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Onasemnogene Abeparvovec as New Gene Therapy in Patients with Spinal Muscular Atrophy – a Review of the Literature

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Abstract

Introduction: *Spinal muscular atrophy is an autosomal recessive neurodegenerative disease that mainly affects children. It is caused by mutation in the SMN1 gene, which results in degeneration and loss of alpha motor neurons innervating skeletal muscles. Without any intervention, spinal muscular atrophy progresses and leads to disability or even early death.*

Material and methods: *The latest available literature accessible on the PubMed database was reviewed. Thirty papers, which were published in English, available as full-text publications, and published since 2015, were selected for analysis.*

Results: *Depending on the level of motor development and the age of onset, spinal muscular atrophy is divided into 4 or 5 subtypes. Onasemnogene abeparvovec is a gene replacement therapy and consists of a vector of the serotype 9 adeno-associated virus, which delivers a functional copy of the SMN1 gene to the cells of the motor neuron. Important advantage of the drug is single administration via an intravenous route. The limitation is the high price and the lack of studies in older children. Several studies confirmed the efficacy and safety of using onesamnogene abeparvovec in children who afterward made progress in respiratory functions, swallowing, and motor milestones, like head control and sitting independently.*

Conclusions: *Onasemnogene abeparvovec is an innovative and effective drug with great potential for present and future use. Therapy in spinal muscular atrophy should be implemented as early as possible to avoid muscle cell loss. It is important to conduct universal screening tests of newborns to detect the disease before the first symptoms appear.*

Key words: *gene therapy, spinal muscular atrophy.*

Introduction and objective

Spinal muscular atrophy (SMA) is a group of severe inherited neurodegenerative diseases caused by a mutation in the *SMN1* gene (survival of motor neuron) on chromosome 5q13. It results in degeneration and loss of alpha motor neurons of the spinal cord innervating skeletal muscles, which is manifested by progressive muscle weakness and atrophy [1, 2]. The gene codes SMN protein, without which it is impossible to survive. Patients with SMA live due to the small amount of SMN protein produced from the *SMN2* gene. SMA is an autosomal recessive disease that mainly affects children. Depending on the level of motor development and the age of onset, spinal muscular atrophy is divided into 4 subtypes [3]. Sometimes type 0 is also enumerated or classified as 1A by some authors [4]. The incidence of SMA in the population is estimated at 1 in 10,000 live births [5]. Patient support consists of the symptomatic treatment of the disease in order to prevent further deterioration of health [1]. Without any intervention, spinal muscular atrophy progresses and leads to disability or even early death [1, 5].

The first disease-modifying drug approved for the treatment of spinal muscular atrophy was nusinersen. It consists of antisense oligonucleotides and interacts with the *SMN2* gene, resulting in increased production of the SMN protein and requires multiple for life intrathecal administration [6]. There are trials of treatment with other drugs possible for use in SMA therapy, for example, risdiplam [7].

In recent years, scientists have been looking for other, more effective, safe, and easier to administer drugs in the treatment of spinal muscular atrophy. In May 2019, new gene therapy was approved in the United States for the treatment of paediatric patients under 2 years old [8]. It appeared on the market as the most expensive drug currently in the world – onasemnogene abeparvovec. In 2020 the European Medicine Agency approved it for the treatment of patients with the clinical presentation of SMA type 1 or SMA with up to three copies of the *SMN2* gene [9].

The aim of the study is to present the current state of knowledge on the effectiveness of the new gene therapy with the use of onasemnogene abeparvovec in the treatment of SMA.

Material and methods

The latest available literature was reviewed. The materials accessible in the PubMed database were used. The following inclusion criteria were applied: papers published in English, available as full-text publications, and published since 2015. Original and review papers were chosen whereas letters to the editor were not included. The literature review was carried out on 7 November 2020, using the following keywords: "gene therapy" and "spinal muscular atrophy", from which 150 results were received. Using the brand name of the drug "Zolgensma" 49 results were obtained, while using the pharmaceutical name of the preparation "onasemnogen abeparvovec" – 33 publications. After reading abstracts, 30 papers, which met the adopted criteria, were selected for analysis.

Results

SMA as a genetic disease with a different clinical picture

The clinical picture of the disease varies depending on the type of disease and includes problems such as general motor muscle weakness, limited mobility, muscle contractures, and respiratory failure [2]. Intellectual development is normal. Type 0 of spinal muscular atrophy is recognized prenatal or at birth, in which profound hypotension and respiratory distress are present soon after birth, and life expectancy in the absence of treatment is up to one month [4]. In infants with type 1 SMA, the first symptoms appear before the age of 6 months and include respiratory problems, hypotonia, and motor delays. Patients never sit up. It is the most severe form and the most common genetic disease with high mortality even before the age of 2. Children with SMA type 2 are able to sit, but they cannot walk. Symptoms of the disease appear later and before the

age of 18 months. In patients with type 3 SMA, symptoms of the disease are relatively mild and begin after 18 months of age. Children can walk independently, but there is a risk of losing this ability later. The symptoms of type 4 SMA appear in adults and are characterized by slow progress. It is the mildest form of the disease, in which patients walk, and their life expectancy is usually normal [10]. The strongest genetic modifier of SMA severity is the *SMN2* gene copy number. The more copies of the gene, the milder the course of SMA. However, this inversely proportional relationship is not absolute, and we cannot always predict the course of the disease [2, 11].

Molecular basis of gene therapy in SMA

Gene therapy is a very effective method of treating neurodegenerative diseases, which also includes disorders of the motor neuron. It involves the introduction of nucleic acids into cells and enables treatment at the molecular level [12, 13]. SMA is a result of a single gene defect, therefore gene therapy can be extremely effective in the treatment of this disease [14]. It prevents the death of neuronal cells and inhibits the progression of SMA [6]. Onasemnogene abeparvovec is a one-time gene replacement therapy. It consists of a vector of the serotype 9 adeno-associated virus (AAV9) [6]. AAV is a non-enveloped small virus of the *Dependovirus* genus of the *Parvoviridae* family. The length of a single-stranded, linear DNA genome is ~ 4.7 Kb. It is encased in a 25-nm icosahedral capsid. This virus cannot replicate itself, but can infect dividing and non-dividing host cells. The AAV genome then integrates with the host cell's DNA and remains hidden there [15]. AAV9 crosses the blood-brain barrier allowing a single intravenous infusion, which is a significant advantage of the drug [14, 16]. The dose is selected strictly according to the patient's weight. Multiple dosing cannot be used, because the patient might develop the AAV antibodies [17]. The advantage of the AAV vector is efficacy, safety, and the induction of a limited immune response [13]. Its task is to deliver a functional copy of the *SMN1* gene to the cells of the motor neuron directly. This replaces the faulty or missing *SMN1* gene. DNA self-com-

plementation technology enables the rapid formation of a functional episome by a vector delivered in the form of double-stranded DNA [14]. Administration of the drug increases protein expression in the central and peripheral nervous system [18]. As a result, onasemnogene abeparvovec has a very fast onset of action [14].

The effectiveness of gene therapy in the treatment of SMA in research

Numerous studies confirm the effectiveness of onasemnogene abeparvovec therapy in children. Waldrop et al. assessed the safety and early outcome data from 21 children aged 1–23 months and proved that in this population, due to screening and careful post-gene transfer management, replacement therapy with onasemnogene abeparvovec-xioi was efficient and safe. An asymptomatic drop in platelets in the first week after treatment was experienced by 19 out of 21 children. Two patients experienced stabilization and 17 experienced improvements in motor function in a group of 19 children with repeated outcome assessments. Due to the hepatotropic properties of the drug vector adenovirus, post-drug liver enzyme levels should be monitored and steroids administered. Gene transfer was well tolerated in children below 6 months. In this group, serum aspartate aminotransferase and alanine aminotransferase elevations were modest and an association with γ glutamyl transpeptidase elevations was not seen. Initial prednisolone was administered. In children over 6 months, a higher dose of prednisolone was required due to more common elevations in serum transaminases and γ glutamyl transpeptidase, but all patients did not present clinical symptoms [19].

Al-Zaidy et al. evaluated the effectiveness of onasemnogene abeparvovec therapy (previously known as AVXS-101) in infants with spinal muscular atrophy type 1 (n = 12) and compared the results with a cohort of healthy infants (n = 27) and a prospective natural history cohort of SMA1 infants (n = 16) from the NeuroNEXT (NN101) study. Event-free survival, CHOP-INTEND scores (scale for assessing neuromuscular efficiency of infants), compound muscle action potential, motor milestone achievements, and adverse events were compared. All onasemnogene

abeparvovec treated infants survived by 24 months of follow-up. In the NN101 study, the percentage was 38%. Independent sitting and walking were achieved by infants receiving AVXS-101. SMA1 infants from NN101 study presented the average baseline CHOP-INTEND score 20.3, which worsened to 5.3 by age 24 months. In patients receiving AVSX-101 the average baseline score was 28.2 and improved to 56.5 by age two years. AVXS-101-treated infants at 6 and 24 months had improvements in compound muscle action potential peak area (means of 1.1 and 3.2 millivolts/second) [20].

In another study, Al-Zaidy et al. assessed the effectiveness of AVXS-101 gene replacement therapy among twelve SMA1 infants with homozygous deletions of the *SMN1* gene and two *SMN2* gene copies. Patients received a one-time intravenous AVXS-101 between December 2014 and 2017 and were followed for 2-years post-treatment for outcomes. Eleven children were able to swallow, which allows orally feeding. Seven patients did not require noninvasive ventilation and eleven achieved the ability to speak. Eleven patients were able to control the head position and sit independently. Two of them could walk without help. The mean length of hospitalization was assessed as 6.7 days. The mean unadjusted annualized hospitalization rate was 2.1. The mean proportion of time hospitalized was 4.4%, which showed the decline and contributed to the improvement of the quality of life of patients and their parents [21].

Lowes et al. conducted a study on the effect on motor function of onasemnogene abeparvovec administration in one-time gene replacement therapy in infants with severe spinal muscular atrophy type 1. The therapeutic dose of AVXS-101 was administered to 12 infants. The infants were grouped according to age at the time of AVXS-101 administration and baseline values from the Philadelphia Children's Hospital neuromuscular disorder test. The first group of children was less than 3 months old, with a score < 20 (n = 3) and weak motor skills. Early dosing was used which resulted in a mean increase of 35 points from a mean baseline value of 15.7. The next group consisted of children aged 3 months or older (n = 6). Late dosing was performed which resulted in a mean increase of

23.3 points compared to a mean starting value of 26.5. The last group consisted of children under 3 months of age with a score of ≥ 20 (n = 3) and strong motor skills. As a result of early dosing compared to a mean baseline of 44.0, a mean score of 60.3 was rapidly achieved. Children with strong motor skills who received early dosing with AVXS-101 were the earliest of the 3 groups tested to start sitting up alone. The group of children with lower motor skills who used the dosing earlier despite a lower value of the initial motor score started to sit up faster than the group of children who used the latter dosing. The results of these studies have shown that early treatment is important and that improvement in the quality of life is independent of baseline motor function [22].

The concern issue of combining molecular therapies in patients with SMA1 was addressed by Yohei Harada et al. Five patients (age: 17––29 months) who had homozygous *SMN1* deletions and two copies of *SMN2* were tested. All received nusinersen and onasemnogene abeparvovec-xioi and four of them (1, 2, 4, 5) had received nusinersen prior to onasemnogene. Nusinersen was continued in three of them. The treatment of the fifth patient was sequential, but not concurrent. As a result of the increase in liver enzymes, the first and second patients had to stay in the hospital and undergo longer corticosteroid therapy. The second patient had a liver biopsy, and his symptoms indicated a liver failure. In the fourth and fifth patients, the increase in liver enzymes was found to be milder, they were normalized after treatment with corticosteroids. In addition, transient thrombocytopenia was observed in both of these patients. The third patient was taking onasemnogene abeparvovec-xioi, which was the first drug, and then he was given nusinersen. No side effects were observed. Improvement was seen in all patients with SMA1 after combination therapy [23].

Paul et al. highlighted in their review that the level of improvement in muscle strength and respiratory health differs depending on SMA genotype, treatment applied, the timing of the first dose, and intensity of baseline neuromuscular and pulmonary impairment. The authors after analyzing data from several studies claimed that although some patients

might still require escalation of respiratory support during illnesses, overall pulmonary morbidity might have decreased after a single intravenous infusion of onasemnogene. The number of patients who acquired the ability to safe swallow function to allow partial oral feeding increased from 58% to 92%, assessed in video-fluoroscopy. Percentage of children able to drink thin liquids increased from 33% before treatment to 83% after it [24].

In the study conducted by Dabbous et al., treatment efficacy of onasemnogene abeparvovec (AVXS-101) relative to nusinersen for the treatment of SMA type 1 was evaluated. The possibility of preventing death was 20% higher for children treated with onesamnogene abeparvovec than nusinersen (risk ratio (RR) = 1.2). Among symptomatic infants with SMA type 1, the number needed to treat to prevent (NNT) one more death with AVXS-101 instead of nusinersen was 6.2. For event-free survival, the NNT to prevent one more event was 2.6 (RR = 1.6). For improvement in motor function, NNT was 3.5 (RR = 1.4). For milestone achievements, the NNTs were 1.4, 1.5, and 1.2 (RR = 4.2, 7.8, and 11.2) for head control, rolling over, and sitting independently, respectively. Each outcome was reported with 95% confidence intervals. Results suggest that AVXS-101 may have an efficacy advantage in comparison to nusinersen for independence from permanent assisted ventilation, motor function, milestones, and overall survival [25].

In the study by Waldrop et al., several case reports of patients with SMA were presented. In one of them, the patient received onasemnogene abeparvovec-xioi at 6 months of age, and nusinersen was stopped. His general gross and fine motor development has improved to be at the appropriate time or even early. Patients' CHOP-INTEND score has stabilized at 64 about 2 months after gene transfer (5 months since the last dose of nusinersen). The second patient with CHOP-INTEND = 37 received onasemnogene abeparvovec-xioi at 10 months of age. Her clinical outcomes have improved, with a CHOP-INTEND score of 54 at 13 months. Onasemnogene abeparvovec-xioi performs very well with minimal liver toxicity, but the sample size in research is much smaller compared to

nusinersen and the data are only in infants. Due to possible side effects throughout the body after systemic administration (an ability of AAV9 to transduce also other than neurons cells types and use a promoter in all types of cells in the body) and possible higher exposure of the motor neurons to the delivered *SMN1* directly to central nervous system, the intrathecal administration may be considered in clinical trials [26]. A lower dose would be sufficient with such a method of administration and the drug potentially might be used in older patients.

Rashnonejad A. et al. assessed the efficacy of human SMN gene expression after delivering gene therapy in SMA mouse embryos in the context of possibilities of fetal treatment for early-onset SMA. Intrauterine intracerebroventricular injection of AAV9-EGFP led to the vast expression of EGFP protein in the central nervous system with a huge amount of transduced neural stem cells. Mouse fetuses received a single intracerebroventricular injection of a single-stranded or self-complementary AAV9-SMN vector that led to a lifespan of 93 (median of 63) or 171 (median 105) days for ill mice. In both study groups, the muscle pathology and number of the motor neurons improved. Little better results come from self-complementary AAV treatment [27]. In the study conducted by Hinderer et al., three juvenile nonhuman primates and three piglets were treated with an intravenous injection of an AAVhu68 vector (an AAV9 variant) which carried a human SMN transgene. In both species, wide transduction of spinal motor neurons was achieved after administration of $2x10^{14}$ genome copies/kilogram of body weight. The dose was close to that used in the SMA clinical trials. Nonhuman primates exhibited increased transaminases. All animals presented with features of degeneration of dorsal root ganglia sensory neurons. Authors conclude that research involving high systemic doses of AAV vectors should include precise control for toxicity [28]. However, among children under the age of two, onesamnogene abeparvovec visibly changes the natural history of spinal muscular atrophy with minimal side effects [26].

Limitations of the drug therapy

Unfortunately, onasemnogene abeparvovec is not refunded by the National Health Fund now in 2020 in Poland. Its cost makes it impossible to use in any child with SMA who would be qualified for the therapy. Onasemnogene abeparvovec treatment costs (brand name – Zolgensma) were estimated at $2.1 million per one dose or an annualized cost of $425,000/year for 5 years [29]. Nevertheless, the 5-year costs for Zolgensma, which is a one-time treatment, are lower in comparison to nusinersen, which is the only approved therapy for SMA and costs $750,000 in the first year of treatment and $375,000 annually thereafter for life [29].

Future perspectives

There is presently no treatment that can revive muscle cell loss due to the disease, because currently used drugs can only increase the availability of the SMN protein in motor neurons and prevent them from dying further. The early diagnosis of the disease and the use of the drug help to stop the progression of the disease. Australian experience with the introduction of wide-ranging newborn screening for SMA between 1 August 2018 and 31 July 2019 shows that in the first year of the program, 10 out of 103,903 newborns were screened positive for SMA using polymerase chain reaction (PCR). The median time for ending the screening and diagnostic process was 13.5 days (from 8 to 21 days) and therapeutic intervention was implemented by the median of 26.5 days after birth (from 16 to 37 days). Early commencement of treatment with nusinersen offers the best prognosis for survival and clinical outcomes, particularly treatment within the presymptomatic period [30]. If children were early detected, the implementation of onasemnogene abeparvovec treatment as well would be more effective than using the drug after the onset of symptoms. There is a need for conducting further analyses on the efficacy of screening in newborns prior to onasemnogene abeparvovec treatment.

Conclusions

Gene therapy with the use of onasemnogene abeparvovec is an innovative and effective method of treating spinal muscular atrophy, which is confirmed by clinical observations. It is extremely important to implement therapy in spinal muscular atrophy as early as possible and introduce universal screening tests of newborns for mutations in the SMN gene in order to detect the disease before the first symptoms appear. Onesamnogene abeparvovec has great potential to make significant progress in clinical outcomes among patients with spinal muscular atrophy in the future. Due to the novelty of the described gene therapy, further depth research in its field should be conducted.

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