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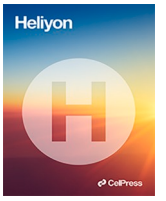

Research article

Effect of nusinersen on pulmonary function in children with spinal muscular atrophy in the plateau region: A pilot study

Jicai Zhu, Xiaofang Chen, Haoke Sang, Minming Ma, Chunhui Tang *

Department of Pediatrics, The First People's Hospital of Yunnan Province, Medical School & Affiliated Hospital, Kunming University of Science and Technology, Kunming, Yunnan, China

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ABSTRACT

Background: The drug nusinersen is applied to improve motor function in patients with spinal muscle atrophy (SMA). However, research on the effects of this treatment on lung function is lacking.
Aim: To investigate the effect of nusinersen on lung function in children with SMA in the Plateau.
Methods: A total of 20 patients with SMA (types 1, 2, or 3) who started nusinersen treatment at the Department of Pediatrics at Yunnan First People's Hospital from March 2022 and February 2024 were studied. A retrospective study was conducted to investigate changes in lung function parameters (including forced vital capacity, forced expiratory volume at 1 s, forced expiratory volume at 1 s/forced vital capacity, and peak expiratory flow) in patients with SMA treated with nusinersen.
Results: 20 patients (13 male, 7 female; aged 5–16 years) were enrolled, including 2, 9, and 9 with SMA types 1, 2, and 3, respectively. The mean value of FVC % and FEV1/FVC % did not decrease further following nusinersen treatment in any patients. The mean value of FEV1% was 4.4 % and 5.0 % higher than before treatment in all patients ($P = 0.03$), and those with type 2 SMA ($P = 0.04$), respectively. The overall mean PEF % did not decrease any further after treatment. However, the average level in the type 2 group increased by 2.9 % ($P = 0.03$).
Conclusion: Patients with SMA, particularly those classified as type 2, showed a trend of improvement in lung function following nusinersen treatment.

1. Introduction

Spinal muscle atrophy (SMA) is an autosomal recessive neuromuscular disorder characterised by the degeneration of alpha motor neurones in the anterior horn of the spinal cord, resulting in progressive and symmetrical proximal muscle weakness and atrophy [1]. Clinically, patients with SMA are typically categorised into five types (0–4, from severe to mild) based on age at onset and the maximum motor function achieved [2–4]. The basic classifications are as follows: Type 0, severely affected foetuses or newborns exhibiting no motor function other than eyeball movements; Type 1, infants unable to sit independently; Type 2, individuals who can sit, but are unable to walk; Type 3, individuals who can walk independently; Type 4, patients with mild motor disorders that manifest during adulthood. The primary causes of death in patients with severe SMA phenotypes are respiratory involvement and complications [5].

* Corresponding author. Department of Pediatrics, The First People's Hospital of Yunnan Province, Kunming, 650021, Yunnan, China.
E-mail address: ynkmtch@163.com (C. Tang).

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Reduced levels of surviving motor neuron (SMN) proteins lead to atrophy of the anterior horn cells of the spinal cord, triggering skeletal muscle atrophy, and impaired motor function [6]. SMA is caused by reduced levels of full-length surviving motor neuron (FL SMN) proteins due to the deletion or mutation of SMN1. Although modified SMN2 produces less FL SMN protein than the SMN1 gene, in situations where the SMN1 gene is deleted, the protein produced by SMN 2 can influence SMA severity, depending on the SMN2 cope number [5]. As such, SMN2 is considered a potential therapeutic target. Increasing SMN2 expression can increase the production of functional SMN proteins to overcome genetic defects in the SMA.

However, symptoms and prognosis have improved following the introduction of treatment drugs. Nusinersen is an 18-polymer 2′-MOE thiophosphate antisense oligonucleotide (ASO) that alters SMN2 splicing to promote stable FL SMN protein expression, and thus can be used in patients with SMA [7]. In clinical trials, intrathecal injection of nusinersen has shown positive efficacy in improving motor function among children with SMA [8,9]. Consequently, it has received approval from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of SMA. In April 2019, nusinersen was launched in China to treat SMA. However, treatment with nusinersen is both expensive and demanding, requiring regular intrasheath administration, while its long-term efficacy and effects on lung function have not been systematically evaluated. Considering that respiratory complications are a major cause of morbidity and mortality [10], it is important to clarify the effects of treatment on lung function.

In plateau regions, the elevation gain leads to a decrease in atmospheric oxygen levels, which in turn increases the demand on respiratory function compared to areas at lower altitudes. This study aimed to assess the effects of nusinersen on lung function in children with SMA in the Plateau region.

2. Methods

2.1. Subjects and data collection

This study retrospectively analysed the data of 20 children with 5q-associated SMA (types 1, 2, and 3) admitted to the Department of Paediatrics at the First People's Hospital of Yunnan Province between March 2022 and February 2024. All cases in this study were from Yunnan plateau region.

Inclusion criteria:

1. Pediatric patients diagnosed with 5q-SMA.
2. Number of successful nusinersen injections $\geq$5 times.
3. Pulmonary ventilatory function was measured before and after nusinersen treatment $\geq$1 times.
4. Statistical data, clinical manifestations, and medical history of the patients were obtained.

Exclusion criteria:

1. Patients with incomplete clinical data.
2. Patients who refused to participate in the study.
3. Presence or history of bacterial meningitis or viral encephalitis, diagnosis with hypoxic–ischemic encephalopathy, and neurological sequelae due to hypoxic birth or participation in another clinical trial.
4. The patient also had a lower respiratory tract infection during pulmonary function test.

Intrathecal administration of nusinersen was performed following the drug-labelled dosing regimen, comprising four loading doses (L) performed on days 0 (L1 = baseline), 14 (L2), 28 (L3), and 63 (L4), followed by a maintenance dose (M) every four months (M1 to M8). Each dose comprised 12 mg of nusinersen.

2.2. Pulmonary function test

The flow-volume curve was obtained using the CareFusion pulmonary function instrument (Model:Master Screen-Paediatric, Germany). Height measurement before lung function measurement: Patients who could walk upright underwent height measurement in the standing position, involving measurement of the vertical distance from the top of their head to the sole of their feet. In patients who could not walk, height measurement was replaced with a measurement of shoulder and arm lengths, i.e., the distance between the tips of the two middle fingers when the arms were extended horizontally to the maximum extent.

For the lung function test, Patients who could walk upright were placed in a standing position, whereas those who could not stand were placed in a sitting position. According to conventional operation specifications, for at least three tests, the repeatability of each test curve was good. The following measurement parameters were assessed: Forced vital capacity (FVC), Forced expiratory volume at 1 s (FEV1), FEV1/FVC, and Peak expiratory flow (PEF). The measurement result is expressed as the percentage of the measured value to the estimated value. FVC, FEV1, PEF were classified as follows: measured value/estimated value $\geq$ 80 %, normal; 60 % to <80 %, mild decline; 40 % to <60 %, moderate decline; and <40 %, severe decline. FEV1/FVC was deemed normal at a measured value/estimated value $\geq$ 92 % [11,12].

2.3. Statistical analyses

Continuous variables are described as means, medians, standard deviations, quartiles, and ranges. Categorical data were described using absolute and relative frequencies. Comparisons before and after nusinersen treatment were performed using paired mean t-tests or Wilcoxon signed-rank tests. Statistical significance was set at $P < 0.05$. Data were analysed using SPSS 23.0.

3. Results

3.1. Patient and treatment characteristics

The present study enrolled 20 children with SMA, with 2, 9, and 9 cases classified as SMA type 1, 2, and 3. The detailed data and treatment information are presented in Table 1. Baseline values of pulmonary function tests and changes in children after nusinersen treatment are presented in Table 2.

20 patients with an average observation time of 12.7 months were included in this study. Owing to the small number of children with SMA type 1, a statistical analysis was not performed.

The mean baseline FVC in the entire cohort was 73.7 %. Following treatment with nusinersen, the mean FVC showed no significant difference in all children with SMA.

The mean baseline FEV1 in this cohort was 75.8 %. After nusinersen treatment, the average FEV1 level in all children with SMA increased by 4.4 % ($P = 0.03$). This change was most significant in children with SMA type 2, who showed a 5.0 % increase % ($P = 0.04$). Conversely, there was no significant change in mean FEV1 levels in the type 3 SMA group.

The baseline FEV1/FVC% ratio in the entire cohort was within a normal range. Following treatment with nusinersen, there was no significant change in mean FEV1/FVC% in any of the children with SMA.

The mean baseline PEF% in the entire cohort was 68.1 %. Following treatment with nusinersen, there was no significant change in the mean PEF% in all children with SMA, or in the type 3 subgroup. However, the mean PEF% in children with SMA type 2 increased by 2.9 % ($P = 0.03$).

4. Discussion

The impact of the SMA on the respiratory system primarily involves the intercostal and expiratory muscles. As this disease progresses, patients often develop respiratory muscle weakness, thoracic malformations, and impaired lung function [13–15]. Nusinersen is currently used to treat patients with SMA. One systematic review by Danish researchers, published in 2020, which performed a literature search for studies investigating nusinersen treatment in the clinic until November 13, 2019, showed that nusinersen significantly improved respiratory function in children with SMA [16]. In 2021, Chacko et al. [5]. studied the effect of 1 year of nusinersen treatment on lung function in 28 Australian children, finding that nusinersen could stabilize the further decline of FVC in patients with SMA. In 2023, Pane et al. [17]. published a multicentre study of changes in respiratory function in 48 patients with type 1 SMA after 4 years of treatment with nusinersen, showing that nusinersen could effectively stabilize respiratory function in patients with type 1 SMA.

FVC is an important index of lung volume, and an indicator of restrictive ventilation dysfunction. FEV1 is defined as the volume of air exhaled with the maximum force and speed within 1s of maximum inhalation to the total lung level. As such, it is both a volume indicator and a flow rate indicator. The FEV1/FVC ratio was used to determine the presence of obstructive lesions. The PEF has the highest flow rate during forced exhalation, and is an important indicator of airway patency and respiratory muscle strength. Patients with neuromuscular diseases may have a lower PEF [18]. However, patients with different SMA subtypes exhibit varying changes in lung function parameters, and may further display different changes in response to therapeutic drugs [19].

Table 1
Patient and treatment characteristics.

	SMA type 1	SMA type 2	SMA type 3	Total
Number of patients, n	2	9	9	20
Male, n (%)	0 (0.0 %)	7 (77.8 %)	6 (66.7 %)	13 (65.0 %)
Female, n (%)	2 (100.0 %)	2 (22.2 %)	3 (33.3 %)	7 (35.0 %)
Age, years				
Mean ± SD	5.9 ± 0.8	10.4 ± 3.2	11.4 ± 2.4	10.4 ± 3.1
Range	5–6	6–16	7–15	5–16
Scoliosis, n (%)	2 (100.0 %)	8 (88.9 %)	7 (77.8 %)	17 (85.0 %)
Treatment duration				
Patients with 9 injections = 22 months (M5), n		3	1	4
Patients with 8 injections = 18 months (M4), n		3	3	6
Patients with 7 injections = 14 months (M3), n		1		1
Patients with 6 injections = 10 months (M2), n	1	1	1	3
Patients with 5 injections = 6 months (M1), n	1	1	4	6
Total observation period, patient-years	1.3	12.5	9.2	23

Abbreviations: SD = standard deviation; SMA = Spinal muscular atrophy.

Table 2
Mean change from baseline following nusinersen therapy (last available versus baseline values).

Lung Function Parameter (%Predicted value)	SMA subtype	N	Observation period Mean (months)	Baseline Mean	Change[a] Mean	t value	P value
FVC	1	2	4.5	57.2	−0.3	/	/
	2	9	15.8	75.3	+5.2	−1.95	0.09
	3	9	11.4	75.7	−4.1	0.62	0.55
	Total	20	12.7	73.7	+0.4	−0.14	0.90
FEV1	1	2	4.5	52.7	−1.3	/	/
	2	9	15.8	76.1	+5.0	−2.48	0.04
	3	9	11.4	80.6	+4.9	−1.38	0.20
	Total	20	12.7	75.8	+4.4	−2.36	0.03
FEV1/FVC	1	2	4.5	94.7	+0.25	/	/
	2	9	15.8	99.8	+4.6	−2.30	0.05
	3	9	11.4	103.3	+1.8	−0.78	0.46
	Total	20	12.7	100.9	+2.9	−2.03	0.06
PEF	1	2	4.5	52.5	+1.5	/	/
	2	9	15.8	66.5	+2.9	−2.71	0.03
	3	9	11.4	73.2	+2.1	−0.60	0.57
	Total	20	12.7	68.1	+2.4	−1.47	0.16

Abbreviations: "–" indicates lower,"+" indicates an increase, "/" indicates that data is missing and statistical analysis was not performed due to insufficient data.

[a] For each patient, the last measured value was compared with the respective baseline value.

This study aimed to investigate the impact of nusinersen treatment on the lung function of 20 children with SMA residing in these high-altitude areas.The results of this study showed that the overall mean level of FEV1 in all children with SMA increased by 4.4 % ($P = 0.03$) after a mean follow-up of 1 year following the initiation of nusinersen treatment. The average level in the type 2 SMA group increased by 5.0 % ($P = 0.03$), whereas the average level in the type 3 SMA group did not change significantly. The overall PEF average did not decline further, whereas the mean level in the type 2 SMA group increased by 2.9 % ($P = 0.03$). The average FVC and FEV1/FVC ratio remained stable. These preliminary real-world results suggest that nusinersen can improve lung function in children with SMA, which is consistent with the results of many prior studies from other regions.

Chacko et al. [5] observed that the initial year of nusinersen treatment was associated with a significant reduction in the decline of lung function, particularly in patients with Type 2 spinal muscular atrophy.In contrast,the results of this study further showed that nusinersen significantly improved FEV1 and PEF in patients with type 2 SMA. A study on the natural progression of pulmonary function in 170 SMA patients by Wijngaarde CA et al. [19] observed that FVC and FEV1 were typically within normal limits for those with type 3 SMA.This result may be related to the smaller impact on lung function and the consequent lower room for improvement in patients with type 3 SMA. Further, the relatively slow improvement in peripheral muscle function in patients with type 3 SMA may also be an explanation [20]. Nusinersen may have arrested the anticipated disease progression, which, according to the natural history, would suggest a continuous decline. It is plausible that substantial improvements in pulmonary function could be detected in type 3 SMA patients who have been administered nusinersen over an extended period. Consequently, there is a need for larger-scale, long-term, multi-center studies to better understand the impact of nusinersen on pulmonary function, particularly in SMA type 3 patients.

4.1. Limitation

The number of cases in this study was small and the observation time was limited; therefore, some children may not have had time to experience significant improvements in lung function, particularly those with type 1 SMA.Additionally, the study lacked a control group.As nusinersen is available and offered to all children in most regions, all future trials will likely involve children receiving a disease-modifying medication. Furthermore, the study did not account for other variables that could have influenced the outcomes, such as the impact of rehabilitation, the occurrence of recurrent respiratory infections and the presence of other concurrent diseases throughout the observation period.

5. Conclusion

These preliminary findings show that nusinersen enhances FEV1 and prevents the further deterioration of FVC, PEF in patients with SMA, especially those with type 2. However, the improvement was not statistically significant in patients with type 3. The limitations of this study necessitate confirmation through a larger-scale clinical trial.

CRediT authorship contribution statement

Jicai Zhu: Writing – original draft, Investigation, Data curation, Conceptualization. **Xiaofang Chen:** Data curation. **Haoke Sang:** Data curation. **Minming Ma:** Data curation. **Chunhui Tang:** Writing – review & editing, Resources, Project administration, Conceptualization.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Ethics statement

This study was approved by the Ethics Committee of the First People's Hospital of Yunnan Province (KHLL2024-KY137), and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants and/or their legal guardians.

Funding information

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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