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Single Case

Eculizumab for Thrombotic Microangiopathy Induced by Onasemnogene Abeparvovec in Spinal Muscular Atrophy

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Keywords
Spinal muscular atrophy · Gene replacement therapy · Onasemnogene abeparvovec · Thrombotic microangiopathy · Eculizumab

Abstract
Introduction: Onasemnogene abeparvovec is one of the three disease-modifying therapies available that can significantly improve the outcome of patients with 5q-spinal muscular atrophy. Therapy-induced thrombotic microangiopathy is an ultra-rare, but potentially life-threatening condition of not yet clearly defined aetiology. ***Case Presentation:*** A case of a 2-year-old patient with 5q-spinal muscular atrophy, who developed thrombotic microangiopathy after gene replacement therapy with onasemnogene abeparvovec, is described. This severe adverse event was promptly recognized and successfully treated with the complement C5 inhibitor. ***Conclusion:*** Thrombotic microangiopathy is an ultra-rare, but potentially life-threatening condition that can occur after onasemnogene abeparvovec therapy. Anticipation of these serious adverse events, its prompt recognition and treatment is crucial for a better outcome.

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Introduction

5q-spinal muscular atrophy (SMA) is an autosomal recessive disease that causes degeneration and loss of lower motor neurons, leading to progressive muscle weakness and skeletal muscle atrophy [1]. Onasemnogene abeparvovec (OA; Zolgensma, Novartis) is one of the three disease-modifying therapies available that can significantly improve the outcome of patients with SMA, particularly if they are treated early, ideally when the symptoms of the disease are not yet clearly visible (so-called presymptomatic phase), although the disease processes may have already started [2].

OA is an adeno-associated virus vector 9 (AAV9)-based therapy carrying a functional copy of the survival motor neuron 1 (SMN1) transgene. A strong immune response is expected after AVV9-associated treatment [3], especially when infused systemically [4]. The most frequently reported adverse reactions to OA in clinical trials are elevated aminotransferase levels, pyrexia, thrombocytopenia, and vomiting [5]. The frequency of adverse events has been shown to increase with age and weight [6].

OA therapy-induced thrombotic microangiopathy (TMA) is an ultra-rare, but potentially life-threatening condition of not yet clearly defined aetiology [7], affecting 1.0–3.3 per million patients treated with OA per year [7]. There are two potential mechanisms of TMA in the OA therapy setting. The first is an increased platelet aggregation or activation of the coagulation cascade, as in ADAMTS-13 deficiency-related TMA or thrombotic thrombocytopenic purpura and disseminated intravascular coagulation. The haemolytic uremic syndrome, i.e., the direct activation or lesion of the endothelial cells with a transition from a quiescent state to a proinflammatory and prothrombotic state, as in the predominantly renal TMA, is the second potential mechanism [4]. In the latter case, the complement is also activated and exhibits a second hit to the endothelial cell. It has been previously reported that concurrent or recent infections are often related to TMA after treatment with OA, while the role of vaccine exposure prior to OA treatment is less clear [7].

We describe the case of a 2-year-old female patient with SMA type II, who developed TMA after gene replacement therapy with OA. She was successfully treated with the complement C5 inhibitor, a recombinant humanized monoclonal antibody eculizumab.

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient parents for publication of the details of this medical case. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000546114).

Case Report

A 26-month-old girl was referred to the University Children's Hospital, University Medical Centre Ljubljana (UMCL), Slovenia, because of generalized hypotonia and a significant delay in achieving gross motor skills, which became apparent after the first year of life. Her antenatal and perinatal history were uneventful; the family history of neuromuscular disorders was negative.

At 18 months of age, progressive hypotonia and gross motor delay became evident. At our hospital, a neurological assessment revealed an absence of deep tendon reflexes on the lower limbs and decreased muscular strength. Gower's sign was positive, she was not able to walk without support, and her gait was waddling. Her Hammersmith Functional Motor Scale-Expanded (HFMSE) scale score was 34. A general physical examination was otherwise unremarkable. SMA type II was suspected and confirmed with genetic testing 14 days after her

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referral to UMCL. An MLPA analysis revealed homozygous deletion for SMN1 and gene conversions at exons 7 and 8. Three copies of the SMN2 gene were identified. All three treatment options with nusinersen, risdiplam, and OA were discussed in detail with the parents, underlining the benefits and potential adverse events of each treatment option. The parents opted for treatment with OA. European Medicines Agency (EMA) and the Health Insurance Institute of Slovenia, who finances the treatment costs including the costs of potential complications, have approved treatment with OA for patients with variants affecting *SMN1* gene, who have either been diagnosed with SMA type 1 (the most severe type) or have up to 3 copies of another *SMN2* gene. We have explained to the parents that although there was previous experience with OA treatment of children with SMA, there was limited experience in treating SMA patients older than 2 years of age or with body weight above 13.5 kg [6]. It was made clear to them that the likelihood of experiencing more adverse events was higher in heavier/older children – a risk they accepted. The girl was tested for the presence of anti-AAV IgG antibodies. The endpoint dilution ratio was 1:12.5, which was inferred as clinically insignificant. Compound muscle action potential measurements were performed, showing significantly decreased values. Infections were excluded and she stayed in isolation with her mother for 3 days prior to treatment to avoid the risk of infection. Supportive treatment with prednisolone was started 1 day prior to treatment with OA.

On the day of treatment, the patient was 26 months old and weighted 11.4 kg. She was infused with OA at a dose of 63.3 mL = 1.27×10^{15} vg/kg (vector genome per kg). 3 days after treatment, her aminotransferase levels expectedly became elevated (×2.6), as well as LDH (Table 1), and thrombocytopenia was present. She had a fever without any clinical signs of infection and inflammatory markers and troponin remained normal. Her fever resolved within the next day and on the 7th day she was discharged from hospital.

On the 9th day, she was readmitted to hospital due to nausea and vomiting, which had started a day before, and the presence of dark urine. She was hypertensive and had oliguria. Laboratory tests revealed haemolytic anaemia, thrombocytopenia, fragmented erythrocytes, high AST, LDH, ferritin, and D-dimer, including signs of acute kidney injury with proteinuria, haemoglobinuria, and reduced glomerular filtration; troponin was not elevated (Table 1). Kidney US revealed higher echogenicity of the kidneys. TMA was suspected. Complement investigations showed a clear activation of terminal complement pathway with elevated C5b-9 and CBb (Table 2). ADAMTS13 activity was normal, and verocytotoxin in stool was negative. As the child was in a serious, potentially life-threatening condition, and TMA after OA treatment can be driven by complement activation, we decided to treat her with eculizumab, a C5 complement inhibitor. All other necessary supportive treatment was also offered (transfusion of concentrated erythrocytes, fluids, electrolytes. . .). Steroid treatment was not escalated as aminotransferase levels did not rise above the levels set in the treatment protocol.

She received the first dose of eculizumab on the 9th day after OA application together with penicillin prophylaxis. Cumulatively, she received 4 doses of eculizumab at 0, 7, 21, and 35 days (9, 16, 30, and 44 after OA treatment). An aHUS treating protocol [8] was used. Molecular genetic testing did not reveal any genetic causes of TMA (we have used next-generation sequencing to analyse target genes for TMA: C3, CD46, CFB, CFH, CFRP1,3,4,5, CFI, DGKE, MMACHC, ADAMTS13, INF2, THBD, VTN).

In the days following the first dose of eculizumab, a shift towards the gradual improvement of haematologic and renal parameters (Table 1) and inhibition of the complement system (Table 2) were noted. The girl also started eating and drinking. She was discharged from hospital on the 24th day. She still needed treatment with amlodipine for high blood pressure, which was gradually discontinued in the next 2 months. She has recovered completely from TMA, with no relapses or sequelae.

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Table 1. Summary of laboratory parameters

Treatment	Day	Anaemia			Thrombocytopenia	Renal impairment			
		Hb, g/L	LDH, µkat/L	haptoglobin, g/L	Pt, $\times 10^{-9}$/L	creatinine, µmol/L	eGFR, mL/min/1.73 m^2	u-prot/kr, g/mol	u-RBC
	−1	109	/	/	384	19		<20	0
OA	0								
	+1	102	5.86	1.70	285	13	>90	<20	0
	2	109	**7.70**	2.40	285	14	>90	/	/
	3	109	/	/	155	16	>90	**43**	0
	4	110	**12.66**	5.70	**80**	16	>90	/	/
	5	113	**12.75**	/	**62**	10	>90	/	/
	6	104	**10**	/	**39**	/		/	/
	7	**97**	**23**	**0.10**	**36**	24	>90	/	/
E1 RBC Tx	9	**81**	**54.65**	**0.07**	**50**	**57**	**72**	**4+** (dipstic)	**7**
	10	138	**40.33**	**0.07**	**39**	/	/	/	/
	11	124	**33.66**	/	**58**	**66**	**62**	/	/
	12	114	**25.20**	/	**62**	**54**	**76**	/	/
	14	103	**18.61**	**0.07**	**99**	41	>90	**1,456**	/
	15	**90**	**14.60**	/	170	29	>90	**3+** (dipstic)	**2+** (dipstic)
E2	16	**91**	**11.61**	**0.20**	172	28	>90	**43**	/
	17	**89**	**10.19**	**0.30**	227	26	>90	/	/
	18	**88**	6.66	**0.10**	301	/		/	/
	21	**88**	/	/	433	25	>90	<20	/
E3	30	102	4.83	0.40	467	16	>90	<20	0
	37	106	4.36	0.63	362	15	>90	<20	0
E4	44	120	5.13	0.69	405	15	>90	<20	0
	56	126	4.42	0.72	439	19	>90	<20	0

Normal values: Hb, 107–139 g/L; LDH, <5.62 µkat/L; haptoglobin, 0.30–2.00 g/L; Pt, 150–410 × 10^{-9}/L; creatinine, 21–41 µmol/L; eGFR, >90 mL/min/1.73 m^2; u-prot/kr, <20 g/mol; u-RBC, >3.

OA, onasemnogene abeparvovec; E, eculizumab; RBC Tx, red blood cells transfusion; Hb, hemoglobin; Pt, platelets.

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Table 2. Complement profile

Day	0	9	16	30	44	69	176
treatment	OA	E1	E2	E3	E4		
Classical pathway (%)[a]		82			**10**	**5**	138
Alternative pathway (%)[a]		104			**1**	**1**	74
Lectin pathway (%)[a]		64			1	1	61
C3, g/L		1.09			1.27	1.25	1.39
C4, g/L		0.13			0.21	0.17	0.20
FH, mg/L		**912**			**714**	**722**	592
FB, mg/L		419			292	255	297
FI, mg/L		39			31	34	30
Anti-FH		Neg			Neg	Neg	Neg
C3Nef		Neg			Neg	Neg	Neg
Anti-C1q		Neg			Neg	Neg	Neg
C5–9 lytic complex, ng/mL		**902**			117	160	93
Bb, µg/mL		**4.18**			0.67	0.88	0.72

Normal values: classical pathway (72–128%), alternative pathway (46–102%), lectin pathway (0–125%), C3 (0.60–1.30 g/L), C4 (0.10–0.30 g/L), FH (380–674 mg/L), FB (183–604 mg/L), FI (21–42 mg/L), C5–9 lytic complex (127–303 ng/mL), Bb (0.49–1.42 µg/mL).

OA, onasemnogene abeparvovec; E, eculizumab.

[a]Classical pathway activity was determined by haemolysis of erythrocytes by complement activation via the classical pathway, while the activity of the alternative and lectin pathways were measured by the functional ELISA-based procedures.

At 28 months of age, 2 months after OA treatment, her compound muscle action potential values were improved, a trend that continued to 6 months after treatment. At 31 months of age, she was tapered of steroids as her aminotransferase levels fell in reference values. At 35 months, her HFMSE scale score was 46 (12 points above the initial 34 points). Hypotonia and decreased muscle strength were still noticeable, particularly in the lower limbs and pelvic muscle girdle. She could make up to ten steps unaided, but her gait was broad based and waddling. Lung spirometry revealed normal values for age.

Discussion

We present the clinical case of a 26-month-old girl with SMA who was treated with OA and developed a clinical picture of TMA a week after treatment. So far, 13 patients have been described who developed TMA after viral vector-based gene therapy, of which 8 were treated with OA due to SMA, while the other 5 received vector-based gene therapy for other indications [4]. In all of the described patients in whom the time from gene therapy to TMA had been recorded, TMA mainly occurred in the first week after gene therapy [4], similarly to our patient. The treatment options are equivocal, while we decided to treat our patient with eculizumab.

Gene therapy with OA offers many hopes for patients with SMA, but although an intense immune response to AAV vectors can be expected it poses a unique challenge that can affect its safety and efficacy. The pathophysiological mechanisms of TMA are not completely understood, but it seems that direct endothelial cell injury induced by a high-dose viral load, potentially exacerbated by complement activation as a "second hit," is the most probable one [4]. All reported SMA patients with TMA due to OA were treated with some kind of complement modifying therapy (plasma exchange, plasma infusion, or eculizumab), which seems logical as complement appears to be a very important player in gene-therapy-induced TMA [4]. Complement activation by AAV is primarily antibody dependent (classical pathway), triggered by anti-capsid IgM and IgG antibodies that can cause complement-mediated cell damage [4, 9]. Complement can also be activated by direct interaction of the C3 protein and AAV capsid proteins (alternative pathway) [4]. All pathways result in the formation of C3 convertase, which cleave C3 into C3a and C3b, the later binds to C4b2b and creates C5 convertase. C5 convertase produces C5a and C5b. The first is a potent mediator of inflammation, while C5b binds to C6, C7, C8, C9 and generates C5b-9 membrane attack complex, leading to cell lysis and cell death. [10]. Both C5a and membrane attack complex can cause acute hepatic, myocardial, and endothelial injury leading to TMA [11]. A complement profile in our patient has shown terminal pathway activation.

The outcome in our patient was excellent, with full renal recovery and no relapses in the 9-month follow-up period, while in 8 reported cases developing TMA after OA the outcome was not always favourable. One patient died, another developed chronic kidney disease, and three remained hypertensive [4, 5]. Patients who received eculizumab had a full TMA resolution, except for the one patient who died and the one who ended up with chronic kidney failure [4]. Based on a detailed analysis of this case, one could conclude that the patient had died because of new-onset sepsis with multiorgan failure and severe dysautonomia, which compromised hemofiltration 1 month after TMA [4, 11]. In this patient, a variant of unknown significance was also found in the complement factor I gene. We found no genetic causes of TMA in our patient, which could be a protective factor. Although evaluating patients for potential additional risk factors for TMA would contribute to minimizing the risks of OA treatment, performing a genetic analysis of these genes before treatment might be too time-consuming or unavailable in certain environments to warrant testing before OA treatment. However, if a variant in one of these genes was found, the patient might be able to have the chance to select a different disease-modifying treatment for SMA that would minimize the risk of TMA. The study by Salabarria [12] suggests that TMA in the setting of AAV gene therapy is antibody dependent (classical pathway) and amplified by the alternative complement pathway, and patients receiving prophylactic immunosuppressive treatment (rituximab and sirolimus) did not have a significant change in IgM or IgG and had minimal complement activation. Such prophylactic treatment could be another strategy to minimize the risk of TMA.

Our patient was treated with OA rather late in her life (at the age of 26 months) due to her late referral to our tertiary paediatric neurology centre. One could speculate that this may have contributed to the development of gene therapy-induced TMA. It was shown that higher doses of AAV (5×10^{13} to 2×10^{14} vg/kg) significantly increase complement activation by direct endothelial cell injury [7, 11]. Age at OA application seemed not to have played a major role in TMA development in the other eight reported OA therapy-induced TMA cases. Only one of these was 4 years old, while the other seven were much younger (from 5 to 23 months) [6–8, 12]. As the frequency and severity of adverse events have been shown to increase with age after OA therapy [5], early diagnosis and treatment is therefore essential not only from the perspective of optimal outcome but also for minimizing the risks of adverse events of gene

replacement therapy with OA. A successful strategy for achieving this, which is being increasingly adopted by many countries, is the implementation of a newborn screening program for SMA [13].

Conclusion

Gene replacement therapy with OA is an important disease-modifying therapy for patients with SMA that is related to significant improvements in outcomes, particularly if used early in life. TMA is a rare condition that can be triggered with OA therapy, whose pathophysiology is not completely understood, but seems to be multifactorial, with the complement system playing an important role. Since a uniform strategy to cope with TMA has not yet been established, further controlled studies are warranted. Inhibition of the complement system seems to be an effective and safe strategy, with eculizumab treatment showing promise to resolve TMA in a timely and effective manner allowing patients to reach complete resolution of TMA, as was the case in our patient.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the parent of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.K.L. and D.O. contributed substantially to the conception and design of the work, critically reviewing the work, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Finally, they approved the final version to be published. N.O.K., C.M.P., E.V., A.V.G., and T.L. contributed substantially to the acquisition, analysis, and interpretation of data for the work, drafting of the work, and finally approving the final version of the work.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding authors.

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