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ISSUES & OPINIONS

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Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy

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Abstract

Spinal muscular atrophy (SMA) is an autosomal recessive, neurodegenerative disease caused by biallelic mutations in the survival motor neuron 1 (*SMN1*) gene. SMA is characterized by motor neuron degeneration, resulting in progressive muscle atrophy and weakness. Before the emergence of disease-modifying therapies, children with the most severe form of SMA would never achieve the ability to sit independently. Only 8% survived beyond 20 months of age without permanent ventilator support. One such therapy, onasemnogene abeparvovec, an adeno-associated virus–based gene replacement therapy, delivers functional human *SMN* through a one-time intravenous infusion. In addition to substantially improving survival, onasemnogene abeparvovec was found to increase motor milestone attainment and reduce the need for respiratory or nutritional support in many patients. This expert opinion provides recommendations and practical considerations on the patient-centered decisions to use onasemnogene abeparvovec. Recommendations include the need for patient-centered multidisciplinary care and patient selection to identify those with underlying medical conditions or active infections to reduce risks. We also describe the importance of retesting patients with elevated anti–adeno-associated virus serotype 9 antibodies. Recommendations for prednisolone tapering and monitoring for potential adverse events, including hepatotoxicity and thrombotic microangiopathy, are described. The need for caregiver education on managing day-to-day care at time of treatment and patient- and family-centered discussions on realistic expectations are also recommended. We detail the importance of following standard-of-care guidance and long-term monitoring of all children with SMA who have received one or more

Abbreviations: AAV, adeno-associated virus; AAV9, adeno-associated virus serotype 9; ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AST, aspartate transaminase; BSL1, biosafety level 1; dsDNA, double-stranded DNA; GGT, gamma-glutamyltransferase; IgG, immunoglobulin G; IV, intravenous; MAP, managed access program; NGT, Novartis Gene Therapies Inc; RG1, National Institutes of Health Risk Group 1; SARS-CoV-2, severe acute respiratory–syndrome coronavirus-2; ssAAV, single-stranded AAV; scAAV, self-complementary AAV; SMA, spinal muscular atrophy; SMN, survival motor neuron; *SMN1*, survival motor neuron 1 gene; *SMN2*, survival motor neuron 2 gene; TMA, thrombotic microangiopathy; ULN, upper limit of normal.

disease-modifying therapy using registries. We also highlight the need for presymptomatic or early symptomatic treatment of this disorder.

KEYWORDS
efficacy, gene therapy, onasemnogene abeparvovec, safety, spinal muscular atrophy

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive, neurodegenerative disease caused by biallelic mutations in the survival motor neuron 1 (*SMN1*) gene. Biallelic *SMN1* mutations lead to survival-motor-neuron (SMN) protein deficiency and degeneration of motor neurons, resulting in progressive muscle atrophy and weakness.[1] SMA occurs in 1 in 11 000 live births in the United States.[2] The severity of SMA is largely dependent on the number of copies of survival motor neuron 2 (*SMN2*) gene, a back-up gene to *SMN1*. Each *SMN2* copy produces approximately 10% of the functional SMN protein produced by a single functional *SMN1* copy,[1] partially compensating for the disrupted *SMN1* genes as SMN protein is essential for life.[3] Patients lacking functional *SMN1* and *SMN2* genes do not survive. Children with two or fewer copies of *SMN2* will typically exhibit the most severe SMA phenotype.[4,5]

Historically, SMA was classified into three major phenotypes (SMA types 1, 2, and 3), differentiated by the child's age at symptom onset and maximum motor milestone achieved.[6,7] SMA types 0 and 4 were added to describe rare congenital and adult-onset forms of SMA, respectively.[8,9] Presymptomatic infants are described by *SMN2* copy number, as type remains a clinical diagnosis. Despite this traditional categorization, SMA patients are on a continuum rather than fitting neatly into distinct types. Moreover, with disease-modifying therapies, this classification system is less relevant, with less predictive value. Experts increasingly recommend that patients with SMA be reclassified as non-sitters, sitters, and walkers.[10,11]

SMA's clinical course is changing. Patients with genotypes historically predictive of SMA type 1 are receiving disease-modifying treatments and achieving independent sitting or walking, particularly if treated early.[12,13] Disease-modifying therapies and supportive care have improved SMA patient prognoses and functional status, and have decreased the likelihood and severity of comorbidities. Three treatments have demonstrated clinical efficacy in SMA by increasing SMN protein expression. Nusinersen and risdiplam alter *SMN2* splicing, resulting in a greater inclusion of exon 7 and increase in full-length SMN protein. Onasemnogene abeparvovec is a gene replacement therapy that delivers functional human *SMN* through a one-time intravenous (IV) infusion.[14]

As of June 2021, more than 1200 patients had been treated with onasemnogene abeparvovec globally. As more countries and regions approve IV onasemnogene abeparvovec, questions have arisen regarding its implementation in practice that are not covered in the prescribing information or a review describing the clinical trial experience.[15] This expert opinion provides recommendations in key areas by an expert panel of neuromuscular specialists who have treated SMA patients with onasemnogene abeparvovec.

2 | METHODS

To address questions encountered with the use of onasemnogene abeparvovec, Novartis Gene Therapies, Inc. (NGT) invited the coauthors to develop this expert opinion. Coauthors, representing five countries and four continents, included seven pediatric neurologists and neuromuscular specialists who have experience treating children with SMA, six of whom were site investigators for onasemnogene abeparvovec clinical trials. They have each treated approximately 5 to 21 patients in both clinical trials and post-approval clinical treatment as of January 2021. Each coauthor demonstrated a leadership role in clinical trials with onasemnogene abeparvovec and/or early introduction of gene replacement therapy in their respective countries. Experts established key areas for these recommendations through a series of virtual meetings from September 2020 to November 2020, where knowledge was exchanged and experiences were shared. For example, intrathecal administration of onasemnogene abeparvovec was outside the scope of these recommendations because this would be evaluated in future clinical trials. Because vector shedding was considered an area of interest, NGT agreed to share these data with the coauthors. After review of the relevant medical literature, the authors worked collaboratively to carefully construct recommendations to provide their expert consensus after the discussion. The authors agreed with the recommendations made within this article, and also identified areas of uncertainty and gaps.

3 | WHAT IS ONASEMNOGENE ABEPARVOVEC?

Onasemnogene abeparvovec is an *in vivo* adeno-associated virus serotype 9 (AAV9) gene replacement therapy that delivers the *SMN* transgene under a ubiquitous promoter into target cells, through a one-time IV infusion.[14] Indications for onasemnogene abeparvovec are presented in Table 1 for each jurisdiction where it is currently approved.

AAV gene therapy platforms offer several advantages over other viral vectors. For example, AAVs are not known to cause human disease. Compared with adenovirus vectors, activation of innate immunity is lower with AAVs.[16] In addition, AAVs have a low risk of genomic integration because the transgene is maintained as an episome.[17] However, with limited reports of AAV integration,[18-21] there is a theoretical risk of malignancy should the insertion occur near a proto-oncogene. Recent deaths of patients with X-linked myotubular myopathy related to progressive liver dysfunction after AAV8-based gene therapy highlight potential safety concerns.[22] All three patients treated with the high dose

TABLE 1 Key indications for onasemnogene abeparvovec by country

	United States[14]	Japan[83]	European Union[84]	Brazil[85]	Australia[86]	Canada[87]
Age	<2 years	<2 years	No upper age limit	<2 years	<9 months	No upper age limit
Weight	—	—	Explicitly states there is limited experience in patients with body weight >13.5 kg	Explicitly states there is limited experience in patients with body weight >13.5 kg	—	—
SMN2 copy number	No restrictions	No restrictions	≤3 *SMN2* copies	≤3 *SMN2* copies	≤3 *SMN2* copies	≤3 *SMN2* copies
Anti-AAV9 antibody titers	—	Explicitly excludes patients with seropositive anti-AAV9 antibody titers	—	—	—	—

Abbreviations: AAV9, adeno-associated virus serotype 9; *SMN2*, survival motor neuron gene 2.

(3×10^{14} vector genomes/kg) had evidence of pre-existing liver disease, underscoring importance of dose selection and identifying patients with underlying hepatic disease.

AAV9 can cross the blood-brain barrier (Figure 1).[23,24] The self-complementary feature of onasemnogene abeparvovec allows for rapid transgene expression.[25] The hybrid cytomegalovirus enhancer–chicken beta-actin promoter drives sustained SMN protein expression,[26] which may enable lifelong transgene expression. Analysis of two human case studies confirmed that IV administration of onasemnogene abeparvovec results in generalized cell transduction and expression of SMN protein in spinal motor neurons, neurons, glial cells, heart, liver, skeletal muscles, and other tissues.[14]

In the phase I START study, treatment of SMA patients less than 8 months of age with onasemnogene abeparvovec demonstrated improvements in survival, as well as achievement of motor milestones not observed in natural history, without the need for permanent ventilation.[27,28] The phase III STR1VE-US study demonstrated the favorable benefit-risk profile observed in the phase I study for a larger group.[29] Long-term evaluation for up to 5.6 years has indicated the maintenance of motor milestones without any new safety signals in patients who received the targeted therapeutic dose in START.[30]

Onasemnogene abeparvovec has not been studied for children with profound weakness, including those requiring invasive ventilator support, and the potential benefit of treatment in this subgroup of patients may be low because of irreversible loss of motor neurons as the disease progresses. Treatment of patients, including those with the most severe form of SMA who required invasive mechanical ventilation and tracheostomy before receiving onasemnogene abeparvovec, has also been reported.[31,32]

4 | NEED FOR PRESYMPTOMATIC OR EARLY SYMPTOMATIC TREATMENT

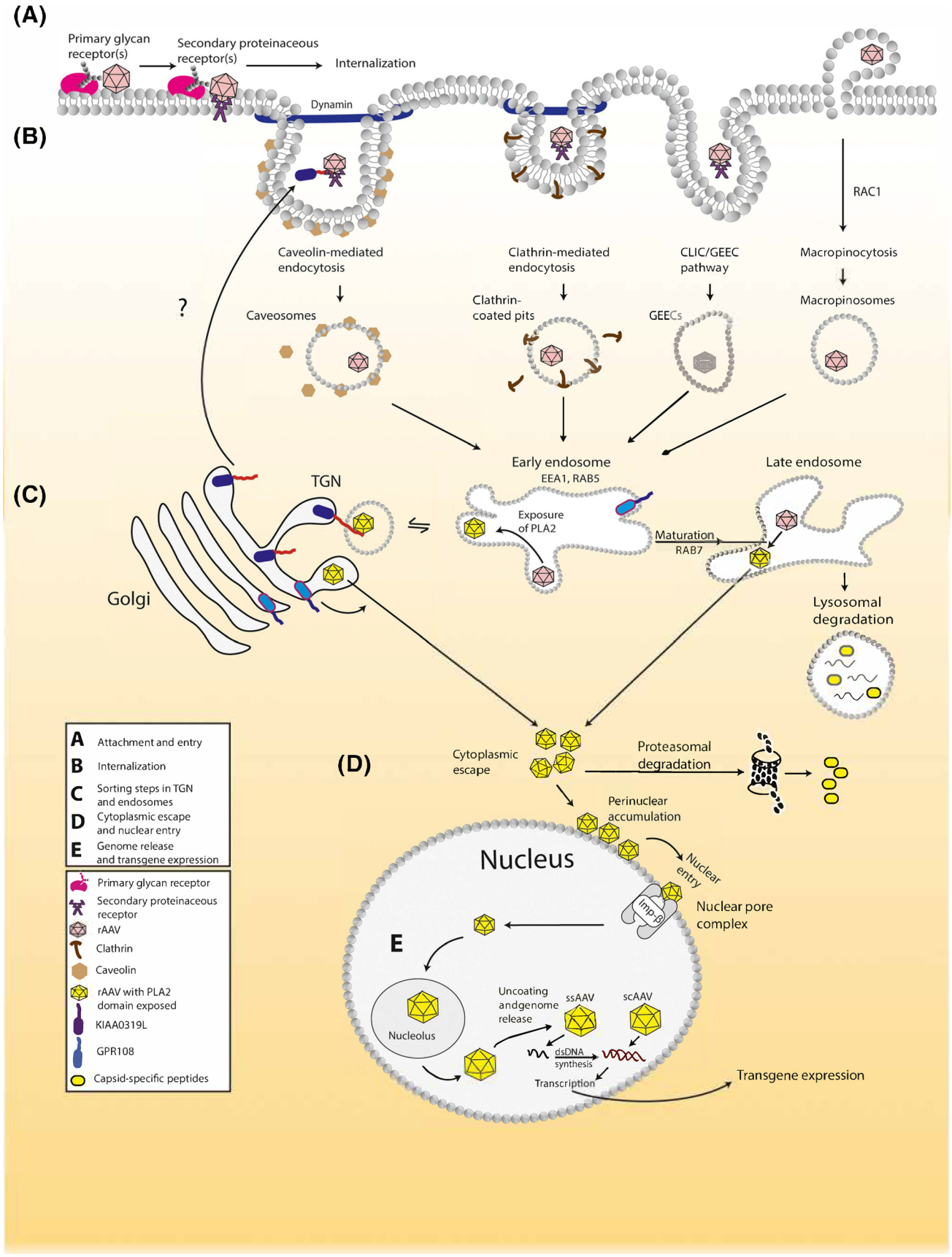
Clinical studies have consistently demonstrated the benefits of early treatment initiation in SMA, before irreversible loss of motor neurons.[12,13] Although the clinical benefits of early treatment in the presymptomatic phase are known, diagnostic delays occur. A systematic literature review revealed that lags between symptom onset to diagnosis were 3.6, 14.3, and 43.6 months for SMA types 1, 2, and 3, respectively.[33] To expedite treatment initiation, the United States, Europe, Taiwan, Japan, and Australia, among other countries and regions, have introduced newborn screening programs or pilot studies (Figure 2).[34-39] Current guidelines recommend immediate treatment for all infants with two, three, or four copies of *SMN2*.[40-42]

Recommendation: Treating physicians should discuss timing of therapeutic initiation with families, highlighting treatment urgency given that motor neuron degeneration largely occurs in the first few months and rapid decreases in motor unit number estimation and maximum compound motor action potential amplitude occur within 2 postnatal months, demonstrating irreversible loss of motor units.[43] Physicians should also highlight the benefits of early treatment[12,13] to prevent treatment delays in newly diagnosed patients.[44] Treatment decisions for presymptomatic patients may be guided by clinical context, in addition to *SMN2* copy number.[40]

Recommendation: Widespread adoption of newborn screening will facilitate early SMA diagnosis and treatment initiation, which holds the potential to improve outcomes.

5 | PATIENT- AND FAMILY-CENTERED CARE

Discussions on factors that predict treatment response are important to provide realistic expectations and goals. Although gene therapy may stabilize SMA, parents should be counseled that ongoing disability may be expected, and possibly become clinically evident for presymptomatic children. Although outcomes are improved with treatment, complications, particularly for patients with long disease duration, may arise. Discussions of potential benefits and risks or burdens of treatment are needed to manage expectations, especially for those patients with severe motor weakness, respiratory insufficiency, and bulbar dysfunction.[45] Discussions should emphasize need for continual multidisciplinary coordinated care throughout the patient's life



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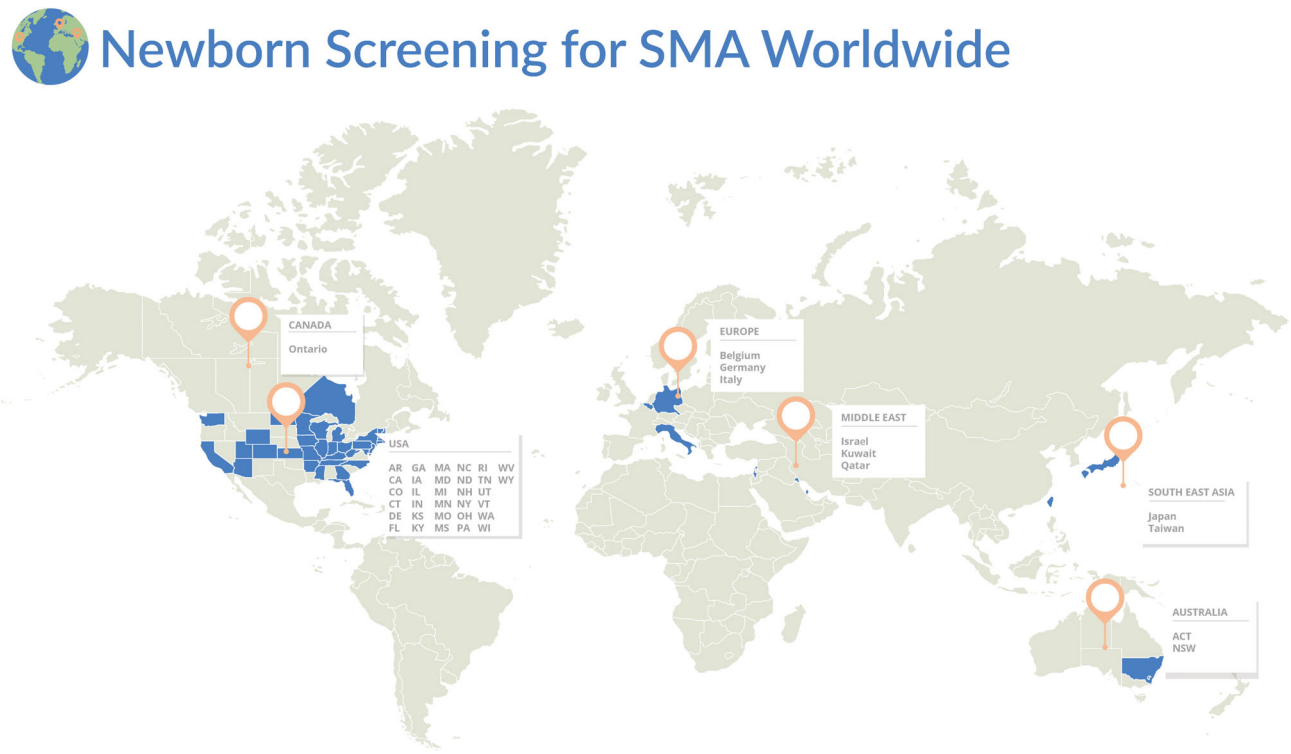

FIGURE 2 Newborn screening programs for SMA implemented globally; this includes all countries conducting newborn screening for SMA as of November 2020

and that, in agreeing to treatment, the family is also agreeing to all recommended safety monitoring. In some countries (eg, France), expert committees are used to guide treatment decisions.

Recommendation: Patient-centered multidisciplinary care should continue after treatment to optimize outcomes for patients and families.

6 | PATIENT SELECTION AND PREPARATION

Before AAV9 administration, children should be evaluated for underlying medical conditions, including severe or symptomatic liver disease, thrombocytopenia, or any other serious underlying medical conditions, that may heighten the risk of AAV9 therapy. Active infection may be a risk factor for developing thrombotic microangiopathy (TMA).[46] In the STR1VE-EU study, respiratory infection was observed in a patient who died after treatment with onasemnogene abeparvovec. This patient's death indicates that viral illness can cause severe illness, even in individuals with treated SMA. This may be exacerbated for those who have recently received gene therapy, because of corticosteroid treatment and potential adrenal insufficiency.[47]

Although age and weight limits for onasemnogene abeparvovec treatment differ by jurisdiction (Table 1), limited evidence exists on safety and efficacy in older, heavier patients, and those with advanced disease. Further research is needed to evaluate onasemnogene abeparvovec for these patients. Risk-benefit has to be carefully assessed before treatment.

Counseling on possible adverse events is also required before dosing, and close clinical and laboratory monitoring is required in the weeks to months after treatment. Although gene therapy only requires a single administration, close follow-up and safety monitoring are essential.

FIGURE 1 After intravenous administration of onasemnogene abeparvovec, the *SMN* transgene is maintained as a non-integrating episome in the nuclei of target cells. A, Attachment and entry. Cell-surface attachment of rAAV is mediated by primary glycan receptors and stabilized by proteinaceous secondary receptors. B, Internalization. AAV-based vectors utilize multiple endocytic routes during their journey towards the nucleus. C, Sorting steps. The rAAV capsid undergoes substantial conformational changes in the sorting compartments (endosomes and the Golgi). D, Cytoplasmic escape and nuclear import. After escaping the sorting compartments, vector particles accumulate around the perinuclear space and enter the nucleus via nuclear pore complexes. E, Genome release and transgene expression. Inside the nucleus, the vector genome is released and transcribed, resulting in the expression of the transgene. Abbreviations: dsDNA, double-stranded DNA; GEEC, glycosylphosphatidylinositol-anchored protein (GPI-AP)-enriched compartment; scAAV, self-complementary AAV; ssAAV, single-stranded AAV; TGN, trans-Golgi network. Reprinted from *Trends in Molecular Medicine*, Dhungel BP, Bailey CG, and Rasko JEJ, Journey to the center of the cell: tracing the path of AAV transduction, p4, 2020, with permission from Elsevier

7 | ANTI-AAV9 ANTIBODY TITERS

To be eligible to receive onasemnogene abeparvovec, SMA patients must be tested for the presence of pre-existing anti-AAV9 antibodies,[14] which can, in theory, increase the risk of immune responses, resulting in reduced transduction and limited therapeutic efficacy. SMA patients must have anti-AAV9 antibody titers of no greater than 1:50, as measured by enzyme-linked immunosorbent assay.[14]

Prevalence of antibodies against AAVs is relatively low, particularly in infants.[48,49] In infants, particularly neonates, anti-AAV9 antibodies may result from maternal transplacental transfer. Exposure to maternal neutralizing antibodies to AAV serotypes during breastfeeding may occur. However, the risk of entering the infant circulation through the intestinal mucosa is low.[50] More commonly in older children, anti-AAV9 antibodies may arise also from environmental exposure to naturally occurring AAV9.[51] Screening results from the onasemnogene abeparvovec clinical trials and the managed access program through December 31, 2019, yielded 15 of 196 patients (7.7%) with exclusionary titers (>1:50).[52,53]

When onasemnogene abeparvovec treatment is within the goals of the family and treating physician, retesting titers for patients with elevated baseline anti-AAV9 antibody titers may also be considered. Although the half-life of passively acquired immunoglobulin G (IgG) antibodies ranges from 35 to 40 days,[54] the time course of the clearance of anti-AAV9 antibodies has not been established. Retesting frequency is at the discretion of the treating physician. The extent to which baseline titers are elevated and patient age may be useful in predicting whether titers will fall, as younger patients likely have elevations because of maternal transplacental transfer vs environmental exposure. Some authors have repeated testing as frequently as weekly, typically every 2 weeks, in settings in which they anticipated titers to decrease. For young patients with baseline anti-AAV9 antibody titers of at least 1:50, titers may fall enough to permit dosing within 1 week. In the interim, other treatments may be considered. Two of three patients in START, one of six patients in STR1VE-EU, one patient in the managed access programs (MAPs), and one patient in the US commercial program (personal correspondence from Dr Proud) who initially had exclusionary anti-AAV9 antibody titers were subsequently enrolled after antibody titers had declined to 1:50 with repeat testing.[52,53]

Samples used for anti-AAV9 antibody testing (serum vs whole blood) and reference ranges differ between laboratories, which are of relevance in interpreting the results. Furthermore, differences in sample collection, processing, storage, and shipment make it difficult to easily compare results across studies. To reduce assay variability, all AAV9 antibody tests performed for eligibility of onasemnogene abeparvovec were centralized in four laboratories: two in the United States, one in Japan, and one in Europe. One US and one European laboratory defined samples less than or equal to 1:50 titers as seronegative. The other US laboratory defined samples with less than 1:25 titers as seronegative.[53]

Recommendation: The interpretation of anti-AAV9 antibody titers is based on assay and laboratory cutoffs. Repeat testing can be considered for those who initially have elevated titers depending on the specific clinical scenario. Repeat testing should also be considered if there is a prolonged period between original testing and onasemnogene abeparvovec dosing, given the risk of a new exposure. In waiting for titers to decrease, consideration of treatment with other agents, such as nusinersen, is reasonable. It should be noted that pretreatment with nusinersen leads to the dilemma of whether to continue with nusinersen after onasemnogene abeparvovec dosing. Criteria for doing so are not firmly established and pretreatment may be best considered if there are concerns about imminent deterioration of clinical status.

8 | BREASTFEEDING

Breastfeeding offers many advantages to infants, including nourishment, protective immunity, and enhanced mother-infant bonding.[55] Breast milk contains cytokines, secretory immunoglobulins, and immune cells that are transferred from the mother to the infant's gastrointestinal lumen.[56] Secretory immunoglobulin A comprises approximately 90% of total antibodies in human breast milk.[57] In humans, breast milk antibodies do not enter an infant's circulation in any substantial amount because humans lack the intestinal Fc receptor, which other mammals possess, that actively transports IgG subtypes to their circulation.[50] Immunoglobulins contained within breast milk instead remain within the intestinal lumen of human infants, acting as an important line of mucosal defense along with bactericidal lactoferrin.[58]

Recommendation: The potential benefits of breastfeeding are many. With no known risk of active transfer of immunoglobulins from the infants' intestinal lumen to circulation, we recommend infants continue breastfeeding before and after administration of onasemnogene abeparvovec, unless other contraindications exist.

9 | SCREENING FOR UNDERLYING LIVER OR CARDIAC DISEASE

The importance of evaluating baseline liver function has been highlighted in the recent tragic deaths of three patients in the phase I/II ASPIRO clinical trial, who experienced serious liver problems that appeared related to high-dose IV AT132 (AAV8-based gene therapy) for X-linked myotubular myopathy.[22] All three patients had preexisting hepatobiliary disease.[22] Liver transaminase elevations are a known risk factor with AAV vectors.[28] For patients with significant increases in transaminase concentrations, hepatic fibrosis may occur and pose a risk of liver-related complications later in life.

Assessment of liver function is particularly important given that SMA patients may have a greater risk of impaired fatty acid metabolism and/or hepatic dysfunction.[59] In identifying patients with elevated baseline concentrations of alanine aminotransferase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (GGT), and

bilirubin, one should note that reference ranges differ between neonates and older children.[60] Of the patients treated with onasemnogene abeparvovec in clinical trials, 61% had baseline elevations in ALT and/or AST and/or bilirubin, but these elevations were less than threshold values for study exclusion before dosing (greater than two- or three times the upper limit of normal [ULN]).[61]

Recommendation: Baseline ALT and AST concentrations should be evaluated to foster appropriate discussions between families and treating physicians within a reasonable time frame to dosing. When a delay in dosing is necessary, retesting baseline safety assessments should be strongly considered.

Because cardiac toxicity was observed in neonatal mice after IV onasemnogene abeparvovec infusion,[14] patients are evaluated for baseline cardiac function, including clinical examination and analysis of cardiac troponin I, a sensitive biomarker of myocardial injury,[62] before dosing. Patients with the severe phenotype may have coincident structural cardiac abnormalities.[63,64]

The troponin complex consists of three subunits, troponin I, T, and C, and is required for contraction of skeletal and cardiac muscle regulated by calcium. Both cardiac troponin I and T are increasingly used as diagnostic indicators of myocardial infarction.[62] In clinical trials, minor transient increases in troponin I along with changes in heart rate were observed after onasemnogene abeparvovec.[65] However, they were without clinical sequelae, and the clinical significance of these elevations is not known.[14] In addition, normative data on troponin I in infants and young children are limited,[66,67] and the clinical importance of mild elevations is unknown. Although baseline values are important for subsequent comparison after dosing, elevations at baseline typically do not delay dosing, and clinicians should react when appropriate.

Recommendation: Evaluation of troponin I concentration should include a comparison of results with those of age-appropriate normal ranges, as infants less than 6 months of age have greater troponin concentrations compared with older children.[66,67] Although the significance of mild elevations in baseline troponin I is unknown, consultation with a cardiologist is recommended for thorough evaluation and multidisciplinary care of those patients with abnormal baseline cardiology assessments.

Recommendation: Troponin T concentration may increase in patients with skeletal muscle diseases, including those with SMA,[68,69] further increasing with disease severity.[70] As with troponin I, its use for monitoring cardiac function in SMA patients is unknown. Consultation with a cardiologist is recommended for patients with persistently abnormal troponins.

10 | RESPIRATORY INFECTIONS AND OTHER CONDITIONS

Because infection before or after infusion could lead to more serious complications, physicians should advise caregivers of possible viral infection signs.[14] To avoid potential illness, the authors recommend families limit potential contacts and practice good hand hygiene both pre- and post-infusion.

Recommendation: In the event of an infection (eg, rhinovirus infection), patients should wait at least 2 weeks after illness resolves before initiating treatment with onasemnogene abeparvovec.

11 | POTENTIAL ADVERSE EVENTS

Adverse events have been reported after administration of onasemnogene abeparvovec. For example, treatment may result in aminotransferase elevations, particularly in older, heavier patients.[71,72] In clinical trials, 90% of children had elevations in ALT and/or AST, often occurring at week 1 as well as month 1 after therapy.[61] Two of 44 patients in clinical trials had increased AST and ALT concentrations of up to 48-times the ULN after onasemnogene abeparvovec infusion. These patients, who were otherwise asymptomatic with normal total bilirubin, were managed with systemic corticosteroids, and the abnormalities resolved without clinical sequelae. In addition, two cases of subacute liver failure after treatment with onasemnogene abeparvovec have been reported.[73]

Current prescribing information recommends liver function should be monitored for at least 3 months after onasemnogene abeparvovec infusion (weekly for the first month, and then at a minimum every other week for the second and third months, until results have normalized).

12 | ROLE OF PROPHYLACTIC PREDNISOLONE

SMA patients are treated with prophylactic prednisolone with the goal of attenuating serum aminotransferase elevations.[28] Starting 1 day before onasemnogene abeparvovec infusion, systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight/day should be administered for a total of 30 days.[14] For patients with unremarkable findings (normal clinical examination, total bilirubin, and prothrombin time, and ALT and AST concentrations below two-times ULN), the corticosteroid dose should be tapered over the next 28 days (eg, 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/kg/day). Steroid taper should not proceed faster than this recommended approach and may need to be longer and slower if more persistent abnormalities occur (discussed later).

13 | POST-DOSAGE MONITORING AND MANAGEMENT OF CORTICOSTEROIDS

13.1 | Serum transaminase elevations

Some patients, particularly older (≥8 months) patients,[72] may experience serum transaminase elevations, occurring as early as 1 to 2 weeks after infusion, with a second occurrence often observed later at 1 to 2 months post-dosing.[61] Transaminase elevations may persist for as long as 6 months in some patients, requiring a prolonged course

of prednisolone. For these patients, systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) should be continued until AST and ALT values are both below two-times the ULN and all other assessments return to normal range. Taper of corticosteroid dosage over the next 28 days should follow (Table 2).

Serum transaminase elevations may be successfully managed using different assessments and treatment regimens. In France, where 18 SMA type 1 patients (3–10 months of age) were treated, some patients experienced elevated transaminases that persisted over 8 weeks after infusion without severe hepatic failure (personal correspondence from Professor I. Desguerre). A hepatologist was consulted and echography was performed to exclude other potential causes for the elevated serum transaminase concentrations. Echography was normal in all cases, and serum transaminase concentrations were monitored. Prednisolone dosing did not need to be increased for these patients.

Recommendation: Patients with marked or persistent transaminase elevation (eg, three- or four-times ULN) may require an increased prednisolone dosage (up to 1.5 or 2 mg/kg/day), followed by close monitoring. Treating physicians may also consider pulsing with IV methylprednisolone (30-mg/kg infusion) in those patients who continue to have further increases in transaminases despite increasing their daily steroid dosages. Insufficient data exist regarding the optimal scenario on when to pulse IV methylprednisolone. We suggest that the rate of rise and height of rise should be considered on a case-by-case basis.

Recommendation: In the presence of AST and ALT elevations, we recommend analyzing synthetic liver function (international normalized ratio, prothrombin time, albumin, bilirubin, and GGT tests), as it is more indicative of liver injury. For patients with abnormalities in synthetic liver function and/or elevated bilirubin, consultation with a gastroenterologist may be required.

Recommendation: Treating physicians should counsel families on the importance of monitoring laboratory results after onasemnogene abeparvovec, and the need for potentially longer steroid dosing schedules in response to abnormal laboratory values.

Recommendation: Given the long duration of steroid treatment that may be required for some patients, consultation with an endocrinologist may be considered when pursuing treatment, given the risk of adrenal insufficiency.[74] This is important to ensure adrenal function is normal in treated patients, especially in context of a respiratory infection or other physiological stress. Examinations in older children may include a morning (8:00 AM) cortisol test and adrenocorticotropic hormone (ACTH) stimulation tests to ensure patients have recovered normal adrenal function after steroid exposure. Newborns may require additional testing to detect adrenal insufficiency because of residual adrenal reserve that can respond to synthetic ACTH[75] and lack of normal circadian rhythm in morning cortisol concentration.

Recommendation: For patients receiving prolonged corticosteroids, physicians should consider using injectable stress dosing hydrocortisone if evidence of acute illness presents in the post-dosage period. Physicians may also consider consultation with an endocrinologist in the context of acute illness of a hospitalized child receiving post-dose corticosteroids. After prednisolone is stopped, a sick-day plan for adrenal insufficiency should be provided to families according to institutional guidelines.

TABLE 2 Surveillance blood tests recommended post-dosing for liver function

United States[14]	Assess liver function (clinical examination, AST, ALT, total bilirubin, prothrombin time) at baseline, weekly for the first month, and every other week for the second and third months, until results are unremarkable.
Japan[83]	Assess liver function (clinical symptoms, AST, ALT, total bilirubin, prothrombin time) at baseline, and 3 months following (once a week for 1 month and once every 2 weeks thereafter).
European Union[84]	Assess liver function (clinical examination, AST, ALT, total bilirubin) at baseline, weekly for 30 days, and every 2 weeks for next 60 days.
Brazil[85]	Assess liver function (clinical examination, AST, ALT, total bilirubin) at baseline, weekly for the first month, and every other week for second and third months until results are unremarkable.
Australia[86]	Assess liver function (clinical examination, AST, ALT, total bilirubin, prothrombin time) weekly for the first month, and every other week for the second and third months, until results are unremarkable (normal clinical examination, total bilirubin, and prothrombin results, and ALT and AST concentrations are <2× ULN).
Canada[87]	Assess liver function (clinical examination, AST, ALT, total bilirubin, prothrombin time) weekly for 30 days, and every 2 weeks for at least an additional 60 days through the end of corticosteroid taper. A longer duration or increased dose of corticosteroid treatment may be required. Tapering of corticosteroid should not be considered until AST and ALT concentrations are <2× ULN.

Note: Surveillance recommendations from each country are shown as described in the respective prescribing information.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; ULN, upper limit of normal.

13.2 | Thrombocytopenia

In clinical trials, transient decreases in platelet counts were observed, and some met the criteria for thrombocytopenia (<75 000/μL),[14,76] often within 10 days of infusion. Those that were not attributable to other causes resolved without intervention and were without associated bleeding events.[76] Thrombocytopenia is frequently short-lived. Nevertheless, monitoring platelet counts weekly for the first month and every other week for the second and third months until platelet counts return to baseline is important (Table 3).[14] In cases of thrombocytopenia, particularly in the immediate week post-infusion, immature platelet profile can be used to monitor whether the body is appropriately making new platelets. In these cases, no treatment escalation is needed.

TABLE 3 Surveillance blood tests recommended post-dosing for platelet counts

United States[14]	Measure platelet counts at baseline, weekly for the first month, then every other week for the second and third months, until return to baseline.
Japan[83]	Platelet count should be measured at baseline and for 3 months thereafter (once a week for 1 month and once every 2 weeks thereafter).
European Union[84]	Measure platelet counts weekly for the first month and then every other week for second and third months until platelet counts return to baseline.
Brazil[85]	Measure platelet counts at baseline, weekly for the first month and then every other week for second and third months until platelet counts return to baseline.
Australia[86]	Measure platelet counts weekly for the first month, and then every other week for the second and third months, until platelet counts return to baseline.
Canada[87]	Measure platelet count before infusion and monitor weekly for the first month and then every other week for the second and third months until platelet count results are unremarkable.

Note: Surveillance recommendations from each country are shown as described in the respective prescribing information.

TABLE 4 Surveillance troponin I blood tests recommended post-dosing for troponin I

United States[14]	Measure troponin I at baseline, weekly for the first month, then monthly until return to baseline.
Japan[83]	Cardiac troponin I should be measured at baseline and for 3 months thereafter (once a week for 1 month and once a month thereafter); keep measuring until abnormalities resolve.
European Union[84]	Assess troponin I at baseline and for at least 3 months or until concentrations return to within normal reference range for SMA.
Brazil[85]	Troponin I concentrations should be monitored at baseline and then for at least 3 months or until concentrations return to normal reference range for SMA.
Australia[86]	Assess troponin I weekly for the first month, and then monthly for the second and third months, until troponin I concentrations return to baseline.
Canada[87]	Assess troponin I concentrations infusion and monitor for at least 3 months after until concentrations are unremarkable.

Note: Surveillance recommendations from each country are shown as described in the respective prescribing information.
Abbreviation: SMA, spinal muscular atrophy.

Thrombocytopenia can also be one of the first signs of TMA, along with hemolytic anemia and acute renal impairment, which has been reported in some patients receiving onasemnogene abeparvovec.[46,77] In some cases, TMA may have been precipitated by infections, triggering complement activation or dysregulation and coagulation abnormalities and underpinning recommendations to wait at least 2 weeks after illnesses have resolved before initiating treatment with onasemnogene abeparvovec. If thrombocytopenia is detected, analysis of hemoglobin, hemolysis, and renal dysfunction (including urinalysis) should be undertaken, as early identification of TMA is critical in initiating timely therapeutic intervention.[46] If clinical signs, symptoms, or laboratory findings consistent with TMA occur, physicians should manage as clinically indicated.

Recommendation: Along with clinical assessment for bruising, we recommend conducting broader laboratory analyses, such as complete blood counts, at each time point, as permitted by patient age and size, to detect thrombocytopenia and coincident hematologic abnormalities that may indicate inflammation/infection.

13.3 | Troponin I

Transient increases in troponin I and changes in heart rate without clinical sequelae were observed after onasemnogene abeparvovec.[14,65] In clinical studies, echocardiogram revealed no abnormality of cardiac contractility, as indicated by left ventricle ejection fraction and no thrombus formation in any patients with elevated troponin I concentrations. Baseline to final cardiac function remained normal for all patients. No clinically significant electrocardiogram findings were obtained.[76]

Given cardiac toxicity observed in animal studies, troponin I concentrations should be regularly monitored for at least 3 months after onasemnogene abeparvovec (weekly for the first month, and then monthly for the second and third months until troponin I concentrations return to baseline) (Table 4).[14] Clear clinical significance of troponin I elevations in the absence of other signs of cardiac disease is lacking.

There remains no consensus on increases that are significant. Repeating troponin I tests may be useful. All individuals with elevations should have history and examination reviewed for potential new symptoms. If elevations persist or are associated with accompanying concerns, consultation with a cardiologist should be strongly considered.

The clinical utility of measuring other cardiac biomarkers in place of troponin I is unknown. Original protocols for phase III studies included analyses of creatine kinase-MB. All study protocols were subsequently amended to accommodate additional cardiac safety monitoring, including troponin I measurements, in response to the findings from mouse toxicology studies.

14 | TEMPORARY VECTOR SHEDDING AND WASTE HANDLING

Onasemnogene abeparvovec vector DNA shedding post-infusion was analyzed in samples of saliva, urine, and stool from five patients in the phase I START study through the month 21 (saliva and urine) or

month 18 (stool) visit. Analysis of vector DNA by droplet digital polymerase chain reaction revealed shedding in saliva, urine, and stool after infusion, with much greater concentrations found in stool. Vector shedding decreased rapidly and was undetectable in samples after 60 days (Figure 3). Specifically, the vector DNA could be detected in saliva and urine samples through day 7, with the majority of concentrations below the limit of quantitation on day 14 (1.1×10^6 genome copies/mL) (Figures 3A and 3B, and Tables S1 and S2.). In stool, vector DNA could be detected through day 30, with the majority of concentrations below the limit of quantitation on day 60 (1.1×10^7 genome copies/mL) (Figure 3C and Table S3).

Theoretical risks of vector shedding after onasemnogene abeparvovec are extremely low, including for immunocompromised siblings. Because AAVs are not associated with disease in healthy adult humans, they are classified as a National Institutes of Health Risk Group 1 (RG1) agent,[78] with US Centers for Disease Control and Prevention biosafety level 1 (BSL1) designation.[79] Although these designations are specific to the United States and may have region-specific differences, AAVs are generally considered low risk. Onasemnogene abeparvovec is non-replicating, further adding to the drug's safety profile. Although risks of exposure to onasemnogene abeparvovec are low, the treatment may expose siblings who also have SMA to AAV9, potentially precluding them from receiving AAV9-based therapies.

Recommendation: Given that temporary vector shedding of onasemnogene abeparvovec occurs primarily through body waste, caregivers should be advised on proper handling of patient feces and contact with urine. To avoid the potential for causing a sibling to seroconvert, we recommend patients and siblings avoid bathing together during the period immediately after dosing.

14.1 | Pharmacy considerations

Onasemnogene abeparvovec requires thawing before use either at room temperature or in a refrigerator. It is a clear to slightly opaque, colorless to faint white liquid, and free of particles once thawed. Once IV access is confirmed, onasemnogene abeparvovec can be drawn up in a syringe at the appropriate dose volume, and all transfers should be performed using polypropylene materials only. Onasemnogene abeparvovec is then delivered at room temperature to the infusion location and used within 8 hours. Onasemnogene abeparvovec should be administered as a single-dose IV infusion through a venous catheter over 60 minutes.

Recommendation: The recommended dose of onasemnogene abeparvovec is 1.1×10^{14} vector genomes per kilogram of body weight.[14] Because patients' weights can change in a short period, we recommend obtaining the most up-to-date weight before ordering the medication.

Recommendation: Given onasemnogene abeparvovec's relative safety (RG1 requiring BSL1 safety equipment), personal protective equipment should be used according to institutional guidelines.

Recommendation: Vascular access can be challenging in SMA type 1. Having the best possible team to obtain access is important. Before dosing, placement of two IV lines is preferred (in case one line fails).[15]

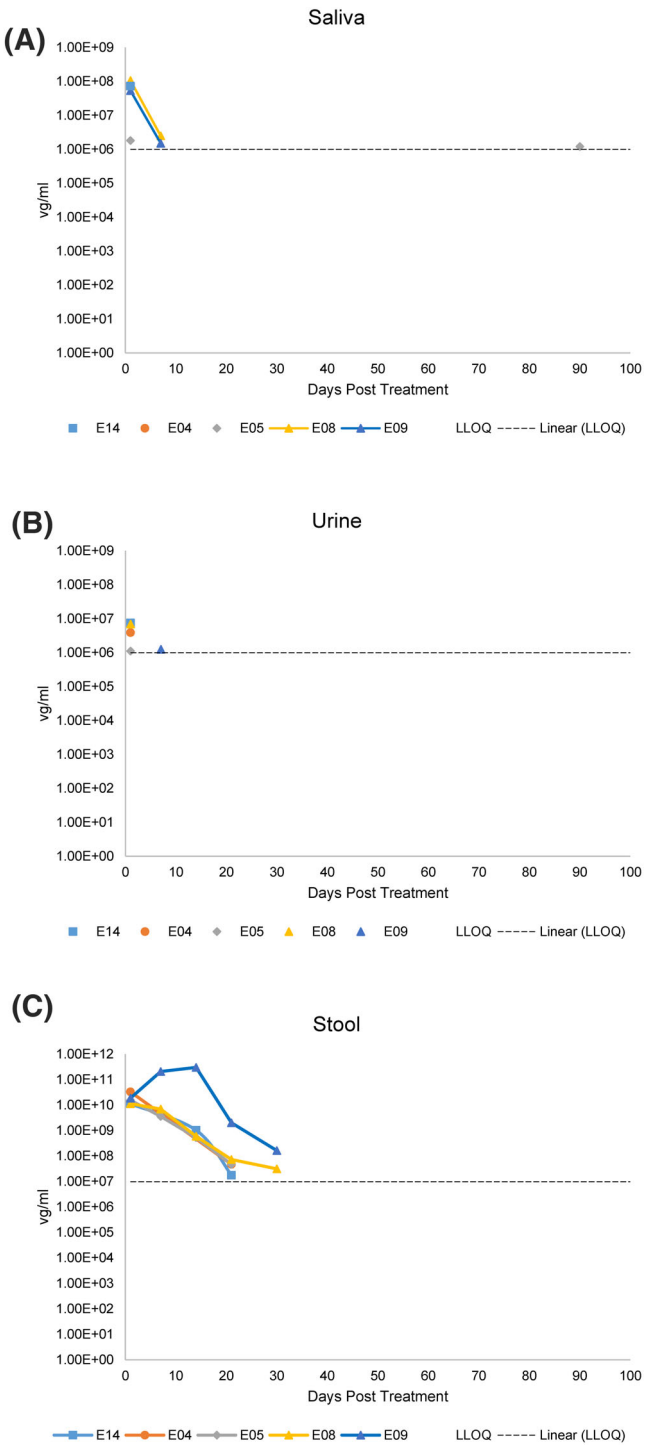

FIGURE 3 Onasemnogene abeparvovec shedding in START study patient samples over time. Viral particle titers in saliva (A), urine (B), and stool (C) samples were examined by droplet digital polymerase chain reaction. The lower limit of quantification (LLOQ) for the assay is indicated by the hatched line. Samples were taken at visit days 1, 2, 7, 14, 21, 30, 60, and 90 (shown) and monthly until month 21 post-dose (Table S1). Only those values above the LLOQ are presented

Note: There are certain circumstances in which a single line may be chosen as a result of venous access challenges. In France, 90% of SMA type 1 patients (n = 18; 3–10 months old) required a transient

central line (jugular or femoral) with local anesthesia because of difficulties with peripheral venous access.

Recommendation: All transfers must be performed using polypropylene syringes and tubing, as stability studies have been conducted to confirm drug product compatibility with those materials. Compatibility of onasemnogene abeparvovec has not been analyzed when stored in polystyrene or polycarbonate syringes.

15 | POTENTIAL DRUG INTERACTIONS

15.1 | Vaccinations

Scheduled and seasonal vaccination of patients should be adjusted to accommodate concomitant prednisolone administration (ideally a minimum of 2 weeks before infusion). Vaccines such as measles, mumps, rubella, and varicella are contraindicated for patients receiving substantially immunosuppressive steroids. Oral rotavirus vaccines are also live attenuated viruses and should be adjusted to accommodate dosing and prednisolone tapering.

Recommendation: Children should be current on all recommended vaccinations before administration of onasemnogene abeparvovec. Vaccinations should be avoided within 2 weeks before or after administration to avoid systemic inflammatory events and potential issues with thrombocytopenia. Live virus vaccines, such as vaccination against rotavirus, are contraindicated during higher-dosage prednisolone.

Recommendation: Seasonal respiratory syncytial virus prophylaxis (palivizumab) is recommended for symptomatic SMA infants. Vaccination against seasonal influenza is also recommended.

Recommendation: We recommend family members and caregivers be current on vaccines and avoid live attenuated vaccines after onasemnogene abeparvovec. We also recommend all eligible family members be vaccinated against SARS-CoV-2.

15.2 | Combination treatment

Some SMA patients have been treated with both nusinersen and onasemnogene abeparvovec. This includes patients who transitioned from nusinersen to onasemnogene abeparvovec and those who received nusinersen after gene therapy.[31,72,80] In a retrospective review of the first 21 children with SMA treated with onasemnogene abeparvovec in Ohio, 11 had been previously treated with nusinersen.[72] A 3-month gap between last nusinersen dose and onasemnogene abeparvovec infusions was implemented after one patient developed thrombocytopenia after nusinersen, followed with onasemnogene abeparvovec 1 month later.[72]

Older patients, many of whom were previously treated with nusinersen, were more likely to have had transaminase elevations and require a prolonged prednisolone course.[72] Three of these patients experienced drops in platelet counts. None had thrombocytopenia that required treatment.[72] In another case series, the clinical courses were described for two patients, one with a delayed diagnosis and the other diagnosed through newborn screening, who were initially treated with nusinersen and later treated with onasemnogene abeparvovec.[80] Improvements in both children were observed.[80] Three of four patients initially treated with nusinersen continued nusinersen after onasemnogene abeparvovec in another case series of patients treated with both nusinersen and onasemnogene abeparvovec.[31] The authors highlighted the importance of monitoring liver function. Thrombocytopenia was the main overlapping potential adverse effect, which caused more issues with potential lumbar puncture than with IV infusion. Although improvement with combination therapy was observed in these individual cases, the effect relative to monotherapy was not established. The impact of combination therapy on patient outcomes and safety is unknown and is being evaluated in clinical trials. Currently, there are no published data on combination treatment with risdiplam and onasemnogene abeparvovec, although some patients have received both treatments.

Recommendation: There is no evidence that combination therapy improves efficacy. Until evaluated in a clinical trial, no recommendations can be made regarding combination therapy. It could be considered for patients who demonstrate suboptimal responses to initial therapy. Consideration should be given to timing between treatments. Given thrombocytopenia can be an adverse effect of both onasemnogene abeparvovec and nusinersen, we recommend an interval of at least 2 weeks before and 1 month after onasemnogene abeparvovec before nusinersen is administered. Platelets should be monitored in between treatments with potential for increasing the interval of dosing if thrombocytopenia occurs. Risdiplam should not be administered until serum transaminases have normalized after onasemnogene abeparvovec.

Recommendation: Long-term registry studies will be necessary to understand the durability and safety of this treatment both alone and in combination with other therapies.

16 | ISOLATION BEFORE AND AFTER DOSING

Given the potential for treatment postponement for respiratory or other systemic infections, or the immunosuppressive effects of prednisolone, it may be beneficial for patients to be isolated to limit potential contact with other viruses (eg, flu season). This is particularly critical immediately before scheduled infusions and immediately afterward, when coinfection with another virus may increase inflammatory responses. Contact with anyone exhibiting any symptoms should be avoided, and family members should practice appropriate handwashing hygiene.

Recommendation: We recommend limiting contact with others for 2 weeks before dosing to avoid infection that would delay the dosing.

Recommendation: Although patients are immunosuppressed with steroids, especially during the first 4 to 6 weeks, we advise families to minimize exposure to other viruses that may increase risk and severity of adverse events.

17 | POST-INFUSION VOMITING AND ACUTE VIRAL REACTIONS

Vomiting is one of the most frequently observed adverse events with onasemnogene abeparvovec,[27,28] similar to other AAV gene therapy platforms. Although the exact etiology for this specific adverse event is not known, acid reflux resulting from the prednisolone may be involved, as well as an acute viral response.[81] Important clinical factors include maintaining hydration, sustaining urine output, and absorbing prednisolone.

Recommendation: Treating physicians should educate parents about the potential for vomiting after infusion, fluid management, and red flags for dehydration, and should plan around this adverse event. Parents should also be counseled on the importance of oral prednisolone. If the patient vomits within 30 minutes of prednisolone, the dose should be readministered when vomiting has ceased. Consideration may be given to use of famotidine for gastric protection and ondansetron as needed for vomiting. Hospitalization should be recommended if concerns for adequate hydration or an inability to keep down corticosteroids are observed.

Recommendation: Patients may also have acute viral reactions, including fever, with onasemnogene abeparvovec. Fever can be controlled using age-appropriate dosing of antipyretics. Ibuprofen is preferred if platelets are normal. If there is concern for thrombocytopenia, or the patient is less than 6 months of age, then acetaminophen is preferred.

18 | STANDARD-OF-CARE GUIDELINES AND NEED FOR LONG-TERM FOLLOW-UP

Despite recent advancements in SMA management, patients continue to require multidisciplinary care directed by a neurologist or other specialist with expertise in neuromuscular disease, facilitating multidisciplinary interventions. Specifically, respiratory care must be established to monitor cough, airway clearance, and potential hypoventilation. Rehabilitative therapies are recommended to improve motor skills, and may include physical, occupational, and speech therapy. Orthopedic management should also be in place to monitor contractures and scoliosis; nutrition evaluations are also required to ensure adequate feeding, growth, and swallow function.[10,82]

Recommendation: The treating physician should counsel families on the importance of multidisciplinary and long-term care after treatment, even in those who may appear to be only minimally symptomatic.

Recommendation: Long-term monitoring of treated patients through registries is important for collaboration and dissemination of outcome and safety data. Physicians should discuss the importance of participation in long-term registries with their patients' parents or guardians.

19 | CONCLUSIONS

Onasemnogene abeparvovec provides a novel, effective, single-dose treatment for SMA patients and has the potential to significantly alter the course of the disease. As more patients receive this innovative therapy, treatment centers must be prepared to handle and administer the drug. Given the progressive nature of SMA and the need to initiate treatment before irreversible motor neuron loss, physicians must be able to identify those patients eligible to receive onasemnogene abeparvovec through newborn screening whenever possible, make careful baseline assessments, conduct follow-up assessments, and educate caregivers. Long-term registry studies will be necessary to understand the durability and safety of this therapy both alone and in combination with other therapies.

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CONFLICT OF INTEREST

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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