

Preliminary Safety and Tolerability of a Novel Subcutaneous Intrathecal Catheter System for Repeated Outpatient Dosing of Nusinersen to Children and Adults With Spinal Muscular Atrophy

Kevin A. Strauss, MD,* Vincent J. Carson, MD,* Karlla W. Brigatti, MS, LCGC,*
Millie Young, RNC,* Donna L. Robinson, CRNP,* Christine Hendrickson, RNC,*
Michael D. Fox, MD,†‡ Robert M. Reed, MD,§ Erik G. Puffenberger, PhD,*
William Mackenzie, MD,†|| and Freeman Miller, MD†||

Background: Many patients with spinal muscular atrophy (SMA) who might benefit from intrathecal antisense oligonucleotide (nusinersen) therapy have scoliosis or spinal fusion that precludes safe drug delivery. To circumvent spinal pathology, we designed a novel subcutaneous intrathecal catheter (SIC) system by connecting an intrathecal catheter to an implantable infusion port.

Methods: Device safety and tolerability were tested in 10 SMA patients (age, 5.4 to 30.5 y; 80% with 3 copies of *SMN2*); each received 3 sequential doses of nusinersen (n = 30 doses). Pretreatment disease burden was evaluated using the Revised Hammer-smith Scale, dynamometry, National Institutes of Health pegboard, pulmonary function testing, electromyography, and 2 health-related quality of life tools.

Results: Device implantation took ≤ 2 hours and was well tolerated. All outpatient nusinersen doses were successfully administered via SIC within 20 minutes on the first attempt, and required no regional or systemic analgesia, cognitive distraction, ultrasound guidance, respiratory precautions, or sedation. Cerebrospinal fluid withdrawn from the SIC had normal levels of glucose and protein; cerebrospinal fluid white blood cells were slightly elevated in 2 (22%) of 9 specimens (median, 1 cell/ μL ; range, 0 to 12 cells/ μL) and red blood cells were detected in 7 (78%) specimens (median, 4; range, 0 to 2930 cells/ μL).

Discussion: Preliminary observations reveal the SIC to be relatively safe and well tolerated in SMA patients with advanced disease and spinal fusion. The SIC warrants further study and, if proven effective in larger trials of longer duration, could double the number of patients able to receive nusinersen worldwide while reducing administration costs 5- to 10-fold.

Key Words: intrathecal catheter, nusinersen, *SMN1*, spinal muscular atrophy

(*J Pediatr Orthop* 2018;38:e610–e617)

From the *Clinic for Special Children, Strasburg; ‡Department of Pediatrics, Sidney Kimmel Medical College at Thomas Jefferson University; ||Department of Orthopedics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA; †Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE; and §University of Maryland School of Medicine, Baltimore, MD.

This study was funded in part by a grant from Biogen, the manufacturer of nusinersen. The authors received no direct or indirect compensation from Biogen and have no personal financial interests in the company. Author Robert M. Reed reports grants from Flight Attendants Medical Research Institute (FAMRI) during the conduct of the study. Funding from FAMRI did not influence the collection or analysis of data.

The authors declare no conflicts of interest.

Reprints: Kevin A. Strauss, MD, Clinic for Special Children, 535 Bunker Hill Road, Strasburg, PA 17579. E-mail: kstrauss@clinicforspecialchildren.org.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.pedorthopaedics.com.

Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/BPO.0000000000001247

Spinal muscular atrophy (SMA; MIM# 253300) is a common monogenic cause of spinal motor neuron (SMN) degeneration caused by biallelic deletions of *SMN1*, which encodes SMN protein.^{1–4} Within the *SMN1* locus on chromosome 5q13, humans have a second SMN-encoding gene (*SMN2*) that can be present in multiple copies. *SMN2* contains a base difference (c.850C > T) that excludes exon 7 from ~90% of mRNA transcripts to produce an unstable protein fragment (SMN Δ 7) that is rapidly degraded.^{5,6} Residual intact SMN translated from each *SMN2* copy partially compensates for *SMN1* deficiency such that genomic *SMN2* copy number correlates inversely with disease timing and severity.^{7–9}

Functional overlap between *SMN1* and *SMN2* inspired the design of nusinersen, an antisense oligonucleotide engineered to alter splicing of *SMN2* pre-mRNA and thereby increase expression of stable SMN protein.¹⁰

Repeated intrathecal injections of nusinersen improve survival and motor development among infants with severe SMA (2 copies of *SMN2*) treated between 30 and 262 days of age, and also benefit patients started on therapy between 2 and 9 years of age as observed in CHERISH, a study to assess the efficacy and safety of nusinersen in participants with later-onset SMA (NCT02292537).¹¹

The CHERISH trial excluded older symptomatic patients with joint contractures, severe scoliosis (radiographic Cobb angle >40 degrees), gastrostomy, or dependence on mechanical ventilatory support.¹¹ Unfortunately, such complications are common among surviving SMA patients, many of whom have skeletal deformity or instrumentation that hinders repeated interlaminar nusinersen dosing.^{12,13} This has prompted a search for alternative nusinersen dosing strategies¹⁴ and engenders related questions about how to structure functional assessments for patients who have advanced neuromuscular disability and its attendant skeletal and respiratory complications.^{12,13,15–17} We were confronted with this problem in March 2017, when an 11-year-old Mennonite boy with advanced SMA was denied intrathecal nusinersen at 2 different academic medical centers because of spinal fusion.

To circumvent spinal pathology, we devised a novel subcutaneous intrathecal catheter (SIC) system using an off-label configuration of 2 Food and Drug Administration (FDA)-approved devices: an intrathecal catheter and power injectable implantable infusion port. This allowed for repeated nusinersen dosing via subcutaneous port (Fig. 1). Following successful implantation in the sentinel patient, we designed a prospective study to evaluate 20 SMA participants treated via SIC for 14 months (through 4 loading and 3 maintenance doses of nusinersen) and tailored functional assessments to older individuals with moderate to severe neuromuscular disease.^{11,18} Here we report preliminary safety and tolerability of the SIC for the first 10 participants, each of whom received 3 loading doses over 4 weeks, and discuss the implications for future studies.

METHODS

Patients

Ten study participants born between 1987 and 2012 shared homozygous exon 7 deletions of *SMN1* that traced to common ancestral founders across 11 generations and segregated into individuals with 2 ($n=1$), 3 ($n=8$), or 4 ($n=1$) copies of *SMN2* (Table 1). The 6 eldest patients (age, 12.1 to 30.5 y) had spinal fusion that precluded repeated lumbar puncture; the 4 youngest (age, 5.4 to 10.4 y) had no spinal pathology, but parents elected the SIC based on its perceived administration safety, convenience, and cost. The study was approved by Penn Medicine-Lancaster General Hospital Institutional Review Board. Adults consented in writing to participate and parents consented on behalf of their children. In accordance with journal policy, a separate signed consent was obtained for reproduction of the photograph in Figure 1. This interim

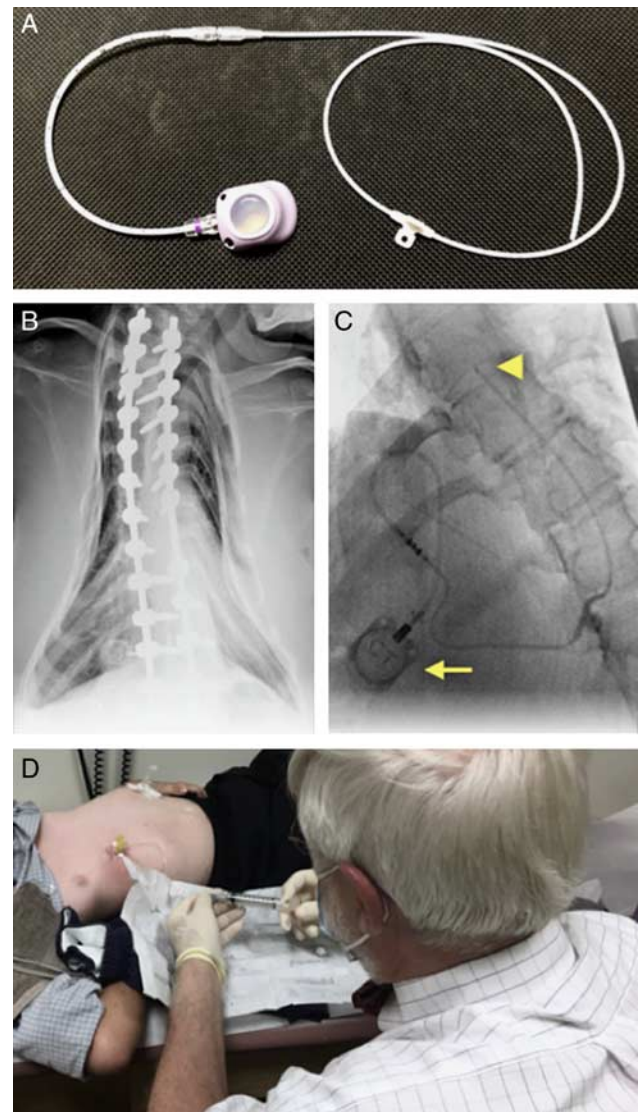


FIGURE 1. SIC system. A, The interlocked intrathecal catheter and subcutaneous infusion port used to construct the hybrid nusinersen delivery system. B, Distortions of spinal and pulmonary anatomy, commonly observed among older SMA patients, that inspired design of the SIC system. C, The SIC system in situ, with the infusion port and intrathecal catheter tip marked by a yellow arrow and arrowhead, respectively. D, The SIC allows for safe, low-cost, repeated outpatient nusinersen dosing. SIC indicates subcutaneous intrathecal catheter; SMA, spinal muscular atrophy.

analysis, focused upon initial safety and tolerability of the SIC, was conducted between June 2017 and January 2018.

Surgical Procedure and Nusinersen Dosing

We constructed a hybrid infusion system using 2 FDA-approved devices: a catheter commonly utilized for continuous or repeated intrathecal infusion (Medtronic) and a power injectable implantable infusion port (Med-Comp) designed for repetitive blood sampling or chemotherapy (Fig. 1). The infusion port locked firmly into the

TABLE 1. Patient Characteristics (n = 10), Comorbidities, and Cerebrospinal Fluid Indices

Patient Number	Age (y)	Sex	SMN2 Copies	Motor Baseline*	Mean CMAP (mV)	Cerebrospinal Fluid From SIC								
						Wheelchair	Scoliosis	Spinal Fusion	G-tube	BiPAP	RBC/ μ L	WBC/ μ L	Glucose (mg/dL)	Protein (mg/dL)
1	6.3	F	4	65	6.6						4	8	49	68
2	5.4	M	3	30	1.5	•					0	0	53	19
3	7.9	M	3	26	1.1	•	•				1	5	58	25
4	10.4	F	3	27	1.5	•	•				0	3	76	25
5	13.7	M	3	4	1.2	•	•	•			3	1	67	18
6	15.8	F	3	7	1.7	•	•	•			69	0	53	20
7	20.4	F	3	3	0.6	•	•	•			13	0	53	18
8	23.0	M	3	6	1.1	•	•	•			11	12	53	29
9	30.5	F	3	6	1.9	•	•	•			–	–	–	–
10*	12.1	M	2	16	0.1	•	•	•	•	•	2930	0	62	45

*Motor function was assessed using the RHS (maximum score = 66) with the exception of patient #10, who had 2 copies of SMN2 and could not complete the RHS; he was instead assessed using the CHOP INTEND scale (maximum score = 64).

“–” indicates data not available/test not completed; “•”, the presence of a morbid outcome; BiPAP, bilevel positive airway pressure > 6 hours daily; CMAP, compound muscle action potential; F, female; G-tube, gastrostomy feeding tube; M, male; RBC, red blood cells; RHS, Revised Hammersmith Scale; SIC, subcutaneous intrathecal catheter; WBC, white blood cells.

intrathecal catheter, nonleakage was verified ex vivo, and the implantation procedure was performed under general anesthesia.

We exposed the spine through a 3 to 4 cm incision and drilled a hole (under fluoroscopic guidance) through the spinal fusion to access the epidural space. The catheter was threaded into the midthoracic intrathecal space and the threading needle withdrawn to document free back-flow of cerebrospinal fluid (CSF). Although nusinersen is typically administered in the lumbar region via interlaminar puncture, SMA affects lower motor neurons along the entire neuraxis, and lumbar administration is based on tactical rather than biological considerations.¹⁹ Unlike infants with SMA who spend much of their time supine,¹⁸ most of our patients are upright (ie, on a wheelchair) during waking hours. We therefore chose a higher delivery site to expose thoracic and potentially cervical motor neurons to nusinersen.

Once positioned, an anchor was placed over the catheter and sutured to deep fascia, just a top bone. The infusion port was then placed through a 2 cm incision of the chest wall and implanted subcutaneously, where it was anchored to hard fascia of the chest, flank, or lower back, depending on anatomic considerations and patient preference. The port catheter was tunneled under the fascia to the posterior wound and connected firmly to the intrathecal catheter. Before wound closure, the port was accessed to document CSF flow through the complete hybrid system.

The posterior bone hole was closed with a pressure injection of surgical sealant-coagulant to prevent CSF leak and fascia were closed tightly to further safeguard against leakage. Following complete posterior wound closure, the exposed anterior infusion port was again aspirated to document free flow. A CSF volume of 5 mL was withdrawn from the port followed by injection of 12 mg (5 mL) of nusinersen (loading dose 1; LD1), which was then cleared from the catheter using 0.5 mL of normal saline. The anterior wound was then completely closed.

Patients remained supine for 48 hours postoperatively, after which they were placed in seated position and, if asymptomatic when upright for 12 hours, discharged home. Surgical wound inspection was performed on postoperative day 14 to insure the access port was completely under the skin, readily palpable, and easily accessed via a noncoring needle (Fig. 1). No imaging, sedation, or regional anesthesia was required to access the port or administer drug thereafter.

All subsequent nusinersen doses were given in the outpatient setting by standard procedure: (1) topical lidocaine 2.5%/prilocaine 2.5% was applied over the infusion port at least 30 minutes before dosing; (2) skin overlying the access port was then prepped and draped using sterile technique (Fig. 1); (3) the port reservoir was accessed via noncoring needle and flushed with 0.2 mL saline to float the intrathecal catheter tip free from surrounding pia and arachnoid mater; (4) 3 mL CSF was withdrawn and discarded and an additional 4 mL withdrawn for analysis; and (5) nusinersen 12 mg (5 mL) was infused through the port and the catheter was flushed with 2 mL saline.

Assessments

Each participant received 3 loading doses of nusinersen via SIC (baseline, LD1; week 2, LD2; week 4, LD3). At scheduled doses, we obtained laboratory indices of safety and solicited information about adverse events and concomitant medications. Before administration of LD3, CSF was collected through the SIC and divided into aliquots for measurement of cell counts, protein, and glucose. A structured battery of assessments was conducted at the preimplantation visit and 4 weeks after implantation, before administration of LD3. We did not expect to observe any significant changes in motor function, power, or respiratory performance after just 2 doses of nusinersen, which for infants only improves event-free survival beyond the loading phase.¹⁸

Motor assessments were performed at ~09:00 hours by the same examiner and included tests of neuromuscular

function [Revised Hammersmith Scale (RHS)²⁰ or Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders,²¹ as appropriate to pretreatment functional level]. Nine (90%) participants could be studied using the RHS, for which scores range between 0 and 66 (with higher numbers indicating better motor function). Motor speed and dexterity were assessed using the National Institutes of Health (NIH) Toolbox pegboard,²² and power was measured by 12 dynamometry maneuvers (JTech Medical, Commander Echo MMT Dynamometry). A novel dynamometric parameter, the SMA Force Index (SFI) was devised to capture the distribution of weakness characteristic of SMA (see Supplemental Materials for details, Supplemental Digital Content 1, <http://links.lww.com/BPO/A180>).

Baseline compound muscle action potential (CMAP; mV) was recorded from the distribution of ulnar (abductor digiti minimus), radial (extensor carpi radialis longus), and deep peroneal (extensor digitorum brevis, tibialis anterior) nerves—and used to calculate an average CMAP amplitude for each patient.²³ Pulmonary function testing was performed in the seated position in accordance with American Thoracic Society standards using an EasyOne Pro Lab (NDD). Maximal inspiratory (MIP) and expiratory (MEP) pressures were measured after full exhalation and inhalation, respectively, using a Micro respiratory pressure monitor (RPM; Micro Direct); these are reported as *z*-scores calculated from age-specific and sex-specific reference values,²⁴ where $z = (\text{patient value} / \text{reference mean}) / (\text{reference SD})$ and normal *z*-scores range between -2 and +2. To assess well-being, we administered age-appropriate Pediatric Quality of Life (PedsQL) Acute and Family Impact Modules (www.pedsq.org; parent and child forms)²⁵ and the NIH Toolbox Emotion Domain.²²

Statistics

Functional measures, laboratory indices, and measures of HRQOL at preimplantation and week 4 were compared using a paired *t* test. Relationships of RHS, dynamometer measures, and pulmonary function to patient age were studied with Pearson (*r*) correlations (Prism 7, GraphPad).

RESULTS

Baseline Assessments

Motor function, dexterity, power, mean CMAP, pulmonary function, and HRQOL among 10 study participants are represented in Tables 1 and 2. For 8 patients with 3 copies of *SMN2*, the RHS, weight-adjusted SFI, and select dynamometry maneuvers correlated inversely with age in children below 16 years (Pearson *r* values -0.94 to -0.97). These correlations broke down thereafter, revealing their limits for patients with advanced neuromuscular disease (Fig. 2). Measured parameters did not change significantly after 2 loading doses of nusinersen (Table 2). Baseline mean CMAP varied by *SMN2* copy number: values for patients with 4 (n = 1), 3 (n = 8), and 2 (n = 1) copies of *SMN2* were 6.6 ± 0.8,

TABLE 2. Clinical Assessments Pretreatment and After 2 Loading Doses of Nusinersen (n = 10)

	Preimplantation		Week 4*		P
	Mean	SD	Mean	SD	
Revised Hammersmith Functional Motor Scale†	19.0	19.2	19.5	19.4	ns
Dynamometry, left-right average (N)‡					
Shoulder abductors	10.3	16.4	10.1	15.5	ns
Elbow extensors	9.1	14.9	7.7	12.3	ns
Grip strength	20.9	14.0	21.1	13.2	ns
Three-point pinch	12.9	8.1	12.8	7.5	ns
SMA Force Index§	0.085	0.083	0.080	0.070	ns
NIH Toolbox Pegboard score (s)	33.0	6.2	31.3	7.0	ns
Mean CMAP amplitude (mV)	1.7	1.8	—	—	—
Pulmonary function					
Total lung capacity (L)	3.1	1.3	3.5	1.0	ns
Forced vital capacity (L)	1.6	0.5	1.9	1.6	ns
Maximum inspiratory pressure (cm H ₂ O)	41.8	27.6	49.8	23.0	ns
Maximum expiratory pressure (cm H ₂ O)	30.9	21.3	40.1	15.8	ns
PedsQL physical functioning (scale 0-100)					
Subject report	32	9	36	17	ns
Parent report	45	18	34	22	ns
PedsQL emotional functioning (scale 0-100)					
Subject report	74	18	79	16	ns
Parent report	68	18	75	12	ns
PedsQL Global Family Impact (scale 0-100)	71	13	74	3	ns
NIH toolbox emotion domain (T scores)					
Positive affect	51	9	54	8	ns
Life satisfaction	55	13	57	13	ns
Loneliness	44	7	48	9	ns
Anger	47	10	44	11	ns
Sadness	45	11	46	9	ns

*After 2 loading doses of nusinersen.

†Nine of 10 subjects had 3 copies of *SMN2* and completed the RHS (maximum score, 66). One subject had severe type 1 SMA (2 copies of *SMN2*), was 12 years old at implantation, and unable to generate a score on the RHS. He was instead assessed using the CHOP INTEND (maximum score, 64), on which he scored 16 (preimplantation), and 15 (week 4). These scores were included in the mean statistic.

‡Full dynamometry assessment was comprised of 12 maneuvers, which included neck flexors, shoulder abductors, elbow flexors and extensors, wrist extensors, hand grip, 3-point pinch, hip flexors and abductors, knee flexors and extensors, and foot dorsiflexors. Pearson correlations showed that only 4 among these (shown) had a temporal correlation with disease course (Supplemental Materials, Supplemental Digital Content 1, <http://links.lww.com/BPO/A180>).

§The weight-adjusted SFI was derived from the 4 informative dynamometry maneuvers using the equation: $SFI = (\text{Shoulder Abductors} + \text{Elbow Extensors} + \text{Grip}) / (\text{Pinch})^{0.5}$, and correlated strongly disease course (Pearson $r = -0.94$, $P = 0.0001$).

||Electromyography was only performed at pretreatment baseline and will be conducted again at study conclusion (14 mo).

CMAP indicates compound muscle action potential; LD3, nusinersen loading dose 3; NIH, National Institutes of Health; ns, not significant ($P > 0.05$); PedsQL, Pediatric Quality of Life Inventory; RBC, red blood cells; RHS, Revised Hammersmith Scale; SFI, SMA Force Index; SMA, spinal muscular atrophy; WBC, white blood cells.

1.3 ± 0.7, and 0.2 ± 0.1 mV, respectively. Motor nerve amplitude did not vary as a function of age among patients with 3 copies of *SMN2* (Fig. 2).

Total lung capacity and forced vital capacity were 32% to 78% and 16% to 97% predicted, respectively (Tables 1, 2, and Fig. 2). MIP and MEP pressures decreased with age and MEPs corrected for age and sex were low relative to MIPs (Fig. 2). This reflects a reversal

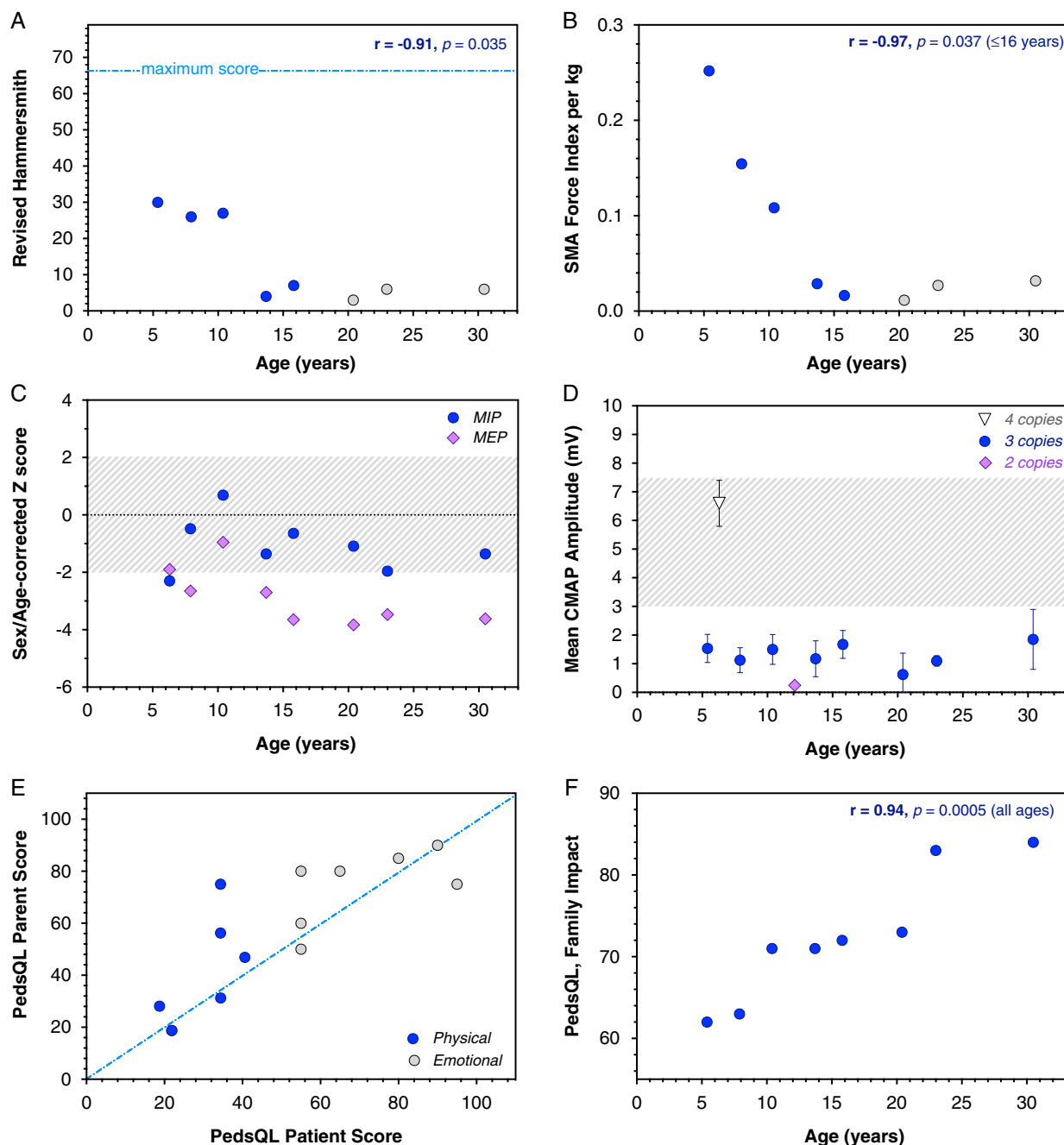


FIGURE 2. Multidomain baseline assessments. Among SMA patients with 3 copies of *SMN2* and below 16 years of age (blue circles), we found strong inverse Pearson correlations between age and Revised Hammersmith Functional Motor Scale (A), weight-adjusted SFI (B), and forced vital capacity. This association broke down after age 16 (gray circles). C, MEP as compared with inspiratory pressure (corrected for age and sex) was low for all patients, reflecting weakness of intercostal muscles relative to the diaphragm. Gray shaded area indicates normal z-scores ranging from -2 to $+2$. D, Baseline mean CMAP, averaged from 4 separate recordings, varied by *SMN2* copy number (white triangle, 4 copies; blue circles, 3 copies; purple diamond, 2 copies) but did not vary as a function of age among patients with 3 *SMN2* copies. Gray shaded area represents the range of CMAP amplitude observed in ambulatory (as compared with nonambulatory) SMA patients (Lewelt et al²³). E, Independent PedsQL responses of participants and their caregivers were generally in good agreement (blue-dashed line represents unity) but there was a tendency for parents to overrate their child’s well-being. F, The overall burden of disease on family functioning (PedsQL family impact module) was strongly associated with patient age. CMAP indicates compound muscle action potential; SMA, spinal muscular atrophy; PedsQL, Pediatric Quality of Life.

of normal physiology characteristic of SMA; the diaphragm is less impaired than intercostal muscles and results in development of a bell-shaped chest (Fig. 1).

PedsQL responses of participants and their caregivers, elicited independently, were generally in good agreement ($r^2 = 0.77$, $P < 0.0001$). Participants and parents alike consistently rated physical function lower than emotional function and parents tended to overrate their child's physical well-being (Fig. 2). Within our cohort of predominantly Old Order Mennonite participants harboring 3 copies of *SMN2*, baseline indices of emotional health were similar to values from healthy pediatric reference populations,^{26,27} whereas physical functioning scores were 60% to 70% lower (Table 2).

Safety and Tolerability of the SIC

For all 10 participants, the SIC was successfully implanted during a single procedure lasting an average 1.4 (range, 1.1 to 2.0) hours followed by a hospital stay of 50 to 55 hours. There were no perioperative or postoperative complications and all wounds were clean and dry by postoperative week 2. Each participant received 3 nusinersen doses over a 4 week postimplantation period (30 doses for the cohort). All outpatient nusinersen doses were successfully administered via SIC with a single attempt through topical anesthesia, and required no regional or systemic analgesia, cognitive distraction, ultrasound guidance, respiratory precautions, or sedation.²⁸ No patient required oropharyngeal suctioning, supplemental oxygen, or noninvasive ventilation before or during receipt of an outpatient SIC dose.

During the interim study period, 3 adverse events occurred among 3 participants. These included: (1) urinary tract infection in a male child, (2) back pain secondary to a protruding spinal rod in an adult female, and (3) inability to withdraw CSF from the SIC port during LD2 in another adult female; nusinersen could, however, be freely administered through this same port, implicating dynamic suction-induced catheter obstruction. None of these events were serious and only the latter was definitely related to the device.

Nine study participants had CSF withdrawn from the SIC. CSF glucose (median, 53 mg/dL; range, 49 to 76 mg/dL) and protein (median, 25 mg/dL; range, 18 to 68 mg/dL) levels were normal. White blood cells were slightly elevated in 2 (22%) of 9 specimens (median, 1 cell/ μ L; range, 0 to 12 cells/ μ L) and red blood cells were detected in 7 (78%) of 9 specimens (median, 4; range, 0 to 2930 cells/ μ L) (Table 1). There were no serum or urine laboratory abnormalities associated with SIC nusinersen administration.

DISCUSSION

Barriers to Nusinersen Administration

Nusinersen has well-documented efficacy for infants and children with SMA,^{11,18} but clinical studies to date do not adequately address older patients who have more advanced neuromuscular disease and its attendant skeletal and pulmonary morbidities. Specifically, scoliosis is observed in as many as 80% of SMA patients with 2 or 3

copies of *SMN2* who survive into late childhood¹² and can preclude safe, repeated interlaminar dosing of nusinersen. These same patients often require sustained mechanical ventilatory support or gastrostomy tube feeding, which were exclusion criteria for CHERISH.¹¹

Absolute anatomic and relative pulmonary barriers to repeated interlaminar dosing have prompted efforts to administer nusinersen by alternative routes. As one recent example, 4 SMA patients with spinal fusion received 15 consecutive nusinersen injections via a transforaminal route guided by cone-beam computed tomography with fluoroscopic navigational overlay.¹⁴ Although the complication rate was low (6.7%), each procedure was technically complex, required sedation, and incurred radiation exposure. Lower complication rates from lumbar puncture (ie, 6% to 17%) might be achieved with conscious sedation^{16,29} but consistently safe, controlled interlaminar access in young people often requires a high degree of technical expertise and/or general anesthesia.²⁹⁻³¹

Even among SMA patients without advanced neuromuscular disease or spinal pathology, repeated interlaminar dosing of nusinersen poses challenges. The overall incidence of traumatic lumbar puncture in children ranges from 20% to 50% and is highest among newborns.³²⁻³⁴ In one series of 73 lumbar punctures for 28 SMA patients (2 to 14 y), headache, back pain, or CSF leak complicated 32% of nusinersen doses.³⁵ In a second series of 84 interlaminar nusinersen doses at an academic neuromuscular center (20 patients, ages 2 to 50 mo),²⁸ the first lumbar puncture attempt failed 33% of the time (mean, 1.5 ± 1.0 attempts/child/dose) and 2 (10%) children below 6 months of age required ultrasound guidance. Oropharyngeal suctioning was regularly performed, and 7 (35%) children received noninvasive ventilation during lumbar puncture. Procedural sedation and postprocedural analgesia were required for 30% and 40% of children, respectively.²⁸

Preliminary Device Safety and Tolerability

In contrast to repeated lumbar puncture, dosing via SIC required only topical anesthetic and took <20 minutes during the course of routine outpatient visit. All doses were administered on the first attempt and patients experienced no significant pain, distress, or clinical instability from the procedure. Accordingly, we found no need to use special respiratory maneuvers, systemic analgesia, conscious sedation, or cognitive distraction. Parents of the four youngest study participants who had no anatomic or pulmonary contraindications to interlaminar dosing—elected SIC implantation as potentially safer, more convenient, and less costly than repeated lumbar puncture.

Efficacy was not an endpoint of the present study. However, consistent with best clinical practice, we used a multidimensional battery to assess patients at pretreatment baseline and at various intervals until study completion (ie 14 mo, after 4 loading and 3 maintenance doses of nusinersen). We expect therapeutic effects of nusinersen in this cohort will be relatively modest, slow to emerge, and observed primarily as an arrest of disease progression.¹¹ Unfortunately, as shown in Figure 2, many

conventional endpoints of motor function used for infants and young children lose their informative value after age 16 years. Thus, different assessment tools might be needed to gauge efficacy of disease-modifying therapies in adolescents and adults with SMA.

Laboratory monitoring supported the safety of the SIC but, on a cautionary note, we detected red blood cells (median, 4; range, 0 to 2930 cells/ μ L) in 7 (78%) of 9 specimens withdrawn from the system (Table 1). A similar phenomenon was observed among newborns with an intrathecal reservoir or ventriculoperitoneal shunt,³⁶ raising the possibility that indwelling CSF catheter tips, when not continuously infusing, can adhere to pial or arachnoid membranes to become dynamically obstructed and/or cause microvascular injury when suction is applied. To safeguard against this, we added an initial 0.2 mL saline flush to the administration protocol to gently dislodge the catheter tip from surrounding thecal membranes before withdrawal of CSF. It is worth noting that CSF withdrawal and examination were a means by which to assess SIC patency and safety for the purpose of this trial, but need not be a routine component of long-term administration protocols.

Clinical and Economic Implications

Since the FDA approved nusinersen for treatment of all forms of SMA in December 2016, there is growing demand for delivery methods adapted to older patients with respiratory and spinal comorbidities. The publication of CHERISH,¹¹ which demonstrated clinical efficacy in an older SMA patient population with later-onset disease, brought the need into sharp relief. In recognition of this fact and its time-sensitivity for many patients with SMA, we chose a relatively short interval to describe device implantation and preliminary safety with the intention to prompt additional research in this area. If the SIC or similar device proves safe and well tolerated in multicenter trials involving more patients over longer intervals, indwelling catheter systems might become a preferred route of nusinersen dosing for patients across the SMA spectrum. This could not only increase the proportion of patients who receive drug, but also reduce its overall administration cost (Fig. 3).

In our office, nusinersen via SIC cost US\$75 per administration. By comparison, 4 Mennonite children (age, 0.7 to 2.9 y) treated contemporaneously by standard lumbar puncture incurred hospital charges of \$5000 and \$9000 per administration, depending on the type and duration of sedation used. On the basis of these data, Figure 3 depicts comparative administration costs (not including drug) for 10 participants over a period of 10 years, assuming an SIC implantation cost of \$22,000 and an annual medical inflation rate of 6%. The SIC yields average savings of \$24,000 per child per year (2.4 million dollars for the cohort over 10 y). Although not a primary endpoint of this study, this simple economic heuristic has unambiguous implications for the overall cost of nusinersen administration worldwide.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, nusinersen via repeated intrathecal injection is effective therapy for all types of SMA,^{11,18} but its

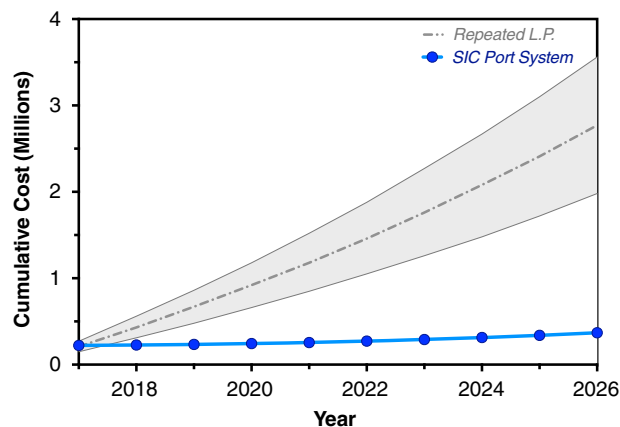


FIGURE 3. Administration economics. Projected nusinersen administration costs (not including drug) for 10 participants were plotted over 10 years, assuming a 1-time SIC implantation cost of \$22,000 and an annual medical inflation rate of 6%. The SIC (blue line) yields average savings of \$24,000 per child per year (2.4 million dollars for the cohort over 10 y) as compared with repeated lumbar puncture (gray shaded area, bounded by upper and lower limits of projected interlaminar administration costs). SIC indicates subcutaneous intrathecal catheter.

standard method of interlaminar delivery poses both absolute and relative challenges for a large proportion of patients. More data are needed to determine if nusinersen has comparable efficacy when delivered by subcutaneous port as compared with the standard interlaminar route. However, our initial observations are promising, and long-term administration of nusinersen via the SIC or similar device has the potential to double the number of children worldwide who can safely receive the drug^{12,14} while simultaneously lowering its long-term administration cost 5- to 10-fold.

Although the SIC was designed for SMA patients with advanced disease and attendant spinal pathology, our preliminary observations have implications for younger, less severely affected patients. As private and government insurers adapt to the extraordinary costs associated with new disease-modifying precision therapies, they will likely seek practical innovations like the SIC, which have the potential to safely control administration costs while preserving therapeutic value.

ACKNOWLEDGMENTS

This work was supported in part by charitable contributions from the communities we serve. We thank SMA patients and their families for their creativity, courage, and partnership in this endeavor.

REFERENCES

- Govoni A, Gagliardi D, Comi GP, et al. Time is motor neuron: therapeutic window and its correlation with pathogenetic mechanisms in spinal muscular atrophy. *Mol Neurobiol*. 2018;55:6307–6318.
- Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80:155–165.

3. Burglen L, Spiegel R, Ignatius J, et al. SMN gene deletion in variant of infantile spinal muscular atrophy. *Lancet*. 1995;346:316–317.
4. Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. *Nat Genet*. 1997;16:265–269.
5. Butchbach ME. Copy number variations in the survival motor neuron genes: implications for spinal muscular atrophy and other neurodegenerative diseases. *Front Mol Biosci*. 2016;3:7.
6. Han KJ, Foster DG, Zhang NY, et al. Ubiquitin-specific protease 9x deubiquitinates and stabilizes the spinal muscular atrophy protein-survival motor neuron. *J Biol Chem*. 2012;287:43741–43752.
7. Kolb SJ, Coffey CS, Yankey JW, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. *Ann Clin Transl Neurol*. 2016;3:132–145.
8. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol*. 2017;82:883–891.
9. Coovert DD, Le TT, McAndrew PE, et al. The survival motor neuron protein in spinal muscular atrophy. *Hum Mol Genet*. 1997;6:1205–1214.
10. Khorkova O, Wahlestedt C. Oligonucleotide therapies for disorders of the nervous system. *Nat Biotechnol*. 2017;35:249–263.
11. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378:625–635.
12. Carter GT, Abresch RT, Fowler WM Jr, et al. Profiles of neuromuscular diseases. Spinal muscular atrophy. *Am J Phys Med Rehabil*. 1995;74:S150–S159.
13. Mayer OH. Scoliosis and the impact in neuromuscular disease. *Paediatr Respir Rev*. 2015;16:35–42.
14. Weaver JJ, Natarajan N, Shaw DWW, et al. Transforaminal intrathecal delivery of nusinersen using cone-beam computed tomography for children with spinal muscular atrophy and extensive surgical instrumentation: early results of technical success and safety. *Pediatr Radiol*. 2018;48:392–397.
15. van der Ploeg AT. The dilemma of two innovative therapies for spinal muscular atrophy. *N Engl J Med*. 2017;377:1786–1787.
16. Bhatt M, Johnson DW, Chan J, et al. Risk factors for adverse events in emergency department procedural sedation for children. *JAMA Pediatr*. 2017;171:957–964.
17. Graham RJ, Athiraman U, Laubach AE, et al. Anesthesia and perioperative medical management of children with spinal muscular atrophy. *Paediatr Anaesth*. 2009;19:1054–1063.
18. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377:1723–1732.
19. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388:3017–3026.
20. Ramsey D, Scoto M, Mayhew A, et al. Revised Hammersmith Scale for spinal muscular atrophy: A SMA specific clinical outcome assessment tool. *PLoS One*. 2017;12:e0172346.
21. Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia infant test of neuromuscular disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord*. 2010;20:155–161.
22. Gershon RC, Wagster MV, Hendrie HC, et al. NIH toolbox for assessment of neurological and behavioral function. *Neurology*. 2013;80:S2–S6.
23. Lewelt A, Krossschell KJ, Scott C, et al. Compound muscle action potential and motor function in children with spinal muscular atrophy. *Muscle Nerve*. 2010;42:703–708.
24. Wilson SH, Cooke NT, Edwards RH, et al. Predicted normal values for maximal respiratory pressures in caucasian adults and children. *Thorax*. 1984;39:535–538.
25. Dunaway S, Montes J, Montgomery M, et al. Reliability of telephone administration of the PedsQL generic quality of life inventory and neuromuscular module in spinal muscular atrophy (SMA). *Neuromuscul Disord*. 2010;20:162–165.
26. Panepinto JA, Pajewski NM, Foerster LM, et al. The performance of the PedsQL generic core scales in children with sickle cell disease. *J Pediatr Hematol Oncol*. 2008;30:666–673.
27. Lam KC, Valier AR, Bay RC, et al. A unique patient population? Health-related quality of life in adolescent athletes versus general, healthy adolescent individuals. *J Athl Train*. 2013;48:233–241.
28. Pechmann A, Langer T, Wider S, et al. Single-center experience with intrathecal administration of Nusinersen in children with spinal muscular atrophy type 1. *Eur J Paediatr Neurol*. 2018;22:122–127.
29. Iannalfi A, Bernini G, Caprilli S, et al. Painful procedures in children with cancer: comparison of moderate sedation and general anesthesia for lumbar puncture and bone marrow aspiration. *Pediatr Blood Cancer*. 2005;45:933–938.
30. Chiaretti A, Benini F, Pierri F, et al. Safety and efficacy of propofol administered by paediatricians during procedural sedation in children. *Acta Paediatr*. 2014;103:182–187.
31. Crock C, Olsson C, Phillips R, et al. General anaesthesia or conscious sedation for painful procedures in childhood cancer: the family's perspective. *Arch Dis Child*. 2003;88:253–257.
32. Glatstein MM, Zucker-Toledano M, Arik A, et al. Incidence of traumatic lumbar puncture: experience of a large, tertiary care pediatric hospital. *Clin Pediatr (Phila)*. 2011;50:1005–1009.
33. Howard SC, Gajjar AJ, Cheng C, et al. Risk factors for traumatic and bloody lumbar puncture in children with acute lymphoblastic leukemia. *JAMA*. 2002;288:2001–2007.
34. Bonadio W. Pediatric lumbar puncture and cerebrospinal fluid analysis. *J Emerg Med*. 2014;46:141–150.
35. Hache M, Swoboda KJ, Sethna N, et al. Intrathecal injections in children with spinal muscular atrophy: nusinersen clinical trial experience. *J Child Neurol*. 2016;31:899–906.
36. Lenfestey RW, Smith PB, Moody MA, et al. Predictive value of cerebrospinal fluid parameters in neonates with intraventricular drainage devices. *J Neurosurg*. 2007;107:209–212.