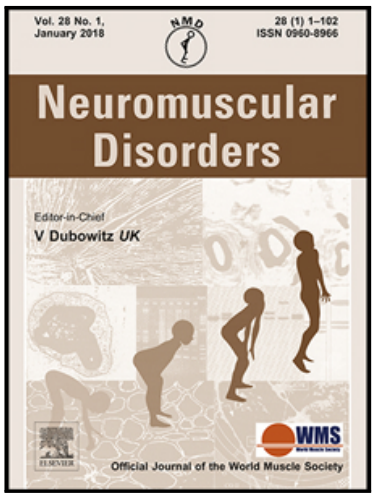

Nusinersen in type 1 SMA infants, children and young adults: preliminary results on motor function

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Highlights

- Report longitudinal experience of using Nusinersen in 104 type 1 SMA patients.
- Patients were assessed using the CHOP INTEND and the HINE-II.
- Improvements were found in 55.7% (CHOP INTEND) and in 20.19% (HINE-II).
- Significant difference at 6-months were found on both CHOP INTEND and HINE-II.
- Motor improvements are observed in treated SMA type 1 patients.

Nusinersen in type 1 SMA infants, children and young adults: preliminary results on motor function

Marika Pane[a*], Concetta Palermo[a*], Sonia Messina[b], Valeria A Sansone[c], Claudio Bruno[d], Michela Catteruccia [e], Maria Sframeli[b], Emilio Albamonte [c], Marina Pedemonte[d], Adele D'Amico [e], Giorgia Brigati [d], Roberto de Sanctis[a], Giorgia Coratti[a], Simona Lucibello[a], Enrico Bertini[e], Giuseppe Vita[b], Francesco Danilo Tiziano[f], Eugenio Mercuri[b], on behalf of the Italian EAP working group

*both first authors

[a] Paediatric Neurology and Centro Clinico Nemo, Catholic University and Policlinico Gemelli, Rome, Italy;

[b] Department of Clinical and Experimental Medicine, University of Messina and Centro Clinico Nemo, Messina, Italy;

[c] Neurorehabilitation Unit, University of Milan, Centro Clinico Nemo, Niguarda Hospital, Milano, Italy;

[d] Center of Myology and Neurodegenerative Disorders, Istituto Giannina Gaslini, Genoa, Italy;

[e] Unit of Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital, Rome, Italy;

[f] Institute of Genomic Medicine, Catholic University, Rome, Italy.

Corresponding author:

Eugenio Mercuri, Pediatric Neurology Unit , Policlinico Gemelli, Largo Gemelli 00168, Roma, Italy.

Tel.: +39 06 30155340; fax: +39 06 30154363. E-mail address: eugeniomaria.mercuri@unicatt.it

Italian EAP working group

Daniela Lauro, Luca Binetti, Anita Pallara, Simona Spinoglio, Maria Letizia Solinas, Grazia Zappa Francesca Penno, Cristina Ponzanelli, Jacopo Casiraghi.

Neuropsichiatria Infantile/Centro Clinico Nemo Pediatrico, Roma: Daniela Leone, Gloria Ferrantini, Beatrice Berti, Maria Carmela Pera, Nicola Forcina, Sara Carnicella, Giulia Norcia, Marco Piastra, Orazio Genovese, Alessandro Pedicelli.

Centro Clinico Nemo Sud and University of Messina : Antonio Versaci, Imma Rulli, Eloisa Gitto, Cristina Faraone, Stefania La Foresta, Maria Macrì.

Ospedale Bambino Gesù, Roma: Giulia Colia, Anna Maria Bonetti, Adelina Carlesi, Renato Cutrera, Maria Beatrice Chiarini

Istituto Giannina Gaslini, Genova: Marta Ferretti, Alberto Garaventa, Giovanni Montobbio, Carlo Gandolfo, Valentina Iurilli, Paola Tacchetti , Emilia Bobeica, Valentina Lanzillotta

Neurorehabilitation Unit, University of Milan/Centro Clinico NEMO, Milano: Alice Pirola, Sara Lupone, Elisa De Mattia, Elisa Falcier, Fabrizio Rao, Elisabetta Roma, Caterina Conti, Francesca Salmin, Cristina Grandi, Fausto Fedeli, Luca Mancini, Nicola Tovaglieri, Paolo Stoia, Maurizio Heinen, Valeria Cozzi, Beatrice Travaglia, Emma Mizzotti

Abstract

We report preliminary data on the six month use of Nusinersen in 104 type 1 patients of age ranging from three months to 19 years, 9 months. Ten of the 104 were classified as 1.1, 58 as 1.5 and 36 as 1.9.

Three patients had one *SMN2* copy, 65 had two and 24 had three copies. In 12 the *SMN2* copy number was not available.

After six months an improvement of more than two points was found in 58 of the 104 (55.7%) on the CHOP INTEND and in 21 of the 104 (20.19%) on the Hammersmith Infant Neurological Examination. Changes more than two points were found in 26/71 patients older than two years, and in seven of the 20 older than 10 years. Changes $\geq$ four points were found in 20/71 older than two years, and in six of the 20 patients older than 10 years.

The difference between baseline and six months on both CHOP INTEND and Hammersmith was significant for the whole group ($p<0.001$) as well as for the subgroups with two ($p<0.001$), and three *SMN2* copies ($p<0.001$).

Our preliminary results suggest that functional improvement can be observed in type 1 patients outside the range of the inclusion criteria used in the Endear study.

Keywords:

Spinal Muscular Atrophy; Nusinersen; CHOP INTEND; Hammersmith Infant Neurological Examination; Werdnig Hoffmann disease.

Introduction

In the last few years two Phase 3 sham-controlled studies using Nusinersen, an antisense oligonucleotide designed to increase full-length SMN protein levels and gene replacement, have shown significant improvements on motor functional scales in both infantile and late onset SMA [1, 2]. This has led to the approval of the drug in several countries worldwide. Before regulatory approval, Nusinersen was made available as part of an Expanded Access Programme (EAP) for compassionate use to patients with the infantile form[3]. The EAP allowed to use the drug in all type 1 patients, therefore also including patients with the neonatal severe form and those older than seven months who were excluded in the Phase 3 clinical trial. Both the Nusinersen infant clinical trial [1] and a recently published gene replacement trial [4] have strongly suggested that, even within the restricted window of enrollment in the first seven months of age, the treatment appears to be more efficacious in the younger infants. There has therefore been concern that the treatment may show limited effect when administered after the age of seven months. As the drug is expensive and the intrathecal injections require frequent visits to the hospital, a systematic assessment of possible changes in the EAP patients is needed. This will help to understand if there is a positive effect in patients treated at different ages and whether this is sufficient to justify the costs and the burden of traveling and of the procedure for the severely affected fragile patients and for their families.

We report our experience of the first six months of treatment with Nusinersen in in a cohort of 104 type 1 patients of age ranging from three months to 19 years, 9 months, with 95 of the 104 older than seven months.

Materials and methods

Details of the cohort assessed at baseline and of the search procedure have already been reported[3]. The patients were all treated in the five Italian centers previously involved in Nusinersen trials.

The study was approved by the Ethics committee in each centre. Written informed consent was obtained from all participants (or guardians of participants) in the study (consent for research).

All patients were assessed using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), and the developmental section of the Hammersmith Infant Neurological Examination (HINE). The CHOP INTEND is a functional scale specifically designed to assess motor function weak infants, [5-7], including 16 items with a total score ranging from 0 to 64. The module of the HINE [8], is a short assessment, including eight selected motor items which document developmental progress. Each item provides the opportunity to score the level of development according to the gradient of normal maturation.

Both measures were performed by clinical evaluators after training and reliability sessions.

Results

One hundred and four of the 122 patients who agreed to participate to the EAP completed the first six months and had assessments performed at both baseline and six months. Ten could not receive the infusion due to severe scoliosis and were rescheduled for further assessments, and five decided to withdraw their consent within three months from the first administration. In two siblings the functional assessment were not performed at six months. One infant died within the first six months. He had a neonatal early onset and parents refused ventilatory or nutritional support.

The age of the remaining 104 ranged between 0 and 19 years. Ten of the 104 were classified as 1.1, 58 as 1.5 and 36 as 1.9.

Three of the 104 had 1 *SMN2* copy: one had 1.1 SMA, one had 1,5 and one had 1.9 SMA ; 65 patients had 2 *SMN2* copies: eight had 1.1, 42 had 1,5 and 15 had 1.9 SMA; 24 had 3 *SMN2* copies: seven had 1,5 and 17 had 1.9 SMA. In 12 the *SMN2* copy number was not available.

At baseline the mean CHOP INTEND scores ranged between 0 and 52 (mean: 15.08, SD: 13.53), the mean HINE score ranged between 0 and 7 (mean: 0.82, SD: 1.58).

After 6 months the mean CHOP INTEND scores ranged between 0 and 56 (mean: 19.59, SD: 16.37).

The CHOP INTEND changes ranged between -7 and 27 (mean: 4.51, SD: 5.80). Only two patients (1.92%) showed negative changes (-3 and -7 respectively), another 44 (42.3%) remained stable (n=27) or had one point improvement (n=17). The remaining 58 (55.7%) improved two points (n=6) or more than two points (n=52).

Of the nine patients younger than seven months, seven had an improvement of more than four points (77.77%). In the 95 older than seven months, 45 (47.36%) had an improvement of more than two points , and 37 (38.94%) more than four points.

Seventy-one patients were older than two years: 26/71 had an improvement of more than two points (36.6%), and in 20 (28.16%) more than four points. Twenty patients were older than 10 years: seven had an improvement of more than two points (35%) and six (30%) more than four points.

After six months the mean HINE score ranged between 0 and 12 (mean: 2.08, SD: 3.07).

The HINE changes ranged between 0 and 10 (mean: 1.26, SD: 2.18). 64 (61.5 %) remained stable and 11 (10.5) had one point improvement. Seven (6.7%) improved two points and 21 (20.19%) more than two points.

Using a T-test, there was a significant difference between baseline and six month scores on both

the CHOP INTEND and the HINE for the whole group ($p<0.001$) as well as for the patients with two SMN2 copies ($p<0.001$), and for those with three SMN2 copies ($p<0.001$).

Discussion

Even if limited to the first 6 months of treatment, our preliminary results suggest that a motor functional improvement can be frequently observed in patients outside the range of the inclusion criteria used in the Endear study[1].

The improvements did not appear to be specifically related to the number of SMN2 copies as they occurred in both subgroups with two and three SMN2 copies. The improvements on CHOP INTEND (more than two points) were frequent both in patients with the milder type 1.9 phenotype (24%) and among those with the more common 1.5 phenotype (24%). The patients with less response to treatment were those with the early onset 1.1 severe phenotype who showed little changes after six months.

In our cohort the changes appeared to be more obvious on the CHOP INTEND than on the HINE as an improvement of more than two points on the HINE were observed in approximately 27% compared to the 55.8% on the CHOP INTEND. This may be due partly to the short duration of treatment as achieving a milestone may require longer.

These preliminary results raise some questions about the therapeutical window in type 1 infants. A narrow window has been suggested by electrophysiological tests in infants with SMA type 1 showing a rapid loss of motor units occurring in the first three months after birth and loss of more than 95% of motor units within the first six months [9-11]. The rapid early loss of motoneurons has been confirmed by animal studies [11] and postnatal autopsy studies[12].

A narrow therapeutic window has also been confirmed by the recent experience with clinical trials [1, 4] suggesting that intervention is more effective when performed in the first few months.

Our results suggest that some therapeutic efficacy is possible even after the first seven months even if the consistency or the magnitude of response was variable and often smaller than those observed with early intervention. Unfortunately, neurophysiological tests were not systematically performed as part of the EAP as they could have provided information whether there is a baseline value of motoneurons activity compatible with the possibility of improvement or whether the clinical improvements, when observed, were associated with compensatory collateral sprouting or with different profiles of motor unit loss.

A longer follow up will allow to establish and better quantify the magnitude and frequency of motor changes over a longer exposure to treatment, to draw more conclusions on the respiratory and nutritional aspects and to compare the results of the EAP cohort to the ENDEAR study.

A recent study has also reported the results after six months of treatment with Nusinersen in type 1 patients [13]. They also report a remarkable improvement on both CHOP INTEND and HINE but their results are not easily comparable to ours because of differences in the age range, with our study reporting an overall older cohort. The possibility to compare our results to further cohorts that are being treated in other countries, will allow to have larger numbers and to establish the possible role of other clinical aspects (scoliosis, contractures) that are more frequent in older patients and may contribute to reduce the possibility to see an improvement.

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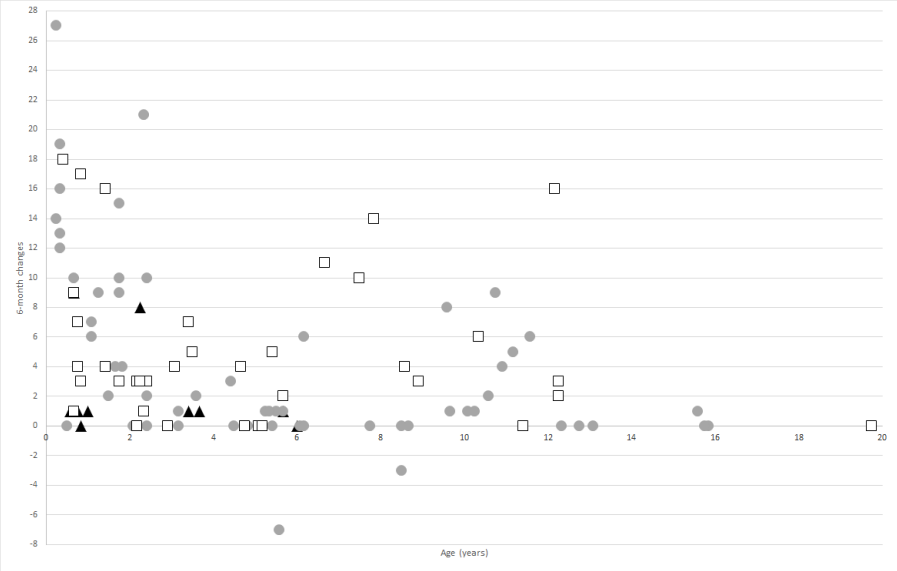

Fig. 1 shows individual details of the CHOP INTEND changes according to severity, age (1a) and baseline (1b) values. Legend to figures: ▲: 1.1 ; ●: 1.5, □: 1.9.