ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

CASE STUDY

Successful weaning from mechanical ventilation in a patient with SMA type 1 treated with nusinersen

Jiwon Lee[1], Se Eun Park[1], Dajeong Lee[1], Joo Young Song[2] & Jeehun Lee[1]

[1]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Pediatrics, CHA Gangnam Medical Center, CHA University, Seoul, Korea

Correspondence
Jeehun Lee, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. Tel: +82-2-3410-0910; Fax: +82-2-3410-0043; E-mail: jhlee0101@skku.edu; leejeehunmd@gmail.com

Funding Information
No funding information provided.

Received: 31 December 2020; Revised: 31 January 2021; Accepted: 2 February 2021

Annals of Clinical and Translational Neurology **2021; 8(4): 964–967**

doi: 10.1002/acn3.51321

Abstract

SMA type 1 is the most severe type, characterized by early onset at <6 months of age, and rapid progression resulting in permanent assisted ventilation before 2 years of life. Supportive care was the only treatment until the approval of nusinersen, an antisense oligonucleotide drug that increases functional SMN protein levels. We present a case of successful weaning from permanent ventilation via tracheostomy with nusinersen in an infant who had been diagnosed with SMA type 1 at the age of one month and had become ventilator-dependent from the age of 3 months.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by degeneration of motor neurons of anterior horn cells of the spinal cord, leading to progressive muscle weakness and hypotonia.[1] Homozygous deletion of the survival motor neuron (SMN) 1 gene on chromosome 5q13 resulting in SMN protein deficiency is the cause of 95% cases of SMA. The *SMN2* gene, which is homologous to the *SMN1* gene, produces approximately 10% of the functional SMN protein through alternative splicing. Fewer copies of *SMN2* are associated with more severe phenotypes and earlier onset of disease.[2,3] SMA type 1 has the most severe phenotype characterized by onset at an age <6 months, and a rapid progression resulting in respiratory failure. These patients require permanent assisted ventilation within 2 years of life.[4] Nusinersen is an antisense oligonucleotide drug that modifies pre-mRNA splicing of the *SMN2* gene, increasing functional SMN protein levels.[5,6] It is known to improve motor function in patients with SMA. However, there have been limited studies that report weaning from permanent mechanical ventilation in patients with SMA type 1 treated with nusinersen.[7] We report the case of a patient with SMA type 1 treated with nusinersen and weaned successfully from permanent mechanical ventilation.

Case Report

A 1-month-old male infant was referred to the pediatric neurology outpatient clinic for decreased limb movement and hypotonia. He was born by cesarean section at 40 weeks of gestation, weighing 3670 g and had no perinatal problems. He had no family history of neuromuscular, metabolic, or genetic disorder. On neurologic examination, he showed global hypotonia and inability to move both arms and legs fully against gravity. Tongue fasciculations were observed, and deep tendon reflexes were absent. Although his grasp power was weak, sucking power was sufficient for feeding and gaining weight. His weight, height, and head circumference were 5.1 kg (75th percentile), 54.7 cm (25th percentile), and 37.8 cm (95th percentile), respectively. Homozygous *SMN1* deletion and 2 copies of *SMN2* were found with multiplex ligation-dependent probe amplification test. At the age of 2 months,

© 2021 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals LLC on behalf of American Neurological Association
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

he was admitted with respiratory difficulty and treated with high-flow nasal cannula therapy. He was transferred to the pediatric intensive care unit on the 2nd day of admission and required a mechanical ventilator on the 6th hospital day due to aggravated respiratory difficulty. After three failed attempts at weaning despite the use of a nasal continuous positive airway pressure device, a tracheostomy was performed at 3 months of age and he was discharged with a home ventilator. He was given the first dose of nusinersen at the age of 4 months after being enrolled in an early access program by Biogen. He completed four loading doses by 6 months of age, and thereafter, maintenance doses were administered at 4-month intervals. We evaluated his respiratory status by the duration of ventilator support, parameters of home ventilation, and blood gas analysis at each nusinersen therapy session. Motor function was evaluated using the Hammersmith Infant Neurological Examination (HINE-2) score. The progression of his respiratory status and motor function after administering nusinersen is shown in Table 1. The first trial of weaning off the ventilator was done at 10 months of age, after the 5th dose of nusinersen, and he tolerated 3 h without the aid of the ventilator. At 14 months of age, he could be weaned from the ventilator during the day and needed ventilation only during sleep for about 10–12 h. On each trial of weaning,

Table 1. Respiratory and motor function of the patient with spinal muscular atrophy type 1 at each nusinersen therapy.

		Respiratory state					Motor function (score)					
Age (mo)	Number of nusinersen	Duration of ventilator support (hr)	Ventilator mode	PIP (cmH_2O)	pH	pCO_2 (mmHg)	Total HINE-2	Voluntary grasp	Ability to kick	Head control	Rolling	Sitting, crawling, standing, walking
4	1	24	P-SIMV	17	7.38	31.4	0	(0)	(0)	(0)	(0)	(0)
5	2	24	P-SIMV	16	7.46	24.6	1	Grasp with whole hand (1)	(0)	(0)	(0)	(0)
5.5	3	24	P-SIMV	14	7.47	23.8	1	Grasp with whole hand (1)	(0)	(0)	(0)	(0)
6	4	24	P-SIMV	14	7.44	25.8	2	Grasp with whole hand (1)	Kick horizontally (1)	(0)	(0)	(0)
10	5	16	P(A)CV	20	7.46	25.0	2	Grasp with whole hand (1)	Kick horizontally (1)	(0)	(0)	(0)
14	6	10–12	P(A)CV	15	7.50	21.2	2	Grasp with whole hand (1)	Kick horizontally (1)	(0)	(0)	(0)
18	7	10–12	P(A)CV	11	7.47	22.8	4	Grasp with whole hand (1)	Kick upward (2)	(0)	Rolling to side (1)	(0)
22	8	10–12	P(A)CV	14	7.42	23.6	8	Index finger and thumb but immature grasp (2)	Touch leg (3)	(0)	Supine to prone (3)	(0)
26	9	10–12	P(A)CV	12	7.44	31.4	10	Pincer grasp (3)	Touch leg (3)	Wobble (1)	Supine to prone (3)	(0)
30	10	8–10	P(A)CV	10	7.46	32.0	10	Pincer grasp (3)	Touch leg (3)	Wobble (1)	Supine to prone (3)	(0)

Abbreviations: HINE, Hammersmith Infant Neurologic Examination; hr, hours; mo, month; P(A)CV, Pressure control ventilation; PIP, peak inspiratory pressure; P-SIMV, Pressure-synchronized intermittent mandatory ventilation.

© 2021 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals LLC on behalf of American Neurological Association

he was admitted and monitored for more than 24 h of respiratory condition and oxygen saturation. Also, we evaluated the occurrence of respiratory acidosis or difficulty through blood gas analysis and chest X-ray before and after weaning from a mechanical ventilator. At 30 months of age, there was no respiratory difficulty and his oxygen saturation was maintained above 90% without ventilatory support during the daytime, including daytime naps for 2-4 h, although the home ventilator was applied during nighttime sleep for the patient's safety. His HINE-2 score increased by 10 points from the first treatment, and he was able to move his limbs against gravity. He also performed pincer-grasp and rolled from a supine to prone position with head control, with some support. Independent sitting posture was not possible.

This study was approved by the Institutional Review Board (IRB) of Samsung Seoul Hospital (IRB No. 2020-04-154-001) and written informed consent was obtained from the patient's parents.

Discussion

The indication for nusinersen covered by national or public insurance, including that of South Korea, is patients who are not fully dependent on a mechanical ventilator. This is based on the initial clinical trial. This case report shows that even if the patient is completely dependent on mechanical ventilation, they can be partially weaned off the ventilator with nusinersen treatment. This report supports the evidence expanding the indication of nusinersen to patients dependent on a permanent ventilator in the early stage of the disease. Several studies have shown the effects of nusinersen on motor function or survival rate in SMA type 1 patients, however, they did not focus on respiratory function or weaning from the ventilator in patients with a tracheostomy before treatment[7–13] Other studies on SMA type 1 patients with ventilatory support via a tracheostomy reported an improvement in respiratory function with nusinersen treatment[14–16] (Table 2). Among them, there was no patient with ventilatory support via tracheostomy who was weaned from permanent assisted ventilation, even though they showed a decreased duration and termination of noninvasive ventilatory support. A case report of a male infant with SMA type 1 who had undergone a tracheostomy at 75 days of age and treated with nusinersen at 99 days of age demonstrated that he could be weaned from the ventilator for 1.5 h/day after 6 months of nusinersen treatment.[17] In our case, the duration of self-breathing without ventilatory support was over 12 h/day. Although we applied the ventilator during nighttime for patient safety, under close observation, he can maintain stable respiration during sleep. Because, there are few reports proving the effectiveness of the treatment on respiration, it is difficult to perform parallel comparison taking into account various factors that may affect treatment response. However, the patient in this study showed remarkable improvement in respiratory capacity that he could spend more than half of the day without respiratory assistance after early treatment.

We report a case of successful weaning from a mechanical ventilator for more than 12 h/day after early nusinersen treatment for SMA type 1. Further clinical evidence is necessary to prove the possibility of weaning off the ventilator by starting nusinersen treatment at an early stage of disease, even in SMA type 1 patients on ventilatory support via tracheostomy.

Table 2. Literature review: progression of respiratory and motor function in patients with spinal muscular atrophy type 1 treated with nusinersen.

		Pechmann et al.	Pane et al.	Sansone et al.
Total patients, n		61	85	118
Duration of follow-up, months		6	12	10
At 1st nusinersen	Mean age (range)	21.08 months (1–93 months)	4.7 years (2 months–15 years)	42.8 months (11.0–102.8 months)
	NIV > 16 h/d (A.pechmann et al.) or > 10 h/d (Pane et al. and Sansone et al.), n	6	19	24
	Tracheostomy, n	12	8	46
Assessment of respiratory function	Decreased duration or termination of NIV support, n	4 (6.6%)	2 (2.4%)	3 (2.5%)
	Removal of tracheostomy tube, n	0	0	0
Assessment of motor function	Mean improvement of HINE-2 score	1.4	1.34	N/A
	Mean improvement of CHOP INTEND score	9	5.46	N/A

Abbreviation: NIV, noninvasive ventilation; HINE, Hammersmith Infant Neurologic Examination; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; N/A, not available.

 © 2021 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals LLC on behalf of American Neurological Association

Acknowledgment

We appreciate the patient and their parents for their participation in this study.

Conflict of Interest

The authors have no potential conflicts of interest to disclose.

Authors' Contributions

Se Eun Park reviewed the case and prepared the manuscript. Dajeong Lee and Joo Young Song clinically managed and evaluated the patient with functional assessment. Jiwon Lee managed the patient and prepared and reviewed the manuscript. Jeehun Lee leaded the clinical team, and designed and reviewed the manuscript.

References

1. Arnold ES, Fischbeck KH. Spinal muscular atrophy. Handb Clin Neurol 2018;148:591–601.
2. Melki J, Abdelhak S, Sheth P, et al. Gene for chronic proximal spinal muscular atrophies maps to chromosome 5q. Nature 1990;344:767–768.
3. Mailman MD, Heinz JW, Papp AC, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. Genet Med 2002;4:20–26.
4. Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. Arch Neurol 1995;52:518–523.
5. Hua Y, Vickers TA, Okunola HL, et al. Antisense masking of an hnRNP A1/A2 intronic splicing silencer corrects SMN2 splicing in transgenic mice. Am J Hum Genet 2008;82:834–848.
6. Li Q. Nusinersen as a therapeutic agent for spinal muscular atrophy. Yonsei Med J 2020;61:273–283.
7. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–1732.
8. Aragon-Gawinska K, Daron A, Ulinici A, et al. Sitting in patients with spinal muscular atrophy type 1 treated with nusinersen. Dev Med Child Neurol 2020;62:310–314.
9. Aragon-Gawinska K, Seferian AM, Daron A, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: a cohort study. Neurology 2018;91:e1312–e1318.
10. Farrar MA, Teoh HL, Carey KA, et al. Nusinersen for SMA: expanded access programme. J Neurol Neurosurg Psychiatry 2018;89:937–942.
11. Pane M, Palermo C, Messina S, et al. Nusinersen in type 1 SMA infants, children and young adults: preliminary results on motor function. Neuromuscul Disord 2018;28:582–585.
12. Szabo L, Gergely A, Jakus R, et al. Efficacy of nusinersen in type 1, 2 and 3 spinal muscular atrophy: real world data from Hungarian patients. Eur J Paediatr Neurol 2020;27:37–42.
13. Audic F, de la Banda MGG, Bernoux D, et al. Effects of nusinersen after one year of treatment in 123 children with SMA type 1 or 2: a French real-life observational study. Orphanet J Rare Dis 2020;15:148.
14. Pechmann A, Langer T, Schorling D, et al. Evaluation of children with SMA type 1 under treatment with nusinersen within the expanded access program in Germany. J Neuromuscul Dis 2018;5:135–143.
15. Pane M, Coratti G, Sansone VA, et al. Nusinersen in type 1 spinal muscular atrophy: twelve-month real-world data. Ann Neurol 2019;86:443–451.
16. Sansone VA, Pirola A, Albamonte E, et al. Respiratory needs in patients with type 1 spinal muscular atrophy treated with nusinersen. J Pediatr 2020;219:223–228 e224.
17. Ogawa K, Okanari K, Kobayashi O, et al. Respiratory assessment in a spinal muscular atrophy infant treated with nusinersen. Pediatr Int 2019;61:1051–1053.

© 2021 The Authors. *Annals of Clinical and Translational Neurology* published by Wiley Periodicals LLC on behalf of American Neurological Association