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Functional and structural analysis of SITTER patients with spinal muscular atrophy

Aleksandra Bieniaszewska[1]✉, Magdalena Sobieska[2] & Ewa Gajewska[1]

In recent years, three disease-modifying therapies have been approved and fully reimbursed in Poland since September 2023. Those therapies have significantly improved the disease outcome but led to new uncertainties. Doubts mainly concern older patients who have already developed complications occurring because of a lack of previous access to therapy. Joint contractures or trunk deformation are the most noticeable changes that should be examined. This work examines functional and structural changes in SMA sitter patients between the ages of 5 and 20 years during the 12-month follow-up. Twenty-one SMA patients were divided depending on the drug program in which they participated. The study protocol included functional and structural assessments. Most of the subjects experienced an improvement in cervical rotation parameter and increased contracture of the hip and knee joints. There are differences between the patients' body sides. Neither the contractures nor their gradual decrease or increase occur symmetrically. We conclude that all patients under study improved their motor function after 12 months. In both groups, more significant improvement occurred in the assessment of the RULM scale than in the HFMSE scale. Improvement in function was not dependent on improvement in structural parameters.

Keywords Spinal muscular atrophy, Sitter patients, Functional assessment, Structural assessment, Joint contractures

Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disorder with an estimated incidence of 1: 6—10,000 live births[1,2]. It is associated with degeneration of the spinal cord's anterior horn cells, resulting in muscle weakness and progressive muscle atrophy. The disease manifests as a general deterioration of motor function, progressive joint contractures, and scoliosis or respiratory disorders. Until recently, no specific therapy was available[1,3]

In recent years, three disease-modifying therapies, Spinraza (Nusinersen), Zolgensma (Onasemnogen abeparvovek, a gene therapy), and Evrysdi (Risdiplam), have been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It has been fully reimbursed in Poland since September 2023[2,4–8]. The effects of the treatment can be seen in improved respiratory function, reduced hospitalizations or achievement of new milestones that were not possible before the introduction of the treatment[7,9–13]. The altered clinical picture of the disease led to a new classification, dividing patients into non-sitter, sitter, or walker based on the functional level presented by the child[7,14,15].

The first Polish data on treatment satisfaction and quality of life of sick children with SMA published in the 2024 Report (in this case, treatment with Nusinersen) show that more than 80% of patients are satisfied with the treatment received. Among the important effects of the therapy, increased strength and endurance, improved motor and hand function, and the ability to breathe independently or perform activities of daily living were mentioned. More than 70% of pediatric patients note that some of the symptoms of the disease have disappeared, significantly improving their quality of life[16].

In contrast to the natural course of SMA observed so far and the course in children who receive treatment immediately after birth (diagnosed with screening), there is still an intermediate group who also began effective treatment but not immediately after birth. These patients have already experienced the natural course of the disease with progressive deficits. It has become interesting for us to estimate the effect of treatment on previously formed abnormalities of structural parameters, especially for thoracic deformities, joint contractures or limitations of range of motion in the trunk and limbs.

This work examines functional and structural changes in SMA sitter patients during the 12-month follow-up.

[1]Department of Developmental Neurology, Poznan University of Medical Sciences, 60-355 Poznan, Poland. [2]Department of Rehabilitation and Physiotherapy, Poznan University of Medical Sciences, 61-545 Poznan, Poland. ✉email: aleksandra.bieniaszewska.22@gmail.com

Material and methods

The study consisted of a 12-month prospective follow-up of SMA sitter patients. Patients were enrolled at admission to the Clinic, evaluated (initial examination) and re-evaluated after 12 months (follow-up examination). Data were collected between May 2020 and February 2023.

Material

Twenty-one sitter participants with SMA were recruited for the study. Patients' enrollment as a sitter was related to maintaining a stable sitting position for at least 5 s without upper limb support[17]. Because the disease entity involved in this study belongs to rare diseases, the possibility of obtaining a larger group size was limited, and the sample size is similar to those reported in world publications[2,18,19]. All consecutively admitted patients were enrolled if they met inclusion criteria and did not meet exclusion criteria. The patients were treated with Nusinersen or Risdiplam (dependent on clinical assessment, beyond our decision). After 12 months, all patients were re-evaluated. Inclusion criteria were a genetically confirmed diagnosis of SMA, sitter patients, participation in a Nusinersen or Risdiplam drug program for at least one year (without changing the drug during observation), age between 5 and 20 years, and informed consent of participants/parents. The Risdiplam group had previously participated in clinical trials, so their recruitment was only possible when they entered the reimbursed treatment program in Poland. Exclusion criteria were non-sitter or walker patients with SMA, another genetic or metabolic disease affecting the child's functional level, surgery during follow-up (e.i. due to scoliosis), treatment with a drug other than Nusinersen or Risdiplam, age younger than five and older than 20, patients with a diagnosis obtained by screening and treated right after birth, and lack of informed consent of participants/parents. Patients were retrospectively divided into two groups—depending on the drug program they participated in: the Nusinersen group (n = 9) and the Risdiplam group (n = 12). It should be stressed that the paper was not intended to evaluate the effectiveness of treatment but to show the functional and structural changes in the sitter SMA patients. Because they were treated with these two drugs, we show the two groups' evaluation over time. The groups were similar in size, age, time of diagnosis, and time elapsed between diagnosis and treatment initiation. The recruited patients are a group that was not screened or treated immediately after diagnosis.

The study includes eleven females and ten males. According to the functional level classification, all patients belong to the sitter group. Eighteen of them have SMA2 and three—SMA3. Eighteen patients have scoliosis; three had an operation on the scoliosis before the first examination, and five are qualified for surgery in the future. Importantly, patients with SMA3 due to the disease have lost the ability to walk; therefore, they are classified as sitter SMA. Table 1 presents the detailed characteristics of the group.

Methods:

The study protocol included three components: an in-person questionnaire completed at the first visit (questionnaire answers are presented in Table 1) and functional and structural assessments performed at admission and after one-year follow-up. The functional evaluation included examining the child's motor level and measuring fine motor skills. Both were performed using validated functional scales[20–22]. The Hammersmith Functional Motor Scale—Expanded (HFMSE) was used to assess the motor level, while the Revised Upper Limb Module (RULM) scale assessed the fine motor skills[20–22].

The HFMSE scale is designed for patients who can at least sit unsupported. The scale consists of two parts: a basic one assessing 20 items and an extended one containing 13 more complex motor activities. Exemplary activities assessed encompass long sitting, rolling, changing position from sitting to lying, propping on forearms and extended arms, standing, squatting, or jumping forward. Each element can be repeated three times and is scored from 0 to 2, where 2 means a fully completed task, 1—a task completed with compensation, and 0—no task completed. Sixty-six points is the maximum number of points that can be scored[21–23]. The RULM scale is used to assess the function of the upper limb. Patients are tested in a sitting position using a specialized test set consisting of coins, a button light, metal weights of various weights, or a Ziploc container. The test consists of 20 items and a pre-task (A), which does not count towards the overall score but is designed to determine the child's functional level. The remaining 18 tasks are scored from 0 to 2, where 0 indicates no task performance, 1 means a task performed with compensation or less efficiency, and 2 indicates complete task performance. The exception is item I, assessing the opening of a Ziploc container, evaluated with a score of 0 to 1. The maximum number of points to be obtained is 37. The RULM assessed skills such as putting hands on the table from the lap, completing the path, placing a coin into a cup, tearing paper, or opening a Ziploc container[20,24]. A minimally clinically significant change in the HFMSE and the RULM scale is considered an improvement of at least 2 points in the total scale score[25,26]. We understand an improvement of 2 points in an individual HFMSE and RULM scale item as achieving a new motor function (milestone). Such an improvement automatically also means a clinically significant change in the total HFMSE or RULM score. A deterioration of the score of the same item by 2 points means a loss of the motor function in question.

The structural assessment included parameters in the trunk and upper and lower limbs. Tests were evaluated within the trunk parameters, such as the cervical rotation (CR) and supine angle of trunk rotation (SATR)[24,27–30]. CR checked the extent of cervical rotation during passive movement while stabilizing the ribs on the opposite side. The SATR angle was assessed at two levels: the first at the sternum and second rib level (SATR-U) and the second in the lower torso at the xiphoid process level (SATR-L). A scoliometer assessed SATR, while a plurimeter was used for CR[24,27–30]. Evaluation of upper and lower limbs was done using a goniometer. Ranges of passive motion and the joint's neutral position were evaluated for the following: arm flexion (AF), arm abduction (AB), elbow flexion (EF), forearm supination (FS), hip flexion (HF), knee flexion (KF), and ankle dorsiflexion (ADF). Joint contractures were diagnosed if the neutral position value varied from 0 (i.e., the patient could not achieve the proper initial position). The severity of the contracture increases with the neutral position's value. In the goniometer test, we assumed a 5-degree measurement error.

Parameters	All SMA sitter (n = 21)	Nusinersen (n = 9)	Risdiplam (n = 12)
Sex			
Female	11	4	7
Male	10	5	5
Age (given in years)			
Mean ± SD	9 ± 4	9 ± 4	9 ± 4
Age at the start of treatment (given in years)			
Mean ± SD	7 ± 4	8 ± 4	6 ± 4
SMN2 copy number			
2 copies	1	0	1
3 copies	17	7	10
4 copies	3	2	1
SMA type			
SMA2	18	6	12
SMA3	3	3	0
Child's functional level			
Sits unassisted	6	3	3
Rolls over	6	1	5
Crawls	4	3	1
Stands with assistance	3	1	2
Stands unassisted	2	1	1
Presence of scoliosis	18	8	10
Operation of scoliosis before the first examination	3	1	2
qualification to the scoliosis operation (after examination)	5	2	3
The duration between the diagnosis to the start of the treatment (given in months):			
Mean ± SD	85 ± 52	102 ± 47	72 ± 53
The duration between the start of treatment to the first examination (given in months)			
Mean ± SD	26 ± 12	13 ± 5	36 ± 4
Rehabilitation intensity			
1–3 times a week	1	1	0
4–6 times a week	10	5	5
Each day	10	3	7

Table 1. Study group characteristics.

Physiotherapeutic evaluation of scoliosis using a scoliometer in children with SMA is subject to too much error, so the present study does not consider these data. In earlier work, we attempted to evaluate scoliosis in these patients by measuring with a tailor's tape the distance between the inferior angle of the scapula and the posterior superior iliac spine during the sitting position. However, in the end, this parameter did not show any relationship with the functions tested on scales[23,24].

The bioethics committee accepted the study (No. 1035/19).

Statistical analysis

According to the type of the analyzed variables, mean with standard deviation was used for interval variables, median with quartile range, and minimum and maximum values were used for ordinal variables. No comparison between the groups treated with distinct drugs was performed, only the change of the analyzed variables over time (the Wilcoxon test was used). Correlations were tested with Spearman's non-parametric test, and the correction for the multiplicity of the tests was checked. A Bonferroni correction was conducted. No precise alpha risk could be defined for our study as we did not conduct any intervention; we just performed the measurements. Statistical analysis was performed using the Statistica.pl package.

Results

Below are the results of a 12-month follow-up in the SMA sitter patients undergoing disease-modifying therapies. Functional assessment of patients based on scales, structural assessment, and correlations between functional and structural changes in sitter SMA patients were analyzed sequentially. Patients were evaluated collectively and according to the type of treatment applied to them.

Functional assessment based on validated functional scales

Patients were examined using the HFMSE scale and the RULM scale. Initial results (initial examination) and after 12 months (follow-up examination) were analyzed. Due to the nature of the variables, median, min–max

Parameter	All SMA sitter (n = 21)		Nusinersen (n = 9)		Risdiplam (n = 12)	
	HFMSE	RULM	HFMSE	RULM	HFMSE	RULM
Initial examination (0-month)						
Median	23	30	32	30	22	31
Min–max	5–45	14–43	5–42	14–41	8–45	24–43
Q25–Q75	14–35	27–36	14–35	27–37	15–32	28–35
Follow-up examination (12-month)						
Median	23	32	34	34	23	32
Min–max	6–46	17–43	6–43	17–42	9–46	24–43
Q25–Q75	14–36	29–37	14–36	30–37	14–34	28–36
The difference between examinations						
Wilcoxon test	z = 0.62	**z = 2.34**	z = 1.33	**z = 2.31**	z = 0.16	z = 1.02
	$p = 0.538$	$\boldsymbol{p = 0.02}$	$p = 0.183$	$\boldsymbol{p = 0.02}$	$p = 0.875$	$p = 0.308$

Table 2. The values of functional scale scores for all patients and by Nusinersen and Risdiplam group. Statistically significant differences are marked in bold.

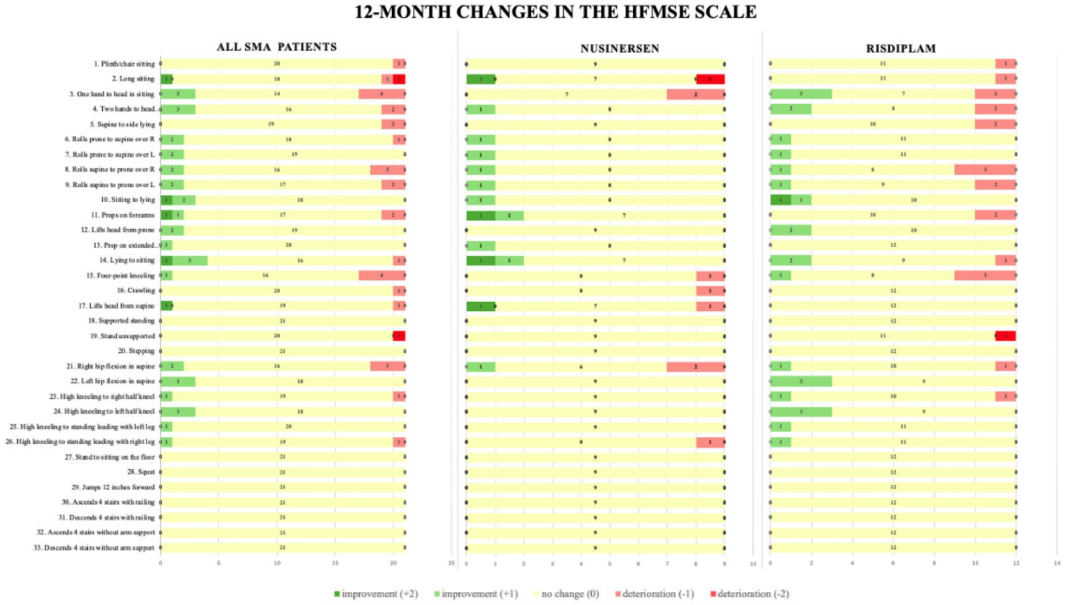

Fig. 1. Number of patients with improvement, no change or deterioration in the HFMSE scale.

value, and upper and lower quartiles were used. The difference in time (between examinations) for all patients and each group was calculated using the Wilcoxon test. A detailed description of the functional scale results is presented in Table 2.

There was no change in the HFMSE scale over time for the total study group, while scores on the RULM scale improved significantly. A similarly significant improvement was obtained for the group treated with Nusinersen.

The improvement values of individual functions on the HFMSE and RULM scales

Subsequently, it was verified how many patients experienced changes in individual motor functions measured using specific items of the HFMSE and the RULM scales over 12 months. It was analyzed how many patients showed an improvement of 1 or 2 points, how many showed no change and how many showed a deterioration of 1 or 2 points. These data are presented for all SMA patients and separately for the Nusinersen and Risdiplam groups (Figs. 1 and 2).

According to our data, 2 points of improvement (what we understand as a reaching new milestone) were visible in five HFMSE scale functions—long sitting, changing position from sitting to lying, props on the forearm, changing position from lying to sitting and lifting the head from the supine. This change affected five different patients. Considering the 2 points of deterioration, losses of function were seen in two functions: long sitting and standing unsupported, which happened to two different patients.

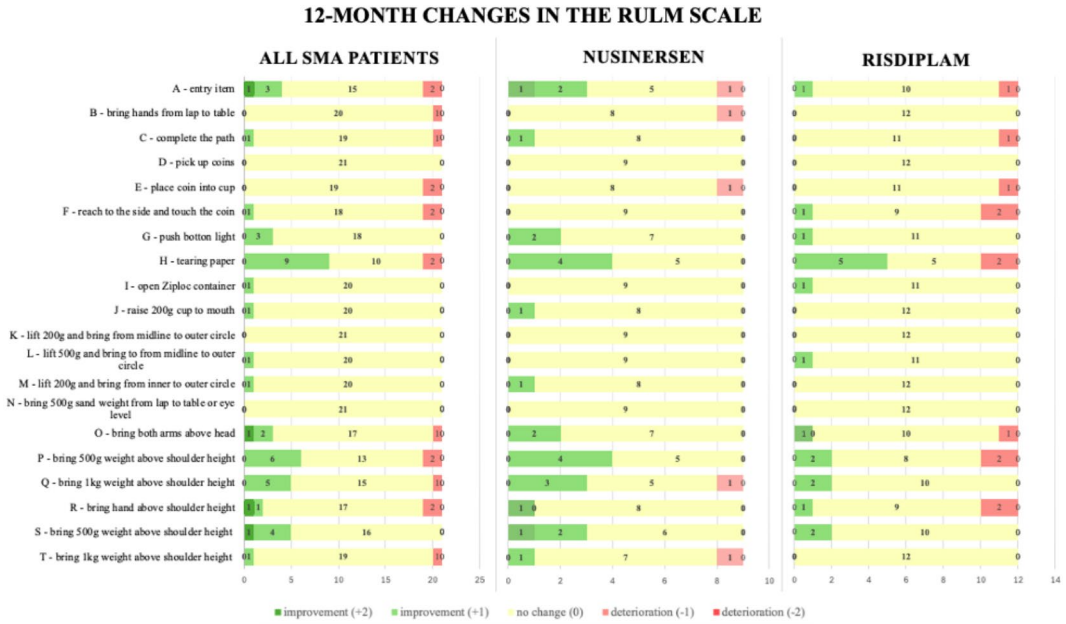

Fig. 2. Number of patients with improvement, no change or deterioration in the RULM scale.

According to the RULM scale, 2-point improvement was seen in four patients, but in each, it involved a different function: entry item, bringing both arms above the head and hand above shoulder height with and without 500 g weight. Most patients improved tearing paper function (Fig. 2).

Considering the total number of patients showing improvement, no change, and deterioration of function in the Nusinersen group, most patients showed improvement in functional scale scores (HFMSE—6 patients, RULM—8 patients). In the case of the Risdiplam group, most patients showed deterioration of function in the HFMSE scale (7 patients), while in the RULM, the ratio of improvement to deterioration was 7:3, and two patients showed no change in scores.

Structural assessment

The study protocol included structural parameters in the trunk and upper and lower limbs. Regarding the upper and lower limb joints, both ranges of motion and joint contractures defined as differences from the neutral position were measured.

In one patient, a normal neutral position was observed at the shoulder joint, contracture at the elbow joint at the level of the right elbow joint (30 degrees in the first examination and 35 degrees in the second), and left elbow joint (15 and 30 degrees, respectively); normal neutral position regarding the forearm. In the examined child, the range of motion limitation of flexion in the right shoulder joint was 20 degrees in the first examination and decreased to 10 in the second examination; the abduction was limited by 40 degrees in the right upper limb during the first examination and decreased to 20 degrees, while we observed the most significant deterioration in forearm supination (deficit increased from 15 to 40) by 25 degrees. The overall RULM score was 30 and 25, respectively; the deterioration was probably due to worsening scoliosis, and the patient was qualified for surgery. The other patients had neither contractures nor limited mobility in the upper limb joints.

The results shown in Table 3 present differences in the parameters of the trunk and lower limbs. The mean and standard deviation present the results of specific structural parameters. The Wilcoxon test was used to compare changes over time.

Analyzing the changes in the values of structural parameters in all SMA patients during the 12-month follow-up, a significant statistical improvement was observed in the cervical rotation parameter (CR-R and CR-L). The values of neutral positions in the hip and knee joints increased slightly, indicating the deterioration of contractures. In the case of the hip joints, the change was statistically significant. However, the values of knee joint ranges of motion increased, and in the case of the left knee, the change was statistically significant.

For the Nusinersen group, the most remarkable improvement was in cervical rotation (CR-R and CR-L). The value of SATR-L decreased significantly, indicating improvement. Contractures in the hip joints have worsened, and the range of motion has not changed, while contractures in the knee joints have not changed. The range of motion of both knee joints increased, and the change for the left knee was statistically significant.

In the group treated with Risdiplam, there were no changes in trunk parameters. There was a very slight deterioration of contractures and a slight (not significant) improvement in the ranges of motion in the hip joints. As for the knee joints, the increase in contracture was significant only for the right joint, but the range of motion improved significantly for both knee joints.

All investigated parameters in 0 time point and after 12-month (0;12)			All SMA sitter	NUSIN	RISDIP	The difference in time 0 point vs. 12 months		
						All SMA sitter	NUSIN	RISDIP
Trunk parameters: magnitude—degrees; at 0 point and after 12 months (Mean ± SD)	CR-R	0	64 ± 14	60 ± 9	67 ± 17	**z = 2.40**	**z = 2.38**	z = 0.56
		12	70 ± 12	71 ± 10	70 ± 14	***p* = 0.016**	***p* = 0.017**	*p* = 0.575
	CR–L	0	72 ± 12	69 ± 10	75 ± 13	**z = 2.22**	**z = 1.96**	z = 1.27
		12	78 ± 11	76 ± 11	80 ± 11	***p* = 0.026**	***p* = 0.050**	*p* = 0.203
	SATR-U	0	4 ± 3	4 ± 2	3 ± 3	z = 0.28	z = 1.60	z = 1.35
		12	4 ± 4	3 ± 3	5 ± 5	*p* = 0.779	*p* = 0.109	*p* = 0.178
	SATR-L	0	5 ± 4	6 ± 4	3 ± 4	z = 0.89	**z = 2.02**	z = 0.91
		12	4 ± 4	3 ± 4	4 ± 4	*p* = 0.374	***p* = 0.043**	*p* = 0.361
Lower limb parameters: ranges of motion (ROM) and neutral position (NP) Magnitude—degrees; at 0 point and after 12 months (Mean ± SD)	HF-R (ROM)	0	122 ± 11	117 ± 10	125 ± 10	z = 0.88	z = 0.28	z = 1.01
		12	124 ± 10	119 ± 10	128 ± 9	*p* = 0.379	*p* = 0.799	*p* = 0.310
	HF-R (NP)	0	20 ± 16	13 ± 11	24 ± 17	**z = 2.58**	**z = 0.23**	z = 1.78
		12	23 ± 15	18 ± 13	27 ± 16	***p* = 0.009**	***p* = 0.043**	*p* = 0.075
	HF-L (ROM)	0	122 ± 9	117 ± 8	125 ± 8	z = 1.41	**z = 2.02**	z = 0.17
		12	123 ± 10	119 ± 9	126 ± 11	*p* = 0.158	***p* = 0.043**	*p* = 0.866
	HF-L (NP)	0	22 ± 18	13 ± 11	29 ± 19	**z = 2.48**	z = 1.36	**z = 2.37**
		12	25 ± 16	21 ± 17	28 ± 15	***p* = 0.013**	*p* = 0.173	***p* = 0.018**
	KF-R (ROM)	0	146 ± 11	140 ± 13	151 ± 6	z = 0.44	z = 1.36	**z = 2.37**
		12	150 ± 9	144 ± 11	155 ± 5	*p* = 0.663	*p* = 0.173	***p* = 0.018**
	KF-R (NP)	0	39 ± 27	29 ± 19	46 ± 31	z = 0.44	z = 1.36	**z = 2.37**
		12	40 ± 24	29 ± 16	48 ± 28	*p* = 0.663	*p* = 0.173	***p* = 0.018**
	KF-L (ROM)	0	145 ± 11	139 ± 12	150 ± 8	**z = 3.07**	**z = 2.37**	**z = 1.96**
		12	150 ± 8	146 ± 8	153 ± 8	***p* = 0.002**	***p* = 0.018**	***p* = 0.050**
	KF-L (NP)	0	39 ± 25	31 ± 19	45 ± 27	z = 1.10	z = 0.73	z = 0.84
		12	42 ± 25	32 ± 19	49 ± 28	*p* = 0.272	*p* = 0.465	*p* = 0.401

Table 3. The presence of structural parameters of the trunk and lower limbs joints and their change over time. Nusin.—the Nusinersen group; Risdip.—the Risdiplam group; CR-R—right cervical rotation; CR–L—left cervical rotation; SATR-U—supine angle of upper trunk rotation; SATR-L—supine angle of lower trunk rotation; HF-R (ROM)—right hip flexion (range of motion); HF-R (NP)—right hip flexion (neutral position); HF-L (ROM)—left hip flexion (range of motion); HF-L (NP)—left hip flexion (neutral position); KF-R (ROM)—right knee flexion (range of motion); KF-R (NP)—right knee flexion (neutral position); KF-L (ROM)—left knee flexion (range of motion); KF-L (NP)—left knee flexion (neutral position). Statistically significant differences are marked in bold.

In six patients, the feet were positioned in plantar flexion (−15 to −5 degrees below the neutral position), and no dorsiflexion movement was possible. The range of motion did not differ from expected values in the remaining patients, so the statistical analysis results were not presented.

Then, it was measured how many patients showed improvement, with no change or worsening of structural parameters.

Considering all SMA patients, improvement dominated the parameters of cervical rotation and ranges of motion of the right hip and the left and right knee. The SATR parameters (SATR-U and SATR-L) mostly showed no change. Deterioration was most evident in the neutral positions of the hip and knee.

In the Nusinersen group, improvement dominated the cervical rotation parameter and the range of motion of the left knee. Deterioration dominated for neutral hip joint positions. The ratio of no change to deterioration for left knee neutral positions was 5:4.

For the Risdiplam group, improvements were observed in the parameters of left cervical rotation and the right hip joint range of motion. Deterioration predominated primarily in neutral knee joint positions. The results are presented in Fig. 3.

As the patients' age was quite diverse, we also analyzed the possible influence of this variable on the changes observed in motor performance, contractures or ROM. Neither the patients' age nor the time from diagnosis to the first examination influenced the change in any of the described parameters.

Correlations between scores on functional scales and joint contracture values

The final element of observation was to examine whether there was a relationship between the values of changes in the scores obtained on the functional scales and the changes in the value of the structural parameters during the 12-month follow-up. Since the most significant changes were observed within the hip flexion, this parameter was included in the correlation analysis. The results of Spearman correlations are presented in Table 4.

In the Nusinersen group, a statistically significant correlation was observed between the 12-month change in HFMSE (a weak one) and RULM scores (a moderate one) and right hip contracture (a weak one, change of

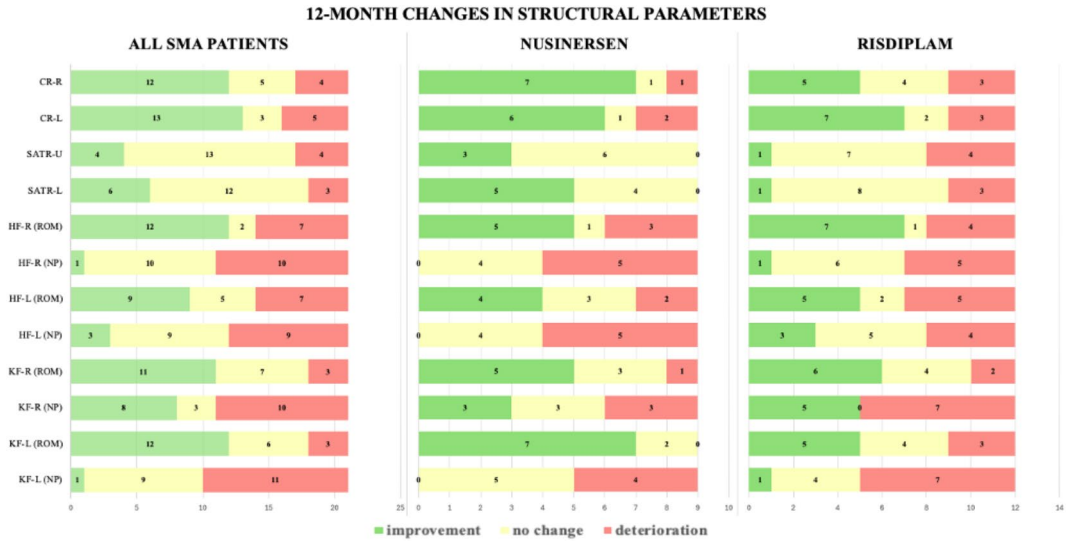

Fig. 3. Number of patients with improvement, no change or deterioration of structural parameters. CR-R—right cervical rotation; CR–L—left cervical rotation; SATR-U—supine angle of upper trunk rotation; SATR-L—supine angle of lower trunk rotation; HF-R (ROM)—right hip flexion (range of motion); HF-R (NP)—right hip flexion (neutral position); HF-L (ROM)—left hip flexion (range of motion); HF-L (NP)—left hip flexion (neutral position); KF-R (ROM)—right knee flexion (range of motion); KF-R (NP)—right knee flexion (neutral position); KF-L (ROM)—left knee flexion (range of motion); KF-L (NP)—left knee flexion (neutral position).

	ALL SMA SITTER		NUSINERSEN		RISDIPLAM	
PARAMETERS	change of HFMSE	change of RULM	change of HFMSE	change of RULM	change of HFMSE	change of RULM
change of HF-R (NP)	0.24	0.12	**−0.37**	**−0.15**	0.39	0.14
change of HF-L (NP)	0.25	0.20	0.02	0.13	0.26	**−0.23**

Table 4. Correlation between the functional scales and the magnitude of joint contracture in hip. Abbreviations: change of HF-R (NP)—change of neutral position of right hip; change of HF-L (NP)—change of neutral position of left hip. The value of Spearman's rho is given, and statistically significant values are marked in bold ($p < 0.05$).

HF-R (NP)). This change indicates that as the scale score increases, the value of contracture decreases. There was a similar correlation between the left hip contracture value and the RULM score in the RISDIPLAM group.

Discussion

The two groups (Nusinersen and Risdiplam) had different timing of treatment initiation since entering our study. This was particularly evident in the Risdiplam group, whose recruitment began at the end of the clinical trial, which may have flattened the therapeutic effect. Therefore, we refrained from comparing the two groups and focused on presenting the changing functional and structural parameters over time.

Disease-modifying therapies have changed the previously known clinical picture of the disease[31–33]. One particular interest has been the motor development of patients who have experienced the natural course of the disease by receiving treatment after the onset of the first symptoms, and they were the focus of this study. As a result of the lack of effective therapy, they first experienced a weakening of muscle strength and then gradual muscle atrophy. This resulted in a loss of motor function, leading to a gradual reduction in mobility, the need to use a wheelchair, and, as a result of the forced position, the formation of joint contractures. It should be stated once again that the study was not intended to compare the effect of a particular drug, only to investigate the relationship between structural parameters and the motor performance estimated using two widely used scales. To date, there have been only a handful of papers on how therapies have affected the structural changes occurring in SMA patients, and the effect of treatment on skeletal changes is still unclear[18,23,24,27,32,34].

Historically, patients with SMA deteriorated motorically despite the rehabilitation used. Nowadays, patients taking the drug have stopped deteriorating. At the same time, rehabilitation is carried out in most patients with similar intensity and aims, for example, to improve the quality of function and slow down ongoing structural disorders.

At 12-month follow-up, we showed that patients achieved functional improvement as measured by the HFMSE and RULM scales. However, the extent of improvement was more pronounced in the Nusinersen group. This observation is consistent with the results of Chen and co-authors, who also showed functional improvement

in patients treated with Nusinersen and Risdiplam. The authors also highlighted that in patients treated with Nusinersen, in addition to improvements in gross motor skills, improvements in upper limb function were observed, which is consistent with our observations showing a greater extent of improvement in RULM in the Nusinersen group[35]. However, given that assessment with functional scales is still subjective, and the RULM and HFMSE scales may not be sensitive enough, further research is needed[31]. The greater extent of improvement in the upper limb may also be due to its more intense activity, as opposed to the lower limbs remaining at rest. This observation agrees with a publication by Oude Lansink and co-authors, whose participants noted that contractures did not develop in joints they used regularly and that changes in the upper limbs were more noticeable by them than changes in the lower limbs[36].

The second question tested in the study was the 12-month follow-up of structural changes occurring in SMA patients. Data on clinically significant changes in structural parameters have not been previously discussed. Only a few papers present the basic results of such measurements. However, publications are demonstrating structure–function relationships in patients with SMA. The number of movements with a limited range of motion correlates positively with age and the degree of upper limb function. The study was performed on patients with SMA type 2[37]. Montes and co-authors showed that lower limb contractures are common in patients with SMA types 2 and 3, and even minimal hip and knee flexion contractures are associated with reduced gross motor function[38]. In another paper, Salazar emphasized that minimal contractures of the hip and knee joints are associated with reduced motor ability. Therefore, all clinical trial designs should consider the impact of contractures on motor function[39].

We aimed to find any relationship between the contractures and structural or motor changes. t is known from the natural course of the disease that the sequence of the appearance of contractures in the limbs has a specific, well-defined pattern. The sitter patients we described were previously mainly classified as SMA type 2 patients, in whom contractures appear sequentially at the knees, through the ankle to the hip, according to Harding et al.[40]. One could conclude that the order of reduction of these changes should occur in reverse order. However, the characteristics of the patients we described deviate from this pattern: most subjects had hip contractures, although not of the ankle joint, and the left range of motion improved the most. The publications also did not highlight the differences between the sides of the body, and neither the contractures nor their gradual decrease or increase occur symmetrically. This issue, too, requires further research involving a wider group of patients. Characteristics of SMA patients during movement observation are the various compensations they create, including the formation of forced positions and contractures. Therefore, it can be challenging to designate standard therapeutic management for SMA patients, and the approach should be highly individual. Compensations seem to be a necessary cost of their own to improve function despite the existence of structural changes. Other modern therapies are likely to increase muscle strength[33]. However, this does not necessarily reduce structural changes. Some changes may even be exacerbated because, for example, the hip flexors will strengthen faster than the extensors due to the forced sitting position in patients classified as sitter. It is also necessary to consider asymmetrical changes that can lead to scoliosis in young patients despite the treatment used[34].

A limited group of patients is presented in the paper due to the desire to show the transitional period of SMA therapy before the screening program and starting therapy as soon as the diagnosis is made. Due to the nature of the drugs used, the start of the study did not completely coincide with the start of the drug and differed between the two groups. Another limitation of the work is the lack of objective tools for assessing function (subjective rating scales, in many cases also affected by ceiling effect) and the difficulty of using objective measurement tools due to specific structural disorders. e also state clearly that the study could not be blinded: due to the clinical program of treatment the patients were involved it was clear which drug they received. Nevertheless, all measurements were conducted by two experienced physiotherapists according to best clinical practice.

Conclusions

All patients under study improved their motor function after 12 months. In both groups, more remarkable improvement was seen in the assessment of upper limb function (RULM scale) than in overall function as measured by the HFMSE scale. Improvement in function was not dependent on improvement in structural parameters. Structural abnormalities change individually and require urgent observation in each patient. In the future, this group will be the basis for comparison for patients whose treatment was implemented immediately after birth, and we hope that structural disorders will not appear in them.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions
A.B.: Conceptualization, Methodology, Design, Data Acquisition, Data Interpretation. Article Drafting, Article Revision; M.S.: Conceptualization, Methodology, Data Analysis, Data Interpretation, Article Revision; E.G.: Conceptualization, Methodology, Design, Data Acquisition, Data Interpretation, and Article Revision. All authors have read and agreed to the published version of the manuscript.

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Declarations

Ethics approval and consent to participate
The study was conducted by the Declaration of Helsinki and approved by the bioethics committee (no. 1035/19 date of approval is 7 November 2019). All participants and their parents gave informed consent to the study.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to A.B.