Informational materials

Consensus on Gene Replacement Therapy for the Treatment for Spinal Muscular Atrophy (Version N 2)

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Proximal spinal muscular atrophy (SMA) is a severe, disabling autosomal recessive neuromuscular disorder caused by chromosome 5 abnormalities (5q). The genetic cause of SMA is homozygous deletions or loss of function as a result of mutations in the survival motor neuron (*SMN1*) gene [1]. The highly homologous reserve *SMN2* gene ensures the production of only 10% of full-length SMN protein. There is evidence that having more copies of the *SMN2* gene results in less severe

phenotypes [2]. The prevalence of proximal SMA is 1 case per 6,000–10,000 newborns [3].

The disease is characterized by motor neuron degeneration, which results in progressive muscle atrophy, as well as swallowing and breathing difficulties [3].

Clinically, SMA is divided into 5 types based on the age of onset, the severity of phenotypic manifestations, and the degree of motor skill acquisition, which may be lost later as the disease progresses [4].

SMA type 1 is found in 60% of patients, with the first symptoms appearing before the age of six months. SMA type 2 (30% of cases) manifests at 6–18 months of age, SMA type 3 beyond 18 months, and SMA type 4 in adulthood [5].

There is also SMA type 0, in which severe muscular hypotension and a sharp decrease in motor activity, as well as other clinical manifestations, occur in utero and can result in fetal death. Patients with SMA type 1 require respiratory and nutritional support, with continuous lung ventilation by the age of 2, and only 8% survive to the age of 20 months [6, 7].

SMA diagnosis and treatment have recently advanced significantly. Various disease-modifying therapies are currently available, which allows for a better prognosis in SMA patients. Pathogenetic therapy that increases protein production by modifying the *SMN2* gene splicing should be received for life. It includes nusinersen, an antisense oligonucleotide administered intrathecally, and risdiplam, a small molecule administered orally [8].

Onasemnogene abeparvovec (OA), a single-dose gene replacement therapy, is an alternative treatment option for SMA. Its mechanism of action is based on the introduction of a functional copy of the gene, which replaces the function of the defective *SMN1* gene and restores SMN protein synthesis [9].

Russia has been conducting expanded newborn screening since 2023, including the identification of presymptomatic SMA patients [10]. This diagnostic approach has the potential to reduce infant mortality and improve prognosis and quality of life in patients with hereditary diseases. The issue of selecting the best therapy for SMA patients, including those identified through newborn screening, is critical and necessitates a thorough medical evaluation in terms of efficacy, safety, and tolerability. This consensus statement compiles the views of leading SMA experts on the use of gene replacement therapy in clinical practice.

OA is now on the Circle of Kindness Foundation's list of medicinal products for the treatment of SMA.

1. Categories of children eligible for the prescription of OA (trade name: Zolgensma®)

Currently, the Circle of Kindness Foundation has adopted the following criteria for the use of OA:

I. Patients who have not previously received other pathogenetic therapies:

1) patients with a genetically confirmed diagnosis of SMA type 1 (with biallelic mutations in the *SMN1* gene);

2) patients with a genetically confirmed diagnosis of other types of SMA (with biallelic mutations in the *SMN1* gene) and not more than 3 copies of the *SMN2* gene.

Conditions:

• the medicinal product is prescribed by the decision of the medical commission of the healthcare facility;

• the opinion of one of the four federal centers with experience in gene replacement therapy (National Medical Research Center for Children's Health, Research Clinical Institute of Pediatrics and Pediatric Surgery named after Yu.E. Veltishchev, Russian Children's Clinical Hospital of the Russian National Research Medical University named after N.I. Pirogov, or Institute of Perinatology and Pediatrics named after V.A. Almazov) is required;

• legal representatives must be willing to refuse another pathogenetic therapy after using gene replacement therapy.

II. Patients who have previously received other pathogenetic therapies:

1) patients with a genetically confirmed diagnosis of SMA type 1 (with biallelic mutations in the *SMN1* gene);

2) patients with other types of SMA and not more than 3 copies of the *SMN2* gene.

Conditions:

• the medicinal product is prescribed by the decision of the medical commission of the healthcare facility, based on the decision of the council of physicians involving at least three healthcare facilities subordinate to the federal executive authorities;

• legal representatives must be willing to refuse another pathogenetic therapy after using gene replacement therapy.

Criteria limiting the use of OA:

• age over 2 years;

• anti-adeno-associated virus *AAV9* antibody titer above 1:50;

• body weight above 13.5 kg;

• the need for mechanical ventilation for more than 16 hours per day for 14 consecutive days or more, excluding infectious and other acute diseases;

• the use of a gastrostomy tube, or constant use of a nasogastric tube, or inability to swallow.

When making a decision on the provision of OA to children, it is necessary to follow the instructions for use of this medicinal product. For children above the age of two and weighing more than 13.5 kg, the decision should be made on a case-by-case basis, taking into account the decisions of the federal council of physicians.

Consensus opinion

The criteria for using Zolgensma must be expanded in accordance with the Summary of Product Characteristics (product label). Experts recommend removing the age criteria for the product prescription and expanding the use of gene replacement therapy in patients with SMA weighing up to 21 kg.

Inability to swallow should be one of the criteria limiting the prescription of the medicinal product, since the use of a gastrostomy tube or a nasogastric tube does not necessarily correlate with the severity of bulbar function disorders.

Rationale

The use of intravenous gene replacement therapy was studied in symptomatic and presymptomatic SMA patients in 5 clinical trials: phase I study (**START**), [12] three phase III studies STRIVE (**STRIVE-US**, [13] **STRIVE-EU**, [14] and **STRIVE-AP** [15]), as well as the **SPRINT** study [16, 17]. In addition, a long-term 15-year follow-up of patients who completed participation in clinical trials is ongoing, and a registry of patients who received gene replacement therapy in real-world clinical practice (**RESTORE** [23]) has been created.

In contrast to the natural course of the disease, a single infusion of OA provides a rapid therapeutic effect that increases over time, improves motor function, and increases survival in SMA patients.

2. Gene replacement therapy can be prescribed to patients with homozygous deletion of the *SMN1* gene without clinical manifestations identified through newborn screening. In patients with 4 copies of the *SMN2* gene without clinical manifestations identified through newborn screening, gene replacement therapy can be prescribed by a collective decision of experts from at least three federal institutions

Rationale

Newborn screening for SMA allows detecting the disease before the onset of symptoms, within one week after birth. In this case, pathogenetic therapy can be prescribed before the first symptoms of the disease appear, for the best effect [18].

The safety and efficacy of OA were studied in an open-label, multicenter, phase III SPRINT study [16, 17] in presymptomatic SMA patients aged <6 weeks with a biallelic mutation in the *SMN1* gene and two (*n*=14) or three (*n*=15) copies of the *SMN2* gene. The endpoints were assessed after 18 months in patients with two copies of the *SMN2* gene and after 24 months in patients with three copies of the *SMN2* gene.

The primary endpoints included the ability to sit without support for ≥30 s (for patients with two copies of the *SMN2* gene) and stand without support (for patients with three copies of the *SMN2* gene). The improvement of motor function according to the CHOP INTEND scale and the safety of therapy were also assessed. The following results were obtained: event-free survival (survival without the needs for permanent ventilation) was 100%, and none of the patients required respiratory support.

In the group with two copies of the *SMN2* gene, 14 (100%) patients in the ITT population could sit without support for ≥30 s, 11 (79%) could stand without support (with 7 [50%] patients acquiring this skill within the age norm), 9 (64%) could take at least five steps independently, and 14 (100%) had a mean CHOP INTEND score of ≥58 points.

In the group with three copies of the *SMN2* gene, 15 (100%) patients could stand without support (with 14 [93%] patients acquiring this skill within the age norm), and 14 (93%) patients could take at least five steps independently (with 11 [73%] patients acquiring this skill within the age norm).

All 15 children acquired the ability to sit and stand without support (within the WHO reference range in most cases), and none of them required respiratory support.

The SPR1NT study confirmed the favorable safety profile and good tolerability of gene replacement therapy. According to the researchers, none of the serious adverse events was associated with gene replacement therapy.

Thus, the SPR1NT study shows an increase in survival rate with no need for respiratory support and age-appropriate motor development in presymptomatic SMA patients who received OA, emphasizing the importance of initiating treatment before the onset of symptoms.

At the same time, according to pilot newborn screening projects in various countries, 5.0–39.5% of patients have more than three copies of the *SMN2* gene [18]. There is currently a lot of evidence suggesting patients with four copies of the *SMN2* gene are at risk and may develop symptoms in early childhood [19, 20]. In this regard, international experts reviewed the recommendations on the treatment of patients with SMA identified through newborn screening, adding the requirement for urgent treatment for patients with four copies of the *SMN2* gene [21].

Consensus opinion

Because the mechanism of action of gene replacement therapy is based on the introduction of a functional copy of the *SMN1* gene into transduced cells, the number of copies of the *SMN2* gene is not a determining factor in the use of OA. The mechanism of action, as well as single-dose administration of OA, make it possible to use it in patients with four copies of the *SMN2* gene.

A number of foreign publications present data on the efficacy and safety of gene replacement therapy in patients with four copies of the *SMN2* gene identified through newborn screening [22, 23].

3. All patients with planned gene replacement therapy infusion should be tested for antibodies to adeno-associated viral vector serotype 9 (*AAV9*). Patients with a baseline anti-*AAV9* antibody titer greater than 1:50 should be retested, or alternative pathogenetic treatment options should be considered. If the titer decreases below 1:50, the prescription of gene replacement therapy can be considered

Rationale

Patients should be tested for anti-*AAV9* antibodies before OA infusion [24]. Anti-*AAV9* antibody production can be due to natural exposure to the virus. Several studies on the prevalence of anti-*AAV9* antibodies in the general population showed low rates of prior exposure to *AAV9* in the pediatric population [24]. Nevertheless, it can reach 14% in newborns in the first month of life, which is most often associated with transplacental transmission of antibodies from the mother [25]. According to the published data, the half-life of transplacentally transmitted antibodies is approximately 6 weeks [26]. During newborn screening in patients with planned gene replacement therapy infusion, testing for anti-*AAV9* antibodies can be performed simultaneously with confirmatory diagnosis. Retesting can be performed if the anti-*AAV9* antibody titer exceeds 1:50. The timing of retesting depends on the titer of anti-*AAV9* antibodies and is determined by the attending physician. The efficacy and safety of OA in patients with anti-*AAV9* antibody titer above 1:50 are unknown [24]. No dose adjustment is required in patients with baseline anti-*AAV9* antibody titer exceeding 1:50.

4. Laboratory parameters and possible adverse events should be closely monitored in the post-infusion period in all patients who have received gene replacement therapy with OA. If the patient's clinical condition deteriorates as a result of an adverse event or negative changes in laboratory parameters during the post-infusion period following gene replacement therapy, it is necessary to decide on the need for hospitalization

in a multidisciplinary healthcare facility

Rationale

Gene therapy has a well-established safety and efficacy profile [12–17]. Before using OA, the following laboratory tests should be performed [24]:

• liver function test: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, prothrombin time, activated partial thromboplastin time (APTT), and international normalized ratio (INR);

• complete blood count (including hemoglobin and platelet count);

• troponin I test;

• creatinine level.

Glucocorticosteroids must be prescribed in the post-infusion period after gene replacement therapy due to the immune response to the capsid proteins of the *AAV*9-based vector. This can lead to elevated liver transaminases, elevated troponin I, or a decrease in platelet count. Immunomodulation with glucocorticosteroids is indicated to suppress the immune response; the dose can be adjusted in case of adverse events and changes in laboratory parameters.

The most common post-infusion adverse reactions (ARs) were elevated liver enzymes (24.2%), hepatotoxicity (9.1%), vomiting (8.1%), thrombocytopenia (6.1%), elevated troponin I (5.1%), and pyrexia (5.1%) [24].

All patients should receive prednisolone 1 mg/kg/day *per os* 24 hours before OA infusion. In case of intolerance to prednisolone *per os*, its parenteral administration may be considered. Following gene replacement therapy, glucocorticosteroid therapy regimen may need to be adjusted, such as using glucocorticosteroids for a longer period of time or increasing the dose. In some cases, pulse therapy or a slower dose reduction may be required.

Prednisolone 1 mg/kg/day should then be continued for 30 days following the OA infusion (including the day of infusion). Over the next 28 days, the dose of systemic glucocorticosteroid should be reduced gradually; therapy with these drugs should not be abruptly discontinued. For patients with insignificant changes (clinical parameters within the normal range; total bilirubin, ALT, and AST below 2×ULN at the end of the 30-day period), a gradual reduction in the dose of prednisolone (or an equivalent dose of another glucocorticosteroid) is recommended: for example, 0.5 mg/kg/day for 2 weeks, then 0.25 mg/kg/day for 2 weeks.

Liver function should be monitored by assessing ALT, AST, and total bilirubin levels for at least 3 months after OA infusion or as clinically indicated. Patients with deteriorated liver function tests and/or signs or symptoms of an acute disease should be promptly examined and closely monitored [24]. In the absence of an adequate response to glucocorticosteroids at a dose equivalent to oral prednisolone 1 mg/kg/day, the patient should be immediately consulted by a pediatric gastroenterologist or hepatologist. In case of intolerance to oral glucocorticosteroids, parenteral administration may be considered.

Platelet count should be determined prior to OA infusion and carefully monitored for a significant decrease in platelet count within 2 weeks after the infusion and regularly thereafter; at least once a week in the first month and once in 2 weeks in the second and third months, until the platelet count returns to baseline values [24].

Cases of thrombotic microangiopathy (TMA) have been reported in the post-marketing period. As a rule, TMA was reported within the first 2 weeks after OA administration. TMA is characterized by thrombocytopenia and microangiopathic hemolytic anemia [24]. Acute kidney injury has also been observed. In some cases, concurrent immune system activation (e.g., due to infections or vaccination) was a contributing factor.

It is recommended to pay close attention to the signs and symptoms of TMA because it can result in life-threatening consequences or death.

Thrombocytopenia is a key sign of TMA. Therefore, the platelet count must be carefully monitored for a significant decrease during the first 2 weeks after the infusion and regularly thereafter, along with other signs and symptoms, such as arterial hypertension, skin and subcutaneous hemorrhages, convulsions, or decreased urine output. If these signs and symptoms occur against the background of thrombocytopenia, further diagnostic evaluation is required to detect hemolytic anemia and impaired renal function [24].

If clinical signs, symptoms and/or laboratory parameters of TMA are detected, the patient should be immediately consulted by a pediatric hematologist and pediatric nephrologist in order to select TMA therapy according to clinical indications.

Increases in cardiac troponin I following OA infusion have been reported. Elevated troponin I may suggest myocardial tissue injury in some patients. Based on these findings and the cardiotoxicity observed in preclinical studies in mice, troponin I levels should be measured before OA infusion and monitored for at least 3 months thereafter, until they return to the normal range for SMA patients [24]. Where necessary, a cardiologist consultation should be considered.

Thus, in the post-infusion period after gene replacement therapy, patients should be followed up in a healthcare facility at the place of residence or at the center that infused gene replacement therapy in order to monitor laboratory parameters and clinical condition. In case of clinically significant adverse events following gene replacement therapy, it is necessary to decide on the need for emergency hospitalization in a multidisciplinary healthcare facility at the place of residence or the federal center that infused gene replacement therapy.

5. In some patients with a suboptimal response to the prescribed pathogenetic therapy (insufficient efficacy),
sequential therapy (switching from another pathogenetic therapy to gene replacement therapy) can be considered. The decision
on the switching should be approved by a group of experts from several federal healthcare facilities

Rationale

Management of SMA patients, as well as approaches to prescribing and selecting the best drug therapy, are complicated. To assess the efficacy of pathogenetic therapy, a dynamic evaluation of motor skills using various scales is required [3]. To ensure uniformity of results and eliminate erroneous data interpretation in complex clinical cases, the assessment should be performed on a regular basis in specialized healthcare facilities (in some cases, federal healthcare facilities) that have extensive experience in testing patients with various types of SMA.

The criteria of suboptimal response to therapy (insufficient treatment efficacy) in SMA patients are as follows:

1) Total worsening in scale score, confirmed by two consecutive measurements on any two of the following three scales:

• the patient loses >2 points for the ability to kick whilst lying on the back or 1 point on other HINE scales, excluding voluntary grasp;

• the patient loses >4 points on the CHOP INTEND scale;

• the patient loses >3 points on the HFMSE scale.

2) and/or deterioration of respiratory function:

• increased need for respiratory support during the day and/or for this patient;

• an uncharacteristic increase in the number of respiratory infections requiring hospital treatment that cannot be explained by aspiration or lung disease.

The assessment should be performed 12 months after the initiation of therapy compared to baseline. In this case, the patient's general condition and motor status at baseline are important.

Regarding the timing of switching, the following time intervals are recommended: the prescription of gene replacement therapy can be considered 3–5 days after the last dose in the case of previous therapy with risdiplam and at least 30 days after the last dose in the case of previous therapy with nusinersen, based on the pharmacokinetics of these medicinal products.

It should be kept in mind that switching from another pathogenetic therapy to gene replacement therapy may increase the risk of adverse events, according to real-world evidence.

In any case, the issue of insufficient treatment efficacy and the need to switch from another pathogenetic therapy to gene replacement therapy should be resolved on a case-by-case basis, based on the collective opinion of a group of experts from several healthcare facilities, taking into account the assessment of the risk-benefit ratio.

6. Combination therapy of SMA currently has limitations in real-world clinical practice

Rationale

Combination disease-modifying therapy should include the prescription of pathogenetic therapy (risdiplam or nusinersen) after a single-dose gene replacement therapy, the effect of which, presumably, persists throughout the patient's life [9]. At the moment, there is no evidence of the efficacy and safety of combination disease-modifying therapy for SMA compared to OA monotherapy. Therefore, combination therapy should not be used in routine clinical practice, and experts should prefer monotherapy with an effective drug. However, exceptions may be made in some cases by the decision of a council of physicians [28].

All disease-modifying therapies affect SMN protein production. There are currently no clinical study or systematic review data on the relationship between the degree of SMN protein expression and the clinical effect size [9, 28].

It should be noted that irreversible degeneration of motor neurons and muscle tissue in patients with severe symptoms is probably the most important factor resulting from the lack of expected efficacy or phenotypic recovery, regardless of the amount of SMN protein produced, which is observed with any therapy option [28].

7. Vaccination

It is recommended to pay special attention to the prevention, monitoring, and treatment of infectious diseases before and after OA infusion.

Timely seasonal prevention of infections caused by respiratory syncytial virus (RSV) is recommended. If possible, the patient's vaccination schedule should be adjusted taking into account the use of glucocorticosteroids in the pre- and post-infusion period of OA therapy.

Rationale

During newborn screening, BCG vaccination in presymptomatic SMA patients is recommended in the first days of life, according to the national immunization schedule [29]. Gene replacement therapy with subsequent corticosteroid therapy can be performed no earlier than 2 weeks after BCG vaccination [30].

If possible, the patient's vaccination schedule should be adjusted taking into account the use of glucocorticosteroids before and after OA infusion [24]. Seasonal vaccination against RSV is recommended [24]. Patients receiving glucocorticosteroids in immunosuppressive doses (for example, prednisolone 20 mg or 2 mg/kg body weight or another glucocorticosteroid at an equivalent dose daily for ≥2 weeks) should not receive live vaccines, such as measles-mumps-rubella vaccine and varicella vaccine [24].

The experts recommend mandatory vaccination against RSV in children with symptomatic SMA; the timing of preventive therapy should not depend on the timing of gene replacement therapy. In presymptomatic children with SMA, the prevention of RSV infection is not mandatory.

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