

Nusinersen in spinal muscular atrophy type 1 from neonates to young adult: 1-year data from three Asia-Pacific regions

INTRODUCTION

Spinal muscular atrophy type I (SMA1) is the most common and severest form of SMA. According to natural history studies, affected babies never achieve independent sitting, and the combined median age of death or permanent ventilation is 13.5 months.¹ Nusinersen, an antisense oligonucleotide that modifies survival motor neuron (SMN2) splicing to enhance full-length SMN protein expression, is the first of many promising approved SMA treatments. The ENDEAR nusinersen clinical trial on SMA1 in patients aged <7 months showed promising motor milestone achievements and improved survival.² Through this multinational study, we provide the first Asian real-world data on patients with SMA1 after 1 year of nusinersen treatment.

METHODS

This retrospective observational cohort study, involving eight institutes in three Asian regions (Hong Kong SAR, Taiwan and South Korea) evaluated the baseline clinical characteristics, motor outcomes and changes in ventilation needs of participating patients with SMA1, from pre-treatment (M0) to 6 months (M6) and 10 months (M10) post-treatment. All participants started nusinersen under the Expanded Access Programme (EAP) between 2017 and 2019. Baseline information—newborn screening where applicable, SMN1 mutation, SMN2 copies, gestational age at birth, sex, age of symptom onset, body weight, respiratory support, feeding status, musculoskeletal status and age of first nusinersen—was collected. The motor outcomes before and after nusinersen initiation, measured by Hammersmith Infant Neurologic Examination Part 2 motor milestones score (HINE-2), CHOP INTEND and motor milestone achievements, were recorded. We used CHOP INTEND increased ≥ 4 points and HINE-2 gained ≥ 5 points as clinical meaningful improvement.² The study was approved by the ethics committees of individual regions.

Statistical analysis

Baseline demographics and clinical characteristics were presented using descriptive

statistics. Changes in the median scores of HINE-2 and CHOP INTEND were calculated using one-way repeated measures ANOVA and paired t-test for quantitative and qualitative variables, respectively. Missing data were excluded. A p value of <0.05 was regarded as statistically significant. A multiple regression model was performed to find the predictor variables of motor outcomes. We used IBM SPSS Statistics V.25 for analyses.

RESULTS

Online supplemental table 1 presents the demographic data and clinical characteristics of the 40 patients with SMA1. Two-thirds of patients had two SMN2 copies. Over half of the cohort (57%) began nusinersen ≤ 2 years old. For the nine patients (22.5%) identified by newborn screening, eight started nusinersen <7 months. All patients started nusinersen at the symptomatic stage. The median nusinersen initiation age was 20 months (range 0.35–294 months).

Survival and motor outcome

1. 95% of patients continued the EAP programme

One patient died before M6 due to respiratory failure. Another patient dropped out before M10 due to lack of improvement. Both had two SMN2 copies (online supplemental table 2).

2. Patients who started nusinersen at aged ≤ 2 years had better motor milestone gains

Of the patients who started nusinersen at ≤ 2 years old, 36.4% (8/22 patients) achieved unassisted sitting; three (13.6%) also attained assisted standing. At M10, 61.1% (11/18 patients) gained ≥ 5 points in HINE-2, with the median gain of 7.5. In contrast, for those who started nusinersen >2 years old, only 6.7% (1/15 patients) achieved unassisted sitting. At M10, only 7.1% (1/14 patients) gained ≥ 5 points in HINE-2 with the median gain of 0.5 only (table 1) (online supplemental figure 1). Despite having one SMN2 copy, the patient who started nusinersen aged 2 months gained 5 HINE-2 points at M10.

3. Patients with three copies of SMN2 had better motor responses than those with two copies.

In table 1, patient with three SMN2 copies had greater increases in median HINE-2 scores from baseline at M6 and M10 compared with those with two copies (p=0.003). A more significant difference was observed in CHOP INTEND (p<0.001) (online supplemental table 3,

figure 2). At M10, more patients (87.5%; 7/8) with three SMN2 copies had CHOP INTEND gained ≥ 4 points, compared with only 54.5% (6/11 patients) in those with two SMN2 copies. The only patient with nusinersen started >2 years of age and achieved independent sitting was an adult patient with spinal fusion, with three SMN2 copies who first received nusinersen at 24 1/2 years old.

2. Newborn screening, disease duration and HINE-2 baseline scores predict milestone gains.

We used Pearson correlation to check the correlation of each risk factor with delta HINE-2 (M10–M0) and delta CHOP INTEND (M10–M0) scores. A multiple linear regression model was used to understand whether disease duration (period between symptom onset and treatment initiation), SMN2 copies, baseline scores and newborn screening if present, accounted for the variability in Delta HINE-2 and Delta CHOP INTEND scores. The univariate analysis showed that Delta HINE-2 scores were negatively correlated with disease duration (r=−0.391, p=0.027, n=32) and positively correlated with baseline HINE-2 scores (r=0.377, p=0.033, n=32) and newborn screening (r=0.557, p=0.001, n=32). The multiple linear regression showed that only newborn screening was independently associated with delta HINE-2 scores (r²:0.479, adjusted beta:0.424, p=0.009). We could not find any predictor variable for the Delta CHOP INTEND (M10–M0) (online supplemental table 4).

5. Different needs of respiratory support post-treatment (online supplemental table 5).

DISCUSSION

We found patients with SMA1 from the neonatal to adult age benefit from nusinersen treatment. Newborn screening, shorter disease duration and higher baseline HINE-2 score may predict better milestone gains. In the ENDEAR study,² 28% of patients gained ≥ 5 HINE-2 points (M10) and a mean nusinersen starting age of 5.4 months. For our eight patients who started nusinersen at <7 months old and with two SMN2 copies, they had an earlier mean nusinersen starting age at 2.7 months, and a higher percentage (61.1%; 5/8 patients) gained ≥ 5 HINE-2 points (M10). While newborn screenings enable the identification of affected pre-symptomatic babies,³ our patients began treatment only after symptom onset. As illustrated by the NURTURE study⁴ and the AVXS-101 phase 1/2A clinical trials,⁵ the best motor outcomes for SMA1 treatment are to asymptomatic affected babies and those with earlier dosing aged <3 months.

Table 1 HINE-2 evolution of the patients according to *SMN2* copy number and age of nusinersen initiation

Characteristics	Total (n=40)	One copy of <i>SMN2</i> (n=1)	Two copies of <i>SMN2</i> (n=25)	Three copies of <i>SMN2</i> (n=14)
Sex, M:F, n	18:22	1:0	10:15	7:7
Age at symptom onset	3.0 (0.0–6.0)	0.0	2.0 (0.0–6.0)	4.5 (1.0–6.0)
Age at nusinersen initiation	20.0 (0.35–294.0)	2.0	19.0 (0.35–140.0)	25.3 (4.0–294.0)
Disease duration before nusinersen	17.5 (0.0–291.5)	2.0	16.0 (0.35–140.0)	17.5 (0.0–291.5)
HINE-2 score				
M0	0.0 (0.0–4.0), n=37	0.0, n=1	0.0 (0.0–2.0), n=24	2.0 (0.0–4.0), n=12
M6	2.5 (0.0–17.0), n=34	4.0, n=1	1.0 (0.0–11.0), n=22	4.0 (1.0–17.0), n=11
M10	4.0 (0.0–24.0), n=32	5.0, n=1	2.5 (0.0–20.0), n=20	4.0 (1.0–24.0), n=11
Time effect p value	<0.001	/	<0.001	0.002
Delta M6–M0	2.0 (0.0–16.0), p<0.001	4.0	1.0 (0.0–11.0), p=0.002	2.0 (1.0–16.0), p=0.019
Delta M10–M0	3.0 (0.0–20.0), p<0.001	5.0	2.5 (0.0–20.0), p=0.003	3.0 (1.0–20.0), p=0.010
HINE-2 score (age ≤7 months old at onset of treatment)				
M0	0.0 (0.0–4.0), n=13			
M6	6.0 (2.0–16.0), n=11			
M10	11.0 (3.0–24.0), n=11			
Time effect p value	<0.001			
Delta M6–M0	6.0 (2.0–12.0), p<0.001			
Delta M10–M0	9.0 (3.0–20.0), p<0.001			
HINE-2 score (age ≤2 years old at onset of treatment)				
M0	0.0 (0.0–4.0), n=22			
M6	5.0 (0.0–17.0), n=19			
M10	9.0 (0.0–24.0), n=18			
Time effect p value	<0.001			
Delta M6–M0	4.0 (0.0–16.0), p<0.001			
Delta M10–M0	7.5 (0.0–20.0), p<0.001			
HINE-2 score (age >2 years old at onset of treatment)				
M0	0.0 (0.0–2.0), n=15			
M6	1.0 (0.0–4.0), n=15			
M10	0.5 (0.0–7.0), n=14			
Time effect p value	0.002			
Delta M6–M0	1.0 (0.0–2.0), p=0.003			
Delta M10–M0	0.5 (0.0–5.0), p=0.013			

* Data are listed as median (range) in months.

‡ One-way repeated measures ANOVA.

§ Paired t-test.

¶ Multiple regression demonstrated that there was significant difference in the changes of the HINE-2 scores, delta M6–M0 and delta M10–M0, between the two groups with two and three *SMN2* copies with the standard coefficients β of 0.263 (p=0.003).

† Three patients were not included in the HINE-2 M0 analysis, due to the following reasons: one patient did not have baseline HINE-2 performed; two patients did not have HINE-2 performed.

HINE-2, Hammersmith Infant Neurologic Examination Part 2 motor milestones score; M0, before treatment; M6, 6 months of treatment; M10, 10 months of treatment; SMN, survival motor neuron.

Support for earliest treatment is therefore necessary.

CONCLUSION

This multinational collaborative retrospective observational cohort study in Asia provides real-world data on first-year treatment that nusinersen is safe and beneficial to patients with SMA1 from the neonatal to adult age. Newborn screening that promotes early treatment initiation can maximise treatment efficacy.

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Acknowledgements The authors would like to thank all the SMA patients and their families for their participation in this SMA EAP study; Mr Wilfred Wong for his advice on the data analysis; Ms Rachel BY Lee for her professional English editing support.

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Funding This study is supported by a donation funding on 'Diagnosis and therapy development of rare neurological diseases and neuromuscular diseases' (20009121) received by SHS Chan.

Competing interests SH-SC received honorarium for serving on scientific advisory board of Biogen and Novartis; for presentations at academic meetings. J-HC received honorarium for serving on scientific advisory board from Biogen and Novartis; and research grant

from Biogen. Y-HC received research funding and honorarium for presentations and consultancy from Biogen. Y-JJ received honorarium for consulting, serving on a scientific advisory board, speaking, or other activities for Biogen and Novartis; research grants for SMA natural history in Taiwan, and clinical trial funding from Biogen. He is also the president of non-profit organisation Taiwan SMA Families.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2020-324532>).



To cite Chan SH-S, Chae J-H, Chien Y-H, *et al.* *J Neurol Neurosurg Psychiatry* 2021;**92**:1244–1246.

Received 9 July 2020

Revised 4 January 2021

Accepted 18 January 2021

Published Online First 11 February 2021

J Neurol Neurosurg Psychiatry 2021;**92**:1244–1246.

doi:10.1136/jnnp-2020-324532

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