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RESEARCH ARTICLE

Nusinersen in pediatric and adult patients with type III spinal muscular atrophy

Maria Carmela Pera[1,2,*], Giorgia Coratti[1,2,*], Francesca Bovis[3], Marika Pane[1,2], Amy Pasternak[4], Jacqueline Montes[5,6], Valeria A. Sansone[7], Sally Dunaway Young[8], Tina Duong[8], Sonia Messina[9], Irene Mizzoni[10], Adele D'Amico[10], Matthew Civitello[11,12], Allan M. Glanzman[13], Claudio Bruno[14], Francesca Salmin[7], Simone Morando[14], Roberto De Sanctis[2], Maria Sframeli[9], Laura Antonaci[1,2], Anna Lia Frongia[1], Annemarie Rohwer[15], Mariacristina Scoto[15], Darryl C. De Vivo[5], Basil T. Darras[4], John Day[8], William Martens[16], Katia A. Patanella[17], Enrico Bertini[10], Francesco Muntoni[15,18,†], Richard Finkel[11,12,†], Eugenio Mercuri[1,2,†] on behalf of the iSMAC group

[1]Pediatric Neurology, Università Cattolica del Sacro Cuore, Rome, Italy
[2]Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[3]Biostatistics Unit, Department of Health Sciences, University of Genoa, Genoa, Italy
[4]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts
[5]Departments of Neurology and Pediatrics, Columbia University Irving Medical Center, New York, New York
[6]Departments of Rehabilitation and Regenerative Medicine and Neurology, Columbia University Irving Medical Center, New York, New York
[7]Neurorehabilitation Unit, University of Milan, Neuromuscular Omnicentre Clinical Center, Niguarda Hospital, Milan, Italy
[8]Department of Neurology, Stanford University, Palo Alto, California
[9]Department of Clinical and Experimental Medicine and Centro Clinico Nemo Sud, University of Messina, Messina, Italy
[10]Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy
[11]Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando,
[12]St. Jude Children's Research Hospital, Memphis,
[13]Department of Physical Therapy, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
[14]Center of Experimental and Translational Myology, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[15]Dubowitz Neuromuscular Centre, UCL Institute of Child Health & Great Ormond Street Hospital, London, United Kingdom
[16]University of Rochester Medical Center, Rochester, New York
[17]Department of Neurosciences, Institute of Neurology, Catholic University, Rome, Italy
[18]NIHR Great Ormond Street Hospital Biomedical Research Centre, London, United Kingdom

Correspondence
Eugenio Mercuri, Pediatric Neurology, Catholic University, Largo Gemelli 8, 00168 Rome, Italy. Tel: +390630155340; Fax: +390630154363; E-mail: eugeniomaria.mercuri@unicatt.it

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Abstract

Objective: We report longitudinal data from 144 type III SMA pediatric and adult patients treated with nusinersen as part of an international effort. **Methods**: Patients were assessed using Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), and 6-Minute Walk Test (6MWT) with a mean follow-up of 1.83 years after nusinersen treatment. **Results**: Over 75% of the 144 patients had a 12-month follow-up. There was an increase in the mean scores from baseline to 12 months on both HFMSE (1.18 points, $p = 0.004$) and RULM scores (0.58 points, $p = 0.014$) but not on the 6MWT (mean difference = 6.65 m, $p = 0.33$). When the 12-month HFMSE changes in the treated cohort were compared to an external cohort of untreated patients, in all untreated patients older than 7 years, the mean changes were always negative, while always positive in the treated ones. To reduce a selection bias, we also used a multivariable analysis. On the HFMSE scale, age, gender, baseline value, and functional status contributed significantly to the changes, while the number of SMN2 copies did not contribute. The effect of these variables was less obvious on the RULM and 6MWT. **Interpretation**: Our results expand the available data on the

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*Pera and Coratti contributed equally to this paper.

†All co-last authors.

effect of Nusinersen on type III patients, so far mostly limited to data from adult type III patients.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by mutations in the survival motor neuron 1 gene (*SMN1*), characterized by the degeneration of the α-motor neurons of the anterior horn cells of the spinal cord resulting in progressive muscle weakness.[1] Classically, three types with pediatric onset (SMA I–III) and one adult type have been identified (SMA IV) based on the age of symptoms onset and maximum motor achievement.[2] Type III SMA, or Kugelberg–Welander disease, is the mildest form and is characterized by clinical heterogeneity. Clinical presentation generally occurs between 18 months and 18 years when patients have reached all the early motor development milestones, including walking.[3] A proportion of them loses this ability, while others will maintain it indefinitely, showing only minimal muscle weakness. Type III patients are further subdivided according to the onset of clinical signs in types IIIA and IIIB including based on the onset of symptoms before and after 3 years of age.[4]

Nusinersen, an antisense oligonucleotide administered intrathecally, targets pre-mRNA splicing of the *SMN2* gene, increasing inclusion of exon 7 in the *SMN2* mRNA splicing and the amount of functional SMN protein.[5] It was approved by the United States Food and Drug Administration (FDA) in 2016 and by the European Medicines Agency (EMA) in 2017, based on two pivotal clinical trials demonstrating the effectiveness in different types of SMA[6,7] in infants and young children. While the early real-world data have mainly focused on type I patients,[8–11] and more recent studies have reported data in adults,[12–18] less has been reported in pediatric patients or, more generally, to cover the spectrum of treated younger and older type III patients who were also not included in the pivotal trials.[19] Furthermore, as there is reported evidence of the variability of the progression of type III in relation to a number of variables, such as age and functional status,[20–22] the interpretation of the limited real-world data available is also affected by the lack of comparison with reference data from untreated patients.

The aim of this study was to report real-world data in a large cohort of ambulant and non-ambulant type III patients treated with nusinersen in order to establish 12-month changes and the possible effect of different variables, such as baseline values, age, and others on the magnitude of changes. For the measures for which reference data were available, we also wished to correlate the changes observed in the treated cohort to recent longitudinal data collected in untreated patients.

Methods

The data used in this study were collected from the International SMA Registry (United States, Italy, and United Kingdom)[23] or, in a few cases from datasets belonging to the same ISMAR centers but collected before June 2018. The study was approved by the institutional review board (ethics committee) in each center (No. 0030504/18). Written informed consent was obtained from all participants (or guardians of participants) in the study.

All patients with a genetically confirmed diagnosis of SMA and a clinically confirmed diagnosis of type III SMA and on treatment with nusinersen for at least 12 months were included in the study. Type III SMA was subdivided into IIIA or IIIB according to the age at symptom onset (before or after 3 years)[4] In accordance with the clinical routine of each center, patients were assessed using the Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), and 6-Minute Walk Test (6MWT) by trained clinical evaluators.

HFMSE

The scale consists of 33 items, investigating the child's ability to perform various activities.[24] Each item is scored on a 3-point scoring system, with a score of 2 for

"performs without modification," 1 "performs with modification/ adaptation," and 0 for "unable to perform." The total score can range from 0, if all the activities are failed, to 66, if all the activities are achieved.

RULM

The scale consists of an entry item to establish functional levels and 19 items covering distal to proximal movements of the upper extremities.[25] Of the 19 items, 18 are scored on a 3-point scoring system and 1 item is scored on a 2-point scoring system. The total score ranges from 0, if all the items cannot be performed, to 37, if all the activities are achieved fully without any compensation.

6MWT

The 6MWT measures the maximum distance a person can walk in 6 min over a 25-m linear course. It has been shown to be a valid and reliable assessment of exercise capacity and functional walking ability in SMA patients.[26] Distance walked over the entire 6-minute time period, distance covered each minute, and the time to complete each 25-m interval was recorded. Clinical evaluators used common procedure manuals and were trained at in-person meetings. Details of the training and reliability sessions have already been reported.[22,27,28]

Each center had a different schedule of assessments, according to their routine clinical practice but it was agreed that all patients should have at least one assessment after 12 months from the first dose of nusinersen, between the 6th and 7th dose of nusinersen.

Statistical analysis

Demographic and clinical characteristics were summarized using frequencies (percentage) for categorical variables and mean (standard deviation (SD)) or median (1st–3rd quartile) for continuous variables, unless otherwise stated.

In this manuscript, we present two different analyses. First, we analyzed all the patients with a follow-up at 1 year of treatment in order to evaluate the 12-month changes in the functional measures. Comparisons of measurements from baseline to 12-months were performed using the estimates and 95% confidence intervals (CI) of pre–post-differences and the Wilcoxon signed-rank test. Twelve-month changes were also analyzed subdividing the cohort according to the functional status (sitters vs. walkers), SMA type III subtypes (IIIA and IIIB), and according to the age (pediatric (<18 years) vs. adults). Following the previous literature, we also reported details on 12-month trajectories with changes grouped as stable ($\pm$2 points), improved (>+2) or declined (>−2).[22]

As a number of patients failed the 12-month assessment because of restricted access to hospitals during the COVID-19 pandemic or for other reasons, and since no imputation was performed on missing data, we also added a second analysis using a mixed model to estimate the changes for the whole type III population in order to exclude possible selection bias. The model was set up with measurements at baseline, age, sex, time, disease duration, SMN2 copy number, disease onset, and SMA function as fixed effects and patient as a random effect. To make inferences about mean slopes according to the age of onset, the model was expanded by including appropriate main effect and interaction terms in the model.

Results

One-hundred forty-four SMA type III patients (age range: 30 months–68.27 years) were enrolled in the study. Of the 144, 139 had an SMN1 homozygous deletion of exon 7/8, 4 had an SMN1 compound heterozygous deletion and a point mutation, and 1 had a compound heterozygous or homozygous point mutation in SMN1.

All patients were treatment naïve at baseline. The mean duration of follow-up was 1.83 ($\pm$0.61) years. Table 1 describes the baseline characteristics and demographics of the cohort.

No serious adverse events (S-AE) were reported at the time of data collection, most frequent AE were all related to the procedure (headache, nausea, back pain), and have not been reported consistently by all patients.

One hundred and four of the 144 had 12-month assessments on at least one measure and were analyzed for the primary analysis on the 12-month changes. Other 26 patients had at least 6-months follow-up and were retained for the mixed model analysis. In these cases, clinical follow-up visits were missed because of restrictions to the access to clinics related to the COVID-19 pandemic. A flow chart describing patient selection from the whole cohort is available in Figure 1.

HFMSE

12-month changes

Complete data both at baseline and at 12 months were available in 104/144 (72.22%) patients for the HFMSE.

In the 104 patients with HFMSE scores available at baseline and after 12 months/6 infusions (median days from baseline = 359.5 (range 286–436 days)), the HFMSE scores significantly increased between the two assessments (mean difference = 1.18 (95%CI: 0.37–1.99), p = 0.004).

Table 1. Baseline characteristics of the SMA type III-treated patients according to the disease onset.

	All	IIIA	IIIB
N	144	74	70
Sex, *n* (%)			
Male	84 (58.33)	40 (54.05)	44 (62.86)
Female	60 (41.67)	34 (45.95)	26 (37.14)
Age at baseline (years), median (1st–3rd quartile)	16.42 (9.14–35.69)	12.60 (5.5–26.27)	23.22 (13.07–43.94)
Age < 18 years, *n* (%)	77 (53.47)	51 (68.92)	26 (37.14)
Median age in pediatric population (1st–3rd quartile), years	9.50 (5.50–13.43)	8.01 (4.40–13.11)	11.74 (9.24–15.08)
Age ≥ 18 years, *n* (%)	67 (46.53)	23 (31.08)	44 (62.86)
Median age in adult population (1st–3rd quartile), years	36.60 (26.27–47.08)	35.40 (27.10–39.00)	38.84 (25.51–49.35)
Disease duration (years), median (1st–3rd quartile)	12.10 (4.4–28.89)	10.41 (3.51–25.11)	13.33 (4.66–31.43)
SMN2 copy number, *n* (%)			
1	0 (0.00)	0 (0.00)	0 (0.00)
2	11 (7.64)	4 (5.41)	7 (10.00)
3	56 (38.88)	40 (54.05)	16 (22.85)
4	14 (9.72)	8 (10.81)	6 (8.57)
4+	29 (20.14)	6 (8.11)	23 (32.86)
Unknown	34 (23.61)	16 (21.62)	18 (25.71)
SMA function, *n* (%)			
Non-sitter	3 (2.08)	3 (4.05)	0 (0.00)
Sitter	62 (43.06)	40 (54.05)	22 (31.43)
Walker	79 (54.86)	31 (41.89)	48 (68.57)
Baseline HFMSE score, median (1st–3rd quartile)	41 (23–54)	32.50 (15–50)	48.5 (28.0–58.5)
	N = 130	*N* = 66	*N* = 64
Baseline RULM score, median (1st–3rd quartile)	31 (24–37)	27 (22–32)	35.5 (29.5–37.0)
	N = 116	*N* = 56	*N* = 60
Baseline 6MWT meter, median (1st–3rd quartile)	321.5 (166–425)	283 (107–397)	356 (236–434)
	N = 62	*N* = 23	*N* = 39
Follow-up (years), mean (SD)	1.83 (0.61)	1.91 (0.63)	1.75 (0.58)
No of visits, median (range)	5 (2–11)	6 (2–11)	5 (3–11)

The mean 12-month increase in the HFMSE scores was significant in both sitters and walkers. A sensitivity analysis was performed excluding the three non-sitter patients and the results did not change.

When subdivided into IIIA and IIIB subtypes, the increase in scores was significant in IIIB patients and showed only a trend of significance in IIIA. Details of the analysis are reported in Table 2 and Table S1.

Details on 12-month trajectories with changes grouped as stable (±2 points), improved (>+2) or declined (>−2) are reported in Table S2.

Longitudinal data analysis

In a multivariable analysis including 130/144 (90.28%) patients with at least 6-months follow-up (median follow-up of 1.86 years (range 0.5–3.11 years), no significant differences between the different SMA III subtypes (p for interaction between time and SMA type = 0.541) (Fig. 2A,B). Age, SMA functional status, HFMSE at baseline, and SMA III subtype were all factors significantly contributing to the changes, while SMN2 copy was not (Table S3).

RULM

12-month changes

Complete data both at baseline and at 12 months were available in 100/144 (69.44%) patients for the RULM.

In the 100 patients with RULM score available after 12 months/6 infusions (median days from baseline = 363.00 (range 286–436 days), RULM scores significantly increased from baseline to 12 months (mean difference = 0.58 (95%CI: 0.12–1.04)). The mean 12-month RULM increase was significant in sitters but not in walkers. A sensitivity analysis was performed excluding the three non-sitter patients and the results did not change.

When subdivided into subtypes, the increase was significant in IIIA patients but not in IIIB. Details of the analysis are reported in Table 2 and Table S4.

At 12 months, of the 100 patients analyzed, 8.0% (n = 8) declined more than 2 points, 75.0% (n = 75) remained stable, and 17.0% (n = 17) improved more than 2 points. Details on 12-month trajectories with changes grouped as stable (±2 points), improved (>+2) or declined (>−2) are reported in Table S2.

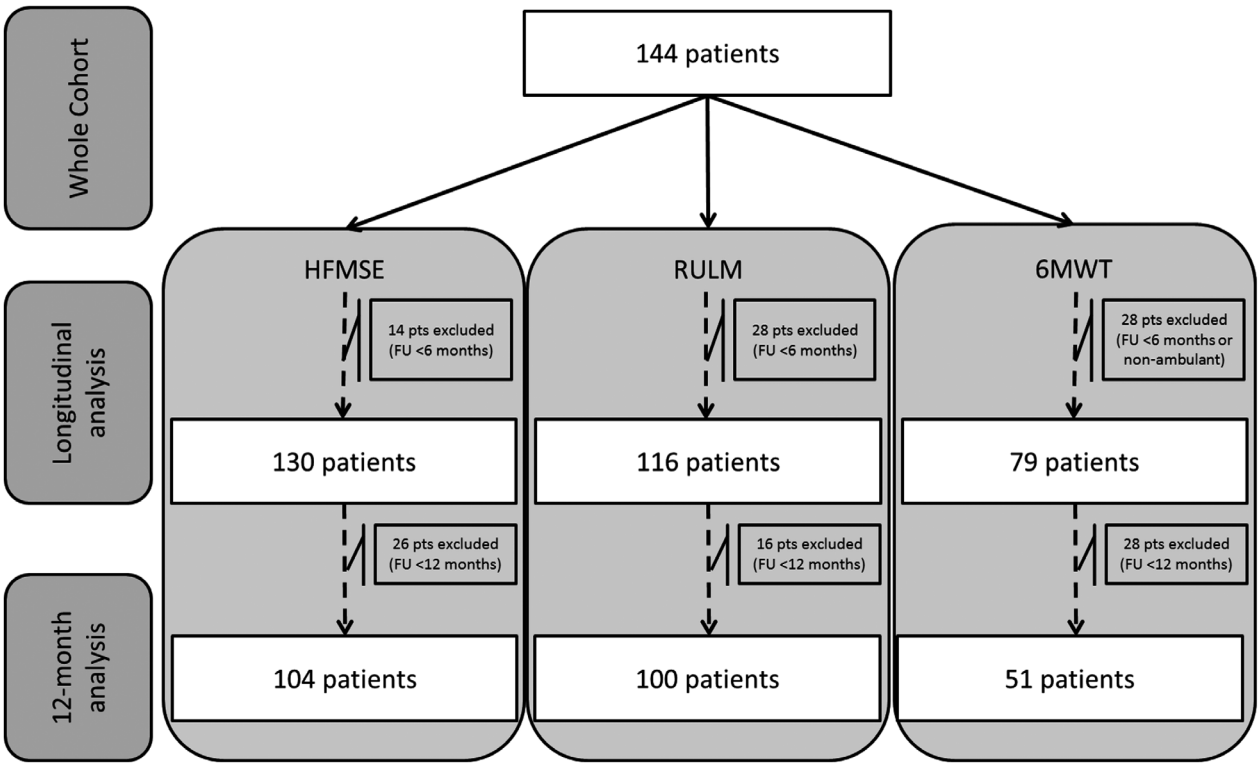


Figure 1. Flow chart of patient selection.

In a sensitivity analysis excluding 27 patients with baseline RULM scores equal to 37, the 12-month changes were slightly larger (0.89 vs. 0.58).

Longitudinal data analysis

In a multivariable analysis including 116/144 (80.55%) patients who had at least 6-months follow-up (and a median follow-up of 1.88 years (range 0.5–3.11 years), there was no significant differences between the different SMA III subtypes (p for interaction between time and SMA type = 0.269) (Fig. 2C,D). Age and RULM at baseline were significantly contributing to the changes, while SMA functional status, RULM at baseline, and SMA III subtype and SMN2 copy were not (Table S5).

6MWT

12-month changes

Complete data both at baseline and at 12 months were available in 51/79 (64.56%) walker patients for the 6MWT assessment.

In 51 patients with 6MWD available at baseline and after 12 months/6 infusions (median days from baseline = 306 (range 286–436 days)), the 6MWT did not significantly increase from baseline to 12 months (mean difference = 6.65 (95%CI: −7.08–20.37)).

When subdivided into subtypes, the increase showed a trend in significance in both type IIIA and IIIB patients. Details of the analysis are reported in Table 2 and Table S6.

Longitudinal data analysis

In a multivariable analysis including the 79 walker patients who had at least 6-months follow-up (median length of follow-up equal to 1.90 years (range 0.77–3.11 years)), there was a difference in the slope according to the SMA subtype (p for interaction between time and SMA type = 0.002) (Fig. 2E,F). Age, 6MWT at baseline were significantly contributing to the changes, while SMA III subtype and SMN2 copy were not (Table S7).

Figure 3 shows the changes in treated patients subdivided according to age groups in relation to published natural history data in untreated patients also subdivided according to the same criteria. Table S8 reports the details of the two cohorts.

Table 2. Changes in HFMSE, 6-minute walk test, and RULM score (12 months vs. baseline) in the overall SMA III population, according to the patient onset, ambulatory status, and age groups.

	N	Baseline Mean Score (95%CI)	12-month Mean Score (95%CI)	Mean difference (95%CI)	*p*-value
HFMSE score					
All	104	37.56 (36.98–38.13)	38.74 (38.17–39.31)	1.18 (0.37–1.99)	0.004
Type IIIA	49	33.55 (32.49–34.61)	34.57 (33.51–35.63)	1.02 (−0.47–2.51)	0.179
Type IIIB	55	41.13 (40.56–41.69)	42.45 (41.89–43.02)	1.33 (0.53–2.12)	0.001
Non-ambulant	43	19.79 (18.82–20.76)	21.27 (20.27–22.28)	1.48 (0.09–2.88)	0.038
Ambulant	60	50.55 (49.85–51.25)	51.61 (50.92–52.30)	1.06 (0.08–2.04)	0.034
Pediatric	59	43.05 (42.22–43.88)	44.58 (43.73–45.44)	1.53 (0.34–2.72)	0.0123
Adults	45	30.75 (29.97–31.53)	31.54 (30.79–32.30)	0.79 (−0.29–1.87)	0.148
RULM score					
All	100	29.33 (29.00–29.66)	29.91 (29.58–30.24)	0.58 (0.12–1.04)	0.014
Type IIIA	44	26.52 (26.02–27.02)	27.77 (27.27–28.27)	1.25 (0.54–1.96)	0.001
Type IIIB	56	31.53 (31.12–31.95)	31.59 (31.17–32.01)	0.05 (−0.53–0.64)	0.857
Non-ambulant	46	24.65 (24.16–25.15)	25.61 (25.10–26.12)	0.95 (0.24–1.66)	0.0009
Ambulant	53	33.98 (33.54–34.42)	34.30 (33.86–34.73)	0.32 (−0.30–0.94)	0.313
Pediatric	45	31.90 (31.40–32.39)	33.15 (32.65–33.66)	1.26 (0.55–1.97)	0.0007
Adults	55	27.31 (26.91–27.71)	27.38 (26.99–27.78)	0.07 (−0.48–0.63)	0.792
RULM score (baseline RULM score <37)					
All	73	26.49 (26.06–26.93)	27.38 (26.95–27.82)	0.89 (0.28–1.50)	0.005
Type IIIA	39	25.17 (24.63–25.73)	26.61 (26.06–27.17)	1.44 (0.65–2.22)	0.0005
Type IIIB	34	28.00 (27.33–28.67)	28.26 (27.59–28.94)	0.26 (−0.68–1.22)	0.581
Non-ambulant	43	23.62 (23.12–24.13)	24.80 (24.28–25.33)	1.18 (0.45–1.91)	0.002
Ambulant	29	31.61 (30.80–32.41)	32.21 (31.43–32.99)	0.60 (−0.52–1.72)	0.289
Pediatric	31	29.52 (28.82–30.22)	31.41 (30.68–32.13)	1.88 (0.87–2.90)	0.0004
Adults	42	24.38 (23.87–24.88)	24.62 (24.12–25.11)	0.24 (−0.47–0.94)	0.505
6MWT score					
All	51	321.00 (311.29–330.71)	327.65 (317.94–337.35)	6.65 (−7.08–20.37)	0.339
Type IIIA	18	279.89 (264.90–294.88)	269.83 (254.84–284.82)	−10.06 (−31.25–11.14)	0.341
Type IIIB	33	343.42 (330.98–355.87)	359.18 (346.74–371.63)	15.76 (−1.84–33.36)	0.078
Pediatric	34	319.87 (306.92–332.82)	330.20 (316.85–343.55)	10.32 (−8.28–28.93)	0.272
Adults	17	323.03 (308.23–337.83)	323.55 (309.55–337.55)	0.52 (−19.85–20.89)	0.959

Dark grey shaded cells: statistical significance.

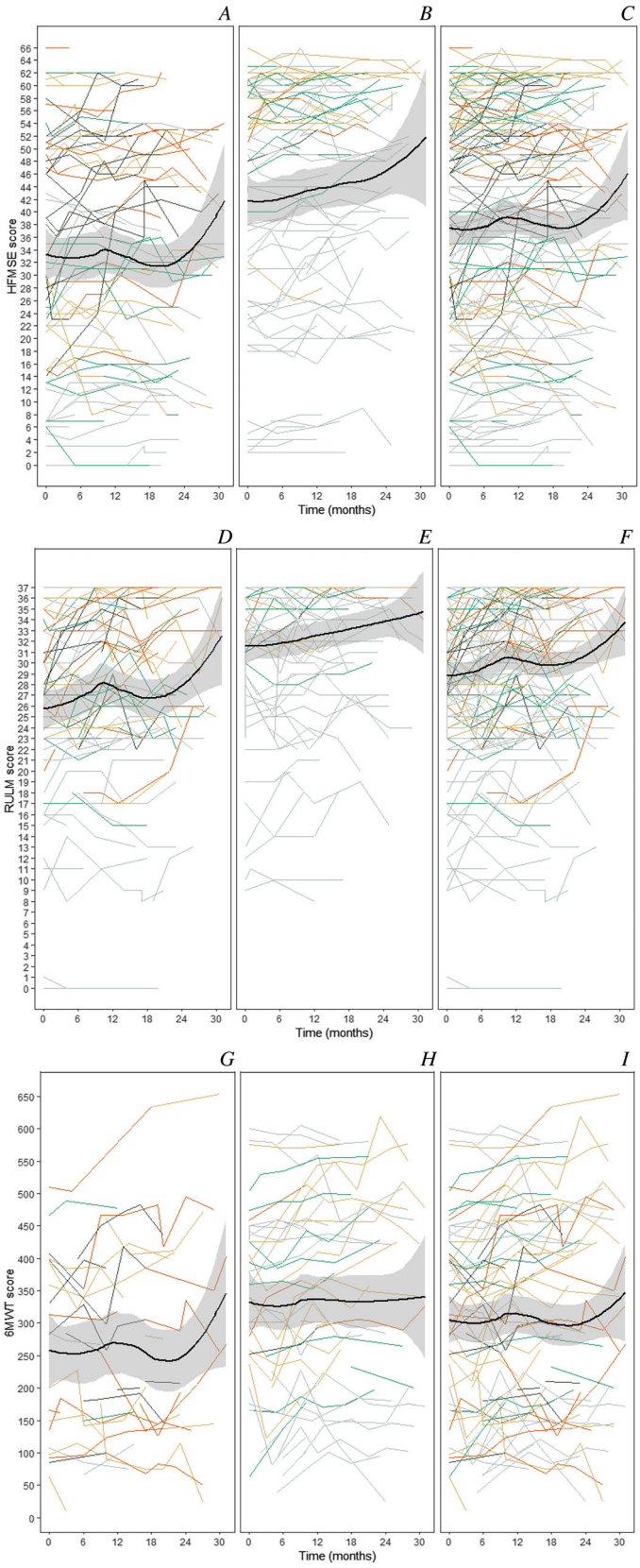
DISCUSSION

The aim of this study was to report real-world data in a large cohort of type III patients treated with nusinersen, including both pediatric and adult patients, filling a gap in the literature that has mainly focused on adult type III patients[12–18] or on types I and II SMA in the pediatric age.[29,30] The analysis of this data, however, should be interpreted with caution as should consider the clinical heterogeneity of type III SMA, as well as the number of variables such as wide age range, age of onset (types IIIA and IIIB), functional status (from non-sitters to fully ambulant), baseline functional scores, duration of disease before the initiation of nusinersen, and genotype (number of SMN2 copies) that could all play a role in determining the response. Because of this, rather than providing just a single estimate of the changes in the whole cohort, we analyzed the data identifying subgroups based on these variables.

As over 75% had two assessments at a 12-month distance, we first looked at the 12-month changes, reporting positive changes in all three measures. These results are at variance with natural history studies in type III patients showing a 12-month decline on all the three measures used in the present study.[22,31,32]

A more detailed comparison with untreated patients was possible for the HFMSE because of the availability of recently published 12-month HFMSE longitudinal data

Figure 2. Mean rate of changes in assessments. Panels (A–C): Mean rate of change in HFMSE scores for all type III (C) and subtypes (IIIA: A, IIIB: B). Panels (D–F): Mean rate of change in RULM score for all type III (F) and subtypes (IIIA: D, IIIB: E). Panels (G–I) Mean rate of change in 6MWT for all type III (I) and subtypes (IIIA: G, IIIB: H). Polynomial line (ribbon: 95% CI) describes progression overtime. Color coding for age at baseline: dark grey line: <5 years; orange line: 5–7 years; dark yellow line: 8–14 years; green line: 15–19 years; light grey line: >20 years.



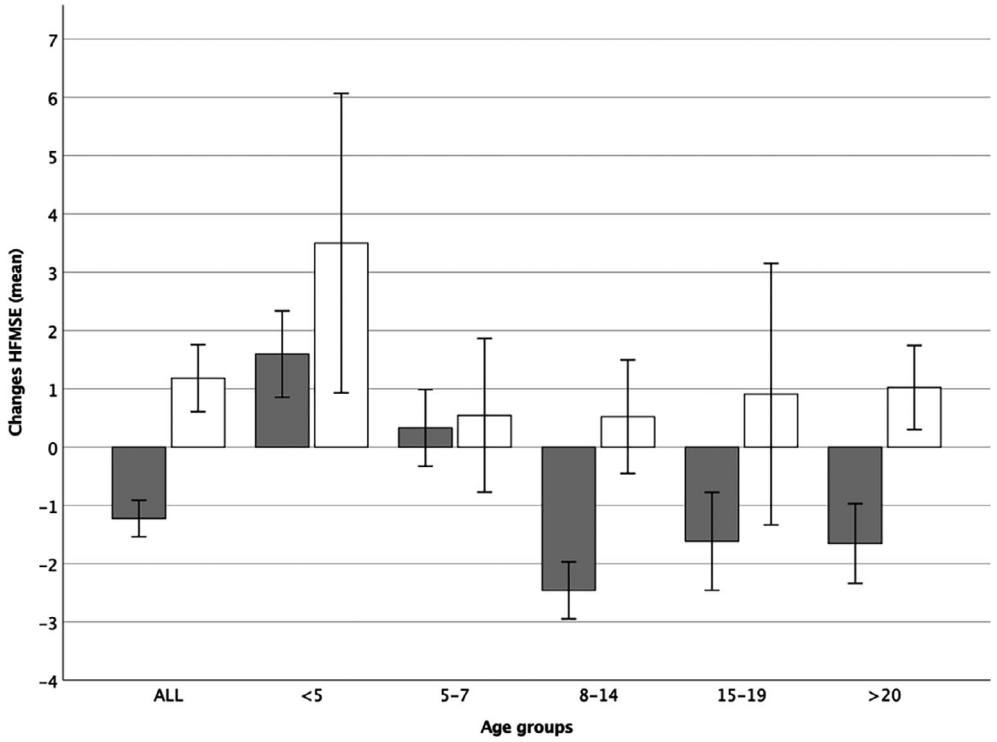


Figure 3. Mean 12-months changes in external untreated controls and treated cohort. Color coding: dark grey: untreated controls,[22] white: treated cohort.

collected in untreated patients.[22] As in the natural history study, untreated patients were subdivided according to age groups and functional status, this allowed a much more accurate matching of the subgroups than an overall comparison between two groups with a wide age and functional range.

The analysis of the different age subgroups allowed further considerations. After the age of 7 years, the mean HFMSE 12-month changes in the untreated patients were always negative and none of the patients showed any improvement.[22] This was significantly different from what was observed in the treated patients in whom the mean changes were always positive and the number of individual patients with negative changes was limited. Irrespective of the absolute values of positive changes, the delta between treated and untreated after the age of 7 was always between 2.5 and 3 points. Before the age of 7 years, type III untreated patients had positive mean 12-month changes but the treated group had a larger improvement. Before the age of 5, there was a delta of 1.9 points between treated and untreated, but the difference did not reach significance. This comparison could not be replicated with the RULM and the 6MWT as the limited reference data[31,32] would not have allowed an appropriate matching of the age and functional subgroups.

Our results in a large cohort including both adults and patients confirm previous findings in adult patients,[14,16–18,33] suggesting that there is a 12-month treatment effect in type III patients irrespective of their ambulatory status and that the changes can be observed on one or more functional measures, depending on age and functional status.

It is of note that each functional subgroup showed some improvement on at least one scale and that none of the scales in isolation was able to identify all patients who had a functional improvement, likely reflecting the large variability of the functional characteristics of the individuals studied. The RULM changes were larger and achieved significance in type IIIA rather than in type IIIB and in non-ambulant patients, while the HFMSE was significant in both ambulant and non-ambulant and in type IIIB. These results suggest that the different scales should be used in combination as each of them contributes to detect possible changes in different groups of patients.

A number of patients had longer follow-up, with a mean duration of follow-up of 1.8 years. Although the data collected after 12 months are still incomplete, our results suggest that the improvement observed in the first year is maintained over time with a further increase in scores after the first year.

In order to reduce the possibility of a selection bias, we also performed a different analysis including all assessments from all the type III patients who had at least 6-months follow-up, in an attempt to identify which variable contributed to the possible changes in the individual measures. On the HFMSE scale, age, gender, baseline value, and functional status all contributed to the changes, while the number of SMN2 copies did not but this should be interpreted with caution as data on SMN2 copy number were not available in 24% of the patients.

The effect of the different variables was less obvious on the RULM and even less on the 6MWT. This probably reflects the different constructs of these measures as the HFMSE covers a wider spectrum of abilities than the other two that are partly targeting distinct functional groups. While the 6MWT can only be performed in ambulant patients,[13] the RULM is more appropriate for weaker patients as it often reaches ceiling scores in stronger ambulant type III patients. Another possible explanation is that changes in the 6MWT may be better appreciated with a longer follow up, as previously reported In the CS12 Nusinersen study, long term extension of the CS2 open-label study.[13] Further studies in larger cohort using the 6MWT may also help to better understand how to use the 6MWT in SMA. Following recent recommendations,[34] we used the raw 6MWD scores as the optimal reference equations for calculating % predicted 6MWD in this patient population is not known.

In conclusion, our findings expand the available data on the effect of Nusinersen on type III patients, so far mostly limited to adult patients. Our results also highlight the variability of responses in relation to treatment and the need for a comprehensive assessment of various functional aspects. As the pattern of changes varies in relation to age and functional severity, the relevance of the response to treatment is better appreciated if the observed changes are compared to the changes observed in untreated patients with similar age and functional status. The topic of minimal clinically important difference warrants further study and will assist the clinician in presenting reasonable expectations to an SMA type III patient treated with nusinersen.

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Conflict of Interest

Coratti, De Sanctis, Montes, Glanzman, Dunaway Young, Pane, Messina, D'Amico, Darras, Bertini, Sansone, Day, Bovis, Muntoni, De Vivo, Finkel, Bruno, Mercuri, and Duong report personal fees from BIOGEN S.R.L. outside the submitted work; Coratti, Pera, De Sanctis, Montes, Glanzman, Dunaway Young, Duong, Sframeli, Scoto, Darras, Bertini, Day, Muntoni, De Vivo, Finkel, Bruno, and Mercuri report personal fees from ROCHE outside the submitted work; Coratti, De Sanctis, Glanzman, Pane, Messina, Darras, Bertini, Sansone, Day, Muntoni, De Vivo, Finkel, Bruno, and Mercuri report from personal fees AVEXIS outside the submitted work; Dunaway Young reports personal fees SMA FOUNDATION outside the submitted work; Dunaway Young, Montes, and Pasternak report personal fees from SCHOLAR ROCK outside the submitted work; D'Amico, Day, Finkel, Mercuri, and Duong report from personal fees NOVARTIS outside the submitted work; Martens, Salmin, Morando, Rohwer, Mizzoni, Antonaci, Frongia, Civitello, and Patanella have nothing to disclose.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. HFMSE descriptive statistics (Mean, SD, Min, Max) of the 12-month cohort.
Table S2. 12-month trajectories grouped as stable (+2 points), improved (>+2) or declined (>−2) HFMSE and RULM.
Table S3. Change in HFMSE score for type III. Dark grey cells: statistical significance
Table S4. RULM descriptive statistics (Mean, SD, Min, Max) of the 12-month cohort.
Table S5. Change in RULM score for type III. Dark grey cells: statistical significance
Table S6. 6MWT descriptive statistics (Mean, SD, Min, Max) of the 12-month cohort.
Table S7. Change in 6MWT distance for type III walkers. Dark grey cells: statistical significance.
Table S8. Mean and standard deviations comparison of the treated population and external untreated controls. Dark grey shaded cells: statistical significance.

Appendix A: iSMAC group

Name	Location	Role	Contribution
Gian Luca Vita	Department of Clinical and Experimental Medicine and Centro Clinico Nemo Sud, University of Messina, Messina, Italy	MD	Clinical support and coordination among the team
Emilio Albamonte	Neurorehabilitation Unit, University of Milan, Neuromuscular Omnicentre Clinical Center, Niguarda Hospital, Milan	MD	Clinical support and coordination among the team
Marina Pedemonte	Center of Experimental and Translational Myology, IRCCS Istituto Giannina Gaslini, Genoa, Italy	MD	Clinical support and coordination among the team
Noemi Brolatti	Center of Experimental and Translational Myology, IRCCS Istituto Giannina Gaslini, Genoa, Italy	MD	Clinical support and coordination among the team
Giulia Norcia	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	PT	Performed the assessments
Lavinia Fanelli	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	PT	Performed the assessments
Nicola Forcina	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	PT	Performed the assessments
Sara Carnicella	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	PT	Performed the assessments
Adelina Carlesi	Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy	PT	Performed the assessments
Annamaria Bonetti	Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy	PT	Performed the assessments
Giulia Colia	Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy	PT	Performed the assessments
Vincenzo Di Bella	Department of Clinical and Experimental Medicine and	PT	Performed the assessments

(*Continued*)

Appendix A: Continued.

(*Continued*)

Appendix A: Continued.

Name	Location	Role	Contribution
	Centro Clinico Nemo Sud, University of Messina, Messina, Italy		
Gloria Ferrantini	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	MD	Clinical support and coordination among the team
Diletta Rossi	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	Study nurse	Data entry and clinical support
Antonella Longo	Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy	Study nurse	Data entry and clinical support
Simona Lucibello	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	MD	Clinical support and coordination among the team
Katia Agata Patanella	Institute of Neurology, Department of Neurosciences, Catholic University, Rome, Italy.	MD	Clinical support and coordination among the team
Chiara Bravetti	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	Study nurse	Data entry and clinical support
Michela Catteruccia	Unit of Neuromuscular and Neurodegenerative Disorders, Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy	MD	Clinical support and coordination among the team
Daniela Leone	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	MD	Clinical support and coordination among the team
Beatrice Berti	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	MD	Clinical support and coordination among the team
Concetta Palermo	Centro Clinico Nemo, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy	MD	Clinical support and coordination among the team
Tim Estilow	Department of Occupational Therapy, The Children's Hospital of Philadelphia, Pennsylvania.	PT	Performed the assessments
Donnielle Rome-Martin	Departments of Neurology and Pediatrics, Columbia University Irving Medical Center, New York, USA	PT	Performed the assessments
Elizabeth Maczek	Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	PT	Performed the assessments
Courtney Dias	Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	PT	Performed the assessments
Alessandra Di Bari	Neurorehabilitation Unit, University of Milan, Neuromuscular Omnicentre Clinical Center, Niguarda Hospital, Milan	Study nurse	Data entry and clinical support
Amelia Signorino	Department of Clinical and Experimental Medicine and Centro Clinico Nemo Sud, University of	PT	Data entry and clinical support

(*Continued*)

Appendix A: Continued.

Name	Location	Role	Contribution
	Messina, Messina, Italy		
Alexis Levine	Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA	Coordinators	Data entry and clinical support
Nancy Videon	Departments of Neurology and Pediatrics, Columbia University Irving Medical Center, New York, USA	Coordinators	Data entry and clinical support
Aixa Rodriguez	Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando, USA	Coordinators	Data entry and clinical support
Julia Balashkina	Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando, USA	Coordinators	Data entry and clinical support
Katharine Hagerman	Departments of Neurology and Pediatrics, Stanford University School of Medicine, Stanford, CA, United States of America	Coordinators	Data entry and clinical support
Richard Gee	Departments of Neurology and Pediatrics, Stanford University School of Medicine, Stanford, CA, United States of America.	PT	Performed the assessments
Bill Martens	Neuromuscular Disease Center, Strong Memorial Hospital, University of Rochester, Rochester, NY	IT team	Provided IT support, reports, and descriptive analysis
Felice Catania	Astir s.r.l., Milan, Italy.	IT team	Provided IT support, reports, and descriptive analysis

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