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Muscle quantitative MRI in adult SMA patients on nusinersen treatment: a longitudinal study

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The recent approval of disease-modifying therapies for spinal muscular atrophy (SMA) raised the need of alternative outcome measures to evaluate treatment efficacy. In this study, we investigated the potential of muscle quantitative MRI (qMRI) as a biomarker of disease progression in adult SMA3 patients during nusinersen treatment. Six adult SMA3 patients (age ranging from 19 to 65 years) underwent 2-point Dixon muscle qMRI at beginning of nusinersen treatment (T0) and after 14 months (T14) to evaluate the muscle fat fraction (FF) at thigh and leg levels; patients were clinically assessed at T0 and T14 with the Hammersmith Functional Rating Scale Expanded (HFMSE), the Revised Upper Limb Module (RULM) and the 6-minute walk test (6MWT). At T0, vastus lateralis muscle displayed the highest mean FF (67.5%), while tibialis anterior was the most preserved one (mean FF = 35.2%). At T0, a slightly significant correlation of FF with HFMSE ($p = 0.042$) and disease duration ($p = 0.042$) at thigh level and only with HFMSE ($p = 0.042$) at leg level was found. At T14, no significant change of mean FF values at thigh and leg muscles was found compared to T0. Conversely, a statistically significant ($p = 0.042$) improvement of HFMSE was reported at T14. We observed no significant change of FF in thigh and leg muscles after 14 months of nusinersen therapy despite a significant clinical improvement of HFMSE. Further studies with longer follow-up and larger cohorts are needed to better investigate the role of qMRI as marker of disease progression in SMA patients.

Key words: SMA, qMRI, fat fraction, outcome measures, biomarker

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Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by a homozygous deletion or smaller mutations of *SMN1* gene causing a reduction of survival motor neuron (SMN) protein, and leading to bulbar and spinal motor neuron degeneration. Four clinical SMA subgroups have been described according to age at onset and maximal motor function achieved, with SMA1 being the most severe phenotype and SMA4 presenting in adult age and characterised by non-progressive mild muscle weakness [1]. Recently, the introduction of new therapeutic approaches has changed the disease natural history [2-4]. The first dis-

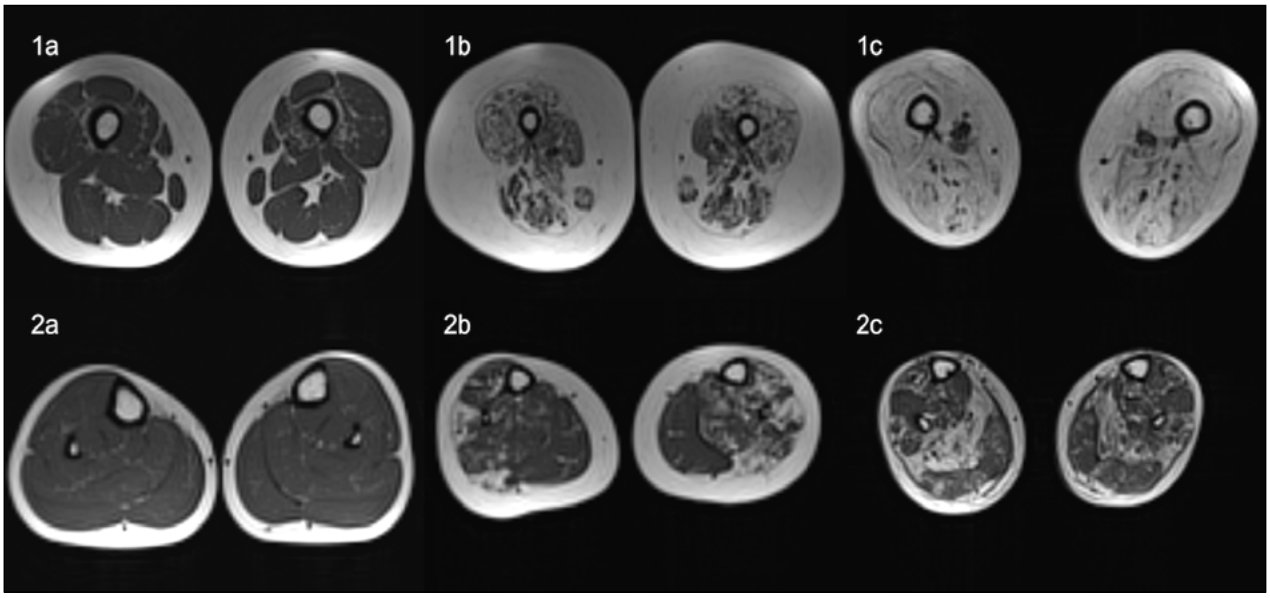

Figure 1. Examples of muscular involvement at thigh (1) and leg level (2) in SMA3 patient with mild (A), medium (b) or severe (c) muscular fat infiltration.

ease-modifying treatment approved in US and EU was the antisense oligonucleotide nusinersen, as reported by two randomized double-blind clinical trials in infantile and later-onset SMA [2,3]. Furthermore, nusinersen has been proved to be effective even in adult age according to observational studies [5,6].

The progression of SMA2 and SMA3 in untreated adult patients is typically slow over the years, regardless the age [7]. However, available clinical outcome measures to assess SMA progression have been validated in pediatric patients and mainly focused on motor function; in addition, they are not always able to catch clinical changes reported by patients [8]. Hence, alternative clinical and nonclinical outcome measures are needed to assess disease progression and evaluate treatment effects in adult SMA patients. In this regard, muscle quantitative magnetic resonance imaging (qMRI) represents a promising biomarker in neuromuscular disorders, being able to discriminate and quantify sub-clinical modifications of the fatty changes in the muscle tissue due to disease progression or treatment response. Indeed, muscle qMRI has been already included as outcome measures in pharmacological clinical trials or natural history studies, particularly in Duchenne muscular dystrophy [9-11]. To date, 4 studies investigating SMA disease progression through qMRI have been reported [12-15]; among them, only 2 focused on nusinersen treatment effect, including respectively 3 and 2 adult SMA3 patients [15,12].

Here, we aimed to study clinical and qMRI modifications in 6 adult SMA3 patients treated with nusinersen over a 14-month period.

Methods

Patients

In this longitudinal study inclusion criteria were the following: (1) clinical and molecular diagnosis of SMA3; (2) ongoing treatment with nusinersen. Patients with contraindications to MRI were excluded.

Standard protocol approvals, registrations and patient consents

This monocentric study has been approved by the Ethics Committee of Fondazione IRCCS Istituto Neurologico 'Carlo Besta', on 17 March 2021. Written informed consent was obtained from all the participants, according to the Helsinki declaration.

Nusinersen administration

All patients received nusinersen intrathecal loading doses of 12 mg at baseline (T0), day 14, day 28 and day 63, followed by maintenance doses every 4 months according to the standard protocol.

Intrathecal injections were performed with standard lumbar access or via X-ray-guided procedure.

qMRI protocol

Patients underwent 2 muscle qMRI (Fig. 1), at baseline (T0) and after 14 months of treatment (T14), respectively. The study focused on the proportion of fatty infil-

tration of the thigh and leg muscles, defined as fat fraction (FF) and measured using the 2-point Dixon imaging technique, as follows. The subject images were acquired with a 1.5T MRI scanner (Avanto, Siemens, Erlangen, Germany). The MRI protocol included the following sequences: 1) a standard axial T1-weighted sequence (TR/TE = 550/8.6 ms, matrix = 192 × 192 × 30, flip angle = 146°, voxel size = 1.98 × 1.98 × 5 mm); 2) a 2-point Dixon sequence for fat/water fraction quantification (TR = 11.1 ms, TE = 2.39/4.78 ms, matrix = 352 × 260 × 192, flip angle = 10°, voxel size = 1.13 × 1.13 × 1.1 mm). The mean duration of the muscle MRI protocol was around 30 minutes.

Post-processing

The fat fraction (FF), expressed as F/(F+ W) × 100 (F = signal of the fat-only image, W = signal of the water-only image), was estimated from the Dixon sequence using Matlab (www.mathworks.com).

Regions of interest (ROIs) were traced on water images by a neurologist (AG) and a neuroradiologist (MM) on two slices, at the midlevel of thighs and at the midlevel of calves, covering all the cross-sectional area of a muscle (Fig. 2). ROIs were traced on 11 muscles in the thighs: rectus femoris, vastus lateralis, vastus medialis, vastus intermedius, sartorius, gracilis, adductor magnus, adductor longus, semimembranosus, semitendinosus and biceps femoris. Six muscles were included for the calves: tibialis anterior, medial head of gastrocnemius, lateral head of gastrocnemius, soleus, tibialis posterior, peroneus longus. Then, using ROIs as binary masks and applying them to the maps, all the metrics were extracted. Mean FF in each muscle of both sides were averaged together (global mean) at thigh and calf levels.

Clinical assessments

The following clinical outcome measures were assessed by trained evaluators at T0 and T14: the Hammersmith Functional Rating Scale Expanded (HFMSE) [16]; the Revised Upper Limb Module (RULM) [17]; the 6 minute walk test (6MWT) [18]. HFMSE assesses the global motor performance and includes 33 items, each scored from 0 to 2, up to a maximum of 66 points. RULM is a scale focused on the upper limb motor function and consists of 20 items with a maximum score of 37. Higher scores correspond to a better motor performance for both scales. The 6MWT test measures the distance in meters walked by the patient in 6 minutes.

Clinically meaningful changes were considered as an improvement from T0 to T14 by at least 3 points with HFMSE, 2 points with RULM or 30 meters with 6MWT, as defined in previous studies [16,19,20].

The patients were considered as wheelchair-bound when not able to walk at least few steps without the aid of other people.

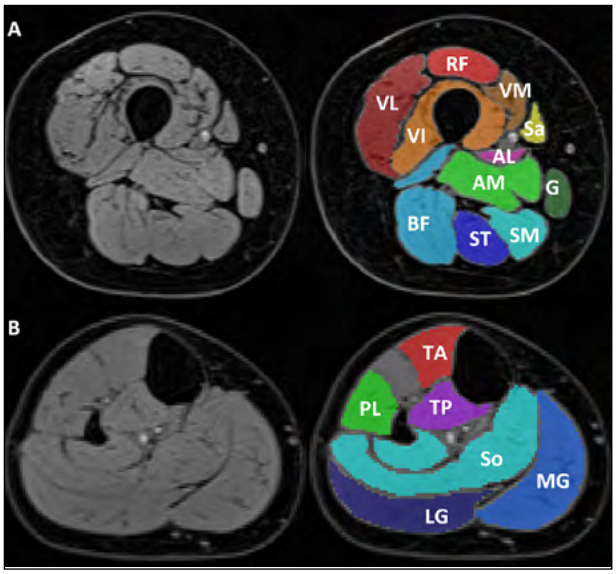

Figure 2. Examples of water images at middle thigh level (A) and middle calf level (B) in a SMA3 patient before and after drawing the muscle regions of interest (ROIs). SM: semimembranosus; ST: semitendinosus; BF: biceps femoris; VI: vastus intermedius; VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis; Sa: sartorius; G: gracilis; AM: adductor magnus; AL: adductor longus; TA: tibialis anterior; PL: peroneus longus; TP: tibialis posterior; So: soleus; MG: medial head of gastrocnemius; LG: lateral head of gastrocnemius.

Statistical analysis

This study was exploratory, thus, a formal sample size was not provided. The number of patients recruited was based pragmatically on the number of patients known to have the disease of interest and eligible for enrolment.

Wilcoxon Signed Rank test was used to research possible significant modification of fat fraction and clinical measures between T0 and T14 assessments. The association between muscle FF and disease duration or clinical variables has been described with the use of Spearman correlation coefficients. Statistical significance was set at $p < 0.05$.

Results

All included patients (4 females and 2 males) were affected by SMA3 caused by a homozygous deletion of exons 7 and 8. Mean age at onset was 7 ± 6.6 years and mean age at T0 was 40.7 ± 18.8 years. At baseline, no patient had received ventilator support or spinal surgery for scoliosis. Clinical and molecular features of patients and their performance on clinical assessments at T0 and T14 are shown in Table I.

Table I. Clinical and molecular features of patients.

Patient/ gender	SMN2 copy number	Age at onset (y)	Ability to walk/age at loss of ambulation (y)	Comorbidities	Age at T0 (y)	Disease duration at T0 (y)	HFMSE		RULM		6MWT	
							T0	T14	T0	T14	T0	T14
1/F	4	16	yes	no	17	1	66	66	37	37	536 m	640 m
2/F	4	15	yes	bipolar disorder	65	50	45	49	36	37	375 m	400 m
3/M	4	3	no/16	no	32	29	12	18	19	22	wb	wb
4/F	3	2	no/45	no	55	53	14	23	21	25	wb	wb
5/F	4	3	yes	no	25	22	54	57	37	36	275 m	300 m
6/M	4	3	yes	no	50	47	44	47	29	27	172 m	182 m

n: number; y: years; HFMSE: Hammersmith Functional Motor Scale Expanded (score); 6MWT: six-minute walk test distance (m); RULM: Revised Upper Limb Module (score); wb: wheelchair-bound; T0: baseline; T14: 14 months of therapy. Clinically meaningful changes at T14 are underlined.

Clinical scores

HFMSE scores were significantly (p = 0.042) improved in our cohort at T14, with a median change of 3.5 (range = 0-9); except for patient 1, displaying normal HFMSE and RULM scores already at T0, HFMSE score improved in all patients by at least 3 points. RULM score did not significantly improved during the follow-up (median change = 1.5; range = 0-4); clinically meaningful improvement with RULM was found at T14 only in patients 3 and 4. Similarly, 6MWT did not significantly improve at T14 (median change = 25; range = 10-104); clinically meaningful improvement with 6MWT was observed only in patient 1.

qMRI

Pattern of muscle involvement at T0

FF for thigh and leg muscles at baseline was reported in Figure 3 and 4, respectively. At thigh level the anterior compartment (vastus intermedius, vastus lateralis, rectus femoris and vastus medialis) was the most involved at baseline, showing a mean FF of 65.4%, with vastus lateralis (mean FF = 67.5%; range = 11.0-87.4%) representing the most impaired muscle. The posterior (semimembranosus, semitendinosus, biceps femoris) and middle compartment (sartorius, gracilis, adductor magnus and adductor longus) displayed a comparable mean FF (respectively 56.8 and 55.5%). At the thigh level the adductor longus was the most preserved muscle (mean FF = 47.9%; range = 7.2-91.2%). At leg level the extensor compartment (tibialis anterior and peroneus longus) showed a mean FF of 40.4%, comparable to the mean FF (41.3%) of the flexor compartment (soleus, medial head of gastrocnemius, lateral head of gastrocnemius and tibialis posterior). Soleus was the most fat-replaced muscle in the leg (mean FF = 47.0%; range = 6.4-90.7%), while tibialis anterior showed the lowest mean FF value (35.2%) with a range of 4.5-74.5%.

Leg muscles were more preserved in ambulant patients compared to wheelchair-bound patients (patients 3 and 4),

pt/muscle	SM	ST	BF	VI	VL	RF	VM	Sa	G	AM	AL
1	6,2%	6,4%	7,7%	24,1%	11,0%	6,4%	11,5%	8,7%	6,8%	7,4%	7,2%
2	22,4%	75,8%	33,4%	78,7%	87,4%	85,0%	84,7%	87,3%	69,1%	29,8%	59,0%
3	83,3%	77,6%	84,6%	74,6%	78,3%	82,6%	69,0%	69,3%	80,7%	74,4%	55,4%
4	76,0%	77,5%	70,0%	87,9%	80,4%	85,5%	75,2%	88,1%	81,5%	81,7%	91,2%
5	48,0%	61,7%	52,8%	55,4%	64,5%	61,4%	37,5%	34,5%	55,9%	35,3%	34,0%
6	80,0%	78,5%	80,4%	84,3%	83,6%	83,0%	78,6%	83,7%	72,1%	78,3%	40,8%

Figure 3. Heatmap of muscle fat fractions at thigh level (baseline). Values are an average of right and left FF. Red colour corresponds to the highest FF levels, green colour to the lowest one; orange and yellow colours correspond to intermediate values of fat fraction. Pt: patient; Muscles: SM: semimembranosus; ST: semitendinosus; BF: biceps femoris; VI: vastus intermedius; VL: vastus lateralis; RF: rectus femoris; VM: vastus medialis; Sa: sartorius; G: gracilis; AM: adductor magnus; AL: adductor longus.

pt/muscle	TA	PL	TP	So	MG	LG
1	4,5%	7,5%	5,9%	6,4%	5,2%	4,0%
2	6,2%	11,3%	13,0%	18,0%	13,8%	13,2%
3	74,5%	83,2%	72,1%	90,7%	85,9%	89,5%
4	61,2%	73,7%	66,9%	80,3%	78,5%	84,1%
5	41,4%	55,8%	34,1%	24,4%	9,2%	71,7%
6	23,6%	42,3%	22,9%	62,3%	19,6%	18,6%

Figure 4. Heatmap of muscle fat fractions at leg level (baseline). Values are an average of right and left FF. Red colour corresponds to the highest FF levels, green colour to the lowest one; orange and yellow colours correspond to intermediate values of fat fraction. Pt, patient. Muscles: TA: tibialis anterior; PL: peroneus longus; TP: tibialis posterior; So: soleus; MG: medial head of gastrocnemius; LG: lateral head of gastrocnemius.

showing severe fatty changes in both proximal and distal muscles. Notably, patient 1 displayed overall a mild muscle fat replacement, with the greatest FF in the vastus intermedius (24.1%), in agreement with the short disease duration and the normal motor performance by HFMSE and RULM. Conversely, patients with the longest disease duration (patients 2, 4 and 6) exhibited the highest FF in sartorius (range: 83.7%-88.1%). In this subgroup patient 2 had a lower global FF at thigh (64.8%) and leg (12.6%) level compared to patients 4 and 6, mainly as a consequence of a lower fat infiltration of semimembranosus, biceps femoris, adductor magnus and of all the leg muscles. These data are probably related to a relatively mild disease severity, being this patient still able to walk after a 50-year disease duration.

FF at thigh level resulted slightly correlated with disease duration ($p = 0.044$) and HFMSE ($p = 0.042$) score; conversely, FF at leg level was slightly associated only with the HFMSE ($p = 0.042$) score (Tab. II).

FF changes at T14

Total mean FF at thigh and calf levels at T0 and T14 are shown for each patient in Table III. Considering the whole cohort, the mean thigh FF resulted unchanged from baseline (59.8%) to T14 (60.9%); similarly, no significant change of mean FF at leg level was detected between T0 (41.0%) and T14 (41.8%). Although not significant, the mean increase of FF across the 2 timepoints was higher in vastus intermedius (3.9%), vastus medialis (3.6%) and adductor longus (3.3%). All remaining muscle showed mean FF modifications below 3%.

Discussion

SMA natural history in adult age still needs to be completely elucidated. Moreover, better comprehension of factors predicting disease progression and response to new treatments is needed. In this regard, qMRI is increasingly recognised as a promising biomarker for disease severity and progression in different neuromuscular disorders. However, poor data on qMRI have been reported in SMA, especially in patients under treatment.

In our study, we did not find any significant change of FF values at thigh and leg levels after a 14-month period of treatment with nusinersen, regardless clinically meaningful changes detected by HFMSE and RULM. Lack of significant modification of FF and concordance with clinical improvement may be related to different factors, as the small sample size, the relatively short observational period and the high muscle fat fraction detected at the baseline in our cohort (thigh FF > 50% in 5/6 patients and leg FF > 30% in 3/6 patients), suggesting a relevant muscle fat replacement before the beginning of the treatment. However, we cannot exclude that unchanged FF values in our co-

Table II. Correlation between FF and clinical scores or disease duration at T0.

		Spearman p-values	Correlation coefficients
FF at thighs	**HFMSE**	**0.042**	- 0.829
	RULM	0.050	- 0.812
	6MWT	0.200	- 0.800
	DD	**0.044**	0.829
FF at legs	**HFMSE**	**0.042**	- 0.829
	RULM	0.084	- 0.754
	6MWT	0.200	- 0.800
	DD	0.544	0.314

Significant p values are highlighted in bold. FF, fat fraction; HFMSE, Hammersmith Functional Rating Scale Expanded; RULM, Revised Upper Limb Module; 6MWT, six-minute walk test; DD, disease duration

hort may be the result of the ongoing treatment with nusinersen. The discrepancy between qMRI data and the small clinical improvement could be related to the inability of FF to catch the positive treatment effect, which could instead be linked to other mechanisms acting on the spared muscle tissue. Savini and colleagues [15] reported a progression of FF in thigh muscles of 3 SMA3 adult patients during 21 months of treatment and a concurrent slight reduction of wT2 over time. This apparent mismatch with our data could be related to the longer follow-up period in the aforementioned study (21 months against 14 months in our study) and a smaller sample size. In this landscape, considering also literature data about nusinersen efficacy in adult SMA patients during the first 14 months of treatment [6], we cannot exclude that nusinersen could be more effective in preventing the muscle degeneration during the first year of therapy, followed by possible resumption of the muscle deterioration. Conversely, Barp and colleagues [12] showed a reduction of fractional anisotropy through diffusion tensor imaging MRI after 24 months of nusinersen therapy in 2 SMA3 adult patients, suggesting a disease stabilization during the treatment, in agreement with our data. However, the application of different qMRI techniques (DTI *vs* 2-point Dixon) do not allow a real comparison among the two studies.

Furthermore, a considerable limitation of all the aforementioned studies, including the present one, is the absence of a control group of untreated SMA patients. In this regard, 2 longitudinal studies investigated muscle deterioration through qMRI in SMA patients, providing contrasting data [13,14]. Bonati and colleagues [13] did not report any significant progression of muscle FF in 18 SMA3 patients over a period of 13 months, suggesting that a longer observation period could be necessary to detect possible FF modifications. Conversely, Otto and colleagues [14] showed a significant increase of FF and a significant decrease of T2 over a 13-month follow-up in a cohort of 10 (5 SMA3 and 5 SMA2) patients, despite any decline of muscle power and motor function scores. The discrepancies between these two studies could be partially explained by the inclusion of more severe patients in the study by Otto and colleagues. Indeed, a further limitation of data from literature and our study is represented by the heterogeneity of the investigated population in terms of age and disease severity.

In addition, considering that the pattern of muscle involvement in SMA could be the result of a degeneration more prominent in specific groups of motor neurons [21], the different study design in the aforementioned studies represent a further confounding factor. Barp and colleagues [12] focused their analyses on 4 leg muscles, without including thigh muscles; on the other side, the remaining 3 longitudinal studies [13-15] were limited to thigh muscles. To our knowledge, thigh and leg muscles were both investigated for the first time in the present study. Higher FF values were detected in leg muscles in wheelchair-bound than in ambulant SMA3 patients at T0, regardless the disease duration, without any apparent difference at the thigh level. With the limitations of the small sample size, these data may suggest that focusing qMRI on leg muscles could be more helpful to predict clinical decline and loss of walking ability; further studies are needed in this regard on large cohort of patients. Besides, longitudinal studies are needed to investigate the role of the upper limb muscle qMRI, particularly in patients with severe phenotypes characterized by residual upper limb motor function and loss of lower limb motor abilities.

Table III. Total mean fat fractions for each patient.

	Total mean FF THIGHS		**Total mean FF LEGS**	
Pt	**T0**	**T14**	**T0**	**T14**
1	9.4% ± 27.1%	10.4% ± 27.4%	5.6% ± 31.6%	6.1% ± 31.4%
2	64.8% ± 27.1%	64.4% ± 27.4%	12.6% ± 31.6%	11.8% ± 31.4%
3	75.4% ± 27.1%	80.8% ± 27.4%	82.6% ± 31.6%	82.8% ± 31.4%
4	81.4% ± 27.1%	81.6% ± 27.4%	74.1% ± 31.6%	73.7% ± 31.4%
5	49.2% ± 27.1%	51.1% ± 27.4%	39.4% ± 31.6%	43.3% ± 31.4%
6	76.7% ± 27.1%	77.2% ± 27.4%	31.5% ± 31.6%	33.4% ± 31.4%

FF, fat fraction; T0, baseline; T14, 14 months of therapy; pt, patient

A correlation at baseline between FF and HFMSE score and between FF and disease duration at thigh level and between FF and HFMSE at legs further strengthen the role of FF as a marker of disease severity, as already reported in SMA patients [22].

Our study revealed a pattern of muscle involvement in agreement with data already reported in literature [21,23-25], although in our cohort sartorius was severely involved as the gracilis and the adductor magnus was relatively preserved. However, utilization of semiquantitative scales in place of qMRI to assess the amount of fatty degeneration in most of these studies, may explain some discrepancies with our data. Notably, vastus intermedius displayed the highest FF in our patient with only a 1-year disease duration, suggesting that this muscle is early involved in the pathological process.

Conclusions

Our study showed stability of fatty infiltration values in thigh and leg muscles of SMA3 adult patients during

14 months of therapy with nusinersen, regardless the clinical improvement. Further studies with longer follow-up, larger cohorts of patients and including other techniques as T2 and DTI or upper limb muscles are needed to better investigate muscle qMRI value as marker of disease severity and progression in SMA patients.

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Conflict of interest statement

LM has received honoraria for speaking and compensation for congress participations from: Sanofi Genzyme, Roche and Biogen; SV received honoraria for advisory board activities, and compensation for travel and congress participation from Sanofi Genzyme, Biogen and Roche; RZ received funds for travel and congress participation from Biogen.

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Authors' contributions

AG performed data analysis and their interpretation, drafted the manuscript; FM performed data analysis and their interpretation and revised the manuscript. SB collected data and revised the manuscript. RZ collected data; MM performed data analysis and their interpretation and revised the manuscript; DA performed data analysis and their interpretation and revised the manuscript; LM planned the study, performed data analysis and their interpretation, drafted and submitted the manuscript.

Ethical consideration

The study was approved by by the Ethics Committee of Fondazione IRCCS Istituto Neurologico 'Carlo Besta', on 17 March 2021 (No. 24/2022). This study was performed in line with the principles of the Declaration of Helsinki.

References

1 Mercuri E, Pera MC, Scoto M, et al. Spinal muscular atrophy – insights and challenges in the treatment era. Nat Rev Neurol 2020;12:706-715. https://doi.org/10.1038/s41582-020-00413-4

2 Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723-1732. https://doi.org/10.1056/NEJMoa1702752

3 Mercuri E, Darras MT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018 378:625-635 https://doi.org/10.1056/NEJMoa1710504

4 Baranello G, Darras BT, Day JV, et al. Risdiplam in type 1 spinal muscular atrophy. N Engl J Med 2021;384:915-923; https://doi.org/10.1056/NEJMoa2009965

5 Hagenacker T, Wurster CD, Günther R, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol 2020;19:317-325. https://doi.org/10.1016/S1474-4422(20)30037-5

6 Maggi L, Bello L, Bonanno S, et al. Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3. J Neurol Neurosurg Psychiatry 2020;91:1166-1174. http://dx.doi.org/10.1136/jnnp-2020-324036

7 Wijngaarde CA, Stam M, Otto LAM, et al. Population-based analysis of survival in spinal muscular atrophy. Neurology 2020;94:e1634-e1644. http://dx.doi.10.1212/WNL.0000000000009248

8 Sansone VA, Walter MC, Attarian S, et al. Measuring outcomes in adults with spinal muscular atrophy - challenges and future directions. Meeting Report. J Neuromuscul Dis 2020;7:523-534. https://doi.org/10.3233/JND-200534

9 Wokke BH, van den Bergen JC, Versluis MJ, et al. Quantitative MRI and strength measurements in the assessment of muscle quality in Duchenne muscular dystrophy. Neuromuscul Disord 2014;24:409-416. https://doi.org/10.1016/j.nmd.2014.01.015

10 Willcocks RJ, Rooney WD, Triplett WT, et al. Multicenter prospective longitudinal study of magnetic resonance biomarkers in a large Duchenne muscular dystrophy cohort. Ann Neurol 2016;79:535-547. https://doi.org/10.1002/ana.24599

11 Keller S, Wang ZJ, Aigner A, et al. Diffusion tensor imaging of dystrophic skeletal muscle. Clin Neuroradiol 2019;29:231-242. https://doi.org/10.1007/s00062-018-0667-3

12 Barp A, Carraro E, Albamonte E, et al. Muscle MRI in two SMA patients on nusinersen treatment: a two years follow-up. J. Neurol Sci 2020;417:117067. https://doi.org/10.1016/j.jns.2020.117067

13 Bonati U, Holiga S, Hellbach N, et al. Longitudinal characterization of biomarkers for spinal muscular atrophy. Ann Clin Transl Neurol 2017;4:292-304. https://doi.org/10.1002/acn3.406

14 Otto LAM, Froeling M, van Eijk RPA, et al. Quantification of disease progression in spinal muscular atrophy with muscle MRI – a pilot study. NMR Biomed 2021;34:e4473. https://doi.org/10.1002/nbm.4473

15 Savini G, Asteggiano C, Paoletti M, et al. Pilot study on quantitative cervical cord and muscular MRI in spinal muscular atrophy: promising biomarkers of disease evolution and treatment? Front Neurol 2021;12:613834. https://doi.org/10.3389/fneur.2021.613834

16 Pera MC, Coratti G, Forcina N, et al. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. BMC Neurol 2017;17:39. https://doi.org/10.1186/s12883-017-0790-9

[17] Mazzone E, Bianco F, Martinelli D, et al. Assessing upper limb function in nonambulant SMA patients: development of a new module. Neuromuscul Disord 2011;21:406-412. https://doi.org/10.1016/j.nmd.2011.02.014

[18] Montes J, McDermott MP, Martens WB, et al. MD Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. Neurology 2010;74:833-838. https://doi.org/10.1212/WNL.0b013e3181d3e308

[19] Dunaway Young S, Montes J, Kramer SS et al. Six-minute walk test is reliable and valid in spinal muscular atrophy. Muscle Nerve 2016;84(14 Suppl):P7.075. http://dx.doi.org/10.1002/mus.25120

[20] Pera MC, Coratti G, Mazzone ES, et al. Revised upper limb module for spinal muscular atrophy: 12 month changes. Muscle Nerve 2019;59:426-430. http://dx.doi.org/10.1002/mus.26419

[21] Brogna C, Cristiano L, Verdolotti T, et al. MRI patterns of muscle involvement in type 2 and 3 spinal muscular atrophy patients. J Neurol 2020;267:898-912. https://doi.org/10.1007/s00415-019-09646-w

[22] Hooijmans MT, Habets LE, van den Berg-Faay SAM, et al. Multi-parametric quantitative magnetic resonance imaging of the upper arm muscles of patients with spinal muscular atrophy. NMR Biomed 2022:e4696. http://dx.doi.org/10.1002/nbm.4696

[23] Otto LAM, van der Pol W-L, Schlaffke L, et al. Quantitative MRI of skeletal muscle in a cross-sectional cohort of patients with spinal muscular atrophy types 2 and 3. NMR Biomed 2020;33:e4357 https://doi.org/10.1002/nbm.4357

[24] Ueno T, Yoshioka H, Iwasaki N, et al. MR findings of spinal muscular atrophy Type II: sibling cases. Magn Reson Med Sci 2003;2:195-198. https://doi.org/10.2463/mrms.2.195

[25] Inoue M, Ishiyama A, Komaki H, et al. Type-specific selectivity pattern of skeletal muscle images in spinal muscular atrophy. Neuromuscul Disord 2015;25(Suppl 2):S194. http://dx.doi.org/10.1016/j.nmd.2015.06.042