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Onasemnogene Abeparvovec Therapy Following Nusinersen Treatment in Eight Patients with Spinal Muscular Atrophy Type 1

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Abstract

Introduction: Innovative gene-modifying therapy can improve motor achievements of patients with spinal muscular atrophy (SMA). Onasemnogene abeparvovec (OAV101) is an adeno-associated viral vector gene therapy that introduces a functional copy of the SMN1 gene, which produces SMA protein that is essential for normal motor neuron function.

Aim: To report our single-center clinical experience using OAV101 in patients with SMA Type 1 previously treated with nusinersen.

Methods: Between October 2019 and September 2020, eight patients (aged 3-23 months) with SMA Type 1 were administered a single intravenous infusion of OAV101, individualized according to bodyweight (1.1 x 1014 vg/kg), and prophylactic immunosuppression. Change in motor function achievements was assessed using Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores. Laboratory parameters, including liver enzymes and troponin were monitored.

Results: OAV101 improved motor function in all eight patients. The average increase in CHOP INTEND scores were 11.14 points (range 3-21 points) 10 weeks after OAV101, with the highest score of 21 points in a child aged 13 weeks. The weekly increase in CHOP INTEND score following OAV101 was 1.11 points, 2.5-fold higher than that achieved with prior nusinersen treatment (0.42 points) (p=0.69; paired t-probe). Any increase in laboratory parameters occurred early after OAV101 and typically resolved to normal levels. Noninvasive ventilation use was decreased in two patients.

Conclusion: OAV101 improved motor function in patients with SMA aged 3 23 months, with a manageable safety profile. Our report contributes real-world evidence of OAV101 treatment for SMA.

Keywords: Spinal muscular atrophy; Onasemnogene abeparvovec; Nusinersen; SMN1; Gene therapy; OAV101

Introduction

Spinal muscular atrophy (SMA) is a progressive neurodegenerative disease caused by autosomal recessive deletions and/or mutations in the survival motor neuron (SMN1) gene [1-3]. SMA is characterized by loss of motor neurons, progressive muscle weakness, and atrophy [1,2,4]. The clinical phenotype of SMA occupies a broad spectrum, with phenotypes historically classified based on age of onset and maximum-achieved motor function: Type 0 and Type 1 are typically earlier onset and more severe from a younger age, Type 4 is typically a milder phenotype [1,2,4-6]. SMA Type 1 represents approximately 60% of patients with SMA and is characterized by symptom onset at ≤6 months and median life expectancy of <2 years in the absence of respiratory support [1,7]. Although SMA is historically one of the most common causes of infant mortality, drug development and the emergence of SMA disease-modifying treatments (DMTs) in the last decade have improved disease outcomes for patients [1,2,5,6].

The positive impact of DMTs on SMA prognosis, means that newer classifications based on the highest level of ambulatory milestone achievement (nonsitter, sitter, and walker) are

increasingly used to better inform disease management [5]. Nusinersen (Spinraza®, Biogen) is an SMA DMT that was first approved in 2016 by the US Food and Drug Administration (FDA), and in 2017 by the European Medicines Agency (EMA) for the treatment of SMA in pediatric and adult patients [8,9]. Nusinersen, an intrathecally delivered SMN2-directed antisense oligonucleotide, modifies pre-mRNA splicing of SMN2 to promote increased production of full-length SMN protein [8,10]. As an SMN2 splicing modifier, nusinersen maintenance dosing every 4 months is required following the initial four loading doses administered over 2 months [8,9]. As nusinersen is administered directly into the cerebrospinal fluid, lumbar puncture can be challenging, particularly in patients with deformed spines, and may require CT-guided puncture under deep sedation [11,12].

Gene therapy with onasemnogene abeparvovec (OAV101, Zolgensma®; formerly AVXS-101, Novartis Gene Therapies) is designed to provide sustained expression of functional SMN protein following a single intravenous (i.v.) dose, with the aim of halting disease progression and preserving motor function. OAV101 was approved for the treatment of patients with SMA with bi-allelic mutations in SMN1 by the FDA and EMA in 2019 and 2020, respectively [13,14]. In the US, OAV101 is specifically indicated in pediatric patients <2 years of age [13]. OAV101 is designed to address the genetic root cause of SMA by delivering a fully functional copy of human SMN, as a transgene, via a self-complementary adeno-associated virus serotype 9 (AAV9) vector, which can cross the blood–brain barrier and target delivery of transgene to neurons in the central nervous system [15]. The design of the OAV101 vector includes a hybrid cytomegalovirus enhancer and chicken beta-actin promotor designed for rapid and sustained SMN protein expression, allowing rapid onset and a durable therapeutic effect [15]. The transgene is designed to exist as episomal DNA in the nucleus of transduced cells and without site-specific integration in the genome of the patient, reducing oncogenic potential [16,17]. OAV101 should be administered to patients who have 5q SMA with a bi-allelic mutation in SMN1 and a clinical diagnosis of SMA Type 1 or, in addition to a bi-allelic mutation in SMN1, have up to three copies of SMN2 gene [13,14]; use or benefit/risk of OAV101 in patients on permanent ventilation has not been established [13,14].

Safety considerations for OAV101 associated with the AAV9 viral vector include thrombocytopenia, thrombotic microangiopathy, and elevated troponin-I [13,14] and, due to the potential for hepatic injury following AAV-based gene therapy, prophylactic systemic corticosteroids are recommended before and after gene therapy administration [14]. Systemic (i.v.) administration of OAV101 means it can affect multiple cell types, and adverse events, including thrombocytopenia and liver, renal, and central nervous system involvement, have been reported in clinical settings [13-15]. Common adverse events identified with OAV101 treatment include elevated liver enzymes and vomiting [13, 14]. Patient liver function should continue to be monitored for at least 3 months after OAV101 infusion [13,14]. Between October 2019 and September 2020, eight patients with SMA Type 1 received OAV101 at the Bethesda Children's Hospital (Budapest, Hungary). This paper summarizes our single-center clinical experience of treatment and follow-up of these patients.

Materials and Methods

Study overview/design

The families of patients with SMA Type 1 previously treated with nusinersen came to the Bethesda Children's Hospital requesting that their child receive OAV101, which they self-funded. As OAV101 did not receive European approval until May 2020, a hospital multidisciplinary project team, which comprised of intensive care physicians, neurologists, a cardiologist, gastroenterologist, pulmonologist, pharmacist, and physiotherapists, was created to establish a professional protocol and delivery procedure. Novartis Gene Therapies provided full access to the OAV101 administration policy and training for the relevant healthcare professionals. OAV101 drug production was specifically adjusted for each patient's weight and age and transported to the hospital under strict safety regulations. Due to the COVID-19 pandemic, treatment and hospital care were executed under strict epidemiological safety arrangements. Parents provided written consent for their children to undergo treatment prior to treatment administration. The parents also consented to the publication of any emerging scientific or clinically relevant anonymized data.

Treatment

Each patient included in this single-center study had genetic documentation of a homozygous deletion or mutation in the SMN1 gene, with the onset of SMA-related clinical symptoms evident from as early as 9 weeks of age. Each patient had received prior nusinersen treatment; however, parents requested a change to single-dose OAV101 treatment. Details of therapies are summarized in Table 1. Each patient received OAV101 treatment in the same order. On day 1 of hospital admission children were settled in an isolated sterile ward and initiated on immunosuppressive prednisolone (1 mg/kg/day) therapy combined with famotidine (1 mg/kg/day) for gastric mucous protection. Prednisolone 1 mg/kg/day was administered in the first month then progressively tapered over the next 28 days in accordance with treatment instructions (13,14). Two peripheral i.v. lines were introduced, one to administer OAV101 and the other to provide a route for additional medications if needed to manage adverse events. On day 2, OAV101, which was thawed and prepared under sterile conditions, was administered to each patient over a 1-hour period via i.v. infusion, with continuous multi-parameter noninvasive monitoring. Treatment was administered as an individualized volume, according to bodyweight (1.1×10^{14} vg/kg). On day 3, the patients were discharged to nearby accommodation for easy hospital access in case of emergencies and followed-up for 12 weeks.

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Table 1: Patient demographics and baseline treatment characteristics.

Patient number	Sex	Age at SMA Type 1 diagnosis (weeks)	SMN2 number of copies	Age at first nusinersen treatment (months)	Number of nusinersen doses	Age at OAV101 administration (months)	Body weight at OAV101 administration	Time between last nusinersen and start of OAV101 (weeks)
1	Male	23	2	10	6	21	9.2 kg	9.8
2	Male	54	3	14	5	23	10.6 kg	4.7
3	Male	26	2	14	7	23	6.8 kg	2.5
4	Male	25	3	11	6	22	9.7 kg	5.8
5	Female	9	2	2.1	2	3	5.1 kg	2
6	Female	10	2	4	6	17	9.0 kg	10.8
7	Male	30	2	8	5	15	9.5 kg	5.8
8	Male	13	2	5	6	14	7.5 kg	23.8
Mean	-	23.8	-	8.5	5.4	17.3	84.1 kg	8.15
Range	-	9.0-54.0	3-Feb	2.1-14.0	7-Feb	3.0-23.0	5.1 – 10.6 kg	2.0-23.8

OAV101, onasemnogene abeparvovec; SMA, spinal muscular atrophy.

Clinical responses and safety monitoring

Patients were examined every week during the first month of treatment with OAV101 and every 2 weeks in the second and third months. The clinical response of patients receiving OAV101 was assessed by changes in motor function achievements using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores. The weekly increases in CHOP INTEND scores during nusinersen treatment and in 10 weeks following OAV101 were compared and statistically analyzed by paired t-probe. Respiratory dependency, specifically the need for noninvasive ventilation (NIV) during both night and day was also assessed.

Over the first 3 months following OAV101 infusion, the patients were closely monitored for potential adverse events of both OAV101 and concomitant prednisolone immunosuppression treatment, as well as for any effects during tapering of the steroid immunosuppression treatment (main objective of second month follow-up). Laboratory parameters, including liver enzyme levels (aspartate transaminase [AST], alanine transaminase [ALT], and lactate dehydrogenase [LDH]), serum blood cell levels (thrombocytes, granulocytes, and leukocytes), and troponin-I, were also assessed.

Analyses

The average weekly change in CHOP INTEND scores over the treatment periods with nusinersen and OAV101 were calculated and compared.

Results

Patient demographics and baseline characteristics

Subsequent data focus on our first eight patients (six males) who were administered a single i.v. infusion of OAV101 at our center between October 2019 and September 2020 with an appropriate-length of follow-up. Demographics and baseline characteristics of these patients are summarized in Table 1. All patients were diagnosed with SMA Type 1 between 9 and 54 weeks of age and initiated nusinersen treatment at a mean age of 8.5 months (range, 9 weeks-14 months). They received an average of 5.4 (range, 2-7) nusinersen doses and had an average CHOP INTEND score of 27.5 (range, 16-40) points at the start of nusinersen treatment. The first infusion of OAV101 was given at an average age of 17.3 (range, 3-23) months; the average volume of OAV101 administered to each child was 5.67 (range: 5.61-5.71) mL (Table 1). Change from nusinersen to OAV101 therapy happened due to parental initiative in all cases.

Clinical response with OAV101

The average time between the last nusinersen dose and OAV101 was 8.15 (range, 2-23.8) weeks. Clinical responses assessed as improvements in motor achievements are shown in Table 2. Motor achievements improved in all patients, as assessed by various capabilities, including ability to hold their heads, reach for targeted objects, swallow, and sit unaided. CHOP INTEND scores increased by an average of 11.1 (range, 3-21) points at 10 weeks after OAV101 infusion; (Table 2; Figure 1); a weekly

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increase with OAV101 that was more than 2.5-fold greater than that achieved with nusinersen (1.11 vs. 0.42 points, respectively). The mean CHOP INTEND score at 10 weeks post-OAV101 infusion was 45.86 points.

Table 2: Clinical outcomes following nusinersen and OAV101 administration

Patient number	CHOP INTEND OAV101 score (points)							
	At first nusinersen dose	Change over nusinersen treatment period	Average weekly increase over nusinersen treatment period	At first OAV101 dose	At 10 weeks post-OAV101 infusion	Change over 10 weeks post-OAV101 infusion	Average weekly increase over OAV101 treatment period	Status at last check-up (at 12-weeks post-OAV101 infusion)
1	40	20	0.42	60	Not measured as patient was able to sit	-	-	• Kept head up, crawled on all four limbs, stood with assistance • Chewed and swallowed unaided • Required NIV for 1-2 h/day (during afternoon nap)
2	38	18	0.62	56	59	3	0.3	• Sat alone, unaided, and stood for a few seconds alone • Chewed and swallowed unaided • Uses a wheelchair • Does not like NIV
3	21	5	0.19	26	40	14	1.4	• Lifted both arms beside head, rolled over, sat for 90 mins, and turned left, and kept legs up for 5 mins • Had chewing difficulties (uses PEG) • Required NIV for 11-13 h/day
4	40	6	0.27	46	52	6	0.6	• Chewed, ate with hands, drank from a glass unaided • Sat unsupported and held head up
5	16	9	1.25	25	46	21	2.1	• Lifted head and both arms and took toys from one hand to the other • Has a strong crying voice and no difficulties swallowing or oral feeding • Required NIV for 10 h/day

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6	16	8	0.14	24	42	18	1.8	• Coughed effectively and had a strong crying voice • Sat up with support and was able to keep head up for 3s • Could swallow a few sips but still needs a feeding tube
7	21	1	0.05	22	34	12	1.2	• Coughed effectively and could cry loudly • Rolled over and manipulated his hands • Partially fed by tube but could swallow purees
8	24	20	0.52	44	48	4	0.4	• Performed antigravity movements with all extremities • Controlled head and sat unaided for 15 mins • Lifted and placed toys • Has a strong voice and can mimic
Average	27.5	12.2	0.42	31.63	45.86	11.14	1.11	
Range	16-40	-19	0.05-0.62	22-56	34-52	-18	0.3-2.1	

CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder; h, hours; mins, minutes; NIV, noninvasive ventilation; OAV101, onasemnogene abeparvovec; PEG, percutaneous endoscopic gastrostomy; s, seconds.

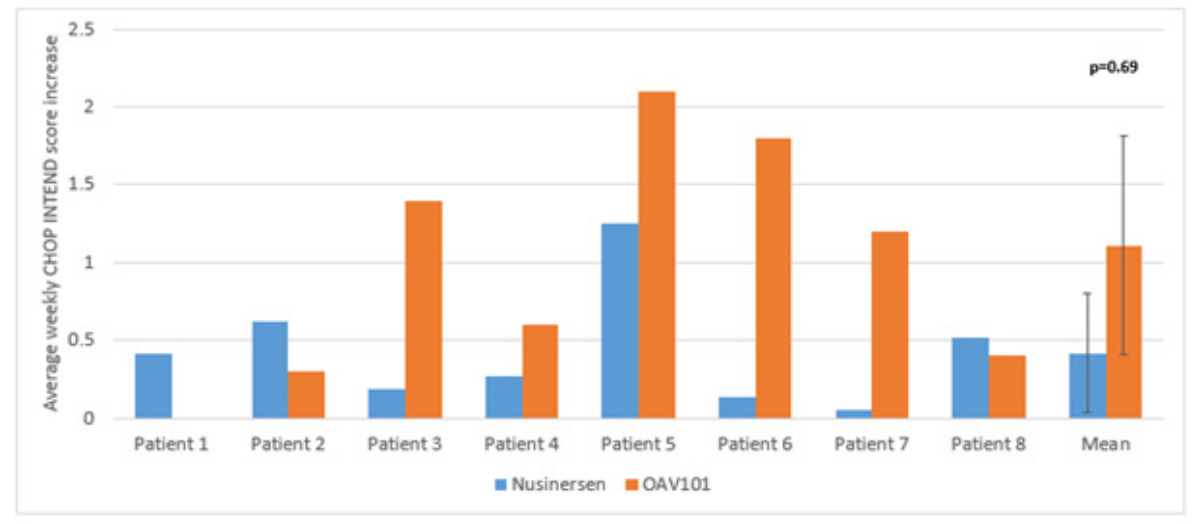

Figure 1: Average weekly increase in CHOP INTEND score over the nusinersen and OAV101 treatment periods.
CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder; OAV101, onasemnogene abeparvovec.

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Patient 3, who arrived at the hospital with protein-energy malnutrition and low body weight and length, and who required targeted nutritional therapy to ensure sufficient weight gain, also showed a 14-point improvement in his CHOP INTEND score at 10 weeks (Table 1 and 2). Patient 5, the youngest of the eight children included in this analysis, was 9 weeks of age at SMA Type 1 diagnosis and 13 weeks of age when OAV101 was administered, had the quickest and most profound improvements in motor functioning at last follow-up, with a 21 point increase in CHOP INTEND score (Table 2; Figure 1). Most patients continued to have respirator dependency, with NIV use, after OAV101. However, for the two patients who were able to sit up, continuous NIV use was reduced from 8-10 hours to 1-2 hours per night (Patient 1 and Patient 2). Reduction in NIV dependency was not expected in patient 1, who suffered from severe malnutrition and chest deformity, or in patient 2 who started NIV therapy less than 3 weeks before OAV101 (Table 2).

Safety and Tolerability

All patients experienced a non-infectious, high body temperature (38.3-38.8°C), which lasted for 1-2 days after OAV101 infusion. Three days post-OAV101 infusion, Patient 6 had vomiting, feeding difficulties, fever, and exsiccation requiring admission into the intensive care unit for 4 days. In addition to high fever (39°C), Patient 8 had macular skin rash and vomiting but no other infectious symptoms. Over 12 weeks of follow-up, Patient 1 had a fever (38-38.7°C) due to a mild upper respiratory infection, while Patient 2 presented with a serous otogenic infection. All eight patients showed changes in laboratory parameters 1 week after OAV101 infusion, including thrombocytopenia and elevated serum LDH and AST levels. Overall, following OAV101 infusion, there was a steady decline in liver enzyme levels over the 12-week follow-up. The youngest patient (Patient 5) showed AST elevation 25 times higher than normal upper limit 1 week after OAV101 infusion, but this subsequently returned to normal. Patient 3 and Patient 7 showed progressive elevation of liver enzymes at Week 6 and prednisolone dose was increased to 1.5 mg/kg/day for 1 week and 2 mg/kg/day for an additional 2 weeks. Prednisolone steroid immunosuppression was tapered over 28 days 1 month after OAV101 in the other six patients.

Laboratory value abnormalities related to leukopenia and granulocytopenia were prolonged in our patients but were not associated with severe or systemic infection. Renal functions and coagulation parameters did not deviate from normal range during the follow-up. There were transient mild troponin-I elevations in 5/8 patients. Significant elevation in troponin-I was reported for Patient 1, which normalized within 2 weeks without hemodynamic or conduction abnormality. Patient 5, the youngest, showed significant elevation in troponin-I (49.3 pg/mL; normal upper range, 17.5 pg/mL) during the first week after OAV101 infusion. Due to simultaneously presenting bradycardia (80-95/min frequency in sleep) she was observed in the intensive care unit for 3 days. Cardiological examination did not confirm any hemodynamic or conduction abnormality and her troponin-I level normalized in 2 weeks.

Discussion

In 2020, an ad hoc European consensus statement on gene therapy for SMA provided guidance on qualification, patient selection, safety, and long-term monitoring required for gene therapy treatment in SMA, including OAV101 [2]. The phase 1 clinical trial (START) demonstrated that 12 infants with SMA Type 1 had an increased probability of survival, rapidly improved motor functions, and achieved motor milestones following a single-dose infusion of the therapeutic dose of OAV101, with a durability of effect demonstrated with nearly 5 years of follow-up [18]. The safety and efficacy of OAV101 are being investigated in the completed phase 3 STR1VE-US [19,20] and STR1VE-EU [21] studies, and the ongoing SPR1NT [22] clinical trial. Patients from these clinical trials can volunteer to participate in a 15-year long-term follow-up (LT-002) [23] and eligible patients from START will enter a long-term safety study with up to 15 years of follow-up [24]. The ongoing RESTORE REGISTRY aims to assess real-world long-term effectiveness and safety outcomes for patients with SMA [25,26].

In our single-center experience of treating eight patients with SMA Type 1 with OAV101, the age at which treatment was administered ranged from 3 to 23 months. We observed improved motor achievements in all OAV101-treated patients with an average CHOP INTEND score increase of 11.14 points over 10 weeks – a weekly increase of 1.11 points. Although it was 2.5 times higher than during prior nusinersen treatment, the difference was not significant. This comparison, however, could be misleading because the onset on nusinersen effect can be slower than that for OAV101. Six patients had a CHOP INTEND score ≥40 points 10 weeks after OAV101 infusion. According to natural history, patients with SMA Type 1 do not achieve/maintain CHOP INTEND scores >40 points [27]. Furthermore, in our experience, the youngest patient in the series showed the quickest and most effective response, which may suggest a beneficial role of early treatment. Previous studies have shown that permanent NIV dependency can be prevented with early OAV101 [28]. Four of the eight patients received OAV101 close to 2 years of age, two of whom were subsequently able to sit up and had reduced continuous night-time NIV dependency from 8-10 hours to 1-2 hours per night. One patient was able to heave and self-self-eliminated his gastric tube after 10 weeks, indicative of returning pharyngeal reflux.

There were no unexpected adverse events observed either with OAV101 or with concomitant steroid immunosuppression during the 3-month monitoring post-treatment. Although increased liver enzymes were observed, these returned to normal levels within a short time, and in certain patients, these elevations

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were manageable with corticosteroid use. Normal levels in liver enzymes were sustained over the 3 months of monitoring. All other laboratory parameters assessed were largely within the normal range, and any increases typically returned to normal levels within 1 week. The mild troponin-I elevations also normalized without any deleterious cardiovascular effects. In our experience, the youngest patient and the one with the worst nutritional status were the most susceptible to potential adverse events. Our experience agrees, with the findings reported from a recent single-center study in Germany, which assessed safety monitoring of OAV101 in patients aged 10-37 months who had previously received nusinersen [29]. These patients underwent close monitoring and adaptation of an immunosuppressive regimen to manage adverse events associated with OAV101 and no long-term immune response-related side effects were reported [29-31].

Conclusion

In conclusion, findings from our single-center experience showed that OAV101 improved the clinical outcomes of eight patients with SMA Type 1 who were previously treated with nusinersen. We observed improvement in both the youngest patient, but also in those who received the OAV101 infusion at almost 2 years of age. Our findings support the use of OAV101 in older infants. However, as the number of patients receiving OAV101 is still limited, single-center experiences, and ongoing and future trials, will continue to provide invaluable insights on using OAV101 for physicians managing patients with SMA. Efforts toward preclinical diagnosis, followed by early treatment initiation may be a way to advance improved quality of life in patients with SMA Type 1.

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