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Thrombotic Microangiopathy Following Onasemnogene Abeparvovec for Spinal Muscular Atrophy: A Case Series

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Spinal muscular atrophy is treated with onasemnogene abeparvovec, which replaces the missing *survival motor neuron 1* gene via an adeno-associated virus vector. As of July 1, 2020, we had identified 3 infants who developed thrombotic microangiopathy following onasemnogene abeparvovec. Early recognition and treatment of drug-induced thrombotic microangiopathy may lessen mortality and morbidity. *(J Pediatr 2021;231:265-8).*

Onasemnogene abeparvovec (Zolgensma) is an adeno-associated virus vector-based *survival motor neuron 1* gene (*SMN1*) therapy, approved in the US, Europe, Japan, Brazil, Israel, and Canada for the treatment of children with spinal muscular atrophy (SMA). This therapy helps patients with SMA produce adequate SMN protein. It is a one-time intravenous infusion, administered concomitantly with corticosteroid (followed by subsequent taper) to ameliorate CD8+ T-cell–mediated immunity against adeno-associated virus capsids in host liver cells. The most common adverse reactions associated with onasemnogene abeparvovec reported in clinical trials were elevated aminotransferases and vomiting.[1] Warnings and precautions listed in the US prescribing information are acute serious liver injury, elevated aminotransferases, thrombocytopenia, and elevated troponin-I.[1] Acute liver injury can occur, and serial monitoring of liver function, platelets, and troponin-I concentrations are recommended.

Thrombotic microangiopathy (TMA) is characterized by arteriole and capillary endothelial pathology and microvascular thrombosis. TMA presents clinically as a syndrome of hemolytic anemia, thrombocytopenia, and acute kidney injury. TMA is rare, occurring in 1.0-3.3 cases/million/year,[2,3] and can result from either genetic or acquired etiologies, such as exposure to toxins or infections and adverse drug reactions,[4] resulting in dysregulation of the alternative pathway of complement. Some features of TMA overlap with thrombotic thrombocytopenic purpura. However, activation of the alternate complement pathway and resultant acute kidney injury differentiates TMA from thrombotic thrombocytopenic purpura. Drug-induced TMA has been reported in association with many pharmaceutical products, including vaccines, immunosuppressive agents, and antibiotics, as well as nonprescription substances, such as herbal or alternative therapies.[4]

SMA	Spinal muscular atrophy
TMA	Thrombotic microangiopathy
vWF	von Willebrand factor

Although the actual mechanisms of TMA can vary, some reports have suggested etiologies that include direct toxic effects (sometimes dose- and duration-dependent) as well as immune-mediated reactions.[4] Neurologic, cardiovascular, and respiratory complications may occur. Treatment of TMA includes withdrawal of the trigger agent, when possible, and supportive care. Refractory or progressive cases also may require plasmapheresis, dialysis, or anticomplement monoclonal antibody therapy, such as eculizumab.[5]

We report 3 children with new adverse reactions of TMA following onasemnogene abeparvovec infusion and discuss potential etiologies, with the aim to increase awareness to optimize early recognition and treatment of TMA in these children.

Methods

Using data from the Novartis Global Safety Database, we conducted a search of all cases who were administered onasemnogene abeparvovec for SMA through July 1, 2020, using the search terms "haemolytic uraemic syndrome," "microangiopathic haemolytic anaemia," "thrombotic microangiopathy," "thrombotic thrombocytopenic purpura," "microangiopathy," "acute kidney injury," and "haemolytic anaemia" to identify any cases of TMA reported. This database includes safety information from the clinical trials, managed access programs, and postmarketing (commercial) settings. Three cases were identified and the corresponding child neurologist and pediatric nephrologist from each center were contacted to provide complementary data from the patient's medical record in a deidentified manner.

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Table. Overview of thrombotic microangiopathy reports for SMA patients treated with onasemnogene abeparvovec

Variables	Case 1	Case 2	Case 3
Country	US	Australia	US
Source of report	RESTORE	MAP	RESTORE
Demographics	5 mo, female	12 mo, female	14 mo, female
Patient weight at dosing	6.5 kg	12.1 kg	8.7 kg
Time to onset and first symptom following onasemnogene abeparvovec	7 d; hypertension, decreased urine output	8 d; vomiting, reduced oral intake and urine output	7 d; vomiting, dehydration
Nusinersen (most recent dose)	No	Yes (1 mo previously)	Yes (4 mo previously)
Laboratory evidence of TMA (baseline and following onasemnogene abeparvovec)			
Hemoglobin	Baseline: 10.3 g/dL Nadir: 7 g/dL (day 7)	Baseline: 11.4 g/dL Nadir: 9.6 g/dL (day 10)	Baseline: 12.5 g/dL Nadir: 6.1 g/dL (day 13)
Platelet	Baseline: 503 k/μL Nadir: 17 k/μL	Baseline: 378 k/μL Nadir: 11 k/μL	Baseline: 506 k/μL Nadir: 17 k/μL
Creatinine	Baseline: 0.1 mg/dL Peak: 0.7 mg/dL	Baseline 0.28mg/dL Peak: 0.93 mg/dL	Baseline: 0.1 mg/dL Peak: 0.3 mg/dL
LDH	Peak: 4208 U/L	Peak: 2902 U/L	Peak: 1677 UL
Urinalysis	Protein and blood	Protein and blood	Protein and blood
PT, PTT, and INR	Normal	Normal	Normal
Vaccines within 1 mo of onasemnogene abeparvovec	Yes (influenza, Prevnar, and Haemophilus influenzae type B, given 6 days after therapy	Yes (10 days previously)	No
Concurrent infections	Aspiration pneumonia 4 d before dosing; (*Acinetobacter baumannii* and *Pasteurella*) Second event of pneumonia 3 d after dosing	No	Urinary tract infection 3 d after presentation (*Escherichia coli*)
Acute complement pathway investigations (classic/alternative) at presentation of TMA	**Complement (C3)** 1.1 g/L (ref 0.9-1.8) **Complement (C4)** 0.07 (ref 0.15-0.57) **Bb fragment concentration** 3.8 mg/L (ref <2.2) **Soluble C5b-9** 0.9 mg/L (ref <0.3) **CH50** 160 U eq/mL (ref >70) **FH autoantibody** <50 AU (ref <200 AU) **Factor B** 32.3 mg/dL (ref 22-50) **Factor H** 369 mg/L (ref 180-420) **Factor I** 34 mg/L (ref 16-40)	**Complement (C3)** 0.62 g/L (ref 0.72-1.64) **Complement (C4)** 0.05 g/L (ref 0.14-0.42)	**Complement (C3)** 57.8 mg/dL (ref 90-180) **Complement (C4)** 0.13 g/L (ref 0.15-0.57), **Bb fragment concentration** 2.8 mg/L (ref <2.2) **Soluble C5b-9** 0.95 mg/L (ref <0.3) **CH50eq** 134 U Eq/mL (ref >70) **Alternative pathway functional assay** 62% (ref 50%–130%) **Hemolytic assay** 0.6% (ref <3%) **FH autoantibody** <50 AU (ref <200) **Factor B** 30.7 mg/dL (22-50) **Factor H** 330 mg/L (ref 180-420) **Factor I** 35.5 mg/L (ref 18-44)
Treatments	PRBC and platelet transfusions, glucocorticoids, plasmapheresis, diuretic for fluid overload, antihypertensives	IV methylprednisolone, low-potassium diet, furosemide for fluid overload, antihypertensives, close clinical and laboratory monitoring	PRBC transfusion, methylprednisolone followed by PO prednisolone, 25% albumin, furosemide, antihypertensives, eculizumab (single dose)
Outcome (time from diagnosis)	Recovered (2 wk) with persistent hypertension	Recovered (4 wk)	Recovered (4 wk) with resolution of hypertension and nephrotic syndrome (3 mo)
Investigations concerning potential predisposition factors (hereditary or acquired)	Functional complement assay with low C4, and normal C3, CFH, I, neg CFHAb, CH50, high C3b-9 (SMAC) ADAMTS13 normal No genetic testing completed Stool and urine cultures negative	Functional complement assays normal (C3, C4, CFH and I, neg anti-CFHAb, CD46) ADAMTS13 normal No genetic testing completed Stool and urine cultures negative	Functional complement assay with low C3 and C4, and normal CFH, I, neg CFHAb, CH50 ADAMTS13 normal *ACTN4* gene and Heterozygous missense variant p.G855R in *FAT1* gene Stool culture negative; urine culture + for *E coli*

ACTN4, alpha-actinin-4; *ADAMTS*, a disintegrin and metalloproteinase with thrombospondin motifs; *CFHAb*, anti-complement factor H autoantibody; *FH*, factor H; *INR*, international normalized ratio; *IV*, intravenous; *LDH*, lactate dehydrogenase; *MAP*, managed access program; *PO*, by mouth; *PRBC*, packed red blood cell; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *RESTORE*, registry of patients with spinal muscular atrophy receiving disease-modifying therapies.

Results

All 3 children received prednisolone 1 day prior to and for a minimum of 30 days following treatment with 1.1×10^{14} vg/kg of onasemnogene abeparvovec (Table).

Case 1

A 5-month-old female patient was treated with onasemnogene abeparvovec while hospitalized and undergoing treatment for aspiration pneumonia. Four days before dosing, her sputum culture grew *Proteus* and *Acinetobacter* species. She had another episode of pneumonia 3 days after onasemnogene infusion. Seven days after onasemnogene infusion, she developed TMA with hemolytic anemia, hematuria, proteinuria, leukocytosis, thrombocytopenia, and severe hypertension. Renal ultrasound scan indicated diffuse increase in cortical echogenicity bilaterally. The features of TMA resolved within 2 weeks following plasmapheresis, except hypertension, which continues to persist 1 year later. Functional TMA panel indicated evidence of complement pathway activation with no autoantibodies or abnormal complement components. Genetic evaluation was not performed.

Case 2

A 12-month-old female patient was at her baseline with no active infections when she received onasemnogene abeparvovec. Six days following onasemnogene abeparvovec infusion, she developed twice-daily vomiting, although she tolerated oral corticosteroid dosing. Eight days postinfusion, she presented with reduced oral intake and urine output and was hypertensive. Laboratory tests showed hemolysis, thrombocytopenia, transaminitis, and acute kidney injury with microscopic hematuria and significant albuminuria. Renal ultrasound scan indicated increased echotexture and reduced corticomedullary differentiation. Echocardiogram indicated mild pericardial effusion. However, by day 12 after infusion, she began to improve with supportive care, and complete resolution occurred within 4 weeks.

Case 3

A 14-month-old female patient with a family history of chronic kidney disease of unknown etiology in 2 second-degree relatives received onasemnogene abeparvovec while in her usual state of health without active infection. She developed intermittent vomiting 1 day after infusion, which persisted, although she tolerated oral corticosteroid dosing with the use of ondansetron as needed. One week following onasemnogene abeparvovec infusion, she presented with dehydration, thrombocytopenia, hemolytic anemia, hypoalbuminemia, and acute kidney injury. Complement (C3) was depressed. Initial urinalysis revealed proteinuria, but urine culture was negative. The patient became febrile 3 days after initial presentation, and repeat urine culture at that time grew *Escherichia coli* ≥100 000 colonies/mL. Treatment included blood transfusion, eculizumab (single dose), increased corticosteroids (5 mg/kg/day intravenous methylprednisolone), and other supportive therapy. TMA resolved after 4 weeks and nephrotic-range proteinuria resolved 3 months after initial presentation, but hypertension persists. Genetic testing showed heterozygous variants of unknown significance in the actinin alpha-4 (*ACTN4*) and *FAT* atypical cadherin 1 genes.

Discussion

We have reported 3 children with SMA who developed TMA following onasemnogene abeparvovec therapy. These cases share several similarities. TMA developed approximately 1 week following onasemnogene abeparvovec infusion, 2 of the 3 children suffered from vomiting, 2 of the 3 had previous exposure to nusinersen, and 2 had infections with encapsulated organisms. Patient 1 had an infection preceding TMA with a new infection shortly after infusion, and patient 3 developed an infection shortly after infusion. All 3 children recovered from TMA. One recovered with supportive measures only. The other 2 resolved with additional therapies such as plasmapheresis, increased corticosteroids, and/or transfusions.

TMA is a syndrome of microvascular hemolysis and kidney injury that results from various etiologies, including drug exposure. Several medications and herbal supplements have been associated with TMA, including quinine, cyclosporine, and tacrolimus.[4] Drug-induced TMA is theorized to result from immune-mediated reactions or a dose-/duration-dependent direct toxic effect. Differentiating criteria include early temporal association with drug administration in the former as opposed to a delayed onset from a cumulative exposure in the latter. Our 3 patients developed TMA approximately 1 week after administration, suggesting an immune-mediated etiology.

Other causes and presentations of TMA include hemolytic uremic syndrome resulting from shiga toxin-positive *E coli*; thrombotic thrombocytopenic purpura resulting from a reduction of ADAMTS13, the protease that cleaves von Willebrand factor (vWF); hereditary deficiencies in regulation of coagulation or alternative complement pathways[3]; and a wide variety of infectious pathogens, including encapsulated organisms.[6]

In addition to exposure to onasemnogene abeparvovec, each of the 3 patients had contributory factors that could be putatively associated with TMA. Potential triggering factors include concurrent infection with encapsulated bacteria and recent vaccine exposure. It is unknown what additional risks to onasemnogene abeparvovec, if any, previous exposure to nusinersen confers. One patient had a gap of 4 months between the most recent nusinersen exposure and treatment with onasemnogene abeparvovec. Few studies have specifically addressed the safety of onasemnogene abeparvovec following exposure to nusinersen, and vice versa.[7,8] Two of three children first developed vomiting, which may have been an early symptom of TMA and potentially resulted in inadequate prednisolone absorption. Two of the cases were

associated with increased complement activation by the alternate pathway. One patient had received eculizumab, a humanized monoclonal antibody targeted against complement C5, without subsequent improvement in symptoms.[5]

Whether children with SMA are at increased risk for TMA is unknown. Children with SMA have been reported to have coagulation abnormalities. Specifically, Wijngaarde et al reported data from 98 patients with SMA (types 1-4; median age of 7.4 years), revealing significant prolongation of both activated partial thromboplastin time and prothrombin time, as well as increased platelet counts.[9] The vWF antigen and vWF activity were also significantly decreased, and this was related to disease severity. No other significant abnormalities in coagulation factors II, V, VII, VIII, or X were observed. Future studies are needed to elucidate the role of genetic complement-mediated predisposing factors and coagulation abnormalities in the pathogenesis of TMA in SMA.

Nephrotic syndrome at presentation is not a classic feature of TMA. Patient 3, who had persistent nephrotic syndrome, did not have proteinuria or other signs of nephrotic syndrome during nusinersen treatment. She did, however, have a family history of chronic kidney disease and was found to have heterozygous *ACTN4* and *FAT1* variants of unknown significance. These variants are not clearly pathogenic, but *ACTN4* mutations are associated with familial focal segmental glomerulosclerosis.

Irrespective of contributory factors, these 3 case reports, from approximately 500 patients exposed, indicate a plausible association between onasemnogene abeparvovec with TMA based on their temporal association. Of note, TMA has been reported following treatment with other gene therapies using an adeno-associated vector, including cases in a Duchenne muscular dystrophy program.[10] These cases have been reported in a clinical trial of adeno-associated viral vector human gene therapy for Duchenne muscular dystrophy, but case details are not available to determine whether there are further similarities with our cases.[10]

Because thrombocytopenia is a key feature of TMA, platelet counts should be monitored, as already recommended in the onasemnogene abeparvovec US prescribing information.[1] If thrombocytopenia is present and there is a clinical suspicion of TMA, further evaluation including hemoglobin and testing for hemolysis and renal dysfunction (including urinalysis) also should be obtained. Early recognition of TMA is imperative, as TMA may require therapeutic intervention such as plasmapheresis, dialysis, or pharmacotherapy, to lessen associated morbidity and mortality. ■

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