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Nusinersen for Spinal Muscular Atrophy Type I with Chronic Respiratory Failure: A Retrospective Study in South Korea

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Purpose: To analyze the efficacy and safety of nusinersen in patients with spinal muscular atrophy (SMA) type I with chronic respiratory failure.
Materials and Methods: We retrospectively reviewed seven patients diagnosed with SMA type I and chronic respiratory failure who were on permanent ventilation and treated with nusinersen at Gangnam Severance Hospital between January 2018 and July 2023. Patient demographics and clinical characteristics were recorded, and treatment progress was evaluated according to Hammersmith Infant Neurological Examination (HINE-2) and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores.
Results: Patients initially developed hypotonia at a mean age of 3.7 months. Mean age at start of nusinersen was 7.3 years; the mean duration of follow-up after starting nusinersen was 46.2 months. At 6-, 18-, 38-, 58-, and 74-month follow-up, the mean changes in CHOP-INTEND scores were 1.0, 2.9, 1.8, 1.5, and 1.5, respectively, and the proportions of patients who showed disease amelioration were 28.6%, 71.4%, 75.0%, 100%, and 100%, respectively.
Conclusion: Nusinersen is safe and effective in patients with SMA type I, even those with chronic respiratory failure and those on permanent ventilation. No significant adverse effects of nusinersen were observed.

Key Words: Spinal muscular atrophy, respiratory failure, motor function, nusinersen, South Korea

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive disease involving muscular atrophy and weakness of the limbs and the bulbar and respiratory muscles. SMA is primarily caused by deletions or mutations in the survival motor neuron-1 (*SMN1*) gene (OMIM:600354). The coding sequence of *SMN2* (OMIM:601627) is nearly identical to that of *SMN1*, except for 11 nucleotides, which synthesize a rapidly degrading SMN protein.[1] In SMA, *SMN2* pre-mRNA editing involves an exon 7-skipping splicing defect. As a consequence, *SMN2* produces transcripts that do not include exon 7, which translate into a truncated form of SMN protein. SMN protein is normally located in the cytoplasm and nucleus of all cells[2] and plays a role in mRNA synthesis in motor neurons and neuronal apoptosis inhibition. Low levels of SMN protein in patients with SMA cause motor neuron degeneration in the anterior horn cells of the spinal cord, which results in progressive muscle atrophy, weakness, and paralysis.[3]

Nusinersen consists of a modified antisense oligonucleotide that pairs with a specific sequence within *SMN2* pre-mRNA, thereby inducing the inclusion of exon 7 in the mature mRNA transcript. This leads to an increase in functional SMN protein production. Nusinersen is administered by intrathecal injection, as it is unable to cross the blood–brain barrier when delivered systemically.[4,5]

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Nusinersen was initially shown to be effective in infants.[6] Subsequently, children with pre-symptomatic and later-onset SMA and adults aged 16–65 years were treated with nusinersen and were found to exhibit considerable improvement in motor function.[7-11] Those with less severe clinical manifestations at baseline tended to have greater improvements in motor function.[10]

Nusinersen administration in patients with poor baseline functional status is controversial. Ergenekon, et al.[12] showed that nusinersen administration in patients with complications, such as those on ventilatory support or gastrostomy tube feeding, led to improved motor function scores, calculated using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores. Moshe-Lilie, et al.[11] demonstrated that although half of such patients treated with nusinersen showed subtle improvement in motor function, there were no statistically significant effects in terms of motor function or complication rates. This study aimed to provide further insights into the efficacy and safety of nusinersen in SMA type I patients with chronic respiratory failure.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed 40 patients diagnosed with SMA and treated with nusinersen at Gangnam Severance Hospital between January 2018 and July 2023. Among them, 7 patients who met the inclusion criteria were genetically and clinically diagnosed with SMA type I and chronic respiratory failure. Exclusion criteria were diagnoses of additional congenital structural anomalies or neurological diseases and a history of medication other than nusinersen to treat SMA. The demographic and clinical characteristics of the patients were recorded.

The requirement for informed consent was waived by our Institutional Review Board (IRB). The study was conducted in accordance with the ethical standards of the IRB of our hospital (3-2022-0111) and the Helsinki Declaration of 1964, as revised in 2000.

Diagnosis of SMA type I

SMA type I was diagnosed according to age of onset and maximum motor milestones achieved and copy numbers of *SMN2*.[13] Molecular genetic testing, in particular targeted mutation analysis, consisted of either single gene or multi-gene panel testing. Multiplex ligation-dependent probe amplification (MLPA) was used to quantify variations in *SMN1* and *SMN2* copy numbers. MLPA was performed using SALSA MLPA Probemix P021 SMA from MRC-Holland (NL): this kit contains specific probes for exons 7 and 8 of *SMN1* and *SMN2*, neuronal apoptosis inhibitory protein, and additional gene sequences within the 5q chromosome region. Homozygous deletions of exons 7 and 8 of *SMN1* on the 5q13.2 locus were identified in the included patients.

Diagnosis of chronic respiratory failure

Chronic respiratory failure was defined as the need for mechanical ventilation lasting for more than 28 days.[14] Permanent ventilation was defined as ventilatory support for more than 16 h per day for more than 21 continuous days, invasive or non-invasive.[6,15] Pulmonary function tests and arterial blood gas monitoring were performed regularly by a pulmonary rehabilitation specialist every 3–6 months. Oxygen dependence, as well as the need for different ventilator settings or tracheostomy, was also evaluated.

Administration of nusinersen

Nusinersen was administered via either direct or computed tomography (CT)-guided intrathecal injection. Patients received 12 mg (5 mL) of nusinersen in each dose, regardless of age or body weight. Four loading doses of nusinersen were administered, the first three doses being 14 days apart and the fourth dose 30 days after the third one. After the loading doses were completed, maintenance doses of nusinersen were administered every 4 months. During treatment with nusinersen, no other treatment or therapies were given concurrently.

Lumbar puncture was performed by a pediatrician or pediatric neurologist while patients were monitored by another physician for procedural complications or need of sedation. Nusinersen was administered via CT-guided intrathecal injection whenever lumbar puncture was difficult to perform, mostly in patients with severe scoliosis or significant post-procedural side effects. Interventional radiologists with at least 5 years of experience in CT-guided interventional procedures administered the injection. The method of approach was selected by interventional radiologists according to the patient's spinal anatomy.

If the patient was more likely to demonstrate poor co-operation during the CT-guided procedure, sedation was performed using midazolam 0.1 mg/kg or ketamine 1 mg/kg, with a maximum of two doses for each sedative. Before, during, and at least 4 hours after the procedure, full monitoring was performed, including EKG, pulse oximetry, and non-invasive BP monitoring.

Assessment of motor function

Motor function was assessed according to Hammersmith Infant Neurological Examination (HINE-2) and CHOP-INTEND scores. Physical therapists trained in evaluating both pediatric and adult patients evaluated motor function in patients with SMA. The primary treatment outcome was an improvement in motor function, measured as the difference between HINE-2 and CHOP-INTEND scores. Baseline motor function assessments were performed before nusinersen administration. Thereafter, motor function was assessed at 2 months after completion of the loading doses and then repeated every 4 months before each nusinersen maintenance dose. Adverse events

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were monitored using electronic medical records and questionnaires.

Statistical analyses

IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Wilcoxon signed-rank test was performed to verify the significance of changes in HINE-2 and CHOP-INTEND scores. Descriptive statistics are reported as medians, standard deviations, and interquartile ranges. Proportions of patients are reported as percentages.

RESULTS

Patient characteristics

Patients initially developed hypotonia at a mean age of 3.7 months. Genetic testing showed that 71% (5/7) of the patients had three copies, and 29% (2/7) had two copies of *SMN2* exons 7 and 8. All patients were on permanent ventilation. Six patients (6/7, 86%) underwent invasive mechanical ventilation via tracheostomy; the median age at first tracheostomy was 9.3 years. One patient (1/7, 14%) was on non-invasive nasal intermittent positive pressure ventilation with the help of a nasal prong for at least 16 h per day. All patients were diagnosed with scoliosis, but none had undergone orthopedic surgery due to high risk of general anesthesia or refusal of surgery by legal guardians (Table 1).

Table 1. General Characteristics of the Patients (n=7)

Characteristics	Values
Sex (male: female)	6:1 (86%:14%)
Onset age of 1st symptom (month)	3.7±1.4 (3–4.4)
1st symptom	
Hypotonia	7 (100)
Delayed development	0 (0)
Genetic testing	
SMN2 exon 7 copy number	2 (29)
2	
3	5 (71)
SMN2 exon 8 copy number	
2	2 (29)
3	5 (71)
Pulmonary function	
Invasive ventilation	6 (86)
Duration of ventilation use (h)	24
Age at 1st tracheostomy (yr)	9.3±6.4 (0–16)
Gastrointestinal function	
Gastrostomy	6 (86)
Orogastric tube	1 (14)
Age at 1st gastrostomy (month)	17.0±7.4 (13.5–20.5)
Musculoskeletal abnormalities	
Scoliosis	6 (86)
Cobb's angle	26.4±13.2 (16.9–30.8)
Administration of nusinersen	
Age at start of nusinersen (yr)	7.3±4.0 (6.4–9.4)
Duration of follow-up (month)	46.2±15.4 (34.2–58.0)
Total number of nusinersen doses	15.0±3.9 (12–18)
Direct intrathecal injection	5 (71)
CT-guided intrathecal injection	2 (29)
Transforaminal	1 (50)
Interlaminar	1 (50)
Change from direct to CT-guided injection	2 (100)

Data are presented as mean±standard deviation (range) or n (%).

The mean age at the initial nusinersen dose was 7.3 years. Five patients received nusinersen via direct intrathecal injection (5/7, 71%). Two patients underwent CT-guided intrathecal injections using either a transforaminal or interlaminar approach. These patients were switched from direct to CT-guided injection because of difficult access for direct lumbar puncture, which can result in severe post-procedural headache and back pain (Table 1).

Treatment progress

The mean duration of follow-up after start of nusinersen was 46.2 months. At baseline, the mean HINE-2 score was 0; at an 18-month follow-up, the mean interval change from baseline HINE-2 score was 0.1 and showed gradual increases to 0.2 at 38-month and 0.3 at 58- and 74-month follow-up. The baseline mean score for CHOP-INTEND score was 2.3. At 18-month follow-up, the mean interval difference from baseline increased to 2.9 (p=0.042) and decreased to 1.8 at 38 months. At 58- and 74-month follow-up, the mean interval difference in CHOP-INTEND score decreased to 1.5. Overall, both HINE-2 and CHOP-INTEND scores gradually increased over time. Four of seven patients showed improvement in CHOP-INTEND scores. Meanwhile, one patient maintained the same CHOP-INTEND score without deterioration, and two patients showed aggravation. Towards the end of the study, one patient discontinued treatment due to the high cost of treatment, and two patients died due to infectious causes, such as pneumonia (Tables 2 and 3).

Respiratory, gastrointestinal, and musculoskeletal status for SMA type I patients did not change significantly before or after nusinersen treatment (Table 4). All patients remained on ventilation, with the duration of use remaining the same. Feeding support remained to tube feeding and gastrostomy in most patients.

Although scoliosis in these patients did appear to worsen in the majority of patients (5/7, 71%); interestingly, the mean increase in Cobb's angle was only 7.9 degrees. Patient 1 received nusinersen treatment at 0.5 years old; this infant did not have scoliosis at the beginning of treatment and only developed mild scoliosis with a Cobb's angle of 10.5 degrees. Patients 6 and 7, who started treatment at early adolescence, showed the most severe scoliosis, but did not show much aggravation, compared to the natural history of SMA type I. Two patients

Table 2. Treatment Progress According to HINE-2, and CHOP-INTEND Scores

	At Baseline (n=7)	At 6 mo (n=7)	At 18 mo (n=7)	At 38 mo (n=5)	At 58 mo (n=4)	At 74 mo (n=4)
HINE						
Mean score	0	0	0.1±0.4 (0–1)	0.2±0.45 (0–1)	0.3±0.5 (0–1)	0.3±0.5 (0–1)
Interval change from baseline		0	0.1±0.38 (0–1)	0.2±0.45 (0–1)	0.3±0.5 (0–1)	0.3±0.5 (0–1)
Improvement (%)		0/7 (0.0)	1/7 (14.3)	1/5 (20.0)	1/4 (25.0)	1/4 (25.0)
CHOP-INTEND						
Mean score	2.3±1.5 (0-4)	3.3±2.5 (0–8)	5.1±4.14 (1–13)	3.6±2.70 (1–8)	4.0±2.9 (1–8)	4.0±2.9 (1–8)
Interval change from baseline		1.0±1.73 (0–4)	2.9±4.26 (0–12)*	1.8±1.71 (0–4)	1.5±2.1 (1–4)	1.5±2.1 (1–4)
Improvement (%)		2/7 (28.6)	5/7 (71.4)	3/4 (75.0)	4/4 (100)	4/4 (100)

HINE-2, Hammersmith Infant Neurological Examination; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
*p<0.05 (p=0.042), according to Wilcoxon signed-rank test.

Table 3. Changes in Motor Function for Each Patient

Patient	Age at start of nusinersen (yr)	Duration of follow-up (yr)	Number of nusinersen doses	SMN2 copy number (exon7/8)		Baseline	At 6 mo	At 18 mo	At 38 mo	At 58 mo	At 74 mo
1	0.5	29.90	11	2/2	HINE-2	0/26	0/26	0/26			
					CHOP-INTEND	1/64	4/64	13/64			
2	6.4	58.01	18	3/3	HINE-2	0/26	0/26	1/26	0/26	0/26	0/26
					CHOP-INTEND	4/64	4/64	5/64	3/64	0/64	0/64
3	6.4	57.60	18	2/2	HINE-2	0/26	0/26	0/26	0/26	0/26	0/26
					CHOP-INTEND	0/64	0/64	1/64	1/64	1/64	1/64
4	6.7	58.00	18	3/3	HINE-2	0/26	0/26	0/26	1/26	1/26	1/26
					CHOP-INTEND	2/64	2/64	4/64	4/64	4/64	4/64
5	6.8	38.50	13	3/3	HINE-2	0/26	0/26	0/26	0/26		
					CHOP-INTEND	2/64	2/64	2/64	2/64		
6	11.6	23.10	9	3/3	HINE-2	0/26	0/26	0/26			
					CHOP-INTEND	4/64	3/64	3/64			
7	12.8	58.30	18	3/3	HINE-2	0/26	0/26	0/26	0/26	0/26	0/26
					CHOP-INTEND	4/64	8/64	8/64	8/64	8/64	8/64

HINE-2, Hammersmith Infant Neurological Examination; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

with moderate and severe scoliosis at last follow-up, proceeded with CT-guided intrathecal injections. The progression of scoliosis during the follow-up period deterred the patient from receiving direct intrathecal injections. Five of the seven patients who continued to be administered with nusinersen via a direct intrathecal method exhibited a broad spectrum of scoliosis severity: one patient showed mild scoliosis, two showed moderated scoliosis, and the remaining one showed severe scoliosis (Table 4).

Adverse events

No serious adverse events related to nusinersen administration were observed. Adverse events included post-procedural headache and back pain in one patient, which led to a modification of the drug administration procedure from direct to CT-guided intrathecal injection. Symptoms of headache and back pain did not deter patients from continuing the treatment. Patients were treated with pain medication, such as acetaminophen and ibuprofen; at times, intravenous mannitol was infused for treatment of possible increased intracranial pressure. After changing the method of administration, nusinersen was injected to a more precise location with easier access via a less timing consuming process. However, the high cost of treatment posed to be a barrier to continuing treatment with nusinersen. Patients 1 and 5 died due to pneumonia at age 3 and 10 years old, respectively, which was not associated with the administration of nusinersen.

DISCUSSION

In this study, we investigated the efficacy and safety of nusinersen for treating patients with SMA type I with chronic respiratory failure. This retrospective study involved 7 patients who were permanently on ventilation and treated with nusinersen and were followed for approximately 4 years. Our results revealed a modest improvement in motor function over time with no significant adverse effects.

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Table 4. Changes in Respiratory, Gastrointestinal, and Musculoskeletal Status for Each Patient

Patient	Age at start of nusinersen (yr)	Functional status	At baseline	At last follow-up
1	0.5	Duration of ventilation use	24 (non-invasive)	24 (non-invasive)
		Feeding support	Orogastric	Orogastric
		Scoliosis status (Cobb's angle)	<10.0	11.0
2	6.4	Duration of ventilation use	24	24
		Feeding support	Gastrostomy	Gastrostomy
		Scoliosis status (Cobb's angle)	13.0	10.0
3	6.4	Duration of ventilation use	24	24
		Feeding support	Gastrostomy	Gastrostomy
		Scoliosis status (Cobb's angle)	20.0	45.0
4*	6.7	Duration of ventilation use	24	24
		Feeding support	Gastrostomy	Gastrostomy
		Scoliosis status (Cobb's angle)	16.0	25.0
5	6.8	Duration of ventilation use	24	24
		Feeding support	Gastrostomy	Gastrostomy
		Scoliosis status (Cobb's angle)	35.0	33.0
6	11.6	Duration of ventilation use	24	24
		Feeding support	Gastrostomy	Gastrostomy
		Scoliosis status (Cobb's angle)	27.0	29.0
7*	12.8	Duration of ventilation use	24	24
		Feeding support	Gastrostomy	Gastrostomy
		Scoliosis status (Cobb's angle)	48.0	50.0

*Change from direct to CT-guided intrathecal injection.

Therapeutic agents for SMA type I are continuously being developed and diversified. Currently, three therapeutic drugs for SMA have been approved by the Korean Ministry of Food and Drug Safety. These are nusinersen (Spinraza), described in this study; risdiplam (Evrysdi), an orally administered RNA-targeting small molecule that acts as an *SMN2* pre-mRNA splicing modifier; and onasemnogene abeparvovec (Zolgensma), an intravenous adeno-associated virus serotype 9 vector that replaces *SMN1*. However, these drugs pose a significant economic burden for overt use in various patient groups.[16,17] Therefore, risdiplam and onasemnogene abeparvovec have only been approved for newly diagnosed SMA patients in Korea. Furthermore, nusinersen has only been approved for SMA patients who are not on permanent ventilation. However, this study showed that nusinersen is therapeutically effective, and it can be safely administered without major complications in patients with SMA type I and chronic respiratory failure.

Previous studies suggested a more remarkable improvement of HINE-2 scores among SMA type I patients, especially in those with better baseline motor function, but a therapeutic window within 6 months after birth is the most critical factor.[18,19] Interestingly, our study data reveals no deterioration in motor function in most patients post-nusinersen administration, even with the mean time to treatment initiation being 48 months.

Our patients were all diagnosed with chronic respiratory failure at the start of treatment, with the mean time to treatment initiation being 48 months. Finkel, et al.[6] showed that patients with a treatment duration of more than 13 weeks are more likely to require permanent ventilation. However, some studies showed that nusinersen may induce improvements in respiratory function in patients less than 6 months of age and in motor function in all age groups.[12,20] Unfortunately, our patients did not show any significant improvement in respiratory function after nusinersen treatment. More data needs to be accumulated in larger studies of SMA patients with chronic respiratory failure.

In this study, improvement in motor function was reflected more definitively in CHOP-INTEND scores than in HINE-2 scores. However, because patients with SMA type I have serious limitations in motor function, a precise evaluation of any treatment effect is usually difficult. The effect of the treatment could be more accurately evaluated if more sensitive motor-outcome measures were available for patients with SMA type I. Various scales could be utilized according to severity, ambulatory status, and age, some of which can be generalized to other diseases. Generalized scales include Gross Motor Function Measure, Motor Function Measure, and Egen Klassification. Disease-specific measurements include the Hammersmith Functional Motor Scale (HFMS), the HFMS Extended, and the Revised Upper Limb Module (RULM).[21] While clinically meaningful improvements have been reported by patient family members, these are not accompanied by objective measurements.[22] This suggests that a more sensitive scale is need-

ed to assess the motor function of patients with SMA. Subtle improvements in clinical progress of SMA patients, such as louder voice and better fine motor function of the hands, should be recognized and assessed to determine how much a treatment may impact patient quality of life. Including more qualitative data from patients and families would provide a richer understanding of the therapeutic impact of nusinersen.

In this study, no serious adverse events related to nusinersen administration were observed. Finkel, et al.[6] reported that nusinersen treatment elicited relatively lower rates of both severe and serious adverse events, compared to a sham procedure. The potential adverse effects of nusinersen treatment include headache, nausea, and back pain, which may be more associated with the lumbar puncture than with the drug itself.[10]

To the best of our knowledge, this is the first observational study of patients with SMA type I in South Korea only. Kim, et al.[23] reported 7 Korean patients who were diagnosed with SMA type I (n=4) and type II (n=3) and demonstrated that nusinersen was effective even in patients with a median disease duration before treatment of 37 months. Chan, et al.[24] reported on 40 SMA type I patients from three Asian regions, including South Korea, who were treated with nusinersen. Their study showed that nusinersen is safe and effective in patients at various ages, from neonatal to adult age.

Notably, our study included a homogeneous group of Korean patients with SMA type I with chronic respiratory failure on permanent-assisted ventilation. Moreover, this study was systematically conducted at a single center using a unified protocol, with one of the longest observation periods (46 months). However, this study has several limitations. First, the number of patients included was small. In addition, the accuracy of motor function assessment in our patients was limited to HINE-2 and CHOP-INTEND scores. A more comprehensive evaluation might have been possible if the RULM module was included.

In conclusion, our study indicated that nusinersen can be effectively and safely administered to SMA type I patients even with low baseline motor and pulmonary function. Our study provides valuable real-world data on severe SMA type 1. If more data is accumulated to prove the therapeutic efficacy of nusinersen in high-risk patients, such as those with chronic respiratory failure, more patients will have the opportunity to be treated. For more effective treatment, there are needs for a more sensitive scale with which to measure the clinical status of SMA patients and for precise biomarkers highly correlated with the pathophysiology of SMA.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article. Raw data that support the findings of this study are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

Conceptualization: Young-Mock Lee. Data curation: Hyunjoo Lee and Young-Mock Lee. Formal analysis: Hui Jin Shin and Ji-Hoon Na. Investigation: Hui Jin Shin and Ji-Hoon Na. Methodology: Hui Jin Shin and Ji-Hoon Na. Project administration: Young-Mock Lee. Resources: Hyunjoo Lee and Young-Mock Lee. Supervision: Young-Mock Lee. Validation: Hui Jin Shin and Ji-Hoon Na. Visualization: Hui Jin Shin and Ji-Hoon Na. Writing—original draft: Hui Jin Shin and Ji-Hoon Na. Writing—review & editing: Young-Mock Lee. Approval of final manuscript: all authors.

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