Respiratory Needs in Patients with Type 1 Spinal Muscular Atrophy Treated with Nusinersen

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Objective To evaluate the effects of nusinersen on respiratory function of patients with type 1 spinal muscular atrophy.

Study design Observational, longitudinal cohort study. We collected respiratory data from 118 children with type 1 spinal muscular atrophy and differing pulmonary requirements and conducted a semistructured qualitative interview among a subsample of caregivers at baseline, 6 months, and 10 months after the first nusinersen treatment. Patients were stratified according to ventilation modalities and age at study entry.

Results Most patients in our cohort remained stable (84/109 = 77%). More than 80% of the children treated before age 2 years survived, in contrast to the lower survival reported in natural history studies, and did so without tracheostomy or noninvasive ventilation (NIV) ≥16 hours. In those less than 2 years old, only 3 patients shifted from NIV ≤10 hours to NIV >10 hours, and the other 3 reduced the hours of NIV required. Most of the older patients remained stable; this included not only those on tracheostomy or NIV >10 hours but also 75% of those on NIV ≤10 hours.

Conclusions Our results suggest that nusinersen may produce some improvement in the progression of respiratory impairment, both in terms of survival and need for respiratory support ≥16 hours, especially before the age of 2 years. *(J Pediatr 2020;219:223-8)*.

Respiratory disease is a typical feature of type 1 spinal muscular atrophy (SMA), occurring at birth or, more frequently, in the first months of life.[1-3] Recent natural history studies show that even when respiratory management and ventilatory support are fully implemented according to standards of care, progressive decline of respiratory function always ensues.[4] By age 20 months, over 90% of the patients do not survive or need more than 16 hours of noninvasive ventilation (NIV).[5,6] Generally, even the few patients who survive beyond age 2 years without 16 hours ventilation/tracheostomy, will eventually show some pulmonary decline and only those who attained 200 mL vital capacity at any time in life (those with milder SMA 1C phenotype) retain some ability to breathe after 10 years of age.[7]

The advent of new therapeutic approaches may have a positive effect on not only survival but also respiratory status. Following 2 successful double-blind clinical trials in early onset and late onset SMA,[8,9] nusinersen has recently become commercially available. The data from the ENDEAR study of type 1 SMA, including infants enrolled before the age of 7 months, showed a significant increase in survival and an overall improvement of motor function in patients treated with nusinersen, compared with a sham procedure. These results focused on specific cohorts, without significant respiratory involvement. On the other hand, the nontrial experience data, obtained in several countries as part of the worldwide expanded access program (EAP),[10,11] also report an increase in survival and functional motor improvements,[10,11] but again, mainly

EAP	Expanded access program
IMV	Invasive mechanical ventilation
MIE	Mechanical in-exsufflator
NEMO	Neuromuscular omniservice
NIV	Noninvasive ventilation
SB	Spontaneous breathing
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
T0	Time point 0 (baseline)
T180	Time point 180 (180 days-6 months from initial infusion)
T300	Time point 300 (300 days-10 months from initial infusion)

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focused on motor function.[9-13] Overall, less has been reported on the impact of nusinersen on respiratory function,[8,9] particularly in those children with the most severe form of SMA.

We report here longitudinal respiratory data of a large cohort of patients followed as part of the EAP in Italy. This provided an opportunity to assess the efficacy of the drug in a real-world setting in a large number of patients with type 1 SMA, with a much wider range of age, severity, and survival motor neuron (*SMN*)*2* copy numbers than those selected for the ENDEAR study.[9] More specifically, we wished to establish whether the survival and respiratory data in the infants assessed below the age of 7 months (210 days) were consistent with the ENDEAR study, while extending our investigation to children treated at an older age, also in relation to severity or number of *SMN2* copies. We also aimed to establish, using dedicated patient reported questionnaires, whether possible respiratory changes were related to the caregiver's perception.

Methods

All the patients with type 1 SMA who participated in the EAP program with nusinersen from baseline to 300 days after first infusion (T300) were included for our analysis. Details of the EAP Italian experience have already been reported.[10,14] Intrathecal injections with nusinersen were administered on days 1, 15, 30, 60 (loading doses), and then every 4 months (maintenance doses). Institutional review board approval and parents' consents were obtained at each site. The design of the study and patient flow is shown in **Figure 1** (available at www.jpeds.com).

To stratify better this heterogeneous population, we used the decimal type 1 SMA classification suggested by Dubowitz (1995), deployed in our previous studies in this cohort[10,15]: 1.1 including the infants at the more severe end of the spectrum, with severely reduced mobility at birth and early respiratory and bulbar difficulties; 1.5 including those with the most common type 1 phenotype, with inability to raise the legs against gravity or maintain the head posture but having, at diagnosis, no difficulty with feeding and swallowing, and no obvious respiratory distress; and 1.9 the mildest phenotype, often diagnosed after the first few months, who achieve some head control and have less respiratory compromise. The number of *SMN2* copies was also registered, whenever available.

Patients were subjected to motor function tests (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP INTEND] scores) at baseline, after the loading dose and then every 4 months as previously described.[10] Lastly, the presence of feeding aids (namely a nasogastric tube or a percutaneous endoscopic gastrostomy) was also registered.

Respiratory Intervention and Monitoring

NIV indication and any other ventilatory intervention (including the introduction of the mechanical in-exsufflator [MIE]) was based on standards of care for SMA[4] and was provided by pulmonologists and respiratory therapists with experience in SMA at each site. Respiratory assessments included physical examination, gas exchange assessments, sleep studies, and number of respiratory infections at baseline and each follow-up visit. When gas exchange and nocturnal oximetry suggested inadequate ventilation or increased work of breathing, pulmonologists and therapists modified the ventilator requirements according to standards of care[4] and patient and family choices.[2] This was discussed as part of a multidisciplinary team, including neurologists and child neurologists. Invasive mechanical ventilation (IMV) was an option in selected patients in whom NIV was insufficient or failed or there was no effective interface to allow appropriate gas exchange.[4]

Our sample was then stratified based upon the modality (spontaneous breathing [SB], NIV, and NIV plus IMV) as well as the number of hours of ventilation required. We arbitrarily chose NIV ≤10 hours/day as this would include patients in whom NIV is used mostly during nocturnal sleep. In contrast, 16 hours/day is commonly an indicator of a prolonged need for ventilation. The need and prescription of MIE was also registered.

Respiratory assessments were performed at baseline, prior to the first nusinersen infusion (T0) and repeated at 6 (T180) and at 10 months (T300) from treatment. Respiratory assessments are detailed in **Table I**.

Qualitative Interviews

Parent/Caregiver Reported Questionnaires. A questionnaire was developed and administered to parents or primary caregivers to identify their perception on whether there had been any change that was clinically meaningful to them after 1 year of treatment. Parents or caregivers were asked to report whether they felt their child's general function had (1) remained stable; (2) improved; or (3) deteriorated. If they did report on an improvement or a deterioration, parents had to clarify whether this was mainly related to (1) respiratory function; (2) motor function; or (3) swallowing and speech. Additional respiratory items addressed in the semi-structured ad hoc questionnaire are provided in **Table II** (available at www.jpeds.com).

Statistical Analyses

Data were described using mean and SD, median, and IQR, absolute number, and percentage. Descriptive analyses were performed through frequency analysis, in detail studying the frequency distribution using both numbers and percentages with graphic representations, and the central tendency of distribution, using mean ± SD and median (IQR) as appropriate. Our sample was divided according to the modality of ventilation, and each group was stratified into subgroups on

Table I. Respiratory assessments performed at baseline, at T180, and at T300

Ventilatory status assessment and stratification	(1) SB (2) NIV (3) IMV (tracheostomy)
Daytime monitoring	Hours of ventilation/d Oxygen supplementation
Ventilatory support	Ventilator settings and parameters H of ventilation recorded/d
Respiratory Infections	Number of respiratory tract infections requiring hospitalization or antibiotic treatment in the 3 mo prior to nusinersen treatment

the bases of age at evaluation. Analyses were conducted using SAS v 9.3 software (SAS Institute, Cary, North Carolina).

Results

One hundred eighteen patients had their first infusion successfully performed at baseline (median age 42.8 months; IQR 11.0-102.8 months). Four patients died, and another 6 withdrew their participation before the tenth month, either because of difficulties related to the administration procedure, or because the effects of treatment were not as evident as expected. Five had to be re-directed to local centers in Italy for the treatment and were, therefore, considered lost to follow-up because it was not possible to ascertain the uniformity of standards of care and/or monitoring at these other sites. However, by means of telephone calls between the pulmonologists of our and other centers, we managed to collect data concerning the current type of ventilatory support of those 5.

Using the decimal classification already mentioned, out of the 118 patients, 12 could be classified as SMA 1.1; 65 as SMA 1.5, and 38 as SMA 1.9. As for the remaining 3, who were referred to us after the third month of life, previous clinical information on the first months were ambiguous and these infants were not classified (**Figure 2**; available at www.jpeds.com). Regarding the *SMN2* copy number, 3 had only 1 *SMN2* copy, 82 had 2 copies, 27 had 3, and 2 had 4 copies. It was not possible to obtain the number of *SMN2* copies for 4 children. Further clinical, genetic, and demographic data of this cohort are presented in **Table III** (available at www.jpeds.com).

Respiratory Status at Baseline and Over Time

Patients were stratified based on the modality and hours of ventilation into the following cohorts: (1) SB, (2) NIV for a maximum of 10 hours/day, (3) NIV for more than 10 hours, and (4) IMV with tracheotomy. In particular, the group using NIV ≤10 hours/day included both patients who used it for a few hours/day for prophylactic purposes[16] and those who only required it during sleep.

Nine of 21 patients on SB on first nusinersen administration were still on SB at T300 (42.9%). Eighteen of 24 using NIV ≤10 hours/day remained stable (75%); 15 of 22 patients who used NIV >10 hours/day remained stable (68.2%). None of the patients on IMV could remove the cannula and switch to NIV. Three children improved their respiratory status from T0 to T300 (**Table IV**). **Figure 3** (available at www.jpeds.com) shows the number of patients who remained stable, improved, worsened, or died over time. In regards to the prescription of MIE, at baseline 101 (85.6%) of children had already initiated use of this assistive aid; 100% of patients on IMV were already using this device. At T300, data from 106 of the initial 118 patients were collected and, out of these, only 3 patients (2.8%) still had not initiated MIE, all of them not belonging to the most severe end of the spectrum. Changes in individual patients at T0, T180, and T300 stratified by age at enrollment are presented in detail below and summarized in **Figure 4** (available at www.jpeds.com).

At baseline age below 7 months, 9 of the 12 children were on SB, 2 were on NIV ≤10 hours/day, 1 on NIV >10 (but <16) hours/day, and none was on IMV. At T300 (age range: 12.3 months; median age: 13.8 months; IQR = 13.1; 14.9 months) 10 out of the 12 children survived, with 3 of the 10 still with SB, 3 on NIV ≤10 hours/day, and 3 on NIV >10 hours/day (with 2 requiring NIV <16 hours/day). One patient required IMV at T180. In the children <7 months of age at baseline, none improved, 3 remained stable (25.0%), and 7 (58.3%) required further ventilatory assistance, and 2 (16.7%) died.

Table IV. Respiratory status at baseline and over time

Baseline data	T0	Lost to follow-up	T0	Worsened or died at T300	Stable at T300	Improved at T300
SB, n (%)	22 (18.64)	1	21 (19.27)	12 (57.14)	9 (42.86)	0 (0.00)
NIV ≤10 h/d, n (%)	26 (22.03)	2	24 (22.02)	6 (25.00)	18 (75.00)	0 (0.00)
NIV >10 h/d, n (%)	24 (20.34)	2	22 (20.18)	4 (18.18)	15 (68.18)	3 (13.64)
Invasive ventilation, n (%)	46 (38.98)	4	42 (38.53)	0 (0.00)	42 (100.00)	0 (0.00)

Table V. Respiratory infections occurrence at T0, T180, and T300, in the population as a whole and in the different subgroups, stratified per ventilatory support

Patient poulation	Baseline (T0)	6th mo (T180)	10th mo (T300)	*P* (T300-T0)
Total population (%)	118 (100.0)	109 (100.0)	103 (100.0)	
Total population reporting infection(s) (%)*	39 (33.1)	40 (36.7)	39 (37.9)	>.05
Number patients on SB (%)	22 (18.6)	10 (9.2)	9 (8.7)	
Patients on SB reporting infection(s) (%)*	6 (27.3)	3 (30.0)	1 (11.1)	>.05
Number patients on NIV (%)	50 (42.4)	52 (47.7)	50 (48.5)	
Patients on NIV reporting infection(s) (%)*	20 (40.0)	21 (40.4)	23 (46.0)	>.05
Number patients on IMV (%)	46 (39.0)	47 (43.1)	44 (42.7)	
Patients on IMV reporting infection(s) (%)*	13 (28.3)	16 (34.0)	15 (34.1)	>.05

*Respiratory infection defined as any respiratory infection occuring in the previous 3 months prior to assessment and requiring antibiotics or hospitalization.

At baseline age between 7 and 24 months, 11 of the 32 children were with SB, 4 were on NIV ≤10 hours/day, and 9 on NIV >10 hours/day (with 6 requiring NIV <16 hours/day), and 8 were on IMV. At T300 (age range 17.2-34.0 months; median age: 20.5 months; IQR 18.7; 24.3 months), 5 were still on SB, 9 on NIV ≤10 hours/day, and 6 on NIV >10 hours/day (with 5 on NIV <16 hours/day), and 10 required IMV. Three patients in this age group had a reduction of required hours of NIV from more than 10 to 10 or less hours/day. In this age group, 4 (12.5%) improved, 20 remained stable (62.5%), and 6 (18.8%) required further ventilatory assistance, and 1 child (3.1%) died and 1 (3.1%) was lost to follow-up.

Among those at baseline age between 24 months and 5 years, 2 of the 24 children of age between 24 months and 5 years were with SB, 6 on NIV ≤10 hours/day, and 6 on NIV >10 hours/day (all of them <16 hours/day); 10 required IMV. At T300 (age range 35.1-71.3 months; median age: 46.5 months; IQR 38.1; 55.6 months), 1 child was still with SB, 7 were on NIV ≤10 hours/day, and 5 on NIV >10 hours/day (all of them <16 hours/day), and 10 required IMV; 1 child died. One patient in this age group had a reduction of required hours of NIV from more than 10 to 10 or less hours/day. In this age group, 1 child (4.2%) improved, 20 remained stable (83.3%), 2 (8.3%) required further ventilatory assistance, and 1 died (4.2%).

For those at baseline age of 5 up to 10 years, none of the 29 children was with SB, 10 were on NIV ≤10 hours/day, and 5 required NIV >10 hours/day (with 4 requiring NIV <16 hours/day), and 14 had a tracheostomy. At T300 (age range 5.6-10.6 years; median: 7.7 years; IQR 6.3-9.3), no patient was with SB, 7 were on NIV ≤ 10 hours/day, and 6 on NIV >10 hours/day (with 4 requiring NIV<16 hours/day). No additional tracheostomies were required. In this age group, none improved nor died, 24 remained stable (82.8%), 2 (6.9%) required further ventilatory assistance, and 3 (10.3%) were considered lost to follow-up.

Among the 21 children at baseline age of 10 years or greater, none of the children were with SB; 4 were on NIV ≤10 hours/day, 3 on NIV >10 hours/day (with 2 requiring NIV <16 hours/day), and the remaining 14 on IMV. At T300 (age range 11.0-16.7 years; median: 12.6 years; IQR 12.0-13.3 years), 3 were on NIV ≤10 hours/day, 2 on NIV >10 hours/day (with 1 requiring NIV ≥16 hours/day), and 11 on IMV. The remaining 5 were lost at follow-up. In this age group, none improved, worsened, or died, 16 remained stable (76.2%), and the remaining 5 (23.8%) were considered lost to follow-up.

Correlation of Respiratory Health with Gross Motor Function

Motor response to nusinersen treatment has already been found to be clinically relevant in patients with less severe SMA,[10] yet with some degrees of variability within the same age group and decimal type. Figure 4 illustrates the gross motor function trajectory for each patient, compared with the respiratory course. Besides the evident differences of improvement in these 2 areas, it can also be observed that although the majority of those who worsened from the respiratory point of view belonged to the youngest age groups, those who did so in the gross motor area were more evenly distributed.

Correlation of Respiratory Health with Nutritional Status

At baseline, 12 (10.2%) and 64 (54.2%) of children were fed, respectively, via nasogastric tube or percutaneous endoscopic gastrostomy; quite expectedly, 100% of patients on IMV were fed by either one of these modalities. At T300, data from 105 of the initial 118 patients could be collected and 6 (5.7%) and 69 (65.7%) patients were fed, respectively, via nasogastric tube or gastrostomy. None of those who retained the ability to feed independently exhibited a severe phenotype.

Qualitative Interviews–Parents-Proxy Perceptions

Results from 46 parent interviews at T300 are presented in Figure 5 (available at www.jpeds.com). A general improvement was reported by three-quarters of parents/caregivers. From a respiratory point of view, an improvement was noted in 37%, with over 50% reporting stability and less than 10% a worsening. In those who reported an improvement, this was mainly accounted for by the rate of infections, although no objective statistical difference in the infection rate could be appreciated from baseline, as evidenced in Table IV and Table V, which describe the number of respiratory infection events according to mode of ventilation at baseline and over time.

Discussion

Longitudinal natural history data on respiratory function in type 1 SMA are scanty, as until recently most studies focused on survival or time to respiratory event (ie, tracheostomy or ventilation >16 hours). In the last decade, 2 natural history studies, reflecting data collected after care recommendations had become available,[17] showed limited survival in the first 2 years of life.[5,6,18] Only a few studies reported respiratory data, especially in cohorts including older patients with type 1 SMA[5,18] or subdivided according to respiratory criteria (IMV, NIV, untreated). The baseline findings in our cohort, obtained at different ages are in line with previous observations that the majority of the patients who survive after the age of 2 years are on NIV >16 hours or have a tracheostomy, require assistance with airway clearance (usually in the form of MIE), and are not able to feed safely independently, thus, requiring either nasogastric or gastrostomy feeding. Few exceptions, however, can be observed, generally in patients with milder forms and 3 *SMN2* copies.[5]

The results of the pivotal ENDEAR study[9] suggest that nusinersen can increase survival in patients treated before 7 months of age. Although the results are not entirely comparable because our data endpoint is at day 300, we also found that in the youngest patients, who started nusinersen before 7 months of age, survival was increased compared with natural history data. Only 2 of the 12 patients younger than 7 months of age died, and 1 had a tracheostomy. When we looked at the survival in patients who were younger than 2 years at baseline and reached the age of 2 years at T300, only 3 of 43 (6.98%) died and 5 additional patients required ventilatory support for more than 10 hours, with a survival of over 80%, as opposed to the estimated survival of 8% that has been reported for untreated patients older than 20 months.[5,6]

Three patients younger than 2 years of age were able to reduce the need of ventilator support from more than 10 to less than 10 hours of NIV/day after 6 (n = 1) and 10 months from treatment (n = 2). All 3 patients were SMA 1.5, and 2 additional ones who also improved were SMA 1.9. None of the patients with SMA 1.1 improved. Although it could be argued that the improvement seen could have been determined by a better stabilization of the clinical condition, possibly because of a more consistent application of the standards of care, we cannot rule out that, in addition to a better proactive respiratory management, there may be a beneficial effect of the pharmacologic treatment alone. On the other hand, the 12 children with SMA 1.1 were weaker at baseline and respiratory improvement could not be demonstrated, perhaps in part because of the level of support they required at baseline. A similar variability of response, was reported for gross motor function,[10] both in terms of clinical phenotype and age at baseline (**Table III**) and was also observed for the feeding function requirements. When we look at the respiratory status at enrollment, it is of interest that of the patients on SB at baseline, 42.9% were still on SB after 10 months, and this included some older patients (age range at T300, 12.5-39.0 months) with SMA type 1.5 or 1.9.

No objective respiratory changes could be observed in the more chronic patients having a tracheostomy or who had been on NIV for many years, although on the qualitative interviews, one-third of the families of patients on tracheostomy or on NIV for many years reported a respiratory improvement. In general, the fact that the stability was perceived as a subjective improvement, is in line with results from a recent large survey[19] reporting that most patients with SMA (81.3%) would be satisfied with a drug, which would stabilize their condition, including respiratory function.

Our results suggest that the use of nusinersen seems to produce some improvement on the progression of the respiratory impairment, in terms of both survival and need for respiratory support ≥16 hours in patients treated before the age of 2 years. The observation that a limited number of patients showed a reduction in the number of hours on NIV is promising and appears unexpected in infants with type 1 SMA; its value, however, cannot be easily interpreted as there are no systematic respiratory longitudinal data for comparison.

The lack of natural history data in the older groups (≥24 months old at baseline) makes the interpretation of the data difficult. In general, little or no changes were registered among those patients characterized by a more severe respiratory involvement and most requiring either IMV or NIV >10 hours/day since baseline.

On the other hand, the progression in those with less severe impairment (and a limited use of NIV) showed less decline of what we would have expected on the basis of the few data available[20] and of personal experience: although it is expected that about 10% of children with type 1 SMA will not develop respiratory failure, thus, necessitating NIV or IMV, until after the 24th month of life, this applied to more than 17% of our population.

Although these results appear to be encouraging, there are several limitations that need to be considered. Particularly, modality and hours of ventilation may not be the best surrogate for respiratory function as they are highly dependent on proactive respiratory care and management, including specialists' experience, timing of NIV launching and its proper setting, cough assistance maneuvers, and machines.[2,4] Although all the centers participating reporting data in this study had similar protocols of care, we cannot exclude that some of these factors, as well as patients' overall status, compliance, and their families' attitude may confound distinguishing between the exclusive effect of the drug and the influence of the respiratory care. Furthermore, it may be argued that the overall stability and the few cases of improvement observed in this study may, at least in part, be due to the fact that a number of patients started treatment as part of their pathway of care at one of the tertiary sites involved in the EAP, where experience with SMA possibly resulted in better compliance with the standards of care. Another point is that our results may not be reproducible in other countries with more limited resources or in more peripheral clinical sites, where there still may be a need to implement standards of care and in which expertise in SMA may still be limited. Lastly, families who

decide to opt for treatment are also more likely to become more pro-active in the use of NIV and cough machine. Larger studies including data from different countries will help to establish better the value of our data.

Overall, our study emphasizes the importance and range of ventilatory support in SMA, especially in the most severe forms, and calibrates family and providers to adhere to standards of care. Children with SMA are vulnerable and optimizing support will allow them to achieve maximum benefit from nusinersen or any other treatment. It is also important to consider that, similarly to the variable motor response here observed and reported by Pane et al,[10] the variability in more complex functions (ie, breathing) is to be expected and should be accounted for during counseling. As neonatal screening for SMA moves forward, future studies will be able to focus on larger homogeneous populations with SB at outset to assess clearly the effects of the drug and to be able to discriminate the potential contribution of mechanical ventilation to respiratory measures and clinical outcome. ■

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Appendix

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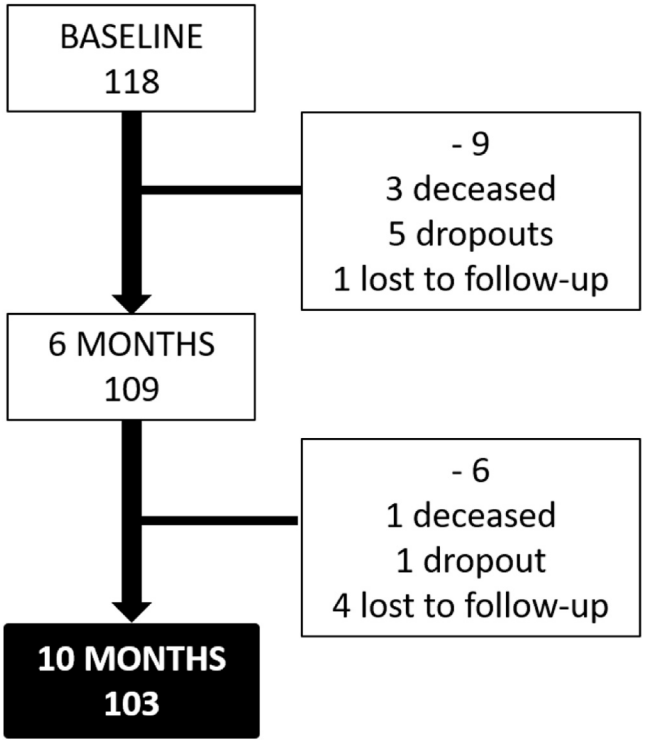

Figure 1. Patient flow from baseline to T300.

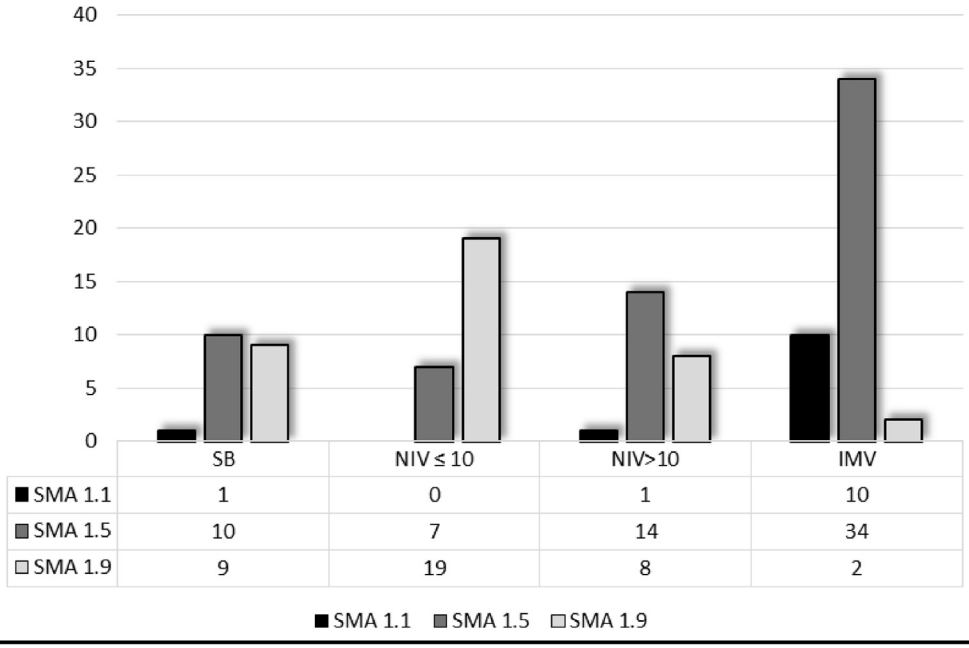

Figure 2. Patient respiratory characteristics at baseline according to SMA type.

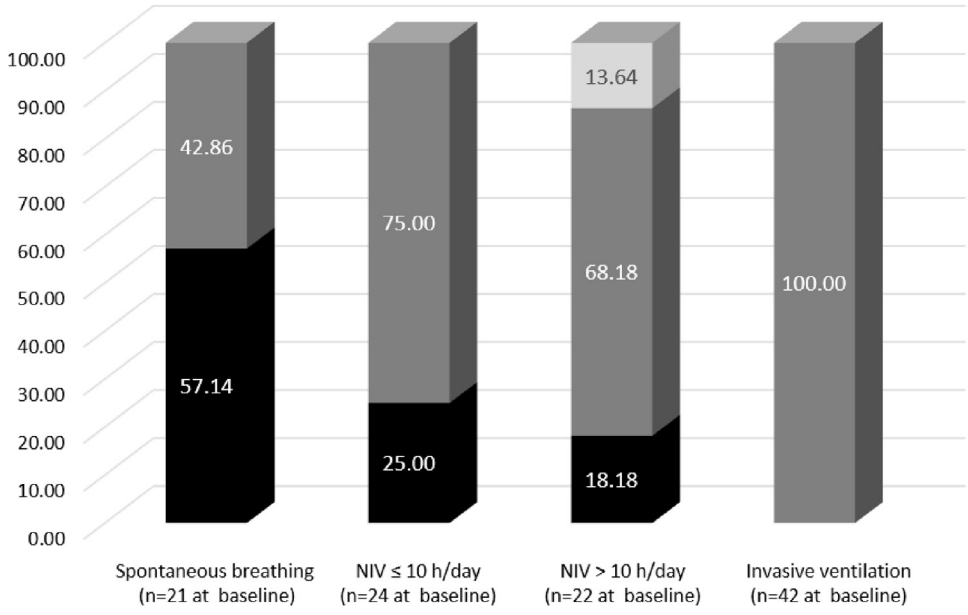

Figure 3. Summary of patients who remained stable, improved, worsened, or died over time.

Age at baseline	SMA		BASELINE (T0)	10th MONTH (T300)
<7 months	1.1	R	Δ	†
		M	15[1]	†
	1.5	R	Δ° Δ° ○ Δ° Δ° Δ° Δ ●	† ○° ● ○ ● ○ Δ ϕ
		M	22 14 21 23 17 27 42[2] 37[1]	† . . 50[1] 34[2] 45[2] 56[2] 40[2]
	1.9	R	○° Δ°	● Δ°
		M	33 24	45[1] 55
	n/a	R	Δ°	Δ
		M	.	.
≥7 months; <24 months	1.1	R	● ϕ ϕ ϕ ϕ ϕ	ϕ ϕ ϕ ϕ ϕ ϕ
		M	13[1] 5[2] 5[2] 7[2] 5[2] 0[2]	12[2] 0[2] 11[2] 6[2] .[2] .[2]
	1.5	R	Δ° ● Δ ● ● Δ ϕ ϕ ○ ○ ϕ ● ● ● Δ°	† ϕ ϕ ● ● Δ ϕ ϕ ○ ○ ϕ ● ○ ○ L
		M	12 32 19[2] 15[1] 14[1] 6[2] 4[2] 14[2] 27 22[2] 5[1] 14 16 16 26	† 51 18[2] 7[2] .[1] 7[2] 13[2] .[2] . 35[2] 7[2] . 28 44 L
	1.9	R	Δ° Δ° Δ ○ ○ Δ° Δ° Δ ●	○ ○ ● ● ○ Δ Δ Δ ○
		M	31 32 52 38[1] 39 44 40 29[1] 36	47 41 64 .[1] 54 53 . .[2] 47
	n/a	R	●° Δ°	●° Δ
		M	29 31	36 .
≥24 months; <5 years	1.1	R	ϕ ϕ ϕ	ϕ ϕ ϕ
		M	7[1] 1[2] 0[2]	.[1] 1[2] .[2]
	1.5	R	● ϕ ϕ ○ ● ϕ ϕ ϕ ϕ ●	† ϕ ϕ ○ ● ϕ ϕ ϕ ϕ ●
		M	5[1] 1[2] 4[2] 16[1] 17 13[2] 20[2] 14[2] 1[2] 12[2]	† 3[2] 3[2] . . 15[2] .[2] 17[2] 1[2] 10[2]
	1.9	R	Δ ○ ○ ○ Δ ϕ ● ● ● ○ ○	○ ○ ○ ○ Δ ϕ ● ● ● ○ ○
		M	43 35 15 21[2] 42 1[2] 5[2] 28[2] 17[2] 23 28	46 39 17 26[2] 47 2[2] 10[2] 35[2] 19[2] . 33
≥5 years; <10 years	1.1	R	ϕ ϕ	ϕ ϕ
		M	8[2] 0[2]	7[2] 0[2]
	1.5	R	○ ● ϕ ϕ ϕ ϕ ϕ ϕ ● ϕ ϕ ϕ ϕ ● ○ ϕ ϕ	● ● ϕ ϕ ϕ ϕ ϕ ϕ ● ϕ ϕ ϕ ϕ ● ○ ϕ L
		M	12[2] 3[2] 7[2] 0[2] 3[2] 3[2] 3[1] 3[2] 7[2] 12[2] 3[2] 0[2] 0[2] 1[2] 6[2] 0[2] 0[2]	14[2] .[2] 8[2] 1[2] 4[2] 5[2] 3[1] .[2] .[2] 6[2] 1[2] 0[2] .[2] 0[2] 6[2] .[2] L[2]
	1.9	R	○ ○ ○ ○ ● ○ ○ ○ ● ○	● ○ ○ ○ ● ○ ○ ○ L L
		M	24 43[2] 18 30 31[2] 32 19 18[2] 22[2] 36	31 .[2] 23[1] 32 .[2] 31 28 0[2] L[2] L
≥10 years	1.5	R	ϕ ○ ϕ ϕ ϕ ϕ ϕ ϕ ϕ ϕ ϕ ● ϕ ϕ ϕ	ϕ ○ ϕ ϕ ϕ ϕ ϕ ϕ ϕ ϕ ϕ ● L L L
		M	5[2] 3 2[2] 0[2] 3[2] 2[2] 2[2] 0[2] 7[2] 10[2] 7[2] 2[2] 2[2] 0[2] 0[2]	9[2] 3 3[2] 0[2] 4[2] 9[2] 8[2] 1[2] 7[2] .[2] .[2] 5[2] L[2] L[2] L[2]
	1.9	R	○ ● ϕ ○ ○ ●	○ ● ϕ ○ L L
		M	33 8[2] 4[2] 26[2] 18 6	. 5[2] 6[2] 1[2] L L

Figure 4. Respiratory (R) and motor (M) statuses at baseline and over time. Improvements at T180 and T300 are highlighted in *green*, worsening in *red*, stability in *gray* and deaths in *black*. CHOP-INTEND scores are provided for each patient. Δ, Spontaneous Breathing, SB; ○, NIV ≤10 hours/day; ●, NIV ≥ 10 hours/day; ϕ, IMV; †, deceased; L, not available, lost to follow-up; ., not evaluated; °, not using Mechanical In-Exsufflator (MIE); [1], feeding via nasogastric tube (SNG); [2], feeding via percutaneous endoscopic gastrostomy.

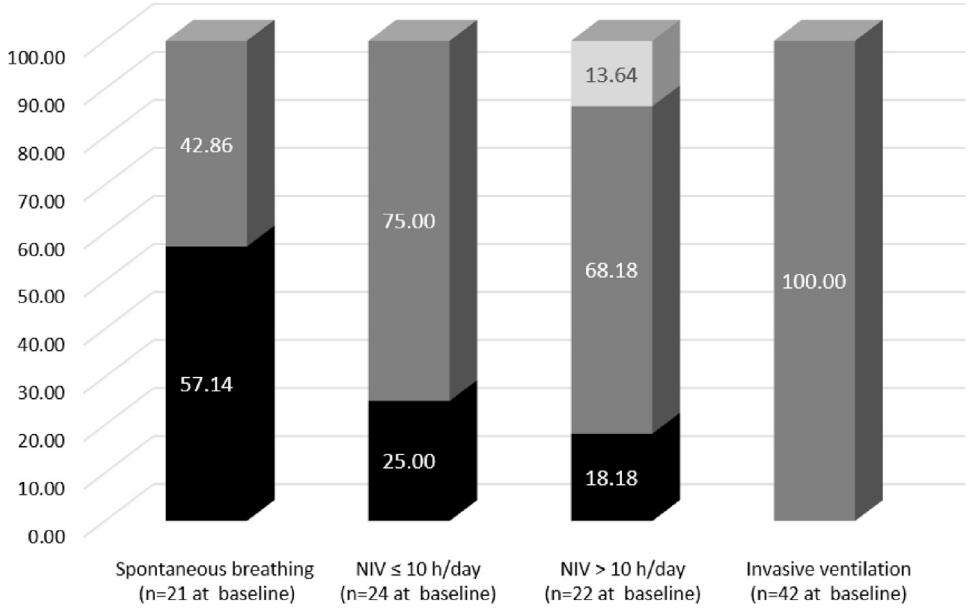

Figure 5. Subjective perception as resulting from parent-proxy interview vs objective data. Numbers are expressed as percentages (%).

Table II. Qualitative interviews–respiratory questions

(1) In the last month, did your child have a respiratory tract infection requiring antibiotic treatment?
☐ YES. Please indicate how many……..
☐ NO
(2) In the last month, did you have to take your child to the emergency department or have him/her admitted to hospital for an acute respiratory event?
☐ YES. Please indicate what the reason was for hospital admission……..
☐ NO
(3) In the last month, did you have to increase the number of hours of ventilation or the number of times your child required cough assistance?
☐ YES. Please indicate how many times you had to use cough assisted devices……
Please indicate how many additional hours of ventilation had to be implemented
☐ NO
(4) In the last month, did you have to increase the number of secretion aspirations/day for your child?
☐ YES.
Did this occur during an acute respiratory event? YES / NO
☐ NO

Table III. Clinical, genetic, and demographic data of the whole cohort at baseline

Baseline data	n (%)
Total population	118 (100)
Sex	
Female	62 (52.5)
Male	56 (47.5)
SMN2 copy number	
1 *SMN2*	3 (2.5)
2 *SMN2*	82 (69.5)
3 *SMN2*	27 (22.9)
4 *SMN2*	2 (1.7)
not assessed	4 (3.4)
Decimal classification	
SMA 1.1	12 (10.2)
SMA 1.5	65 (55.1)
SMA 1.9	38 (32.2)
not assessed	3 (2.5)
ABC classification	
SMA 1	14 (11.9)
SMA 1B	66 (55.9)
SMA 1C	35 (29.7)
not assessed	3 (2.5)
Clinical features	
MIE	101 (85.6)
Nasogastric feeding	12 (10.2)
Gastrostomy feeding	64 (54.2)