CASE STUDY

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Is gene therapy in spinal muscular atrophy safe? A casereport of thrombotic microangiopathy following onasemnogene abeparvovec

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Abstract

Spinal muscular atrophy is a neuromuscular disorder caused by a mutation in the survival of SMN1 gene. Diagnosis of the disease is based mainly on the presence of hypotonia and symmetrical [1]. A five-month-old male with SMA type 1 was admitted to the Children's Neurology Clinic for gene therapy with onasemnogene abeparvovec. He was diagnosed with spinal muscular atrophy in newborn screening.Neurological examination of the patient revealed abolition of deep tendon reflexes. Administration of the medication proceeded without complications. Two weeks after gene therapy, abnormal test results were observed. The patient experienced several adverse effects of the therapy, which indicated thrombotic microangiopathy (TMA). Gene therapy with onasemnogene abeparvovec provides many hopes for patients with SMA. On the other hand, its safety remains uncertain and patients require comprehensive long-term monitoring for possible side-effects.

Key words

microangiopathy, SMA, genetherapy

INTRODUCTION

Spinal muscular atrophy is a neuromuscular disorder caused by a mutation in the survival of motor neuron 1 (SMN1) gene. Clinical features depend on the onset of symptoms and the maximal motor function achieved. Diagnosis of the disease is based mainly on the presence of hypotonia and symmetrical, progressive weakness of the proximal muscles of the lower limbs or, less frequently, the upper limbs. Other symptoms include numerous spinal lesions, such as scoliosis, and weakening of the intercostal muscles, which is life-threatening. In addition, molecular genetic testing for the SMN1/SMN2 gene is performed. The absence of both full copies of SMN1 confirms the diagnosis of SMA [1].

CASE REPORT

A five-month-old male with SMA type 1 was admitted to the Children's Neurology Clinic for gene therapy with onasemnogene abeparvovec. He was diagnosed with spinal muscular atrophy in newborn screening. Initially, no abnormalities of the psychomotor development were observed. Neurological examination of the patient revealed abolition of deep tendon reflexes.

Administration of the medication proceeded without complications. However, on the following day, the patient presented a slight weakness, elevated body temperature and vomiting, which lasted for two consecutive days. A drop in platelets (35×10^9/L) and elevation of ALT, AST, D-dimers and serum urea were observed. Cardiac troponin I, GGTP and bilirubin levels, however, were normal. Treatment with prednisone and etamsylate was administered. After a week, the boy was discharged in good condition.

In the follow-up visits conducted during the first month after administration of onasemnogene abeparvovec, the patient presented no clinical symptoms or abnormalities in the physical examination. An ultrasound of the abdominal cavity was performed and no abnormalities were found. Two weeks after gene therapy, however, microcytic anaemia with reticulocytosis, increased total cholesterol, serum cystatin C and LDH levels were observed. Urinalysis revealed mild haematuria and proteinuria. Serum transaminase and urea levels remained unchanged, while the amount of platelets increased (125×10^9/L). A one-week hospitalization was necessary to rebalance the above-mentioned abnormalities. Treatment with prednisone was sustained. Total cholesterol level remained increased, while other parameters stabilized.

Treatment for SMA has historically been supportive. In recent years, a long-awaited development of disease-modifying therapies for SMA has been seen. These new options for treatment include: nusinersen, onasemnogene abeparvovec and risdiplam [2]. While nusinersen and risdiplam enhance the function of the pseudogene SMN2 by interfering with the mRNA splicing process, gene therapy aims to provide ready-made, functional copies of the SMN1 gene. Moreover, onasemnogene abeparvovec is given in one intravenous dose, while nusinersen needs to be repeatedly administered intrathecally to maintain sufficient levels of SMN protein [2]. Onasemnogene abeparvovec gene therapy uses self-complementary adeno-associated virus serotype 9 (scAAV9) – a viral vector capable of transducing motor neurons and thereby launching functional SMN transgene

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Table 1. Results of the patient's diagnostic tests

Day after treatment	**0**	**3**	**6**	**9**	**12**	**14**	**15**	**17**	**18**	**21**	**28**
plateletes (10^9/L)	327	**120**	**82**	**35**	**120**	**108**	**125**	**138**	325	**138**	**480**
haemoglobin (g/dL)	13,1	**11,3**	12,3	**9,1**	**9,8**	**8,9**	**7,9**	**8,5**	**8,5**	**9,3**	**10,8**
D-dimer (ng/mL)	NM	**1103**	**4234**	**4775**	**5664**	**2413**	NM	NM	**1676**	**916**	**1100**
ALT (U/L)	18	20	**184**	**138**	53	32	NM	NM	NM	15	13
AST (U/L)	41	**87**	**460**	**297**	**123**	**87**	NM	NM	NM	45	44
urea (mg/dL)	**12,4**	**15,8**	29,8	70,4	85,4	61,4	50	44	25,4	**20**	**17,9**
proteinuria (mg/dL)	NM	NM	none	NM	<4,0	**285**	**230**	**35,3**	**100,8**	**53,6**	**69,8**
haematuria (RBC/HPF)	NM	NM	none	NM	**5–10**	3–5	5	**8–10**	none	1–3	3–5
LDH (U/L)	NM	NM	NM	NM	NM	378	185	**145**	**771**	**573**	380
cystatin C (mg/L)	NM	NM	NM	NM	NM	**3,43**	**2,99**	NM	**2,22**	**1,7**	1,1
total cholesterol (mg/dL)	NM	NM	NM	NM	NM	**281**	NM	NM	NM	**328**	**349**
dose of prednisone (mg)	14	14	14	14	14	14	14	14	14	14	7

as an episome in their nuclei. The formulation also includes chicken-β-actin promoter, which enables permanent transgene expression [3]. Clinical studies show the greatest efficacy of gene therapy in infants with type 1 SMA below 6 months of age [3]. However, the innovative therapy raises many questions concerning its safety [2][3].

Our patient experienced many adverse effects of the therapy: post-infusion vomiting and transient fever, increased serum transaminase levels, thrombocytopenia, microcytic anemia with reticulocytosis, hypercholesterolaemia, hyperlipidaemia, proteinuria and haematuria. Platelet drop (to the lowest level of 35×10^9/L), along with regenerative anemia and elevated markers of kidney injury (elevated serum levels of urea, proteinuria and hematuria) are indicative of thrombotic microangiopathy (TMA).

TMA is an extremely rare complication of gene therapy in SMA, affecting 1.0 – 3.3 per million patients treated with onasemnogene abeparvovec per year [4].This may result both from genetic and acquired (e.g. infectious) etiologic factors, which altogether lead to activation and dysregulation of the alternate complement pathway [3][4]. The severity of the symptoms of TMA vary (it is especially dangerous when it occurs rapidly after treatment) [5]. Our patient experienced mild TMA with few physical signs. However, reviewing the literature, we found cases of patients with TMA after onasemnogene abeparvovec therapy complicated with infections, pericardial effusion and severe hypertension [4]. A case of death in the course of post-gene therapy TMA has also been reported [5]. It is therefore recommended to evaluate predisposing factors for TMA, such as infections (shiga toxin), ADAMTS-13 activity and gene mutations [3] [5]. The possible mutations responsible for the severe course of TMA involve the CFI, FAT1 and ACTN4 genes [5]. Since no gene screening for these mutations is available, parents should be informed about the risks of gene therapy [5].

A thorough clinical evaluation of patients concerning potential underlying conditions before the administration of AAV9-based gene therapy is recommended to reduce the risk of severe complications. It should include screening for pre-existing immunity against adeno-associated virus serotype 9 (anti-AAV9 antibodies), underlying liver or cardiac disease (ALT, AST, GGT and bilirubin levels, cardiac troponin I), thrombocytopenia and symptoms of active infection, which may increase the risk of thrombotic microangiopathy [3].

As the adverse effects of onasemnogene abeparvovec gene therapy are often asymptomatic, patients require long-term post-infusion monitoring, including assessment of liver function, platelets and troponin I [3].

CONCLUSION

Gene therapy with onasemnogene abeparvovec provides many hopes for patients with SMA (especially those who have not developed symptoms of motor neuron degeneration yet). On the other hand, its safety remains uncertain and patients require comprehensive long-term monitoring for possible side-effects. More research needs to be carried out to fully understand the nature and prevalence of thrombotic microangiopathy and other adverse effects of the gene therapy in patients with spinal muscular atrophy

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