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Keywords: Spinal Muscular Atrophy type 1, Respiratory management, Nocturnal gas exchange, Non Invasive Ventilation, Nusinersen, Children

Funding Source: No fundings were secured for this study.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Data Availability Statement: data available on request from the authors

Conflict of Interest: JT: Coinvestigator for the ENDEAR study group and Avexis; LS has conducted consultancy/attented board for Roche, Novartis, Biogen, Scholar Rock. He is coordinating investigator of studies funded by Biogen, Roche and Avexis; CV has conducted consultancy/attented board for Roche, Novartis, biogen, is coordinating investigator of studies funded by Biogen and Roche. JM, EF, AB, AB, GL, LC, MBB, MGGB and HC have no conflict of interest to disclose.

Meetings: This paper was presented to the "Congrès de Pneumologie et d'Allergologie Pédiatrique" 2021 during a poster session.

Abbreviated title: Respiratory management of Spinal Muscular Atrophy type 1

Abstract

The recent development of disease-modifying treatments in Spinal Muscular Atrophy (SMA) type 1 shifted these patients' management from palliative to proactive. The aim of this study was to assess patients' nocturnal gas exchanges prior to NIV initiation and their clinical evolution in order to determine if capnia is a good criterion to decide when to introduce respiratory support. This multicentric retrospective study reports the respiratory management and evolution of 17 SMA type 1 children (10 females) for whom treatment with Nusinersen was initiated between 2016 and 2018. Median [IQR] age at diagnosis and at first Nusinersen injection was of 4 [3;8] and 4 [3;9] months, respectively. Patients were followed during 38 [24;44] months. Thirteen (76%) patients were started on Non-Invasive Ventilation (NIV) at a median [IQR] age of 12 [9;18] months. Repeated hospitalizations and ICU admissions were needed for 11 of them. Blood gas and nocturnal gas exchange recordings performed prior to NIV initiation were always normal. 9/13 X-ray performed prior to NIV showed atelectasis and/or acute lower respiratory tract infections. There was a significant decrease in the total number of hospital admissions between the first and second year of treatment ($p=0.04$). This study shows that patients do not present with nocturnal hypoventilation before respiratory decompensations and NIV initiation, and suggests that a delay in NIV initiation might result in respiratory complications. There is a need for disease-centered guidelines for the respiratory management of these patients, including NIV indications.

Introduction

Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disease resulting from an autosomal recessive mutation in the *Survival Motor Neuron 1* gene (*SMN1*) [1]. With an incidence of approximately 1 in 10 000 newborns and a carrier frequency of 1:40 in the Caucasian population, it is the most common genetic cause of death in infancy [2-4].

SMA is characterized by progressive muscle atrophy and proximal muscle weakness causing chronic respiratory insufficiency [5,6]. Clinical presentation varies according to the functional status - illustrated by the highest motor milestone achieved - and age at onset [7,8]. Thus, SMA is clinically classified into five subtypes (SMA types 0-4). SMA type 1 is the most frequent subtype, affecting approximately 58% of all SMA patients [9,10]. These children present with severe hypotonia and muscle weakness, usually diagnosed during the first 6 months of life. Natural history studies have described a death rate of 68% in the first 2 years of life and 82% before the age of 4 years old without treatment [8,11].

SMN1 gene is located on chromosome 5q [12]. Its mutation causes insufficient SMN protein production. In humans a second gene – named *SMN2* - can also lead to the production of SMN protein but in insufficient quantities to compensate for the absence in *SMN1* and maintain muscle function, due to alternative splicing of SMN2 mRNA [3,13]. Copy number of *SMN2* gene is correlated with disease severity [14,15]. Children with SMA type 1 usually present with two - sometimes three - copies of *SMN*2, those with three copies being usually less progressive or with later onset (type 1c) than those with two (type 1a or 1b) [14,16].

The emergence of new disease-modifying treatments in the last decade has dramatically changed SMA natural history, in particular in SMA1 children treated at an early stage of the disease [17-20].

Nusinersen (Spinraza®), an antisense oligonucleotide administrated intrathecally and designed to increase the expression of SMN2 protein, was the first drug to be approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2017 and 2016. It is given in repeated doses, starting by four close doses in 2 months and maintenance doses thereafter every four months. The phase 3 efficacy and safety trial of Nusinersen showed a significant motor-milestone response and higher survival in treated patients [18]. Respiratory evolution, however, remains less impressive, with 31% of treated patients on continuous respiratory support by 13 months of age, compared to 48% in the control group [18].

Along with these new therapies, the standards of care for SMA patients, and in particular in type 1 patients, have shifted from palliative to proactive. This is especially true for respiratory care, which now includes respiratory physiotherapy for airway clearance and, for most patients, nocturnal ventilatory support using Non-Invasive Ventilation (NIV) [21]. For most neuromuscular diseases, the decision to start NIV is based on nocturnal gas exchange recordings and the presence of nocturnal hypoventilation [22], however, no study has evaluated the nocturnal gas exchange in SMA type 1 children treated with Nusinersen. There is currently a need for disease-centered guidelines on when to start NIV, as recommendations used in other neuromuscular diseases do not seem to be appropriate for these patients.

In this study, we report the respiratory management and evolution of SMA type 1 children treated with Nusinersen, with the aim of assessing patients' nocturnal gas exchanges prior to NIV initiation and their subsequent clinical evolution in order to determine if capnia is a good criterion to decide when to introduce it.

Patients and Methods

Our retrospective multicenter study included SMA type 1 patients for whom treatment with Nusinersen was initiated between 2016 and 2018. We considered two centers where Nusinersen injections were first started (Paris, Lille) for patients who were afterwards followed in 8 French reference centers for neuromuscular diseases. All patients had a genetically confirmed diagnosis of SMA and onset before the age of 6 months, with no sitting position acquired before Nusinersen treatment.

The study was approved by the institutional Review Board of the French learned society for respiratory medicine – Société de Pneumologie de Langue Française-. Parental/legal representative consent was obtained prior to inclusion in the study.

Data collection

Data are part of the French Reference Center for Rare Lung Diseases (Respirare®) database. The database and data collection from the RespiRare® database have been approved by French national data protection authorities (CNIL n°908,324 and CCTIRS n°08.015bis).

At inclusion, the following data were collected and analyzed: sex, number of *SMN2* copies, age at symptoms onset, at diagnosis, at first Nusinersen injection and at last visit or at death and baseline motor function evaluation score using CHOP INTEND. Data collected during follow-up include: number of Nusinersen injections, CHOP INTEND scores, respiratory evolution (assessed by the number of hospitalizations, including the ones in intensive care unit (ICU) before Nusinersen and during the first two years of treatment), and thoracic circumference/head circumference (TC/HC) ratio. Data collected on respiratory assessment were: blood gas analyses and nocturnal gas exchange recordings (mean and maximum transcutaneous PCO_2 - $PtcCO_2$ - and

percentage of total sleep time spent with a $PtcCO_2$ > 50 mmHg, mean and minimum pulse oxygen saturation - SpO_2 - and percentage of total sleep time spent with a SpO_2 < 90%) before NIV initiation, number of regular sessions of respiratory physiotherapy and airway secretion management techniques, use of NIV use and patient's age at onset of ventilation .

Statistical analysis

Statistical analyses were performed using the GraphPadPrism® software. Categorical variables are expressed as numbers and percentages. Data are presented as median [IQR], minimum and maximum. The difference in the number of hospital admissions during treatment was tested using the Student *t*-test. Value of $p < 0.05$ was considered statistically significant.

Results

Between September 2016 and October 2018, 18 SMA type 1 patients were treated with Nusinersen in these two centers. One patient was excluded from the analysis because treatment was rapidly discontinued. General characteristics of the seventeen patients and their motor functional evaluations at baseline and at the end of the study are included in **Table 1**.

Median [IQR] length of follow-up was 38 [24;44] months, with a maximum of 64 and a minimum of 2 months. Only one patient died after a 2 months follow-up, at age 4.5 months.

NIV initiation

In total, thirteen (76%) patients were started on NIV. Median [IQR] age at NIV initiation was 12 [9;18] months. For two patients NIV was started before Nusinersen (five and six months respectively). Median [IQR] time between the first Nusinersen injection and NIV initiation was 4

[3;9] months, with NIV initiated more than one year after the first injection in only two patients (14 and 15 months after starting the treatment, respectively).

NIV indications

Eleven (65%) patients were started on NIV after requiring repeated hospitalizations and ICU admissions. In one patient NIV was started because of important airway secretions and, in another one, NIV was started with a proactive/preventive approach without any respiratory decompensation or sign of hypoventilation (at the age of six months, three months after Nusinersen was started). Nine (69%) patients had increased respiratory rate before NIV was initiated, with a mean (range) of 40 (25;80). Ten (77%) patients presented with paradoxical breathing and 6 (46%) with signs of increased work of breathing (i.e. subcostal or intercostal recession). No patient was discontinued from the NIV once initiated, four patients were not on ventilatory support at the end of the study.

Respiratory explorations before NIV

Blood gases were performed before NIV initiation in eight patients, and they did not show hypercapnia (maximum $PaCO_2$ of 42 mmHg). Nocturnal gas exchange recordings were performed prior to NIV initiation in eight patients, without showing markers of hypoventilation, nor spending time with $PtcCO_2$ > 50 mmHg during sleep. Respiratory explorations and their results before NIV are included in **Table 2**. All nocturnal gas exchange recording were performed in a hospital setting.

A chest X-ray was performed in 11/13 patients prior to ventilation initiation. It was either normal (n=4) or showed atelectasis (n=5) and/or signs of acute lower respiratory tract infection with images of lobar consolidation and alveolar pattern (n=4).

Hospitalizations secondary to respiratory decompensations

The number of hospitalizations before and during the first and second years of treatment is shown in **Figure 1.** We found a significant decrease (p = 0.04) in the total number of hospital admissions between the first and second year of treatment. The number of hospitalizations decreased for all patients but two in whom it increased, from 2 to 6 (including 3 hospitalizations in ICU) in one patient, and from 0 to 5 in the other one. For these two children, NIV was started following ICU hospitalization at 18 and 26 months of age and after 14 and 15 months of treatment with Nusinersen, respectively. They were the only patients started on NIV more than one year after Nusinersen was initiated. Interestingly, the child who was started on prophylactic NIV (patient 10) did not need any hospitalization for respiratory decompensation during follow-up.

Respiratory management (excluding NIV)

Respiratory physiotherapy and airway secretion management techniques are described in **Table 3**. By the end of follow-up, all patients but four were using a secretion management device (cough assist or intra-pulmonary percussive ventilation). The evolution of respiratory physiotherapy management between baseline and follow-up is shown in **Table 4**.

All patients received customary immunizations according to French recommendations, and 7 (41%) received additional RSV immunization. One patient received nebulized corticosteroids, and four were started on continuous antibiotics. Hypertonic saline nebulizations were not prescribed in our population. The use of a nasofeeding tube was necessary in 9 (53%) patients at a median [IQR] age of 10 [4;15] months. At the end of follow-up, 11 (65%) patients needed a gastric feeding tube at a median [IQR] age of 16 [14;23.5] months old.

Thoracic circumference/Head circumference ratio

TC/HC at inclusion was available in five (29%) patients, with an initial median [IQR] ratio of 1.0 [0.91;1.02]. TC/HC at the end of follow-up was available in nine (53%) patients, with a median [IQR] ratio of 1.03 [1.02;1.10]. For all these patients, TC/HC was stable or increased during follow-up.

Discussion

In this study we report results of nocturnal gas exchange prior to NIV initiation in SMA type 1 patients treated with Nusinersen. We observed that patients do not present with nocturnal hypoventilation before respiratory decompensations. More importantly, this study shows that a delay in ventilatory support initiation might result in pulmonary atelectasis and other respiratory complications that will negatively impact the patients' respiratory evolution.

Seventeen SMA type 1 patients treated with Nusinersen were included in this retrospective multicenter study, focusing on the respiratory management and outcome. Despite an increasing number of studies on respiratory outcomes and evolution since the development of disease-modifying treatments, information on respiratory explorations and nocturnal gas exchange results before NIV initiation are very scarce. Here, we highlight that most children were started on NIV because of repeated respiratory exacerbations requiring hospitalizations, but not because of hypoventilation.

In our study, 13 (76%) children were started on NIV following repeated hospitalizations for respiratory failure (including in ICU) and one due to important airway secretions. This is in line

with Chen et al. who reported that in three out of four newly-diagnosed SMA type 1 patients started on NIV, treatment initiation was decided after repeated hospitalizations. The median age at ventilatory support initiation was 12 months old in our study, similar to that reported by Chen et al. and Lavie et al. (13.8 and 13.5 months, respectively) [23,24]. Unfortunately these studies do not provide information on nocturnal gas exchange prior to NIV [23].

Nocturnal gas exchange recordings were performed before NIV initiation in eight out of 13 (61%) children, none of whom presented with hypoventilation prior to hospitalizations and NIV initiation, as shown by normal $PtcCO_2$ values. This is an important finding as none of the studies describing respiratory management and evolution in SMA type 1 patients treated with Nusinersen have provided results of nocturnal gas exchange recordings. Considering the recent shift in the standard of care for patients, namely the recommendation for a more proactive respiratory management, there is a need for new guidelines on when to consider ventilatory support in SMA type 1 patients [21]. Our results would encourage clinicians not to wait for signs of hypoventilation to initiate NIV, as opposed to recommendations for other neuromuscular diseases [22]. Indeed it is likely, as we show here, that patients will present with pulmonary atelectasis and repeated respiratory infections before showing signs of nocturnal hypoventilation. The two patients for whom the frequency of hospitalizations increased after one year of Nusinersen were those for whom NIV was started later (at 18 and 26 months of age). This underlines an increased risk of respiratory morbidity in case of postponing NIV, and favors a more proactive management.

Nocturnal recordings should be part of the decision-making but only as one of many tools including (but not limited to) clinical examination looking for paradoxical breathing, TC/HC ratio measurement, nutritional status assessment, and the necessity for hospitalizations secondary to respiratory distress. In five patients for whom we had TC/HC measures, NIV was started when

the ratio had fallen under one. The ratio increased after treatment initiation for all patients. This suggests a favorable respiratory evolution under Nusinersen and/or NIV treatment. Ropars et al. have previously suggested using TC/HC ratio as a specific respiratory outcome measure, as they found that SMA type 1 patients with a TC/HC ratio < 0.85 died within 3 months [25]. We suggest using this measure to guide the clinician on when to start NIV and provide an indication on treatment efficiency by means of chest wall growth. Respiratory scoring based on clinical observations could also be of great help to decide on the most appropriate respiratory management method. As an example, the Great Ormond Street Respiratory (GSR) score includes main clinical criteria (acute and recurrent chest infections, increased work of breathing, chronic or acute respiratory failure) and supportive clinical criteria (poor weight gain, chest wall deformity) to guide the decision-making [26].

Our results are in agreement with the findings of other groups who evaluated the respiratory muscles function, showing that Nusinersen improves inspiratory muscle strength and increases accessory muscles performance [27,28]. However, these findings were reported in less severe (type 1c and type 2) patients. Chacko et al. also showed a reduction in lung function decline in older SMA type 2 and 3 patients [29]. Objective respiratory muscle function evaluation is difficult in this population as it involves invasive tests available only in a few centers. Nighttime recordings, such as polysomnography (PSG) and nocturnal gas exchange recordings, on the contrary, are more available and easier to perform in younger children. However, our results suggest that nocturnal gas exchanges might not be good indicators of when to start NIV in SMA type 1 patients. PSG recordings could be of interest as they provide information on hypopnea, the presence of paradoxical breathing and sleep structure.

Apart from two patients who presented with a more complicated respiratory evolution, all the remaining study patients had a significant decrease in the number of hospitalizations between the first and the second year of treatment. These results are in agreement with those reported by other authors [23,29]. The reduction in the hospitalization rate is probably multifactorial, resulting from not only the stabilization of lung function due to Nusinersen treatment, but also from a combination of early NIV initiation, respiratory physiotherapy with secretion management techniques and oral suctioning. This result emphasizes the importance of a proactive approach in this population.

All patients except one had regular sessions of respiratory physiotherapy, including airway secretion management techniques (assisted cough or percussions). This is in line with what has been described in other studies and with standards of care recommendations [24,21]. Conversely, only 1/3 of our patients received RSV immunization treatment. This could be explained by the fact that the standards of care recommending RSV immunization were published after the inclusion period of our study [21].

This study has several limitations, mainly the low number of patients or incomplete or missing information, for example in TC/HC ratio measures, because of its retrospective nature. Along with the heterogeneity in the patients' management in the 8 national reference centers, which illustrates the lack of guidelines for the respiratory care for SMA type 1 patients. The small number of patients also makes it difficult to draw recommendations.

Respiratory management of SMA type 1 patients treated post-symptomatically remains nevertheless burdensome and resource-consuming. Inversely, pre-symptomatically treated patients present with much lower needs in terms of respiratory management [30]. The high cost and

burden for families and for patients should constitute additional reasons to rapidly move towards generalized newborn screening and presymptomatic treatment [31].

Conclusion

The latest recommendations of standards of care for SMA emphasize the fact that NIV should be started in all symptomatic SMA type 1 patients [21]. In line with these recommendations, our results are in favor of not basing the decision to start NIV on nighttime recordings only. Clinical examination, TC/HC ratio and respiratory scoring systems are essential to decide when to start NIV in these patients.

When it comes to respiratory management, the burden of treatment should always be balanced with the risk of respiratory morbidity and socioeconomic impact in case of delayed treatment [32]. Currently, too much is left to the clinicians' judgement and we are in need for additional, clear recommendations specific to SMA type 1, especially as several of these patients might not benefit from the clinical expertise of reference centers. Further studies are needed to evaluate respiratory function evolution in this population, and to apprehend the long-term quality of life of patients, families and caregivers.

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Acknowledgements

We thank all the patients and families. This research did not receive any funding from public, commercial or not-for-profit agencies.

Table 1. General characteristics and CHOP-intend score evolution of the 17 patients

Table 2. Respiratory explorations before non-invasive ventilation initiation

Table 3. Respiratory physiotherapy management at the end of follow-up

Table 4. Age at initiation of respiratory and physiotherapy management - evolution between baseline and the end of study

Figure 1. Hospitalizations during the first and second years of Nusinersen

ICU: Intensive Care Unit, * $p < 0.05$