**Anna A. Kokorina1, Sergei S. Nikitin2**

1 Children’s treatment and rehabilitation center “Nadezhda”, Tyumen, Russian Federation

2 Research Centre for Medical Genetics, Moscow, Russian Federation

**Interim Analysis of Treatment Outcomes of Young Children with 5q Spinal Muscular Atrophy on Viral Vector Therapy (Onasemnogene Abeparvovec). Clinical Observations**

**Contact information:**

*Kokorina Anna Alexandrovna*, neurologist in Children’s treatment and rehabilitation center “Nadezhda”

**Address:** 625048, Tyumen, Khokhryakova Street, 80/1, **tel.:** +7 (3452) 25-72-95, **e-mail:** ChAA01@yandex.ru

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***Background.*** *Onasemnogene abeparvovec is the first gene therapy medication based on the adeno-associated viral vector (AAV9). One injection to a patient with 5q spinal muscular atrophy (SMA) leads to replacement of the missing or defective SMN1 gene with its functional copy. It leads to normalization of survival motor neuron protein (SMN) production.* ***Objective. The aim of the study is to*** *to evaluate efficacy, safety, and causes of different responses to therapy after single administration of onasemnogene abeparvovec in 5 patients with 5q SMA (types I and II) comparing the baseline status with the results of continued monitoring in real clinical practice in Russian Federation.* ***Methods.*** *Interim results of continued follow-up of children with 5q SMA with 2-3 copies of the SMN2 gene are presented: 2 boys and 1 girl with type I who received single dose of onasemnogene abeparvovec at 4 and 7 months of age; and 2 girls with type II who received therapy at 11 and 16 months of age.* ***Results****. Short-term controlled fever was observed in 4 out of 5 patients during first 2 weeks after viral vector therapy administration (max in patient 5 — up to 38.5 ° C). All 5 children had transaminases increase, 1 patient — significant transaminases increase during the sensitisation period (>10 from upper normal level (UNL)), 1 patient — delayed significant transaminases increase (> 20 UNL), 1 patient — transaminases increase (> 3 UNL) after discontinuation of long-term therapy with glucocorticosteroids (according to prescribing information). All patients had shown positive and sustained response to therapy over time at motor status assessment via CHOP INTEND/HFMSE scales. The more significant response was observed in patients with less aggressive baseline 5q SMA type II with 3 copies of the SMN2 gene.* ***Conclusion.*** *Onasemnogene abeparvovec is relatively safe medication for management of children with 5q SMA. Thus, the development of adverse events and their mechanisms should be further studied, as well as long-term follow-up of recipients is required to gather experience on this medication effects on human body.*

***Keywords:*** *spinal muscular atrophy, children, gene replacement therapy, onasemnogene abeparvovec, adverse events, efficacy, safety, CHOP INTEND, HFMSE*

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**Table 1.** Patients’ characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Indicators** | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** |
| Sex | female | male | female | male | female |
| Onset age, months | 6 | 1 | 6 | 1,5 | 1 |
| Therapy initiation age, months | 16 | 4 | 11 | 7 | 7 |
| SMA type | II | I | II | I | I |
| *SMN2* gene copies | 3 | 2 | 3 | 3 | 2 |
| CHOP INTEND scale score | н/п | 17 | 39 | 20 | 23 |
| HFMSE scale score | 26 | n/a | n/a | n/a | n/a |
| Body weight at therapy initiation, g | 9030 | 5650 | 8000 | 8364 | 6300 |
| Maximum scale change in points | HFMSE 34 | CHOP INTEND 36 | HFMSE 24\* | CHOP INTEND 41 | CHOP INTEND 33 |
| Platelet count (reference range) | 49 × 109/l  (150–580) | 253 × 109/l  (150–580) | 42 × 109/l  (150–580) | 461 × 109/l  (150–580) | 245 × 109/l  (150–580) |
| Monocyte count (reference range) | 2,8 × 109/l  (0,38–1,26) | 1,9 × 109/l  (0,53–1,8) | 2,66 × 109/l  (0,38–1,26) | 2,4 × 109/l  (0,00–1,00) | 0,30 × 109/l  (0,09–0,60) |
| Neutrophil count (reference range) | 1,42 × 109/l  (1,1–5,8) | 1,07 × 109/l  (0,8–3,8) | 1,07 × 109/l  (0,8–3,8) | 0,6 × 109/l  (n/a) | 2,71 × 109/  (2,04–5,08) |
| AST level (reference range) | 959 u/l  (< 42) | 79 u/l  (< 42) | 807 u/l  (< 42) | 131 u/l  (9–80) | 323 u/l  (15–60) |
| ALT level (reference range) | 853 u/l  (< 40) | normal values | 1044 u/l  (< 40) | 142 u/l  (13–45) | 208 u/l  (13–48) |
| LDH level (reference range) | 1030 u/l  (91–295) | 582 u/l  (91–295) | 529 u/l  (91–295) | 567 u/l  (195–450) | 623 u/l  (180–430) |
| GGT level (reference range) | 41,39 u/l  (3–30) | 21 u/l  (3–30) | 125 u/l  (< 38,0) | 20 МЕ/l  (6–92) | 21,60 u/l  (1,00–39,00) |
| AP level (reference range) | 145,12 u/l  (60–400) | 271 u/l  (50–350) | 595 u/l  (50–350) | 135,7 МЕ/l  (113–443) | 117 u/l  (124–341) |
| Coagulation parameter (reference range) | PI 108%  (70–120) | PI 153%  (70–120) | PI 151%  (70–120) | PT 10,0 sec  (9,5–12,8) | PT 12,1 sec  (9,9–13,4) |
| Duration of GCS administration, weeks | 36 | 12 | 18 | 12 | 12 |
| Abdominal ultrasound | no changes | no changes | hepatomegaly, secondary pancreatic changes | splenomegaly, cleaved calices-pelvis system, pyeloectasia of the lower segment of left kidney, calices-pelvis system induration | hepatomegaly |
| Duration of post-administration follow-up, months | 9 | 3 | 12 | 10 | 10 |

*Note.* SMA (СМА) —5q spinal muscular atrophy; CHOP INTEND — Children’s Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders; HFMSE — Hammersmith Functional Motor Scale – Expanded; n/a (н/п) — not applicable for HFMSE (due to the fact that patients did not reach the functional status of " sedentary patient" by the time of motor functions testing), NA (н/д) — no data available; AST (АсТ) — aspartate transaminase; ALT (АлТ) — alanine transaminase; LDH (ЛДГ) — lactate dehydrogenase; GGT (ГГТП) — gamma-glutamyltranspeptidase; AP (ЩФ) — alkaline phosphatase; PI (ПТИ) — prothrombin index; PT (ПВ) — prothrombin time; GCS (ГКС) — glucocorticosteroids; US (УЗИ) — ultrasound; CPS (ЧЛС) — calices-pelvis system; <\*> — patient achieved the ability to sit on his own, it has allowed to assess him on HFMSE scale.

**Table 2.** Laboratory differences in 5 patients who received single dose of gene replacement therapy with onasemnogene abeparvovec according to CTCAE 5.0 (2017)

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient** | **Sensitisation period / postponed period** | | |
| **AST** | **ALT** | **GGT** |
| 1 | > 10 UNL (grade 3) / > 5ВГН (grade 3) | > 10 UNL (grade 3) / > 5 UNL (grade 3) | grade 1 / normal |
| 2 | < 3 UNL (grade 1) / < 3 UNL (grade 1) | normal / normal | normal / normal |
| 3 | 3 UNL (grade 1) / > 10 UNL (grade 3) | normal / > 20 UNL (grade 4) | > 4 UNL (grade 2) |
| 4 | < 3 UNL (grade 1) / < 3 UNL (grade 1) | normal / > 3 – < 5 UNL (grade 2) | normal / normal |
| 5 | > 3 – < 5 UNL (grade 2) / < 3 UNL (grade 1) | > 3 – < 5 UNL (grade 2) / normal | normal / normal |

*Note.* AST (АсТ) — aspartate transaminase; ALT (АлТ) — alanine transaminase; GGT (ГГТП) — gamma-glutamyltranspeptidase; UNL (ВГН) — upper normal level. CTCAE 5.0 (2017): grade 1 – grade 5 (fatal outcome) — Common Terminology Criteria for Adverse Events 5.0 (2017): grade 1 – grade 5 (fatal outcome); for AST/ALT: grade 1 – to 3 UNL, grade 2 — > 3 – 5 UNL, grade 3 — > 5 – 20 UNL, grade 4 — > 20 UNL; for GGT: grade 1 — up to 2,5 UNL, grade 2 — 2,5–5 UNL, grade 3 — > 5 – 20 UNL, grade 4 — > 20 UNL.

**Table 3.** Patients’ characteristics before gene replacement therapy

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Indicators** | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** |
| SMA type | II | I | II | I | I |
| *SMN2* gene copies | 3 | 2 | 3 | 3 | 2 |
| Onset age, months | 6 | 1 | 6 | 1,5 | 1 |
| Initial functional status | “sedentary patient” | “bed-bound / non-sedentary patient” | “bed-bound / non-sedentary patient” | “bed-bound / non-sedentary patient” | “bed-bound / non-sedentary patient” |
| Maximum initial large motor skills | Crawling (not reciprocal), self-acting sitting, sitting without support, cruising up to 6 steps | no skills | Lifting and holding the head in face-down position | no skills | no skills |
| Leading symptom complex at disease onset emphasized by the doctor at examination | Motor skill developmental delays, abnormal sleepiness due to rapid physical fatigue, muscular hypotonia, hand tremors | Minimal motor activity with regression, muscular hypotonia, areflexia, fast fatigue while feeding, tongue fasciculation, paradoxical breathing pattern, chest deformity | Regression of acquired motor skills, muscular hypotonia with voluntary movements deficiency, hypo-/areflexia, tongue fasciculation, paradoxical breathing pattern | Motor skill developmental delays, muscular hypotonia, tongue fasciculation | Tongue fasciculation, minimal motor activity, muscular hypotonia, areflexia, malnutrition (eat a little, choking while swallowing), constipation |
| Time from symptoms onset to diagnosis, months | 8 | 38 days | 3 | 3,5 | 5 |
| Prior pathogenetic therapy | Risdiplam | Risdiplam | Risdiplam | No | No |
| Orthopaedic manifestations | Hip dysplasia, genu valgum, plano-valgus foot posture | Hip dysplasia | Hip dysplasia | Hip dysplasia | Hip dysplasia |

**Table 4.** Major motor skills dynamics in 5 patients with 5q SMA on therapy

|  |  |  |
| --- | --- | --- |
| **Patient** | **Skills before treatment** | **Observation end point** |
| 1 | Stands with support | Walks without support |
| 2 | Cannot hold the head upright | Can hold the head upright for up to 2 minutes |
| 3 | Can hold the head upright, turns from back to sides, does not maintain passively set "sitting" position | Sits readily after passively set, stands on all fours with raised head, can turn into the "sitting" position by himself from the "standing on all fours" position |
| 4 | Cannot hold head even in upright position, cannot not raise head in face-down position | Can maintain face-down position with support on the forearms and holding the head up to 20 seconds, in the position "sitting on the parent's lap" can raise the lowered head, turns the head from side to side, sits readily after passive set, can stand in the tutors on ankle joints without support for up to 2 minutes |
| 5 | Cannot hold the head upright, cannot not raise head in face-down position | Learned to turn from back to stomach; can hold the head without for up to an hour and a half in support chair, can raise the head |

**Fig.** Motor skills dynamics in 4 patients with 5q SMA after single dose of onasemnogene abeparvovec according to CHOP INTEND scale

*Note.* Patient 2 — number of *SMN2* gene copies = 2; patient 3 — number of *SMN2* gene copies = 3 (patient 3 reached the ability to sit during observation, achieved maximum score according to CHOP INTEND, was transferred to HFMSE scoring system and achieved score of 24 points); patient 4 — number of *SMN2* gene copies = 3, patient 5 — number of *SMN2* gene copies = 2. Patient 1 (number of *SMN2* gene copies = 3) scored + 8 points on HFMSE scale (from 26 to 34 points) 6 months after viral vector administration.

**RESEARCH LIMITATIONS**

Sampling limitations:

* insufficient sample size: vector of possible deviations may be significant in this case;
* different compliance and follow-up frequency in patients within the sample due to different distance from the place of residence to the observer; taking into account the first and end point of follow-up, interim analysis through data collection, continued analysis of large motor skills development via video recording, even at no possibility for testing according to functional scales, the vector of possible deviations should not be significant for the obtained study results;
* different duration of patients’ follow-up from the moment of exposure at outcomes evaluation (3-12 months): vector of possible deviations may be significant for study results reliability.

Limitations related to the studied indicators:

* there was not enough data for accurate analysis when studied retrospective data from patients; medical records: vector of possible deviations in this case should not affect the result of the study, therefore, this fact may interfere understanding of the mechanisms of adverse events development;
* the fact of test results comparison by functional scales by different specialists and the presence of artifacts during some cases of functional testing (considering detailed description of major motor skills and video recording) should not lead to significant deviations in the study results.

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Not specified.

**DISCLOSURE OF INTEREST**

Not declared.