

# Chronic respiratory failure after the first dose of nusinersen treatment: A case report

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## Abstract

Spinal muscular atrophy (SMA) is a disease characterized by progressive nerve cell loss in the spinal cord and brainstem. It can be fatal if left untreated, particularly in infantile forms. Nusinersen became the first disease-modifying agent to be approved in 2016 for the treatment of all types of 5q-associated SMA, across all age groups. Trials have shown that the drug has an acceptable safety profile and has significantly improved clinical care for patients; however, data on long-term risks and benefits are limited. Respiratory problems following use of the drug are an important potential complication and the mechanisms of action are not fully understood. This study reports on a patient with type 1 SMA who developed chronic respiratory failure after the first dose of nusinersen, a condition not previously reported. Although nusinersen significantly improves patients' quality of life, its long-term or rare side effects are not well understood. Patients should be closely monitored for respiratory side effects, especially after the first dose, and families should be thoroughly informed about potential respiratory complications.

**Keywords:** Adverse effects, chronic lung disease, nusinersen, spinal muscular atrophy

## Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterized by the progressive loss of  $\alpha$ -motor neurons in the spinal cord and brainstem, with an incidence rate of 1 in 6000 to 11000 live births (1, 2). Among patients, 95% exhibit a homozygous deletion of the SMN1 gene, which is situated on chromosome 5q13.2. The remaining patients either exhibit a heterozygous deletion of SMN1 or harbor an intragenic pathogenic variant on the other allele that leads to the inactivation of SMN1. The clinical phenotype of SMA is heterogeneous. Moreover, severity of the condition is inversely correlated with the number of copies of SMN2, a non-functional copy to SMN1 (3).

Until 2016, only supportive therapies were available for SMA. However, in 2016, the FDA approved nusinersen as a disease-modifying agent for the treatment of all 5q-related SMA types in all age groups, followed by approval from the EMA in 2017. Nusinersen, along with other currently used therapies, is not curative; moreover, it only alleviates the severity of the disease. Furthermore, insufficient data are available regarding the long-term effects and side effects of these therapies (4).

Nusinersen, an antisense oligonucleotide, is administered intrathecally at a dosage of 12 mg/5 ml. After the initial four loading doses administered over the first two months, maintenance doses are administered every four months (1, 5). Studies evaluating efficacy and safety profiles commonly report side effects, such as upper and lower respiratory tract infections, atelectasis, constipation, headache, back pain, and post-lumbar puncture syndrome. Additionally, side effects such as respiratory distress, acute respiratory failure, decreased

oxygen saturation, cough, vomiting, dysphagia, and gastroesophageal reflux have been reported in a small number of cases (6-8). No patient with chronic respiratory failure has been reported in the literature.

This study reports on a type 1 SMA patient who experienced acute respiratory distress after receiving the first dose of nusinersen without evidence of pulmonary infection, and subsequently, developed chronic respiratory failure within approximately two weeks.

## Case Report

A 13-day-old boy was found to have a homozygous deletion in exon 7 of SMN1, with an SMN2 copy number of 2, as determined by the newborn screening program. The neurological examination findings were consistent with type 1 SMA. As nusinersen is the treatment covered for all SMA types in our country, the patient was included in the treatment program and his medication was provided. No clinical or laboratory findings were identified during the pretreatment evaluation that would act a contraindication for the use of this drug. Nusinersen, at a dosage of 12 mg/5 ml, was administered intrathecally when the patient was 28-days-old. No complications were observed during the 4-hour post-procedure follow-up, and the patient was discharged.

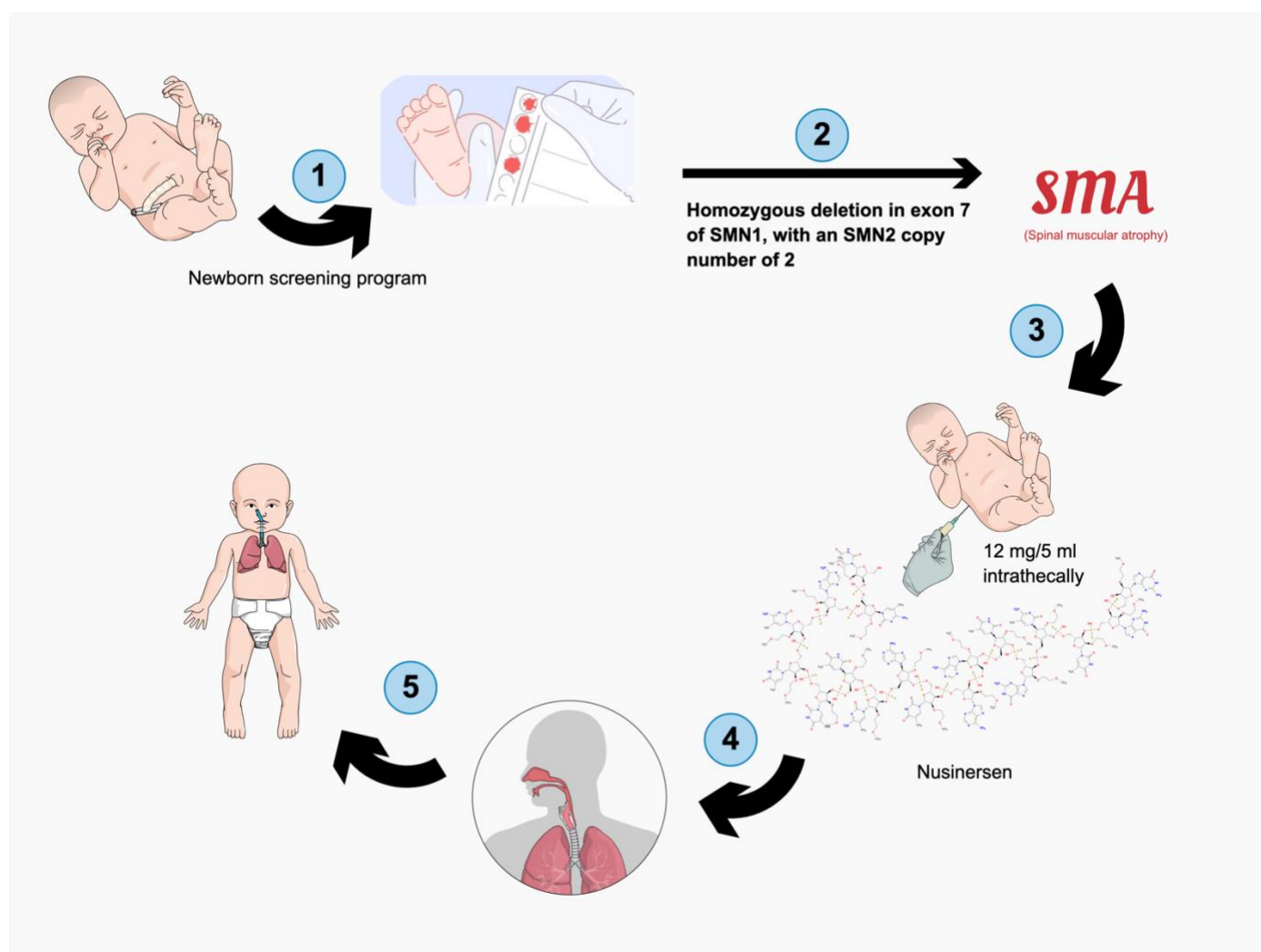
The patient presented with respiratory distress 24 hours after drug administration. On admission, the patient's pulse oximetry reading was 82%, and he was subsequently admitted to the ward. No infiltration was found on chest radiography (Fig. 1).



**Figure 1.** The patient's chest radiograph reported as normal at the time of hospitalization

Blood gas analysis revealed a pH of 7.12, a partial pressure of carbon dioxide ( $p\text{CO}_2$ ) of 71 mmHg, and a partial pressure of oxygen ( $p\text{O}_2$ ) of 56 mmHg. The white blood cell count was  $17.77 \times 10^3/\mu\text{L}$ , with a C-reactive protein level of 2 mg/L, procalcitonin level of 0.08 ng/dL, and erythrocyte sedimentation rate of 4 mm/hr. The patient's laboratory findings are summarized in Table 1. Patient did not meet the criteria for diagnosis with Pediatric Acute Respiratory Distress Syndrome (9). The patient was connected to the monitor, and oxygen therapy at 100% was initiated using a non-rebreather mask. Given that the patient's saturation did not increase on pulse oximetry and his general condition continued to deteriorate; thus, the patient was promptly transferred to the pediatric intensive care unit. In the intensive care unit, high-flow nasal cannula (HFNC) oxygen therapy was initiated. The patient's oxygen

saturations returned to normal values following HFNC oxygen therapy. On the 5th day of hospitalization, the patient was switched from HFNC oxygen therapy to oxygen support via a mask. On the 7th day of hospitalization, the patient underwent testing to assess tolerance to room air. The patient's oxygen saturation dropped to  $\leq 80\%$  in room air, and the patient did not tolerate it. Repeated attempts were made to administer room oxygen inhalation; however, the patient's oxygen saturations dropped below 80% each time. The patient was reassessed by a pediatric chest diseases specialist. On the 12th day of hospitalization, it was decided to discharge the patient with a home mechanical ventilator and oxygen concentrator due to chronic respiratory failure. This case report schematically illustrated in Figure 2.



**Figure 2.** SMA was detected in a 13-day-old male infant during the newborn screening program (1). During the genetic analysis for definitive diagnosis, homozygous deletion in exon 7 of the SMN1 gene and 2 copies of the SMN2 gene were detected (2). The baby was included in the Nusinersen treatment program due to the diagnosis of type 1 SMA (3). Treatment of 12 mg/5ml Nusinersen was administered intrathecally to the baby at the 28th day of born (4). Chronic respiratory failure developed in the baby who was admitted to the intensive care unit due to respiratory symptoms 24 hours after the beginning of the treatment (5). This case report reveals a question that if is this a side effect of Nusinersen treatment?

Table 1. Laboratory findings of the patient

|                                | Application time | 24. hour | 48. hour | 5. day | 7. day | Discharge time |
|--------------------------------|------------------|----------|----------|--------|--------|----------------|
| pH                             | 7.36             | 7.12     | 7.28     | 7.35   | 7.45   | 7.39           |
| pCO <sub>2</sub> (mmHg)        | 36.3             | 71       | 56.6     | 42     | 33.2   | 44             |
| pO <sub>2</sub> (mmHg)         | 77               | 56       | 55       | 76     | 67     | 68             |
| HCO <sub>3</sub>               | 21               | 17       | 19       | 23     | 23     | 27             |
| Lactate                        | 1.2              | 6.6      | 5.3      | 1.4    | 1      | 1.1            |
| Procalcitonine (ng/dl)         | 0.04             | 0.08     | -        | 0.1    | -      | 0.02           |
| CRP (mg/L)                     | 1.9              | 2        | 0.3      | 0.2    | 0.3    | 0.7            |
| WBC (10 <sup>3</sup> /uL)      | 12.99            | 17.77    | 15.59    | 9.51   | 13.52  | 12.48          |
| Hemoglobin(g/dL)               | 16.8             | 14.3     | 14.6     | 13.2   | 11.6   | 10.7           |
| Platelet (10 <sup>3</sup> /uL) | 409              | 368      | 348      | 333    | 503    | 547            |
| NLR                            | 0.75             | 0.77     | 1.95     | 0.17   | 0.67   | 0.44           |
| Glukoz (mg/L)                  | 114              | 138      | 91       | 83     | 91     | 81             |
| Urea (mg/dL)                   | 23.54            | 25.68    | 17.12    | 8.56   | 4.28   | 10.7           |
| Creatinine (mg/dL)             | 0.2              | 0.4      | 0.28     | 0.25   | 0.13   | 0.2            |
| Sodium                         | 135              | 132      | 136      | 137    | 133    | 136            |
| Potassium                      | 4.2              | 5.3      | 4.7      | 5      | 4.7    | 5.5            |

Abbreviations: CRP: C Reactive Protein, WBC: White Blood Cell, NLR: Neutrophil lymphocyte ratio

Discussion

Nusinersen therapy has significantly enhanced the clinical care of infants and children with SMA. While it has been demonstrated to enhance quality and duration of life in numerous studies, data on the long-term risks and benefits of the drug remain very limited in the published literature to date. However, available studies have found that the drug has an acceptable safety profile (6, 7). It is understandable that families are willing to accept the risks and complications of this supportive treatment for a disease that, if left untreated, can quickly prove fatal.

Although clinical trials are ongoing, there are still numerous unanswered questions regarding nusinersen. There is insufficient data on the long-term side effects of the drug. In a meta-analysis study, the rate of SMA or drug-related adverse events was 83.51%, the rate of possible drug-related adverse events was 7.76%, and the rate of definite drug-related adverse events was 0.57% (10). Recent studies have reported improvements in lung and respiratory functions associated with the treatment (11, 12). However, one of the important potential side effects of the drug is respiratory complications. During the administration phase of the drug, an increase in paradoxical breathing, respiratory symptoms, pneumonia, and respiratory support requirements have been reported in treated patients compared to placebo (13). Approximately 700 drugs, mostly

chemotherapeutics, have been reported to cause undesirable side effects on the lungs through toxic or immunologic mechanisms (14). In studies evaluating the immunologic response to nusinersen, pretreatment and post-treatment comparisons revealed that approximately 4% of patients developed antidrug antibodies after treatment. Antidrug antibodies developed transiently in half of the patients, whereas they persisted for a prolonged duration in the other half (10). Based on the available data, there is insufficient information to evaluate the effect of antidrug antibodies on the pharmacokinetics, efficacy, or tolerability of nusinersen. The precise mechanism by which nusinersen induces respiratory complications is not completely understood. Immune-mediated response or hypersensitivity reactions may be responsible for respiratory complications (14, 15).

Some patients may experience rare complications that have not been observed in any other cases. It was reported that severe hyponatremia developed in one patient, necessitating salt supplementation for 14 months to correct the electrolyte disorder (16). To date, despite tens of thousands of patients in our country and worldwide receiving this treatment, there have been no reports of rapid deterioration and chronic respiratory failure after the first dose, as observed in our patient.

Limitation of our study: Respiratory viral panel could not be performed in our hospital during the patient's hospitalization. The patient's relatives could not have the respiratory viral panel performed in an

external laboratory due to economic reasons. However, we still thought that the event was a complication of the drug because the patient's clinical findings, infection markers remained negative throughout the entire follow-up, and the symptoms started immediately after the drug administration.

## Conclusion

In conclusion, although nusinersen significantly improves patients' quality of life, its long-term side effects or rare side effects are not well known. Especially after the first dose, patients should be monitored more closely for respiratory side effects, and families should be thoroughly informed about potential respiratory complications.

## Disclosures

**Informed Consent:** Written informed consent was obtained from the patient's family.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - Ö.O, N.Ö., M.N.T.; Design - Ö.O, N.Ö., H.N.B., A.D.; Supervision - Ö.O, N.Ö., M.N.T., M.N.Ö., H.N.B.; Materials - Ö.O, N.Ö., M.N.T., M.N.Ö., H.N.B.; Data collection &/or processing - Ö.O, N.Ö., M.N.T., M.N.Ö., H.N.B.; Analysis and/or interpretation - Ö.O, N.Ö., M.N.T., M.N.Ö.; Literature search - Ö.O, N.Ö., M.N.T., M.N.Ö.; Writing - Ö.O, N.Ö., H.N.B., A.D.; Critical review - Ö.O, N.Ö., M.N.T., M.N.Ö., A.D.

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## References

- Ramdas S, Servais L. New treatments in spinal muscular atrophy: an overview of currently available data. *Expert Opin Pharmacother* 2020;21(3):307-315. <https://doi.org/10.1080/14656566.2019.1704732>
- Su YN, Hung CC, Lin SY, Chen FY, Chern JP, Tsai C et al. Carrier screening for spinal muscular atrophy (SMA) in 107,611 pregnant women during the period 2005-2009: a prospective population-based cohort study. *PLoS One* 2011;6(2): e17067. <https://doi.org/10.1371/journal.pone.0017067>
- Rouzier C, Chaussonnet A, Paquis-Flucklinger V. Molecular diagnosis and genetic counseling for spinal muscular atrophy (SMA) *Arch Pediatr*. 2020;27(7S):7S9-7S14. [https://doi.org/10.1016/S0929-693X\(20\)30270-0](https://doi.org/10.1016/S0929-693X(20)30270-0)
- Saracaloğlu A, Demiryürek AD. Spinal Musküler Atrofi (SMA) Tedavisinde Yeni Yaklaşımlar ve Onaylı İlaçlar. *J Curr Pediatr* 2021;19:248-258. <https://doi.org/10.4274/jcp.2021.0031>
- Lavie M, Diamant N, Cahal M, Yahav I, Veber M, Sarafy-Levy T. Nusinersen for spinal muscular atrophy type 1: Real-world respiratory experience. *Pediatr Pulmonol* 2021;56(1):291-298. <https://doi.org/10.1002/ppul.25140>
- De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS et al. 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(11):842-856. <https://doi.org/10.1016/j.nmd.2019.09.007>
- Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med* 2017;377(18):1723-1732. <https://doi.org/10.1056/NEJMoa1702752>
- Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med* 2018;378(7):625-635. <https://doi.org/10.1056/NEJMoa1710504>
- Emeriaud G, López-Fernández YM, Iyer NP, Bembea MM, Agulnik A, Barbaro RP, et al. Executive Summary of the Second International Guidelines for the Diagnosis and Management of Pediatric Acute Respiratory Distress Syndrome (PALICC-2). *Pediatr Crit Care Med* 2023;24(2):143-168. <https://doi.org/10.1097/PCC.0000000000003147>
- Zhong ZJ, Zheng PM, Dou HH, Wang JG. Adverse events in the treatment of spinal muscular atrophy in children and adolescents with nusinersen: A systematic review and meta-analysis. *Front Pediatr* 2023;11:1152318. <https://doi.org/10.3389/fped.2023.1152318>
- Chacko A, Sly PD, Ware RS, Willoughby R, Rosenthal M, Waters KA. Effect of nusinersen on respiratory function in paediatric spinal muscular atrophy types 1-3. *Thorax* 2022;77(1):40-46. <https://doi.org/10.1136/thoraxjnl-2020-216564>
- Neil EE, Bisaccia EK. Nusinersen: A Novel Antisense Oligonucleotide for the Treatment of Spinal Muscular Atrophy. *J Pediatr Pharmacol Ther* 2019;24(3):194-203. <https://doi.org/10.5863/1551-6776-24.3.194>
- Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. *Respir Res* 2012;13(1):39. <https://doi.org/10.1186/1465-9921-13-39>
- Darras BT, Chiriboga CA, Iannaccone ST, Shieh PB, Montes J, Mignon L, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. *Neurology* 2019;92(21):e2492-e2506. <https://doi.org/10.1212/WNL.0000000000007527>
- Finkel RS, Chiriboga CA, Vajsaar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet* 2016;388(10063):3017-3026. [https://doi.org/10.1016/S0140-6736\(16\)31408-8](https://doi.org/10.1016/S0140-6736(16)31408-8)
- Hoy SM. Nusinersen: First Global Approval. *Drugs* 2017;77(4):473-479. <https://doi.org/10.1007/s40265-017-0711-7>