

Scoliosis in Spinal Muscular Atrophy Type 1 in the Nusinersen Era

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Abstract

Background and Objectives

The introduction of spinal muscular dystrophy (SMA)-modifying therapies, such as antisense oligonucleotide therapy, has changed the natural history of SMA. Most reports on treatment outcomes have focused on motor scores and respiratory function. The objective of this study is to document the development and progression of scoliosis in patients with SMA1 treated with nusinersen.

Methods

A descriptive single-center study was conducted in patients with SMA1 who were treated with nusinersen before 6 months of age. Data were collected on patients who met criteria, including age at the first nusinersen dose, number of nusinersen doses, degree of scoliosis, respiratory parameters, feeding route, and motor scores at baseline and follow-up. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was subanalyzed using axial (AxS) and appendicular motor (ApS) scores to evaluate a possible correlation between scoliosis and axial muscle strength.

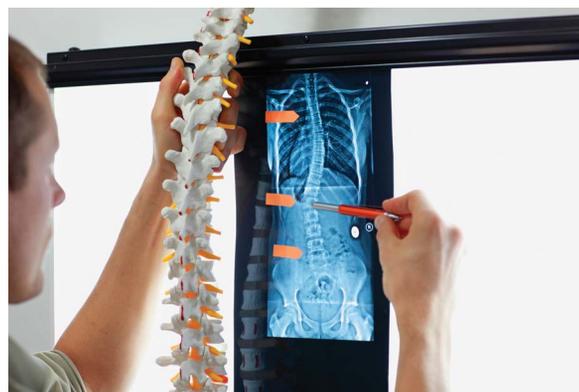
Results

From our cohort, 31 percent (11/35) of patients had a diagnosis of SMA1. Sixty-three percent (7/11) met the inclusion criteria. All patients (7/7) showed initial improvement in their CHOP-INTEND scores in correlation with improvement on the ApS. Despite this, most patients did not show improvement in the AxS. Subsequently, all patients developed scoliosis in the first year of life with Cobb angles that ranged between 18° and 60°. Furthermore, total CHOP-INTEND scores had dropped in 2 patients alongside the development of a Cobb angle of >40°.

Discussion

Despite the significant improvement in functional motor assessment in patients with SMA1, there is a progression of significant scoliosis despite treatment. Subsequently, lack or minimal improvement on the axial CHOP-INTEND scores may predict worsening on the total motor scores.

Scoliosis is a challenging comorbidity associated with many neuromuscular disorders.^{1,2} It is defined as a 3-dimensional deformity of the spine. Scoliosis can be idiopathic or congenital or can develop secondary to vertebral deformity or tumor-related deformity or neuromuscular



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Coinvestigators are listed in Appendix 2.

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disease.¹ Scoliosis prevalence among patients with neuromuscular disorders differs from one condition to the other.¹ Neuromuscular scoliosis is more severe, with a rapid progression in most cases, and is usually associated with increased comorbidities.² The combination of scoliosis and the limitation resulting from the underlying neuromuscular condition can lead to significant impairment in limb movements, cardiopulmonary function, gait, standing, sitting, balance, trunk stability, activities of daily living, pain, concerns about self-image, and social interactions.¹

Furthermore, progressive scoliosis due to rapidly deteriorating axial muscle tone is a critical factor in all patients with spinal muscular atrophy (SMA) types 1 and 2, significantly affecting both respiratory and motor function.³⁻⁷ Historically, SMA had no curative or disease-modifying treatment. The mortality was almost 100% in SMA1 without respiratory support before 2 years old.⁸ Over the past decade, there have been significant advancements in understanding the genetics and pathogenesis of SMA, which have led to the development of novel therapies for this devastating disorder. In 2016, the first disease-modifying drug for SMA was approved by the Food and Drug Administration, and it was the first drug approved for patients with SMA in Canada.⁹ Nusinersen is an antisense oligonucleotide intrathecal therapy that enhances the inclusion of exon 7 into the mRNA transcript from the survival motor neuron 2 (*SMN2*) gene, thus resulting in full-length SMN protein production.¹⁰

The ENDEAR clinical trial of intrathecal nusinersen in SMA1 demonstrated improved motor function in treated patients and promoted prolonged survival of infants with SMA1.¹¹ However, the assessment of treatment outcome focused on motor scores and respiratory function. Little is known about the impact of nusinersen on the progression of scoliosis. Recently, Young described a high correlation between the degree of scoliosis and the Revised Upper Limb Model and Hammersmith Functional Motor Scale Expanded for SMA (HFMSE) in patients who participated on the CHERISSH and SHINE studies.¹² Exploring the effect of novel therapies on scoliosis progression is needed because findings will likely affect the current guidelines of care for this group of patients.

We hypothesized that scoliosis progression would be highly correlated with motor outcomes in the SMA1 population treated with nusinersen. Our aim was to document the development and progression of scoliosis in patients with SMA1 who started treatment with nusinersen before 6 months of age.

Methods

Study Population

We conducted a descriptive study of patients with a confirmed genetic diagnosis of SMA, who were treated with nusinersen in our institution. The inclusion criteria were

(1) a confirmed genetic diagnosis of SMA with 2 homozygous deletions of exon 7 in the *SMN1* gene and 2 copies of *SMN2* and (2) patients who initiated treatment with nusinersen before 6 months of age. All patients received the standard of care according to the 2017 international SMA guidelines.^{13,14} SMA diagnosis was confirmed genetically by the detection of homozygous loss of function of the *SMN1* gene and determined *SMN2* gene copy numbers by multiplex ligation-dependent probe amplification analysis using the SALSA multiplex ligation-dependent probe amplification. Patients who met the inclusion criteria had received 4 loading doses (12 mg) of intrathecal nusinersen at day 1, 14, 30, and 60, followed by a maintenance dose of 12 mg every 4 months.

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional research ethics board approved this study at the Hospital for Sick Children (REB#1000069140).

Clinical Data

Deidentified patient information was collected and managed using REDCap tools hosted at the Hospital for Sick Children.^{1,2} REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

The clinical data gathered included SMA type, *SMN1* and *SMN2* copy number, age at symptom onset, age at the first dose, duration of the disease at the time of treatment initiation, treatment duration to date, the total number of nusinersen doses, and feeding route at the time of the first dose and the last dose.

Scoliosis Evaluation

The presence of scoliosis was evaluated clinically at baseline using spinal X-rays and followed serially every 6 to 9 months. The Cobb angle was used as the measure of scoliosis progression. Ideally, the radiographs were taken in the sitting position if possible or in the supine position if sitting position radiographs were challenging to obtain. Two views were obtained: anterior-posterior and lateral. In the case of S-shape scoliosis, the highest degree angle was the one used for assessment.

Respiratory Function

The patient's respiratory status at the first nusinersen dose and most recent nusinersen dose was obtained from the electronic health record. Respiratory parameters, including whether the patient required invasive or noninvasive ventilation, age when noninvasive or invasive ventilation was

Table 1 Patients' Demographics and Clinical Characteristics (n = 7 Patients)

Patient	1	2	3	4	5	6	7
Sex	M	F	F	M	F	M	M
Age at the end of the study (mo)	14	14	17	51	24	32	53
SMN1 copy no.	0	0	0	0	0	0	0
SMN2 copy no.	2	2	2	2	2	2	2
Age at symptom onset (wk)	4	2	4	4	8	7	4
Age at the 1st dose (wk)	16	8	20	12	12	12	23
Total no. of doses	6	7	5	15	8	10	14
Follow-up period (mo)	10	12	12	48	21	39	57
Route of feeding at the 1st dose	Oral	Oral	Oral	Oral	Oral	Oral	NG tube
Route of feeding at the last dose	GJ-tube	GJ-tube	G-tube	G-tube	Oral	G-tube	G-tube
Ventilation at the 1st dose	None	None	None	None	None	None	Invasive V
Ventilation at the last dose	NIV	NIV	NIV*	NIV	NIV*	NIV*	Invasive V
Age at initiation (m)	5	4	14	5	21	24	7
Use of cough assist at the 1st dose	No	No	Yes	No	No	No	Yes
Use of cough assist at the last dose	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pectus excavatum	No	No	No	No	No	Yes	Yes

Abbreviations: GJ-tube = gastrojejunostomy tube; G-tube = gastrostomy tube; invasive V = invasive ventilation; NG tube = nasogastric tube; NIV = noninvasive ventilation; SMN1 = survival motor neuron 1; SMN2 = survival motor neuron 2.

initiated, the indication for the initiation, and the number of hours per day, were all documented. We documented the use of cough assist therapy, the number of times used per day, and the timing of the first and most recent dose of nusinersen. The presence of pectus excavatum and polysomnography results was documented at baseline, around the starting nusinersen dose and during the most recent visit to the respiratory clinic.

Nutrition

We also documented the use of a gastrostomy tube (G-tube) and swallowing assessment results.

Motor Function Evaluation

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) is a validated measure to evaluate SMA patients' motor function.¹⁵ A trained physiotherapist used the CHOP-INTEND to evaluate each patient and determine a score at baseline and every 4 months. Because the development of scoliosis in neuromuscular disorders is related to the axial muscles, CHOP-INTEND scores were divided into (1) axial muscle scores (AxS) (items 4, 12, 14, 15, and 16) with a maximum score of 20 points and (2) appendicular muscle scores (ApS) (the rest of the items) with a maximum score of 44 points. Clinical status was compared with the most recent follow-up visit in the neuromuscular and respiratory clinics.

Data Analysis

Clinical and demographic characteristics were used to summarize the study population. For the primary analysis data, we used median, range, and proportions using Excel.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Among a total of 35 patients with SMA who were followed at the neuromuscular clinic in our institution, 11 (31%) had SMA type I. All 11 patients (100%) had 2 copies of SMN2. Seven patients met our inclusion criteria. Two patients were excluded because nusinersen was started after 6 months of age (1 at 63 months and 1 at 108 months). Two additional patients were excluded from analysis because care was withdrawn after a prolonged intensive care unit admission, and they died after elective extubation. Both patients were on the loading phase of nusinersen treatment. Seven of 11 (63.6%) were followed during the study period (Table 1).

Four males and 3 females met the study criteria. The onset of symptoms ranged between 2 and 8 weeks (median 4 weeks). All patients presented with axial hypotonia and weakness in the upper and lower extremities. Four of 7 patients presented

Table 2 CHOP-INTEND Scores Subdivided by Axial and Appendicular Scores in Correlation With the Cobb Angle

Patient	Age (mo)	CHOP-INTEND (total)	Axial	Appendicular	Cobb angle	Age at first nusinersen (mo)	Total no. of nusinersen doses
1	5	15	4	11	0	4	6
	10	28	4	24	11		
	14	33	4	28	18		
2	2	24	4	20	0	2	7
	7	40	5	35	17		
	13	57	16	41	20		
3	5	26	6	20	0	5	5
	11	30	4	26	12		
	15	35	4	31	38		
5	4	—	—	—	0	3	8
	8	44	10	34	19		
	13	45	11	34	—		
	16	47	12	35	29		
	21	49	8	41	34		
6	1	—	—	—	0	3	10
	8	37	6	31	—		
	16	49	10	39	34		
	19	50	10	40	—		
	24	44	8	36	61		
7	4	—	—	—	0	6	14
	6	11	3	9	—		
	9	26	6	20	40		
	40	42	6	36	—		
	44	38	4	34	80		

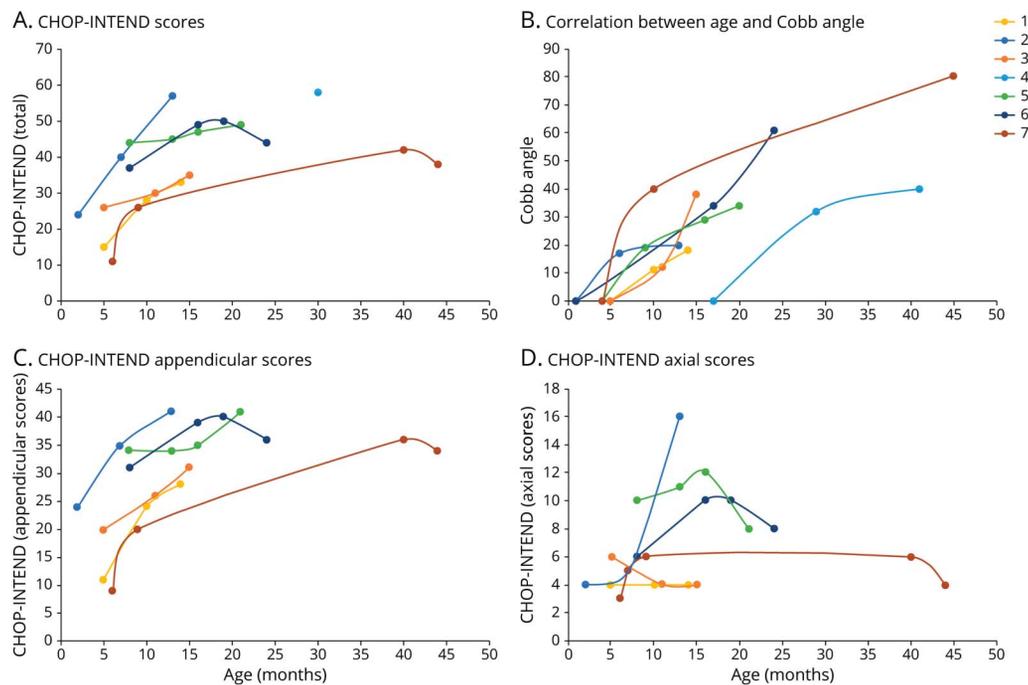
Abbreviation: CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

with bulbar symptoms, including choking with feeds, regurgitation, coughing, and swallowing difficulties. The age for receiving the first nusinersen dose ranged between 8 and 23 weeks (median of 12 weeks). The time from symptom onset to the first nusinersen dose ranged between 4 and 19 weeks, with a median of 8 weeks. Treatment was started for all of them except patient 7 before 12 weeks of disease progression. Each study participant received an average of 9 doses of nusinersen ranging between 5 and 15 doses. The follow-up period ranged between 10 and 57 months, with a median of 21 months. All patients were feeding orally at the first nusinersen dose (Table 1).

Six of the 7 patients were breathing spontaneously when they received the first nusinersen dose, whereas patient 7 needed invasive ventilation at the first dose and remained on invasive

ventilation at the most recent nusinersen dose (Table 1). Patients 1, 2, and 4 were initiated on nocturnal noninvasive ventilation at the last nusinersen dose, 2 for nocturnal hypoventilation (patients 1 and 2) and 1 for chest wall remodeling (patient 4). There were plans at the time of the most recent nusinersen dose for 3 of 7 patients to start noninvasive ventilation, 1 for nocturnal hypoventilation (patient 6) and 2 for chest wall remodeling (patients 3 and 5). Patients 3 and 7 were on cough assist at the first nusinersen dose, and all patients were on cough assist at the time of their most recent nusinersen dose. No patients had pectus excavatum at the first nusinersen dose, and patients 6 and 7 presented it at their most recent nusinersen dose (Table 2). Patient 7 underwent tracheostomy because of the ongoing need for invasive ventilation. Furthermore, this patient had received the first nusinersen dose at 23 weeks of age (19 weeks after symptom onset). The second

Figure 1 (A) Correlation Between the Age in Months (X-Axis) and the Total CHOP-INTEND Score (TChS; Total 64 Points) (Y-Axis), (B) Correlation Between the Age in Months (X-Axis) and Cobb Angle (Y-Axis), (C) Correlation Between the Age in Months (X-Axis) and the Appendicular CHOP-INTEND Score (ApS; Total 44 Points) (Y-Axis), and (D) Correlation Between the Age in Months (X-Axis) and the CHOP-INTEND Axial Scores (AxS; 4, 12, 14, 15, and 16 With a Total of 20 Points) (Y-Axis)



(A) All patients showed improvement in their total scores with subsequent nusinersen doses. Note that patient 6 and patient 7 had drop in their last scores in correlation with an increment on their scoliosis (B). There is a high resemblance on the progression between the TChS and the ApS (A-C), whereas the AxS seems to follow an independent pattern (D). Although the TChS improves, the AxS is mainly stable or tend to drop over time. Patients presenting with a Cobb angle of $>40^\circ$ the TChS drops (patients 6 and 7) dragged by the drop on the ApS. The drop on the AxS seems to predict the drop on the total scores in correlation with the progression of the scoliosis. CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

patient with pectus excavatum (patient 6) showed evidence of obstructive sleep apnea on polysomnography at the age of 8 months, indicating the need for bilevel positive airway pressure initiation; however, compliance with therapy was not optimal until the age of 24 months.

All 7 patients, except 1, were orally feeding at the time of the first nusinersen dose. The 1 patient (patient 7) who was not feeding orally had a nasogastric tube and subsequently acquired a gastrostomy tube. Furthermore, 4 of these patients had bulbar symptoms at the first nusinersen dose. All patients except one were provided enteral feeds at the most recent nusinersen dose. Five of these patients were exclusively on enteral feeds and were deemed unsafe to orally feed because of the risk of aspiration. One patient (patient 6) received both enteral and oral feeds. Only 1 patient (patient 5) remained on oral feeds and did not show any bulbar symptoms.

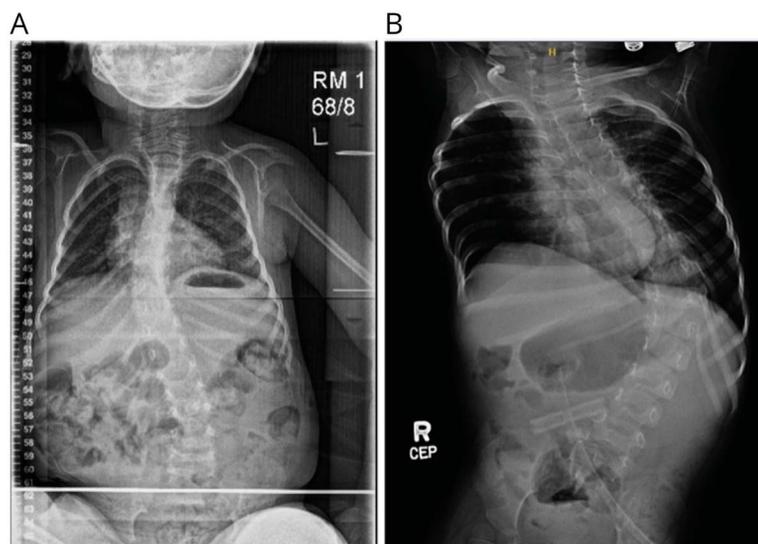
Four of 7 participants had CHOP-INTEND testing completed at baseline and subsequently for follow-ups. Two patients (patients 6 and 7) had Hammersmith Infant Neurologic Examination (HINE) initially followed by CHOP-INTEND assessments. Patient 4 had HINE assessment initially followed by the HFMSE for subsequent follow-ups because independent

sitting was achieved and was considered too advanced for the CHOP-INTEND assessment. This last patient was excluded from the CHOP-INTEND analysis (Table 2).

All patients showed initial improvement in the motor scores between baseline and their assessment performed 5–10 months after the first loading dose (median age 8 months). The initial increment in CHOP-INTEND scores ranged between 1 and 16 points (average increase of 6.1 points). The 1 patient with HFMSE scores showed initial improvement by 12 points. Maximum increment on the total CHOP-INTEND scores varied between 4 to 33 points. On follow-ups, 2 of 6 patients (patients 6 and 7) showed a drop in their CHOP-INTEND scores by 4 points and 1 point at 24 and 42 months of age, respectively (16 months and 34 months after nusinersen initiation, respectively) (Figure 1A). Patient 5, who had HFMSE assessments, had dropped their score by 5 points at 45-month evaluation.

The subanalysis of the AxS and ApS in the 6 patients who had completed CHOP-INTEND assessments showed that 3 of 6 presented improvement in the AxS (patients 2, 5, and 6) initially, 2 of 6 did not change (patients 1 and 7), and 1 of 6 (patient 3) showed a drop by 2 points in follow-up

Figure 2 Scoliosis in 2 Patients With Spinal Muscular Atrophy



(A) S-shape scoliosis on patient 4. (B) C-shape scoliosis on patient 6.

(Figure 1D). Only patient 2 had an increment of more than 5 points on the AxS. All patients had improvements in the CHOP-INTEND ApS initially with a median of 9.5 points (range 1–28). However, 2 patients (patients 6 and 7) presented a decline of 4 and 1 point at 24 and 42 months, respectively, in correlation with the total scores (Figure 1C).

None of the patients had scoliosis at baseline when clinically evaluated in the neuromuscular clinic, but all patients developed scoliosis on subsequent follow-up (Figure 1B). Three of 7 (43%) had S-shape scoliosis, and 4 of 7 (57%) had C-shape scoliosis (3/4 to the left side and 1/4 to the right side) (Figure 2). All the patients (7/7) had a thoracolumbar scoliosis. We observed a rapid worsening of the spine curvature for most patients starting at 5 months of age with an average progression of 2.3° per month (range 1.1–3.8) (Figure 1B). All patients had scoliosis defined as Cobb angle >15° by 12 months of age. Patient 2 was the only one with an ApS of >15 points (16), with a total score of 57. At the same time, this child showed a reduction in the progression of scoliosis from down to 0.4° from 7 to 13 months of age. On the other hand, patients 6 and 7 who had >40° of scoliosis started to show a drop in their total CHOP-INTEND scores and their ApS. At the same time, patient 4 who had HFMSE showed a drop in the total score when a Cobb angle of >40° was reached.

Discussion

Here, we are reporting on the progression of scoliosis in a cohort of children with SMA1 treated with nusinersen. All the children in our study developed scoliosis in the first year of life. We observed that the total CHOP score was highly influenced by the appendicular scores, and the lack or mild improvement of the axial scores correlated with the onset

and/or progression of scoliosis. Furthermore, motor scores dropped in all patients who developed a Cobb angle of >40°, highlighting the clinical relevance of scoliosis even in children with SMA1 treated with nusinersen.

Scoliosis emerges in nearly all nonambulatory neuromuscular patients, leading to chest wall deformities, severely reduced vital capacities, tilted hips, and loss of ambulation.¹⁶ One study showed that scoliosis progresses by 8° per year in patients with SMA2, 3° per year in nonambulatory SMA3 patients, and 0.6° per year in ambulatory type-III patients.^{17,18} On the other hand, another study evaluated the progression of scoliosis in ambulatory patients and showed that scoliosis progressed by 5°–15° per year in these patients.¹⁹ In addition, reference 20 reports on a cohort of patients with SMA2 who developed scoliosis with the main Cobb curvature for patients between 0 and 4 years was 26° with a median of 25°. It was recently shown that scoliosis progressed by 7.2° per year, and this progression markedly increased in the 18 months before scoliosis surgery by 10.1° per year.^{18,20} The average age at onset of scoliosis was 2 years or less in SMA1, between 1 and 7 years in type-II, and 4–14 years in type-III patients.²¹

All our patients developed scoliosis, which is similar to what has been reported in the medical literature. We observed a rapid progression in the first year of life, with a curvature increment of 2.3° per month starting around 5 months of age for most patients. It is unclear what the rate of scoliosis progression was in the natural history pretreatment era of patients with SMA1. However, comparing what has been reported in the literature for patients with SMA2, the progression of our cohort of patients with SMA1 appears significantly higher.^{18–20,22} We did not observe differences in

severity in terms of the shape of the scoliosis between our patients.

As anticipated, all our patients showed initial improvements in CHOP-INTEND total scores after receiving treatment with nusinersen. This parallels the effect of nusinersen reported in the ENDEAR study.¹¹ We know from natural history studies that patients with SMA1 initially present with CHOP-INTEND scores of 20 and rarely achieve any score above 40.⁸

Within our cohort, 3 patients had a decline of the motor scores with subsequent doses despite a dramatic initial improvement. These 3 patients had Cobb angles of 40° or more when the decline in their motor scores was observed (Figure 1B). Patient 7 was already with invasive ventilation and with more than 12 weeks of progression at the moment of starting the intrathecal infusion. This last child presented the fastest worsening on the scoliosis. We know that patients with severe respiratory component and more than 12 weeks of progression will present poor outcome despite the initiation of treatment.

As a secondary objective, we wanted to analyze the contribution of ApS vs AxS in the total CHOP-INTEND scores. Analysis of the AxS (items 4, 12, 14, 15, and 16) showed either stabilization or decline in the first 6 months after initiation of treatment for the 6 of 7 patients, although there was an overall improvement in the total CHOP-INTEND score. On the other hand, the CHOP-INTEND ApS initially showed dramatic improvement in parallel with the total CHOP-INTEND initial scores (Figure 1, A–C).

Likewise, the 2 patients who showed decline in the total score (16 and 34 months after therapy initiation, respectively) presented parallel worsening in the ApS. Moreover, the only patient who presented an increment of more than 5 points on the AxS presented a reduction on the progression of the scoliosis. These observations have shed light on 4 main points. First, in proportion, the contribution of the CHOP-INTEND ApS outweighed the one originated from the AxS, creating an unintended bias. Second, scoliosis progression is likely a natural result of the deterioration of axial muscle scores that have not improved with nusinersen subsequent doses. Third, the lack of improvement of the AxS might be an important indicator for the onset of severe progression of scoliosis. Finally, a worsening of the Cobb angle ($\geq 40^\circ$) precedes the worsening of the total scores and ApS subscore.

Deterioration in respiratory function is a significant cause of morbidity and mortality in SMA, especially in children with SMA1. In addition to the respiratory muscle weakness resulting from motor neuron degeneration, scoliosis causes mechanical restriction of the chest wall and results in restrictive lung disease. There is a well-documented correlation between the decline of respiratory function and progression of scoliosis (Cobb angle); a decline in forced

vital capacity (FVC) % predicted by 7.7% per year has been observed.⁵ Furthermore, another study documented a decline in FVC % predicted by 4.7% and similar 3.3% decrease in the peak flow for each 10° increase in the Cobb angle.⁷ Although our study is limited by the lack of a pulmonary function test because of the age of our participants, the development of scoliosis compounded with neuromuscular weakness may have contributed to the need for respiratory support in some of our patients, particularly those with more rapidly progressing scoliosis.

Six of 7 of our patients did not improve their swallowing function independent of age at the initiation of treatment or improvement of the motor scores. This feature might be an independent factor of assessment that could be related to the lack of homogenous distribution of nusinersen through the spine.²³

Despite the small sample of our cohort ($n = 7$), our population is a homogenous group and representative of the general SMA1 population receiving nusinersen. We have observed the rapid progression of scoliosis in patients with SMA1 who received nusinersen. All our patients with SMA1 who received nusinersen at <6 months of age developed scoliosis in the first year of life and had a Cobb angle of $>15^\circ$ by the end of the first year of life despite improvement in motor function. This may have a considerable impact on these patients' respiratory parameters and CHOP-INTEND scores. Moreover, the initial improvement in the CHOP-INTEND scores seems to be falsely reassuring and reflects mainly the ApS improvement.

Scoliosis is a major factor that directly affects the prognosis of patients with SMA and warrants regular monitoring. Our study highlights the importance of understanding the sub-components of the motor functional assessment. Based on the ENDEAR clinical trial, nusinersen improves the initial motor function scores; however, it does not seem to stop or slow down the progression of scoliosis in symptomatic individuals. In treated patients with SMA1, the improvement in the total CHOP-INTEND score seems to be primarily led by the rise in the ApS subscore, whereas AxS scores appear to be influenced by the presence of scoliosis. Although these results will need validation, it sheds light on the possible effect of this novel therapy on one of the most critical SMA comorbidities.

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TAKE-HOME POINTS

- Scoliosis has huge impact on respiratory function and mobilization in patients with SMA.
- Nusinersen improves the motor function in patients with SMA; however, nusinersen does not seem to slow the progression of scoliosis in patients with SMA.
- Improvement in CHOP-INTEND scores can be falsely reassuring for physicians and caregivers because it is primarily driven by appendicular scores but not axial scores.

Disclosure

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Appendix 1 (continued)

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Lauren Weinstock, BSc, MScPT	Department of Rehabilitation Services, Hospital for Sick Children, University of Toronto, Toronto, Canada	Major role in the acquisition of data
Ana Stosic, BSc, MSc	Genetics and Genome Biology Program, PGCL, University of Toronto, Toronto, Canada	Drafting/revision of the manuscript for content, including medical writing for content
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Appendix 2 Coinvestigators

Name	Location	Role	Contribution
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Appendix 2 (continued)

Name	Location	Role	Contribution
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