

Sitting in patients with spinal muscular atrophy type 1 treated with nusinersen

KAROLINA ARAGON-GAWINSKA^{1,2}  | AURORE DARON³ | ANA ULINICI³ | LAURA VANDEN BRANDE¹ | ANDREEA SEFERIAN¹ | TERESA GIDARO¹ | MARIACRISTINA SCOTO⁴ | NICOLAS DECONINCK^{5,6} | LAURENT SERVAIS^{1,3}  | SMA-REGISTRY STUDY GROUP*

1 Institute I-motion, Armand Trousseau Hospital, Paris, France. **2** Department of Neurology, Warsaw Medical University, Warsaw, Poland. **3** Neuromuscular Reference Centre, Citadelle Hospital, Liege, Belgium. **4** Neuromuscular Centre UCL Great Ormond Street Institute of Child Health, London, UK. **5** Department of Paediatric Neurology and Neuromuscular Centre, Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), ULB, Brussels; **6** Department of Paediatric Neurology, Neuromuscular Reference Centre, UZ Gent, Ghent, Belgium.

Correspondence to Laurent Servais at Centre de Référence liégeois des Maladies Neuromusculaires, Centre Hospitalier Régional de la Citadelle, Boulevard du 12ème de Ligne 1, 4000 Liège, Belgium. E-mail: lservais@chuliege.be

*Members of the SMA-Registry Study Group are listed in the Acknowledgements.

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ABBREVIATIONS

CHOP-	Children's Hospital of
INTEND	Philadelphia Infant Test of Neuromuscular Disorders
HINE-2	Hammersmith Infant Neurological Examination, Section 2
SMA1	Spinal muscular atrophy type 1
SMN	Survival motor neuron

AIM To determine factors associated with acquisition of a sitting position in patients with spinal muscular atrophy type 1 (SMA1) treated with nusinersen.

METHOD Using data from the registry of patients with SMA1 treated with nusinersen, we compared the subgroups of sitters and non-sitters after 14 months of therapy as a function of baseline level, *SMN2* copy number, age at treatment initiation, and improvement at 2 and 6 months post-treatment initiation. We used Hammersmith Infant Neurological Examination, Section 2 (HINE-2) and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders for motor evaluation.

RESULTS Fifty children (22 females, 28 males), mean age 22 months (SD 20.7; range 2.5–102.8mo) were treated. Data on sitting position acquisition were collected for 47 patients at month 14. Fifteen patients were able to sit unassisted; 11 of 15 had a baseline HINE-2 score of at least 2 points and 11 of 14 had an improvement over baseline of at least 2 points at month 6. Patients who improved by 2 or more points at month 6 were three times more likely to be sitters at month 14 than those who did not.

INTERPRETATION High baseline motor function and improvement in HINE-2 score after 6 months of treatment are associated with the probability of acquiring a sitting position in patients with SMA1 treated with nusinersen.

Spinal muscular atrophy type 1 (SMA1) is the most common genetic cause of infant mortality. SMA1 is caused by a homozygous deletion of the *SMN1* gene, which encodes the protein called survival motor neuron (SMN).¹ Symptoms are observed within the first 6 months of life and include global hypotonia and severe muscle weakness.² Patients do not acquire a stable sitting position and only some achieve head control.^{2–4} Patients usually have two or three copies of the pseudogene *SMN2*.^{3,4} Patients with three *SMN2* copies usually have later onset of symptoms and have prolonged survival relative to those with fewer copies.^{3,4}

Nusinersen is an intrathecally injected antisense oligonucleotide approved for treatment of SMA1. The only identified positive prognostic factor of treatment response is initiation of the therapy soon after the onset of symptoms, but patient prognosis remains difficult to predict.^{5–9} Given the high cost of the drug and patient burdens related to

intrathecal injection,⁷ early identification of likely responders is necessary.

To date, patient response has been reported in terms of survival and improvement on motor scales, such as the Hammersmith Infant Neurological Examination, Section 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). HINE-2 is a motor milestone test that assesses eight items: head control, sitting, voluntary grasp, ability to kick, ability to roll, ability to crawl, ability to stand, and ability to walk. The maximum score on the HINE-2 is 26 points. The scale is simple to implement and has been used in a number of SMA clinical trials and reports, with the exclusion of the voluntary grasp section.^{5–7,10} CHOP-INTEND is a 16-item motor scale with each item scored from 0 to 4 points. CHOP-INTEND is a reliable and validated tool of assessment of patients with SMA1.^{11,12} Acquisition of important milestones, such as ability to sit

unassisted or ambulation, is more meaningful to parents and health service providers than a change on a motor scale. In the Phase 3 study of nusinersen, 8% of 73 treated patients were able to sit independently at the end of the study,⁵ but factors that distinguish these patients from the other treated participants have not been identified. We evaluated a cohort of patients with SMA1 treated with nusinersen to identify factors that are predictive of acquisition of the sitting position at 14 months after initiation of treatment.

METHOD

Participants

We analysed data of patients with SMA1 treated with nusinersen in three centres: Paris (France) and Liege and Gent (Belgium). The first patients were treated in October 2016. All patients had clinically and genetically confirmed diagnoses and were treated with the accepted standard of care in addition to nusinersen. All data are part of European Registry of Patients with Infantile-onset Spinal Muscular Atrophy (trial no. NCT03339830), which was accepted by the local ethical committee (Comité de Protection des Personnes) Ile de France 3 (3539-NI). According to French law, patients and representatives were informed of data collection and were given the opportunity to drop out. They gave written consent for biological data collection.

Study design

Nusinersen was administered as previously reported.⁵ Data were collected at the following time points: before treatment (month 0), after 2 months of treatment (month 2, end of the loading dose), and after months 6, 10, and 14 of treatment. Patients were assessed using HINE-2, excluding voluntary grasp,⁵ and CHOP-INTEND. A stable sitting position was defined as sitting for at least 30 seconds without support, and patients who scored 3 ('stable sit') or 4 points ('pivots', which indicates that the patient can rotate while in sitting position) in the sitting section of HINE-2 scale were classified as 'sitters'.

Statistical analysis

All statistical analyses were performed with SPSS software, version 22 (IBM Corp., Armonk, NY, USA). Differences between sitters and non-sitters were assessed using the Mann–Whitney *U* test and χ^2 tests for quantitative and qualitative variables respectively. Missing data were not taken into account.

RESULTS

Of 53 patients included in the study, 47 completed 14 months of treatment and sitting status was known. Two patients died: one after five injections (month 6) and one after six injections (month 10); in both cases death was due to respiratory failure unrelated to treatment. One patient was withdrawn from the treatment after the loading dose (month 2) because of lack of motor gain and respiratory

What this paper adds

- Fifteen of 47 patients with spinal muscular atrophy could sit unaided 14 months after treatment with nusinersen.
- The number of *SMN2* copies were not predictive of acquisition of a sitting position.
- Baseline condition and clinical response after 6 months of treatment were most predictive of sitting position acquisition.

degradation. HINE-2 scores were obtained for 52 patients at baseline for 51 patients at month 2, 49 at month 6, 50 at month 10, and 47 at month 14. CHOP-INTEND results were obtained for 36 patients at baseline, 35 at month 2, 31 at month 6, 33 at month 10, and 30 at month 14. After month 14 month of treatment 15 of 47 patients were able to sit independently. Five patients were able to sit after only 6 months of treatment. The median age at first symptoms, age at the start of the treatment (and, therefore, disease duration before treatment), and number of *SMN2* copies were similar in both sitters and non-sitters, and there was no statistically significant difference between the two groups in those categories (Table S1, online supporting information). Table 1 shows baseline characteristics of our cohort compared to those of the patients enrolled in the Phase 3 trial and other open-label studies.

Sitters had statistically significantly higher baseline scores in HINE-2 (2 vs 1, $p < 0.01$) and CHOP-INTEND (35.5 vs 26.5, $p < 0.05$) and larger changes in the median HINE-2 score after 6 months of treatment than non-sitters (3 vs 1, $p < 0.05$, Table S1, Fig. 1). We found that a high baseline score was associated with an increased probability of acquisition of the sitting position. Patients with an initial HINE-2 score of greater than or equal to 2 had a three-fold higher likelihood of being able to sit than those patients with lower HINE-2 scores (relative risk 3, 95% confidence interval [CI] 1.1–8.1; odds ratio [OR] 5, 95% CI 2.1–8.7). We found similar correlations between the magnitude of change in HINE-2 score and acquisition of the sitting position. This relationship was more robust for the difference between baseline and month 6 than for the difference between baseline and month 2 (Table S1, Fig. 1). The frequency of sitters was three-fold higher in the group that gained 2 or more points in HINE-2 score at month 6 relative to baseline than in the group without this gain (relative risk 3.06, 95% CI 1.0–9.5; OR 4.8, 95% CI 2.1–6.9). Patients with both an initial HINE-2 score greater than or equal to 2 and a gain of 2 or more points in HINE-2 score at month 6 had a three-fold higher probability of becoming sitters than the remaining patients (relative risk 4.29, 95% CI 1.8–10.4; OR 11.7, 95% CI 2.1–29.7).

DISCUSSION

We found that high baseline motor function and improvement in HINE-2 score by more than 2 points after 6 months were positive predictive factors for the acquisition of a sitting position in patients with SMA1 treated with nusinersen. Previously, the only positive predictive factor of nusinersen treatment efficacy in SMA1 was the time between symptom onset and treatment initiation.^{5,6}

Table 1: Baseline characteristics of patients with spinal muscular atrophy (SMA1) treated with nusinersen in our cohort and in recent studies

	Present study					Australia ⁷	
	Sitters (n=15)	Non-sitters (n=32)	ENDEAR ⁵ (n=73)	Italy ⁸ (n=104)	Germany ⁶ (n=61)	New (n=8) ^a	Chronic (n=8) ^b
Age at initiation treatment initiation	21.9mo	23.3mo	5.4mo ^c	0–19y	21.08mo	7.5mo	102.4mo
≤2 <i>SMN2</i> copies, %	53	62	100	65	62	50	25
Respiratory support, %	20 (NIV)	50 (44 NIV/6 IV)	26 (NIV)	50 (IV) ^d	58 (28 NIV/30 IV)	None	88 (NIV)
Nutritional support, %	13 (PEG)	22 (9 NG/13 PEG)	9 (NG)	NR	56 (NG and PEG)	None	75 (PEG)
HINE-2 score	3.07	1.23	1.29	0.82	0.8	NR	NR
CHOP-INTEND score	33.7	26.9	26	15	22	NR	NR

^aNew diagnosis of SMA1 made during the expanded access programme (EAP). ^bSMA diagnosis made preceding the EAP. ^c7.9 weeks (converted to months to facilitate comparisons). ^dUnpublished data, presented by E. Bertini at EVELAM, December 2018. SMN, survival motor neuron; NIV, non-invasive ventilation <16h/d; IV, invasive ventilation or NIV >16h/d; NG, nasogastric tube; PEG, percutaneous gastrostomy; NR, not reported; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Section 2.

Recent publicly disclosed follow-up data from the open-label extension study, SHINE, suggests that age at treatment initiation (<5.5mo) is the main predictive factor of motor improvement.¹³ The importance of early treatment in the efficacy of gene therapy and small-molecular splicing modifiers has also been reported.¹⁴

In the present study, patients who would go on to sit independently had a 1-point higher median score in HINE-2 at baseline and almost 10 points more in the CHOP-INTEND scale than non-sitters. In the ENDEAR Phase 3 study of nusinersen, 8% of 73 treated patients achieved an independent sitting position at the end-point analysis.⁵ Although baseline features of independent sitters corresponded more closely to those of our group of non-sitters than to the sitters, in the follow-up study of ENDEAR, the sitters have characteristics between those of our groups of sitters and non-sitters (Table 1, Fig. 2). In the German⁶ and Australian⁷ open-label studies, 3.3% (2 of 61) and 3 of 16 patients treated with nusinersen were able to sit independently respectively after 6 months.

Because of a longer follow-up of 14 months, we observed a remarkably higher percentage of sitters (15 of 47) than reported for previous studies. Indeed, only five of our patients had achieved an independent sitting position at 6 months. It is worth noting that the majority of sitters showed no objective motor progress after 2 months of treatment as measured by the HINE-2 scale. Yet, sitters had a significantly higher HINE-2 score after 6 months of treatment compared to non-sitters. Therefore, we recommend that patients should be treated for at least 6 months before it is determined whether or not a patient has responded to treatment.

In the clinical trial of the gene therapy onasemnogene abeparvovec, the baseline CHOP-INTEND score in conjunction with age was demonstrated to be a strong predictive factor of walking acquisition.¹⁵ However, correlation was based on two infants who had very high baseline function at 1 month of age, who are not representative of the population of postsymptomatically identified patients.^{16,17}

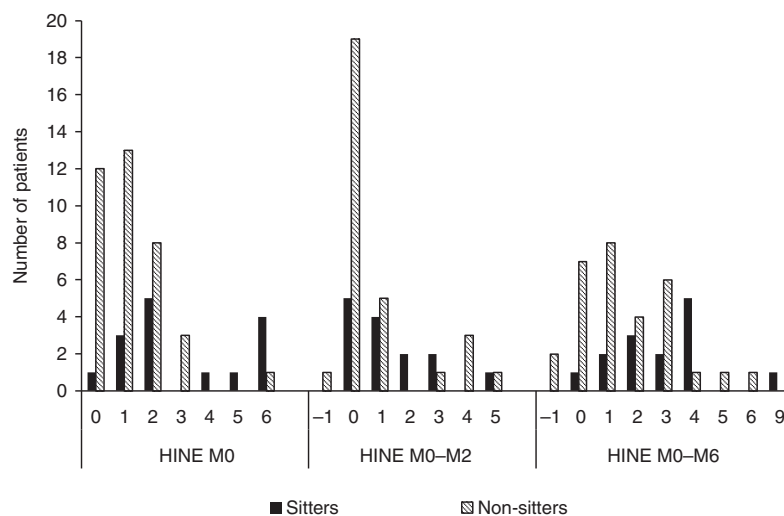


Figure 1: Hammersmith Infant Neurological Examination, Section 2 (HINE-2) scores before treatment (HINE M0), change in HINE-2 at 2 months (HINE M0–M2), and change in HINE-2 at 6 months (HINE M0–M6).

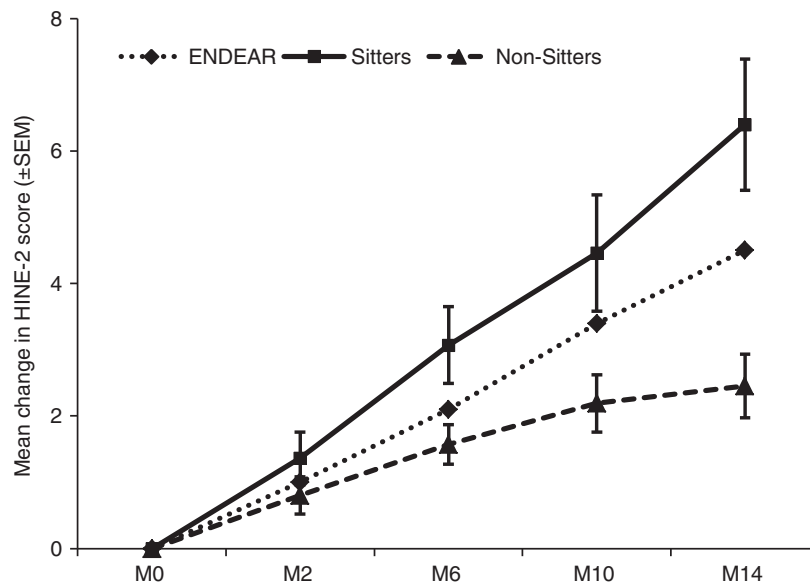


Figure 2: Results for nusinersen-treated cohort in the ENDEAR study ($n=73$ at baseline, $n=26$ at M14) adapted from Finkel et al.⁵ SEM, standard error of the mean; M0, baseline; M2, 2 months of treatment; M6, 6 months of treatment; M10, 10 months of treatment; M14, 14 months of treatment.

SMN2 copy number was not significantly correlated with attainment of the sitting position. Although three copies of *SMN2* are not associated with a better prognosis in patients with symptomatic SMA1 treated with nusinersen,^{6,8,9} preliminary results from a study of infants treated presymptomatically with nusinersen indicated that patients with three *SMN2* copies have better improvement than patients with two copies.¹⁸ Neither the median age at first appearance of symptoms nor the age at the start of the treatment was correlated with the achievement of an independent sitting position in our cohort. This is probably related to the fact that our population included patients who were naturally long-term survivors and much younger patients. There is evidence from different clinical trials that early treatment is associated with better outcome, and, therefore, newborn screening for SMA has been initiated in several countries.^{14,19,20}

The limitations of our study are the small number of participants and the broad range of ages, covering newly diagnosed patients and long-term survivors. This is, however, representative of the overall population of patients with SMA1. Choosing a scale for an objective evaluation of this cohort is challenging. Although the HINE-2 was developed for infants aged 0 to 24 months, it has become a widely used assessment tool for patients with SMA.^{5-8,10} In contrast, the CHOP-INTEND was validated in patients of a broad age range.¹² Patients with SMA1 given standard care have not been reported to acquire the ability to sit independently,^{3,4} but it is a reasonable expectation that successful treatment will enable these patients to sit independently. Sitting was chosen as a primary outcome in an open-label trial of a new splicing modifier that will be given orally to treat infants with SMA1 (trial no.

NCT02913482), and it is also the primary endpoint of the Phase 3 trial of the gene replacement therapy onasemnogene abeparvovec (trial no NCT03461289).

Even though acquiring a sitting position constitutes an important milestone, it is worth noting that there are other significant motor milestones, such as the ability to turn around or to better use the upper limbs, that are also of importance to patients, their caregivers, and health service providers. Several open-label studies^{6,8,9,13} have demonstrated that even if treated patients are not able to sit, patients may progress on motor scales. Longer follow-up of larger cohorts will be required to better define predictive factors, not only of sitting position but also of other important outcomes, such as standing, rolling, independent breathing, and independent feeding.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Characteristics of sitters and non-sitters 14 months after treatment initiation

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