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Original Article

Impact of Age and Motor Function in a Phase 1/2A Study of Infants With SMA Type 1 Receiving Single-Dose Gene Replacement Therapy

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ABSTRACT

Background: This study characterizes motor function responses after early dosing of AVXS-101 (onasemnogene abeparvovec) in gene replacement therapy in infants with severe spinal muscular atrophy type 1 (SMA1).
Methods: This study is a follow-up analysis of 12 infants with SMA1 who received the proposed therapeutic dose of AVXS-101 in a Phase 1 open-label study (NCT02122952). Infants were grouped according to age at dosing and baseline Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scores: (1) early dosing/low motor, dosed age less than three months with scores <20 (n = 3), (2) late dosing, dosed at age three months or greater (n = 6), and (3) early dosing/high motor, dosed age less than three months with scores ≥20 (n = 3).
Results: Early dosing/low motor group demonstrated a mean gain of 35.0 points from a mean baseline of 15.7, whereas the late dosing group had a mean gain of 23.3 from a mean baseline of 26.5. The early dosing/high motor group quickly reached a mean score of 60.3, near the scale maximum (64), from a mean baseline of 44.0. Despite a lower baseline motor score, the early dosing/low motor group achieved sitting unassisted earlier than the late dosing group (mean age: 17.0 vs 22.0 months). The early dosing/high motor group reached this milestone earliest (mean age: 9.4 months).
Conclusions: The rapid, significant motor improvements among infants with severe SMA1 treated with AVXS-101 at an early age highlight the importance of newborn screening and early treatment and demonstrate the therapeutic potential of AVXS-101 regardless of baseline motor function.

Introduction

Spinal muscular atrophy (SMA), a devastating, rapidly progressive neuromuscular disease, is caused by the loss of the *survival motor neuron* (*SMN*) gene. The *SMN* gene is found in duplicate copies, *SMN1* and *SMN2*, on chromosome 5q13 in humans.[1] Both are capable of encoding SMN, the life-saving RNA-binding protein; however, because of a mutation in exon 7 resulting in a truncated protein, *SMN2* can only partially compensate for the loss of *SMN1*. Thus with no *SMN1* copies, higher copy number of *SMN2* can modify disease severity. Of the four SMA types, SMA type 1 (SMA1) is the most severe, with patients commonly having one or two *SMN2* copies, symptom onset before age six months, and early loss of motor neurons, resulting in progressive muscle weakness, paralysis, respiratory failure, and death.[1,2] The clinical hallmark of SMA1 is an inability to ever achieve independent sitting.[2,3] Several natural history studies have demonstrated that patients with SMA1 treated with standard of care have a median time to either death or permanent ventilation of age eight to 10 months.[3,4] Given the rapid

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progression of SMA1, it could be hypothesized that infants with more severe disease or those treated later in the disease course would likely have greater irreversible loss of function, and as a result, a reduced motor response to treatment. Finding disease-modifying treatments is challenging, and in the past, clinicians have raised concerns suggesting the futility of medical intervention.

For assessment of motor function in clinical trials, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale provides a sensitive measure of meaningful changes.[5,6] The CHOP-INTEND uses a 0- to 64-point scale in which higher scores indicate better motor function; it has been used to reliably quantify the natural decline of motor function in infants with SMA1.[3,7] In a natural history analysis of patients with SMA1, almost none reached a CHOP-INTEND score of ≥40 after age six months.[3] In the NeuroNEXT cohort of patients with SMA1 with two copies of *SMN2*, CHOP-INTEND scores decreased by a mean of 10.7 points from age six to 12 months, and none reached above a score of 33 points.[4]

Therapeutic strategies with promising clinical data for SMA have focused on increasing the levels of SMN protein in motor neurons. AVXS-101 (onasemnogene abeparvovec) gene replacement therapy aims to increase SMN expression by delivering a functional copy of the *SMN* gene via a self-complementary (sc)AAV9 vector that crosses the blood-brain barrier. The cDNA carried to neurons avoids the need to convert single-stranded to double-stranded cDNA, facilitating the rapid production of SMN protein.[8] One-time systemic delivery of AVXS-101 corrects the phenotype in a severe SMA murine model (SMNΔ7 murine model), increasing survival to more than 250 days when dosed early in disease progression at postnatal day 1 (P1) compared with a median survival of 15.5 days in control animals.[9] Animals injected at P2 had survival similar to those dosed at P1.[9] In contrast, dosing at P5 modestly increased survival by ~15 days versus control and the survival of P10-injected animals was no greater than that of SMNΔ7 controls.[9]

Loss of motor function in patients with SMA1 is driven by the loss of motor neurons, and thus one may expect that patients with progressed disease (i.e., low motor function) at the time of therapeutic intervention may not experience significant gains in motor function. In a Phase 1, single-arm, open-label, gene replacement therapy trial, all patients treated with a one-time intravenous dose of AVXS-101 were alive and free of permanent ventilation at age 24 months[10,11]; this finding contrasts with the results of a natural history study in which only 8% of infants with SMA1 surviving to age 20 months were free of permanent ventilation.[3] In this study, we investigate whether age at dosing and baseline motor function are associated with motor function improvements in cohort 2 of the previously published AVXS-101 gene replacement therapy study. The current study is a subgroup analysis of the 12 infants with SMA1 (cohort 2) who received the proposed therapeutic dose of AVXS-101 in the Phase 1 open-label study (NCT02122952) in which infants were stratified by age at dosing and CHOP-INTEND score activity at baseline.[11]

Using the Bayley Motor Scales of Infant and Toddler Development-Third Edition (Bayley-III) criteria to assess gross motor function,[12] 11 of 12 patients receiving the proposed therapeutic dose of AVXS-101 assessed at the 24-month post-treatment visit had achieved sitting unassisted for more than five seconds, a milestone rarely or never seen in this population.[11]

Interestingly, among infants with SMA1 treated with the currently available treatment, nusinersen, those with shorter disease duration experienced greater benefit.[13] To investigate whether age at dosing and baseline motor function were associated with any difference in motor function improvements, we characterized the CHOP-INTEND changes in infants participating in the AVXS-101 gene replacement therapy trial, in particular the response of patients with low motor function when dosed at an early age.

Methods

Study participants

A cohort of 12 genetically confirmed symptomatic infants with SMA1 having homozygous deletions of *SMN1*, two copies of *SMN2*, and no c.859G>C *SMN2* modifier mutation predicting a milder phenotype received a one-time intravenous infusion of AVXS-101 gene replacement therapy at the proposed therapeutic dose in an open-label study between December 2014 and December 2015 (NCT02122952).[11] For purposes of this analysis, the patients were grouped according to age at dosing (Early less than three months or Late three months or greater) and baseline CHOP-INTEND scores (Low <20 points or High ≥20 points). Three groups are described: Early Dosing/Low Motor (n = 3), Late Dosing (n = 6), and Early Dosing/High Motor (n = 3).

The study protocol was approved by the institutional review board at Nationwide Children's Hospital in Columbus, Ohio, and study procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki. All parents or guardians provided written informed consent before any study procedures were performed.

Study endpoint

The composite endpoint was event-free survival, defined as death or ≥16 hours of ventilation per day for more than two consecutive weeks without a reversible illness. A full description of study endpoints and study design were previously published.[11]

Assessments

Exploratory objectives included the motor milestone achievement of sitting unassisted and improvements in CHOP-INTEND scores. The CHOP-INTEND is a functional scale shown to reliably assess motor function in patients with SMA1 and other neuromuscular disorders presenting in infancy.[5,6] This scale includes 16 items with a total score ranging from 0 to 64. The achievement and maintenance of scores greater than 40 points have been considered to be clinically meaningful because patients with SMA1 rarely achieve and never maintain this level of motor function.[3] The achievement of sitting unassisted as defined by the Bayley-III[14] was confirmed by examination of video recordings of the patients by an independent reviewer as follows: (1) five seconds or more according to item 22 of the Bayley-III gross motor subtest and (2) ≥30 seconds according to item 26 of the Bayley-III.

Follow-up analysis

CHOP-INTEND scores were reported at each monthly visit according to protocol, provided participants were able to safely complete assessments. The gross and fine motor portions of the Bayley-III were administered monthly through 24 months postdose if a patient reached or exceeded a score of 60 of 64 on the CHOP-INTEND scale.

Statistical analysis

Outcomes of interest were reported with descriptive statistics: either numbers with percentages or means with S.D.s. Patients were grouped by age at dosing of AVXS-101 (less than three months or three months or more) and by baseline CHOP-INTEND scores

(<20 or ≥20) as described above. A comparison of each group's achievement of sitting unassisted was analyzed descriptively.

Results

Baseline demographics and motor function of patients receiving proposed therapeutic dose

Baseline demographics and motor function for all 12 patients who received the proposed therapeutic dose of AVXS-101 are shown in Table 1. Patients were grouped by a combination of age at dosing (less than three months versus three months or more) and baseline CHOP-INTEND scores (<20 vs ≥20). The Early Dosing/Low Motor group was dosed early (mean 1.8 [S.D. 0.76] months) and had a mean baseline CHOP-INTEND score <20 points (mean 15.7 [S.D. 1.53] points). All the patients in the Early Dosing/Low Motor group had severe early impairment at baseline, including swallowing dysfunction requiring nutritional support (nasojejunal tubes), although they were not receiving noninvasive ventilatory support. The Late Dosing group was dosed later (mean 5.1 [S.D. 1.56] months) and had a higher baseline CHOP-INTEND score (mean 26.5 [S.D. 7.66] points). Two patients (33%) in the Late Dosing group were receiving nutritional support at baseline, and two (33%) were receiving noninvasive ventilatory support at baseline. The Early Dosing/High Motor group was also dosed early (mean 1.8 [S.D. 0.85] months) and had a high mean baseline CHOP-INTEND score of ≥20 points (mean 44.0 [S.D. 7.94] points); none were receiving nutritional or noninvasive ventilatory support at baseline.

CHOP-INTEND improvements following AVXS-101 dosing

As shown in Fig 1, all patients showed rapid, early CHOP-INTEND improvements compared with baseline, one, three, and 24 months after AVXS-101 dosing (Table 2). In the first month postdosing, a greater increase was observed in the Early Dosing/Low Motor group (mean increase 13.7, S.D. 2.08), who had severe disease progression at enrollment; the Late Dosing group had a mean increase of 7.3 (S.D. 3.56). The Early Dosing/High Motor group had a mean increase of 10.7 (S.D. 2.52); however, this group started at a higher baseline, limiting achievable increases in scores.

At 24 months follow-up, the Early Dosing/Low Motor group reached a mean total CHOP-INTEND score of 50.7 (S.D. 5.77) from a mean baseline of 15.7 (S.D. 1.53). Patients in the Late Dosing group reached a mean total CHOP-INTEND score of 49.8 (S.D. 16.64) from a mean baseline of 26.5 (SD 7.66). Of note, patients in the Early Dosing/Low Motor group reached a mean CHOP-INTEND score similar to that of the Late Dosing group despite having a lower mean baseline motor function. Patients in the Early Dosing/High Motor group reached a mean total CHOP-INTEND score of 60.3 (S.D. 6.35) from a mean baseline of 44.0 (S.D. 7.94), and two patients in this group reached the ceiling of 64 points after achieving 14- and 17-point increases.

Motor milestone attainment

In contrast to the expected natural history for SMA1, nearly all patients achieved sitting unassisted following AVXS-101 treatment: 11 of 12 patients (92%) sat unassisted for five seconds or more at 24 months post-treatment, including all three patients (100%) in the Early Dosing/Low Motor group. In addition, nine of 12 patients (75%) achieved sitting unassisted for ≥30 seconds by 24 months follow-up. Only one patient, with the lowest baseline CHOP-INTEND score in the Late Dosing group, who happened to be the oldest child in the study, did not achieve sitting unassisted.

As shown in Fig 2, younger age at sitting unassisted was associated with baseline CHOP-INTEND scores in the two groups that started with higher scores (≥20 points); higher baseline CHOP-INTEND scores were associated with achievement of sitting unassisted at a younger age. However, all three patients with SMA in the Early Dosing/Low Motor group were not on the trend line of baseline CHOP-INTEND score and age at sitting unassisted—these patients achieved sitting unassisted earlier than would be predicted by the trend for the Late Dosing group despite having lower motor function at baseline.

As shown in Fig 3, patients achieved sitting unassisted (less than five seconds) regardless of baseline motor function and age at dosing. Two patients in the Early Dosing/High Motor group were able to achieve standing with and without assistance during the 24-month follow-up. Of note, these two patients had baseline CHOP-INTEND scores around 50. Despite the relatively strong baseline CHOP-INTEND scores, both were evaluated and documented as having clinical symptoms, including hypotonia as early as days 17 and 49. These patients were both diagnosed based on a family history of SMA, one whose parents were both carriers and the other with an affected sibling who died at age 13 months.

Descriptions of patients in the Early Dosing/Low Motor group with severe SMA1

Patient A: This patient's severe SMA1 was diagnosed at age four weeks, supported by a genetic profile demonstrating biallelic *SMN1* exon 7 deletion with two copies of *SMN2* (Table 3). The parents reported constipation, poor swallowing, and hypotonia.

At enrollment, patient A had hypotonia and limb weakness with a baseline CHOP-INTEND score of 16 at 2.3 months of age. Patient A received AVXS-101 therapy at age 2.3 months. Although patient A

TABLE 1.
Baseline Characteristics

Characteristic	Early Dosing/Low Motor Group (n = 3)	Late Dosing Group (n = 6)	Early Dosing/High Motor Group (n = 3)
Age at dosing, months, mean (S.D.)	1.8 (0.76)	5.1 (1.56)	1.8 (0.85)
Weight, kg, mean (S.D.)	5.2 (0.15)	6.7 (1.02)	4.2 (0.87)
Proportion of females (%)	33.3	66.7	66.7
Age at symptom onset, months, mean (S.D.)	0.7 (0.58)	2.0 (0.89)	1.0 (1.00)
CHOP-INTEND score, mean (S.D.)	15.7 (1.53)	26.5 (7.66)	44.0 (7.94)
Clinical support			
Free from nutritional support (%)	0	66.7	100
Free from NIV support (%)	100	66.7	100

Abbreviations:
CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
NIV = Noninvasive ventilation

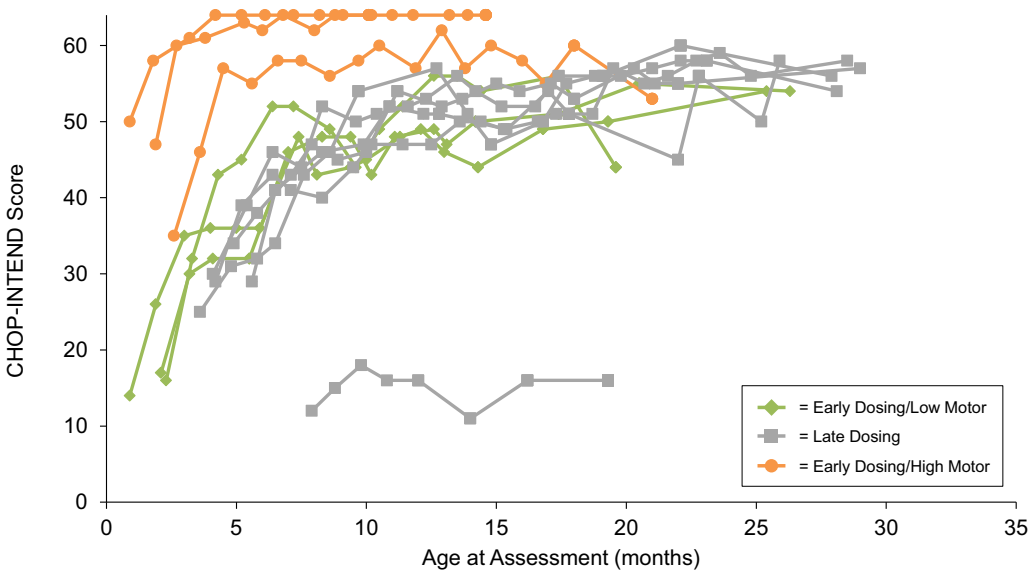

FIGURE 1. CHOP-INTEND assessments were conducted for each patient at each monthly visit if the participants were able to perform the assessments. Assessments were discontinued for patients who reached or exceeded a score of 60 of 64 on the CHOP-INTEND. Green lines: patients in the Early Dosing/Low Motor group were dosed early (less than three months), and each had a CHOP-INTEND score <20 at baseline. Gray lines: patients in the Late Dosing group were dosed at three months or greater, and five of six had CHOP-INTEND score ≥20. Orange lines: patients in the Early Dosing/High Motor group were dosed early (less than three months), and each had CHOP-INTEND scores ≥20 at baseline. CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. Adapted from *New England Journal of Medicin*e, Mendell J, Al-Zaidy S, Shell R, et al., Single-dose gene-replacement therapy for spinal muscular atrophy, volume 377, issue 18, pages 1713-1722, Copyright © 2017 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.

did not require noninvasive ventilation at baseline, it was recommended as support at age 12 months. A swallowing test at screening revealed that the patient was at risk for aspiration. Accordingly, a nasojejunal tube was placed between the screening and baseline period of the study for nutritional support. A gastrostomy tube was placed six months after dosing to optimize nutritional support. Patient A was able to feed orally at end of study and achieved the ability to speak.

Motor function improved after treatment with AVXS-101 from a total CHOP-INTEND score of 16 at baseline to 32 at month one and 44 at month 24. The achievement of sitting unassisted for more than five seconds was observed at age 17.6 months.

Patient B: This infant's severe SMA1 was diagnosed during prenatal screening via amniocentesis based on *SMN1* exon 7 deletion with two copies of *SMN2* (Table 3). Patient B developed pathognomonic symptoms of hypotonia and limb weakness with onset at birth. In addition to these symptoms, the parents conveyed a medical history including gastroesophageal reflux with onset at birth and transient hyperbilirubinemia (day one to day 17).

This patient demonstrated impaired motor function at baseline, as indicated by a total score of 14 on the CHOP-INTEND at age 0.9 months. Patient B was dosed with AVXS-101 at age 0.9 months. Results of a swallow test conducted about two weeks before study enrollment revealed risk of aspiration, prompting insertion of a nasojejunal tube, which was optimized with gastrostomy tube/Nissen fundoplication during the study. However, patient B was able to feed orally and had normal swallow function test results by end of study, as well as the ability to speak. The patient did not require noninvasive ventilation at enrollment; however, it was recommended as support at age seven months.

Motor function improved after treatment with AVXS-101 from a baseline CHOP-INTEND score of 14 to 26 at month one and 54 at month 24. The patient achieved sitting unassisted for five seconds or more at age 13.0 months and sitting unassisted for 30 seconds at age 22.1 months (Fig 3).

Patient C: This infant's severe SMA1 was diagnosed at age about one month by the local pediatrician, accompanied by a genetic profile demonstrating biallelic *SMN1* exon 7 deletion with two copies of *SMN2* (Table 3). The parents conveyed a medical history, including patent foramen ovale, poor swallow function requiring nasojejunal tube support, generalized pain, hypotonia, mild intercostal retractions, and moderate belly breathing.

TABLE 2.
Motor Function Assessments

	Early Dosing/ Low Motor Group (n = 3)	Late Dosing (n = 6)	Early Dosing/ High Motor Group (n = 3)
CHOP-INTEND increase 1 month post-dosing, mean score change (S.D.)	13.7 (2.08)	7.3 (3.56)	10.7 (2.52)
CHOP-INTEND increase 3 months post-dosing, mean score change (S.D.)	22.0 (7.00)	11.5 (4.51)	16.7* (3.06)
CHOP-INTEND increase at end of study, mean score change (S.D.)	35.0 (6.24)	23.3 (9.77)	16.3* (2.08)
CHOP-INTEND scores at end of study, mean score (S.D.)	50.7 (5.77)	49.8 (16.64)	60.3 (6.35)
Sitting unassisted ≥5 seconds, n (%)	3 (100%)	5 (83%)	3 (100%)
Mean age, months (S.D.)	17.0 (3.78)	22.0 (3.48)	9.4 (2.20)
Sitting unassisted ≥30 seconds, n, (%)	3 (100%)	3 (50%)	3 (100%)
Mean age, months (S.D.)	21.2 (1.86)	23.1 (2.46)	10.0 (1.95)

Abbreviation:
CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
* Two patients in this group quickly reached the maximum CHOP-INTEND score after 14- and 17-point increases.

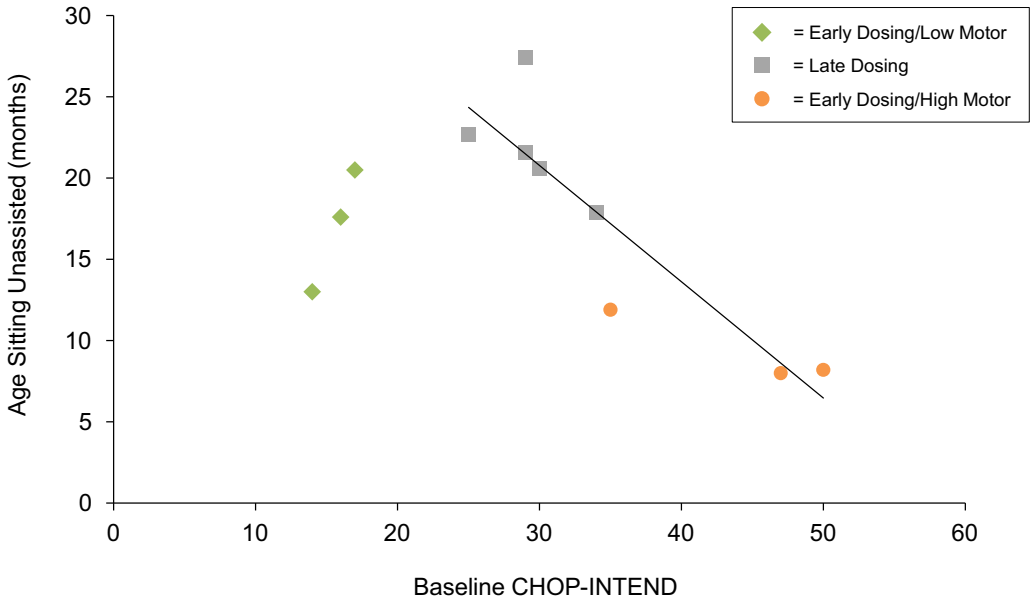

FIGURE 2. Association between age when patients sat unassisted and baseline CHOP-INTEND score. Green diamonds: patients dosed early (less than three months) with low motor function; gray square: patients dosed later (three months or greater) with high motor function; and orange circle, patients dosed early (less than three months) with high motor function. Three patients in the Early Dosing/Low Motor group sat relatively early despite having low CHOP-INTEND scores at baseline (green diamonds). CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

Baseline examination showed symptoms of hypotonia, limb weakness, and swallowing or feeding difficulties. The baseline CHOP-INTEND score was 17 at enrollment. Patient C received AVXS-101 treatment at age 2.1 months. Nasojejunal tube feeding at enrollment was later optimized with a gastrostomy tube at age about four months. However, patient C was able to feed orally at end of study and achieved the ability to speak. Given moderately abnormal pulmonary function (intercostal retractions, paradoxical abdominal breathing), noninvasive ventilatory support was initiated two months after dosing and used over the ensuing 22 months following treatment with AVXS-101.

Motor function improved after treatment with AVXS-101, as evidenced by a total CHOP-INTEND score of 17 at baseline, increasing to 30 at month one and 54 at month 24. Post-baseline swallowing tests revealed risk of aspiration but functional swallowing at month 12, and functional swallowing at all

FIGURE 3. Patients with high baseline CHOP-INTEND who were dosed early (Early Dosing/High Motor) are shown in the orange quadrant; these patients achieved sitting unassisted earliest, and two were standing with assistance and walking. In the green quadrant, patients with low baseline CHOP-INTEND scores (Early Dosing/Low Motor) who were dosed early (less than three months) achieved independent sitting. In the gray quadrant, patients were treated at age three months or greater (Late Dosing). CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

TABLE 3.
Clinical Characteristics of Infants With Severe SMA1 Disease

Patient	Age at Onset and Age at Dosing	Symptoms	Motor Function Achievements	Gastrointestinal Status	Pulmonary Status
	Clinical Characteristics at Baseline		Clinical Characteristics at End of Study		
A	Onset: ~4 weeks Dosing: 2.3 months	Motor function: CHOP-INTEND: 16 Swallow function: aspiration detected, feeding support implemented Respiratory status: no support	CHOP-INTEND: 44 Sitting unassisted for ≥5 seconds (17.6 months) ≥30 seconds (19.1 months), standing with assistance*	Swallow function: feeding orally Speaking	Respiratory status: NIV support at night (5 hr/night)
B	Onset: Birth Dosing: 0.9 months	CHOP-INTEND: 14 Swallow function: aspiration detected, feeding support implemented Respiratory status: no support	CHOP-INTEND: 54 Sitting unassisted for ≥5 seconds (13.0 months), ≥30 seconds (22.1 months)	Swallow function: feeding orally Speaking	Respiratory status: NIV support at night (12 hr/night)
C	Onset: ~4 weeks Dosing: 2.1 months	CHOP-INTEND: 17 Swallow function: aspiration detected, feeding support implemented Respiratory status: no support	CHOP-INTEND: 54 Sitting unassisted for ≥5 seconds (20.5 months), ≥30 seconds (22.5 months)	Swallow function: feeding orally Speaking	Respiratory status: NIV support (8 hr/night; 2 hr/day)

Abbreviations:
CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
LTFU = Long-Term Follow-up
NIV = Noninvasive ventilation
SMA1 = Spinal muscular atrophy type 1
* Achieved after enrollment into the LTFU study.

assessments thereafter. Patient C also achieved sitting unassisted for five seconds or more at age 20.5 months and sitting for more than 30 seconds at age 22.5 months (Fig 3).

Discussion

Typically, patients with SMA1 have respiratory symptoms and motor function decline before age six months. A recent natural history study reported that only 50% of untreated infants with SMA1 with two copies of *SMN2* reached a median age of eight months free of permanent ventilation.[4] In contrast to natural history, in which no patient achieved a CHOP-INTEND score above 40,[15] 11 of 12 patients in this study achieved and maintained a CHOP-INTEND score of ≥40. Patients in the Early Dosing/Low Motor group had rapid mean increases in CHOP-INTEND of 13.7 and 22.0 points at one and three months, respectively. Untreated patients with SMA1 with severe motor function who decline shortly after dosing are known to have a poorer prognosis; however, all the patients in the Early Dosing/Low Motor group were able to achieve sitting unassisted and could speak by the end of the study. In the LTFU study of patients beyond the 24-month study period, as of March 8, 2019, all patients in cohort 2 (N = 10) remain alive and free of permanent ventilation.[16] No previously achieved motor milestone has been lost among the children enrolled.[16] Patients maintained or improved ventilatory status (aside from in the context of acute reversible illness).[16] Of the 4 patients who used noninvasive ventilation at the start of the LTFU study, 2 no longer require it regularly.[16] All patients maintained their ability to swallow.16 Mean (range) age at last follow-up is 3.9 (3.4 to 4.8) years. Mean (range) time since start of treatment is 3.7 (3.3 to 4.3) years.[16] No new treatment-related adverse events emerged during this LTFU.[16]

All subjects receiving the proposed therapeutic dose of AVXS-101 in the current study improved in CHOP-INTEND at early time points postdosing (mean of 9.8 points by one month). This finding is in contrast to that reported in the NeuroNEXT natural history cohort (SMA1 with two copies of *SMN2*), in which CHOP-INTEND scores decreased by a mean of 10.7 points from age six to 12 months.[7] Rapid onset of protein production due to the self-complementary nature of AVXS-101 could account for the rapid increase in motor function seen in the CHOP-INTEND scores.

Dosing early in disease progression, irrespective of disease severity, can allow for significant motor function gains and motor milestone attainment. Two children in the Early Dosing group achieved sitting unassisted within the range of general developmental timeline (i.e., four to nine months).[14] Efficacy in motor function is further validated when compared with the poor outcomes associated with severe variants of SMA1 (mean CHOP-INTEND scores of 4.1 to 5.4 and death by age 14 months).[15] These results show the efficacy of using AVXS-101 and support identifying infants via newborn screening to maximize the therapeutic benefit of early treatment, as recently recommended by a panel of SMA experts.[17] The findings also indicate that gene transfer with AVXS-101 is highly relevant and effective for patients with early onset and low CHOP-INTEND scores. It is important to note that attention to standard of care and appropriate incorporation of ventilatory and nutritional support are critical for infants with SMA1 to fully maximize the impact of AVXS-101 therapy. Indeed, all three infants in the Early Dosing/Low Motor group utilized noninvasive ventilatory support and went on to achieve independent sitting, with one patient achieving standing with support in the follow-up study after 24 months.

One limitation of the current study is the sample size of 12 infants. However, the clinical benefits of early treatment reported here are further underscored by similar results obtained with nusinersen. In fact, children treated with nusinersen at an earlier point in their disease, marked by younger age and greater baseline motor function, respond remarkably better to treatment.[13] Given the rapid early disease progression seen at enrollment in the three children with SMA in the Early Dosing/Low Motor group, one might assume that such children were beyond the scope of adequate treatment. However, we show that such infants who were dosed early in age were able to achieve CHOP-INTEND scores ≥40 and were able to sit unassisted, an unlikely milestone in the natural history of SMA1. These data suggest that infants with severe disease can make significant motor function gains if dosed early in disease progression with a therapy that has a rapid onset of effect, as AVXS-101 does.

Consensus expert opinion recommends treating patients with two to three copies of *SMN2* as soon as possible, as these patients are likely to have severe disease without treatment.[17] These data also emphasize the need for therapies with rapid onset of effect in addition to newborn screening for SMA. Current diagnostic delays can result in the initiation of treatment at points past the time when maximal therapeutic benefits may be achievable.[17] Advances in newborn screening assays will permit identification of infants with SMA before they show symptoms.

The present study is limited by the enrollment restrictions, which were used to obtain a homogeneous group. Specifically excluded were presymptomatic patients and those with the c.859G>C genetic modifier, which predicts a milder SMA phenotype.[18] Given the unprecedented gains in motor function observed in patients in this study—even in those with significant disease progression at enrollment—rapid achievements are expected to be obtained in presymptomatic patients, as well as in those with the genetic modifier.

Conclusions

The vast majority of patients with SMA1 treated with the proposed therapeutic dose of AVXS-101 achieved sitting unassisted irrespective of age at dosing; however, those dosed early achieved this milestone much more quickly regardless of baseline motor function. Clinically significant and rapid motor function improvements, as well as the ability to sit unassisted, were observed among children with low motor function at baseline. These data highlight the potential impact of early treatment and rapid onset of AVXS-101 and emphasize the need for newborn screening in SMA1 as critical for maximal outcomes.

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