Combinatorial Surgical and Neuroprotective Therapy for Cervical Spondylotic Myelopathy Results in Improved Neurological Function: From Preclinical Proof of Concept to a Phase III Randomized Controlled Trial

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Introduction

Surgical decompression is an effective treatment for cervical spondylotic myelopathy (CSM). However, a number of patients continue to experience substantial neurological impairment post surgery. Riluzole has neuroprotective effects in injuries of the central nervous system. To determine the efficacy of riluzole for promoting neurological improvement in CSM following decompression, we performed a pre-clinical proof of concept experiment and then we translated our work and established a Phase III multi-center randomized controlled clinical trial (CSM-Protect).

Methods

Surgical decompression was performed in a rat CSM model and riluzole, or control, was administered. Spinal cord blood flow (SCBF) was evaluated in all CSM rats, in vivo, before and after decompression using FAIR MRI. The long-term outcomes of decompression with or without riluzole treatment determined using neurobehavioural and neuroanatomical assessments.

Methods Phase III

A total of 270 (300 to adjust for loss-to follow up) patients undergoing surgical decompression for CSM will be randomized in this ongoing prospective double-blinded controlled trial involving 15 sites in North America. Randomization will be 1:1 to riluzole 2x50mg daily for 14 days before the surgery and 28 days after the surgery or to the same regimen of placebo. Primary outcome measure is change in mJOA between baseline and 6 months following the surgery. Secondary outcomes include ASIA, SF36v2, NDI, EQ5D, Pain VAS and complications. Outcomes evaluations will occur at 6 and 12 months.

Statistical Design

Plan ID	Parameter
Type of the hypothesis	1-Sided
Type I Error (α)	0.025
Power (1 - β)	0.80
Randomization Ratio (Investigational vs. Control)	1:1
Planned Number of Interim Looks	2
Spacing of Looks	65%, 100%
Hypothesis to be Rejected	H0 or H1 (binding)
Boundary Family	Published Function
Boundary to Reject H0	O'Brien-Fleming
Boundary to Reject H1	Gamma (-2)
Difference of Means Assuming H_1	0.9
Standard Deviation (σ)	2.57
Sample Size	270 (135 per arm)

mJOA score will determine the effectiveness of the combinatorial treatment at 6 months following surgery. Statistical analysis will be performed as a sequential adaptive trial with interim analysis.

Results

Rats receiving combinatorial treatment displayed long-term significant neurological improvements associated with preservation of motor neurons and corticospinal tracts compared to rats treated with decompression alone. Riluzole also dramatically reduced the extent of ischemia-reperfusion injury post surgical decompression in our animal model.

At present, 299 subjects have been enrolled into the CSM-Protect trial. A planned interim analysis using this sample has commenced.

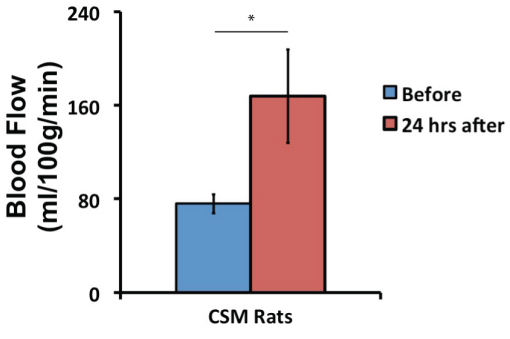
Primary and Secondary Outcomes

Outcome Measure		Mean (Standard Deviation)
mJOA (N = 298)		11.8 (1.5)
ASIA	Motor Total (N = 293)	95.3 (6.0)
	Sensory Light Touch (N = 289)	105.9 (10.8)
	Sensory Pin Prick (N = 290)	105.9 (10.5)
SF36v2 PCS (N = 294)		32.8 (9.4)
Pain VAS	Pain in Arm and Shoulder (N = 296)	4.8 (2.9)
	Pain in Neck (N = 296)	4.9 (2.9)
NDI (N = 295)		42.9 (20.6)
EQ-5D (N = 297)		0.6 (0.2)

Demographics

Demographics		N (%)
Age (N = 298)		57.9 (10.1)
Gender	Female	131 (44%)
	Male	167 (56%)
Race	White	241 (80.9%)
	African-American	28 (9.4%)
	Asian	15 (5.0%)
	Pacific Islander	1 (0.3%)
	Alaska Native	1 (0.3%)
	Unknown	4 (1.3%)
	Other	7 (2.4%)
	Did not answer	1 (0.3)
Surgery	Anterior	131 (45.8%)
	Posterior	148 (51.8%)
	Ant + Pos	7 (2.5%)

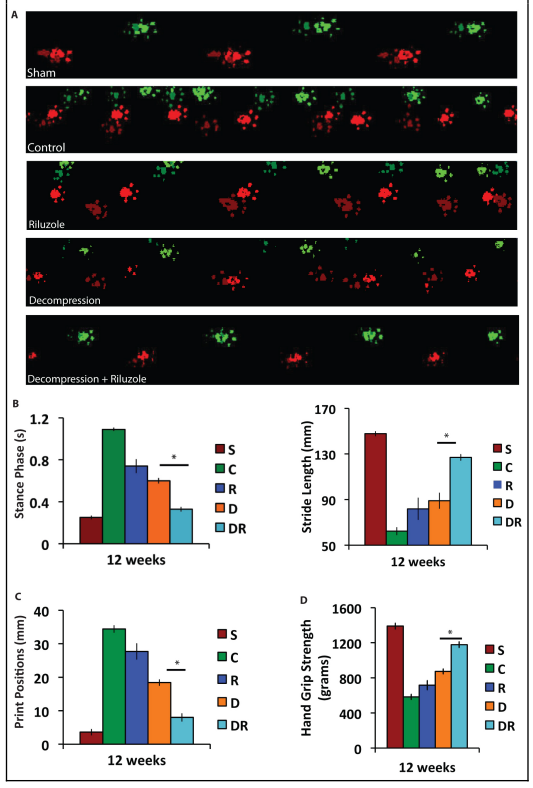
Reperfusion of the spinal cordparenchyma 24 hours afterdecompression surgery.



References

Sci Transl Med. 2015 Dec 2;7(316):316ra194. Karadimas SK. et al Riluzole blocks perioperative ischemiareperfusion injury and enhances postdecompression outcomes in cervical spondylotic myelopathy.

CSM rats receiving combinationtreatment showed improved long-term forelimb function andcoordinated locomotion.



Conclusions

The proposed combinatorial therapy promotes neurological recovery in CSM rats. Confirmation of this proof of concept has been translated from bench to the bedside and we are currently running the CSM-Protect trial to determine the efficacy of this combinatorial treatment option for use in CSM patients.

Acknowledgements

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