Treatment with nusinersen in a girl with spinal muscular atrophy type 1: Case report

Zdravljenje z nusinersenom pri deklici s spinalno mišično atrofijo tip 1: Prikaz primera

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Abstract

We report the case of a girl with spinal muscular atrophy (SMA) type 1, who is the first patient with SMA in Slovenia treated with nusinersen, the first disease modifying therapy available for these patients. SMA is an autosomal recessive neuromuscular disorder characterized by muscle weakness, atrophy and paralysis due to the degeneration of the anterior horn cells, leading to premature death, most commonly due to respiratory infections. Nusinersen, an antisense oligonucleotide, was clinically approved based on clinical trials showing dramatic improvement in the natural course of infantile-onset SMA. After the genetic confirmation of SMA, our girl was the first child in Slovenia to receive nusinersen, which was provided through an expanded access programme. She received intrathecal applications of nusinersen according to the protocol. No serious adverse events were observed. Assessment of her motor skills was performed using The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP – INTEND) before the beginning of treatment and after completing the first 7 applications of nusinersen. She scored 21/64 points before the introduction of treatment and 32/64 after the completion of treatment. In conclusion, nusinersen improved the CHOP – INTEND motor function score and has been effective in delaying the expected natural course of SMA in our patient.

Izvleček

Predstavljamo primer deklice s spinalno mišično atrofijo (SMA) tipa 1, prve bolnice v Sloveniji, ki se zdravi z zdravilom nusinersen, ki spreminja naravni potek bolezni. SMA je avtosomno recesivna živčno-mišična bolezen, za katero je značilno propadanje motoričnih nevronov sprednjih rogov hrbtenjače, kar vodi v mišično šibkost, atrofijo, paralizo in prezgodnjo smrt; slednja je v večini primerov posledica okužbe dihal. Protismiselni oligonukleotid nusinersen je bil odobren za zdravljenje na osnovi kliničnih študij, ki so pokazale izboljšanje v naravnem poteku infantilne oblike SMA. Po genetski potrditvi klinične diagnoze SMA je naša deklica prvi otrok v Sloveniji, pri kateri smo uvedli zdravljenje z nusinersenom. Zdravilo smo, še pred registracijo v Sloveniji, dobili s pomočjo programa sočutne rabe. Deklica v skladu s protokolom prejema redno intratekalno nusinersen. Neželenih učinkov ob zdravljenju nismo beležili. Objektivno oceno dekličinih motoričnih sposobnosti smo opravili s pomočjo lestvice CHOP – INTEND pred začetkom in po sedmih vnosih zdravila nusinersen. Deklica je pred uvedbo zdravljenja dosegla 21/64 točk, po sedmih vnosih zdravila pa 32/64 točk. Ugotavljamo, da je nusinersen, glede na lestvico CHOP – INTEND, izboljšal motorične sposobnosti pri naši deklici in se je pri upočasnjevanju naravnega poteka bolezni izkazal kot učinkovit.

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1 Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by the degeneration of anterior horn cells, resulting in muscle atrophy and weakness (1). It is classified into five types based on clinical features, age of onset and the motor functions affected. In all five types of SMA involvement of virtually all skeletal muscles is present, with the exception of the muscles innervated by the first 11 cranial nerves (the XII cranial nerve being an exception among them) (2,3).

The disease is most commonly caused by a mutation in the survival motor neuron (SMN) gene, located on chromosome 5 (5q11.2–13.3). This results in the loss of alpha motor neurons in the ventral horn of the spinal cord, resulting in progressive paralysis and eventually premature death (4). The aforementioned mutation accounts for up to 95 % of cases and has a frequency of 1/11.000 births (5,6). In humans, two forms of the SMN gene exist on each allele: a telomeric form (SMN1) and a centromeric form (SMN2). Transcription of the SMN1 gene produces full-length mRNA transcripts that encode the SMN protein. The SMN2 gene is identical to the SMN1 gene with the exception of a C to T substitution in an exonic splicing enhancer, which results in the exclusion of exon 7 during transcription. The resultant truncated protein is not functional and is rapidly degraded. Importantly, exon 7 is not excluded from all SMN2 mRNAs and so a small fraction of the total mRNA transcripts (~10–15 %) arising from the SMN2 gene does contain exon 7, thus encoding a normal SMN protein (7).

Nusinersen is the first drug approved to treat SMA. It is a 2'-O-methoxyethyl phosphorothioate-modified antisense drug specifically designed to alter splicing of SMN2 pre-mRNA and thus increase the amount of functional SMN protein, which is deficient in patients with SMA (8).

There are many studies evaluating the successfulness of the nusinersen treatment for different types of SMA. NURTURE, an open-label study that began in 2015 and is still ongoing, is assessing the efficacy, safety, tolerability and pharmacokinetics of multiple intrathecal doses of nusinersen administered to presymptomatic SMA infants aged less than 6 weeks. The interim results of the study show that the effects of nusinersen are encouraging with improvement in motor milestones and growth parameters, no fatalities and no ventilation required after 323 days (9).

Mercuri et al. conducted a multicenter, double-blind, sham-controlled, phase 3 trial of nusinersen in 126 children with SMA who had symptom onset after 6 months of age. They concluded that among children with later-onset SMA, those who received nusinersen had significant and clinically meaningful improvement in motor function, compared to those in the control group (10). Short term results that show the successfulness of nusinersen in late onset SMA were also obtained by other study groups (10,11), but for long term effects additional studies and clinical trials are needed.

Known adverse effects of treatment with nusinersen are side effects due to lumbar puncture (headache, back ache, vomiting), and rarely thrombocytopenia, coagulation disturbances, renal toxicity, and communicating hydrocephalus (12).

SMA type 1 is the most common (50–60 %) type. By definition, the onset of symptoms in SMA type 1 is before 6 months of age and the main cause of

mortality in these children is a result of respiratory involvement. From the point in time of diagnosis, infants with SMA type 1 rarely achieve improvement in motor function or acquire new motor developmental milestones (13).

2 Case report

A 9–month-old girl presented to our hospital (University Children's Hospital in Ljubljana, Slovenia) with gross motor delay, hypotonia and diminished spontaneous movement in the lower limbs.

She was born to healthy, non-consanguineous parents, with an unremarkable family and antenatal history. She was born at 39 weeks of gestation, with a birth weight of 2610 g (7^{th} percentile), a birth length of 46 cm (5^{th} percentile), a head circumference of 33 cm (23^{rd} percentile) and APGAR scores of 9/10/10. During her first 2 months of life poor weight gain was observed. She was breastfed for the first 7 weeks of life, thereafter she was fed with a hypoallergenic formula due to skin rashes, gastroesophageal reflux and abdominal cramps, but weight gain was suboptimal.

Until the 4^{th} month of life the parents reported normal development, she was able to prop herself up on her arms and lift her chin when in prone position. After that, the parents began to notice that the child had signs of muscle weakness and fewer spontaneous movements in her legs. At presentation to our institution (at 9 months of age) they reported that she was able to sit unsupported, but was not able to sit up independently. The parents said that her upper limbs and cognitive functions were unaffected; she was able to grasp toys and move them from one hand to the other, she had babbling conversation from 7 months of age and good social contact. They reported no problems with feeding or lower respiratory tract infections.

On first examination, social contact was good, she was smiling. Tongue fasciculations were present with no signs of other cranial nerve involvement. Hearing tests were not performed, but there were no clinical signs of impaired hearing; her newborn hearing screening test had been normal. When presented with a small toy, she reached toward it, grasped it with the forearm in internal rotation and a pincer grasp. She moved the object spontaneously from one hand to the other, without dropping it. There were almost no spontaneous movements of the lower limbs. Severe generalized hypotonia was present and lower limb muscle strength was severely diminished. She had no obvious signs of muscle atrophy, but proximal muscle weakness was present in the upper and lower limbs, the latter were more affected. All deep tendon reflexes were absent. She was not able to roll from prone to supine and back. When lying supine, frog-leg position was seen. When pulled to sitting position, she had no obvious head lag and was able to sit unsupported with thoracolumbar kyphosis. In ventral suspension, her lower limbs hung loosely and she was unable to support her weight when placed in standing position. Otherwise her clinical status was normal and her weight and length were normal for her age (10 kg – 94th percentile and 70 cm – 48th percentile).

2.1 Laboratory findings, diagnostic procedures and genetic study findings

Diagnostic workup included complete blood count and biochemistry, liver and muscle enzymes were done and they were all normal for age.

Her pulmonary function tests and echocardiogram at presentation were normal. Night polygraphy was also performed, the recording lasting 5 hours and 51 minutes, with an average saturation of 94.6 %. It also showed periods of diminished blood oxygen saturation in sleep, lasting up to 2 minutes. Saturation below 90 % was present in 0.1 % of the recording. Because of technical difficulties, it was impossible to say whether the desaturations were of central or obstructive origin. But it was postulated, that these results might be the result of hypoventilation or paradoxical breathing and further close follow-up was planned.

Genetic studies revealed a homozygous mutation in SMN1 gene – the deletion of exon 7 and 8 - and four copies of SMN2 gene, which confirmed the diagnosis of SMA.

2.2 Treatment and follow-up

The girl was the first child in Slovenia to receive nusinersen, which was provided through an expanded access programme. For the purpose of regular follow-up and collection of all the relevant data she was included in the Registry of Slovenian Children with Neuromuscular Diseases, after written consent from her parents had been obtained. She had multidisciplinary clinical assessments prior to starting treatment.

She was given the 1st intrathecal application of nusinersen in the dosage of 11.3 mg under general anaesthesia on 7 March 2017 at the age of 14 months. Intrathecal injections with nusinersen were continued according to the protocol – on treatment days 15, 30, 60 and 180 and thereafter every four months; only the first application was given under general anaesthesia. After each application, she received one dose of analgesic. So far, she has received 8 applications, the dosage being adjusted to 12 mg after the age of two.

The first (and only) adverse effect was observed a few hours after the 6th application, when the girl reported symptoms of headache which subsided after the second dose of paracetamol.

Assessment of her motor skills was performed using The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP - INTEND) (14) before the beginning of treatment and after completing the first 7 applications of nusinersen. CHOP – INTEND is a reference test used in children with SMA, which evaluates spontaneous as well as active movements of the upper and lower limbs and also head and neck control. She scored 21/64 points before the introduction of treatment and 32/64 after the completion of treatment. The child was clinically and neurologically evaluated by the neurologist before every application of nusinersen; her motor skills as well as her general well-being were recorded.

The parents reported improved mobility performance after the 3rd application of nusinersen. They noticed increased muscle strength and more spontaneous movements of lower limbs as well as the capability of lifting her upper limbs above her shoulders. Additionally, they also noticed improvement in head control and reported the child was able to sit independently for 30 minutes. One hundred and eighty days after the introduction of treatment they reported independent rolling to the side, she was able to move her legs, support her weight and bounce when placed in the standing position.

At the age of two and a half years, the child was tested at our institution, where we documented 20 minutes of unassis-

Figure 1: Girl with spinal muscular atrophy type 1 at the age of 33 months. She is the first patient with SMA in Slovenia treated with nusinersen, starting at the age of 14 months. She can sit by herself, can feed herself and can lift objects against gravity, which far exceeds the expectations based on the natural history of the disease.

ted sitting without kyphosis. (Figure 1). She was able to dorsiflect and extend the foot, could activate extensors and abductors of the hips and when motivated, could roll from prone to supine and from supine to the side. She did not show any decrease in her motor functions and there was no regression in the spontaneous movements of the upper limbs. Deep tendon reflexes in lower limbs were still absent, but in the upper limbs, the biceps tendon reflex was present. She had had no serious respiratory infections (which we defined as any respiratory infection of the lower respiratory tract), her respiratory function as well as night polygraphy were normal, with no signs of hypoventilation or paradoxical breathing. She had had no feeding problems and had gained weight normally.

3 Discussion

We report the first child with SMA type 1 in Slovenia, who was treated with nusinersen. Most infants with SMA type 1 are unable to achieve or maintain most motor milestones. In the natural course of infantile onset SMA, regression of motor functions in all children is observed with age and most of the children die within the first two years of life (15). In our patient, we observed no regression of the achieved motor functions during treatment and after completion of first 7 applications of nusinersen, furthermore, she achieved new developmental milestones. The girl was able to sit unsupported, without kyphosis, developed the ability to roll spontaneously from prone to supine position, and was

able to support her weight when placed in the standing position. She could raise her arms above shoulder level and showed a wider range of movement in her upper limbs in general, was capable of grasping objects, including achieving the pincer grasp. A wider range of movement of the lower limbs was also observed, including dorsiflexion, extension of the foot and activation of extensors and abductors of the hip. She could feed herself independently. Improvement of her motor skills was also observed on CHOP – INTEND, she improved by 11 points since the start of treatment. No serious respiratory infections were recorded. Her pulmonary function values remained normal, she had no signs of hypoventilation, no need for ventilatory support and no feeding difficulties. On the follow-up, her night polygraphy was normal.

The girl has 4 copies of SMN2 gene, which is more than normally seen in SMA type 1 patients, however it had been documented before (16). Despite having more copies of SMN2 gene, she presented with regression of her motor functions before the age of 6 months. We know that the number of copies of the SMN2 gene does not define the SMA type and does not necessarily correlate with the severity of clinical phenotype. Nevertheless, having 4 copies might be a contributing factor to the fact that she is doing very well on the therapy with nusinersen, as nusinersen acts on SMN2 gene. Having more copies of this gene might contribute to the production of more functional SMN protein and therefore maintaining more alpha motor neurons in the spinal cord.

She has tolerated nusinersen very well, as no serious adverse events have been observed. After the completion of 7 applications, the girls' cardiopulmonary function is still normal. From our observation, and taking into consideration the expected natural course of untreated SMA type 1, we consider that the treatment with nusinersen has been effective in delaying the natural course of SMA in our patient.

The girls' response to treatment, as well as data from international studies (11,13), have contributed to obtaining support from the Slovenian health care system to fully cover the financial burden of treatment with nusinersen for all paediatric (0–18 years of age) patients with SMA regardless of the type. We have agreed to closely follow the development of all SMA patients treated and stop the treatment in those who fail to respond favourably to treatment. It still remains unclear how nusinersen will change the course of the disease in the long-term. Will the treatment give durable results or will we still see a progression of the disease, but at a slower rate? Are there other factors which contribute to the range of effect in treatment with nusinersen (like the number of SMN2 copies or other genetic factors)? These are the questions that call for further research and long-term follow-up of all treated patients. For now, all patients with a stable motor-developmental status or those who show further improvement, like our patient, will continue with the nusinersen treatment and close follow-ups. Hopefully, by collaborating with other centres treating patients with SMA and sharing our experiences and data, we will be able to offer optimal treatment and achieve favourable outcomes in patients with SMA in the long run.

Consent was obtained from the girl's parents for the publication of this case report.

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