A study of probable benefit of a bioresorbable polymer scaffold for safety and neurological recovery in patients with complete thoracic spinal cord injury: 6-month results from the INSPIRE study

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OBJECTIVE The aim of this study was to evaluate whether the investigational Neuro-Spinal Scaffold (NSS), a highly porous bioresorbable polymer device, demonstrates probable benefit for safety and neurological recovery in patients with complete (AIS grade A) T2–T12 spinal cord injury (SCI) when implanted ≤ 96 hours postinjury.

METHODS This was a prospective, open-label, multicenter, single-arm study in patients with a visible contusion on MRI. The NSS was implanted into the epicenter of the postirrigation intramedullary spinal cord contusion cavity with the intention of providing structural support to the injured spinal cord parenchyma. The primary efficacy endpoint was the proportion of patients who had an improvement of ≥ 1 AIS grade (i.e., conversion from complete paraplegia to incomplete paraplegia) at the 6-month follow-up visit. A preset objective performance criterion established for the study was defined as an AIS grade conversion rate of $\geq 25\%$. Secondary endpoints included change in neurological level of injury (NLI). This analysis reports on data through 6-month follow-up assessments.

RESULTS Nineteen patients underwent NSS implantation. There were 3 early withdrawals due to death, which were all determined by investigators to be unrelated to the NSS or the implantation procedure. Seven of 16 patients (43.8%) who completed the 6-month follow-up visit had conversion of neurological status (AIS grade A to grade B [$n = 5$] or C [$n = 2$]). Five patients showed improvement in NLI of 1 to 2 levels compared with preimplantation assessment, 3 patients showed no change, and 8 patients showed deterioration of 1 to 4 levels. There were no unanticipated or serious adverse device effects or serious adverse events related to the NSS or the implantation procedure as determined by investigators.

CONCLUSIONS In this first-in-human study, implantation of the NSS within the spinal cord appeared to be safe in the setting of surgical decompression and stabilization for complete (AIS grade A) thoracic SCI. It was associated with a 6-month AIS grade conversion rate that exceeded historical controls. The INSPIRE study data demonstrate that the potential benefits of the NSS outweigh the risks in this patient population and support further clinical investigation in a randomized controlled trial.

Clinical trial registration no.: NCT02138110 (clinicaltrials.gov)

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KEYWORDS spinal cord injury; AIS A; ASIA Impairment Scale grade A; Neuro-Spinal Scaffold implant; biopolymer; thoracic

ABBREVIATIONS ADE = adverse device effect; AIS = ASIA Impairment Scale; ASIA = American Spinal Injury Association; EMSCI = European Multicenter Study about Spinal Cord Injury; INSPIRE = InVivo Study of Probable Benefit of the Neuro-Spinal Scaffold for Safety and Neurological Recovery in Patients with Complete Thoracic Spinal Cord Injury; ISNCSCI = International Standards for Neurological Classification of SCI; NACTN = North American Clinical Trials Network; NLI = neurological level of injury; NSS = Neuro-Spinal Scaffold; SCI = spinal cord injury; SCIMS = Spinal Cord Injury Model Systems; TLICS = Thoracolumbar Injury Classification and Severity Score.

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MORE than 17,000 new cases of acute traumatic spinal cord injury (SCI) present to US hospitals each year, with an estimated 291,000 people currently living with chronic SCI.¹⁻⁴ SCI can be devastating to the individual involved but may also have an adverse effect on the family with a huge societal cost. Estimated lifetime costs can vary, but they may amount to millions of dollars.²

The primary SCI is most often caused by direct mechanical trauma resulting in spinal cord contusion or compression.⁵ The secondary injury cascade exacerbates damage within the spinal cord parenchyma. Substantial necrosis immediately follows the primary mechanism and the effects are compounded by continuous neuronal and oligodendroglial apoptosis.^{5,6} Throughout the secondary injury, substantial loss of myelin has also been noted.^{5,7} These secondary injury mechanisms exacerbate the severity of the injury. Treatment standards for SCI have experienced little improvement over recent years, and current treatment options fail to effectively repair or mitigate these destructive processes.^{5,8}

Based on the International Standards for Neurological Classification of SCI (ISNCSCI), an SCI classified as American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A is considered to be complete (i.e., no motor or sensory function is preserved in the sacral segments [S4–5]).⁹ This is the most severe grade of SCI, with complete loss of motor and sensory function below the level of injury. Only a small percentage of patients who sustain a complete SCI ever regain full neurological function.¹⁰

The Neuro-Spinal Scaffold (NSS; InVivo Therapeutics Corp.) is an investigational device that has been developed as an adjunct to standard of care for the treatment of SCI. The NSS is a highly porous bioresorbable polymer composed of poly(lactic-co-glycolic acid)-b-poly-(L-lysine) (Fig. 1),¹¹ a material widely used in US FDA-approved devices, and is designed to provide structural support to injured spinal cord and a supportive matrix for endogenous healing and repair processes following implantation within a spinal cord contusion. In a rat contusion model, NSS implantation reduced cyst volume, spared white matter, and promoted generation of remodeled tissue at 12 weeks versus controls.¹² Remodeled tissue was rich in neuropermissive extracellular matrix and facilitated endogenous sprouting.

This paper presents the 6-month results from the In-Vivo Study of Probable Benefit of the Neuro-Spinal Scaffold for Safety and Neurological Recovery in Patients with Complete Thoracic Spinal Cord Injury (INSPIRE).

Methods

Study Design and Oversight

INSPIRE was a prospective, open-label, single-arm, multicenter study. The NSS has been designated as a Humanitarian Use Device by the US FDA, which requires evidence that probable benefit to health from use of the device outweighs the risk of injury or illness from its use. The first case from this study demonstrating feasibility of implanting the NSS directly into the injured spinal cord

of a human was reported previously.¹³ An interim evaluation performed in the first 5 patients who underwent NSS implantation and completed 6-month postimplantation assessment supported conversion of the study into a pivotal Humanitarian Device Exemption probable benefit study.

The study expansion had a planned total enrollment of up to 30 patients (including patients assessed in the interim evaluation) to achieve 20 patients in the primary endpoint analysis set. The study was put on hold in July 2017 in discussion with the US FDA following 3 deaths that occurred within 2 weeks of implantation; all were determined by investigators to be unrelated to the NSS or its implantation procedure. Enrollment was closed, with 16 patients meeting the primary endpoint analysis criteria.

Key enrollment criteria implemented at the study sites included the following: age ≥ 16 years to ≤ 70 years, traumatic nonpenetrating SCI (contusion injury) no less than 4 mm in diameter on MRI, AIS grade A classification, neurological level of injury (NLI) at T2–12, and requirement for open spine surgery ≤ 96 hours of SCI (as part of standard treatment) allowing access to the dura overlying the injured spinal cord for NSS implantation. Key exclusion criteria were complete transection of the spinal cord or more than one discrete SCI on MRI, significant traumatic brain injury or coma, terminal illness, and clinically significant preexisting neurological or respiratory comorbidities. Full patient eligibility criteria are provided in Table 1.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonization guidelines for Good Clinical Practice, and applicable regulatory requirements. All patients provided signed written informed consent prior to enrollment in the study or undergoing any study procedure. The protocol and all relevant study forms were approved by the respective institutional review board/research ethics board of each institution. An independent Data and Safety Monitoring Board provided recommendations. This study was registered at ClinicalTrials.gov (identifier NCT02138110).

Screening Assessments, Study Procedures, and NSS Implantation

Neurological status was assessed by the investigator or a designated trained medical professional using the ISNCSCI⁹ and ASIA 2015 worksheet at the following time points: screening; within 8 hours prior to open spine surgery (to confirm a reliable ISNCSCI examination and AIS grade A classification); at 24, 48, and 72 hours postimplantation; at hospital discharge; and at 1, 2, 3, 6, 12, and 24 months postimplantation. MRI studies without contrast were performed at screening and at 72 hours and 3, 6, 12, and 24 months postimplantation. Long-term follow-up including general annual health assessment and safety event monitoring continues annually via phone for 3 to 10 years postimplantation.

The ISNCSCI examinations determined sensory and motor levels (left and right sides), NLI, sensory and motor scores, and AIS grade.⁹ The injury was considered complete (AIS grade A) when there was no motor or sensory function in the lowest sacral segments (S4–5). Incomplete injuries were defined as follows: AIS grade B (sensory

FIG. 1. The porous, cylindrical NSS comes in 2 sizes, 2-mm diameter $\times$ 10-mm length and 3-mm diameter $\times$ 10-mm length. The NSS is designed for optimal fit in the intraspinal postirrigation cavity and can be trimmed, if necessary, to a specific length. The NSS is expected to be resorbed from the site of implantation within 4–8 weeks. **Left:** Macroscopic view of a representative 3 $\times$ 10-mm NSS. **Right:** Scanning electron microscopy cross-sectional image of a representative 2 $\times$ 10-mm NSS. Bar = 500 μ m. Reprinted from Layer RT, Ulich TR, Coric D, et al. New clinical-pathological classification of intraspinal injury following traumatic acute complete thoracic spinal cord injury: postdurotomy/myelotomy observations from the INSPIRE trial. *Neurosurgery*. 2017;64(CN_suppl_1):105–109, by permission of Oxford University Press. Copyright © 2017 by the Congress of Neurological Surgeons. All rights reserved. For permissions, please email journals.permissions@oup.com.

incomplete—sensory but not motor function is preserved below the level of injury and includes sacral segments S4–5), AIS grade C (motor incomplete—motor function preserved below level of injury; voluntary anal contraction or sparing of motor function 3 levels below injury), and AIS grade D (motor incomplete—as for grade C, but with at least half of key muscles below injury functioning against gravity). AIS grade E indicated normal function. NLI refers to the most caudal segment of the spinal cord with normal sensory and motor function on both sides of the body. Sensory scores were assessed on a scale from 0 to 2 for each sensory point tested on each side of the body (pinprick maximum score = 112 and light-touch maximum score = 112), and motor scores were assessed on a scale from 0 to 5 for each myotome tested on each side of the body (upper-limb maximum score = 50 and lower-limb maximum score = 50), with higher scores indicating better neurological function.

Open spine surgery was performed (bony decompression, reduction, and/or stabilization). On visualization of the dura, intraoperative ultrasonography was performed to localize the area of maximal damage as initially assessed by preoperative MRI. Durotomy and myelotomy, if needed, were performed to expose the intramedullary contusion site. The contusion cavity was then irrigated with isotonic saline solution to wash away any superficial hemorrhagic material and devitalized tissue. The NSS was soaked in isotonic saline solution and, if necessary, trimmed at one end to the size needed to fit the postirrigation contusion cavity without causing any undue tension on the surrounding spinal cord. The NSS was then gently implanted lengthwise into the epicenter of the intraspinal contusion cavity followed by dural closure. Based on preclinical testing, the NSS is expected to be essentially resorbed (mass loss of $\geq 85\%$) from the site of implant within 4 to 8 weeks (InVivo Therapeutics Corp., unpub-

lished data). All patients were treated according to standard of care at a qualified trauma center and participated in a comprehensive rehabilitation program following hospital discharge.

Representative examples of an MR image demonstrating the preoperative hematoma (Fig. 2), preimplantation and postimplantation ultrasound images (Fig. 3), and an intraoperative video demonstrating myelotomy and implantation of the NSS (Video 1) are provided.

VIDEO 1. Case 14. Intraoperative video of myelotomy and implantation of the NSS in a patient with complete SCI at T2. Copyright InVivo Therapeutics Corp. Published with permission. Click here to view.

Outcomes

The primary efficacy endpoint was the proportion of patients who had an improvement from preimplantation of ≥ 1 AIS grade at the 6-month follow-up visit. An objective performance criterion established for the study was defined as achievement of conversion from complete paraplegia (AIS grade A) to incomplete paraplegia by 6 months in $\geq 25\%$ of patients. This preset benchmark was derived from the natural history rate in a similar patient population from the European Multicenter Study about Spinal Cord Injury (EMSCI) database (15.6%).¹⁴

Secondary endpoints included changes in NLI, sensory scores, and motor scores (all measured using the ISNCSCI classification tool), and changes in spinal cord anatomy as determined by MRI.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 (March 2014) was used to classify all safety events.

Statistical Analysis

The primary endpoint analysis set includes all patients

TABLE 1. INSPIRE study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1) AIS grade A classification of traumatic SCI at T2–12 neurological level of injury confirmed by a qualified medical professional	1) Terminally ill patients not likely to be able to participate in follow-up
2) Recent injury (must receive the NSS within 96 hrs from injury)	2) Incomplete SCI (AIS grade B–E injuries)
3) Nonpenetrating SCI (contusion injury) that is no less than ~4 mm in diameter by MRI	3) Patients with >1 discrete SCI (contusion)
4) Requires open spine surgery allowing access to the injured spinal cord (patients requiring either posterior surgical approach or posterior plus anterior approach will be eligible)	4) No discrete cavity (existing or created by irrigation/myelotomy) in the contused spinal cord in which an NSS can be placed
5) Informed consent obtained	5) Patients with clinically significant preexisting neurological comorbidities that are unrelated to the contusion being treated (e.g., multiple sclerosis, amyotrophic lateral sclerosis, significant prior peripheral nerve dysfunction, residual problems related to previous spine-related neurological pathologies) will be excluded only if it is felt that these preexisting morbidities will increase risk, affect safety monitoring, or confound study results
6) 16–70 yrs of age, inclusive	6) SCI associated with significant traumatic brain injury or coma that, in the opinion of the investigator, would preclude adequate assessment of spinal cord function, brain injury that could be associated on its own with sensory or motor deficits, or patients with any other reason that results in an unreliable ISNCSCI exam
7) Hemodynamically stable and deemed a suitable candidate for surgery	7) Patients with clinically significant preexisting respiratory disease not related to the contusion being treated (e.g., chronic obstructive pulmonary disease)
	8) Patients requiring long-term ongoing mechanical ventilation
	9) Patients with documented immune deficiency disorders, including a known diagnosis of HIV infection/AIDS
	10) Recent (according to DSM IV or V criteria) history of abuse of narcotics or other significant substance abuse
	11) Significant injury complications where, in the view of the investigator, participation in the study could further complicate subject care, limit study follow-up, or confound interpretation of safety or efficacy data
	12) A female who is:
	a) Pregnant, or planning to become pregnant within the next 12 mos; or
	b) Breastfeeding; or
	c) A woman of child-bearing potential (defined as postmenarche and biologically capable of becoming pregnant [i.e., not surgically sterile]) who is engaged in active heterosexual relations and is not willing to use a barrier or hormonal form of birth control for 12 mos following NSS implantation (e.g., oral, injected, implanted contraceptives)
	13) A male who is engaged in active heterosexual relations and is not willing to use birth control for 3 mos following NSS implantation including sperm donation or banking
	14) Current or impending incarceration
	15) Complete spinal cord transection
	16) Patients with SCIs directly due to gunshot, knife, or other penetrating wound
	17) Known hypersensitivity to PLGA or PLL (e.g., hypersensitivity to absorbable sutures containing PLGA)
	18) History of severe mental illness (according to DSM IV or V)
	19) Evidence of pretrauma active local or systemic infection
	20) Participation in another interventional clinical trial for 6 mos after NSS implantation
	21) BMI >39
	22) Having a medical condition (e.g., cardiovascular disease, life-threatening injuries), or receiving medical treatment, or having any other reason that, in the judgment of the investigator, precludes successful participation and follow-up for ≥6 mos or confounds collection or interpretation of study safety, feasibility, or efficacy data
	23) Patients receiving tetracyclines, such as minocycline (patients must discontinue tetracyclines to be enrolled in the study; tetracyclines can be resumed after 6 mos postimplantation)

DSM = *Diagnostic and Statistical Manual of Mental Disorders*; PLGA = poly(lactic-co-glycolic acid); PLL = poly-L-lysine.

who underwent NSS implantation with no major protocol deviations and had completed the 6-month primary endpoint follow-up visit. A sensitivity analysis imputed a value for any missing AIS grade at the 6-month follow-up visit as not having an improvement of ≥ 1 AIS grade. Efficacy and safety analyses are reported for all treated patients.

The preimplantation ISNCSCI examination performed within 8 hours before surgery was used as the baseline

value for ISNCSCI measurements, and the screening MRI was used as the baseline value for changes in spinal cord anatomy.

These results represent a preplanned analysis including data through the 6-month follow-up visit (data cutoff January 10, 2019). Data were analyzed according to the latest protocol version approved by the US FDA prior to database lock using SAS for Windows (version 9.3, SAS Institute Inc.).

FIG. 2. Case 9. Preoperative sagittal T2-weighted MR image showing an upper-thoracic burst fracture at T3 with complete SCI.

Results

Between October 13, 2014, and June 23, 2017, 25 patients were enrolled at 12 study sites in North America (11 sites in the US and 1 in Canada). Nineteen patients underwent NSS implantation, 5 patients did not meet eligibility criteria, and 1 patient was enrolled but not treated with the NSS, and durotomy was not performed. There were 3 early withdrawals due to death determined by investigators to be unrelated to the NSS or its implantation.

Patient Demographics and Baseline Characteristics

Patient demographic and baseline characteristics for enrolled patients are presented in Table 2. Among patients who underwent NSS implantation ($n = 19$), 8 had an upper-thoracic injury (T2–5), 6 had a mid-thoracic injury (T6–9),

and 5 had a lower-thoracic injury (T10–12). All patients had AO Spine type B2 or C fracture,¹⁵ and all required surgical intervention as assessed according to the Thoracolumbar Injury Classification and Severity Score (TLICS)¹⁶ classification system. The mean time from injury to start of surgery was 40.9 hours (range 7–81 hours); most patients underwent surgery within 72 hours postinjury ($n = 16$), including 6 patients within 24 hours and 2 within 8 hours.

Primary Efficacy Analysis

Seven of the 16 patients (43.8%) who completed the 6-month follow-up visit converted to AIS grade B ($n = 5$) or C ($n = 2$).

AIS grades at each time point for patients who were implanted with the NSS are provided in Table 3. Among patients who achieved the 6-month primary endpoint, 3 had initial conversion by the 1-month visit (AIS grade B, $n = 1$; AIS grade C, $n = 2$), 2 patients had converted to AIS grade B by the 2-month visit, and 1 patient each had converted to AIS grade B by the 3- and 6-month visits, respectively. Two patients experienced improvement and deterioration in AIS grade over time: 1 patient converted to AIS grade B by the 2-month visit due to the presence of sacral sensation, reverted back to AIS grade A at the 3-month visit, and then converted again to AIS grade B by the 6-month visit due to the presence of deep anal pressure. Another patient converted to AIS grade C by the 1-month visit due to the presence of voluntary anal contraction and deep anal pressure, and reverted to AIS grade B at the 3-month visit due to the loss of voluntary anal contractions, and then converted back to AIS grade C at the 6-month visit due to sacral sensation and to the presence of both deep anal pressure and voluntary anal contraction. An additional patient had conversion to AIS grade B at the 1-month visit but was assessed as AIS grade A at future assessments.

A sensitivity analysis including all NSS-implanted patients ($n = 19$) resulted in a 6-month AIS grade conversion rate of 36.8%.

FIG. 3. **Left:** Case 18. Preoperative ultrasound study obtained in a patient with complete SCI at T12. **Right:** Case 5. Intraoperative postimplantation ultrasound study obtained in a patient with complete SCI at T4. The arrows indicate the implanted intramedullary NSS.

TABLE 2. Baseline demographics and cause of injury for all enrolled patients who were included after screening

Characteristic	NSS (n = 20)
Mean age (range), years	36 (18–69)
Sex, n (%)	
Female	4 (20.0)
Male	16 (80.0)
Race, n (%)	
American Indian or Alaskan Native	1 (5.0)
Black or African American	2 (10.0)
White	16 (80.0)
Other	1 (5.0)
Ethnicity, n (%)	
Hispanic or Latino	4 (20.0)
Non-Hispanic or Latino	16 (80.0)
Mean height (range), cm	172 (147–185)
Mean weight (range), kg	83 (58–127)
Mean BMI (range), kg/m ²	28 (20–38)
Cause of injury, n (%)	
Fall	5 (25.0)
Other: all-terrain vehicle	1 (5.0)
Vehicular	14 (70.0)

Secondary Efficacy Analyses

Changes in NLI are presented in Table 4. At the 6-month follow-up visit, 5 patients showed an improvement in NLI of 1 to 2 levels compared with preimplantation, 3 patients showed no change, and 8 patients showed a deterioration of 1 to 4 levels.

Among patients who completed the 6-month follow-up visit (n = 16), the mean (SD) change in sensory pinprick score was an improvement of 0.9 (5.5) points compared with preimplantation. Ten patients demonstrated an improvement ranging from 1 to 10 points, and 6 patients demonstrated a deterioration ranging from –2 to –12 points. Sensory pinprick score changes varied over time; 7 patients had improved sensory pinprick scores over time, 4 patients had decreased scores over time, and 5 patients experienced fluctuating scores.

Changes in sensory light-touch scores were generally consistent with sensory pinprick scores. The mean (SD) change in sensory light-touch score among patients who completed the 6-month follow-up visit was an improvement of 2.9 (5.7) points compared with preimplantation. Ten patients demonstrated an improvement in sensory light-touch score compared with preimplantation (1 to 13 points), 4 patients demonstrated a deterioration (–2 to –8 points), and 2 patients demonstrated no change. Sensory light-touch scores were consistent with pinprick scores, except for 1 patient who had an improvement in sensory light-touch score and a deterioration in sensory pinprick score at the 2-month follow-up visit, and 1 patient who had a deterioration in sensory light-touch score and an improvement in sensory pinprick score at the 6-month follow-up visit.

Fourteen patients had no change in motor scores at the 6-month follow-up visit compared with preimplantation, indicating no change in motor function and no lower-ex-

tremity motor function present. One patient demonstrated an improvement in total motor score of 10 points at the 6-month follow-up visit. An additional patient experienced improvement in motor scores in the lower extremities, but the total change was not reportable secondary to the lower-extremity fractures at screening and preimplantation preventing proper testing according to the ISNCSCI. However, a motor score of 61 at the 6-month follow-up visit indicated a minimal improvement of 10 points over the preimplantation motor score of 51.

MRI showed the presence of cysts in 5 of 14 patients with evaluable images at the 6-month follow-up visit, which were first observed at the 3-month visit in 3 patients. One patient had documented spinal cord adhesion at the 6-month visit, and another patient had a documented syrinx on MRI at the 3-month visit with a decrease in size noted at the 6-month visit. None of these events required any additional surgical intervention.

Safety

The following safety events not related to the NSS or its implantation procedure occurred in more than 20% of patients who underwent NSS implantation (n = 19): urinary tract infection (68.4%), muscle spasms (57.9%), neuralgia (47.4%), pyrexia (42.1%), abdominal distention (31.6%), leukocytosis (31.6%), back pain (26.3%), pain in extremity (26.3%), pleural effusion (26.3%), arthralgia (21.1%), atelectasis (21.1%), constipation (21.1%), decubitus ulcer (21.1%), depression (21.1%), hypophosphatemia (21.1%), hypotension (21.1%), incision site pain (21.1%), muscle spasticity (21.1%), and urinary incontinence (21.1%).

There were 22 serious adverse events; none were deemed by investigators to be related to the NSS or its implantation procedure. Intensity was mild for 1 event, moderate for 10 events, severe for 10 events, and not provided for 1 event (decrease in neurological function). The most common serious event was urinary tract infection (n = 3), followed by 2 events each of pleural effusion, pulmonary embolism, respiratory distress, and respiratory failure. One serious event was reported for each of the following: cellulitis, *Clostridium difficile* colitis, postoperative wound infection, sepsis, traumatic pneumothorax, dehydration, necrotizing myositis, CSF leakage, cerebrovascular accident, spinal cord disorder, and deep vein thrombosis. Three deaths determined by investigators not to be related to the NSS or procedure to implant the NSS were reported (1 each due to sepsis, cerebrovascular accident, and pulmonary embolism). There were no other adverse events leading to discontinuation from the study.

No serious or unanticipated adverse device effects (ADEs) were reported. Two ADEs determined to be possibly related to the NSS and the implantation procedure occurred in 1 patient (mild intermittent nerve pain and a single event of mild myelomalacia). An additional 4 ADEs considered to be related to the implantation procedure were reported (severe intermittent increase in generalized pain, moderate continuous declining neurological status, mild continuous acute postoperative pulmonary insufficiency, and moderate continuous incisional pain). There were 2 adverse events of interest in a single patient (thoracic CSF leak of moderate intensity and deep wound infection of

TABLE 3. AIS grades in patients who underwent NSS implantation

Case No.	Age Group	Preimplantation NLI (n = 19)	Time From Injury to Implantation (hrs)	AIS Grade					
				Preimplantation (n = 19)	Hospital Discharge (n = 16)	1 Mo Postimplantation (n = 15)	2 Mos Postimplantation (n = 12)	3 Mos Postimplantation (n = 16)	6 Mos Postimplantation (n = 16)
1*	Adult	T3†	70	A					
2	Adult	T12	67	A	A	A	B	A	B
3	Adult	T11	9	A	A	C	Not done‡	C	C
4	Adult	T7	46	A	A	A	Not done‡	A	A
5	Adult	T4	83	A	A	B	B	B	B
6	Adult	T3	22	A	A	A	A	A	A
7*	Adult	T4	21	A					
8	Pediatric§	T10	21	A	A	B	Not done	A	A
9	Adult	T3	47	A	A	A	A	A	A
10	Pediatric§	T10	9	A	Not done	A	B	B	B
11	Adult	T8	37	A	A	A	A	A	A
12	Adult	T9	77	A	A	A	A	A	A
13	Pediatric§	T8	69	A	A¶	A	A	A	B
14	Adult	T2	79	A	A	Not done	Not done	A	A
15	Adult	T9	29	A	A¶	A	A	A	A
16	Adult	T3	53	A	A	A	A	A	A
17	Adult	T4	40	A	A	A	A	B	B
18*	Adult	T12	28	A	A				
19	Adult	T6	20	A	A	C	C	B	C

* Died prior to hospital discharge; no further follow-up visits.

† T3 at screening assessment; preimplantation assessment not done.

‡ Two-month visit not required per protocol approved at the time.

§ Defined as ≤ 21 years old.

¶ Hospital discharge visit occurred after 1-month visit.

moderate intensity), both of which resolved. Two patients had a deterioration in NLI of > 2 dermatome levels compared with the preimplantation visit on 2 successive examinations ≥ 8 hours apart. However, the Data and Safety Monitoring Board did not recommend stopping the study for either of these cases after careful and thorough review.

Discussion

Key Findings

The INSPIRE study describes the safety and feasibility of NSS implantation in patients with acute complete (AIS grade A) thoracic SCI and reports a 6-month AIS grade conversion rate that exceeded the study objective performance criterion (≥ 25%). Seven of 16 evaluable patients had AIS conversion from complete paraplegia to incomplete injuries classified as either AIS grade B (5 patients) or C (2 patients).

Comparison With Natural History

SCI is a devastating injury, and there are few treatment options for patients beyond standard of care, which include decompression, stabilization, and fusion.^{17,18} The NSS has shown a potential benefit when compared with the natural history of these injuries. The AIS grade conversion rate in the current study (44%) was greater than historical bench-

marks (approximately 16%) for patients with T2–12 complete (AIS grade A) SCI from large natural history databases (EMSCI and the Spinal Cord Injury Model Systems [SCIMS]).^{14,19} A recent study (CONTEMPO) evaluating outcomes for standard-of-care comparator groups from the North American Clinical Trials Network (NACTN), EMSCI, and SCIMS registries, with inclusion and exclusion criteria that closely matched those of INSPIRE, included 170 patients who sustained injuries between 2006 and 2016.²⁰ The spontaneous conversion rate at approximately 6 months postinjury or beyond was 21.1% (weighted average for all registries combined), which is consistent with earlier benchmarks and provides further support to the relevance of the current study results.

In the INSPIRE study, conversion to incomplete paraplegia was reported in a higher proportion of patients with lower-thoracic injuries (T10–12; 3 of 4 patients [75.0%]) than those with upper-thoracic (T2–5; 2 of 6 patients [33.3%]) or mid-thoracic (T6–9; 2 of 6 patients [33.3%]) injuries, which is in line with what can be expected based on natural history data.^{14,19,20} However, it should be noted that the patient distribution in the INSPIRE study did not favor lower-level injuries, as only approximately 25% of patients who underwent NSS implantation had T10–12 injuries. The estimated lifetime hospitalization costs for thoracic AIS grade B patients are substantially less than

TABLE 4. NLI in patients who underwent NSS implantation

Case No.	Age Group	Time From Injury to Implantation (hrs)	NLI					
			Preimplantation (n = 19)	Hospital Discharge (n = 17)	1 Mo Postimplantation (n = 15)	2 Mos Postimplantation (n = 12)	3 Mos Postimplantation (n = 16)	6 Mos Postimplantation (n = 16)
1*	Adult	70	T3†					
2	Adult	67	T12	L1	L1	L1	L1	L1
3	Adult	9	T11	T11	L1	Not done‡	L1	L1
4	Adult	46	T7	T5	T5	Not done‡	T5	T5
5	Adult	83	T4	T4	T4	T3	T5	T4
6	Adult	22	T3	T3	T3	T3	T2	T2
7*	Adult	21	T4					
8	Pediatric§	21	T10	T7	T8	Not done	T7	T6
9	Adult	47	T3	T3	T3	T3	T3	T4
10	Pediatric§	9	T10	T9	T10	T10	T9	T9
11	Adult	37	T8	T9	T10	T10	T10	T10
12	Adult	77	T9	T10	T10	T10	T10	T10
13	Pediatric§	69	T8	T8¶	T7	T7	T7	T7
14	Adult	79	T2	T2	Not done	Not done	T2	C8
15	Adult	29	T9	T9¶	T9	T9	T9	T9
16	Adult	53	T3	T3	T3	T3	T3	T3
17	Adult	40	T4	T4	T4	T4	T4	T3
18*	Adult	28	T12	T12				
19	Adult	20	T6	T3	T5	T4	T4	T4

* Died prior to hospital discharge; no further follow-up visits.

† T3 at screening assessment; preimplantation assessment not done.

‡ Two-month visit not required per protocol approved at the time.

§ Defined as ≤ 21 years old.

¶ Hospital discharge visit occurred after 1-month visit.

for AIS grade A patients, and the risk for SCI-related complications such as pressure ulcers is reduced.^{21,22}

Benefits of the NSS Over Decompression and Myelotomy Alone

Decompression surgery alone can provide benefit to patients, with a trend being seen for increased recovery with earlier surgery.^{23,24} The NSS is intended to serve as an extracellular matrix aiming to provide support to surrounding spared tissue after injury, minimize expansion of areas of necrosis, and support endogenous healing and repair processes following injury, and may harbor the promise of sparing of white matter, increasing neural sprouting, and decreasing posttraumatic cyst formation.¹² In a rat contusion model, benefits of NSS implantation over myelotomy alone (allowing spontaneous extrusion and irrigation of necrotic debris and relieving spinal cord pressure) included new tissue formation, almost no cavitation, and an extensive region of SC-derived P0-positive myelin in the spared tissue, suggesting that implantation of the NSS may provide additional benefit beyond simple decompression and myelotomy.¹²

Timing of Decompression

Balancing the benefits of early surgery against the

risks of operative intervention in critically ill patients is an important issue for physicians treating patients with SCI. Although there are no definitive guidelines regarding the optimal time to decompression,^{24,25} there has been a trend over the past 10–15 years to perform decompressive surgery earlier. The INSPIRE study reflects the current standard of care, which favors early spinal decompression and stabilization. All patients underwent surgery within 96 hours of injury. No formal statistical analysis was performed; however, there did not appear to be any correlation between time to surgery and AIS grade conversion.

Contusion- and Compound-Type Injuries

Early postdurotomy observations from the INSPIRE study provided visual evidence of 2 forms of cord damage: injuries where the cord surface is intact (contusion type) and injuries where the pia is breached and there is visible but incomplete cord parenchymal separation (compound type).¹¹ Successful NSS implantation and subsequent AIS grade improvements were observed in patients with both injury types in this study.

Secondary Endpoints

The NLI results in the current study generally showed

1- and 2-level variations that were not clinically significant. These may be explained by either fluctuation in sensory level seen in the natural history of SCI or the variability in testing related to the thoracic dermatomes.

The sensory changes in the study align with the natural history of recovery in this patient population. Although valuable in understanding the complete neurological status of the patient, it is difficult to conclude any positive or negative effects of changes in sensory scores.

Although motor function is believed to be a valuable endpoint due to its ability to lead to ambulation, its utility as an assessment tool following thoracic injuries may be limited. Spontaneous motor improvement following complete thoracic injuries is extremely limited, and the chance of observing a meaningful therapeutic effect is low.²⁶ Lee et al. reported an average lower-extremity motor score change of 1.5 to 4.1 points, depending on initial NLI, with a median change of 0.¹⁹ Zariffa et al. published an average 2-point improvement in this patient population.¹⁴

Cysts, spinal cord adhesions, and the syrinx in NSS-treated patients, as documented on MRI, are consistent with the natural history of the SCI population. These events did not require any additional surgical intervention.

Safety of the NSS

There were no unanticipated ADEs and no major morbidity related to the NSS or the procedure to implant the NSS as determined by the investigators in this study. All 3 safety events deemed possibly related to the device were of mild severity. There were 2 safety events of interest in a single patient (CSF leak and infection), which were likely related to the severity of the original injury that included a defect in the dura. Overall, the safety events reported in the INSPIRE study were consistent with what would be expected in the routine care of SCI patients.²⁷

Study Limitations and Future Directions

This study had several limitations. The study was non-blinded and nonrandomized with no comparator group, and patient numbers were small (as can be expected given the inherent enrollment challenges associated with this patient population).^{28,29} Patients continue to be followed in this study, including ISNCSCI assessments through 24 months postinjury, and a separate randomized, controlled, single-blind, multicenter study has been initiated to evaluate whether the NSS is safe and demonstrates probable benefit in the treatment of complete (AIS grade A) thoracic SCI versus standard-of-care open spine surgery (INSPIRE 2.0; ClinicalTrials.gov identifier NCT03762655).

Conclusions

In this first-in-human study, implantation of the NSS within the spinal cord appeared to be safe in the setting of surgical decompression and stabilization for complete (AIS grade A) thoracic SCI. It was associated with a 6-month AIS grade conversion rate that exceeded historical controls. The INSPIRE study data demonstrate that the potential benefits of the NSS outweigh the risks in this patient population and support further clinical investigation in a randomized controlled trial.

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Author Contributions

Conception and design: Theodore. Acquisition of data: Kim, Lee, Coric, Chang, Harrop, Theodore. Analysis and interpretation of data: all authors. Drafting the article: Kim. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kim.

Supplemental Information

Videos

Video 1. <https://vimeo.com/463130852>.

Previous Presentations

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