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Salbutamol tolerability and efficacy in patients with spinal muscular atrophy type II

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by homozygous deletions or loss-of-function mutations in *SMN1*, which result in a degeneration of motor neurons in the spinal cord and brain stem. Even without a randomized placebo-controlled trial, salbutamol has been offered to patients with SMA in the neuromuscular clinics of most of hospitals for many years. We describe the response to salbutamol in 48 patients with SMA type II who were not taking any other medication. We investigate the changes over an eighteen-month period in motor functional scales and we analyze side effects and subjective response to treatment. Our results suggest that oral administration of salbutamol might be helpful in the maintenance of motor function in patients with SMA type II. An apparent beneficial effect was observed in functional scales of children under the age of 6, especially during the first 6 months of therapy. The majority of patients of all ages referred some kind of subjective positive effect associated with therapy intake. Salbutamol seemed safe and was well tolerated without serious side effects.

Keywords: Spinal muscular atrophy; Salbutamol; Therapy; Motor function; Side effects; Beta agonists.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by homozygous deletions or loss-of-function mutations in the gene encoding survival motor neuron 1 (*SMN1*), which result in a degeneration of motor neurons in the spinal cord and brain stem [1]. It is the most common genetic cause of childhood mortality [2,3], with an estimated incidence of 1 in 11,000 live births [4] and a carrier frequency of 1 in 40–60 adults [5]. It is classified in several major phenotypes based on the age of onset and maximal motor capacity achieved [6–8]. SMA type II manifests as onset usually between ages 6 and 12 months: patients achieve the ability to sit independently but never walk independently. Although poor muscle tone may be evident at birth or within the first few months of life, individuals with SMA II may gain motor milestones slowly [9]. The life expectancy of persons with SMA II is shortened by respiratory complications in the context of a restrictive pulmonary disease and early onset scoliosis. Despite this, the majority of patients with SMA type II live into adulthood. Data on natural history on SMA type II show a slow decline in motor and pulmonary functions over time, causing substantial disability [10].

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Deletions (identified in 92% of all classical SMA patients) or loss-of-function mutations in the *SMN1* gene, located on chromosome 5q13, are responsible of the disease [11], whilst the phenotype severity is strictly related to the paralogous *SMN2* gene copies number present [12,13]. Basing on the hypothesis that a higher copies number may ameliorate the clinical phenotype; some current treatment strategies are focused on enhance *SMN2* transcript.

Apart from its widespread use in patients with myasthenia due to its effect over the neuromuscular junction [14–16], a beneficial effect on skeletal muscle after treatment with short acting β2-adrenergic agonists has also been reported over the last years. Firstly, Martineau et al. described an improvement on muscle strength after treatment with albuterol for 21 days in healthy volunteers [17]. Later, salbutamol proven to be effective in several types of congenital myasthenic syndromes [18,19], and some kind of increase in the skeletal muscle strength has been documented in patients with other neuromuscular disorders, including central core diseases [20] and facioscapulohumeral dystrophy (FSHD) [21], though subsequent studies suggested that this positive effect on muscle strength in patients with FSHD was not maintained over time [22], was limited [23], or was not detected [24]. Albuterol also appears to partially enhance efficacy from enzyme replacement therapy in Pompe disease [25] and seemed to increase the strength in a placebo-controlled pilot study in 9 boys with dystrophinopathies [26], although these results observed in patients with dystrophinopathy were not confirmed in a larger study [27]. Lastly, some studies indicate that salbutamol may have a beneficial effect on muscle function in patients with SMA type II and III without serious side effects [28–31].

Two different studies have reported that salbutamol increases SMN protein in SMN fibroblast cells [32,33]. However, the precise mechanism by which the salbutamol is able to increase SMN protein remains unclear. A stimulation of the inclusion of exon 7 in *SMN2* mRNA was initially proposed [32], but more recently has been strongly suggested that salbutamol may increase SMN protein levels in SMA by inhibiting ubiquitin-mediated SMN degradation via activating β2-adrenergic receptor-PKA pathways [33]. A third study hypothesizes that the increase in *SMN2* full length transcript levels was directly proportional to *SMN2* gene copy number [34]. More recently, a role of salbutamol on neuromuscular junction has been suggested. It was based on the concordance between clinical and neurophysiological signs of improvement in two patients with SMA treated with salbutamol [35].

Following these data, salbutamol has been offered to patients with SMA in the neuromuscular clinics of most of hospitals for many years, with greater or lesser confidence. In the absence of a randomized placebo-controlled trial, even less likely to be performed in the current radically new therapeutic context, we describe the response to salbutamol in 48 patients with SMA type II who were not taking any other medication. The main aim of this study was to investigate the changes over an eighteen-month period in motor functional scales in individuals with SMA type II under treatment with salbutamol, in order to describe a possible beneficial effect. Secondly, we analyzed side effects and subjective response to treatment.

2. Methods

2.1. Study design and patients

This was a prospective, longitudinal study to characterize the development of motor function in patients with SMA type II treated with oral salbutamol. Results were compared with natural history of the disease and with other previously published patients treated with salbutamol. We hypothesized that individuals who were treated with salbutamol would have a better evolution. Side effects and subjective response were also analyzed.

Forty-eight patients followed-up at Hospital Sant Joan de Déu, Barcelona, were included in this study. All patients had a clinical diagnosis of SMA type II confirmed by genetic analysis with homozygous absence of *SMN1*. None of patients was taking part in any other pharmacological trial or was on other concurrent medication. SMA type II was classified based on age at disease onset and maximal motor capacity achieved, according to the functional criteria of the International SMA Consortium [36]. Phenotype data were collected from family interviews and medical records. Data were collected in accordance with ethical guidelines of the institution.

Oral Salbutamol was initiated after a cardiac evaluation, including electrocardiogram and echocardiography. The dose was progressively increased over five weeks until the target daily dose of 6 mg/day (2 mg three times per day). Weight and Cobb angle variations during the study period, as well as hospitalizations and surgical interventions were registered and taken into account.

2.2. Outcome assessment motor measures and subjective response

To capture disease progression, motor function was longitudinally assessed using three assessment tools over an 18-months period: Hammersmith Functional Motor Scale-Expanded (HFMSE), Revised Upper Limb Module (RULM), and Egen Klassifikation 2 scale (EK2). All evaluations were performed on a single day, every 6 months.

The HFMSE is an expanded version of the original HFMS which includes 13 supplementary items, totaling 33. Total score, obtained by summing scores of each item, can range from 0 (fail of all the activities) to 66 (full activities achieved). The scale is specifically validated for use in patients with SMA to assess motor activities related to daily living [37]. The RULM, specifically designed to assess upper limb function in SMA patients, including non-ambulatory children, consists of 19 items for a maximum score of 37 [38]. EK2 scale assesses the functional capacity of people with spinal

muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) that are in wheelchair phase. It consists of 17 items that can be graded basing on a 4-point system, ranging from 0 (able to perform) to 3 (unable). The lowest level of function is an EK2 sum of 51 [39]. Validated Spanish versions of EK2 and HFMSE are available [40,41]. All the evaluators have been specifically trained for the three scales.

Patients were stratified according to age at the start of treatment (<6 years vs ≥6 years). Mean, median, standard deviation, and range of the scores in functional scales after 6 months, 12 months, and 18 months of treatment were calculated in both groups. We considered ±3 points in HFMSE as a confident interval to estimate changes. It was considered a clinically meaningful increase based on our own experience and its previous use as an end point in clinical trials for SMA [42]. In patients which strictly complied with the timing of follow up, the scores over a period of 18 months were compared adjusting for baseline. Patients included in this group had at least a preliminary assessment before start treatment (T0) and subsequently were evaluated every 6 months after the first dose.

Patients in whom functional assessments had to be temporary suspended due to surgical procedures, hospitalizations, or other reasons, were not excluded. A detailed evaluation of joint mobility was periodically performed in all patients. Scoliosis progression was evaluated by Cobb angle, measured in sitting anterior-posterior X-ray at baseline and at month 12 or 18. Weight at baseline and during follow-up was registered in most of patients. Where possible, number of *SMN2* copies was also studied to eventually correlate with a better response to treatment. To better understand subjective perception of treatment efficacy, patients underwent to an in-depth unstructured interview focused on impact of treatment in their daily life. Items that are not usually captured by functional motor scales were requested, including fatigue, respiratory symptoms (inability to cough/clear lung secretions, respiratory infections, breathing difficulties), feeding/swallowing and chewing difficulties, sleep problems (ability to turn in bed), difficulties transferring to/from wheelchair to bed or toilet.

2.3. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences 22.0 (IBM SPSS Statistics 22.0, Chicago, IL, USA). Descriptive statistics were used to summarize the demographic and medical characteristics of patients. Data are presented as mean ± standard deviation (SD) or median and range where appropriate. Changes in scores of functional scales at months 6, 12, and 18 after the onset of oral salbutamol were our primary interest.

Spearman rank order correlations were performed to examine the concurrent validity between the HFMSE, RULM, and EK2. Correlations were designated as small (0.10–.29), medium (0.30–.49), and large (> 0.50).

Table 1
Characteristics of the patients at baseline. y: years; m: months; n°: number of patients.

Sex	32 male, 16 female
Age at onset of salbutamol (y)	
Mean	10.1 ± 4.8
Median	7
Range	2–21.4
Age at symptom onset (m)	
Mean	9
Range	6–15
Age at diagnosis of SMA (m)	
Mean	15
Range	7–24
Disease duration (m)	
Mean	112.2
Range	16–247
SMN2 copy number (n°.%)	
2	4 (11.4%)
3	28 (80%)
4	3 (8.6%)
Unknown	13
Motor milestones ever achieved (n°.%)	
Ability to sit without support	48 (100%)
Ability to stand with support	13 (27.1%)
Ability to stand without support	5 (10.4%)
Ability to walk independently	0
HFMSE score	5.76 ± 9.42
RULM score	13.27 ± 7.43
EK2 score	19.19 ± 7.06

3. Results

3.1. Demographics

A total of 48 patients (32 male, 16 female) with SMA type II from 47 unrelated families were included in the study. The mean age at the onset of treatment was 10.1 years (SD ± 4.8), ranging from 2 to 21.4 years. Thirteen children (8 male, 5 female) were included in the <6-year-old group and 35 patients (24 male, 11 female) in the ≥6-year-old group. Characteristics of the patients at baseline are summarized in Table 1.

Forty of the patients were treated during at least 18 months, the entire period of the study. Eight of the patients (16.7%) withdrew prematurely, due to a perceived lack of response (12.5%) or adverse effects (4.2%). All the 48 patients received salbutamol during at least 6 months. Protocol deviations occurred and were always related to skip of assessments. Cardiac evaluation, performed before the onset of salbutamol, was normal in all patients.

3.2. Longitudinal motor functional assessment

Table 2 shows details of the scores at baseline, month 6, month 12, and month 18. Table 3 shows the mean scores and changes in the scales during the follow-up.

Mean score in **HFMSE** at baseline assessment was significantly higher in patients younger than 6 years (13.57 points) than in patients aged 6 years or more (4 points)

Table 2
Details of the scores at baseline, month 6, month 12, and month 18 in HFMSE, RULM, and EK2. Patients who underwent a definitive spinal fusion during the follow-up are marked with an asterisk.

	Age	HFMSE_0	HFMSE_6	HFMSE_12	HFMSE_18	RULM_0	RULM_6	RULM_12	RULM_18	EK2_0	EK2_6	EK2_12	EK2_18
1	24	6	9	6		15	15	14		18	16	17	
2	24	29	38	34		21	29	27	23	3	5	3	2
3	31			12	14			12	16			8	24
4	40	10	16	12	22	22	28	28	24.5	25	7	23	11
5	42		17	17	17		20	16.5	21		12	13	8
6	46	17	20	14		19	18	22		9	13	12	
7	51		32				26.5				9		
8	55		10	11	11		21.5	20	23.5		7	14	9
9	57		14	17	14		25.5	25.5	22		7	7	14
10	63		17				22				15		
11	66	6	0	0	0	13	12	16.5	16.5	20	25	18	16
12	67	6	6	7	10	12.5	16		17.5	25	19		18
13	67	21	36	33	35	15.5	21	20	28	21	7	13	12
14	86	0	0	0		1.5	2	2		27	24	26	
15	87	0	0			1	1			30	31		
16	88	7	7			22	21			14	14		
17	91	0	0			7.5	8.5			24	24		
18	94	35	29			26	27			7	6		
19	97	6	7	0		19.5	16.5	20.5		12	12	21	
20	107	0	0		0	2.5	2.5		2	19	28		24
21	109	7	8	4	0	20	21	18	19	15	13	16	13
22	110	16	11	14	13	21	22	21	22	15	19	17	17
23	117	32	28	27	23	31	30	28	31	5	6	6	7
24	121	7	4	0		15.5	16	15		14	16	22	
25*	126	0	0			12	9.5			17	19		
26*	127	0	0	0	0	14.5	11.5	12	9	24	26	24	23
27	132		8	4	0			17	16.5			17	17
28*	138	8	7	6	6	15.5	15	17	10	14	13	11	15
29	143	2	0	0	0	11.5	6	8.5	8.5	23	24	23	24
30	144		0	0			9	14.5			18	12	
31	144		0		0		12.5		12		18		18
32	145	0	0	0		14	11.5	10		19	21	23	
33	151		0	0	0		16	14	13.5		19	18	18
34	153	2	0	0	0	9	12.5	12	5	28	29	27	34
35*	153	0		0	0	12	9.5	8	5.5	14	13	19	13
36	159	0	0	0		11	11.5	13		20	22	18	
37*	164	0	0	0			15	13.5	16		19	19	24
38	168	0	0	0		8	10	6		19	19	24	
39	172	0	0	0	0	13.5	11	5	11.5	15	15	18	18
40	174	0	0			4	7			21	25		
41	190	0		0	0	1		0	0	32		31	36
42	193	0	0		0	0	0		0	24	28	30	29
43	200	0	0			14.5	12			15	15		
44	201	0	0			6	2.5			25	24		
45	204	2	0	0		18.5	16.5	18	17	22	20	19	22
46	207	0	0		0	14	6		7.5	31	28		34
47	216	0			0		15		12	25	23		23
48	257	0	0	0	0		4	4	5		23	25	24

Table 3
Mean score and changes in HFMSE, RULM, and EK2 values at baseline, month 6, month 12, and month 18 after treatment with salbutamol.

	Baseline	Month 6	Month 12	Month 18
HFMSE	5.76 (SD ± 9.42)	7.36 (SD ± 10.85) **(+1.60)**	6.61 (SD ± 9.79) **(+0.85)**	6.35 (SD ± 9.59) **(+0.59)**
RULM	13.27 (SD ± 7.43)	14.35 (SD ± 7.90) **(+1.08)**	14.95 (SD ± 7.26) **(+1.68)**	14.31 (SD ± 8.23) **(+1.04)**
EK2	19.19 (SD ± 7.06)	17.69 (SD ± 7.11) **(−1.50)**	18.00 (SD ± 6.77) **(−1.19)**	18.86 (SD ± 8.25) **(−0.33)**

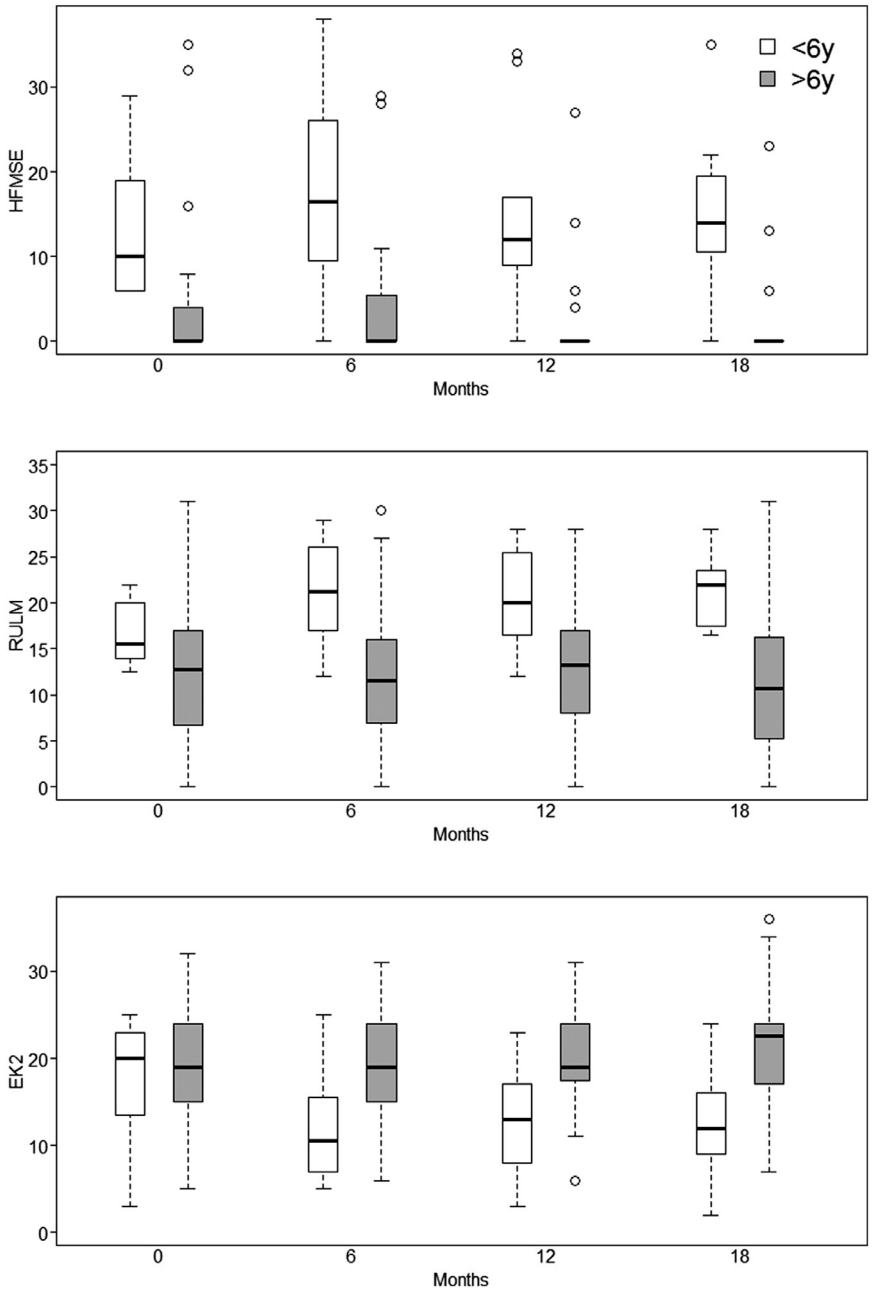

Fig. 1. Change over time in the Hammersmith Functional Motor Scale-Expanded score (A), the Revised Upper Limb Module score (B), and the Egen Klassifikation 2 scale (C). Scores of patients under and over the age of 6 are compared. Note that patients younger than 6 showed a significant clinical improvement in mean HFMSE, RULM, and EK2 scores from baseline to month 6. Better scores compared with baseline were maintained at 12 and 18 months, but in lesser magnitude. In contrast, patients older than 6 years had a decline in mean HFMSE, RULM, and EK2 from the first assessment in spite of the treatment with salbutamol.

(Fig. 1). Patients younger than 6 showed a significant clinical improvement in mean HFMSE score from baseline to month 6 of +4.35 points. This improvement was maintained at 12 and 18 months, but in lesser magnitude (mean change in HFMSE score from baseline to month 12: +1.25 points; from baseline to month 18: +1.81 points). In contrast, patients older than 6 years had a consistent decline in mean HFMSE from the first assessment (−0.59 points from baseline to month 6; −1.5 points from baseline to month 12; −1.7 points from baseline to month 18). An increase of at least 3 points in the HFMSE score from baseline to month 12 was observed in 29% of patients younger than 6 years, whereas any older patient showed an increase in the HFMSE score from baseline to month 12 or 18.

Patients younger than 6 years also had a significantly higher mean score in **RULM** at baseline than patients aged 6 years or more (16.86 vs 12.38). Moreover, a greater improvement in RULM score from baseline to month 6, 12, and 18 was observed in younger patients compared to patients older than 6 years (+4.36 vs −0.53 points from baseline to

month 6; +3.29 vs +0.21 points from baseline to month 12, +4.47 vs −1.21 points from baseline to month 18) (Fig. 1).

In the same vein, an improvement in mean **EK2** score was observed in the <6-year-old group (−5.46 at month 6, −4.49 at month 12, −4.62 at month 18) and a decrease in the ≥6-year-old group (+0.16 at month 6, +0.59 at month 12, +1.99 at month 18) (Fig. 1). Note that higher score in EK2 scale indicates lower function.

The correlations between HFMSE, RULM, and EK2 at baseline and at month 18 were large and significant ($p < 0.01$). Reliability between HFMSE and RULM was 0.82 at baseline and 0.75 at month 18. Reliability between HFMSE and EK2 was −0.55 at baseline and −0.64 at month 18. Reliability between RULM and EK2 was −0.66 at baseline and −0.79 at month 18.

3.3. Motor functional assessment compared with previous studies

A comparison of our results with previously reported patients with SMA treated with salbutamol was performed. Pane et al. published a study in 2008 in which 23 children with SMA type II started treatment with salbutamol before the age of 6 years [29]. Despite a lower increase in our cohort, no statistically significant differences were detected when we compare the mean change in HFMSE score at month 12 in our <6-year-old patients who were assessed both at baseline and at month 12 and those patients from that study (+1.57 vs +3.78. $p = 0.13$). It is remarkable that a significantly higher score in HFMSE at baseline was observed in the patients published by Pane et al. (13.57 vs 24.65. $p < 0.05$).

Given that our study lacked a control group, our results were compared with annual rate of change in motor function in previously published patients without treatment [10,43–46]. The 12-month change in the study published by Mercuri et al. differed significantly in different age groups in non-ambulant patients: the mean 12-month change in HFMS was +0.04 in children below 5 years of age, −0.96 in children between 5 and 15 years, and −0.35 in patients over 15 years of age [43]. Kaufmann et al. observed a slight decline in HFMS score over time, with a mean annual rate of change of −0.47 in non-ambulant patients [44]. Additionally, mean changes in HFMSE and RULM scores at month 12 in our patients below 6 years of age were compared with patients extracted from the sham control group included in the phase 3 trial of nusinersen performed in children with SMA type 2 [42]. This group is composed by 42 patients with a median age of 3.0 years, ranging from 2 to 7 years. A slightly lower mean improvement in HFMSE and RULM at month 12 was observed in these not-treated patients from the sham control group when compared with our patients treated with salbutamol (HFMSE: +1.14 vs +1.25; RULM: +1.36 vs +3.29).

A correlation with the number of *SMN2* copies was not studied since 3 copies were detected in the majority of patients included in our study (80%) (Table 1).

3.4. Subjective response to salbutamol

All the adult patients and parents of those patients under 18 years of age were asked about their subjective perception regarding the impact of treatment over time. A 77% reported initially some kind of improvement (92% in <6 years vs 70.6% in ≥6 years). No beneficial effects were noted in 11 patients. Almost all the patients referred the maximum impact during the first months of treatment, after which a stabilization was appreciated. Interestingly, several patients referred they had realized that they had forgotten to take the medication due to a subjective worsening. Most families (83.3%) refused to stop taking the treatment when they were asked about.

3.5. Adverse effects

Adverse effects were reported in 38.3% of patients (15% in <6 years vs 47% in ≥6 years). Tachycardia and hand tremor were the most frequently reported side effects, disappearing after a few months of treatment in most of cases and not requiring a dosage adjustment. Other less commonly reported side effects were insomnia and dizziness. A perceived lack of response was the main reason to stop the treatment in 6 out of the 8 patients who withdrew prematurely. Two patients, representing a 4.2% of the cohort, stopped the oral salbutamol due to adverse effects (hand tremor and dizziness, respectively). Serious adverse events were not reported in any patient.

3.6. Scoliosis, hospitalizations, and surgical procedures during the study

A scoliotic curve greater than 15° at baseline was detected in 44 out of the 48 patients. Cobb angle at baseline varied from 0° to 94° (mean 56°). Eleven out of the 48 patients had a second X-ray at month 12 (mean change: +5.63°, ranging from 0° to 14°), and 21 patients at month 18 (mean change: +15°; ranging from 0°−49°). A definitive posterior spinal fusion had been performed in 11 patients prior to treatment. During the study period, 5 additional patients underwent a definitive spinal fusion (Table 2). Postoperative complications, including extubation difficulties and surgical wound infection were observed in 2 patients.

Apart from the scoliosis surgical interventions, 13 patients were hospitalized during the study period. Ten of them were admitted to hospital for respiratory infections and the other patient for a bone fracture. In addition, two out of the 48 patients underwent programmed general surgery for phimosis correction and tonsillectomy, respectively.

4. Discussion

Our results suggest that oral administration of salbutamol (6 mg per day) might be helpful in the maintenance of motor function in patients with SMA type II. An apparent beneficial effect was observed in functional scales of children under the age of 6, especially during the first 6 months of therapy.

According to the better results on RULM score at month 18, the benefit on upper limbs seems to be more sustained over time. The majority of patients of all ages referred some kind of subjective positive effect associated with therapy intake. Salbutamol seems safe and was well tolerated without serious side effects.

The overall treatment effect in terms of change from baseline on the 3 scales across all visits was significantly better in the youngest patients (<6 years). These data must be considered with caution since children with SMA without treatment might experience improvements in motor function during their first years of life [43,47] and a possible placebo effect cannot be ruled out, although the improvement observed is different from the typical temporary early response associated with a placebo effect. The main limitation of the study was the absence of a control group. In order to mitigate this defect, we compared our results with those extracted from the natural history [10,43–46] and from patients belonging to the sham control group included in the phase 3 trial of nusinersen [42]. Although a rigorous statistical analysis cannot be undertaken, our impression comparing these data is that the functional progression in our cohort, characterized by a marked improvement in the 6 first months of treatment, is not typical of the natural history of the disease. The subjective perception of patients and families is consistent with this clinical beneficial effect, observed especially during the first months after the onset of oral salbutamol. The long-term effect of oral salbutamol cannot be reliably measured according to available data.

The analysis of overall results was strongly influenced by the heterogeneity of our cohort in terms of age. The impact of the salbutamol is not easy to be assessed in older patients with SMA type 2 since: (1) HFMSE shows a floor effect in non-ambulant patients with a prolonged course, (2) other variables such as scoliosis or contractures are more frequent in older patients, and (3) data on follow-up with RULM and/or EK2 in patients over the age 10 in the literature are scarce. Seen in another way and from an actual perspective, this information about disease progression in older patients provide a significant added value in order to properly assess what impact the new therapies have on them.

The three functional scales used to assess disease progression showed a good correlation, both at baseline and at month 18. As previously observed in other studies [48], HFMSE is an appropriate scale with clear utility in the assessment of ambulant and stronger non-ambulant patients. Nevertheless, the HFMSE is susceptible to floor effects in weaker non-ambulant patients. In these last patients, use of RULM and EK2 appeared to be more sensitive to describe the SMA phenotype and capture changes.

Despite the acknowledged limitations, this study represents a step forward for the analysis of the usefulness of this commonly used treatment. The results we report here are consistent with the results of previous studies and, to our knowledge, it is the longest and largest study so far to collect prospective assessments, including three different functional motor scales. These novel data are useful to improve the design of future studies and highlight the need for a more appropriate randomized placebo-controlled trial investigating the efficacy of salbutamol in SMA, that may be associated with the new therapies.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.04.003.

References

[1] Darras BT, Markowitz JA, Monani UR, De Vivo DC. Spinal muscular atrophies. In: Darras BT, Jones HRJ, Ryan MM, De Vivo DC, editors. Neuromuscular disorders of infancy, childhood, and adolescence: a clinician’s approach. 2nd Ed. San Diego, CA: Academic Press; 2015. p. 117–45.

[2] Wirth B. An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). Hum Mutat 2000;15:228–37.

[3] Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve 2015;51:157–167.

[4] Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20:27–32.

[5] Cusin V, Clermont O, Gérard B, Chantereau D, Elion J. Prevalence of SMN1 deletion and duplication in carrier and normal populations: implication for genetic counselling. J Med Genet 2003;40:e39.

[6] Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120–2133.

[7] Russman BS. Spinal muscular atrophy: clinical classification and disease heterogeneity. J Child Neurol 2007;22:946–51.

[8] Munsat TL, Davies KE. International SMA consortium meeting. (26-28 June 1992, Bonn, Germany). Neuromuscul Disord 1992;2:423–8.

[9] Prior TW, Finanger E. Spinal muscular atrophy. 2000 Feb 24 [updated 2016 Dec 22]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, Eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2018. Available from http://www.ncbi.nlm.nih.gov/books/NBK1352/.

[10] Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology 2012;79:1889–97.

[11] Wirth B, Herz M, Wetter A, Moskau S, Hahnen E, Rudnik-Schöneborn S, et al. Quantitative analysis of survival motor neuron copies: identification of subtle SMN1 mutations in patients with spinal muscular atrophy, genotype-phenotype correlation, and implications for genetic counseling. Am J Hum Genet 1999;64:1340–56.

[12] Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358–68.

[13] Calucho M, Bernal S, Alías L, March F, Venceslá A, Rodríguez-Álvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord 2018;28:208–215.
[14] Burke G, Hiscock A, Klein A, Niks EH, Main M, Manzur AY, et al. Salbutamol benefits children with congenital myasthenic syndrome due to DOK7 mutations. Neuromuscul Disord 2013;23:170–5.
[15] Chan SH, Wong VC, Engel AG. Neuromuscular junction acetylcholinesterase deficiency responsive to albuterol. Pediatr Neurol 2012;47:137–40.
[16] Rodríguez Cruz PM, Palace J, Ramjattan H, Jayawant S, Robb SA, Beeson D. Salbutamol and ephedrine in the treatment of severe AChR deficiency syndromes. Neurology 2015;85:1043–7.
[17] Martineau L, Horan MA, Rothwell NJ, Little RA. Salbutamol, a beta 2-adrenoceptor agonist, increases skeletal muscle strength in young men. Clin Sci (Lond) 1992;83:615–21.
[18] Rodríguez Cruz PM, Palace J, Ramjattan H, Jayawant S, Robb SA, Beeson D. Salbutamol and ephedrine in the treatment of severe AChR deficiency syndromes. Neurology 2015;85:1043–7.
[19] McMacken G, Cox D, Roos A, Müller J, Whittaker R, Lochmüller H. The beta-adrenergic agonist salbutamol modulates neuromuscular junction formation in zebrafish models of human myasthenic syndromes. Hum Mol Genet 2018;27:1556–64.
[20] Messina S, Hartley L, Main M, Kinali M, Jungbluth H, Muntoni F, et al. Pilot trial of salbutamol in central core and multi-minicore diseases. Neuropediatrics 2004;35:262–6.
[21] Kissel JT, Mendell JR, Griggs RC, McDermott M, Tawil R. Open-label clinical trial of albuterol in facioscapulohumeral muscular dystrophy. Neurology 1998;50:1402–6.
[22] Kissel JT, McDermott MP, Mendell JR, King WM, Pandya S, Griggs RC, et al. Randomized, double-blind, placebo-controlled trial of albuterol in facioscapulohumeral dystrophy. Neurology 2001;57:1434–1440.
[23] van der Kooi EL, Vogels OJ, van Asseldonk RJ, Lindeman E, Hendriks JC, Wohlgemuth M, et al. Strength training and albuterol in facioscapulohumeral muscular dystrophy. Neurology 2004;63:702–8.
[24] Payan CA, Hogrel JY, Hammouda EH, Lacomblez L, Ollivier G, Doppler V, et al. Periodic salbutamol in facioscapulohumeral muscular dystrophy: a randomized controlled trial. Arch Phys Med Rehabil 2009;90:1094–101.
[25] Koeberl DD, Li S, Dai J, Thurberg BL, Bali D, Kishnani PS. β2 agonists enhance the efficacy of simultaneous enzyme replacement therapy in murine Pompe disease. Mol Genet Metab 2012;105:221–7.
[26] Fowler EG, Graves MC, Wetzel GT, Spencer MJ. Pilot trial of albuterol in Duchenne and Becker muscular dystrophy. Neurology 2004;62:1006–1008.
[27] Skura CL, Fowler EG, Wetzel GT, Graves M, Spencer MJ. Albuterol increases lean body mass in ambulatory boys with Duchenne or Becker muscular dystrophy. Neurology 2008;70:137–43.
[28] Kinali M, Mercuri E, Main M, De Biasia F, Karatza A, Higgins R, et al. Pilot trial of albuterol in spinal muscular atrophy. Neurology 2002;59:609–10.
[29] Pane M, Staccioli S, Messina S, D'Amico A, Pelliccioni M, Mazzone ES, et al. Daily salbutamol in young patients with SMA type II. Neuromuscul Disord 2008;18:536–40.
[30] Giovannetti AM, Pasanisi MB, Černiauskaitė M, Bussolino C, Leonardi M, Morandi L. Perceived efficacy of salbutamol by persons with spinal muscular atrophy: a mixed methods study. Muscle Nerve 2016;54:843–9.
[31] Khirani S, Dabaj I, Amaddeo A, Olmo Arroyo J, Ropers J, Tirolien S, et al. Effect of salbutamol on respiratory muscle strength in spinal muscular atrophy. Pediatr Neurol 2017;73:78–87.
[32] Angelozzi C, Borgo F, Tiziano FD, Martella A, Neri G, Brahe C. Salbutamol increases SMN mRNA and protein levels in spinal muscular atrophy cells. J Med Genet 2008;45:29–31.
[33] Harahap NIF, Nurputra DK, Ar Rochmah M, Shima A, Morisada N, Takarada T, et al. Salbutamol inhibits ubiquitin-mediated survival motor neuron protein degradation in spinal muscular atrophy cells. Biochem Biophys Rep 2015;4:351–6.
[34] Tiziano FD, Lomastro R, Pinto AM, Messina S, D'Amico A, Fiori S, et al. Salbutamol increases survival motor neuron (SMN) transcript levels in leucocytes of spinal muscular atrophy (SMA) patients: relevance for clinical trial design. J Med Genet 2010;47:856–858.
[35] Pera MC, Luigetti M, Sivo S, Lapenta L, Granata G, Antonaci L, et al. Does albuterol have an effect on neuromuscular junction dysfunction in spinal muscular atrophy? Neuromuscul Disord 2018;28:863–864.
[36] Munsat TL, Davies KS. International SMA consortium meeting (26-28 June 92, Bonn, Germany). Neuromuscul Disord 1992;2:423–8.
[37] Glanzman AM, O'Hagen JM, McDermott MP, Martens WB, Flickinger J, Riley S, lanzman AM, O'Hagen JM, et al. Validation of the expanded Hammersmith functional motor scale in spinal muscular atrophy type II and III. J Child Neurol 2011;26:1499–507.
[38] Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, et al. Revised upper limb module for spinal muscular atrophy: development of a new module. Muscle Nerve 2017;55:869–874.
[39] Mayhew AG, Eagle M, Steffenson B. S.P.6 Exploratory Rasch analysis of the EK2 scale used in a population of Duchenne muscular dystrophy (DMD). Neuromuscul Disord 2012;22:877.
[40] Fagoaga J, Girabent-Farres M, Bagur-Calafat C, Steffensen BF. Evolution of functional capacity, assessed with the Egen Klassifikation scale, in the Spanish population with spinal muscular atrophy or Duchenne muscular dystrophy. A three year longitudinal study. Rev Neurol 2015;61:344–8.
[41] Febrer A, Vigo M, Fagoaga J, Medina-Cantillo J, Rodríguez N, Tizzano E. Hammersmith functional rating scale for children with spinal muscular atrophy. Validation of the Spanish version. Rev Neurol 2011;53:657–63.
[42] Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–35.
[43] Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. Neuromuscul Disord 2016;26:126–31.
[44] Kaufmann P, McDermott MP, Darras BT, Finkel R, Kang P, Oskoui M, et al. Observational study of spinal muscular atrophy type 2 and 3: functional outcomes over 1 year. Arch Neurol 2011;68:779–786.
[45] Seferian AM, Moraux A, Canal A, Decostre V, Diebate O, Le Moing AG, et al. Upper limb evaluation and one-year follow up of non-ambulant patients with spinal muscular atrophy: an observational multicenter trial. PLoS One 2015;10(4):e0121799.
[46] Mercuri E, Messina S, Battini R, Berardinelli A, Boffi P, Bono R, et al. Reliability of the Hammersmith functional motor scale for spinal muscular atrophy in a multicentric study. Neuromuscul Disord 2006;16:93–8.
[47] Iannaccone ST, Browne RH, Samaha FJ, Buncher CR. Prospective study of spinal muscular atrophy before age 6 years. DCN/SMA Group. Pediatr Neurol 1993;9:187–93.
[48] Mazzone E, De Sanctis R, Fanelli L, Bianco F, Main M, van den Hauwe M, et al. Hammersmith functional motor scale and motor function measure-20 in non ambulant SMA patients. Neuromuscul Disord 2014;24:347–52.