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ORIGINAL ARTICLE

Intrathecal nusinersen treatment for SMA in a dedicated neuromuscular clinic: an example of multidisciplinary and integrated care

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Abstract
Nusinsersen is now available in Italy for all SMA types. We describe the experience with intrathecal treatment with nusinersen in 50 patients with SMA at the NEMO Center (NEuroMuscular Omniservice Clinical Center) in Milan, a neuromuscular patient-centered clinic hosted within Niguarda Hospital, a National Public General Hospital. Our results indicate that the pathway of care described outweighs the burden due to the repeated intrathecal injections. Irrespective of age and severity, the treatment is feasible, accessible, and replicable provided that there is a multidisciplinary team having experience and training in SMA.

Keywords Spinal muscular atrophy · Nusinersen · Multidisciplinary · Integrated care · Spinraza

Introduction

Spinal muscular atrophy (SMA) type 1 is a severe motor neuron disease causing death in two thirds of cases within 2 years of age and resulting in severe disability in the remaining ones [1]. SMA types 2 and 3 may be less severe, but in all cases, the disease is progressive and disabling, irrespective of age at onset [2]. Standards of care [3–5] have slowed down the progression of the disease and have to some extent modified its natural history. The recent approval of Spinraza for the treatment of SMA [6–8] and the promising ongoing trials [6, 7] have changed the approach of clinicians and families when a new diagnosis of SMA is now made.

Despite the initial concerns regarding the repeated intrathecal injections, nusinersen has proved to be relatively safe and well-tolerated by patients reported so far. A recent report in a single German center describes the technical details of the procedure and emphasizes that a structured protocol allows to approach the complexity of the therapeutic program [9]. The experience from the Italian EAP working group confirms the need for a structured protocol but also emphasizes that the program can be conducted successfully in different centers provided that the working team has experience with the protocol's procedures and the disease [10, 11].

We describe the experience with Nusinersen at the NEMO Center (NEuroMuscular Omniservice Clinical Center) in Milan, a neuromuscular patient-centered clinic hosted within Niguarda Hospital, a National Public General Hospital in 50 patients with SMA types 1–3.

Methods

Treatment design

The treatment design is described in Fig. 1. Consent to proceed with the intrathecal administrations of nusinersen was obtained from each patient or family. Assent to participate was also required for 8-year-old kids and older ones. All the patients proposed for this treatment accepted to start the therapy with nusinersen. As in the previous randomized trials [11] with intrathecal injections of nusinersen, patients received four injections within 2 months (loading phase) and then every 4 months (maintenance phase). Patients were asked to

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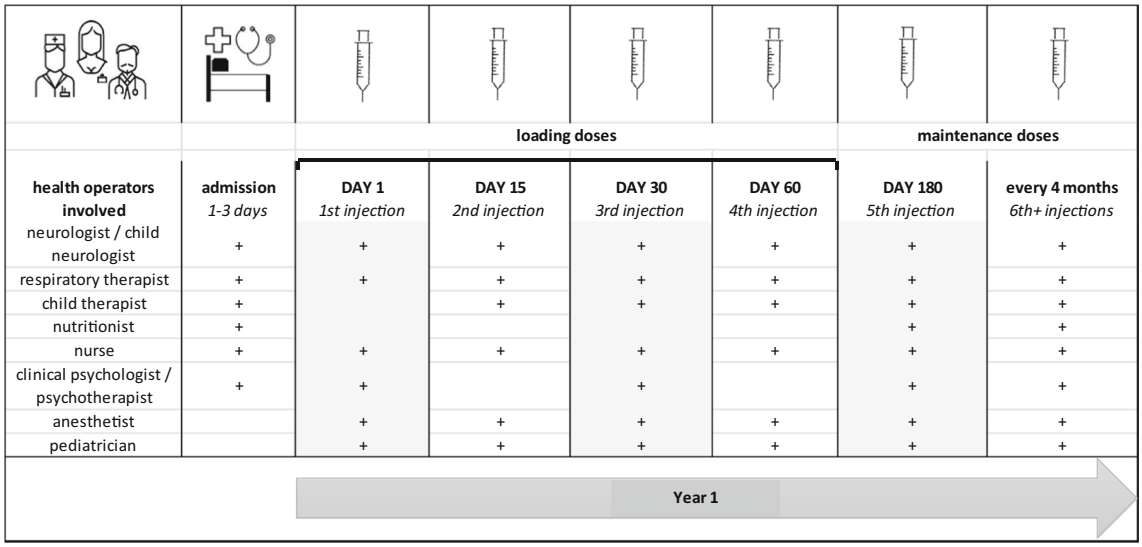

Fig. 1 Treatment design and multiprofessional involvement

come in prior to injection. This was planned according to the general health and respiratory conditions of the patients, usually 1–3 days prior to admission for the first injection and then as a day service care for the subsequent ones, unless the clinical condition required monitoring of the child or adult before and after treatment. Routine laboratory tests, including coagulation screening, were performed prior to the administration.

The multidisciplinary team

At the NEMO Center, patients with neuromuscular disorders, including SMA patients are routinely taken care of by a dedicated team of health professionals including child neurologists or neurologists, pulmonologists, physiatrist, therapists, nutritionist, nurses, and clinical psychologists. This multiprofessional team addresses the multisystem involvement in SMA and applies the Standards of Care for these patients [4, 5]. Nusinersen was administered in the context of this existing multidisciplinary care. An anesthetist and a pediatrician from the Child Department of the National Health System Hospital Niguarda were included in the team during the intrathecal infusions for the infants and kids.

The Italian SMA Family Associations

The Italian SMA Family Associations played an important role in the program. They gave their support during the EAP by taking care of transportation and lodging for those families living at a distance from the referral site. In addition, constant feedback was given to the referral centers on the number of patients waiting for treatment who had been included in a priority list according to age and disease severity based on the criteria that the younger patients and the new diagnosis came first [6]. Feedback was also given to the families on the procedures being performed and on patients' immediate self-generated reports after the procedure. After Spinraza approval, Family Associations supported physicians and families to promote access at the local sites thus trying to accelerate the activation of centers at a distance from the initial EAP sites.

Results

Patient population

We enrolled 50 patients with SMA at the NEMO Center. Twenty-nine SMA1 kids had been included in the EAP (mean age of SMA1 patients 4.96 ± 5.2 months; age range 3 months–15 years and 11 months) and received treatment within 6 months from drug approval. Of these 29, 11 (40%) were known to the Center and 6 of 29 were newly diagnosed SMA1 kids. The remaining 21 patients were SMA2 ($n = 11$; mean age 5.94 ± 5.07 months; age range 12 months–17 years and 7 months) and SMA3 ($n = 10$; mean age 22.52 years ± 20.50 years; age range 4.3–58.7 years).

Fifty-seven percent of the patients included in the EAP came from outside the region hosting the EAP (Lumbardy region) (Fig. 2a). After Spinraza approval in Italy for all SMA types (September 25, 2017, decree no. 1611/2017), 29 additional clinical centers were identified as suitable to administer Spinraza and of these 5 additional ones within Lumbardy region. Starting from November 2017, the new recommendations from the National Health Regulatory Authorities were that Spinraza should be administered locally, at each of the certified sites. The plan was to favor accessibility and reduce the burden on the start-up centers within the EAP and also to reduce the waiting lists. As a result of this, after discussion with the families and the local centers, 12 of the 29 SMA1

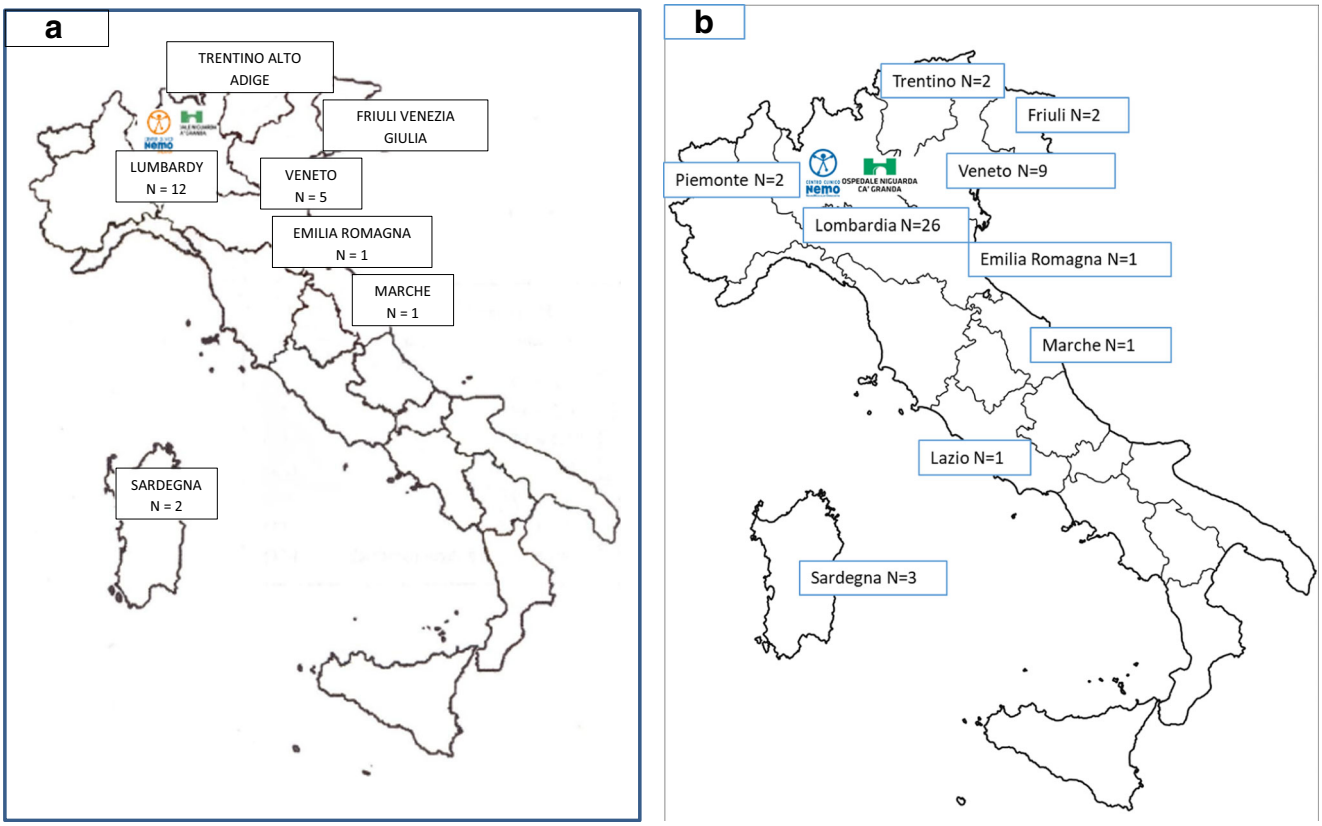

Fig. 2 **a** Regions of origin of SMA1 patients treated at the NEMO Center in Milan during the EAP ($n = 26$). **b** Regions of origin of the patients treated at the NEMO Center after Spinraza approval for all SMA types ($n = 47$)

kids were redirected to their regional sites. Figure 2b describes the actual distribution of patients with SMA currently being treated at the NEMO Center.

Of the 50 patients included in the program so far, 3 dropped out because of technical difficulties with the procedure, despite ultrasound aid. In general, adherence and compliance were high: none of the other patients missed their scheduled injection.

Multidisciplinary involvement

Initial phase

Informing and defining the pathway of care with the family

Information on the preliminary results, expectations and safety profile of nusinersen had been provided to families through SMA Expert Webinars, SMA Association Meetings, and diffusion on media. Despite this, prior to the day of injection, a multidisciplinary team including a neurologist, a child neurologist, a psychologist, and a child therapist met the families and discussed the program and the preliminary results from previous trials including the risk-benefit ratio of going through multiple doses of intrathecal injections. The safety profile of the drug and the possible side effects related to the lumbar puncture were revisited with the family during each meeting and as needed. Time was allocated for questions and additional multidisciplinary meetings were planned as necessary. A dedicated phsychologist was then available for additional time with the family either as a whole, or individually with either one of the parents. This ensured a thorough understanding of the procedure and detected special needs and attention during the whole pathway of care. The pathway of care was delineated at this time and the need to adhere to the standards of care including scheduled visits to assess motor, respiratory, nutritional function, as well as monitoring for scoliosis and growth parameters were discussed and considered mandatory to participate in the program. In case of SMA1, if the kid's respiratory parameters were such that ventilation was recommended, but the parents refused this treatment, the kid was included in the program only if the parents allowed the patient to be placed on NIV at least during the procedure and the kid's respiratory profile was safe enough to go through lumbar puncture.

Assessments/tests and procedures

After enrolment in the program, the day before the injection, patients were subjected to motor functional scales as appropriate per age (Children's Hospital of Philadelphia (CHOP INTEND); Hammersmith Infant Neurological Examination

(HINE)), Range Of Motion, anthropometric measures (ulnar length, weight, cranial, and thoracic circumferences) at baseline, after 15, 30, and 60 days and then every 4 months. Patients were also video-recorded and the source documents saved in the local database according to Privacy and GCP current legislation. Nocturnal oximetry and transcutaneous CO_2 were also recorded at baseline (T0) and after 6 months (T180). A spine X-ray was obtained for all patients while lying.

First injection

For kids, the pediatrician or child neurologist performed the lumbar puncture in a surgery setting in the presence of an anesthetician in case sedation was needed or respiratory complications occurred during the procedure. A dedicated respiratory physiotherapist as well as the child neurologist and/or neurologists were always part of the SMA team during the procedure and helped with ventilation and setting the parameters if sedation or protoxide were used or if the kid's blood oxygen levels went below normal range, sometimes due to crying. For adults, the neurologist performed the lumbar puncture in an out-patient setting in the presence of an anesthetician in case sedation was needed. Propofol or midazolam iv were chosen according to the sedation required and clinical picture.

Monitoring

The child neurologist, neurologists, therapists, and nurses monitored the kid or adult regularly for several hours after the procedure. The psychologist allocated time after the infusion to discuss about the procedure with the patients or family and to identify possible doubts or frailties needing additional support.

Follow-up injections

Between injections patients, parents and caregivers were instructed to take note and inform the referral center about any clinical event that occurred. Whether related or not that was annotated by the clinicians as per report of side effects. Adherence to recommendations (e.g., cough-machine, diet, vaccinations, noninvasive ventilation) was verified by regular phone interviews. Planning of subsequent injections was agreed upon at each visit and verified usually 1 week prior to admission to facilitate compliance to timeline and to make sure that the clinical conditions were such that injection could be maintained. Additional visits or assessments were planned as needed.

Safety

None of the patients had SAEs that were considered to be related to nusinersen. Only three patients experienced transitory increase in body temperature, headache, and nausea. In two patients, there was slight postural reddening and skin edema. Six patients experienced transitory and clinically nonsignificant brady- or tachyarrhythmias after all four administrations of the loading dose. Three adult patients experienced headache, nausea, and vomiting for 48 h after the first lumbar puncture. This was transitory, responded to paracetamol 1 g tid and was not a reason for drop out in any of these patients.

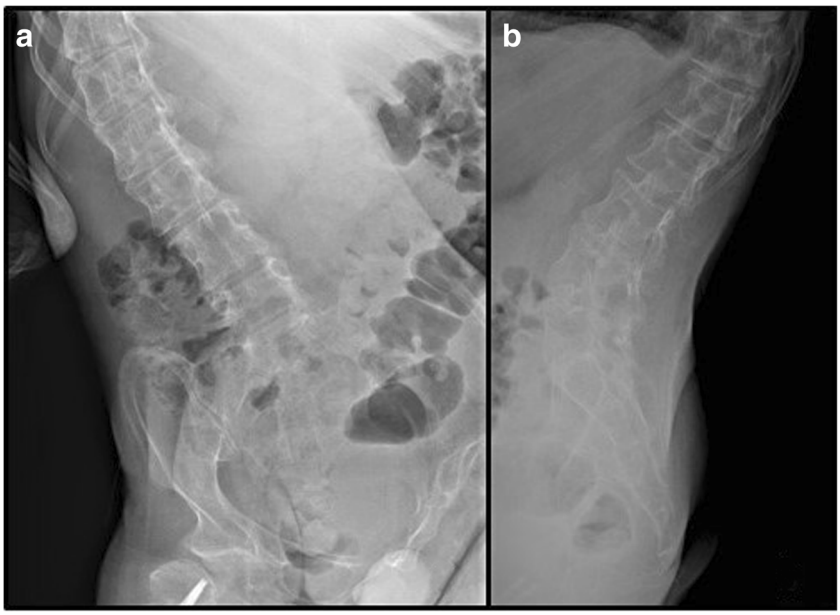

Fig. 3 X-ray images of lumbosacral spine of a patient with severe scoliosis in whom the intrathecal administration was possible with the traditional approach, with no additional neuroimaging or guided procedure. Frontal (**a**) and sagittal (**b**) images

Scoliosis and lumbar puncture

In 30 of the 50 treated patients, there was no scoliosis. In 10 patients, scoliosis was graded as mild (Cobb angle ≥ 10° < 25°), in 4 as moderate (Cobb angle ≥ 25° < 50°), and in 6 as severe (Cobb angle ≥ 50°). In 90% of patients having scoliosis, this was right-curved. Only in 3 of 50 (6%) the procedure was judged as too burdensome for the patients (all SMA1a, having severe disc rotation and scoliosis). In the remaining, including those with severe scoliosis (Fig. 3), we were able to proceed with intrathecal administration with no need for guided support.

Conclusions

The experience with nusinersen at the NEMO Center is that the treatment is feasible, accessible, and replicable provided that there is a multidisciplinary team having experience and training in SMA. This is irrespective of age, disease severity, and degree of scoliosis.

The multidisciplinary team involved at the NEMO Center is part of the patient-centered and omniservice-based approach which is routinely activated at this site during the pathway of care for patients with neuromuscular disorders, including SMA. Dedicating trained staff to apply protocols and procedures was crucial to collect data that proved to be reproducible and reliable and therefore applicable to define the new natural history of these patients.

Yet, there have been difficulties in the process, and not only related to the technical limitations that were expected with intrathecal injections. Not surprisingly when a drug for very disabling and potentially lethal conditions comes into clinical practice the patient and family expectations are very high. It is important to allocate time to discuss about the expected versus the known effects as well as about the procedure. The way the pathway of care and cure was designed was especially structured bearing this in mind. It was important for the team that the concept of cure was conceived by the families and the patients beyond the pharmacological treatment and that patients understood how important it is to comply to the assessments and treatments defined by the Standards of Care no matter how promising the new pharmacological treatment options are.

Despite the safety profile and the very promising results from the previous RCT phase II and III trials, the cost-related issues and risk-benefit ratio have been a matter of debate since approval worldwide [12].

Yet, we believe the approach described outweighs the burden due to the repeated intrathecal injections and assessments required. The initial positive results from the recent papers [13–15] further strengthen this. Regarding the repeated intrathecal injections, reports from the single-centered German experience and from the Italian experience, confirm that the clinical burden for patients, families and health operators is not a limiting factor if the staff is trained, motivated and part of a multidisciplinary infrastructure. In all patients, including all investigated age groups (age range 3 months–58 years old), the lumbar punctures were, in general, well tolerated. The results so far confirm the safety profile of nusinersen. We recommend that treatment occurs within a multidisciplinary setting and that it is conceived as an add-on to their usual clinical practice according to standards of care [16].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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