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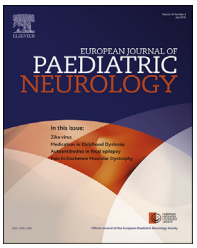

Original article

Single-center experience with intrathecal administration of Nusinersen in children with spinal muscular atrophy type 1

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ABSTRACT

Background: Spinal muscular atrophy (SMA) is a neuromuscular disorder mainly characterized by proximal muscle weakness. There have been enormous advances in therapeutic development with the possibility to influence the clinical course of the disease. Nusinersen is the first approved drug to treat SMA. It is administered intrathecally and acts as splicing modifier of the *SMN2* gene.

Methods: Lumbar punctures were performed using a standardized protocol. To evaluate safety and feasibility of the intrathecal treatment, vital signs and the need for sedation, analgesia or mechanical ventilation during the procedure were monitored. Furthermore, the number of puncture attempts, the injection site and the macroscopic appearance of cerebrospinal fluid were documented.

Results: Treatment with Nusinersen was initiated in 20 children aged from 2 to 50 months. Administration of a local anesthetic cream on the puncture site and a peripheral analgesic led to an adequate pain management. We observed a beneficial distraction through the possibility to watch a movie or listen to music during the procedure. In some cases, an additional sedation was necessary. In patients accustomed to non-invasive ventilation, this was used during lumbar punctures. On average, 1.5 ± 1.0 puncture attempts were performed between L 4/5 and L 2/3. If required, the position of the medullary cone was identified by ultrasound to guarantee a safe puncture above L 3/4.

Conclusions: Lumbar punctures for intrathecal administration of Nusinersen could be performed without any relevant complications. With the described approach lumbar punctures were tolerated well in all investigated age groups.

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Abbreviations: ASO, antisense oligonucleotide; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CNS, central nervous system; CSF, cerebrospinal fluid; EAP, expanded access program; L, lumbar vertebra; NIV, non-invasive ventilation; SMA, spinal muscular atrophy; SMN, survival motor neuron.

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1. Background

Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by degeneration of the anterior horn cells of the spinal cord resulting in muscle atrophy and proximal muscle weakness. It is an autosomal-recessive disorder and the most common genetic cause of death during childhood. SMA type 1 (Werdnig-Hofmann disease) is the most frequent subtype affecting about 50–60% of patients. Children with SMA type 1 develop a severe muscle weakness within the first 6 months of life. Due to the respiratory involvement, mortality is mainly caused by respiratory failure. From the time of diagnosis, infants rarely achieve improvements of motor function or acquire motor developmental milestones.[1] The management of the disease is mainly based on a multidisciplinary management to improve respiratory, gastrointestinal, and orthopedic symptoms. With technical advancements and thus the possibility to provide non-invasive ventilator support and enteral feeding to the affected children, survival has increased.[2,3]

SMA is caused by a homozygous deletion in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13 and has an incidence of about 1:10,000. *SMN2* is a centromeric copy of *SMN1* that produces transcripts of SMN protein lacking exon 7 because of a C-to-T transition in *SMN2* creating an exon-splicing suppressor sequence.[4] The result is an alternatively spliced truncated and non-functional SMN protein (SMNΔ7).[4,5] Based upon a better understanding of the molecular genetics of SMA, there has been a promising approach for the development of novel drugs intervening the pathophysiology of SMA with the main idea to upregulate levels of functional SMN protein. Nusinersen is an antisense oligonucleotide (ASO) that acts as splicing modifier targeting the intronic splicing silencer N1 in *SMN2* intron 7.[6] Preclinical data showed significant increases in exon 7 inclusion and thus an increase in levels of functional SMN protein leading to improved motor function and survival of SMA mice after intrathecal administration.[7,8] The results of a phase III trial were an improvement in muscle function, developmental motor milestones as well as a positive impact on survival and on the need for permanent ventilator support in children with SMA type 1 due to the intrathecal treatment with Nusinersen.[9,10]

Recurrent administration of intrathecal treatment is well established in the pediatric population, especially in the pediatric oncology therapy. During a phase I open-label study in children with SMA type 2 and 3, lumbar punctures and intrathecal administration of Nusinersen were successfully performed and lumbar puncture-related adverse event frequency was similar to that previously reported in children.[11] Adverse events related to lumbar puncture were described as headache, back pain, and a post-lumbar puncture syndrome occurring more often in older children with SMA type 3.[11] Several risk factors can make lumbar punctures in children with SMA type 1 challenging. Age below 12 months was described as major risk factor for failed or traumatic lumbar punctures.[12,13] This is relevant in children with SMA type 1 given that an early initiation of treatment with Nusinersen after diagnosis is important for the success rate of treatment.[14–16] Further, children with SMA type 1 often suffer from respiratory and orthopedic symptoms that have to be considered in performing lumbar punctures and in the decision about general anesthesia or sedation.

Nusinersen has been approved in the United States since 12/2016 and in Europe since 06/2017. Prior to the approval from 11/2016 to 06/2017, Nusinersen was provided to patients with SMA type 1 in Germany within an Expanded Access Program (EAP). In contrast to the previous clinical trials of phase I–III, children of different age groups and different stages of the disease were treated with Nusinersen within the EAP.

Here, we report our single-center experience with the intrathecal administration of Nusinersen in children with SMA type 1.

2. Methods

In the Department of Neuropediatrics and Muscle Disorders, Medical Centre – University of Freiburg, Germany, the treatment with Nusinersen was provided to children with SMA type 1 within an EAP from 11/2016 to 06/2017. Inclusion criteria to participate in the EAP were defined as presence of a genetic documentation of 5q SMA, documentation of an onset of clinical signs and symptoms at less than 6 months of age and that patients' care meets the guidelines published in 2007 as consensus statement for standard of care in SMA.[17] The following criteria were defined as exclusion criteria: a possible participation in an ongoing clinical trial with Nusinersen or participation in a prior Nusinersen study or previous exposure to Nusinersen, history of brain or spinal cord disease that would interfere with lumbar puncture procedures or cerebrospinal fluid (CSF) circulation, presence of an implanted shunt for CSF drainage or implanted central nervous system (CNS) catheter, previous or current participation in a clinical trial with an investigational gene therapy for SMA or participation in a study with an investigational therapy for SMA within the past 6 months.

The intrathecal administration of Nusinersen was performed on treatment days 1, 15, 30, 60 and 180. Dosage of Nusinersen was age-dependent analogous to the preceding clinical trials: 9.6 mg (0–90 days), 10.3 mg (91–182 days), 10.8 mg (183–365 days), 11.3 mg (366–730 days) and 12 mg (>731 days). The drug was administered via intrathecal injection over 1–3 min. All lumbar punctures were performed with a Quincke G22 needle. Children were positioned in a lateral decubitus position.

For preparation of lumbar puncture, all children received a local anesthetic cream on the injection site as well as a peripheral analgesic (e.g. Acetaminophen). Children were offered to watch a movie or listen to music during the procedure. We discussed the need for an additional sedation with the parents in less affected children with a lively moving pattern, generally in children older than 9 months of age or in children showing symptoms of agitation or separation anxiety from parents prior to the procedure. Thus, if necessary we applied a benzodiazepine intranasally (e.g. Midazolam with a dosage of 0.2 mg per kg). Parents were not

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