DOI: 10.17650/2222-8721-2022-12-1-29-38

Experience of using gene replacement therapy with Zolgensma® (onasemnogene abeparvovec) in real clinical practice in Russia

S.B. Artemyeva, Yu.O. Papina, O.A. Shidlovskaya, A.V. Monakhova, D.V. Vlodavets

Research Clinical Pediatric Institute of Pirogov Russian National Research Medical University; 2 Taldomskaya St., Moscow 125412, Russia

Contacts: Svetlana Bronislavovna Artemyeva *artemievasb@gmail.com*

Objective: to analyze the safety and evaluate the effectiveness of therapy with onasemnogene abeparvovec in patients with spinal muscular atrophy in real clinical practice based on the experience of using the drug in the neuromuscular center of Research Clinical Pediatric Institute of Pirogov Russian National Research Medical University.

Materials and methods. Patients with spinal muscular atrophy received therapy with onasemnogene abeparvovec based on the prescription of the drug according to vital indications by a council of physicians of Federal institutions (the availability of the drug was carried out within the framework of the MAP Program (global program of managed access MAP to AVXS-101 for eligible patients in countries, where it is not approved by regulatory authorities (NCT03955679), through funding from the charitable foundations, as well as through funding from the state fund "Circle of Kindness". The drug tolerance was assessed and the analysis of side effects after drug administration was based on the criteria for adverse events (General criteria Adverse Event Terminology (CTCAE) v. 5.0) Patient motor function was assessed prior to treatment initiation and every 3–6 months after therapy using the Philadelphia Pediatric Hospital's CHOP INTEND scale, total motor development based on Hammersmith Hospital Neurological Assessment Scale in Young Children, Part 2 (HINE-2), and the acquisition of new motor skills.

Results. 41 children aged 5 to 47 months (weighing no more than 21 kg) received therapy with onasemnogene abeparvovec in the period from April 2020 to December 2021. Adverse events (hyperthermia, decreased appetite, nausea, vomiting) were registered in all patients with different degree of severity. Elevated levels of transaminases greater than 2 times the upper limit of the normal range were observed in 32 patients (78 %), thrombocytopenia in 9 patients (22 %). 15 patients (36 %) required a dose adjustment of corticosteroids.

17 patients underwent assessment of motor scales after 6 months, 10 children were assessed after a year. The average improvement on the HINE-2 scale was 3.3/4.4 points, respectively. The average improvement on the CHOP INTEND Scale was 7.1/9.4 points after 6/12 months of therapy.

Conclusion. The efficacy and safety of onasemnogene abeparvovec have been demonstrated in real clinical practice in the treatment of spinal muscular atrophy for children in different age groups with a body weight of no more than 21 kg.

Key words: spinal muscular atrophy, onasemnogene abeparvovec, Zolgensma®, safety, MAP program, increased transaminases, *SMN1* gene, gene replacement therapy

For citation: Artemyeva S.B., Papina Yu.O., Shidlovskaya O.A. et al. Experience of using gene replacement therapy with Zolgensma® (onasemnogene abeparvovec) in real clinical practice in Russia. Nervno-myshechnye bolezni = Neuromuscular Diseases 2022;12(1):29–38. (In Russ.). DOI: 10.17650/2222-8721-2022-12-1-29-38.

Introduction

Proximal spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease characterized by degeneration of alpha motor neurons in the anterior horns of the spinal cord, leading to progressive muscle weakness, muscle atrophy, and deformities of the spine and joints [1, 2]. The disease is caused by mutation in the *SMN1* (Survival Motor Neuron) gene localized on the long arm of chromosome 5 (5q13), which leads to a deficiency of the SMN protein [3, 4].

There are several types of proximal SMA, with different age of manifestation of the first clinical symptoms and different severity of movement disorder [5]. SMA type 1 is the most severe. It has a narrow therapeutic window for timely initiation of pathogenetic treatment and leads to early childhood mortality [6–8].

Availability of therapy targeting the disease root cause allows considerably slowing down the disease progression, thus improving the prognosis and preventing further complications [9]. On May 24 2019, US Food and Drug Administration (FDA) approved Zolgensma® (onasemnogene abeparvovec by AveXis Inc.; since September 2020 by Novartis Gene Therapies Inc.), the first gene replacement therapy for SMA in pediatric patients aged under 2 years [10]. The recommended dose is 1.1×10^{14} vector genomes (vg) per 1 kg of body weight administered as an intravenous infusion for 60 min [11].

In 2019, the Global Managed Access Program (GMAP) was started for Zolgensma® (onasemnogene abeparvovec) [12]. The product became available to eligible patients with SMA aged under 2 years in the countries where the product was not approved. In May 2020, the European Medicines Agency (EMA) approved the product for pediatric patients with SMA of different age groups with a body weight up to 21 kg [13].

The safety and efficacy of onasemnogene abeparvovec have been demonstrated in completed clinical trial START that included 15 pediatric patients who had a SMA onset in infancy (SMA type 1; age ≤8 months at baseline) [14] and also in STR1VE-US (22 patients aged ≤6 months with two *SMN2* copies) and STR1VE-EU (33 patients aged ≤6 months with one or two *SMN2* copies) [15, 16].

The clinical study data suggest that children who received onasemnogene abeparvovec demonstrated a rapid onset of therapeutic effect which enhanced with time, higher survival rates, improved motor function as assessed using CHOP INTEND, and significantly improved rates of achieving development milestones (e.g., the ability to hold head, to sit independently, or to stand and walk in some patients) compared to the natural SMA course in infants [14–16].

The most common adverse reactions to onasemnogene abeparvovec reported in the clinical trials were elevated hepatic transaminases, hepatotoxicity, vomit, and pyrexia [14–16].

The data from clinical practice suggest that there may be a greater number of adverse events when onasemnogene abeparvovec is used in older children, who often have received prior treatment with *SMN2* splicing modifiers (e.g., nusinersen, risdiplam). This requires close monitoring and further studies in a more extensive cohort of pediatric patients [17, 18].

A limited number of clinics in Russia have an experience of using Zolgensma®. For instance, recently an article has been published on a study of short-term safety and efficacy of onasemnogene abeparvovec in 10 patients in a hospital of Ekaterinburg [19].

In this paper, we describe the clinical experience with Zolgensma® in 41 patients with clinically and genetically verified diagnosis of proximal 5q SMA in the center for neuromuscular diseases of Autonomous Unit "Veltischev Research and Clinical Institute for Pediatrics" of the Pirogov Russian National Research Medical University.

The aim of the study was to analyze the safety and efficacy of Zolgensma® (onasemnogene abeparvovec) in patients with SMA in the real clinical practice.

Materials and methods

The study included 41 patients with SMA who received an infusion of onasemnogene abeparvovec in the Veltischev Research and Clinical Institute for Pediatrics from April 2020 to December 2021. SMA was diagnosed based on the clinical data and verified with a molecular and genetic testing in the Bochkov Research Center for Medical Genetics. To establish whether a patient was eligible for gene replacement therapy, all patients were tested for anti-AAV9 antibodies not less than 1 months prior to the planned Zolgensma® administration. The determination of anti-AAV9 antibodies in blood was performed by ELISA in the Viroclinics (the Netherlands). The legal representatives of the patients were informed of the onasemnogene abeparvovec mechanism of action and its possible side effects. They also signed the Informed Consent Form for non-approved drug use prior the therapy initiation. The issues of the need for active rehabilitation and correct positioning after the therapy were discussed, the availability of assistive technology was clarified.

Statistical processing of the data obtained was carried out using Microsoft Excel and Statistica 10.0. The quantitative data were expressed as mean values or medians ± root square mean. The Student's t-test was used to compare the mean values of the motor function by analyzing the significance level of p (two levels of statistical significance were established: $p = 0.01$ was regarded as a high significance and $p = 0.05$ was regarded as sufficient significance).

The dose of onasemnogene abeparvovec was calculated as follows: 1.1×10^{14} vg/kg body weight; the whole dose was administered for 1 hour via infusion pump. Twenty-four hours before Zolgensma® infusion, the patients received 1 mg/kg/day prednisolone, and it was continued depending on the laboratory parameters levels.

Safety assessment. All patients underwent a complete medical examination prior to the therapy, including laboratory data (complete blood count, clinical urinalysis, blood chemistry with parameters indicating the function of the liver, heart, and kidneys; if required, tests for hospital-acquired infections indicating the degree of disease activity), instrumental data (electrocardiography, echocardiography, abdominal ultrasound, and kidney ultrasound), and examinations by specialists (cardiologist, gastroenterologist, pulmonologist, orthopedist) for the respective disorders.

Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0 were used for safety evaluation [20]. The degree of laboratory parameter abnormalities were evaluated using CTCAE ver. 5.0 as well.

After the infusion, the patients were followed-up in the Neurological Department for 3 to 7 days. Later on, the laboratory data were followed-up weekly for 1 months, then one time

in two weeks for 2 months or until the values normalization. Additional tests were made if indicated.

The motor development was evaluated using the Hammersmith Infant Neurological Examination Part 2 (HINE-2) [21] and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) [22] before the treatment and 2, 4, and 6 months after it. Also, the age-specific motor skills were assessed in accordance with the WHO motor development milestones [23].

Results

Population characteristics. The data of 41 patients with SMA who received onasemnogene abeparvovec in the Veltischev Research and Clinical Institute for Pediatrics were included in the analysis. The patient body weight was ≤21 kg; the mean body weight was 9.8 (7.2–14.5) kg. SMA type 1 was diagnosed in 31 patients; the mean age of the onset of symptoms was 10 (2–20) weeks. SMA type 2 was diagnosed in 10 patients, with the disease onset after the age of 6 months.

Forty children had a homozygous deletion of exon 7 or 7–8 of the *SMN1* gene; one patient had a heterozygous deletion of exon 7 of the *SMN1* gene and two point mutations in the *SMN1* gene: pThr274lle (c.821C>T) in exon 6 and p.Glh154 = (c.462F>G) in exon 3. The number of copies of the *SMN2* gene was one.

Twenty patients had two copies of *SMN2* (all patients with SMA type 1); 19 patients had three gene copies (9 patients with SMA type 2 and 10 patients with SMA type 1); one patient had four gene copies in one patient with SMA type 1, and there was one *SMN2* copy in one patient with a heterozygous *SMN1* mutation.

The mean age at the initiation of treatment with onasemnogene abeparvovec was 20.3 (5–47) months.

Seventeen patients received previous nusinersen treatment with a positive effect on their motor abilities prior to the onasemnogene abeparvovec treatment. Eight patients received risdiplam as part of early access to the drug for 3–6 months with positive changes in their motor abilities and no side effects. One patient with poor motor abilities received 6 injections of nusinersen without a positive effect and was switched to risdiplam, which was continued for 3 months without positive changes either. Three patients took part in a clinical study of branaplam with a positive response but were switched to gene replacement therapy due to the early study termination. Twelve patients were naive to pathogenetic treatment before the start of onasemnogene abeparvovec.

The patients received onasemnogene abeparvovec as part of GMAP (Global Managed Access Program to AVXS-101 for eligible patients in countries where it is not authorized [NCT03955679]) and with funding from charitable foundations and state fund Circle of Kindness based on the prescription of the drug by the decision of the experts from the federal hospitals [24].

The patient sample characteristics are presented in Table 1.

Table 1. *Baseline patients' characteristics (n = 41)*

Parameter	Value
Sex, *n*: male female	 20 21
Spinal muscular atrophy type I, *n* Spinal muscular atrophy type II, *n*	31 10
Average age at infusion of onasemnogene abeparvovec (range), months	20,3 (5–47)
Number of copies of the *SMN2* genes, *n*: 2 3 4 1 + point mutations	 20 19 1 1
Previous pathogenetic therapy, *n*: yes no	 29 12
Body weight at infusion of onasemnogene abeparvovec, kg	9,8 (7,2–14,5)

Note. *SD – standard deviation.*

Tolerability evaluation results. Table 2 shows the clinical manifestations in the early follow-up period during 7 days after the infusion.

Table 2. *Early clinical manifestations of adverse reactions after onasemnogene abeparvovec administration depending on the age at infusion*

Clinical symptom	Age at infusion less than 1 year (*n* = 7)	Age at infusion over 1 year (*n* = 34)
Pyrexia within 1–3 days	2	33
Decreased appetite	7	34
Vomiting	1	10
Short-term rash	2	–

All children had a decrease in appetite for 3–5 days; 11 children experienced vomiting after taking prednisolone tablets, which required replacing oral dosing with intramuscular injections of prednisolone at a dose of 1 mg/kg of body weight. Four patients required infusion therapy with 5 % glucose solution for hydration. Short-term febrile temperatures up to 38.0–38.5 °C on Day 2–3 was observed in 35 patients but did not require any additional therapy. Transient clinical symptoms during the first week after the infusion were reported in older children.

Abnormal laboratory findings are given in Table 3. Follow-up of laboratory data identified elevated transaminases (ALT, AST) of varying grades.

In 9 patients the transaminase elevation did not exceed ×2 upper limit of normal (ULN), so they were treated with corticosteroids for ≤3 months.

Most patients had elevated transaminases without significant liver dysfunction and with normal bilirubin values, except for one patient.

Table 3. *Changes of laboratory parameters after infusion of onasemnogene abeparvovec*

Laboratory parameter	Number of patients	Comments
ALT, AST <5 ULN	12	Clinical symptoms were not registered, bilirubin level was within normal range. Corticosteroids' dosage wasn't modified
AST, ALT >5 ULN <20	11	Corticosteroids' dosage was modified to 2 mg/kg in 7 patients
ALT, AST >20 ULN	8	Clinical symptoms were not registered, levels of bilirubin were within normal range in 7 patients. All children received pulse-therapy with methylprednisolone
GGT >2 ULN	14	An increase in gammaglutamyltransferase level was registered 2–3 weeks after an increase in transaminase levels >5 times
Thrombocytes <100 × 10^9/l	9	Thrombocytopenia was observed in the first week after infusion in 7 patients, wasn't accompanied by clinical symptoms and didn't require additional treatment. 2 patients had clinically significant symptoms
Troponin I	3	All patients underwent electrocardiography and echocardiography, none of them had heart complications, parameters returned to normal during re-tests
Prothrombin	1	A change in the level of prothrombin was registered in 1 patient with clinical symptoms of drug-induced liver injury

Note. *ULN – upper limit of normal; ALT – alanine aminotransferase; AST – aspartate aminotransferase.*

Out of 41 patients in this cohorts, 6 subjects were in a poor physical condition and had a hospital-acquired infection. These patients had history of recurrent pneumonias, long-term ICU stay with IVL, and long-term enteral feeding or gastrostomy tube feeding, and also poor motor abilities at baseline (low score on the scales). After a thorough examination and management of inflammation associated with the hospital-acquired infection, the patients received an infusion of onasemnogene abeparvovec. The characteristics of this group of the patients are shown in Table 4.

All 6 patients received 1 mg/kg of prednisolone; in three of them the dose was up-titrated to 2 mg/kg due to elevated transaminases. One patient from this group required pulse steroid therapy, but despite the treatment the condition kept on worsening; jaundice of the skin, swelling, and increased bilirubin appeared; anemia and coagulation disorders with a tendency towards hypercoagulation developed. The patient was consulted by a hepatologist; drug-induced liver injury was diagnosed. To reverse the abnormalities, the patient received plasma infusions and packed RBCs, as well as antithrombin III to prevent thrombotic and thromboembolic events. In three weeks, the child's condition was stabilized; in two months the levels of transaminases did not exceed ×3 ULN. Therapy with corticosteriods 5 mg/day is planned to be continued.

None of the patients demonstrated activation of a chronic infection while on corticosteroids; however, acute respiratory

Table 4. *Severe patients with baseline nosocomial infection*

Age at infusion of onasemnogene abeparvovec, months	Previous pathogenetic therapy	HINE-2 before/after 2 months	CHOP INTEND before/after 2 months	Increased transaminases level (upper limit of normal)	Significant adverse events	Dosages of steroids
17	Risdiplam	2/2	18/21	>5	Anemia, coagulogram was normal	1 mg
13	Nusinersen	1/1	8/9	<2	None	1 mg
15	Risdiplam	2/4	31/40	>20	None	1.2 mg
28	Nusinersen (6), risdiplam	1/ –	12/ –	>20	Drug-induced liver injury with moderate changes, nephropathy, edema, coagulopathy, anemia	1.2 mg, pulse therapy
24	Nusinersen since 5 months	7/ –	39/ –	>8	Нет	1 мг
20	Risdiplam since 3 months	7/ –	34/ –	>10	None	1.2 mg

Note. *"–" – assessment of patients' motor skills has not been carried out.*

viral infections were common in the follow-up, which affected the enzyme levels negatively.

In three patients, motor function was assessed 2 months after the infusion; there was a slow positive trend, despite the poor motor abilities at baseline.

Evaluation of onasemnogene abeparvovec efficacy. Motor activity was assessed using CHOP INTEND and HINE-2 at baseline before the start of therapy and after 6 and 12 months from the start of the therapy.

Assessment by CHOP INTEND score. A total of 17 patients were assessed 6 months after the infusion of onasemnogene abeparvovec. The CHOP INTEND mean score increased from 48.0 ± 11.8 to 55.1 ± 8.9 points (Fig. 1). The value changed by 7.1 points (p <0.05). There was a >4 point improvement (considered clinically significant [22, 25]). Two patients reached the maximum number of points on the scale (64 points); one patient showed no improvement in points, despite an increase in muscle strength in the limbs, due to an increase in deformities (scoliosis and contractures); the other patient showed a decrease in CHOP INTEND score, but there was an increase in HINE-2 score.

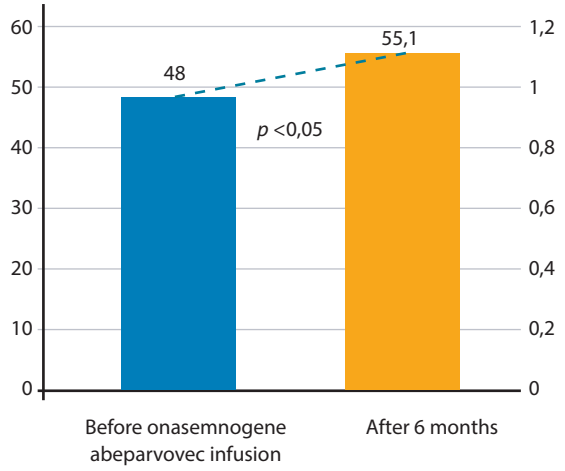

Fig. 1. *Assessment of motor activity according to the CHOP INTEND scale before the infusion of onasemnogene abeparvovec and after 6 months, average score (n = 17). CHOP INTEND – Children's hospital of Philadelphia infant test of neuromuscular disorders*

Assessment using HINE-2. A total of 17 patients were assessed 6 months after the infusion of onasemnogene abeparvovec (Fig. 2). None of the patients showed a regress in the motor abilities by this scale. The mean value increased from 10.3 ± 5.4 to 13.6 ± 5.3 points. A mean HINE-2 change was 3.3 points (p <0.01).

Assessment using CHOP INTEND and HINE-2 in 12 months. The patients continue to improve motor skills 12 months after the infusion of onasemnogene abeparvovec (Fig. 3). The data of 10 patients were analyzed. The mean values of motor activity assessment by CHOP INTEND increased from 50.5 ± 9.1 to 59.9 ± 3.7 points; the change was 9.4 points (p <0.05). The score by HINE-2 changed from 10.8 ± 5.1 to 15.2 ± 4.2, and the change was 4.4 points (p <0.01).

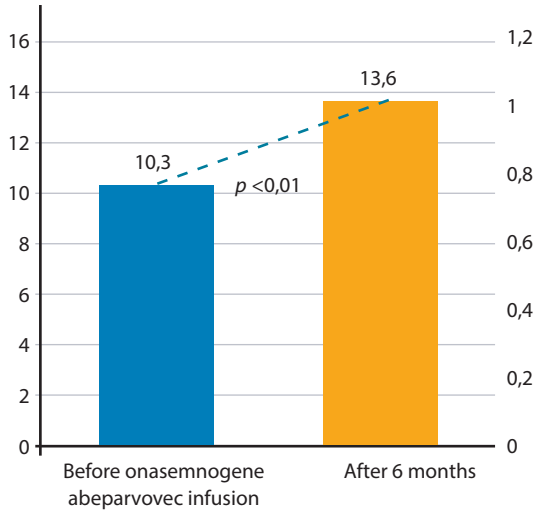

Fig. 2. *Assessment of motor activity according to the HINE-2 scale before the infusion of onasemnogene abeparvovec and after 6 months, average score (n = 17). HINE-2 – Hammersmith infant neurological examination, part 2*

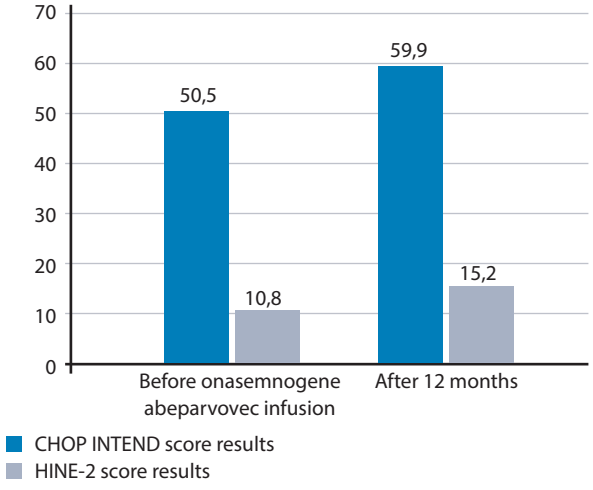

Fig. 3. *Assessment of motor function score results according to the HINE-2 and CHOP INTEND scales before and in 1 year after onasemnogene abeparvovec infusion (n = 10). HINE-2 – Hammersmith infant neurological examination, part 2; CHOP INTEND – Children's hospital of Philadelphia infant test of neuromuscular disorders*

Discussion

This paper sums up the experience with gene replacement therapy for patients with SMA in Russia.

The efficacy and safety of onasemnogene abeparvovec in patients with SMA in routine clinical practice were evaluated. The changes in the motor abilities of patients with SMA were described in 6 and 12 months.

It should be noted that the sample of patients who received gene replacement therapy in our hospital was heterogeneous by age and body weight and included patients with different baseline motor abilities. 70 % of children received previous pathogenetic therapy with various drug products.

Elevated transaminases were detected in all patients; however, clinically significant liver damage with impaired bilirubin metabolism and synthetic liver function was registered in only one patient. Seven patients (17 %) required an up-titration of the corticosteroid dose to 2 mg/kg; eight (19 %) patients with elevated transaminases >20 times required pulse therapy with methylprednisolone 20 mg/kg for 3 days, followed by dose tapering as the level of liver enzymes normalized. Although the exact mechanism of hepatotoxicity is not clear, it is thought to be an immune reaction associated with the uptake of viral vectors by hepatocytes. Prednisolone 24 hours before and after the infusion of gene replacement therapy is used to diminish this effect [26, 27].

Thrombocytopenia was observed on the first week after infusion in 9 patients; it was asymptomatic and did not require additional treatment. One patient with critical decrease in platelet counts developed clinical symptoms on the skin manifesting as subcutaneous hemorrhages on the thighs and on the abdomen in places of compression during the first week after the administration of onasemnogene abeparvovec 11–21–43 × 10^9/L (ref.: 127–520). No mucosal or internal bleeding was observed. The coagulogram remained within the normal range; the patient's state of health remained satisfactory. Elevated liver enzymes did not require corticosteroid dose modification. One week later, this patient's platelet count rose to 150 × 10^9/L, and no new skin lesions were noted.

Moderately to severely elevated transaminases were more often noted on Weeks 2–4 after the administration of onasemnogene abeparvovec with a gradual normalization of the transaminase levels to ≤2 ULN.

In two patients, a repeated increase in the level of liver enzymes was registered on Week 8, which was also noted by other researchers [19, 26].

The literature describes isolated cases of more serious disorders such as subacute liver injury followed by partial fibrosis, as well as isolated cases of thrombotic microangiopathy [28, 29], which is reflected, among other things, in the Package Leaflet [30].

In order to timely identify possible complications and correct hormone therapy, monitoring of patients who received gene replacement therapy is required, with an assessment of laboratory parameters.

In clinical study SPRINT, it was shown that early administration of gene replacement therapy, before the onset of symptoms, has proven advantages in terms of patients achieving age-appropriate motor skills [31, 32]. In addition, the use of gene replacement therapy in patients with SMA at an earlier age may reduce the risk of adverse events. A similar conclusion can be drawn based on the results of START clinical trial, where the use of the drug product was studied in patients with SMA type 1 aged up to 8 months. The data obtained suggest that elevated liver enzymes was not severe and did not require high doses of corticosteroids [14]. In our cohort, only three subjects received an onasemnogene abeparvovec infusion before the age of 8 months, one of whom had previously received risdiplam and another one received nusinersen. In all three patients, there was no increase in the level of liver enzymes >2 ULN. None of the patients required an increase in the dose of corticosteroids; the average duration of corticosteroid use in patients of this age group was 2.0–2.5 months.

In the real-world clinical practice, the use of onasemnogene abeparvovec in older children with SMA and in children with SMA with previous use of other pathogenetic therapy is associated in some cases with higher adverse events incidence rate accompanied by hyperenzymemia and hepatotoxicity [17, 18, 27]. The experience of our hospital also shows a trend towards an increase in the level of liver enzymes in this category of patients, but most of these laboratory changes, as previously noted, were asymptomatic. Adverse events, both clinical and laboratory, are more often reported in patients in poor condition, i.e. with chronic infection, with tracheostomy or gastrostomy, or poor motor skills at baseline, but they may experience an improvement in motor abilities anyway. The follow-up of these patients is currently short; the risk/benefits profile of gene replacement therapy in this category of patients requires further monitoring with a subsequent assessment of feasibility of this type of therapy.

It is impossible to determine conclusive predictors of significant adverse events after the use of gene replacement therapy at this stage. These issues require further research.

Thus, today there is ever more clinical and real-world data indicating the long-term efficacy and safety of single-use gene replacement therapy in patients with various types of SMA [33, 34], which has been confirmed in our observations as well.

Conclusion

The efficacy and safety of onasemnogene abeparvovec in the real-world clinical practice in the treatment of SMA for pediatric patients in different age groups weighing not more than 21 kg has been demonstrated.

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Authors' contributions
S.B. Artemyeva: patient management, analysis of the data obtained, writing the article;
O.A. Shidlovskaya, A.V. Monakhova: assessment on the HINE-2 and CHOP INTEND scales;
Yu.O. Papina: patient management, assessment on the HINE-2 and CHOP INTEND scales;
D.V. Vlodavets: coordination of the study and informed consent with the local ethics committee, writing an article, editing the article.

ORCID of authors
S.B. Artemyeva: https://orcid.org/0000-0002-8876-7462
O.A. Shidlovskaya: https://orcid.org/0000-0003-2017-1651
Yu.O. Papina: https://orcid.org/0000-0003-3794-6855
A.V. Monakhova: https://orcid.org/0000-0001-9828-9348
D.V. Vlodavets: https://orcid.org/0000-0003-2635-2752

Conflict of interest. The authors declare no conflict of interest.

Financing. The study was performed without external funding.

Compliance with the rights of patients and the rules of bioethics. All patients or their legal representatives signed an informed consent to participate in the study and publish the data.

Article submitted: 21.12.2021. **Accepted for publication:** 27.01.2022.