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Article

Patients' Perceptions of Nusinersen Effects According to Their Responder Status

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Abstract: Background and Objective: Patients with spinal muscular atrophy (SMA) treated with a disease-modifying therapy (DMT) are often classified as responders or non-responders based on attainment of a specific improvement threshold on validated functional scales. This categorization may significantly impact treatment reimbursement in some countries. The aim of this research is to evaluate the perception of treatment benefit by patients considered as responder or non-responder. **Methods:** In this non-commercial multicenter study, 99 post-symptomatically treated SMA type I-III patients with a median age of 11.2 (0.39-57.4) years at treatment initiation were stratified into three groups based on their treatment outcomes, i.e. those exhibiting clinically significant improvement (N=41), those with non-clinically significant improvement (N=18), or those showing no improvement (N=40). Fifteen months after treatment initiation patients or patients' caregivers were assessed using a patient-rated scoring system based on the Patient Global Impression of Change (PGIC) scale, comprising 22 questions targeting important aspects and tasks in the daily life of patients with SMA.

Results: We found no statistical difference in patient perception of treatment benefit in 17 out of 22 domains across patient groups. **Conclusion:** Our results suggest that functional motor scales do not recapitulate patients and patients' caregivers experience about the effect of nusinersen treatment in SMA.

Keywords: spinal muscular atrophy; nusinersen; responder; treatment response; patient perception

1. Introduction

Spinal muscular atrophy (SMA) is a severe, progressive, and life-threatening neuromuscular disorder caused by mutations in the survival motor neuron 1 (*SMN1*) gene, leading to a deficiency in the SMN protein, with an incidence of 1:14.848 births[1,2]. The severity of the phenotype is mostly

driven by the low and variable residual levels of SMN protein produced by the autologous gene *SMN2*, for which human beings comprise zero to several copies[3]. Patients with SMA are classified at diagnosis according to the age at onset of symptoms and their highest motor milestone achieved: SMA type I patients show first symptoms before 6 months and are never able to sit independently; SMA type II patients present with first symptoms between 6-18 months and are able to sit independently; SMA type III patients have their first symptoms after 18 months and are able to walk; SMA type IV show first symptoms in adulthood, following achievement of ordinary motor milestones in childhood[4]. As patients may lose their highest motor ability over time, a functional classification between non-sitters, sitters and walkers to indicate the current phenotype of the patient is more commonly used[5]. Nusinersen, an antisense oligonucleotide targeting pre-mRNA splicing of the *SMN2* gene was approved by the United States Food and Drug Administration (FDA) and the European Medical Agency (EMA) in 2016 and 2017, respectively, and is one of the three currently approved DMT for SMA[6,7]. Large real-world data collections have since then provided additional evidence of efficacy in a broad range of patients[8–15]. The vast majority of these controlled and real-world studies were based on the use of well-validated scales such as Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and Hammersmith Infant Neurological Examination – Section 2 (HINE-2) in type I SMA, and Hammersmith Functional Motor Scale Expanded (HFMS-E), Revised Upper Limb Module (RULM), and Motor Function Measure 32 (MFM32) in type II SMA[14,16]. Although these scales have been demonstrated to constitute robust tools to compare populations, individual meaningfulness, especially in older and weaker patients, is not as well established[17]. This becomes an issue in outcome-based agreements when payers and healthcare systems base their judgement to continue funding treatment at the individual patient level using the magnitude of change on these scales determined by the minimal clinically important differences (MCID) as the primary driver in the decision-making process[17,18]. The MCID is usually based on specific population typically validated from homogenous and clinical trial-based research groups, leading to greater variability and potential higher MCID for the real-world population[19]. Indeed, it has been shown that patients and caregivers are perceiving improvements that are not captured by the functional motor scales[9,11,20]. Although such small improvements not captured by standardized scales may appear insignificant, they can have a considerable positive impact on a patient’s daily life[21,22]. The main objective of this study is to compare the treatment benefit as perceived by the patients and caregivers and as measured by current functional scales.

2. Materials and Methods

Participants and Study design: Six Centres in four countries participated in the study: Belgium (Leuven, Gent and Liège - coordinating Centre), Hungary, United States of America, and the Czech Republic. Data were centrally monitored by the coordinating site, and queries were sent for missing or aberrant data. The study was non-commercial (academic), multicentric, and prospective. Patients with 15 months of nusinersen treatment and having been evaluated by standardized assessment were proposed to participate. Ethical approval to conduct the research was granted from relevant bodies within each participating Centre, as dictated by respective local ethics committees. Informed consent was obtained from all subjects and/or legal caregiver involved in the study.

We included patients with genetically confirmed 5q SMA treated post-symptomatically with at least 12 months of a stable dose of nusinersen. Exclusion criteria were patients identified by newborn screening, pregnancy or breastfeeding, presence of any comorbidities interfering with functional scales assessments and scores, patients with no baseline visit unless the patient had a score of zero points on the functional scale at Month 15, assuming the patient was assessed with a scale in which a floor effect was achieved. Given the heterogeneity in real-world data collection related to timings and outcome choices and to increase the robustness of the study population, we defined based on literature; i) clear study windows for treatment initiation and assessments, and ii) an order of priority of functional scales depending on age at treatment initiation and type of SMA based on the literature (Table S1). This enabled us to objectively prioritize scales for each phenotype and age group and to manage heterogeneity across each country due to the large population and the different scales used

across each country. The scales considered were those used in pivotal or phase 2 clinical trials in type I (CHOP-INTEND, HINE-2); type II and type III (HFMSE, RULM, MFM32), and ambulatory type III (6-minute walk test (6MWT)), for which also minimally clinically important differences have been defined[6,7,14,23–25]. To be consistent with the other categories, we prioritized a motor function scale like the HFMSE instead of the 6MWT for the ambulant patients. Furthermore, we also considered the CHOP-INTEND for all non-sitter patients regardless of their age, as it was most widely used[26].

To better understand the individual disease trajectory, events happening in the time frame between baseline and Month 15, such as the implementation of tracheotomy, non-invasive ventilation, or gastrostomy; hospitalization in an intensive care unit; major surgery (e.g., spinal fusion) were considered as adverse events as these can impact the score changes over time [27].

Furthermore, as contracture assessment is usually not harmonized in real-world data collection, we defined contractures as any presence of contracture regardless of degree of range of motion.

Once the study population was identified and included, patients were divided into three groups (Non-responder (NR); Responder non-clinically significant (RNCS); Responder clinically significant (RCS)) according to their responsiveness to treatment related to functional scales scores thresholds commonly used to distinguish treatment efficacy[6,7,23,28] (Table S2).

Assessment: We assessed patients – or caregiving parent in patients younger than 12 years – with a questionnaire composed of 22 questions targeting important aspects and tasks in daily life of patients with SMA. This questionnaire was designed by the authors based on experience in treating and following patients with SMA (Table S3). The objective was not to validate a new questionnaire but to use a well-established method like the Patient Global Impression of Change (PGIC) to measure the perception of change for each item[11,29]. Question 1/22 was about the general impression of change of patient and caregiver after 15 months of treatment. We first explored the presence of an improvement (“Yes/No”) and then asked to score the perceived change with the PGIC. Except for the first one, questions were composed of two sub-questions: a) Baseline question: patients or caregivers were asked to reply by “Yes/No” whether they noticed the symptom or any difficulty with one specific task before treatment initiation; b) PGIC question: patients or caregivers were asked to score a potential change perceived compared to before treatment initiation to correlate their condition before treatment initiation with their condition following the first year of treatment, as reflected by daily tasks. The PGIC scale[29] uses 7 ratings scored from very much improved (rating 1), being the same (rating 4), to very much worse (rating 7) allowing the patient or caregiver to estimate whether a change is perceived after a year of stable nusinersen treatment. To avoid any confusion from the patient, we reversed the scoring system, such that lower scores represented worsening (scores 1-3) and higher scores represented improvement (scores 5-7) of the tested task. Question 22 is related to pain and comprised an additional question about the fact if whether pain was limiting the patient’s activity in daily life. (@Laurent, do we need to keep this question since we do not use it in results?)

Statistical analysis: Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 29.0. Variables were tested for normality using a Shapiro-Wilk test. Descriptive data are expressed as median (minimum – maximum) for non-normally distributed continuous data and as proportions for categorical variables. Differences in demographic characteristics and questionnaire responses across the three groups were examined using the Kruskal-Wallis test for continuous non-normally distributed data and ordinal variables (questionnaire items), whereas chi-square tests were used for categorical variables. Significant results ($p < 0.05$) were followed up with pairwise comparisons with a Bonferroni correction for multiple comparisons.

Initially, we examined the perception of change for each of the 22 questions among all patients across the three patient groups. Subsequently, in the 21 questions in which a baseline question was included, we conducted further analyses by differentiating the number of patients who noticed or did not notice the symptom or any difficulty with one specific task before treatment initiation. Statistical analyses were performed only when each questionnaire item (reporting yes or no) had a minimum of 10 patients represented across at least two patient groups. The PGIC score for each question was used to determine whether patients perceived themselves as worsened (Scores 1-3), unchanged (Score 4,) or improved (Scores 5-7) after 15 months of treatment initiation (Figure S1).

3. Results

A total of 99 participants were studied (see Table 1). Of these, 41 were classified as RCS, 18 as RNCS, and 40 were NR. No statistical difference across the different patient groups was found for sex, SMN2 copies, ambulatory status, patients across outcome groups, adverse events, scoliosis surgery and feeding assistance.

Significant differences were observed in the age at treatment initiation between the RCS and NR groups, with patients in the RCS group initiating treatment at a younger age (median age 5.20 years, range 0.39–47.8) compared to those in the NR group (median age 18.1 years, range 0.83–57.4), $p < 0.001$. Additionally, greater physiotherapy provision was observed for the RCS group compared to the NR group, and interestingly, less provision was observed for the RNCS group compared to the NR ($p < 0.01$).

Except for RCS at neck and right wrist/hand, patients across all groups presented contractures, with statistical differences observed between the right hand/wrist (RNCS > NR, $p < 0.001$) and left hand/wrist (RCS < RNCS, $p < 0.01$).

Ventilatory support and spinal surgery showed statistical differences between the different patient groups, with a higher rate observed in the NR group and a lower rate in the RCS group. However, there were no differences between groups in spinal surgery incidence after nusinersen initiation.

Table 1. Patient characteristics.

	Total (n=99)	RCS(n=41)	RNCS(n=18)	NR(n=40)	Raw p-value
Age at diagnosis (y); [Median (min-max)]	2.36 ; (0.01–28.5)	2.36; (0.01–28.5)	1.77; (0.49–16.5)	3.7; (0.23–22.0)	0.47
Age of first symptoms (y); [Median(min-max)]	1.25; (0.04–16.0)	1.42; (0.08–12.0)	1.0; (0.33–7.0)	1.33; (0.04–16.0)	0.29
Age at treatment initiation (y); [Median(min-max)]	11.16; (0.39–57.4)	5.20; (0.39–47.8)	12.3; (1.41–48.8)	18.1; (0.83–57.4)	RCS<NR, p_{adjusted}=<0.001
Sex, (% male)	51.5 %	48.8 %	50.0 %	55.0 %	0.85
SMN2 copy, n					
2 SMN2 copies	9.0	5.0	2.0	2.0	0.13
3 SMN2 copies	62.0	31.0	10.0	21.0	
4 SMN2 copies	20.0	3.0	6.0	11.0	
>4 SMN2 copies	3.0	1.0	0.0	2.0	
Unknown	5.0	1.0	0.0	4.0	
Patient type, n					
SMA Type 1 from 3-24 months	6.0	4.0	0.0	2.0	
SMA Type 1 from 24 months	5.0	0.0	3.0	2.0	0.17
SMA Type 2 from 6-24 months	2.0	1.0	0.0	1.0	
SMA Type 2 from 24 months	32.0	11.0	8.0	13.0	
SMA Type 3 from 24 months	11.0	7.0	0.0	4.0	

SMA Type 3 from 36 months	44.0	18.0	7.0	18.0	
Ambulatory status, n					
Non-ambulant	58.0	20.0	13.0	25.0	0.30
Loss of ambulation in progress	9.0	6.0	0.0	3.0	
Ambulant	32.0	15.0	5.0	12.0	
AE, n					
Hernia/fractures	12.0 %	43.0%	0%	0%	
Spinal surgery ^a	52.0%	29.0%	88.0%	40.0%	0.06
Hospitalization in ICU	12.0%	14.0%	12.0%	10.0%	
NIV implementation	8.0%	14.0%	0%	10.0%	
Two AEs	4.0%	0.0%	0.0%	10.0%	
Other	12.0%	0.0%	0.0%	30.0%	
Physiotherapy (% with physiotherapy)	78.8%	92.7%	61.1%	72.5%	RCS>NR, RNCS<NR, p _{adjusted} =0.01
Contractures, (% with contracture)					
Left Wrist/Hand	15.2%	2.4%	27.8%	22.5%	RCS < RNCS, p _{adjusted} =0.01
Right Wrist/Hand	15.2%	0.0%	33.3%	22.5%	RNCS > NR, p _{adjusted} =0.001
Left Elbow	23.2%	14.6%	33.3%	27.5%	0.21
Right Elbow	23.2%	14.6%	33.3%	27.5%	0.21
Left Shoulder	10.1%	2.4%	22.2%	12.5%	0.06
Right Shoulder	10.1%	2.4%	22.2%	12.5%	0.06
Left Hip	41.4%	31.7%	61.1%	42.5%	0.11
Right Hip	41.4%	31.7%	61.1%	42.5%	0.11
Left Knee	52.5%	51.2%	50.0%	55.0%	0.92
Right Knee	51.5%	51.2%	44.4%	55.0%	0.76
Left ankle	48.5%	36.6%	55.6%	57.5%	0.14
Right ankle	44.4%	31.7%	50.0%	55.0%	0.09
Neck	10.1%	0.0%	22.2%	15.0%	0.13
Scoliosis (% with scoliosis)	64.6%	56.1%	83.3%	65.0%	0.13
All spinal surgery ^b (% with spinal surgery)	27.3%	9.8%	38.9%	40.0%	RCS < RNCS, RCS < NR, p _{adjusted} =0.03
Ventilatory assistance (% with assistance)	23.2%	14.6%	44.4%	22.5%	RCS < RNCS, RNCS > NR, p _{adjusted} =0.04
% with diurnal assistance	23.0%	17.0%	37.0%	12.5%	0.45
% with nocturnal assistance	87.0%	100.0%	87.0%	78.0%	0.45

Feeding assistance (% with assistance)	7.10%	4.90%	5.60%	10.0%	0.64
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Table 1: Participant characteristics. RCS = responder clinically significant, RNCS = responder non-clinically significant and NR = non-responder. ^aSpinal surgery after treatment initiation. ^bAll spinal surgery before and after treatment initiation. Significant values that survived Bonferroni correction for multiple comparisons are in bold. Adjusted significance with p -value <0.05.

Table 2 presents the difference on the prioritized functional assessment depending on age at treatment initiation after 15 months of nusinersen.

HFMSE was the first in line in our prioritization list (Table S1) in patients older than 2 years (51/99 patients). Using HFMSE, 24 patients were classified as NR with a homogenous distribution between adults (n=13) and children (n=11), while RCS (n=27) comprised of 22 children.

In our cohort, CHOP-INTEND only assessed children, with an equal distribution across the three patient groups (RCS n=5; RNCS n=3; NR n=3).

Considering the entire population, the score differences between baseline and month 15 in the RCS group was higher in children than in adults (Table 2).

Table 2. Difference between baseline and M15 on the prioritized scale in relation to age at treatment initiation, and patient group.

Assessment type	Age category	RCS (n=41)	RNCS (n=18)	NR (n=40)
CHOP-INTEND (Δ)	Children (<18y)	16 \pm 4.74 (n=5)	2.0 1.0 (n=3)	-2.0 \pm 2.0 (n=3)
	Adult (\geq 18y)	–	–	–
HINE-2 (Δ)	Children (<18y)	–	–	-0.50 \pm 0.71 (n=2)
	Adult (\geq 18y)	–	–	–
HFMSE (Δ)	Children (<18y)	8.4 \pm 4.5 (n=22)	1.6 \pm 0.52 (n=10)	-1.82 \pm 2.14 (n=11)
	Adult (\geq 18y)	7.6 \pm 5.4 (n=5)	2.0 (n=1)	-1.54 \pm 1.94 (n=13)
MFM32 (Δ)	Children (<18y)	–	2.0 (n=1)	-6.0 (n=1)
	Adult (\geq 18y)	–	–	–
MFM20 (Δ)	Children (<18y)	8.67 \pm 3.2 (n=3)	–	–
	Adult (\geq 18y)	–	–	–
RULM (Δ)	Children (<18y)	5.0 \pm 2.8 (n=2)	1.0 \pm 0.0 (n=2)	-1.0 \pm 1.4 (n=2)
	Adult (\geq 18y)	3.0 \pm 1.4 (n=2)	1.0 \pm 0.0 (n=1)	-1.0 \pm 1.0 (n=5)
6MWT (Δ)	Children (<18y)	91.0 (n=1)	–	-8.0 (n=1)
	Adult (\geq 18y)	86.0 (n=1)	–	-13.0 \pm 18.4 (n=2)

Table 2: Age category is determined by age at treatment initiation. Functional assessments used to assess the patients: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neuromuscular Examination-Section 2 (HINE-2), Hammersmith Functional Motor Scale – Expanded (HFMSE), Revised Upper Limb Module (RULM), Motor Function Measure (MFM32), 6-minute walk test (6MWT). Delta (Δ) of baseline and Month 15. Score changes (Δ) after 15 months of treatment initiation depending on age category at treatment initiation across the patient groups are presented.

No statistical difference between RCS, RNCS and NR could be found in the general impression of change in quality of life (QoL) (Figure 1; Table S4). More than 78% of patients classified as NR reported an improvement in QoL (PGIC scores >4). On the other hand, approximately 12% of the RCS perceived no change in their QoL.

Figure 1: General Impression of change in quality of life.

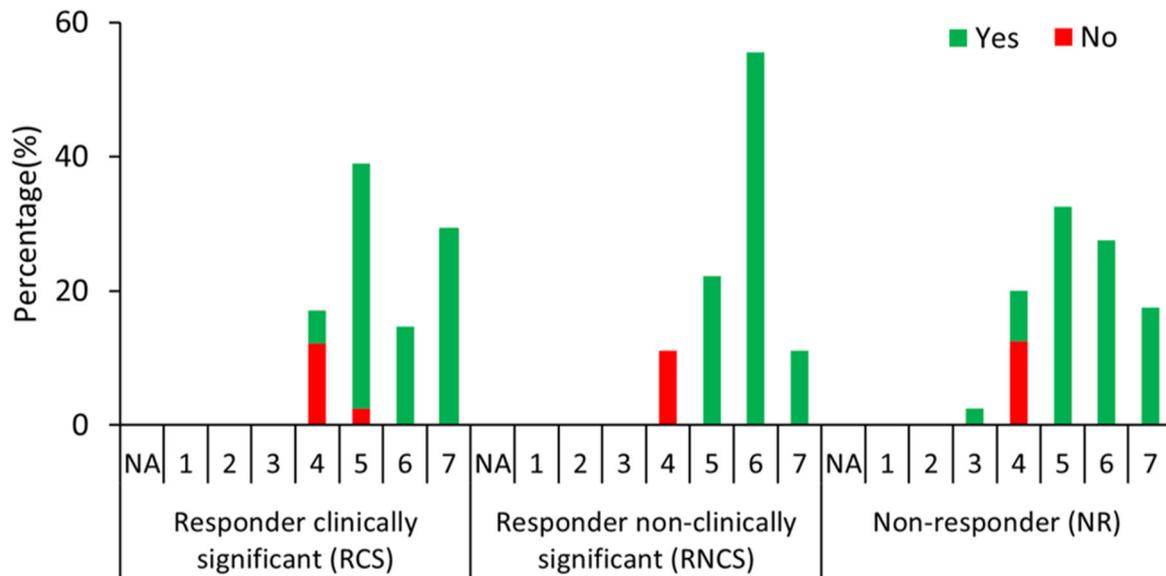


Figure 1. General impression of change in quality of life. 99 Patients were classified as RCS (n=41); RNCS (n=18); NR (n=40). The x-axis shows the PGIC score of 1 to 7 (1 being very much worse, 4 being the same and 7 being very much improved). The number of patients reporting yes/no an improvement after 15 month following treatment initiation are in green and red respectively. The y-axis shows the percentage of participants reporting yes/no to the presence of a symptom or difficulty at baseline, along with their PGIC scores across the three groups. NA = not applicable. No statistical difference was found across the three patient groups.

For the other questions assessing specific fields of potential improvement, we found no statistical difference in 16 out of 21 questions across the three groups (Table S4).

Next, we considered patients who reported difficulties at baseline for each of these 21 questions (baseline question). Again, we did not find any statistical difference between patient groups in 17 out of 21 questions (see Table 3).

Table 3. Perception of patients or caregivers for each of the 21 questions of the questionnaire across the responder groups depending on presence of symptom/difficulty before treatment initiation.

Questions (n=21)	Symptom/difficulty before treatment initiation? (Baseline question)	RCS (n=41)	RNCS (n=18)	NR (n=40)	Raw <i>p</i> -value
		Mean Rank			
Change in tremor	Yes	33.8 (n=32)	40.5 (n=12)	29.3 (n=22)	0.23
	No	– (n=9)	– (n=6)	– (n=18)	
Change in balance while sitting	YES	26.2 (n=18)	19.8 (n=9)	18.5 (n=16)	0.16
	No	32.5 (n=23)	28.7 (n=9)	24.5 (n=24)	RCS > NR, <i>p</i> adjusted=.04
	Yes	43.2 (n=34)	35.1 (n=14)	35.9 (n=29)	0.32

Change in balance while standing/walking	No	– (n=7)	– (n=4)	– (n=11)	
Change in fatigue	Yes	22.0 (n=19)	26.2 (n=9)	17.8 (n=14)	0.22
	No	28.6 (n=22)	31.7 (n=9)	28.4 (n=26)	0.76
Change in function involving hand and wrist muscles	Yes	32.7 (n=23)	29.9 (n=11)	23.4 (n=22)	0.13
	No	24.6 (n=18)	23.2 (n=7)	18.9 (n=18)	0.07
Change in function involving arm muscles	Yes	35.1 (n=22)	21.9 (n=9)	23.7 (n=24)	RCS > NR, $p_{adjusted}=0.04$
	No	24.4 (n=19)	23.4 (n=9)	19.7 (n=16)	0.14
Change in function involving shoulder muscles	Yes	42.7 (n=26)	26.4 (n=13)	29.4 (n=28)	RCS > RNCS, $p_{adjusted}=0.02$ RCS > NR, $p_{adjusted}=0.02$
	No	18.9 (n=15)	18.9 (n=5)	12.5 (n=12)	RCS > NR, $p_{adjusted}=0.04$
Change in ability to eat	Yes	17.7 (n=12)	18.3 (n=7)	15.7 (n=14)	0.79
	No	33.5 (n=29)	33.5 (n=11)	33.5 (n=26)	1.00
Change in appetite	Yes	– (n=9)	– (n=6)	– (n=10)	
	No	40.1 (n=32)	38.1 (n=12)	34.5 (n=30)	0.24
Change in aspiration	Yes	– (n=10)	– (n=5)	– (n=6)	
	No	40.7 (n=31)	39.5 (n=13)	38.4 (n=34)	0.55
Change in swallowing	Yes	– (n=9)	– (n=4)	– (n=11)	
	No	37.5 (n=32)	37.5 (n=14)	38.8 (n=29)	0.76
Change in chewing	Yes	15.5 (n=11)	14.6 (n=6)	12.1 (n=10)	0.59
	No	36.0 (n=30)	36.0 (n=12)	37.2 (n=30)	0.87
Change in loudness of voice	Yes	– (n=8)	– (n=6)	– (n=8)	

	No	42.1 (n=33)	37.5 (n=12)	36.4 (n=32)	RCS > NR, $p_{adjusted}=0.04$
Change in capacity for continuous conversation	Yes	– (n=8)	– (n=6)	– (n=5)	
	No	42.6 (n=33)	39.0 (n=12)	39.0 (n=35)	0.26
Change in quality of sleep	Yes	18.5 (n=19)	22.3 (n=6)	14.6 (n=10)	0.24
	No	33.4 (n=22)	32.0 (n=12)	32.0 (n=30)	0.82
Change in need for nocturnal ventilation	Yes	– (n=6)	– (n=6)	– (n=9)	
	No	40.1 (n=35)	42.3 (n=12)	37.8 (n=31)	0.35
Change in diurnal ventilation	Yes	– (n=2)	– (n=3)	– (n=4)	
	No	45.9 (n=39)	46.0 (n=15)	44.8 (n=36)	0.78
Change in cough	Yes	23.0 (n=15)	21.6 (n=8)	17.7 (n=17)	0.39
	No	29.5 (n=26)	29.5 (n=10)	30.8 (n=23)	0.77
Change in frequency of respiratory infections	Yes	18.9 (n=13)	19.2 (n=8)	18.9 (n=16)	0.99
	No	30.8 (n=28)	33.0 (n=10)	31.7 (n=24)	0.78
Change in the frequency of hospitalization due to respiratory infection	Yes	– (n=7)	– (n=5)	– (n=10)	
	No	39.0 (n=34)	39.0 (n=13)	39.0 (n=30)	1.00
Change in recurrent disease-related pain	Yes	17.7 (n=16)	18.8 (n=3)	13.1 (n=12)	0.33
	No	34.0 (n=25)	34.0 (n=15)	35.2 (n=28)	0.93

Table 3: The number of patients or caregivers who reported (yes or no) with regards to noticing symptom or difficulty changes prior to treatment initiation divided across 3 patient groups. Question 1 is excluded of this analysis; 21 questions remaining. Statistical analysis was performed only when each questionnaire item (reporting yes or no) had a minimum of 10 patients represented across at least two patient groups. Perception of patients scored by using the Patient Global Impression of change (PGIC) presented as mean rank as examined by Kruskal Wallis test. Significant results that survived Bonferroni correction for multiple comparisons are in bold. Adjusted significance with p -value <0.05.

Considering the patients who reported no difficulties at baseline, we did not find any difference between groups in 18 out of 21 questions (see Table 3). The only consistent differences in PGIC for the different groups were change in balance while sitting (RCS > NR, $p_{adjusted}=0.04$) (see Figure 2A), change in function involving shoulder muscles (RCS > NR, $p_{adjusted}=0.04$) (see Figure 2C) and change in loudness of voice (RCS > NR, $p_{adjusted}=0.04$) (see Figure 2D).

Figure 2: Statistical differences of the PGIC scores across the three patient groups depending on baseline question

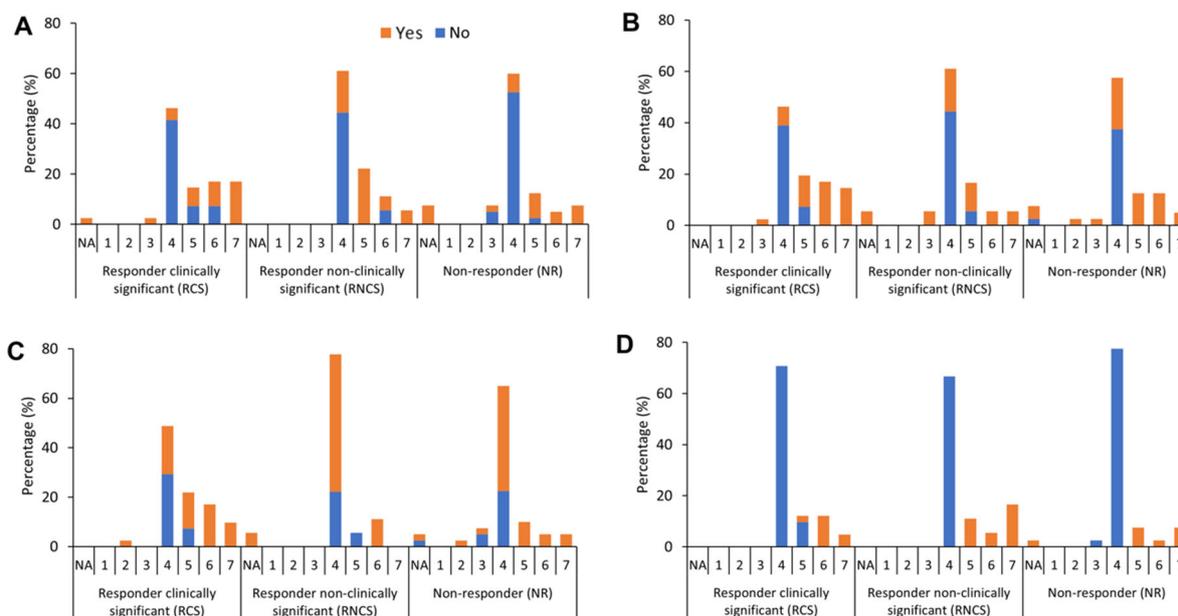


Figure 2. (A) Balance while sitting; (B) Function involving arm muscles; (C) Function involving shoulder muscles; (D) Loudness of voice. 99 Patients were classified as RCS (n=41); RNCS (n=18); NR (n=40). The x-axis shows the PGIC score of 1 to 7 (1 being very much worse, 4 being the same and 7 being very much improved). The number of patients reporting yes/no regarding the symptom/difficulty before treatment initiation are in orange and blue respectively. The y-axis shows the percentage of participants reporting yes/no to the presence of a symptom or difficulty at baseline, along with their PGIC scores across the three groups. NA = not applicable. Statistical differences across the three patient groups depending on baseline question were found for these four domains.

Considering the patients who reported difficulties at baseline, we did find differences in PGIC scores in only two questions amongst the patient groups: change in shoulder muscle function (RCS > RNCS $p_{adjusted}=0.02$; RCS > NR $p_{adjusted}=0.02$) (see Figure C) and change in arm muscle function (RCS > NR, $p_{adjusted}=0.04$) (see Figure B).

Notably, the patients classified as RCS according to the functional scales' thresholds improved not only on the functional scales but also according to their perception.

4. Discussion

We found that global impression of change did not differ between treated patients with SMA classified as responder or non-responder by standardized assessment. Patients' perception of change differed between RCS and NR in only 5 out of 21 questions, with NR reporting improvement in a broad range of domains. Minimal changes considered as not clinically relevant according to functional scales administered by an HCP might nevertheless be perceived as significant by patients themselves as they understand the progressive nature of their condition[30,31]. It must also be noted that a lack of deterioration can be considered as an achievement in SMA even though the MCID is not reached[28].

Another rationale to consider clinical significance at an individual level, rather than relying on absolute thresholds applicable to the entire population, is that the perception of change depends on the patients' functional abilities and age at treatment initiation[30,32–34].

Our findings support the need to change current appellations related to treatment efficiency. "Non-responders" should not be defined as patients who do not improve by a certain score on a certain scale, but as patients for whom the motor, respiratory, and/or bulbar evolution do not diverge from natural history or the expected evolution in absence of treatment.

The main variations in perception were observed in upper limb function and trunk balance.

HFMSE was the most used scale, and trunk strength and upper limb function were captured by several items (e.g., sitting items without support, rolling items, four-point kneeling items) in the total score. Patients across the three groups reporting difficulties at baseline perceived their upper limb function as improved, which aligns with existing findings highlighted by patients treated with nusinersen[35,36]. Patients assigned to the NR group and who experienced significant improvements in upper limb function could possibly have been identified as responders by the RULM which is more sensitive to positive upper limb function change than HFMSE. Indeed, in the pivotal trial of risdiplam, RULM could identify a significant progressive improvement difference in treated patients while HFMSE failed to do so[37].

Our study cohort is broadly heterogeneous in age and types of SMA and composes one of the rare real-world evidence studies including a paediatric and adult population with all types of SMA[16], which can be perceived as a limitation. Compared to RCS, NR were older at treatment initiation with a longer disease duration and less access to physiotherapy, which are known poor prognostic factors to treatment response[27]. Beyond the lower effect size of treatments on classical scales changes, treatment efficacy in older patients is always more challenging to demonstrate. This is linked to the irreversible damage of severe and chronic weakness such as contractures as well as from a respiratory perspective, comprising recurrent infections and pneumonia[38]. Nevertheless, this study clearly highlights that the absence of measurable response in patients when using classical outcomes does not rule out significant benefit as reported by the patients themselves or by their caregivers.

This confirms the need for the use of Patient-Reported Outcome Measures (PROMs)[39] to complement standardized assessments. Several different PROMs and QoL questionnaires have been developed in recent years in SMA[23,39] but also in other neuromuscular conditions[40] to offer a more patient-centric approach. However, the correlation of QoL questionnaire or PROMs with physical abilities can be challenging, especially in a treated adult population demonstrating only small functional changes on functional scales[41]. Several reasons can explain the poor correlation, such as the fact that clinical assessments are time-point evaluations and PROMs are more integrative measures. In addition, PROMs might be impacted by various variables such as social and mental well-being[42–44].

The additional challenge with studying patient perception throughout a clinical trial is that the results can be biased by initial treatment expectations evolving and changing over time. This could explain why patients not reporting the symptom/difficulty before treatment initiation report a positive change 15 months after treatment initiation. Expectations are related to various factors like type of SMA and functional status[34], but it has also been reported that expectations from patients and caregivers increased over time[31]. In addition, caregivers tend to depreciate the actual well-being of patients[42]. This could explain the fact that patients and patients' caregivers' overall impression of change in QoL in the RCS group rated no improvement after 15 months of nusinersen, although their functional scales score changed meaningfully. This suggests that the actual thresholds used for meaningfulness are not applicable to all patients. Meaningfulness should be considered at an individual level where the patient and clinician set goals to provide a balance between a patient-centric approach and objectivity.

Our study has several limitations. First, the choice of outcome measures and scales is not universal. We attempted to minimize this limitation by using a priori strict algorithm for scale selection. The second limitation is related to the possible heterogeneity in patients ranking. Although

the patients were followed up in reference neuromuscular centers, physiotherapists did not undergo study specific and common training. Time points for assessments are less precise in real life than during clinical trials. The baseline point was collected retrospectively from electronic health records. Further, the list of items on which patients answered through the PGIC does not constitute a validated questionnaire or scale, but much more a list of domains usually listed during clinics. Finally, RULM is an outcome measure which is more sensitive to upper limb change and could have captured improvement in the shoulder that is not captured by HFMSE. As HFMSE was prioritized to RULM to classify our patients, this might potentially explain the significant difference between the patient groups.

5. Conclusions

This study demonstrates that the benefit of a treatment, as experienced and reported by patients with SMA and their caregiver, is very poorly related to responder status provided by changes in standardized scales' scores. This supports the identification of patient-adapted therapeutic objectives rather than universal thresholds on standardized scales and questions the use of these thresholds as criteria used by payers to determine treatment continuity.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: Main results Analysis Flowchart; Table S1: Inclusion criteria: Study windows and Functional Scales; Table S2: Assignment to Responder groups; Table S3: Questionnaire; Table S4: Perception of patients for each question of the questionnaire across the responder groups.

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