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ORIGINAL COMMUNICATION

Quality of life assessment in adult spinal muscular atrophy patients treated with nusinersen

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Abstract

Objective To retrospectively evaluate quality of life (QoL) in a large multicenter cohort of adult patients affected by spinal muscular atrophy (SMA) during nusinersen treatment.

Methods We included adult (≥ 18 years) patients clinically and genetically defined as SMA2, SMA3 and SMA4, who started nusinersen treatment in adulthood. QoL was rated by the Individualized Neuromuscular Quality of Life (INQoL) questionnaire. Concurrent motor function evaluation included the Hammersmith Functional Motor Scale Expanded (HFMSE), the Revised Upper Limb Module (RULM), the 6 min walking test (6MWT).

Results 189 completed questionnaires were collected during a 14 months' treatment period. 78 patients were included (7 SMA2 and 69 SMA3 and 2 SMA4) with mean disease duration at first nusinersen administration of 33.2 years (± 12.5 years). All the scores for each INQoL domain (weakness, fatigue, activities, independence, social relationship, emotions, body images) and the derived QoL total score, significantly improved during the observation period, except the muscle locking and pain items. Exploratory analyses suggested that emotions and social relationships were more relevant issues for females compared to males. Social relationships were affected also by a longer disease duration (> 30 years). In SMA3 non-walker patients, activities ameliorate better compared to walkers. The HFMSE and RULM significantly improved from baseline; however, no associations with QoL total score and weakness, activities or independence were demonstrated.

Conclusion In our cohort, adult SMA patients showed a global improvement at the INQoL assessment over 14 months of nusinersen treatment. QoL assessment is relevant to SMA multidisciplinary evaluation.

Keywords Quality of life · Nusinersen · SMA · Adults · INQoL

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Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by weakness and atrophy of voluntary muscles caused by loss of bulbar and spinal motor neurons. SMA is clinically heterogeneous and it is divided into five subtypes (SMA 0–4), ranging from very severe early-onset (< 6 months) phenotypes, representing the most common genetic cause of mortality during infancy, to adult-onset patients with mild motor impairment [1]. The incidence of all SMA types is about 1/10,000 livebirths, with a prevalence of 1–2/100,000 persons [2]. About 98% of patients affected by SMA present homozygous deletions or mutations in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13.2 [3], resulting in defective production of full-length (FL) SMN protein. SMN is a ubiquitous protein that plays key roles in several fundamental pathways within cells [4]. The nearly identical *SMN2* gene undergoes alternative splicing, encoding mostly for a truncated nonfunctional protein, and only about 10–15% of FL SMN protein [5]. The number of *SMN2* copies is variable (0 to ≥ 4 copies) across the population, and increased genomic copies of SMN2 are usually associated with a milder SMA phenotype, making SMN2 the principal phenotype modifier in SMA patients, and the best-known prognostic biomarker to date [6, 7].

In recent years, the implementation of treatments able to alter the splicing pattern of *SMN2* to restore FL SMN transcription levels had revolutionized the approach to SMA, determining motor function improvement and prolonged survival [8, 9].

Relying on this mechanism, antisense oligonucleotide nusinersen (Spinraza®) is the first ever-approved disease-modifying drug for 5q SMA, both in USA and Europe [10, 11]. Antisense oligonucleotides do not cross the blood–brain barrier; thus, nusinersen must be administered intrathecally by multiple lumbar punctures, following a therapy scheme which covers four loading doses (day 0, 14, 28, 63), and a subsequent maintenance phase (every 4 months) [12]. Nusinersen safety and efficacy have been proven in clinical trials across pediatric SMA population [13, 14] and recently confirmed in adult SMA patients by large multicenter observational studies [15, 16]. Nusinersen efficacy in adults was examined by the Hammersmith Functional Motor Scale Expanded (HFMSE), the Revised Upper Limb Motor scale (RULM) and the 6 min walking test (6MWT) which, although pivotal SMA-specific outcome measures, have been designed for the evaluation of the infant SMA population [17]. Adult SMA population is very heterogeneous and it is not infrequent to experience a floor or ceiling effect during HFMSE and RULM assessment [18]; thus, there is a need for more appropriate or complementary outcome measures [19].

In this landscape, patient-reported outcomes (PROs) are emerging as crucial tools for the assessment of patients' health, in association to available motor indexes [20–23]. Among PROs, health-related quality-of-life (HRQoL) measures have been highlighted for their ability to estimate the whole impact of the disease on patients [24, 25], and to evaluate the effectiveness of a specific treatment, as confirmed by QoL assessment inclusion as clinical trial endpoint in neuromuscular diseases [26].

The Individualized Neuromuscular Quality of Life questionnaire (INQoL) was developed in patients affected by different muscle diseases (muscular dystrophies, inflammatory and congenital myopathies) to specifically detect functional limitations relevant to neuromuscular patients [27]. The INQoL has been also validated for the Italian use [28, 29].

A comprehensive quality-of-life assessment in adult SMA patients to monitor disease progression and therapeutic response has not been performed to date. Here, we aimed to retrospectively collect INQoL questionnaires over a long follow-up of a large cohort of adult SMA patients undergoing nusinersen treatment.

Methods

Patients and clinical assessment

We retrospectively included adult (≥ 18 years old) patients clinically and genetically defined as 5q-SMA type 2 and 3, treated with nusinersen, who were followed up across seven secondary or tertiary neuromuscular referral centers in Italy, between 2018 and 2020, in the framework of the SMADU observational study [16]. In addition, two SMA 4 patients excluded from the SMADU study were included here. The study was performed in accordance with the ethical standards of the Declaration of Helsinki. The investigation and use of patients' data for research purposes were approved by Ethics Committees at each center, in accordance with the Declaration of the World Medical Association (ID: SMADU; approved by the Ethics Committee of Fondazione IRCCS Istituto Neurologico 'Carlo Besta', the coordinator center, on 10 July 2019). All patients gave their written informed consent before entering the study. Nusinersen 12 mg/5 ml was administered intrathecally via lumbar puncture, as indicated [12]. Baseline characteristics of enrolled patients (demographics, age of onset, disease duration, SMN2 copy number, ability to walk unaided) were collected. Clinical assessments of motor functions were performed at baseline and every 4 months by trained physical therapists, and included: (1) the Hammersmith Functional Motor Scale Expanded (HFMSE), a 33-item scale for the assessment of physical abilities where each item is scored from 0 to 2, with a best of 66 points [30]; (2) the Revised Upper Limb Module

(RULM), a 20-item scale for upper limb functions, with a maximum score of 37 points [31]; (3) the 6 min walking test (6MWT) where patients are instructed to walk as fast as possible back and forth along a 25 m course, as often as possible for 6 min [32].

QoL assessment

QoL of SMA patients undergoing nusinersen treatment was rated by the Individualized Neuromuscular Quality of Life (INQoL) scale. INQoL consists of 45 self-administered questions within 10 sections related to the physical health domain, and the areas of life and psycho-social aspects. The physical health domain pertains to the impact of common neuromuscular symptoms (i.e., *weakness*, *locking*, *pain* and *fatigue*) on QoL, while *activities*, *dependence*, *body image*, *relationships* and *emotions* evaluate the impact of the disease on psychological and social functioning [27, 28]. Patients respond to each section first with a "yes/no" answer, determining if that specific aspect of the neuromuscular disease (NMD) impacts their daily lives. If yes, it is then asked to determine both the degree of the impact of that topic on their life, and the importance that they attribute to it, by seven-point Likert scales. In this way, the impact of each section of QoL results in a score that is "patient-weighted". The final score for each item is calculated as previously reported [27], and it is presented as a percentage of the maximum negative impact; thus, the closer the score is to 100%, the worse the aspect affects patient QoL. Further, a composite QoL score is drawn combining the five dimensions related to the areas of life and psycho-social aspects, representing the global influence of the NMD on patients' QoL. There is an additional section of the scale that pertains to the effect and expectations of treatment that is not part of this study since it is not included in the calculation of the global INQoL score. The INQoL questionnaire was submitted to patients either before starting the motor evaluation assessment or the day of the infusion.

Statistical analysis

Descriptive statistics were provided in terms of absolute numbers and percentages for categorical data, and means with standard deviations (SDs) and medians with value ranges for continuous data. Changes from baseline of continuous outcomes were analyzed through repeated measure analysis of variance (ANOVA) or a corresponding non-parametric analysis, as appropriate. Associations between HFMSE total score and RULM total score, and QoL score, weakness, activities, and independence items of the scale were investigated through Spearman's correlation coefficients.

Results

Patient cohort

A total of 78 SMA patients receiving nusinersen therapy were enrolled in the study. Patients' demographics and clinical features at baseline are reported in Table 1. Out of 78 (27 females and 51 males), 7 patients were affected by SMA type 2 (9%), whereas 69 were SMA type 3 (88%), and 2 patients were type 4 SMA (3%), with a median age

Table 1 Characteristics of the SMA patients participating in the study

Features	*N* = 78
Gender	
F—*n* (%)	27 (34.6%)
Age (years)	
Mean ± SD	39.4 ± 14.2
Median (range)	38 (18–68)
Age at onset (years)	
Mean ± SD	6.7 ± 6.3
Median (range)	4 (0.3–29)
Disease duration at therapy onset (years)	
Mean ± SD	33.2 ± 12.5
Median (range)	31 (9–55)
SMN2 copy number—*n* (%)	
2	3 (5%)
3	22 (37%)
4	35 (58%)
Unknown	18
SMA type—*n* (%)	
2	7 (9%)
3	69 (88%)
4	2 (3%)
SMA3/4 maximum motor function at baseline—*n* (%)[a]	
Non-walkers	39 (57%)
Walkers	30 (43%)
Motor function scores at baseline	
HFMSE	
Mean ± SD	23.9 ± 21.5
Median (range)	17 (0–64)
RULM	
Mean ± SD	24.5 ± 11.4
Median (range)	25 (0–37)
6MWT	
Mean ± SD	314.4 ± 156.6
Median (range)	328 (0–588)

6MWT 6 min walking test, *F* female, *HFMSE* Hammersmith Functional Motor Scale Expanded, *RULM* Revised Upper Limb Module, *SMA* spinal muscular atrophy, *SD* standard deviation, *SMN2* survival motor neuron 2 gene

[a]The sum does not add up to the total because of some missing values

of 4 years at disease onset, ranging from 6 months to 29 years old.

Among type 3 SMA patients, 30 (43%) were able to walk at least few steps unaided, thus considered walkers, while 39 were non-walkers (57%). Both patients affected by SMA type 4 were walkers, as expected. The two SMA type 4 patients were evaluated together with type 3 SMA patients. The SMN2 gene copy number was determined for 60 (77%) subjects. The median disease duration before treatment with nusinersen (time to treatment) was 31 years (range 9–55). The motor function evaluation at baseline reflected the heterogeneity of the adult SMA population, with a HFMSE ranging from 0 (corresponding to very severe disease) to 62 (corresponding to mild disease) on a total score of 66 points (mean average 23.9 ± 21.5); the mean baseline RULM scale was 24.5 ± 11.4, ranging from 0 to normal (i.e., 37), similarly as for HFMSE. The 6MWT mean score was 314.4 ± 156.6 m. Baseline characteristics of each group of SMA patients providing data at any different time point were comparable (Supplementary Table 1), suggesting no selection bias during the follow-up.

Patient-reported INQoL scores

We collected 189 completed questionnaires across the entire patient cohort during a treatment period of maximum 14 months, subdivided as follow among the different observations: 70 questionnaires at baseline, 48 at 6 months, 41 at 10 months and 30 at the 14th-month evaluation. The scores for each INQoL domain, plus the final QoL score, are reported in Table 2. Patients reported a significant improvement in all the sections of the scale, and in the global QoL score, under nusinersen treatment (Fig. 1), except for the muscle locking and pain sections which overall have not been identified as relevant issues affecting SMA patients. *Weakness* was the section most affected at baseline (66% of the maximum detrimental impact), followed by *activities* (59.5%), *independence* (59%) and *fatigue* (57.2%). After 14 months of nusinersen treatment, patients reported the best improvement in the activities (−9.1%, $p = 0.0004$) likewise in the *fatigue* items (−8.8%, $p = 0.0137$). Notably, a meaningful improvement was already detectable after 6 months of treatment for the *weakness* (T6 vs T0 $p = 0.0273$), *fatigue* (T6 vs T0 $p = 0.0084$), *independence* (T6 vs T0 $p = 0.0454$), *emotions* (T6 vs T0 $p = 0.0260$) and *body image* (T6 vs T0

Table 2 INQoL and motor scores during treatment period

	Mean (95% CI)/median (IQR)[a]				$p^{\#}$
	T0 $n = 70$	T6 $n = 48$	T10 $n = 41$	T14 $n = 30$	
Weakness	66.0 (63.4–68.6)	61.4 (58.3–64.4)	61.5 (58.2–64.8)	58.5 (54.6–62.5)	**0.0176**
Muscle locking	0 (16)	0 (22)	0 (16)	0 (37)	0.2680
Pain	0 (42)	0 (37)	0 (37)	0 (32)	0.1970
Fatigue	57.2 (53.2–61.2)	48.8 (44.1–53.4)	47.9 (42.8–52.9)	48.4 (42.4–54.5)	**0.0137**
Activities	59.5 (57.2–61.8)	57.2 (54.6–60.0)	53.6 (50.7–56.5)	50.4 (46.9–53.9)	**0.0004**
Independence	59.0 (56.4–61.5)	54.8 (51.8–57.8)	54.3 (51.0–57.6)	50.8 (46.8–54.7)	**0.0102**
Soc. relationships	24 (36)	32 (32)	21 (33)	24 (30)	**0.0160**
Emotions	32 (31)	29 (32)	28 (39)	27 (61)	**0.0010**
Body images	54.8 (51.9–57.8)	50.1 (46.7–53.6)	46.5 (42.7–50.2)	46.7 (42.2–51.2)	**0.0049**
QoL total score	47.3 (45.3–49.2)	45.5 (43.2–47.8)	43.3 (40.9–45.8)	42.1 (39.2–45.1)	**0.0286**
HFMSE	17 (41)	22 (46)	27 (42)	25 (38)	**0.0000**
	$n = 68$	$n = 47$	$n = 40$	$n = 29$	
RULM	25 (19)	28 (19)	31 (18)	30 (16)	**0.0000**
	$n = 67$	$n = 47$	$n = 38$	$n = 28$	
6MWT	339.2 (327.9–350.4)	346.8 (334.6–359)	351.9 (339.1–364.7)	343.3 (327.8–358.8)	0.5324
	$n = 26$	$n = 19$	$n = 17$	$n = 12$	

6MWT 6 min walking test, *CI* confidence interval, *HFMSE* Hammersmith Functional Motor Scale Expanded, *IQR* interquartile range, *INQoL* Individualized Neuromuscular Quality of Life questionnaire, *n* number of received questionnaires for time point, *RULM* Revised Upper Limb Module, *T0* baseline, *T6–T10–T14* after 6–10–14 months of nusinersen treatment

[a]Mean with CI from repeated measures analysis for normal distributed variables, and median with IQR for non-normal distributed variables

The sum does not add up to the total because of some missing values

[#]*p* values from repeated measure analysis of variance (ANOVA) or a corresponding non-parametric analysis (i.e., Skillings–Mack test), as appropriate. Bold values denote statistical significance at the $p < 0.05$ level

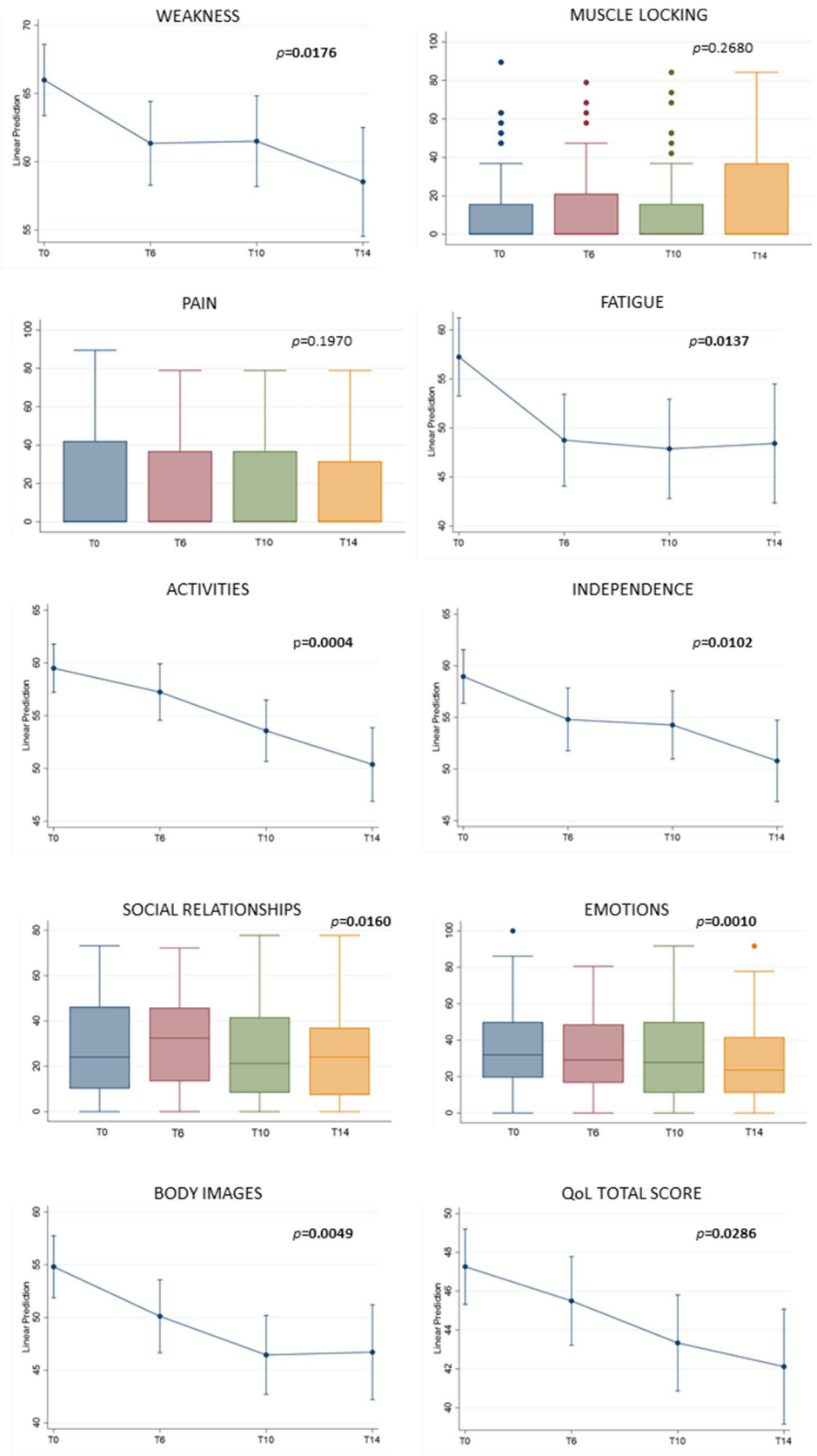

Fig. 1 Changes in the Individualized Neuromuscular Quality of Life (INQoL) scores over 14 months of nusinersen treatment. The INQoL assessment demonstrated an improvement in each section during the observation period, except for the muscle locking and pain aspects. For normally distributed data (i.e., weakness, fatigue, activities, independence, body images and the QoL total score), linear predictions of mean scores with confidence intervals from repeated measure analysis of variance (ANOVA) at baseline (T0), after 6, 10 and 14 months (T6, T10 and T14) are represented. Box plot diagrams graphically depict the medians and the interquartile ranges for non-normally distributed variables (muscle locking, pain, social relationships and emotions) at the mentioned time point of follow-up. *p* values from repeated measure ANOVA or a corresponding non-parametric analysis (i.e., Skillings–Mack test) are reported. Bold values denote statistical significance at the $p < 0.05$ level

$p = 0.0471$) items. Further, a sensitivity analysis considering only patients who underwent 14 months of observation ($n = 30$) did not show substantial differences compared to the analysis performed on the overall dataset (data not shown)".

Subgroup analyses have been performed for each section by sex, by sex and SMN2 copy numbers in patients affected by SMA type (3 vs 4 copies of SMN2), and by disease duration (≤ 30 vs > 30 years, that correspond to the median of disease duration in our cohort) in the whole SMA cohort. Results of the subgroup analyses are detailed in Supplementary Tables S2–S5. A meaningful improvement was seen in females compared with males in the psychosocial domain, particularly in the *relationship* (-3.7 vs $+4.6\%$, respectively, $p = 0.0090$) and in the *emotion* sections (-16.7 vs -2.8% in male, $p = 0.0100$) (Fig. 2). An evident more favorable trend in women compared to men was appreciable for the *weakness*, *fatigue*, *activity* and *independence items*, and in the *QoL total score*, while there was an equal betterment in the *body image* score (supplementary Table1).

No meaningful differences in any sections were detected considering sex and the number of SMN2 copies over the follow-up period.

Dividing the enrolled population by their median of disease duration (i.e., 30 years), a longer disease duration was significantly related to a better outcome in the *social relationships* after treatment (median for disease duration shorter than 30 years 25 vs. 22 for disease duration longer than 30 years, $p = 0.0090$), while a meaningful progressive reduction in the perceived negative impact of *emotions* on QoL was reported by patients with a shorter disease history (median < 30 years 26, median > 30 years 22, $p = 0.0320$) (Fig. 2). A better trend, although not statistically significant, was detected in *independence* acquisition and *QoL total score* reported after nusinersen treatment by patients with a longer disease duration. However, no significant differences were detected in any of the subgroup analyses of the *QoL total score*. Interestingly, *fatigue* was not influenced by disease duration, as for *body image.*

A further analysis among type 3/4 SMA patients based on their maximum motor function achieved at baseline non-walkers vs walkers) was performed for the

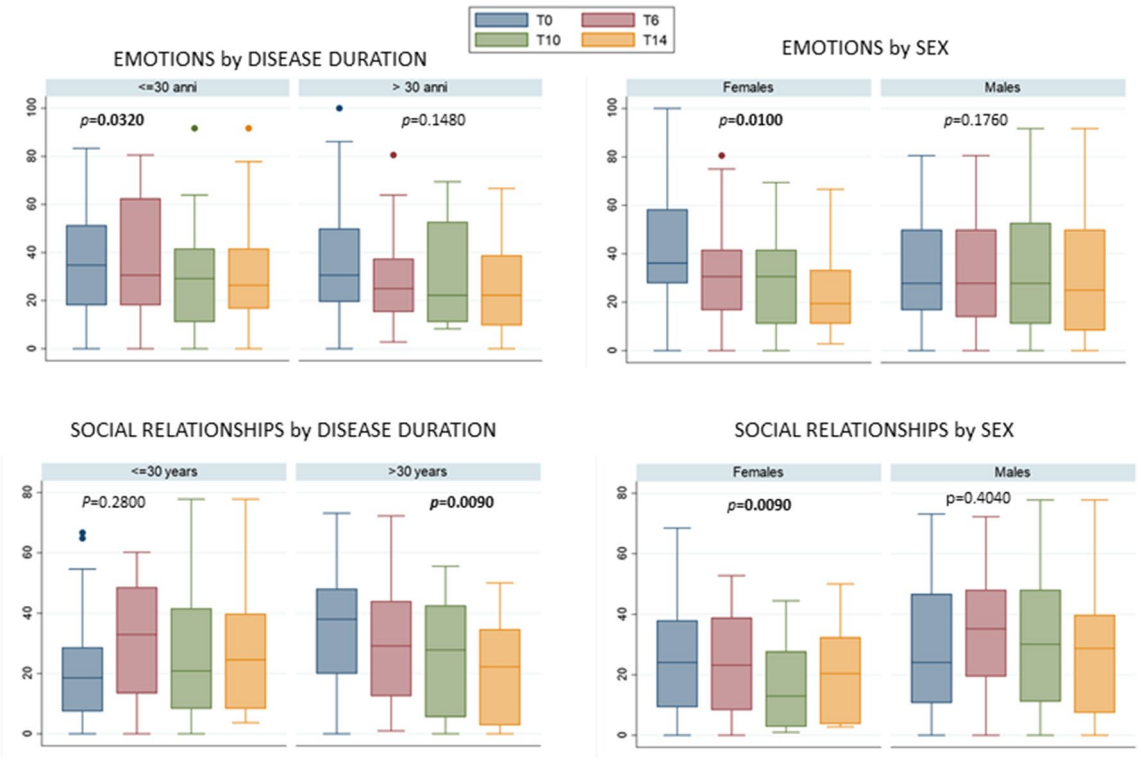

Fig. 2 Changes in the Individualized Neuromuscular Quality of Life (INQoL) scores for specific subgroup analyses. Statistically meaningful subgroup evaluations of the INQoL sections are here represented. Social relationships and emotions resulted to differently impact females, compared to males, during the 14 months of observation, and were also differently perceived by patients with different disease duration (longer and shorter than 30 years, respectively). The median of the score percentages and the interquartile ranges for each time point of follow-up are reported in box plots. *p* values forming a non-parametric repeated measure analysis (i.e., Skillings–Mack test) are reported. Bold values denote statistical significance at the $p < 0.05$ level

Table 3 INQoL analyses of specific section by walker and non-walker SMA type 3–4 patients

	Mean (95% CI)[a]				$p^{\#}$
	T0 $n=63$ (36 non-walkers, 27 walkers)	T6 $n=45$ (24 non-walkers, 21 walkers)	T10 $n=38$ (16 non-walkers, 22 walkers)	T14 $n=28$ (14 non-walkers, 14 walkers)	
Weakness					
Non-walkers	72.2 (66.4–78.1)	64.7 (57.2–71.9)	63.5 (54.7–72.3)	59.4 (50.0–68.8)	0.7388
Walkers	60.0 (53.3–66.8)	55.1 (47.5–62.8)	55.7 (48.3–63.2)	48.9 (39.5–58.3)	
Activities					
Non-walkers	65.8 (59.2–72.3)	64.2 (56.2–72.2)	61.5 (51.7–71.3)	49.2 (38.7–59.7)	**0.0164**
Walkers	49.6 (42.0–57.1)	47.2 (38.6–55.7)	43.6 (35.2–52.0)	42.8 (32.3–53.3)	
Independence					
Non-walkers	73.5 (66.7–80.4)	69.9 (61.5–78.3)	66.7 (56.4–77.0)	62.5 (51.5–73.5)	0.5570
Walkers	34.5 (26.5–42.4)	35.4 (26.5–44.4)	34.3 (25.6–43.1)	31.9 (20.9–43.0)	
QoL total score					
Non-walkers	51.2 (44.7–57.6)	48.7 (40.8–56.5)	47.5 (37.9–57.2)	40.8 (30.5–51.1)	0.1177
Walkers	42.6 (35.2–50.0)	38.6 (30.2–47.0)	36.5 (28.3–44.7)	32.5 (22.2–42.8)	

CI confidence interval, *INQoL* Individualized Neuromuscular Quality of Life questionnaire, *n* number of received questionnaires for time point, *SMA* spinal muscular atrophy, *T0* baseline, *T6–T10–T14* after 6–10–14 months of nusinersen treatment

[a]Mean with CI from repeated measures analysis

[#]*p* values of interaction term from repeated measure analysis of variance (ANOVA). Bold values denote statistical significance at the $p<0.05$ level

weakness, *activity*, *independence* and *QoL total score* items (Table 3). A statistically meaningful amelioration in the *activities* was identified over the follow-up period for the non-walker patients (− 16.6%), compared to the walkers (− 6.8%, $p=0.0164$), consistently with a positive trend in the same population in the independence score, while *weakness* and *QoL total score* improved equally among SMA type 3 patients after treatment (Fig. 3).

Motor function evaluation

The HFMSE and the RULM assessments of SMA patients significantly improved in the SMA population during the treatment period ($p=0.0000$ for both), while the 6MWT did not show a meaningful increase (Fig. 4). Results of motor function evaluations during nusinersen follow-up are shown in Table 2.

Correlation analyses between motor function assessments of SMA patients during the treatment period and specific items of the INQoL scale were conducted (Supplementary Table 2). No correlations were detected between HFMSE total score, or RULM total score, and *QoL total score* at baseline, either after 10 months of follow-up (Supplementary Fig. 1). Similarly, no correlations were found between HFMSE total score, or RULM total score, and *weakness*, *activities*, *independence* items of the scale (data not shown).

Discussion

The data here presented result from the QoL evaluation of adult SMA patients' assessment during nusinersen therapy. Using the Italian validated version of the INQoL questionnaire [28], we were able to capture the degree to which SMA impacts the physical and psycho-social well-being of adult patients (HRQoL) [33], and how this changes over time upon disease-modifying treatment.

At baseline, SMA patients presented higher scores in the muscle symptom-related domain, where *weakness* was the aspect with greater impact, followed by *activities* in the emotional and social sections. These results, including the *QoL total score*, were in line with previous observations obtained by the INQoL questionnaire in an adult cohort of patients affected by Duchenne Muscular Dystrophy (DMD) [34]. Differently, in our cohort, *independence* was much less perceived as impacting on QoL, while the perception of the *fatigue* emerged as a prominent issue for adult SMA population, in accordance with recent studies focused on assessing the relevance of the fatigue, and its relationship with fatigability, in SMA [23, 35, 36]. This reflects, on an average, the different daily life of adult SMA patients, entailing life experiences and expectations often closer to not-affected people if compared to adult DMD patients, which might account for the worse impact of *body image*, *relationships* and *emotions* reported by adult SMA patients

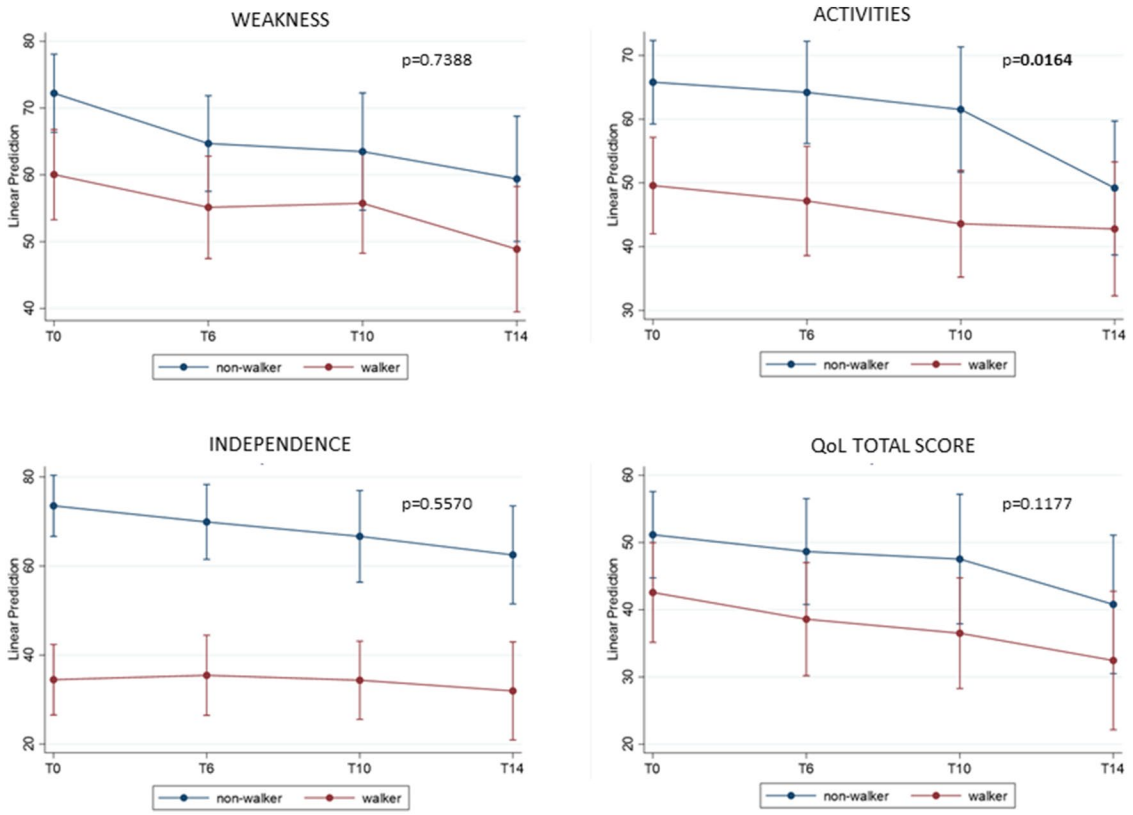

Fig. 3 Changes in the Individualized Neuromuscular Quality of Life (INQoL) score for walker and non-walker spinal muscular atrophy (SMA) type 3–4 patients. Linear predictions of mean scores with confidence intervals from repeated measure analysis of variance (ANOVA) of weakness, activities, independence and QoL total score, by walker and non-walker SMA3 patients, are here represented. Only activities improved differently over the observation period in non-walker patients, compared to walkers. *p* values of interaction term from repeated measure ANOVA are reported. Bold values denote statistical significance at the $p < 0.05$ level

on their lives. This point was also raised in a recent study about patients' treatment expectations, which highlighted that more severely affected patients show different priorities, often less focused on their functional deficits, compared to patients less impacted by the disease [37]. Further, despite the *QoL total score* at baseline being equal between the sexes, males were more affected by the *social relationship* and *emotion* aspects compared to women, in contrast with previous data in other neuromuscular diseases and not [28, 38, 39]. Besides, the greater impact of a longer disease duration on QoL perception at baseline, has been outlined in our population as well as before [27, 28]. Overall, this suggests the possibility to delineate specific QoL patterns of disease impact for different neuromuscular disorders, which could be instrumental for a better multidisciplinary care of patients and better design of pharmacological clinical trials.

The recent advent of nusinersen, the first drug approved for the treatment of 5q-SMA patients of any age [13, 14], opened the discussion on what tools to adopt to correctly measure disease-modifying drug effects, especially in the slowly, chronically progressive adult population [40, 41]. Notably, current-available outcome measures to evaluate adult patients in real-life context are mostly focused on the assessment of the motor function; in addition, they have been validated in pediatric patients and may result not very comfortable for those in adult age. Considering these limitations, attention in this field has been drawn to patient-reported outcome measures (PROMs) for their ability in capturing valuable aspect of patients' health and response to treatments. Even though different scales for the measurement of independence, disease-burden, self-rated improvement and worsening during therapy, are emerging for the evaluation of SMA patients [42], the INQoL remains today the best-known and most used quality-of-life scale specifically validated for adults affected by neuromuscular disorders.

The results obtained by the use of the INQoL scale, administered over 14 months of evaluation during nusinersen treatment, further support the therapy efficacy in adult 5q-SMA patients', as already shown through objective motor outcome measures [15, 16]. Indeed, in our cohort, patients reported a meaningful improvement in all the items of the questionnaire (*weakness*, *fatigue*, *activities*, *independence*, *social relationship*, *emotions*, *body images* and *global QoL*

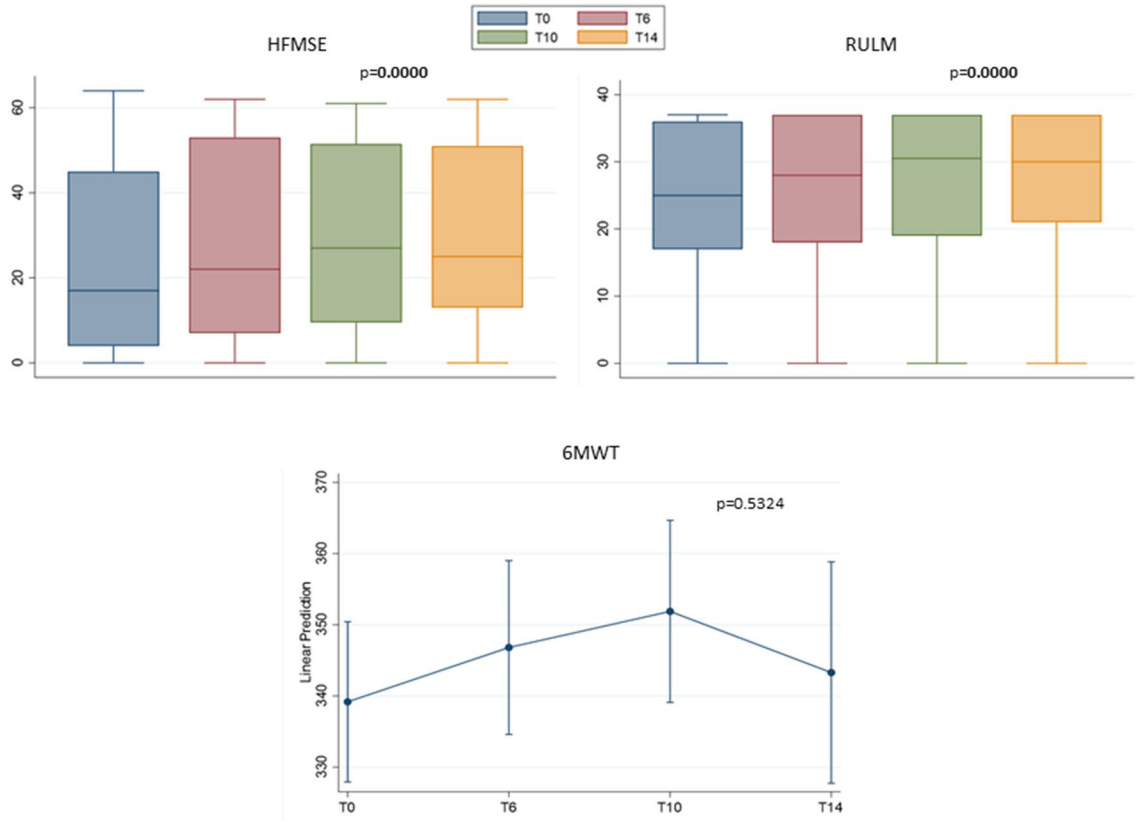

Fig. 4 Changes in the motor scores over 14 months of nusinersen treatment. The Hammersmith Functional Motor Scale Expanded (HFMSE) and the Revised Upper Limb Module (RULM) scores improved after 14 months of treatment. Box plots diagrams graphically depict the medians and the interquartile ranges, at baseline, after 6, 10 and 14 months (T6, T10 and T14). Diversely, the 6 min walking test (6MWT) did not improve during the follow-up period. 6MWT linear prediction graph depicts the mean scores with confidence intervals from repeated measure analysis of variance (ANOVA) at the different time points. *p* values from repeated measure ANOVA or a corresponding non-parametric analysis (i.e., Skillings–Mack test) are reported. Bold values denote statistical significance at the $p < 0.05$ level

score) during the period of observation, except for the *muscle locking*, which is not characteristic of the disease, and for the *pain* that did not emerge as a relevant factor affecting this cohort of adult SMA patients. Notably, there was a substantial equal improvement among each section and the QoL total score throughout nusinersen treatment, although some of the items showed a constant progressive amelioration over time (*activities* and *QoL total score*), others presented a significant improvement in the first 6 months, followed by a stabilization, and a second peak of improvement after one year of treatment (*weakness*, *independence*, *emotions*), while *fatigue* and *body images* positively changed in the first 6 and 10 months, respectively, and then maintained a steady improvement. This differs from what observed by the administration of the Fatigue severity scale (FSS) which recorded a reduction in fatigue after 6 months of nusinersen, but not maintained at 10 months of treatment [43]. This might be related to the different tools to assess fatigue and diverse number of SMA type 2 patients in the mentioned study (36%), compared to our cohort (9%). Indeed, fatigue is not associated to motor function, or rather patients with milder disease can experience it more, as recently reported in a study which also described that FSS does not correlate with HRQOL measures [44]. Looking into the different modifications of the specific items over nusinersen therapy, it is difficult to draw definite conclusions for the various responsiveness to change. However, it is of note that the QoL total score showed a continuous improvement throughout the entire follow-up period and all but the social relationship section clearly improved in the first 6 months of treatment. In this time lapse, patients are subjected to the escalation dose of the drug, which accounts for five intrathecal infusions that might logically affect social relationship experience, but at the same time, the first months after therapy initiation is potentially the moment when patients are more subjected to the placebo effect [45]. A recent study in SMA patients undergoing nusinersen therapy described no correlation between treatment expectations and beneficial treatment outcome; however, the small sample size could not actually allow to exclude it [18]. In the mentioned study,

patients were asked to report the improvement, deterioration or no-modification of specific functions, within the first year of nusinersen treatment, by a self-designed 18 questions score. PROs confirmed once again the beneficial effect of nusinersen on disease course, which was reported by 75% of the patients. Despite strength, that improved better among type 3–4 SMA, the other motor functions evaluated, did not result differently impacted by treatment [18]. Since the number of SMA type 2 patients was very unbalanced in our cohort, but the whole sample size allowed for more stratifications among SMA patients, we looked into other possible features possibly affecting patients QoL. Subgroup analyses in our cohort demonstrated a female's better outcome after therapy compared to male in regards to *pain*, *emotions* and *social relationships*, the latter being positively related also to a longer disease course, which in adult SMA patients might be linked to a milder disease phenotype. Among SMA type 3 patients, neither the number of copies of SMN2, nor the ambulatory status discriminated a category with a specific impact of the disease on QoL. Only SMA type 3 non-walker patients recorded a more evident improvement in the *activities* over time, further suggesting a possible higher effect of nusinersen in SMA sitters as already shown by greater improvement of HFMSE and RULM in this patient subgroup [16]. Even though, given the limited number of patients, the performed subgroup analyses should be considered as just exploratory, clear trends among populations are of note and would benefit of a bigger sample size.

Together with an overall enhancement in the INQoL assessment, the specific motor function outcome measures improved significantly during nusinersen treatment confirming the previously reported data [16]. However, the *QoL total score* did not correlate with HFMSE or with RULM motor function at the baseline, and after ten months of treatment. In a previous paper focused on the efficacy of nusinersen in adult SMA patients, we had already found lack of concordance between motor outcome measures and patients' subjective clinical impression, although a positive trend was observed [16]. This might reflect the possible lack of sensitivity of the available motor functional tests in adult SMA patients, thus the emerging need of tailored instruments to detect meaningful changes to therapy, and supports the fact that the INQoL is able to capture the responsiveness to nusinersen treatment, by means of minor and/or different changes.

Hence, INQoL assessment should be a complementary component of clinical practice in the multidisciplinary evaluation of SMA patients over disease and treatment course for the best comprehensive evaluation, beneficial for physicians in the treatment decision-making process, and when it comes to comparing results across different SMA populations in the studies. This study has some limitations, including its retrospective design and the small sample size of SMA type 2 subgroup, which does not allow definite conclusions for this category, although reflecting real-world data. Furthermore, data have been collected in 2018–2020, right after the availability of nusinersen therapy for adults in Italy, thus the number of evaluations under treatment decreases toward the longer time points of follow-up and, also, some questionnaires are missing, reducing in the end the study sample to about a half of the starting size. Nonetheless, it was possible to detect meaningful improvements. However, SMA disease encompasses a broad range of age and disease severity and, to stratify patients to detect potential QoL modifiers, a bigger sample size is needed. Further, INQoL scale is a validated functional tool for the purpose to measure disease impact on patients with neuromuscular disorders, but in the framework of SMA evaluation, disease-specific, and possibly disease-type-specific QoL scales, are lacking. Although this field is progressing, research in this area is still needed.

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Author contributions SB collected data, performed data analysis and their interpretation, drafted the manuscript. RZ collected data, contributed to data interpretation and manuscript preparation. LB contributed to interpretation of data and revised the manuscript. IT performed data analysis and their interpretation. VB collected data and revised the manuscript. LC collected data and revised the manuscript. GS contributed to interpretation of data and revised the manuscript. MF collected data and revised the manuscript. SB collected data and revised the manuscript. TM contributed to interpretation of data and revised the manuscript. MS contributed to interpretation of data and revised the manuscript. MC collected data, con tribute to data interpretation and revised the manuscript. VV collected data and revised the manuscript. RL contributed to interpretation of data and revised the manuscript. MT collected data and revised the manuscript. RT collected data and revised the manuscript. REM contributed to interpretation of data and revised the manuscript. EP contributed to interpretation of data and drafted the manuscript. LM planned the study, performed data analysis and their interpretation, drafted the manuscript and submitted the manuscript.

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Declarations

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Ethics approval The study involved seven Italian secondary- or tertiary-care centers for SMA and was approved by Ethics Committees at each center (ID: SMADU; approved by the Ethics Committee of Fondazione IRCCS Istituto Neurologico 'Carlo Besta', the coordinator center, on 10 July 2019).

Consent to participate Written informed consent was obtained from all participants, according to the Helsinki declaration.

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