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Safety profile of onasemnogene abeparvovec in children with spinal muscular atrophy

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Goal. To evaluate the safety profile of onasemnogene abeparvovec (Zolgensma®) gene replacement therapy in children with spinal muscular atrophy (SMA) in real clinical practice.

Materials and methods. The study included 30 SMA children who received gene replacement therapy with onasemnogene abeparvovec (Zolgensma®) from December 2020 to December 2021 at the Center for Pediatric Psychoneurology. All children had a diagnosis of SMA confirmed by molecular genetic methods, with no more than 3 copies of the *SMN2* gene and the absence of antibodies to the adeno-associated virus serotype 9. The safety profile was assessed by monitoring the clinical and laboratory data of the patients after administration of onasemnogene abeparvovec. Clinical events included all changes in the child's condition that could be associated with the administration of the drug (hyperthermia, decreased appetite, nausea, vomiting, stool disorders). Laboratory assessment included monitoring of complete blood count, biochemical blood tests, blood coagulation indices. The degree of laboratory changes was estimated according to common terminology criteria for adverse events (CTCAE version 5.0). **Results.** The safety profile of Zolgensma® was studied in 30 children aged from 3 to 39 months, with a weight of 5.2 kg to 14.2 kg. Twenty-eight (93.3%) children had at least one clinical event associated with the administration of the drug. Hyperthermia was observed in 24 (80%) children, nausea and vomiting in 18 (60%) children, decreased appetite in 20 (66.7%) children, stool changes in 4 (13.3%) children. Monitoring of laboratory parameters revealed thrombocytopenia and monocytosis in twenty-two (73.3%) children and neutropenia in twelve (40%) children in the general blood test. An increase in the level of transaminases was noted in all children, the CTCAE grade 1 was detected in fifteen (50%) children, the CTCAE grade 2 in 7 (23.3%) children, CTCAE grade 3 in 6 (20%) children, CTCAE grade 4 in 2 (6.7%) children. Children with CTCAE grade 3 required correction of the prednisolone dose up to 2 mg/kg per day for 2-4 weeks. Two children with CTCAE grade 4 required pulse therapy with methylprednisolone at a dose of 30 mg/kg per day. Regardless of the level of transaminases, no change in the level of total and direct bilirubin was observed in any case. A decrease in prothrombin time was observed in 14 (46.6%) children. An increase in the level of troponin I was detected in four (13.3%) children. In all cases of serious adverse events, according to laboratory parameteres, the clinical condition of the children remained stable. The average duration of prednisolone intake was 17.8 ± 6.6 weeks.

Conclusion. The safety profile of onasemnogene abeparvovec (Zolgensma®) in real clinical practice in children with SMA is presented.

Keywords: *spinal muscular atrophy; children; onasemnogene abeparvovec; Zolgensma; gene therapy; safety; side effects*

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Introduction

Spinal muscular atrophy (SMA) belongs to the group of hereditary neuromuscular diseases. Its major clinical manifestations are progressive muscle weakness and atrophy due to degeneration of α-motor neurons located in the anterior horns of the spinal cord. [1] The genetic cause of the disease is insufficient production of the survival motor neuron protein (SMN) due to a homozygous mutation in the *SMN1* gene located in the short arm of chromosome 5. Biallelic deletion of exon 7 or exons 7 and 8 are the most common (95% cases); sometimes a heterozygous deletion is combined with a point mutation (5% of cases). [2, 3] The existing reserve *SMN2* gene accounts for the production of only 10% of the functional SMN protein. [4]

There are several types of SMA, with different ages of the first symptoms onset and different severity of the motor function disorder:

- In type 0 SMA, severe signs of the disease appear as early as in utero, and most pediatric patients die in the first months after birth.
- Type 1 SMA occurs before the age of 6 months.
- Type 2 SMA occurs at the age of 6–18 months.
- Type 3 SMA occurs at the age of 18 months and older. [5]
- Type 4 SMA occurs in adults.

The incidence of SMA is 1 case per 6,000–10,000 newborns. [1]

Before the registration of disease-modifying therapy, the mortality rate in children with SMA was high. Most children with type 1 SMA (92%), the most severe type, need permanent ventilation after 1 year and did not survive to the age of 2 years. [6]

With the emergence of new types of the pathogenetic therapy, significant progress has been made in improving the clinical outcomes and long-term prognosis in patients with this disease. [7] There are several approaches to drug therapy of SMA in pediatric patients aimed at ensuring the production of SMN protein. [8] The optimal option is gene replacement therapy, which replaces the function of the missing or inactive *SMN1* gene due to the constant expression of the SMN protein. Drugs for gene replacement therapy include onasemnogene abeparvovec (Zolgensma®), the therapeutic effect of which is achieved with a single intravenous infusion. [9] Its high clinical efficacy in terms of patients' survival, achievement of motor development milestones, and prevention of further disease progression has been confirmed. [10–15]

The purpose of the study is to determine the safety profile of onasemnogene abeparvovec (OA) in pediatric patients with SMA who received gene replacement therapy.

Materials and methods

The study included 30 pediatric patients with SMA aged 3–39 months and weighing 5.2–14.2 kg who received gene replacement therapy with OA at the Center for Pediatric Psychoneurology from December 2020 to December 2021.

Inclusion criteria:

- Diagnosis of SMA confirmed by molecular genetic testing (presence of a biallelic deletion of exon 7 of the *SMN1* gene);
- ≤3 copies of the *SMN2* gene;
- <1:50 titer of anti-adenoassociated virus serotype 9 antibodies (ELISA in Viroclinics laboratory, the Netherlands); the assay should be carried out not later than 1 month before the planned date of OA administration;

- Signed Informed Consent for OA therapy from the parents;
- Conclusion of a federal council on the prescription of gene replacement therapy.

Exclusion criteria: failure to meet at least one inclusion criterion.

Gene replacement therapy was granted through several ways (supply of the drug through charity foundations, the state fund "Circle of Kindness") and the global Managed Access Program to AVXS-101.

Before OA administration, all patients underwent a standard examination:

- Complete blood count with WBC differential and platelet count;
- Blood biochemistry;
- Coagulation profile;
- Ultrasound examination of the abdominal cavity and kidneys; echocardiography; electrocardiogram.

Table 1

General characteristics of the examined patients

Parameters	*n*	%
Gender		
male	21	70
female	9	30
Type of spinal muscular atrophy		
1	22	73.3
2	8	26.7
Number of copies of the *SMN2* gene		
2	20	66.7
3	10	33.3
The period from the onset of symptoms to the confirmation of the diagnosis, month	2 (1; 4,5)	
Age at the time of administration of Zolgensma®		
under 1 year old	14	46.7
from 1 year to 2 years	10	33.3
older than 2 years	6	20.0
Median age at the time of Zolgensma®, administration , months	13.25 (6.75; 23.25)	
Body weight at the time of Zolgensma® administration of, kg	9.0 ± 2.8 (5.2-14.2)	
The presence of previous pathogenetic therapy		
yes	17	56.7
no	13	43.3
Previous pathogenetic therapy		
Nusinersen	11	36.7
Risdiplam	3	10.0
Branaplam	3	10.0

As specified in the gene replacement therapy protocol, 1 day before the administration of OA, all patients received hormone therapy with prednisolone at a dose of 1 mg/kg. In addition, gastroprotective drugs were prescribed to reduce the side effects of hormone therapy.

OA was administered at a standard dose of 1.1×10^{14} vector genomes per 1 kg of body weight by a 1-hour intravenous infusion.

The safety of the therapy was assessed by monitoring the clinical and laboratory parameters after the administration of OA. Clinical events included all changes in the condition of the child that could be associated with the drug (as described in SmPC): weakness, apathy, nausea, vomiting, altered bowel habits, loss of appetite or anorexia, and hyperthermia.

Laboratory monitoring included control of complete blood count, blood biochemistry, and coagulogram parameters 1 day after OA administration, then weekly for the first 1.5–2 months, then every 2 weeks until the reference values were obtained and hormone therapy was discontinued. Laboratory abnormalities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Statistical analysis of the results was performed using SPSS Statistics (IBM). The significance of differences (*P*) in all calculations was set at the level of 0.05 and lower.

Results

The general characteristics of the patients' sample are presented in **Table 1**. All 30 children had a homozygous deletion of exons 7 or exons 7–8 of the *SMN1* gene. Nineteen (86.4%) children with type 1 SMA had 2 copies of the *SMN2* gene and 3 (13.6%) children had 3 gene copies. In children with type 2 SMA, the distribution of the *SMN2* gene copies was reversed: 7 (87.5%) children had 3 copies of the *SMN2* gene, and 1 (12.5%) child had 2 *SMN2* gene copies. In 1 patient with a burdened family history of SMA, molecular genetic testing was performed at the pre-symptomatic stage of the disease; the diagnosis was established at the age of 14 days. One child with type 1 SMA with the onset of the disease at the age of 2 months was diagnosed only at the age of 1 year.

Due to the high heterogeneity of the sample, we analyzed the safety of gene replacement therapy depending on the age of the children. At the time of OA administration, all 30 patients had a satisfactory condition without signs of a bacterial and/or viral infection. According to the OA administration protocol, all pediatric patients started glucocorticoids (prednisolone) at a dose of 1 mg/kg/day one day before the OA infusion, and gastroprotective therapy with esomeprazole and aluminum phosphate at age-specific doses was initiated in parallel.

Changes in the clinical condition within 1 week after the administration of OA were noted in 28 (93.3%) patients; the clinical condition remained satisfactory in 2 (6.7%) children. The major clinical manifestations were recorded within 1 week after OA administration and included hyperthermia in 24 (80%) children, nausea and vomiting in 18 (60%), loss of appetite in 20 (66.7%), and altered bowel habits in 4 (13.3%).

Hyperthermia developed in 24 (80%) children on Days 1–4 after OA administration; in most cases (16/24; 66.7%), an increase in body temperature was noted on Day 3. The duration of hyperthermia averaged 2–3 days; antipyretics in age-related doses were used for febrile body temperature. No significant association of hyperthermia with the age at the time of administration of gene replacement therapy was found (P=0.117). Loss of appetite was observed in 20 (66.7%) patients during the first 4–5 days after OA administration and was more severe in children with dyspeptic symptoms (nausea, vomiting, altered bowel habits). Nausea and vomiting were also observed on Days 1–4 after OA administration in 18 (60%) children; their frequency did not exceed 1–2 episodes per day, and they resolved spontaneously by the end of Week 1. Three (10%) children required infusions of antiemetics. One (3.3%) child was switched to injectable prednisolone at a dose of 1 mg/kg/day for 5 days. In children under 1 year of age, nausea and vomiting were noted significantly more often than in children over 1 year of age (P=0.026). Altered bowel habits were observed only in 4 (13.3%) children during the first week after OA administration; they did not require specific treatment and resolved within 1–3 days.

Monitoring of laboratory parameters revealed changes in the complete blood count manifesting as thrombocytopenia, neutropenia, and monocytosis.

Thrombocytopenia was observed mainly at Weeks 1–2 after OA administration in 22 (73.3%) children, of whom CTCAE grade 1 event was recorded in 10 (45.5%), grade 2 in 8 (36.4%), and grade 3 in 4 (18.1%) children. In the vast majority of cases, platelet counts normalized at Weeks 2–3 after OA administration. It should be emphasized that there were no cases of clinical thrombocytopenia. No significant association between the presence of thrombocytopenia and CTCAE grade of thrombocytopenia with the age of OA administration was found.

Neutropenia was observed in 12 (40.0%) children, which is 2 times less common than thrombocytopenia; of the 12 cases, CTCAE grade 2 event was reported in 2 (16.7%) patients, grade 3 in 8 (66.6%), and grade 4 in 2 patients (16.7%). The most severe neutropenia was registered at Weeks 1–2 after the drug administration, which normalized by Weeks 2–4.

Monocytosis at Weeks 1–2 after OA administration was reported in 22 (73.3%) children. The timing of the onset of monocytosis was similar to that of changes in platelet and neutrophil counts. However, monocyte count took longer to normalize: it happened by Weeks 3–5 after OA administration. No association of neutropenia and monocytosis with the age of OA administration was identified.

Elevated liver transaminases were noted in all children; CTCAE grade 1 event (an elevation of ≤ 3 upper limits of normal [ULN]) was detected in 15 (50%) children, grade 2 (×3–5 ULN) in 7 (23.3%) patients, grade 3 (×5–20 ULN) in 6 (20%) patients, and grade 4 (>20 ULN) in 2 (6.7%) patients. Children with CTCAE grade 3 elevated transaminases required prednisolone dose adjustment to 2 mg/kg/day for 2–4 weeks, followed by a decrease to 1 mg/kg. Two children with a transaminase elevation >20 ULN required pulse therapy with methylprednisolone at a dose of 30 mg/kg/day; in one child it was conducted for 5 days and in the other child for 7 days (due to a transaminase elevation up to 2,000 IU/L and the absence of positive changes after administration of 5 doses). The clinical condition of children, regardless of the level of transaminase elevation, remained stable. A significant association between the age at the time of OA administration and the level of transaminase elevation was revealed: the younger the child, the lower the CTCAE grade (**Table 2**).

The average duration of prednisolone therapy until the normalization of the aspartate and alanine aminotransferases level was 17.8±6.6 weeks. Regardless of the transaminase elevation level, there were no cases of increased total and direct bilirubin. An increase in troponin I levels was detected in 4 (13.3%) children, mainly at Weeks 3–5 after OA administration. Follow-up tests within the next 2–4 weeks showed that the troponin I levels normalized. Electrocardiography and echocardiography revealed no pathology in all children.

Monitoring of blood coagulation parameters demonstrated a reduction in prothrombin time in 14 (46.6%) children, in most cases during the first week after gene therapy. The parameters normalized to reference values within 1–2 weeks. In serious adverse events related to the laboratory parameters, the clinical condition of the patients remained stable.

Table 2

Dependence of the degree of increase in the activity of transaminases on the age at the moment of Zolgensma® administration

Age	*n*	The degree of increase in transaminase activity			
		1 (1-3) × UNL	2 (3-5) × UNL	3 (-20) × UNL	4 >20 × UNL
Under 1 year	14	12 (40%)	2 (6.7%)	-	-
From 1 year to 2 years	10	1 (3.3%)	3 (10.0%)	4 (13.3%)	2 (6.7%)
Older than 2 years	6	2 (6.7%)	2 (6.7%)	2 (6.7%)	-

Note. UNL — Upper norm limit. $\chi^2 = 17.3$; $p = 0.05$

Discussion

The safety profile of gene replacement therapy with OA was studied in 30 pediatric patients aged 3 to 39 months with a body weight of 5.2 to 14.2 kg. Most children (93%) had at least one clinical event associated with the administration of OA: hyperthermia, nausea and vomiting, loss of appetite, and altered bowel habits. Clinical events were observed during the 1st week after OA administration and in some cases required symptomatic therapy. Monitoring of laboratory parameters revealed thrombocytopenia, monocytosis, and neutropenia in some children, and elevated transaminase levels in all children. The clinical condition of children, regardless of the level of transaminase elevation, remained stable. The dose of prednisolone was adjusted depending on the levels of transaminase elevation. Two children required pulse therapy with methylprednisolone at a dose of 30 mg/kg/day. It was found that the CTCAE grade of transaminase elevation is lower in younger children, which is consistent with the data of the international and Russian colleagues. [16, 17] It should be noted that in all cases of the serious adverse events related to the laboratory parameters abnormalities, the clinical condition of children remained stable.

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