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Original article

Type 1 spinal muscular atrophy treated with nusinersen in Norway, a five-year follow-up

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ABSTRACT

Background: New treatments for 5q spinal muscular atrophy (SMA) have led to changes in the disease phenotype. Questions about long-term efficacy, however, persist. We present the results from five-year follow-up of the first ten Norwegian patients with SMA type1 treated with nusinersen.

Methods: – Ten patients referred to the expanded access program were included. Standardized assessments with Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), the Hammersmith Infant Neurological Examination (HINE-2), compound muscle action potential (CMAP) examination and cerebrospinal fluid analysis of neurofilament light chain (cNfL) were performed.

Result: Age at baseline ranged from three months to 11 years and eight months. Nine patients were alive and continued to receive treatment at 62 months of follow-up. CHOP INTEND scores increased significantly up to 38 months. Any further increase from 38 to 50 months was not statistically significant, and scores remained almost unchanged from 50 to 62 months. HINE-2 scores increased but the difference from baseline never reached statistical significance.

The youngest patients showed the best motor outcome. The changes in CMAP scores were not statistically significant. cNfL values were significantly reduced after 18 months compared with baseline; the largest difference occurred between baseline and 6 months. There was a significant negative correlation between log cNfL and CHOP INTEND ($p = 0.042$). Bulbar and respiratory function did not improve during the observation period.

Conclusion: Our findings support previously reported results on efficacy and safety of nusinersen. All patients have shown improvement in motor function. The need of respiratory and nutritional support did not improve.

1. Introduction

5q spinal muscular atrophy (SMA) is a severe, autosomal recessive neuromuscular disorder caused by homozygous deletions in the *SMN1* gene, which encodes the survival motor neuron (SMN) protein [1]. Lack of SMN protein leads to degeneration and loss of lower motor neurons. The disease is traditionally classified into four clinical subtypes (SMA 1–4) based on age of onset and milestone achievements. Untreated, SMA type 1 is characterized by onset of symptoms and signs before six months of age with hypotonia, progressive muscular atrophy and weakness, failure to achieve motor milestones, respiratory failure and more than 90 % mortality by two years of age [1].

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Patients with SMA are dependent upon *SMN2*, a gene highly homologous to *SMN1*, but which produces only small amounts of functional SMN protein [2]. The *SMN2* copy number is an important determinant for disease phenotype and correlates with both age at onset and severity of disease so that patients with a higher copy number of *SMN2* will in general have a milder disease [3].

The first disease modifying therapy, nusinersen, was approved for the treatment of SMA in Europe in May 2017. Nusinersen is an antisense oligonucleotide that augments production of SMN protein by modifying *SMN2* gene splicing [4]. Regulatory approval was based primarily upon the results of one completed randomized, controlled multicenter trial in type 1 SMA as well as interim analysis of a phase three study on patients with later-onset SMA [4,5]. Safety and efficacy of nusinersen in SMA type 1 patients has been established [6–11]. A recent real-world data study of type 1 SMA has demonstrated motor stability or mild improvement, over a four year period [12]. Questions remain however, regarding long-term efficacy including potential decline of improvement gained [13].

We report experience and data from five-year follow up of the first ten patients with 5q SMA type 1 treated with nusinersen in Norway. The aim of this study was to assess treatment efficacy and safety using standardized motor- and neurophysiological assessment measurements. Outcome regarding the need of nutritional and respiratory support, in addition to changes in cerebrospinal neurofilament light chain (cNfL), a potential biomarker for neuroaxonal degeneration and disease activity [14], are also reported.

2. Methods

Ten patients with SMA type 1 were referred to assessment for commencement of treatment with nusinersen (Spinraza, Biogen) as part of an expanded access program (EAP) prior to approval of national reimbursement in Norway. All ten patients were consecutively enrolled in this prospective single center observational study.[1] The study was approved by the Regional Ethics Committee (2019/652/REK sør-øst C). Informed consent for treatment and the prospective collection of clinical data and biological material was obtained.

The inclusion criteria were: genetically confirmed 5q SMA with homozygous deletion of *SMN1* on chromosome 5q13.2, onset of clinical disease prior to six months of age and inability to sit independently, consistent with infantile-onset SMA.

Prior to commencement of treatment, the following clinical information regarding: copy number of *SMN2* gene, age at onset of symptoms, age at diagnosis, respiratory support, and use of gastrostomy/feeding tube was collected. Clinical characteristics of the patients are summarized in Table 1. All patients received standardized intrathecal dosage of nusinersen (initially age-adjusted proportional to their cerebrospinal fluid volume), and at intervals recommended by the pharmaceutical company, namely four initial doses over nine weeks followed by one dose every four months. Injections were given under sterile conditions with 22 or 24 G needle with administration of nusinersen over 1–4 min. All procedures were performed by one of three experienced pediatric consultants. In five patients procedures were carried out under sedation.

2.1. Testing of motor function

All tests were performed by a small group of experienced physiotherapists who received special training in the use of the relevant standardized tests. Motor function was assessed using The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Functional Motor Scale Expanded (HFMSE) and the Hammersmith Infant Neurological Exam part II (HINE-2). The primary motor endpoint was change in CHOP INTEND score from baseline.

Table 1
Clinical characteristics. (Age in months).

	Gender	SMN2 copy number	Age symptom onset	Age diagnosis	Age start of treatment
Patient 1	M	2	<1	2	3
Patient 2	F	2	<1	2	3
Patient 3	F	2	<3	5	5.5
Patient 4	F	2	1	4.5	18
Patient 5	M	3	6	15	18
Patient 6	M	2	<1	6	26
Patient 7	F	2	<4	6	34
Patient 8	M	2	<3	4.5	46
Patient 9	F	3	5	12	75
Patient 10	F	3	2	13.5	140

2.1.1 CHOP INTEND is a standardized assessment tool designed to identify small changes in motor function in patients with SMA type 1 [4,15,16]. The maximum score is 64. In this study the last two items of the test were omitted since they were not possible to perform in the older patients, giving a maximal score of 56. Patients who reached the ceiling effect on CHOP INTEND were assessed further with HFMSE. The last recorded CHOP INTEND score is included in the group average.

2.1.2 HFMSE is a standardized assessment tool designed for use in patients with SMA to validate motor function in non-ambulant and ambulant individuals with later-onset SMA. The maximum score is 66 [5,17].

2.1.3 HINE-2 documents developmental progress by examining gross motor milestones. The maximum score is 26 [4,18].

Patients were tested prior to dose one and four, thereafter before every treatment for the first two years, then annually, up to 62 months. Age of the individual child can be found in Table 1, *Clinical characteristics*. The motor tests were performed early in the day, in order to give the patients optimal conditions for performance.

2.2. Biomarkers

2.2.1. CMAP

In the pivotal phase III clinical trial, an increase in CMAP amplitude of 1 mV, or maintenance of an amplitude of >/ = 1 mV was defined as significant [4]. In this single center study, the same experienced neurophysiologist performed all measurements. CMAP measurements of the right ulnar and peroneal nerve were recorded using a Keypoint G4® machine. For the ulnar nerve, supra-threshold stimuli were given at the ulnar crease and the response was registered at the abductor digiti minimi. For the peroneal nerve, the stimulation was given at knee level and registration of maximum amplitude was registered over the tibial anterior muscle. When possible, several attempts were performed in each child and the maximal response was recorded.

2.2.2. cNfL

NfL is an established biomarker of axonal injury and degeneration and can be measured in blood (sNfL) and in cerebro spinal fluid (cNfL) [14]. cNfL has been proposed as a biomarker for treatment response in the patients undergoing treatment with nusinersen [14,19]. The

[1] Treatment of one patient was initiated at Queen Silvia Children's Hospital, Gothenburg, Sweden just before the treatment was established in Oslo.

suitability of cNfL in this respect has yet to be established. cNfL was sampled for analysis at baseline and at dose five and seven (six and 14 months after baseline, respectively). cNfL concentration was measured using an in-house enzyme-linked immunosorbent assay (ELISA) as previously described [20].

2.3. Nutrition and respiratory status

Clinical information about the patients' status regarding tube feeding and respiratory support was obtained from the patients' medical records.

2.4. Statistical analyses

Continuous variables were described with median as well as minimum and maximum values. Categorical data are presented as counts and percentages. To assess the effect of treatment over time and at given time points on selected outcomes (dependent variable) we used linear mixed models for repeated measurements, with baseline as a reference, as all the included individuals were measured several times. Unstructured covariance matrix was used to model these statistical dependencies. All the assessment time points and selected covariates were entered as fixed factors to account for possible confounding. The results are expressed as estimates of regression coefficients B with 95 % confidence intervals (CI). All analyses are considered exploratory so no correction for multiple testing was done and p-values <0.05 were considered statistically significant. All analyses were performed using SPSS version 26.

3. Results

All ten patients with 5q SMA type 1 who were referred for treatment met the inclusion criteria for the study. At 62 months, nine out of ten patients were alive. One patient (patient 3) died of complications related to pneumonia at five years of age, four years and ten months after having started treatment. Age at onset of symptoms varied from third week of life to five months of age. The duration of illness from onset of symptoms to diagnosis ranged between six weeks and ten months. Median age at commencement of nusinersen treatment was 22 months (range 3–140). Six of the included patients were female. Seven had two copies of *SMN2*, three patients had three copies of *SMN2*. Clinical characteristics are summarized in Table 1. Details of motor scores are presented in Table 3. The patients are ranked by age with the youngest patient as number one.

3.1. CHOP INTEND and HFMSE

All patients showed improvement in CHOP INTEND score during the first 26–38 months of the observation period. Only two patients showed improvement after this period of time, and both were three months of age at the start of treatment. The three oldest patients demonstrated a slight decrease in motor score towards the end of the observation period, but their scores remained well above baseline (Fig. 1).

At baseline the CHOP INTEND scores ranged from 11 to 43 (median: 22). After 62 months, scores ranged from 25 to 54 (median: 42). From baseline, improvements in individual CHOP INTEND scores ranged from an increase of ten points to 24 points (median: 14,5). Four children improved by >20 points, four children improved by >10 points and two children improved ten points in CHOP INTEND score. Patients 1 and 2 reached the maximal score (ceiling) at month ten and 14, respectively (dose six and seven). They were thereafter tested with HFMSE (Fig. 2).

With baseline as a reference, there was a statistically significant difference in CHOP INTEND values over the whole follow up period. We observed a steady increase from baseline to 38 months where the increase compared to baseline reached the level of statistical significance. An increase in scores was also seen from 38 to 50 months, but was not statistically significant. The mean motor score remained almost unchanged from 50 to 62 months.

The greatest effect on motor function, as assessed with CHOP INTEND, was observed in the three youngest patients, all of whom were less than six months of age at commencement of treatment. The median improvement in CHOP INTEND in these three children was 19,3. The median improvement for the other seven patients was 14,2.

Patient 1 started treatment at three months of age. He had a score on the HFMSE of 30 at dose 7 and increased to 58 at dose 19. Patient 2, who also initiated treatment at three months of age, had a HFMSE score of 19 at dose 7, increasing to 34 five years after baseline.

Table 2
Status feeding tube and respiratory support.

	Feeding tube status		Nocturnal BiPAP	
	Baseline	62 months	Baseline	62 months
Patient 1	No	No	No	No
Patient 2	No	Yes. Initiated at 25 months	No	Yes. Initiated at 13 months
Patient 3	No	Yes. Initiated at 8 months	No	Yes. Initiated at 7.5 months
Patient 4	Yes	Yes	Yes	Tracheostomy four years after baseline
Patient 5	No	No	No	Yes. Initiated at 23 months
Patient 6	Yes	Yes	Yes	Yes
Patient 7	Yes	Yes	Yes	Yes
Patient 8	Yes	Yes	Yes	Yes
Patient 9	Yes	Yes	No	No
Patient 10	Yes	Yes	Yes	Yes

3.2. HINE-2

Five of ten patients acquired new motor milestones. After 62 months patient 1 could walk, run, walk up stairs and ride a tricycle. Patient 2 was able to sit on her own and walk with support. After 30 months, patients 3, 5 and 9 had achieved the ability to sit independently. This is especially remarkable in patient 9, 75 months of age at commencement of treatment.

At baseline the HINE-2 score ranged from 0 to 5, (median: 1.5). After 62 months the HINE-2 score ranged from 1 to 26, (median: 6). The three patients aged less than six months at baseline showed the greatest improvements of +24, +22 and + 10 points, respectively, at 62 months. The oldest patient, (11 years and 8 months old at baseline) demonstrated an improvement of +6 points at 62 months. Three patients remained stable, one patient gained one point, and one patient showed negative changes from two to one during the observation time (Fig. 3). For the whole group, changes from baseline to 62 months were not, however, statistically significant.

3.3. CMAP

Measurements were obtained from nine children at baseline, while at 26 months, measurements were possible in only five children. Measurements were deemed technically difficult due to lack of cooperation or respiratory problems. During the observation period, seven out of nine patients showed an increase in CMAP of the ulnar nerve and six out of eight patients showed an increase in CMAP of the peroneal nerve. (Fig. 4). Only one patient, patient 1, demonstrated a significant increase in the CMAP response of the ulnar nerve, while three patients demonstrated a significant increase in the peroneal nerve response (patients 1, 2 and 5).

3.4. Cerebrospinal fluid neurofilament light chain (cNfL)

cNfL values were available for eight patients at baseline and at 6 and 14 months (dose five and seven). At baseline, cNfL (pg/ml) ranged from 418 to 7957 (mean 3829, SD 3039). After 14 months, cNfL ranged from

Table 3
Clinical results.

	CHOP-I score		HINE-2 score		CMAP ampl. n.ulnaris mV		CMAP ampl. n.peroneus mV		cNFL pg/ml	
	Baseline	62 months	Baseline	62 months	Baseline	26 months	Baseline	26 months	Baseline	14 months
Patient 1	43	54*****	2	26	0,41	2,9	0,76	2,4	7957	333
Patient 2	28	52*****	1	23	0,32	0,64*	0,33	2,7***	5466	346
Patient 3	24	47****	1	11	0,07	0,28	0,1	0,51	7624	382
Patient 4	15	25	0	1						
Patient 5	37	47	5	11	1,12	1,39***	0,87	1,88***	418	128
Patient 6	16	37	1	1	0,076	0,31	0,29	0,56	3718	211
Patient 7	11	31	1	1	0,1	0,15	0,11	0,12**	965*	77***
Patient 8	18	32	2	1	0,17	0,085**			974	133
Patient 9	37	47	4	10	0,27	0,41	1,16	0,88	179*	81
Patient 10	21	36	2	2	0,51	0,38**	0,2	0,17**	552	156

*Before dose 2/2 weeks. ** Before dose 4/2 months. *** Before dose 6/10 months. **** Before dose 16/50 months.
*****Last score registered.

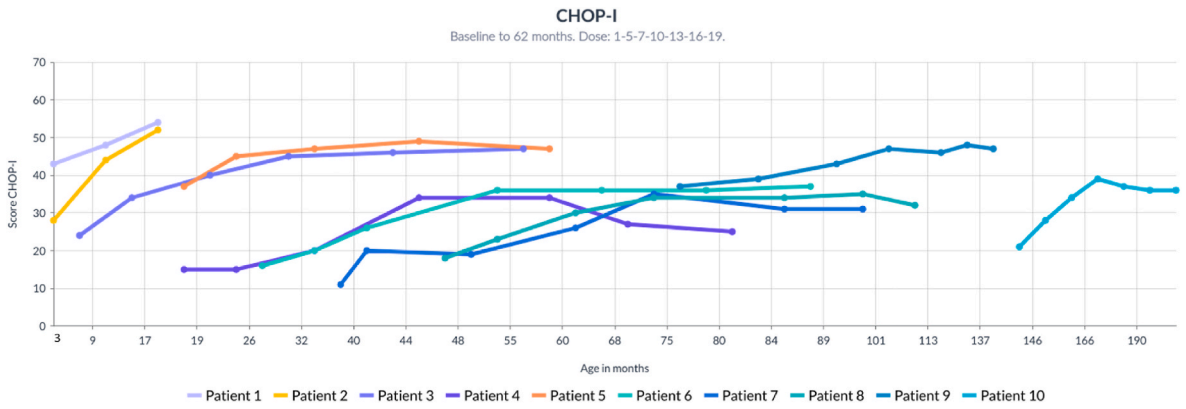

Fig. 1. Patients are ranked by age with the youngest patient as number one. Patient 1 and patient 2 almost reached the top score of CHOP-Intend at 17 months of age. Further assessments of motor skills were therefore made with Hammersmith Functional Motor Scale – Expanded (HFMSE), see Fig. 2. Patient 3 has last score at dose 16.

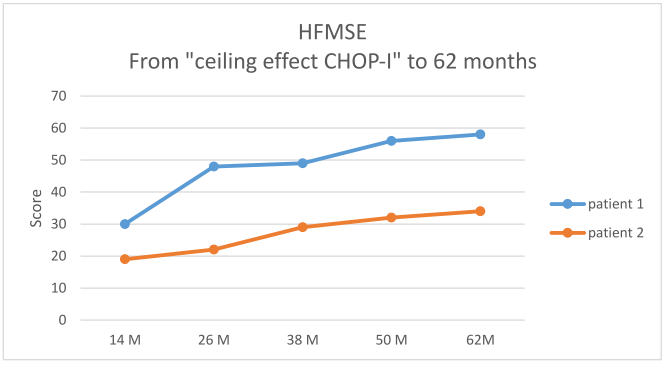

Fig. 2. Patients are ranked by age with the youngest patient as number one (Months after baseline).

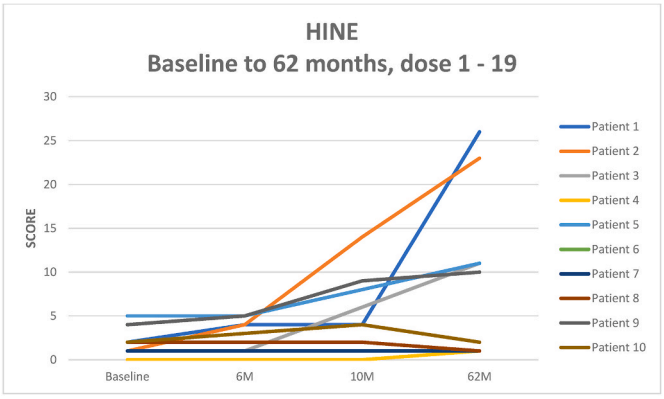

Fig. 3. Patients are ranked by age with the youngest patient as number one.

128 to 382 (mean 270, SD 130) (Fig. 5). Patient 7 and 9 were excluded due to missing values.

When adjusted for age at baseline, cNfL levels were significantly different from baseline assessment at the consecutive assessment points ($p < 0.05$). We did not stratify by age as our sample size was limited, age was entered into the model as a possible confounder. The largest difference was seen between baseline and six months (dose five).

As the cNfL variable was skewed, a logarithmic transformation has been carried out to explore a possible correlation between cNfL and CHOP INTEND. Correlation was assessed using bivariate Spearman correlation, and log cNfL and CHOP INTEND were negatively correlated ($p = 0.042$).

3.5. Nutritional support

At baseline, six patients required tube feeding by nasogastric tube or a gastrostomy. During the observation period, two more patients developed a need for this. These two patients were younger than six months at baseline. Patients 1 and 5 were entirely orally fed during the whole observational time. Clinical data regarding nutritional and respiratory support are summarized in Table 2.

3.6. Respiratory support

At baseline, five patients required noninvasive ventilation (NIV).

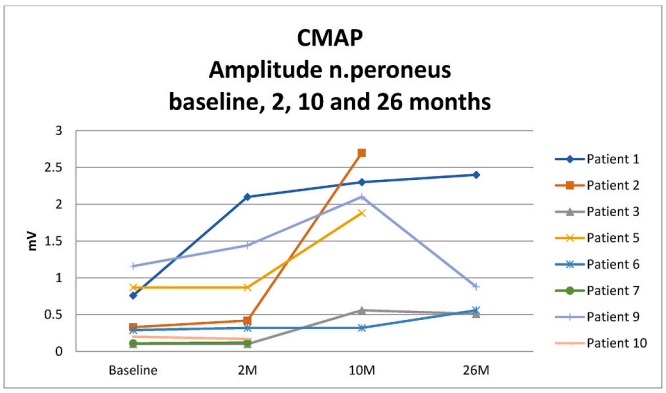

Fig. 4. Patients are ranked by age with the youngest patient as number one. Missing values: patient 3 and 5 are missing values at two months (M), patient 6 at ten months. Patient 8 have just one registered value, 0,42 mV, at ten months. We have no registered CMAP-values on patient 4.

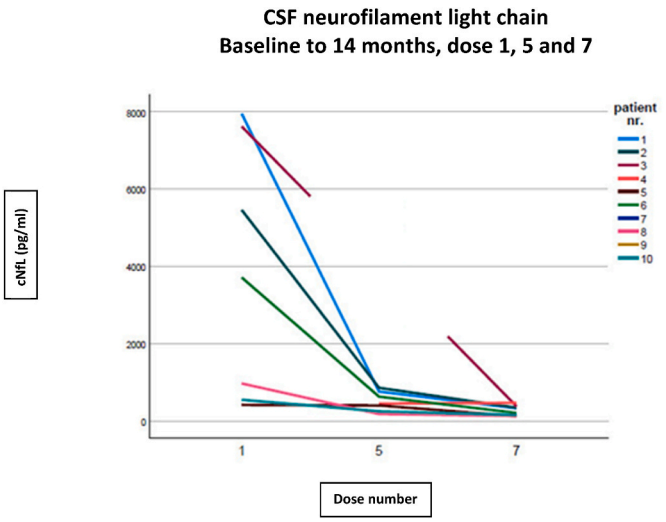

Fig. 5. cNfL at dose one, five and seven. Patients are ranked by age with the youngest patient as number one.

During the observation period, three additional patients developed need for NIV.

Patient 3, who was diagnosed with respiratory failure at initiation of treatment, died due to complications related to pneumonia four years and ten months after initiation of treatment. Patient 4, who was already dependent on bilevel positive airway pressure (BiPAP) more than 16 h per day at the commencement of therapy, underwent tracheostomy almost four years later. Patient 9, despite being 75 months at commencement of treatment, was only using BiPAP as part of her airway clearance regime. Patient 1, who demonstrated symptoms during the first month of life, and had only two copies of the *SMN2* gene, was the only patient who did not require respiratory or nutritional support at the end of the observation period.

Five patients have had recurrent respiratory infections requiring hospitalization. One patient required ventilator support on the pediatric intensive care unit several times. Several patients reported an improvement in cough function.

3.7. Orthopedic

Patient 9 and 10 had scoliosis at baseline and required x-ray guided lumbar puncture for nusinersen injection. Throughout the study period all the remaining eight patients developed scoliosis. Patient 6 developed a need for x-ray guided lumbar puncture due to scoliosis four years after baseline. Patient 9 and 5 underwent surgery for scoliosis two and six years after initiation of treatment, at eight and six years of age, respectively.

Patient 2 underwent hip surgery (osteotomy) due to bilateral hip subluxation with acetabular dysplasia at five years of age, five years after initiation of treatment. She was walking with support at the end of the observation period.

3.8. Additional findings

The parents described improvements in their children's energy levels and appetite. In two of the most severely affected patients, an improvement in social interaction and communication was reported.

3.9. Adverse effects/safety

Drug-related adverse events were not reported while procedure-related adverse events such as headache and back pain did occur due to lumbar puncture. Due to the young age group, we were mainly dependent on parents' report regarding subjective symptoms.

4. Discussion

This prospective, observational study investigated the real-world effect of treatment over a five-year period in the first ten Norwegian patients with SMA type 1 to receive nusinersen. Treatment was associated with an initial improvement in motor function followed by a period of stability within this small group of patients with a wide phenotypic range. This supports a growing body of evidence showing the effectiveness and safety of treatment [6–10,12]. One patient died due to an acute respiratory infection following almost five years of treatment. For the two youngest patients, commenced on treatment at three months of age, a continuous improvement in motor function was observed over five years. No clear improvement in terms of the need for respiratory and nutritional support was observed. This finding is in keeping with a recently published systematic review, albeit it describes a shorter follow-up period. This review concluded that new therapies change the disease phenotype by especially improving motor function rather than respiratory and nutritional function [13]. This is in contrast with the results of the NURTURE study including 25 presymptomatic patients with either two or three copies of *SMN2* treated with nusinersen. At five year follow-up no patients required permanent ventilation and the group showed overall continued improvement in motor function [21].

In a review article, Erdos et al. pointed out that a lack of homogeneity in outcome measures will hamper comparability between different real-world studies [10]. Therefore, in our center, which has the national, centralized responsibility for annual review of children treated with nusinersen, the motor and electrophysiological tests used in the pivotal study, CHOP INTEND, HINE and CMAP were employed [4].

4.1. CHOP INTEND and HFMSE

Our overall findings are in line with results of the pivotal trial [4] and real-world publications on nusinersen treatment in symptomatic patients [6–10]. These studies, however, have shorter observational times than the present study, albeit one of them is looking at the effect after four years of treatment [11]. However, while this study from Italy reported some improvement followed by stability and no evidence of deterioration, in our cohort, three patients showed a slight decline in CHOP INTEND at 62 months, compared to best attained score. They still maintained scores much higher than baseline.

The two patients who started treatment before three months of age, continued to improve and had an increase in the HFMSE motor score at 62 months. There is good evidence and general agreement that the treatment effect is greatest in the youngest patients with shortest

duration of symptoms [7,8,10,12,22]. However, even if motor outcome is most favorable in the youngest patients, our data show that a clinically relevant benefit also can be demonstrated in much older patients. The oldest patient, 11,5 years old at baseline, with three copies of the *SMN2* gene, showed an improvement in CHOP INTEND of 15 points, from 21 at baseline to 36 points after 62 months, which is in striking contrast to the natural history of this disorder [1].

4.2. HINE-2

Attainment of motor-milestones registered as improvement in HINE-2 score during ongoing treatment, also show a development not expected within the natural course of the disease. During the observation time of 62 months, five of ten patients acquired new motor milestones, with the three youngest patients, aged less than six months at baseline, showing the greatest improvements. Of interest, the patient who was aged 11,5 years at baseline also showed improvements with +6 points at 62 months.

With the exception of the two youngest patients, our overall motor results show a tendency towards motor improvement in the initial two to three years, followed by stabilization. Towards the end of the observation period, it may appear that the patients with the most advanced disease tend to deteriorate. More observation time is needed to conclude whether this is a downward trend or a fluctuation of stability.

4.3. Nutritional and respiratory support

Respiratory function and ability to eat are dependent on muscle power and are important abilities for quality of life. These are central outcome measures and should be reported [10]. Observations during these 62 months make us conclude that there are no major changes in terms of need for respiratory or nutritional support. These results are in line with other published studies [7–9].

After this observation period of 62 months, seven out of ten patients have recently changed to oral treatment (risdiplam). Motor function remains stable. Risdiplam has a similar mode of action to nusinersen but has the advantage of oral administration, making lumbar punctures unnecessary. Results have been reported for two-year follow-up of risdiplam treatment in SMA type 1 [23] and have been compared to nusinersen in at least one review [13]. Similar improvements in motor function were demonstrated. Giess et al. have concluded that there is still no evidence for improvement in respiratory or nutritional needs with either treatment [13]. However, with risdiplam there seemed to be a better preservation of swallowing function compared to natural history [23]. Pane et al. reported 20 of 48 patients with preserved oral feeding after 48 months on nusinersen [12]. In our study two of 10 patients were still without a feeding tube at 62 months follow-up.

4.4. Biomarkers: cNfL and CMAP

There is an unmet need to establish reliable biomarkers that can verify disease activity and treatment response in patients with SMA receiving nusinersen. cNfL has been proposed as a biomarker but there is a need for further studies [14,19].

In our cohort, younger patients demonstrated higher levels of cNfL at baseline. However, this does not necessarily correspond with the clinical severity of the patient's condition. A recently published study demonstrates that patients in an acute stage of the disease (defined as less than six months from the onset of symptoms) had markedly increased levels of cNfL, compared to patients in a chronic stage of the disease (defined as more than six months from the onset of symptoms) [19]. In the present study, baseline levels of cNfL were markedly increased in the three patients being under six months at baseline. Patient 4 and 6, with disease duration of 18 and 26 months at baseline, respectively, demonstrated intermediate levels of cNfL at baseline. The remaining patients with longer disease duration had lower baseline values (less than 1000 pg/ml). We also observed that the higher the initial values, the faster the values decreased during the nusinersen loading phase before stabilizing at a lower plateau level from dose five.

We found a statistically significant negative correlation between log cNfL and CHOP INTEND scores when using bivariate Spearman correlation, ($p = 0.042$). These findings are in keeping with other countries' experiences that cNfL might be used as a biomarker of treatment response [14,19]. However, our cohort is small with only a few observations. Thus we had very limited statistical power. Further systematic research is necessary to gain knowledge on the role of cNfL as a possible biomarker.

With increasing use of oral splice modifying treatment (risdiplam), and intravenous gene therapy (onasemnogene abeparvovec), measurement of NFL in blood is also a potential biomarker. Strong correlation between levels in blood and in CSF has been demonstrated [19,24].

Some centers have found CMAP to be a suitable tool for measuring treatment effectiveness [4]. In the present study, only three of the patients demonstrated a significant CMAP response. These were some of the youngest patients (patients 1, 2 and 5). Patient 1 and 2 had the shortest disease course at baseline, while patient 5 was 18 months at the start of treatment. However, he has three *SMN2* copies, which is beneficial in terms of a potentially slower motor neuron degradation. Our findings may indicate that measurement of CMAP as a potential biomarker is more beneficial in the youngest patients with a short disease course and thus better-preserved motor neurons. The experience from newborn screening showing that CMAP may be a sensitive method to detect early findings in presymptomatic patients may support this [25,26].

A recently published article from the Netherlands argues that quantitative MRI of the patients' thigh muscles to gain insight into the microstructure and fat content of the muscles during treatment, can function as a potential tool in monitoring the effect of nusinersen treatment [27]. This is an interesting contributor in the search for a reliable biomarker. However, the disadvantage of this method may be the need for sedation in many of the children.

4.5. Limitations and strengths

The main limitations of this study is the small study size with heterogeneity in patient age and disease duration at baseline. This makes the statistical analyzes challenging as the statistical power was very limited.

An important strength of this study is the follow-up period of five years. Also, this is a single-center study at a hospital with national responsibility for disease modifying treatment for the pediatric SMA cohort. All motor tests were performed by the same group of experienced physiotherapists. This makes it easier to get reliable assessments.

As the cohort was small, it was possible not only to present data at group level, but also to provide a detailed overview of the individual patient trajectories. Long-term results from individual patients in addition to results at a group level are important contributions to the ever-increasing amount of real-world data published on the effect of nusinersen.

5. Conclusion

The results of the present study support the growing body of evidence showing the effectiveness and safety of treatment with nusinersen. No clear improvement in terms of the need for respiratory and nutritional support was observed. The findings presented, which span a five year follow-up period, are similar to other observational studies with a shorter follow-up period.

More research is needed to evaluate the significance of the motor changes we have seen so far and to analyze the long-term effect the treatment has on other areas such as swallowing, ventilation, hip dysplasia and quality of life. The observed improvement in motor

function has resulted in a more proactive approach to monitoring and treatment in areas such as respiratory support, nutrition and orthopedic management. More observation time is needed to be able to conclude whether the downward trend seen in the patients with the most advanced disease at the end of the five-year follow-up period is a real deterioration or a fluctuation of stability.

There is a need for more research on possible biomarkers, to be able to identify possible prognostic factors. In our study the best effect was seen with early treatment in the youngest patients. As screening for 5q SMA now is included in the Norwegian national newborn screening program, most patients with SMA1 will initiate their treatment pre-symptomatically, and thus presumably have a better motor development in the long term than even the best ones in the present study.

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Declaration of competing interest

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