PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Check for updates

Pediatrics International (2022) **64**, e15175 doi: 10.1111/ped.15175

Original Article

Respiratory outcome of spinal muscular atrophy type 1 patients treated with nusinersen

Almala Pinar Ergenekon,[1] Cansu Yilmaz Yegit,[1] Muruvvet Cenk,[1] Yasemin Gokdemir,[1] Ela Erdem Eralp,[1] Gulten Ozturk,[2] Olcay Unver,[2] Ozge Kenis Coskun,[3] Evrim Karadag Saygi,[3] Dilsad Turkdogan[2] and Bulent Karadag[1]

[1]*Division of Pediatric Pulmonology,* [2]*Division of Pediatric Neurology,* [3]*Department of Physical Medicine and Rehabilitation, Marmara University School of Medicine, Istanbul, Turkey*

Abstract ***Background*:** Respiratory failure is the leading cause of mortality in spinal muscular atrophy type 1 (SMA1) children. The current study aims to evaluate the effect of nusinersen treatment on respiratory outcome of the patients with SMA1.

***Methods*:** In this retrospective, single-center study, 52 SMA1 patients treated with nusinersen were included in the analysis. Patients were divided into two groups based on their age at the time of their first nusinersen treatment (Group 1: ≤6 months, Group 2: >6 months). Respiratory outcome on the 180th day of treatment is defined as the type of ventilation support (spontaneous breathing, noninvasive ventilation (NIV), and tracheostomized or intubated on invasive mechanical ventilation). Demographic data, respiratory outcome, and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scores were obtained from medical records.

***Results*:** On the 180th day of treatment, 46 of the 52 (88.4%) children were alive. Prevalence of the mortality was similar in both groups ($P = 0.65$). The comparison of respiratory outcome in patients between group 1 and group 2 was as follows: spontaneous breathing, 7 (43.7%) versus 4 (13.3%) ($P = 0.03$); NIV <16 h/day, 3 (18.7%) versus 4 (13.3%) ($P = 0.68$); invasive mechanical ventilation, 6 (37.5%) versus 22 (73.3%) ($P = 0.01$). There were no patients using NIV ≥16 h/day. There were significant improvements in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scores of the patients at day 180 in comparison with the baseline ($P < 0.001$).

***Conclusions*:** Early initiation of nusinersen treatment in SMA1 patients may alter the disease's natural course.

Key words nusinersen, respiratory follow up, treatment.

Spinal muscular atrophy (SMA) is an autosomal recessive, progressive neuromuscular disorder with an estimated incidence of approximately 1 in 10 000 live births.[1,2] All patients with SMA have a mutation or deletion in the survival motor neuron 1 (SMN1) gene rendering it non-functional.[3,4] More than 94% of SMN1 deletions occur in exon 7.[5] SMA type1 (SMA1) is the most frequent and severe phenotype with an onset of symptoms before six-months.[1,4]

Spinal muscular atrophy impacts the respiratory system, depending on the type of SMA and the severity of loss of muscle function.[6] Weakness of the respiratory muscles presents with ineffective cough reflex and hypoventilation, leading to decreased airway clearance, mucus plugging, atelectasis, and pneumonia with hypoxemia. Impaired secretion clearance and abnormalities in swallowing also leads to aspiration and respiratory infections, resulting in acute respiratory decompensation.[7] Infants with SMA1 develop pulmonary complications early in the disease, and these complications are the leading cause of morbidity and mortality.[8] Respiratory and nutritional support is essential to survive beyond their second year of life.[9] In a previous study, Finkel *et al*. reported that the median time to either death or requirement of at least 16 h/day of noninvasive ventilation support was 13.5 months.[10] Aggressive home management with oral suctioning, assisted airway clearance (e.g., use of a cough-assist device), ventilatory support with bi-level positive airway pressure ventilation (BIPAP) or invasive ventilation through a tracheostomy has notably lengthened the lifespan of children with SMA1.[7]

Advances in therapeutic approaches for SMA treatment have also improved the prognosis for patients with this life-threatening disease.[11] Nusinersen, an antisense oligonucleotide created to increase the SMN protein expression by modifying the transcription of SMN2, is the first approved disease-

Correspondence: Almala Pinar Ergenekon, MD, Division of Pediatric Pulmonology, Marmara University Hospital, Fevzi Cakmak mah. Mimar Sinan Cad. No:41 Pendik/Istanbul, Turkey.
Email: drpergenekon@hotmail.com

Received 3 November 2021; revised 2 February 2022; accepted 21 February 2022.

© 2022 Japan Pediatric Society

modifying therapy.[12] Treatment with nusinersen has demonstrated significant benefits in clinical trials in children with SMA.[13] Limited studies evaluated the effect of the drug on the respiratory system.[1,14–18] A study by Sansone *et al.* demonstrated some improvement by nusinersen in the respiratory impairment progression, both in survival and need for respiratory support >16 h/day, especially before 2 years.[17] More extensive studies are required to assess long-term respiratory outcomes and predictive factors for treatment response.

Nusinersen treatment was covered by the health system for all patients with definitive diagnosis of SMA type 1 as soon as possible after the diagnosis. According to the Ministry of Health regulations in Turkey, all patients, including patients on invasive ventilation, are covered by the health system for the first four loading doses of nusinersen. After completing the four doses, patients are re-evaluated, and improvement in respiratory status and CHOP INTEND scores on the 180th day are assessed. If the patient can tolerate time off from invasive ventilation for more than 4 h and if there is a 4 point increase in the CHOP INTEND score, treatment continues with the fifth dose coverage by the health system.

After the coverage of nusinersen by the health system, all our patients with SMA type 1 started to use nusinersen regardless of their age and respiratory status. So we had the advantage of comparing early nusinersen treatment with older age groups. In this study, we aimed to evaluate the effect of nusinersen on the respiratory outcome of SMA1 patients treated with nusinersen in our center.

Methods

Study protocol

The current study is a retrospective single-center study. There were 56 eligible patients with confirmed genetic diagnosis of SMA1 treated with nusinersen between September 2017 and July 2020. Fifty-two patients, followed for at least 180 days after the first nusinersen dose, were included in the study. The patients whose treatment was stopped by the family ($n = 1$), referred to other centers before reaching the 180th day ($n = 1$), or patients who are still on treatment but did not reach the 180 days ($n = 2$), were excluded from the study. Loading doses of 12 mg nusinersen at day 1 (Baseline), 15, 29, and 60 were administered via intrathecal injection over 1–3 min which was followed by a maintenance dose at 180 days.

In our study, the respiratory outcome at 180 days is defined as the need and the type of ventilation support – spontaneous breathing (SB), noninvasive ventilation (NIV), and tracheostomized or intubated on invasive mechanical ventilation (IMV).

Patients were divided into two groups based on their age at the time of their first nusinersen treatment (Group 1: ≤6 months, Group 2: >6 months). Patients were also classified into subgroups according to age at onset of symptoms and clinical presentation (ABC classification: symptoms in the first two weeks of life: 1A; within the third month: 1B; between 3 and 6 months: 1C).[19]

Clinical assessment

Demographic data, feeding routes (oral feeding/nasogastric feeding/gastrostomy feeding), and SMN2 copy numbers were obtained from medical records. Respiratory assessment data, including physical examination, blood gas results, peripheral capillary oxyhemoglobin saturation (SpO2), oxygen, and respiratory support need (modes and hours of ventilation) at baseline and each follow-up visit were also recorded. A pediatric neurologist evaluated the patients' neurologic status at baseline and on the 180th day using Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). CHOP INTEND is a 16-item test with scores ranging from 0 to 64 points, developed to evaluate motor skills in infants with SMA1, with higher scores indicating better motor function.[18]

Ethical approval

The study was approved by the Ethical Committee of Marmara University Medical Faculty (committee approval number 09.2020.1218), and written informed consent was obtained from the parents of study participants.

Statistical analysis

Descriptive statistical analysis was applied to the demographic data. The continuous variables were described using mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Categorical variables were described with frequencies and percentages. Chi-square tests were used for the comparison of respiratory outcomes between subgroups. McNemar's test was used for the comparison of the feeding routes at the baseline and 180th day. The Mann–Whitney *U*-test was used to compare the CHOP INTEND scores between age groups and respiratory outcomes. The Wilcoxon signed rank test was used to compare the CHOP INTEND test's median scores between baseline and at the 180th day. $P < 0.05$ was considered statistically significant. SPSS v.22 was used for all statistical analyses.

Results

A total of 52 patients with SMA1 were included in the study. The mean age at onset of symptoms was 2.2 ± 1.8 months, and the mean age at diagnosis was 4.1 ± 2.6 months. Of the 52 patients who received nusinersen treatment, 19 (36.5%) were 6 months or younger, and 33 (63.5%) were older than 6 months at the time of the initiation of nusinersen. The median age of nusinersen treatment initiation was 11.3 months (IQR: 4.0–34.8 months). Of the 28 patients on IMV, 24 (46.1%) (4 of them from group 1 and 20 of them from group 2) of them

© 2022 Japan Pediatric Society

1442200x, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ped.15175 by Marmara University, Wiley Online Library on [15/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

were tracheostomized. The median age at the time of tracheostomy surgery was 7 months (IQR: 4–9.5 months). Eleven of the 52 patients (21.1%) had gastrostomy tubes at the initiation of the nusinersen treatment. The median age at the time of nasogastric or gastrostomy tube insertion was 6 months (IQR: 3.0–9.0 months). Due to the lack of coverage by health system in Turkey, only three patients (5.8%) were using the cough-assist device. Two of the patients using the device were from group 1 and one of them was from group 2. Three patients (5.8%) were receiving speech and swallowing therapy. The demographic characteristics of patients are shown in Table 1.

On the 180th day of treatment, 46 children (88.4%) were alive. Three patients died from both groups 1 and 2 (15.8% and 9.1%, respectively). The prevalence of mortality was similar in both groups ($P = 0.65$). Twenty-eight patients were on IMV at baseline, and none of them was able to switch to NIV or SB at the end of the study. Patient flow from baseline to the end of the study is shown in Fig. 1. A comparison of the respiratory outcomes among patient groups is shown in Table 2. As a secondary analysis, while 52.6% of patients from group 1 were on SB or NIV < 16 h/day, 24.2% of patients from group 2 were on SB or NIV < 16 h/day after 180 days of treatment ($P = 0.03$). At the 180th day, the IMV requirement in group 1 (currently all above 6 months of age) was lower than the baseline group 2 (37.5 versus 69.7%) ($P = 0.03$). There were no significant differences in respiratory outcomes according to SMN2 copy numbers and ABC classifications ($P > 0.05$).

Eleven of the 52 patients (21.2%) had gastrostomy tubes when nusinersen treatment was initiated; five additional children required gastrostomy on the 180th day (see Table 3). There was no significant change in the patients' feeding routes on the 180th day than baseline.

Regarding motor function in our cohort, median CHOP INTEND scores at baseline and 180th day were 9.5 (IQR: 3.0–23.7) and 25 (IQR: 11–35), respectively. There was a significant improvement in CHOP INTEND scores of the patients between baseline and day 180 ($P < 0.001$). The patients' median CHOP INTEND scores in group 1 at baseline and 180th day were 18.0 (IQR: 9–25) and 31.0 (IQR: 28.7–43.2), respectively. The median CHOP INTEND scores of the patients in group 2 at baseline and 180th day were 6.0 (IQR: 1–18) and 14 (IQR: 10.5–33.5), respectively. The CHOP INTEND scores of the patients in group 1 were higher than those for group 2 at day 180 ($P = 0.01$). The SB patients' CHOP INTEND scores were significantly higher than patients' on IMV at day 180 ($P < 0.001$). Comparison of CHOP INTEND scores at baseline and 180th day is shown in Fig. 2.

Table 1 The baseline demographic characteristics of the SMA1 patients

Baseline data ($n = 52$)	Group 1 (≤6 months) ($n = 19$)	Group 2 (>6 months) ($n = 33$)	*P*
Gender, male, *n* (%)	11 (57.9)	19 (57.6)	0.9
Age at onset of symptoms, months, mean ± SD	1.1 ± 0.7	2.9 ± 1.9	<0.001
Age at diagnosis, months, mean ± SD	2.5 ± 1.0	5.1 ± 2.8	<0.001
Median age at first nusinersen dose, months, (IQR)	3.7 (2.7–4.6)	23 (12.6–47.5)	<0.001
Respiratory status			
SB, *n* (%)	13 (68.4)	9 (27.3)	0.004
NIV<16 h/day, *n* (%)	1 (5.3)	1 (3.0)	1
IMV, *n* (%)	5 (26.3)	23 (69.7)	0.003
Feeding route			
Oral feeding, *n* (%)	12 (63.2)	10 (30.3)	0.02
Nasogastric feeding, *n* (%)	6 (31.6)	13(39.4)	0.5
Gastrostomy feeding, *n* (%)	1 (5.3)	10 (30.3)	0.04
CHOP-INTEND score, median (IQR)	18.0 (9–25)	6.0 (1–18)	0.02
SMN2 copy number ($n = 40$)			
2 SMN2, *n* (%)	17 (100)	19 (82.6)	0.12
3 SMN2, *n* (%)	0	4 (17.4)	0.12
ABC classification ($n = 47$), *n* (%)			
SMA 1A	3 (16.7)	1 (3.4)	0.15
SMA 1B	15 (83.3)	20 (69)	0.32
SMA 1C	0	8 (27.6)	0.01

Discussion

In this study, we evaluated the respiratory outcomes of our SMA type 1 patients with nusinersen treatment starting below 6 months of age and compared with those above 6 months of age. Early initiation of nusinersen treatment in SMA1 patients may alter the disease's natural course. In most cases, respiratory status remained stable during the study period. Neurological scores improved in all age groups but respiratory outcomes seems to improve only in patients on nusinersen treatment when they were younger than 6 months of age.

Spinal muscular atrophy is characterized by progressive muscle weakness. Early treatment is crucial because the lack of SMN leads to irreversible loss of motor neurons.[20] Some studies evaluating the effect of nusinersen revealed that the treatment efficacy is enhanced when patients are treated before the onset of symptoms.[11,18] Studies evaluating the respiratory status of SMA1 patients treated with nusinersen are scarce. In a pilot project by Vill *et al*., nusinersen treatment was started at the median age of 24 days, and respiratory deterioration was not observed in any of the children who received treatment.[21] A study by De Vivo DC *et al*. (Nurture), including 25 presymptomatic SMA1 patients, early initiation of nusinersen at younger than 6 weeks of age resulted in all 25 infants without the need for permanent ventilation at a median age of 26 months.[18] In our study, the median age of initiation of nusinersen was 3.7 months in patients who started the treatment before 6 months of age. Unlike the Nurture study, only one of our patients received nusinersen treatment before 6

© 2022 Japan Pediatric Society

1442200x, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ped.15175 by Marmara University, Wiley Online Library on [15/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

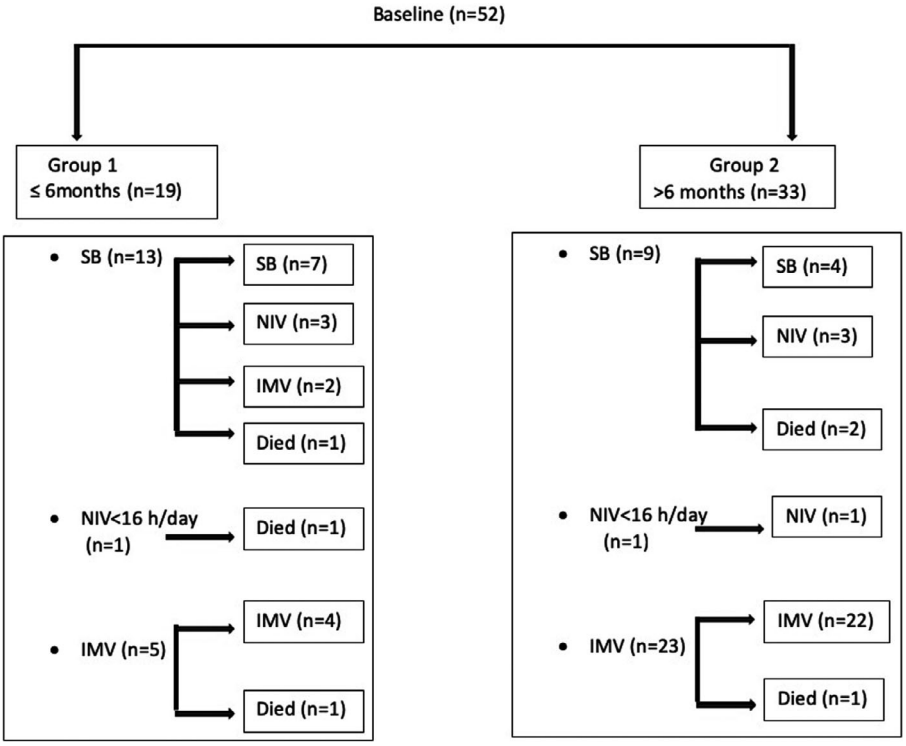

Fig. 1 Patient flow from baseline to the end of the study.

Table 2 Comparison of the respiratory outcomes of the patients on the 180th day (n = 46)

	Group 1 (≤6 months) n = 16	Group 2 (>6 months) n = 30	P
SB, n (%)	7 (43.7)	4 (13.3)	0.03
NIV < 16 h/day, n (%)	3 (18.7)	4 (13.3)	0.68
IMV, n (%)	6 (37.5)	22 (73.3)	0.01

Table 3 Comparison of the feeding routes of the patients

Feeding route	Baseline	At 180th days (n = 46)	P
Oral feeding, n (%)	22 (42.3)	15 (32.6)	0.12
Nasogastric feeding, n (%)	19 (36.5)	15 (32.6)	1.0
Gastrostomy feeding, n (%)	11 (21.2)	16 (34.8)	0.06

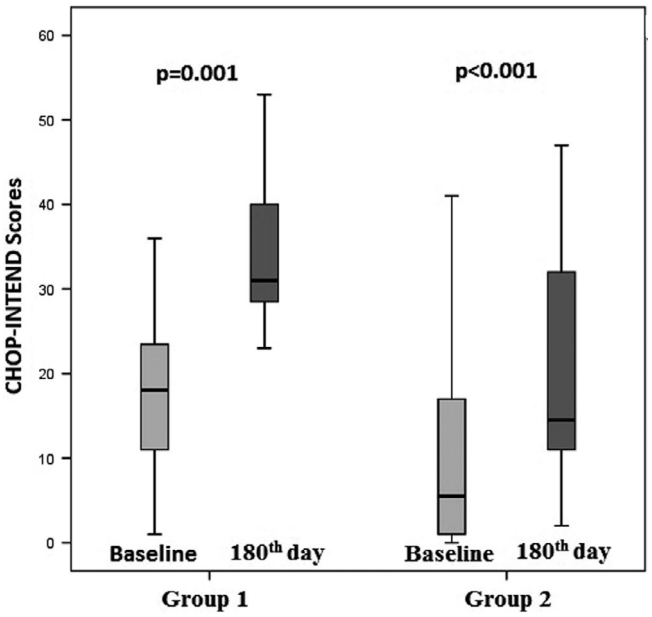

Fig. 2 Comparison of CHOP INTEND scores at the initiation and on the 180th day of nusinersen treatment.

weeks of age, which could explain the lower effectiveness of treatment in our study compared to the Nurture study. A randomized, double-blind, sham-controlled, phase 3 study (ENDEAR) of nusinersen in infants with SMA was stopped early in the interim analysis because a significantly higher percentage of infants in the nusinersen group had a motor-milestone response than in the control group (P < 0.001). In the final analysis, the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; P = 0.005). The mean age at the initiation of the nusinersen treatment was 23 weeks. Infants with a shorter disease

© 2022 Japan Pediatric Society

1442200x, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ped.15175 by Marmara University, Wiley Online Library on [15/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

duration at the initiation of the study were more likely to benefit from nusinersen than those with a longer disease duration. The authors concluded that nusinersen is not a cure in symptomatic patients, and early initiation may be necessary to maximize the drug's efficacy.[16] In the current study, patients with a longer duration of symptoms, i.e., the patients whose treatment was started after 6 months of age, had poorer outcomes. Twenty-five of the 33 patients (75.8%) in this group had either died or required permanent respiratory support. Furthermore, as in our study, the patients' respiratory outcome in ENDEAR study is also inferior compared to the NURTURE study, which can be explained by the later initiation of nusinersen treatment (6 weeks vs. 23 weeks). To show the possible effect of nusinersen on the natural course, we compared baseline group 2 before nusinersen treatment with the final status of group 1. At the 180th day of treatment, patients above 6 months of age mostly did not require IMV (37.5%) in contrast with the baseline group, which required IMV (69.7%) before nusinersen. Early treatment with nusinersen may alter the natural course of the disease, longer term studies are needed.

Currently, SMA is not included in the newborn screening (NBS) program in Turkey. The majority of studies, including our study, point to a better disease course with early diagnosis of the mutation and early initiation of treatment. Thus, implementation of the SMA NBS program should be considered by the health authorities to achieve early diagnosis.

The neurologic outcome with nusinersen treatment is not always correlated with respiratory outcome.[3] In a study by Aragon Gawinska *et al*., the safety and clinical efficacy of nusinersen in patients over 7 months of age was investigated, and respiratory worsening, despite the motor improvement, was observed in some patients. This was partly explained by the slower action of nusinersen on the respiratory system and the possible intercurrent infections that may further compromise the patients' clinical condition with SMA1 and late initiation of treatment.[22] As in this study, we observed a significant improvement in all patients' motor function. However, only patients whose treatment was initiated before 6 months of age had a better respiratory outcome.

Although the evidence is still scarce, differences in response to treatment in different SMA types have been reported in several studies.[23] However, in our study, significant differences regarding respiratory outcomes between the subgroups of SMA1 (1A, 1B, 1C) were not observed. The SMN2 copy number is reported to be the most important predictor of clinical severity in SMA patients; however, a significant difference in terms of respiratory outcome according to the SMN2 copy number was not observed in our study. Limited sample size and type II error may have biased our findings.[24]

Differences in standards of care among the countries could affect treatment outcomes. In recent years, pulmonary management of SMA has shifted from a reactive approach to a proactive approach, including early intervention with noninvasive ventilation, cough-assist devices, gastrostomy tubes, and swallowing therapies.[6] Cough-assist devices combined with manual chest physiotherapy are recommended for airway clearance for all SMA patients with an ineffective cough.[6] Noninvasive ventilation can be used in case of nocturnal hypoventilation before the appearance of respiratory failure.[25] Early NIV can have a beneficial impact on chest shape, reducing the development of pectus excavatum and reverse changes in chest-wall compliance.[26–28] Early initiation of adequate multidisciplinary support and close follow up by specialists may ameliorate disease course and increase the effectiveness of nusinersen therapy. As the multidisciplinary approach and treatment are crucial in SMA management, additional coverage of the evidence-based devices by the health system in this group of patients is vital.[6,7,29,30] Although multiple studies demonstrated the clinical benefit of cough-assist devices, unfortunately, there is no coverage by the health system in our country, and only a small number of our patients use cough-assist devices. Lack of coverage of cough assist device by the health system is unacceptable considering the high cost of nusinersen treatment. This current status may be one of the causes of the reduced effect of the nusinersen treatment, and for this reason, it is also difficult to compare our patient population with other populations.

One of the most important issues to consider for the patient with SMA type 1 is safe swallowing. With the progression of the tongue and pharyngeal muscle weakness, these infants are at increased risk of aspiration and pneumonia. A proactive approach including nasogastric tube feeding is suggested until gastrostomy is performed.[30] Nusinersen may provide improvements in motor milestones and survival rates but the effect on the bulbar functions is unclear.[14,31,32] A study by van der Heul *et al*. evaluating feeding and swallowing problems in infants with spinal muscular atrophy type 1 revealed that the symptoms of abnormal feeding were present in children treated with nusinersen in the first year of their life despite initiating the treatment before the onset of muscle weakness.[33] In the current study, we did not observe any improvement regarding the feeding route after nusinersen treatment.

Major limitations of this single-center study were short duration of follow up and small sample size. At our baseline, there were significant differences between two subgroups, which were divided according to the starting age of nusinersen with regard to the respiratory status. This difference causes difficulties in evaluating the effect of nusinersen treatment in time. Maybe longer term follow up of these patients will prevent this limitation.

Increased number of patients and a longer duration of follow-up may enable detection of nusinersen therapy's effects in subgroups. One hundred-eighty day follow-up duration was chosen, as the coverage by the health system has stopped for some patients before the fifth dose of the treatment due to the respiratory and neurological status.

In conclusion, nusinersen was effective in SMA1 patients as all patients had better neurological scores after treatment. The effect of nusinersen on respiratory outcome was detected only in younger patients when nusinersen was started before 6

© 2022 Japan Pediatric Society

1442200x, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ped.15175 by Marmara University, Wiley Online Library on [15/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

months of age. This finding suggests that the earliest possible intervention after the genetic diagnosis would be ideal for SMA1 patients. The current criteria for continuing of nusinersen treatment should be defined, especially for patients with advanced disease who showed minimal improvement in neurological status in the absence of better respiratory outcomes, considering the cost of nusinersen, particularly for low-income countries where health care resources should be used rationally. Further studies are required to define the efficacy of nusinersen in different subgroups and to define the predictive factors for optimal response to treatment.

Acknowledgement

We thank our SMA nurse, Gulnur Ozel, for her contribution to our study.

Disclosure

The authors declare no conflict of interest.

Author contributions

Almala Pinar Ergenekon, Cansu Yilmaz Yegit, Muruvvet Cenk, Yasemin Gokdemir, Ela Erdem Eralp designed the study, collected the data, performed data interpretation,performed statistical analysis and wrote the first manuscript draft. Gulten Ozturk, Olcay Unver, Ozge Kenis Coskun contributed to the investigation, visualization, writing, review and editing. Evrim Karadag Saygi, Dilsad Turkdogan, Bulent Karadag contributed to validation, writing, review and supervised the study.

References

1 Pechmann A, Langer T, Wider S, Kirschner J. Single-center experience with intrathecal administration of Nusinersen in children with spinal muscular atrophy type 1. *Eur. J. Paediatr. Neurol.* 2018; **22**: 122–7.
2 Lorson CL, Androphy EJ. An exonic enhancer is required for inclusion of an essential exon in the SMA-determining gene SMN. *Hum. Mol. Genet.* 2000; **9**: 259–65.
3 Meylemans A, De Bleecker J. Current evidence for treatment with nusinersen for spinal muscular atrophy: a systematic review. *Acta Neurol. Belg.* 2019; **119**: 523–33.
4 Bortolani S, Stura G, Ventilii G *et al*. Intrathecal administration of nusinersen in adult and adolescent patients with spinal muscular atrophy and scoliosis: Transforaminal versus conventional approach. *Neuromuscul. Disord.* 2019; **29**: 742–6.
5 Haliloglu G. Spinal Muscular Atrophies. In: Kliegman RM, Geme JWS, Blum NJ, Shah SS, Tasker RC, Wilson KM, Behrman RE (eds). *Nelson Textbook of Pediatrics*. Elsevier, Philadelphia, 2020; 12826.
6 Finkel RS, Mercuri E, Meyer OH *et al*. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul. Disord.* 2018; **28**: 197–207.
7 Finkel RS, Weiner DJ, Mayer OH, McDonough JM, Panitch HB. Respiratory muscle function in infants with spinal muscular atrophy type I. *Pediatr. Pulmonol.* 2014; **49**: 1234–42.
8 Wang CH, Finkel RS, Bertini ES *et al*. Participants of the International Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. *J. Child Neurol*. 2007; **22**: 1027–49.
9 Haliloglu G. Spinal Muscular Atrophies. In: Kliegman RM, Geme JWS, Blum NJ, Shah SS, Tasker RC, Wilson KM, Behrman RE (eds). *Nelson Textbook of Pediatrics*. Elsevier, Philadelphia, 2020; 12822.
10 Finkel RS, McDermott MP, Kaufmann P *et al*. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology* 2014; **26**(83): 810–7.
11 Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. *Ther. Clin. Risk Manag.* 2019; **2**(15): 1153–61.
12 Neil EE, Bisaccia EK. Nusinersen: A novel antisense oligonucleotide for the treatment of spinal muscular atrophy. *J. Pediatr. Pharmacol. Ther.* 2019; **24**: 194–203.
13 Darras BT, Farrar MA, Mercuri E *et al*. An integrated safety analysis of infants and children with symptomatic Spinal Muscular Atrophy (SMA) treated with nusinersen in seven clinical trials. *CNS Drugs* 2019; **33**: 919–32.
14 Chen KA, Widger J, Teng A, Fitzgerald DA, D'Silva A, Farrar M. Real-world respiratory and bulbar comorbidities of SMA type 1 children treated with nusinersen: 2-Year single centre Australian experience. *Paediatr. Respir. Rev.* 2021; **39**: 54–60.
15 Messina S, Pane M, Sansone V *et al*. Expanded access program with Nusinersen in SMA type I in Italy: Strengths and pitfalls of a successful experience. *Neuromuscul. Disord.* 2017; **27**: 1084–6.
16 Finkel RS, Mercuri E, Darras BT *et al*. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N. Engl. J. Med.* 2017; **2**(377): 1723–32.
17 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.e4.
18 De Vivo DC, Bertini E, Swoboda KJ *et al*. NURTURE Study Group. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul. Disord.* 2019; **29**: 842–56.
19 Finkel R, Bertini E, Muntoni F, Mercuri E. 209th ENMC international workshop: outcome measures and clinical trial readiness in spinal muscular atrophy 7–9 November 2014, Heemskerk, The Netherlands. *Neuromuscul. Disord.* 2015; **25**: 593–602.
20 Prior TW. Spinal muscular atrophy: a time for screening. *Curr. Opin. Pediatr.* 2010; **22**: 696–702.
21 Vill K, Kölbel H, Schwartz O *et al*. One year of newborn screening for SMA - results of a German pilot project. *J. Neuromuscul. Dis.* 2019; **6**: 503–15.
22 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; **2**(91): e1312–8.
23 LoMauro A, Mastella C, Alberti K, Masson R, Aliverti A, Baranello G. Effect of nusinersen on respiratory muscle function in different subtypes of type 1 spinal muscular atrophy. *Am. J. Respir. Crit. Care Med.* 2019; **15**(200): 1547–50.
24 Kirschner J, Butoianu N, Goemans N *et al*. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. *Eur. J. Paediatr. Neurol.* 2020; **28**: 38–43.

© 2022 Japan Pediatric Society

1442200x, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ped.15175 by Marmara University, Wiley Online Library on [15/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

25 Fauroux B, Griffon L, Amaddeo A *et al*. Respiratory management of children with spinal muscular atrophy (SMA). *Arch. Pediatr.* 2020; **27**: 7S29–7.
26 Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurol. Clin.* 2015; **33**: 831–46.
27 Roper H, Quinlivan R. Workshop Participants. Implementation of "the consensus statement for the standard of care in spinal muscular atrophy" when applied to infants with severe type 1 SMA in the UK. *Arch. Dis. Child.* 2010; **95**: 845.
28 Bach JR, Bianchi C. Prevention of pectus excavatum for children with spinal muscular atrophy type 1. *Am. J. Phys. Med. Rehabil.* 2003; **82**: 815–9.
29 Mercuri E, Bönnemann CG, Muntoni F. Muscular dystrophies. *Lancet* 2019; **30**(394): 2025–38.
30 Mercuri E, Finkel RS, Muntoni F *et al*. SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul. Disord.* 2018; **28**: 103–15.
31 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**: 135–43.
32 Pane M, Coratti G, Sansone VA *et al*. Nusinersen in type 1 spinal muscular atrophy: Twelve-month real-world data. *Ann. Neurol.* 2019; **86**: 443–51.
33 Van der Heul AMB, Cuppen I, Wadman RI *et al*. Feeding and swallowing problems in infants with spinal muscular atrophy type 1: an observational study. *J. Neuromuscul. Dis.* 2020; **7**: 323–30.

© 2022 Japan Pediatric Society

1442200x, 2022, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ped.15175 by Marmara University, Wiley Online Library on [15/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License