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Short-Term Safety and Efficacy of Onasemnogene Abeparvovec in 10 Patients with Spinal Muscular Atrophy: Cohort Study

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Background. *The efficacy and safety of onasemnogene abeparvovec have been demonstrated in patients with spinal muscular atrophy (SMA) in several clinical and observational studies. Gene replacement therapy results in Russian patients with SMA is not investigated yet.* ***Objective. The aim of the study*** *is to study the safety and efficacy of onasemnogene abeparvovec in children with SMA in real clinical practice.* ***Methods.*** *The study included patients with proximal 5q SMA administered with onasemnogene abeparvovec. Diagnosis was verified by biallelic deletion in the 7th exon of the SMN1 gene. Gene replacement therapy was administered according to the decision of neurologists consensus in case of the absence of antibodies to the adeno-associated serotype 9 virus. The therapy safety was estimated via clinical and laboratory data from the hospital (at least 7 days) and from outpatient departments (at least 60 days). Efficacy was estimated via CHOP INTEND scale and mastering new motor skills ⩾ 6 months after therapy onset.* ***Results.*** *Treatment outcomes were studied in 10 SMA patients aged 19 months (15; 21). All patients developed at least one clinical manifestation (hyperthermia, vomiting, lethargy and/or loose stool) associated with drug administration during the first week of follow-up. Increased hepatic transaminases activity and monocytosis was recorded in all patients, thrombocytopenia — in 9, neutropenia — in 5, increased troponin I concentration — in 3. In three cases it was necessary to increase the oral prednisolone dose of to 2 mg/kg, in one case — the dexamethasone pulse therapy dose. The therapy efficacy was monitored ⩾ 6 months after therapy onset via the CHOP INTEND scale in 2 patients (scores increased by 32 and 19 points, respectively), and via mastering new motor skills in 8 patients (positive dynamics was noted in 7 cases).* ***Conclusion.*** *The onasemnogene abeparvovec is relatively safe and quite effective for using in real clinical practice.*

Keywords: *spinal muscular atrophy, children, onasemnogene abeparvovec, safety, liver transaminase, efficacy, CHOP INTEND*

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BACKGROUND

In recent years, a significant breakthrough has been made in the treatment of patients with spinal muscular atrophy (SMA), a disease in which survival motor neuron (SMN) protein deficiency leads to their irreversible degeneration in the spinal cord and brain stem nuclei [1]. Until now, several medicinal products have been developed and put into practice to increase the SMN levels in motor neurons. Of particular interest to the medical community is gene replacement therapy in patients with SMA involving the transfer of the SMN-encoding gene. The medicinal product used for such therapy, onasemnogene abeparvovec, is based on an adeno-associated viral vector carrying a functional copy of the *SMN1* gene [2]. The medicinal product is administered once by intravenous infusion and then penetrates the blood-brain barrier to reach the target cells [3]. The efficacy and safety of onasemnogene abeparvovec have been demonstrated in several clinical trials that have clearly shown the benefits of gene replacement therapy [4, 5]. However, there are few studies on the use of gene replacement therapy in SMA in real-life clinical practice [6, 7] and none in the Russian practice. The need for such research is dictated by the relevance of data regarding the safety and outcomes of gene replacement therapy in view of the future therapy access facilitation, among other things, for the development of the algorithms for its use.

Study Objective

The objective of this study was to evaluate the short-term efficacy and safety of onasemnogene abeparvovec in pediatric patients with SMA in real-life clinical practice.

METHODS

Study Design

We conducted a real-world retrospective cohort study of the gene replacement therapy safety and efficacy.

Study Settings

The study enrolled patients admitted to the Neurology Department of the Regional Children's Clinical Hospital (Yekaterinburg) from December 1, 2020 till August 20, 2021. The planned outcomes were reported in the last patient up to August 30, 2021. Molecular genetic testing for biallelic deletion in the *SMN1* gene was conducted in the laboratory of the Research Center for Medical Genetics (Moscow) or the Molecular Genetic Laboratory of the Republican Medical Genetics Center (Ufa).

Eligibility Criteria

Inclusion Criteria

- Patients with 5q SMA.
- Indications for the use of onasemnogene abeparvovec.
- Voluntary informed consent for treatment and examination provided by the legal representative.

All of the participants had a genetically confirmed diagnosis of SMA based on the detection of biallelic deletion of *SMN1* gene exon 7 by real-time polymerase chain reaction [8]. If the onset of the muscle weakness symptoms occurred before the age of 6 months, the disease was classified as SMA type 1, and if the onset occurred at ⩾ 6 months, it was classified as SMA type 2.

Gene replacement therapy was prescribed based on the decision of the board of neurologists. The medicinal product was prescribed if there were no antibodies to adeno-associated virus serotype 9 (AAV9), as per the package leaflet [3]. The determination of anti-AAV9 antibodies in blood was performed by ELISA in the Viroclinics (the Netherlands). According to the gene replacement therapy protocol, prednisolone was administered at 1 mg/kg/day 24 hours before the infusion of onasemnogene abeparvovec [3]. The dose of onasemnogene abeparvovec was calculated according to the following formula: 1.1×10^{14} viral genomes per 1 kg of patient's body weight. The entire dose of the medicinal product was administered by intravenous drip infusion over 1 hour [3].

Exclusion Criteria

Not stipulated.

Withdrawal Criteria

Not stipulated.

Study Endpoints

Therapy Safety Evaluation

The safety of the gene replacement therapy was evaluated based on the clinical events (any worsening in the patient's state of health related to the administration of the study drug as judged by the attending physician) and laboratory findings observed after the administration of onasemnogene abeparvovec in the hospital within the first week and on day 7, respectively, once a week afterwards within the first month of follow-up in the outpatient settings, and at least once every 14 days until all the parameters reached the reference values, but at least within 60 days after the administration of the study drug. Serious clinical adverse events were defined as any conditions that resulted in the patient's hospitalization and/or death.

Laboratory safety monitoring included the determination of the platelet, neutrophil, and relative monocyte counts, concentrations of total bilirubin and troponin I, gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and prothrombin time (Table 1). The first laboratory monitoring was performed during the patient's stay in the hospital, and follow-up tests were performed by the laboratories in the home area. The information on the therapy safety was retrieved from the patients' medical records (laboratory reports).

To identify the factors associated with the most severe adverse events based on the laboratory findings, the patients were divided into 2 groups based on their maximum elevation in the transaminase (AST and/or ALT) activity — those with the values of < 5 or ⩾ 5 ULN. The groups were compared by their anthropometric parameters, age, sex, and SMA characteristics.

Table 1. Laboratory criteria for onasemnogene abeparvovec side effects

Parameters	Criteria
Platelets	$< 120 \times 10^9$/L
Neutrophils	$< 1.3 \times 10^9$/L
Monocytes	> 11%
Total bilirubin	> 20 mmol/L
ALT	> 2 ULN
AST	> 2 ULN
GGT	> 92 U/L
Troponin I	> 1.0 ng/mL
Prothrombin time	< 9.5 sec

Note. UNL (ВГН) — upper normal level. ALT (АЛТ) — alanine transaminase; AST (АСТ) — aspartate transaminase; GGT (ГГТП) — gammaglutamyltransferase.
Threshold values are given according to reference range used in the laboratory of Regional Children's Clinical Hospital (Ekaterinburg).

Therapy Efficacy Evaluation

Before the initiation of therapy and ⩾ 6 months after the therapy, the patients' functional status was assessed by the CHOP INTEND scale (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) [8]. The efficacy of therapy with onasemnogene abeparvovec was also assessed by mastering new motor skills (holding up the head, rotating the trunk, sitting with support, sitting without support, standing with support, standing without support). The child's legal representatives were asked to report those during a free discussion over the phone or video call ⩾ 6 months after the administration of the study drug (the assessment by the scale, unstructured interview, and interpretation of its results were performed by K.S. Nevmerzhitskaya).

Statistical Procedures

Sample Size Calculation

The sample size was not pre-calculated.

Statistical Methods

STATISTICA software suite, version 10, (StatSoft Inc, USA) was used to describe the data. The quantitative parameters were described using the median (25th; 75th percentiles).

Ethical Review

The study protocol was not subjected to ethical review.

RESULTS

Study Sample (Groups) Characteristics

During the study, 10 patients with SMA aged 19 (15; 21) months were hospitalized to undergo gene replacement therapy with onasemnogene abeparvovec. Six of the children were diagnosed with SMA type 1, and four patients had 2 copies of the SMN2 gene (Table 2). The duration of the disease from the onset of the first symptoms to the administration of the medicinal product was 12.5 (9; 14) months. Four children had been treated with nusinersen before onasemnogene abeparvovec. The median body weight at the initiation of the therapy was 9.3 (8.8; 10.3) kg.

Evaluation of the Gene Replacement Therapy Safety

All of the patients tolerated the intravenous administration of onasemnogene abeparvovec fairly well. Within the first 7 days after the infusion, all of the children had at least one clinical event related to the administration of the medicinal product as judged by the attending physician, including hyperthermia (38.2–39.4 °C) in 9 patients, vomiting in 7, loss of appetite and overall health deterioration in 5, and liquid stools in one patient. In each of the cases, the duration of these symptoms was up to 3 days, and symptomatic therapy was required in all of the cases (antipyretics in 9 patients and antiemetics in three patients). The clinical parameters of the therapy safety were monitored over the entire follow-up period (median duration — 7 (4; 8) months), but the clinical events did not recur in any of the cases.

Laboratory safety parameters were monitored until all of the studied laboratory parameters normalized; the duration was 5 (4; 7) months. In 9 out of the 10 patients, safety monitoring had been completed by the last data-cutoff date. One patient continued to be followed-up due to persistent elevation in transaminase activity. All of the patients had 3 to 6 laboratory abnormalities during the follow-up period (Table 3). The earliest abnormalities to be reported were thrombocytopenia and monocytosis.

In 6 patients, the decrease in the platelet count was detected as early as during the first laboratory monitoring on day 7 after the infusion, but this parameter also normalized earlier than the other ones. Thrombocytopenia was not associated with signs of bleeding and did not require additional therapy. The most severe and persistent were the changes in the liver transaminase (AST and ALT, but

Table 2. Characteristics of SMA patients at onasemnogene abeparvovec therapy initiation

No.	Sex	SMA type	Number of SMN2 copies, abs.	CHOP INTEND score	Age at the onset of SMA symptoms, months	Age, months*	Body weight, kg*
1	F	2	3	22	10	23	11.5
2	F	1	3	10	5	18	8.8
3	F	2	2	38	10	21	9.5
4	F	2	2	34	6	20	8.5
5	M	2	3	43	7	15	10.3
6	M	1	3	18	3	15	9.1
7	F	1	3	6	1	9	6.6
8	M	1	3	20	4	20	8.8
9	F	1	2	24	1	8	11.8
10	M	1	2	47	3	36	10.3

Note. The order of patients in the list is given according to the order of onasemnogene abeparvovec infusions. F (Ж) — female; M (М) — male. SMA (СМА) — spinal muscular atrophy. CHOP INTEND — Children's hospital of Philadelphia infant test of neuromuscular disorders. <*> — at the time of gene replacement therapy initiation.

not GGT) activity. No difference was found in the baseline characteristics of the patients with different maximum liver enzyme activity (Table 4).

Two patients had a two-wave elevation in the transaminase activity, where the first peak was followed by a period of decrease in the enzyme activity with a subsequent significant elevation. Three patients required the dose of oral prednisolone to be increased to 2 mg/kg on weeks 3 and 4 after the infusion of onasemnogene abeparvovec due to an elevation in ALT/AST activity to ⩾ 10 ULN. One patient underwent pulse therapy with dexamethasone over 5 days due to ALT/AST elevation to > 28 ULN, with a subsequent significant decrease in the liver enzyme activity.

The total duration of therapy with glucocorticosteroids (GCSs) in the patients who underwent safety monitoring within the scheduled timeframe (n = 9) was 14 (10.5; 23) weeks. This therapy was discontinued after the liver transaminase activity decreased to < 2 ULN. During the therapy with GCSs, the liver transaminase values returned back to normal in all of the patients.

None of the patients had clinical signs of body organ and system insufficiency. No serious clinical adverse events resulting in patient's hospitalization and/or death were reported during the therapy outcome follow-up period.

Evaluation of Gene Replacement Therapy Efficacy

At the baseline, the motor function score by the CHOP INTEND scale was 23 (18; 38) (see details in Table 2). The efficacy of the therapy by the CHOP INTEND scale in the period of ⩾ 6 months was monitored in two patients. An increase in the score by 32 (patient No. 3) and 19 (patient No. 1) points, respectively, was noted. In the other cases, the patients could not be examined due to the remoteness of their home and/or due to the transportation limitations caused by the spread of COVID-19.

Most of the children could sit before the initiation of the gene replacement therapy (one child could sit without support), four children could only hold up their heads, and one child (patient No. 7) had no motor skills. The development of motor skills in the period of ⩾ 6 months was observed in 8 patients (the age at the administration of gene replacement therapy was 15 to 23 months), and in 7 cases, the formation of new motor skills was noted. One child (patient No. 7) did not demonstrate any new motor skills,

Table 3. Laboratory changes in SMA patients after onasemnogene abeparvovec infusion (n = 10)

Parameter	Patients with an abnormality, abs.	Maximum abnormality value	Time to maximum abnormality, median (25th P; 75th P), weeks	Time to parameter normalization, median (25th P; 75th P), weeks
Platelets, $\times 10^9$/L	9	79 (62; 103)	1 (1; 2)	2 (2; 3)
Neutrophils, $\times 10^9$/L	5	1.06 (1.05; 1.09)	3 (1; 7)	3 (2; 8)
Monocytes, %	10	21.4 (17.2; 25.4)	1 (1; 2)	5 (3; 6)
Total bilirubin, mmol/L	0	–	–	–
ALT, U/L	10	198.7 (104.0; 545.2)	3.5 (1; 5)	11.5 (4; 18)
AST, U/L	10	201.5 (153.0; 609.7)	3 (1; 5)	12 (4; 15)
GGT, U/L	0	–	–	–
Troponin I, ng/mL	3	2.6 (2.0; 3.6)	7 (4; 17)	18 (8; 22)
Prothrombin time, sec	0	–	–	–

Note. You can find threshold values in Table 1.

Table 4. Baseline characteristics of SMA patients with different maximal transaminase activity (AST and/or ALT) after onasemnogene abeparvovec infusion

Attribute	Patients with ALT/AST < 5 ULN, n = 3	Patients with ALT/AST ⩾ 5 ULN, n = 7
Sex, M/F	3/0	6/1
Age, months	15 (15; 36)	20 (9; 21)
Body weight, kg	10.3 (9.1; 10.3)	8.8 (8.5; 11.5)
Dose of onasemnogene abeparvovec, mL	57.0 (52.6; 57.2)	48.7 (46.7; 63.3)
SMA type, 1/2	2/1	4/3
Number of *SMN2* copies, 2/3	1/2	3/4
Duration of therapy with GCSs, months	9 (7; 11)	18 (12; 26)

Note. GCS (ГКС) — glucocorticosteroids, usage period before gene replacement therapy initiation.

Table 5. Dynamics of basic motor skills 6 months after onasemnogene abeparvovec therapy

Case No.	Level of motor skills	
	Baseline	At ⩾ 6 months
1	Sits with support	Sits without support
2	Head control	Sits with support
3	Sits with support	Stands with support
4	Sits with support	Stands with support
5	Sits without support	Stands with support
6	Head control	Sits with support
7	No motor skills	No motor skills
8	Head control	Sits with support
9	Head control	Insufficient time interval for assessment
10	Sits with support	Insufficient time interval for assessment

since their baseline level of motor activity was very low due to the rapidly progressing severe SMA (Table 5).

DISCUSSION

Summary of Primary Study Findings

Gene replacement therapy with onasemnogene abeparvovec in pediatric patients with SMA in real-life clinical practice is relatively safe and fairly efficient in most patients at short-term follow-up.

Study Limitations

The presented study sample of 10 patients with the follow-up duration of less than 1 year demonstrates the most common and the earliest adverse events. Besides, it may be challenging to obtain laboratory findings from various laboratories located in the patients' home areas; it is difficult to interpret any changes in such results. It is also important to note that the safety data after ⩾ 6 months as assessed by the CHOP INTEND scale were only obtained for two patients, and the motor skills assessments — in eight patients. Therefore, these data are not sufficient for a full assessment of the therapy efficacy.

Interpretation of Study Results

This article is the first one to present the outcomes of using onasemnogene abeparvovec in real-life clinical practice in 10 Russian patients with SMA.

Despite the immune response to AAV9 [9] manifested as a transient liver transaminase elevation, none of the 10 patients showed clinical signs of hepatic failure during the entire period of hyperenzymemia. The dose-dependent effect of the therapy on the transaminase activity that had been described earlier was not observed [6]. After a course of therapy with GCSs, the ALT and AST activity decreased to the reference values in different patients within 2 to 25 weeks. No serious clinical adverse events associated with onasemnogene abeparvovec were reported. Besides, the follow-up showed a significant efficacy of the therapy: 7 out of the 8 patients with at least 6 months of follow-up after the gene replacement therapy demonstrated a significant improvement in their motor skills. Further accumulation of data from a long-term follow-up of patients with regular efficacy monitoring is a valuable tool for establishing the profile of an optimal patient for onasemnogene abeparvovec therapy. Timely provision of therapy is nowadays an undisputable trend since the findings of clinical trials and pilot projects aimed at SMA detection have demonstrated that the disease-modifying therapy yields best results in presymptomatic patients; motor development in such children may be almost the same as in their healthy age-mates [10–12]. Therefore, early diagnosis of SMA, specifically before the onset of any symptoms, becomes particularly important during the neonatal screening.

CONCLUSION

Gene replacement therapy is a promising method of etiopathogenetic therapy in SMA. Our experience has demonstrated that therapy with onasemnogene abeparvovec can improve motor skills in SMA types 1 and 2 even in patients older than 12 months of age and at the same time is fairly safe.

FINANCING SOURCE

Not declared.

DISCLOSURE OF INTEREST

Kristina S. Nevmerzhitskaya — speaker in Novartis (lecturing for target audience).

Elena Yu. Sapego — speaker in Novartis (lecturing for target audience).

Daria A. Morozova confirmed the absence of a reportable conflict of interests.

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