



Onasemnogene Abeparvovec (Zolgensma) Decreases Ventilator/Bi-Pap Support in 3 Infants with SMA 1

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Abstract

Spinal muscular atrophy (SMA) type 1 is a rare autosomal recessive disorder that had previously been characterized with progressive and rapid deterioration of muscle function with patients generally becoming ventilator dependent before a year of age. In this paper, we present the case of three infants who had been ventilator or Bi-Pap dependent and treated with a single dose of intravenous (IV) onasemnogene abeparvovec (Zolgensma). Patients from the Children's Hospital of Los Angeles (CHLA), University of Mississippi Medical Center, and Rady's Children's Hospital in San Diego were identified in this retrospective case evaluation. Patients were under the age of 24 months, genetically and clinically confirmed to have SMA type 1, had permanent respiratory support (defined as >16 hours a day of ventilator or BiPap dependence), and received at least 1 bridging dose of nusinersen (Spinraza). All patients received one IV dose of Zolgensma and they were subsequently evaluated for their ability to come off the ventilator or Bi-Pap, and their CHOP-INTEND scores pre-Zolgensma administration and 4-13 months after Zolgensma. All three patients had improvement in their ability to come off the ventilator and were noted to have improved CHOP-INTEND scores. Two of the three patients were no longer considered ventilator dependent.

Keywords: SMA, Ventilator Dependence, Bi-Pap, Zolgensma, CHOP-INTEND, Infant, Retrospective.

Introduction

Spinal Muscular Atrophy (SMA) is an autosomal recessive progressive motor neuron disorder affecting 1 in 10,000 live births. The most common form of SMA affects the Survival Motor Neuron 1 (SMN1) gene on chromosome 5.[1] Affected patients have no functional copy of SMN1. The most severe form, type 1, is diagnosed before 6 months of life. Prior to the widespread use of permanent ventilation and gastrostomy tubes, the majority of patients died by their second birthday.[1-4] In December 2016, the first effective treatment for SMA, nusinersen (Spinraza), was approved in the US.

In a pivotal study, 15 patients received onasemnogene abeparvovec (Zolgensma) intravenously. All patients were under 7 months of age, confirmed genetically to have no functional copies of SMN1, and were not permanently ventilated (less than 16 hours

a day of assisted ventilation). A secondary endpoint of the study was time to death or permanent ventilation. Also evaluated was improvement of motor abilities based on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). At the conclusion of the study, all patients had event-free survival at 20 months of age. All patients improved on their CHOP INTEND scores significantly.[1] Ongoing studies demonstrated that patients continued to gain motor milestones years after the administration of Zolgensma.[4] When Zolgensma was approved by the FDA in May 2019, there was no published data on patients who were already permanently ventilated. The objective of this manuscript is to report on the respiratory effects of Zolgensma in ventilator or Bi-Pap dependent infants who would otherwise fulfil the FDA's criteria to receive this medication.

Methods

Patients were retrospectively identified based on the following: (1) Infants with SMA type 1, (2) genetically and

clinically confirmed to have SMA Type 1 (3), bridged with at least one dose of nusinersen (4), under the age of 2 years (5), under the weight of 13.5 kg, (6) ventilator or Bi-Pap dependent (requiring support for >16 hours a day for 14 or more consecutive days), and (7) treated with onasemnogene abeparvovec as a single IV dose between January 1, 2019 and December 31, 2019 through either the Avexis MAP program or commercially. The patients were seen at Children's Hospital Los Angeles, U. of Mississippi Children's Hospital, or University of San Diego (Rady) Children's Hospital. All patients had received at least one dose of nusinersen prior to onasemnogene abeparvovec. All 3 patients received onasemnogene abeparvovec between January 1, 2019 and December 31, 2019 and reported on up to March 31, 2020. Outcomes that were evaluated were motoric gains based on the CHOP-INTEND score and time off the ventilator/Bi-Pap. Consent was obtained for each patient from their parent/legal guardian. All patients were cared for directly by one or more of the authors listed and follow actively at one of the associated centers listed.

Cases

Case 1

Patient 1 was noted to be floppy at birth and was diagnosed with failure to thrive due to poor oral intake for the first 3 months of life. His initial workup for gastrointestinal and metabolic abnormalities was negative. At 3 months, he had a major choking event while bottle feeding, turned blue and was emergently taken to Rady Children's Hospital. Genetic testing confirmed the clinically suspected SMA type 1 with 2 SMN2 copies at 3 months. Due to multiple failed extubation attempts, he had a tracheostomy and GT placed at 3.5 months. He received his first dose of nusinersen on the day of his tracheostomy. Over the course of the next 6 months, he received a total of 5 injections of nusinersen prior to receiving

Zolgensma at 9 months. His initial CHOP INTEND score was 8 at 3.5 months of age. Once treatment was started, his score improved to 29 after the 5th nusinersen injection; At 12 months of age, his CHOP-INTEND increased to 41, which further increased to 45 points at 16 months of age. After receiving 5 injections of nusinersen, he tolerated being off the ventilator for 45 minutes during the day. He received Zolgensma at 9 months of age, and by 12 months of age he was breathing independently (ventilator-free) for 3 hours each day. At 15 months of age, 6 months post infusion, he was capable of breathing independently for the entire day while awake and only required ventilation at night while asleep or during naps. Nusinersen was not resumed after treatment with SMA gene therapy.

Case 2

Patient 2 first came to medical attention in the US when he was 3 months of age. He was born in California but went to China shortly after birth. His parents were concerned that he was not eating well, not gaining weight, and he had decreased tone. Following his routine 2 month old vaccinations, his pediatrician sent genetic testing for SMA. Testing revealed that he had 0 copies of SMN1 and 2 copies of SMN 2. The patient and his mother took a commercial flight to Los Angeles. He was brought to Children's Hospital Los Angeles ER for evaluation. He was admitted for failure to thrive. At this admission, a head CT was negative. He had mild elevations of his liver enzymes (AST and ALT). A liver ultrasound demonstrated possible coarse echotexture but was otherwise normal. A sleep study demonstrated an AHI of 6.9 without hypoventilation and improved oxygenation with supplemental oxygen. The sleep study was repeated at 3.5 months of age and was unchanged. Strength of the lower extremities was evaluated. He was mostly 2-s with his right hip flexor being weakest (Table 1).

Muscle	3 months	6 months (1 month post Zolgensma)	8 months (3 months post Zolgensma)	17 months (1 year post Zolgensma)
R Hip Flexion	1	1	2-	2-
R Hip Extension	2-	2-	2-	2-
R Knee Flexion	2-	2-	2-	2-
R Knee Extension	2-	2-	2-	2
R Dorsiflexion	2+	2+	2-	3-
R Plantarflexion	2-	2+	2-	2
L Hip Flexion	2-	2-	2-	2-
L Hip Extension	2-	2-	2-	2-
L Knee Flexion	2-	2-	2-	2-

L Knee Extension	2-	2-	2-	2
L Dorsiflexion	2+	2+	2-	3-
L Plantarflexion	2+	2+	2-	2

Table 1: strength of lower extremities in patient 2.

He was admitted on 3 separate occasions. During his first admission, he received a dose of nusinersen when he was 3.5 months old. He was seen and followed by pulmonology. It was recommended at that time for tracheostomy and G-tube placement; however, his family declined. He was sent home with supplemental oxygen at 0.5-1L by Nasal Cannula. He received a second dose of nusinersen as an outpatient. He was admitted a second time to receive onasemnogene abeparvovec through the MAP program given that he was not tolerating feeds and his pulmonary status was tenuous. He also needed to have cardiac monitoring per local MAP protocol that was not possible as an outpatient. He was admitted for a total of 5 days, partly due to nutritional status.

His third admission was 3 days after he was discharged from his second admission, wherein he received Zolgensma. He was admitted from Pulmonology clinic because of continued failure to thrive, recurrent emesis, weight loss, and continued concern for acute on chronic respiratory failure. At this admission, he was not tolerating nasogastric feeds. He needed to be converted to nasal-jejunal feeds. He was trialed on, and failed, Bi-Pap. Thus, the decision was made to go forward with the tracheostomy and gastrostomy tube placement. These were placed 1 month after he received onasemnogene abeparvovec. At the time of this report, he was 17 months of age. Prior to onasemnogene abeparvovec, his CHOP-INTEND score was 15/64. One year after treatment, his CHOP-INTEND score is 28/64. More importantly, his pulmonary function (measured by his sleep studies and ability to come off his ventilator) has improved with time, up to 16 hours a day.

Case 3

Patient 3 initially presented at 2 months due to parental concern for lack of motor progression. Also noted was increased work of breathing at birth which worsened over the first several weeks of life, long feeding times, and a weak cry. Her initial neurological examination demonstrated diffuse and prominent hypotonia with weakness. There was minimal movement seen in the bilateral upper extremities and essentially none in the lower extremities. Deep tendon reflexes were absent. Her Hammersmith Infant Neurologic Exam (HINE) score was 1/26. Genetic testing confirmed the absence of SMN1 with two copies of SMN2.

Due to insurance difficulties, nusinersen administration was delayed by 3 weeks. During this time, her respiratory status deteriorated. She was admitted to the hospital at 3.5 months of

age from the Pulmonology clinic. As an inpatient, she underwent initiation and titration of non-invasive positive pressure ventilation (NIPPV). Her first of 4 loading doses were given during this admission.

During the course of the next several months, there was some improvement in motor function with legs beginning to kick slightly. From a respiratory standpoint, her family noted that she would quickly become tired when off of Bi-PAP (for example during baths) and would have decreases in oxygen saturation levels at night. Even with short sprints she would develop marked increase in work of breathing which prompted her parents to quickly place her back on Bi-Pap.

She was given Zolgensma at 23 months of life. CHOP INTEND at this time was 35. She tolerated Zolgensma infusion well with repeat CHOP INTEND score of 36 at 26 months. Family noted improvement in respiratory status to a greater degree than before Zolgensma. One month after Zolgensma she continued to display distress with being off of BiPAP and using only nasal cannula during the day. Two months after infusion, she had been able to be off Bi-Pap during for 45 minutes during PT and OT sessions and for the duration of baths (approximately 25 minutes). She had a respiratory setback when she had a rhinovirus infection at 28 months. However, she has not required increase in respiratory support, and Bi-PAP settings have remained the same at the time of this report.

Results

All patients received at least 2 doses of nusinersen prior to receiving and stopped receiving this treatment after administration of onasemnogene abeparvovec. At least 4 months passed between when they received gene therapy and the assessment prior to this manuscript. The greatest gains off the ventilator occurred after the administration of onasemnogene abeparvovec. In the first 2 patients, these gains continued even after the washout from nusinersen (typically up to 177 days).[5]

Both patients 1 and 3 had relatively minimal gain in their CHOP-INTEND scores. However, their ability to come off the ventilator or Bi-Pap increased significantly (from 0.75 to 12 hours and from <0.1 to up to 1.2 hours). Patient 2 while having the greatest increase in CHOP-INTEND score, still had the lowest of the 3 patients (28 compared to 45 and 36). Patient 2 had the highest gain on his ability to come off the ventilator (up to 16 hours a day).

Discussion

The respiratory improvement for patients 1 and 2 were more dramatic than what was seen in patient 3. This can be attributed to the age that patients 1 and 2 received the intervention. It has been demonstrated in multiple studies that the sooner an intervention happens, generally, the better the outcome.[6,7] Also, patients 1 and 2 were further from their treatment with onasemnogene abeparovec compared to patient 3 (6.5 and 13 months compared to 4 months). Gains after onasemnogene abeparovec continue beyond 4 month from intervention have been demonstrated. Neither patients 1 or 2 continued to receive nusinersen well beyond 16 weeks past their last dose. This suggests that all gains after onasemnogene abeparovec administration can be attributed to the gene therapy and not from nusinersen.[6,7]

There was a difference in motoric function gain and respiratory gains. While it can be concluded that measures of motoric function and independent respiratory ability improve with onasemnogene abeparovec, one function does not dictate the degree of improvement of the other. This was demonstrated with these 3 patients. It is important to mention that the patients in these cases were among the sickest of SMA type 1 patients. In a recent observational study, the median age for an SMA type 1 patient to either pass or become permanently ventilated was 13.5 months.[4] All three patients required permanent respiratory support before their fourth month of life.

The three patients were from 3 different institutions thus the results that were seen are not because of a particular institution's protocol. All three centers are neuromuscular centers and it can be argued that treatment in one of these centers provides better outcomes. The CHOP-INTEND was used as this is a standard measure in centers that treat SMA.[6,7]

Conclusion

These case studies support the use of both nusinersen and onasemnogene abeparovec in patients despite being trach/

ventilator dependent and demonstrates that weaning off the ventilator is possible even in severe cases of SMA type 1. These cases further highlight the relatively fast weaning off the ventilator within 6 months of onasemnogene abeparovec infusion even in two patients who have been fully tracheostomy and ventilator dependent since 3 months of age. Various degrees of improvement in motor function and independent respiratory abilities suggest that advancement in one area may not be directly proportional to the other. Conversely, in assessing for improvement from onasemnogene abeparovec treatment, these indicators should be evaluated separately.

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