European Journal of Paediatric Neurology 27 (2020) 37–42

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

Efficacy of nusinersen in type 1, 2 and 3 spinal muscular atrophy: Real world data from Hungarian patients

Léna Szabó [a, *], Anita Gergely [b], Rita Jakus [b], András Fogarasi [b], Zoltán Grosz [c], Mária Judit Molnár [c], Ildikó Andor [a], Orsolya Schulcz [b], Ádám Goschler [a], Erika Medveczky [d], Dorottya Czövek [e], Ágnes Herczegfalvi [a]

[a] Semmelweis University 2nd Dept. of Paediatrics, 7-9. Tűzoltó street Budapest, 1094, Hungary
[b] Bethesda Children's Hospital, 3. Bethesda street, Budapest, 1146, Hungary
[c] Semmelweis University Institute of Genomic Medicine and Rare Disorders, 78, Üllői street Budapest, 1083, Hungary
[d] North-Central Buda Centre, New St. John's Hospital and Clinic, 5-9. Bolyai street Budapest, 1023, Hungary
[e] Semmelweis University 1st Dept. of Paediatrics, 53-54. Bókay János street Budapest, 1083, Hungary

ARTICLE INFO

Article history:
Received 21 January 2020
Received in revised form
5 May 2020
Accepted 8 May 2020

Keywords:
Spinal muscular atrophy
Treatment efficacy
Motor function
Nusinersen

ABSTRACT

Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by a homozygous deletion of the survival motor neuron (SMN) 1 gene. Nusinersen is an antisense oligonucleotide enhancing the production of the SMN protein. It has received approval by the European Medicines Agency (EMA) in 2017, based on the clinical trials demonstrating the effectiveness of nusinersen in several types of SMA. In Hungary, the first patient received nusinersen treatment in April 2018. Our aim is to summarize our experience regarding the efficacy, safety and tolerability of nusinersen in our patients.

Methods: Data were collected retrospectively in all types of SMA patients (type 1–3) starting treatment with nusinersen in Hungary between April 2018 and December 2019. Motor functions were evaluated at baseline, at the fourth and all following injections.

Results: By 31st December 2019, nusinersen therapy was initiated in 54 patients at either of the two Hungarian treatment centres. Mean age of the patients at the start of the treatment was 6.3 years (±5,4 range 0.4–17.9). 13 patients are type 1 (mean 0.78 ± 0.27, range 0.4–1.5 yrs), 21 patients are type 2 (mean 4.5 ± 3.3, range 1.3–12 yrs), 23 patients are type 3 (mean 10.9 ± 5.2, range 2.9–17.9 yrs). Fourteen patients had severe scoliosis, four of them underwent spine stabilizing surgery. During the study period 340 injections were administered without any new safety concerns emerging. The data of 38 patients, who had completed the first six treatments, were included in the final statistical analysis. Motor function has improved in most of the children. By the 307th day visit, on average, a 14.9 (±5,1) point improvement was measured on the CHOP INTEND scale in type 1 patients ($p = 0.016$). All patients with type 1 SMA who performed the motor evaluation (7/10) have improved by more than four (7-21) points. Regarding type 2 patients, a 7.2 (range -2- 17) point increase from baseline ($p < 0.001$) on the Hammersmith Functional Motor Scale Expanded (HFMSE) and 4.3 (range: 2–9) point increase ($p = 0.031$) on the Revised Upper Limb Module (RULM) were found. The distance of the 6 min walk test also increased by 33.9 m on average (range -16 – 106), in type 3 patients.

Conclusion: According to our results nusinersen has the same safety and tolerability profile as in the clinical trials. In a heterogenic patient population of SMA type 1 and 2, nusinersen showed similar efficacy as seen in the pivotal studies. A clinically and statistically significant improvement of motor functions was also detectable in type 3 patients with heterogeneous age distribution.

1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive

* Corresponding author.
E-mail address: szabo.lena@med.semmelweis-univ.hu (L. Szabó).

https://doi.org/10.1016/j.ejpn.2020.05.002

disorder caused by a homozygous deletion in the survival motor neuron (SMN) 1 gene on chromosome 5q13 [1,2], characterized by progressive muscle atrophy and weakness, with an estimated incidence of 1 in 7500 live births [3]. The disease severity of SMA is strongly influenced by the copy number of the closely related SMN2 gene, which differs only in two exonic base pairs from the SMN1 gene [4,5]. Depending on the severity of symptoms, the highest level of motor function (i.e. sitting or standing) and age of onset, SMA is classified into five different subtypes (0–4). SMA 0 is the most severe newborn form of the disease. Type 1 is the most common (50–60%) subtype of SMA. Per definition, onset of symptoms is before six months of age and the main cause of mortality of these children is respiratory distress before two years of age. Children with type 2 SMA are able to sit unassisted at some point during their development; however they are never able to walk independently. In type 3 SMA the symptoms occur after 18 months of age, and affected children are able to walk unassisted at some point during their lifetime, but have a high risk of losing their walking ability. Type 4 SMA is the least severe type; it occurs in adult patients with diffuse symmetric proximal muscle weakness and absent or markedly decreased deep tendon reflexes [6].

Nusinersen is the first disease modifying drug approved to treat paediatric and adult patients with SMA [7]. Nusinersen is an antisense oligonucleotide designed to modify the splicing behaviour of the SMN2 gene thereby increasing the inclusion of exon7 and the expression of full length SMN protein [8,9]. It was approved by the US Food and Drug Administration in late December 2016 and by the European Medicines Agency in June 2017 [10]. In Hungary, nusinersen treatment is reimbursed by the National Health Insurance Fund for all three paediatric types of SMA -with certain criteria-for patients under 18 years of age, on a case-by-case basis.

Phase III double-blind placebo-controlled studies proved the efficacy of nusinersen treatment in patients with SMA type 1 and 2 showing an improvement in motor milestones and event-free survival [11,12]. Its efficacy in type 1 SMA population was also demonstrated by the results of the Extended Access Programs (EAP) [13–16]. There is limited data available on the therapeutic effect of nusinersen in type 3 SMA patients [10,17].

2. Methods

We collected data retrospectively for all patients with SMA who received their first dose of nusinersen treatment in Hungary between April 2018 and December 2019. Based on the local administration criteria of nusinersen during our study period, patients were not granted the therapy if a) they were over 18 month of age (SMA types 1), b) they were over 18 years of age (SMA types 2, 3), c) they performed below ten points in HFMSE (SMA types 2 and 3) and d) if they needed permanent ventillation (defined as 16 h or more on the ventilator per day; SMA types 1, 2 and 3). Patients were assessed before administration of the first dose of nusinersen, at the time of the 4th injection (63 days of treatment) and then every four months prior to the administration of the next injection. Before treatment initiation we collected data on clinical history, SMN2 copy numbers and performed a full clinical examination (including evaluation of nutritional, respiratory and body composition via DEXA (Dual Energy X-ray Absorptiometry) evaluation). The patients were categorized into one of the three SMA types based on the start of clinical symptoms and the best motor function achieved. In case of discrepancy, decision was made based on the best motor function. For evaluation of the motor function, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was used in all patients younger than 2 years of age and in all non-sitter patients [11]. For patients who were able to sit without assistance, the Hammersmith Functional Motor Scales Expanded (HFMSE) protocol was used with the addition of the Revised Upper Limb Module (RULM) for those who could sit by a table [12]. For walkers we performed the 6 Minute Walk Test and HFMSE [18,19].

Changes over time were analysed with Wilcoxon matched pairs signed rank test and linear regression analysis with GraphPad Prism version 8.0.1 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com) for all analysis. A p-value < 0.05 was considered as statistically significant difference.

The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics. (SE RKEB 150/2019.). Parents were informed about the data collection and gave written informed consent. We did not perform any procedures outside standard care.

3. Results

3.1. Demography

During the study period 57 patients started nusinersen treatment in Hungary. Three of the patients (5.8%; all SMA I) were excluded from the further analysis due to missing data: two of them started the treatment in the Italian EAP and we could not access the baseline motor functions, one other patient was initially tested with HFMSE and no data on baseline CHOP INTEND was available. Thirty-eight (66.7%) patients who completed the first six treatments and had the assessments performed on Day 307 of the treatment period were included in the final statistical analysis. (Two of the type 1 patients included started their treatment in the French and Belgian EAP) Table 1. shows the baseline characteristics of all treated patients.

Fourteen patients had scoliosis, four of them underwent spine stabilizing surgery (two Growing rod, one Magec, one other) prior to the initiation of the tretment. One patient had percutaneous gastrostomy tube and severe bulbar dysfunction with permanent need of oral suction. All other children were able to feed orally.

Most of the children with type 2 and 3 SMA had annual assessment of their lung function as a part of standard care of neuromuscular patients in Hungary. Prior to or right after the initiation of the treatment, all patients with type 1 and 2 SMA underwent a complex respiratory assessment including polysomnography together with exhaled or transcutaneous CO2 monitoring. Based on this assessment, 18 children required assistance with their breathing overnight in whom BiPAP therapy was initiated. The main indication of BiPAP therapy was hypoventilation during sleep and subsequent hypercapnia during the night. All of these patients were safe to be ventilated non-invasively and none of them needed escalation of treatment (i.e. increasing BiPAP pressures, tracheostomy and invasive ventilation) during the period studied.

4. Motor function

4.1. SMA type 1

Motor function improved in all of the seven patients who performed the motor evaluation at Day 307 and the improvement was >4 points in each case. Detailed data are shown in Table 2. Change from baseline became statistically significant at the time of the 5th injection and remained significant by the time of the Day 307 visit. At this time the average improvement was 14.9 points (±5.1, range 7–21) (Fig. 1). In this relatively small cohort we did not find correlation between the age at treatment initiation and the degree of improvement in motor function (Fig. 2) ($p = 0.559$, R^2 0.072, Slope −0.417 (95% Confidence Intervals −2.13 to 1.3)

Table 1
Baseline demographics prior to treatment of all children including subgroups according to SMA types.

	SMA 1	SMA 2	SMA 3	Total
N (% of total)	10 (18%)	21 (39%)	23 (43%)	54
Mean age (years)	0.78	4.5	10.9	6.3
(SD)	(0.27)	(3.3)	(5.2)	(5.4)
(min-max)	(0.4–1.5)	(1.3–12)	(2.9–17.9)	(0.4–17.9)
Median age (years)	0.8	2.9	13.1	5.26
Male/female	7/3	12/9	15/8	34/20
SMN2 copy number				
2 copies	7	3	1	11
3 copies	3	18	12	33
4 copies	0	0	10	10
Follow up (days) (median)	473 (484)	415 (432)	370 (384)	408 (440)
Baseline motor function (min-max)				
CHOP INTEND score	24.1 (2–43)	–	–	
HFMSE score	–	19.4 (2–33)	48.6 (27–64)	
6MWT (m)	–	–	256.3 (24–426)	

SMA: spinal muscular atrophy, SD: Standard Deviation, SMN: Survival of Motor Neuron, CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HFMSE: Hammersmith Functional Motor Scales Expanded, 6MWT: 6 Minute Walk Test. No patient had one copy of SMN2 gene.

Table 2
The average CHOP INTEND scores by the time points of the injections in SMA type 1 patients.

Time of evaluation (day)	N	CHOP INTEND Mean (SD)	Change from baseline	P value
Before treatment	7	30.0 (7.6)	–	–
63.	7	33.4 (8.6)	3.4	ns.
185.	7	39.0 (7.8)	9.0	0.016
307.	7	44.9 (6.7)	14.9	0.016
429.	6	47.8 (5.9)	20	0.031
551.	3	54.0 (5.3)	27.7	–

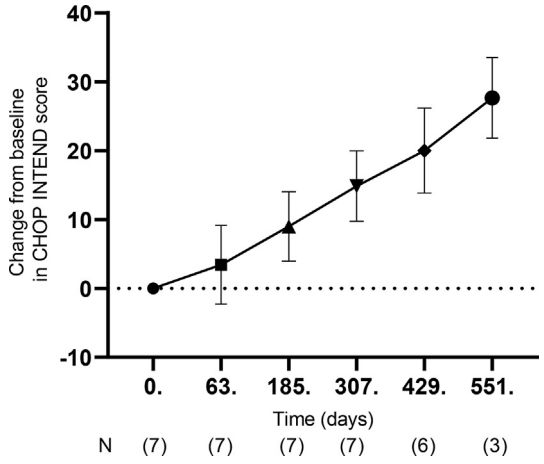

Fig. 1. The change from baseline in CHOP INTEND score in SMA type 1 patients.

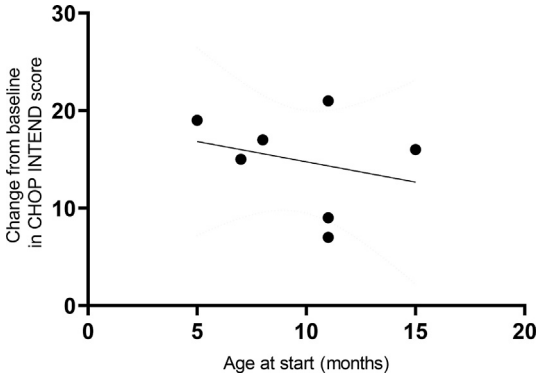

Fig. 2. The relationship between the change from baseline in CHOP INTEND score and the age at treatment initiation.

4.2. SMA type 2

Sixteen patients completed the follow up visit at Day 307. The average motor performance measured by HFMSE improved significantly at the 4th injection and the improvement remained significant at all of the further evaluations. Detailed data are shown in Table 3. At Day 307 of the treatment, average improvement was 7.2 points (±5.0, range -2-17) (Fig. 3). We found a statistically significant correlation between the age at treatment initiation and the change in HFMSE score at Day 307 of the treatment ($p = 0.008$, R^2 0.409, Slope −0.984 (95% Confidence Intervals −1.7 to −0.31) in the group of SMA type 2 patients. The earlier the treatment started, the greater improvement was observed (Fig. 4). Upper extremity function also improved significantly by 4.33 points on average (±2.78, $p = 0.031$) by Day 307 and the improvement remained stable at all consecutive assessments.

4.3. SMA type 3

Fifteen patients completed the follow up visit at Day 307, of whom 12 children were ambulant. Average motor performance measured by HFMSE improved significantly by 5.3 points (±4.4, range -1-13, $p = 0.001$) by the time of the 6th injection (Fig. 5). The distance walked during the 6MWT improved in most of the patients, a significant increase by 33.9 m was found at the 307th day of treatment (±44.0range −16.3–106.5 m, $p = 0.007$). (Fig. 6). The age at treatment initiation did not correlate significantly with either the change in the HFMSE score ($p = 0.428$, R^2 0.092, Slope 0.270 (95% Confidence Intervals −0.41 to −0.86), or the distance in 6MWT ($p = 0.465$, R^2 0.055, Slope 2.19 (95% Confidence Intervals −4.25 to 8.64) at Day 307.

Table 3
The average HFMSE score by the time points of the injections in SMA type 2 patients.

Time of evaluation (day)	N	HFMSE Mean (SD)	Change from baseline	P value
Before treatment	15	21.2 (6.5)	–	–
63.	15	24.2 (9.2)	3.1	0.013
185.	15	25.9 (10.6)	4.0	0.021
307.	16	28.6 (9.7)	7.2	<0.001
429.	11	29.5 (11.4)	7.0	0.012
551.	7	26.1 (14.6)	5.7	Ns

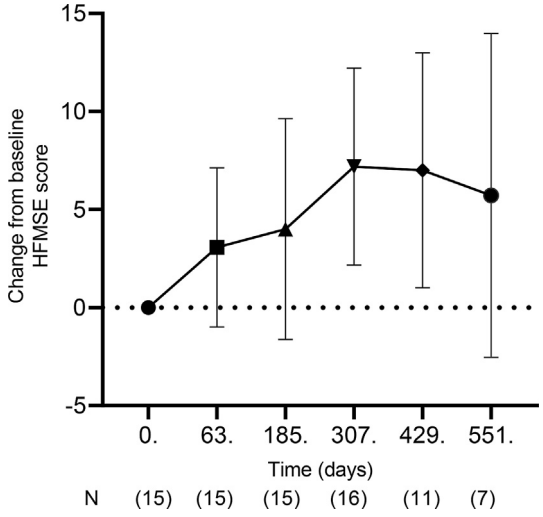

Fig. 3. The change from baseline in HFMSE score in SMA type 2 patients.

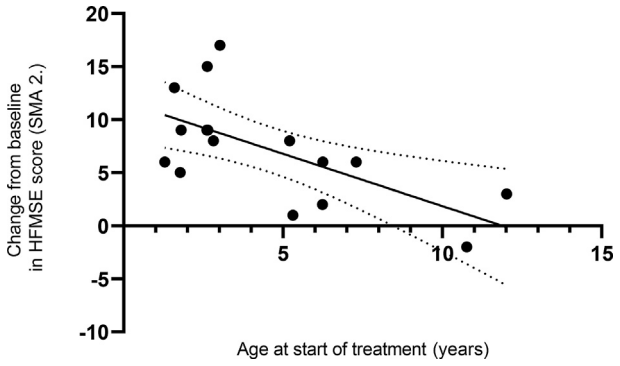

Fig. 4. The change from baseline in HFMSE score and the age at treatment initiation in type 2 SMA patients.

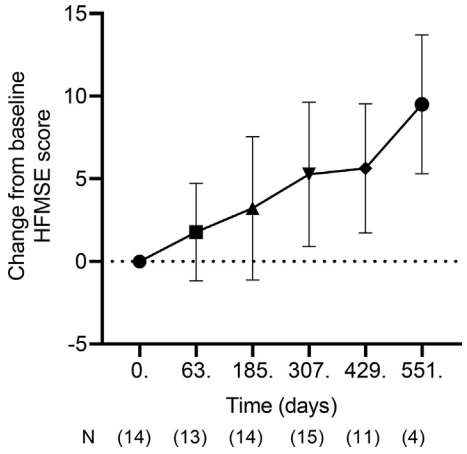

Fig. 5. The change from baseline in HFMSE score in SMA type 3 patients.

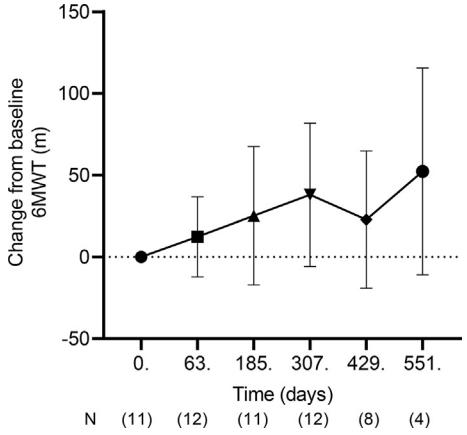

Fig. 6. The change from baseline in 6MWT in SMA type 3 patients.

4.3. Safety

Lumbar punctures were performed without any severe complications and nusinersen was administered intrathecal in all children on all treatment days even in case of severe scoliosis. Commonly used sedation procedure was N_2O 50%; O_2 50% gas combined with a local anaesthetic agent. Occasionally we used midazolam, ketamine or propofol for sedation in patients who could not tolerate the mask or tube for gas administration. We performed 340 injections during the observed period. The most frequent side effects were the common symptoms of post-puncture syndrome [headache (8%), backache (6%), vomiting (6%)]. Medical conditions such as pneumonia, pneumothorax, bone fracture, leg pain, transient and mild thrombocytopaenia, and UTI (Urinary Tract Infection) were occasionally observed during the treatment period. From these conditions above thrombocytopaenia was reported after administration of some antisense oligonucleotides [20]. In our study it only appeared in one patient on one occasion during the treatment period and it was mild and transient. Although the role of nusinersen cannot be ruled out in this condition; it is unlikely that thrombocytopaenia in this case was related to the treatment. No hydrocephalus or any other significant, drug specific side effects were observed. No treatment was terminated because of side effects.

5. Discussion

Our results show that nusinersen is a safe and effective treatment in a heterogeneous population of children with SMA throughout all ages and severity of the disease. After a one year period we observed an improvement in motor function in most of

our type 1, 2 and 3 SMA patients treated with nusinersen in a real world setting in Hungary. These changes were not only statistically significant but also clinically relevant for our patients who all reported an improvement in their quality of life.

In the ENDEAR clinical trial a 71% responder rate (improvement of >4 points in the CHOP INTEND score) was shown after 13 months of follow up in type 1 SMA patients [11]. The open label extension of that clinical trial confirmed a 16.8 point average improvement on the CHOP INTEND scale from baseline by Day 1058. Treatment initiation before the age of 5.4 months resulted in an even greater improvement of 19.3 points from baseline. However, a much broader spectrum of type 1 SMA patients were treated with nusinersen in the EAPs, where the authors described a similar, 42–77% responder rate after a 6 month follow up period which seemed to remain stable for 12 months [13–15]. Pane and colleagues found in the Italian EAP that the improvement was most obvious in patients younger than 7 months, however they also found improvement in the older age group of SMA type1 patients [15]. Pechmann et al. also found a greater change in CHOP INTEND score from baseline in children aged ≤7 months compared to older children (children ≤7 months:14.4 ± 9.2; children>7months of age:7.0 ± 6.6). They experienced slighter improvements in children requiring permanent ventilation support or tracheostomy (change in CHOP INTEND score was 5.6 ± 7.5) [13]. Aragon-Gawinska et al. described an average of 3.5 points improvement in the CHOP INTEND score among children between 8 and 111 months of age after a 6 months follow up period [16]. In our cohort we started the treatment in all children with SMA type 1 before the age of 1.5 years (mean 0.78 ± 0.27y). The average changes in CHOP INTEND score were similar to younger patient group (14.9 ± 5.1 points) in the EAP, even though the mean age at treatment initiation was higher (11 ± 4.4 months) in our cohort. We could not find a statistically significant correlation between the age at treatment initiation and the efficacy of treatment in the type 1 SMA population, most probably because of the small number of patients in this group. All of our treated type 1 patients became responders by the time of the 6th injection. The relatively good therapeutic response could indicate that age at treatment initiation is an important factor of efficacy but not the only one. Since patients with more than 16-hours of ventilation dependency or with tracheostomy cannula were excluded from the treatment according to the Hungarian reimbursement criteria, it is possible that only less severe type 1 patients were alive and without ventilation support and thus available for nusinersen treatment at the time point of treatment initiation. This is also indicated by the fact that the frequency of 3 copies of SMN2 gene in the type 1 group is relatively high (30%). Data from patients, including younger children with more severe symptoms, who started the treatment right after their diagnosis and have not completed the 6th injection yet, were not included in the current statistical analysis. Based on our experience, we believe that the baseline motor function or the progression rate could also influence the treatment outcome, as it was suggested by Pane at al. based on the Italian EAP's data.

There is limited evidence to support the efficacy of nusinersen in type 2 SMA patients beyond the RCT clinical study [10]. In the CHERISH study, Mercuri et al. found an average of 4 points improvement in HFMSE score after 15 months follow up in a cohort involving 84 later onset SMA patients treated by 12 mg of nusinersen. This study included children 2–12 years of age with a motor performance of 10–54 points in HFMSE [12]. The open label extension of the CHERISH study (SHINE) involved 84 patients treated with nusinersen previously and 42 patients who underwent sham procedure. Patients treated with nusinersen from the beginning, showed a 3.7 point improvement in HFMSE at the end of the 1170 day follow up period [21]. A small number of type 2 SMA patients participated in the Phase I study (ISIS-SMNRx) but with a wide age range from 2 to 14 years of age. In this dose-escalating study, 7 patients received the 9 mg nusinersen dose that proved to be effective. During the long term follow up the mean change of HFMSE score was 5.8 points [22]. In our cohort, 7.2 (±5.0) point improvement was experienced by the Day 307 visit. The better results could be explained by the better adherence to care standards alongside the start of nusinersen treatment in the Hungarian patient population.

In type 2 SMA patients, there is limited information available on the factors influencing treatment effectiveness [12]. Our data suggest a negative correlation between the age at treatment initiation and treatment outcomes. As symptoms start between 6 and 18 months in type 2 SMA patients and therapy was started between 1.5 and 12 years of age, disease duration might be a more important factor beside the age itself. This hypothesis is also supported by the fact that we could not find similar correlation between age and efficacy in type 3 patients, in whom the age of the first symptoms and the disease duration are not necessarily linked.

Efficacy of nusinersen treatment in type 3 SMA patients has been suggested by phase 1–2 studies [22], however limited data are available to describe the therapeutic response of this population [10]. Montes et al. summarised patients' follow up data who participated the CS2 or CS12 open labelled clinical trials. Fourteen subjects were ambulatory and performed the 6MWT during these trials. Mean age at screening was 8.6 years. Median distance measured at baseline was 250.5 m (range 0–563 m) and it increased by 17 m range −47-99 m) at Day 253 and 99 m (range 31–150) at Day 1050 [17]. Based on Bohannon findings, a change of 14.0–30.5 m in 6MWT is clinically important across multiple patient groups [23]. Wurster at al. examining 11 type 3 SMA patients between 13 and 60 years of age, could not find a meaningful change in the HFMSE score at the time of the 4th injection [24]. By contrast, in our cohort we found a meaningful increase in the 6 min walk distance (33.9 m range -16-106 m) and a significant improvement in the HFMSE score (mean 5.3, ±4.4, range -1-13 m) in type 3 SMA patients.

6. Limitations

A longer, prospective follow up study with larger number of patient would be necessary to confirm our findings. The clinical protocol followed in the present study did not include the HINE-2 assessment, which could have reflected better the categorical changes in type 1 cases. We measured only motor functions, but additional use of patient reported outcome measures may reflect better the impact of treatment on patients' everyday lives. As nusinersen is a splicing modifier of SMN2 gene, copy number of this gene is a possible influencer of treatment efficacy. However, we could not study the impact of SMN2 gene copy number because of the limited number of patients. Our cohort contains some patients with discordant SMN2 copy number which also might have influenced the treatment efficacy. Type 1 patient with three copies of SMN2 gene may have better outcome. Patients with two SMN2 copies in type 2 or 3 SMA could carry a positive modifier [25,26] which might also influence the outcome.

7. Conclusion

Our data suggest that nusinersen is an effective, life changing treatment in children with a broad disease spectrum of SMA. The drug can be administered intrathecal even in children with severe scoliosis or following spine surgery. In the present study, no significant drug-related side effects were observed over a year-period of treatment and over the administration of 340 injections.

Importantly, there were no children missing a dose because of technical difficulties at either of the two centres. Improvement in the motor functions in patients with SMA is significantly related to their quality of life; thus, further studies are required to establish the long-term effects of nursinersen to optimize the therapy, reduce the morbidity and mortality and hence improve the quality of life of the patients.

Declaration of competing interest

No disclosure.

Acknowledgement

The Authors thank all the patients and their parents for their involvement in the study. Furthermore we would like to say thankyou to all the study nurses and staff of the hospital who significantly contributed to the study.

Czövek D. was supported by János Bolyai Research Scholarship of the Hungarian Academy of Sciences, the ÚNKP-19-4-SE-96 New National Excellence Program of the Ministry of Human Capabilities and NKFI-129237.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2020.05.002.

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