier age, as is the case of our patient.

Other studies on SMA type 1 patients with ventilatory support via a tracheostomy reported an improvement in respiratory function with nusinersen treatment[16-17]. Unfortunately, there were no patients with ventilatory support via tracheostomy who were weaned from permanent assisted ventilation, although they did show a decreased duration of noninvasive ventilatory support.

A case report of a male infant with SMA type 1 who had undergone a tracheostomy at 75 days of age and treated with nusinersen at 99 days of age demonstrated that he could be weaned from the ventilator for 1.5 h/day after 6 months of nusinersen treatment[18].

We report a case of successful weaning from mechanical ventilation in a 17-month-old patient who had started early treatment with nusinersen at the age of 3 months and had received 6 doses before the acute respiratory event that led her to ventilation assistance.

Our case is remarkable because of some particular facts: firstly, she could be weaned from mechanical ventilation without the need of tracheostomy. Secondly, she required a short period of time of continuous ventilation assistance. Noteworthy, she had started the medication at an early age and long before the acute respiratory event. Finally, she is still stable, at the time of this report, and with no need of ventilatory support.

Many studies have failed to prove a significant improvement of respiratory function in patients with SMA type 1 who need mechanical ventilation[1-3,12]. In our patient, the medication had been started long before the invasive mechanical ventilation and this might have played a role in the clinical outcome, making this situation reversible after a short period of ventilatory support. This case might imply that early treatment with nusinersen may improve clinical outcome in type 1 SMA patients who require mechanical ventilation due to an acute respiratory event.

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Conflict of Interest

None of the authors have any potential financial conflict of interest relating to this manuscript.

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