Riluzole for the treatment of acute traumatic spinal cord injury: rationale for and design of the NACTN Phase I clinical trial

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In the immediate period after traumatic spinal cord injury (SCI) a variety of secondary injury mechanisms combine to gradually expand the initial lesion size, potentially leading to diminished neurological outcomes at long-term follow-up. Riluzole, a benzothiazole drug, which has neuroprotective properties based on sodium channel blockade and mitigation of glutamatergic toxicity, is currently an approved drug that attenuates the extent of neuronal degeneration in patients with amyotrophic lateral sclerosis. Moreover, several preclinical SCI studies have associated riluzole administration with improved functional outcomes and increased neural tissue preservation. Based on these findings, riluzole has attracted considerable interest as a potential neuroprotective drug for the treatment of SCI. Currently, a Phase I trial evaluating the safety and pharmacokinetic profile of riluzole in human SCI patients is being conducted by the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury. The current review summarizes the existing preclinical and clinical literature on riluzole, provides a detailed description of the Phase I trial, and suggests potential opportunities for future investigation. Clinical trial registration no.: NCT00876889.

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KEY WORDS • spinal cord injury • riluzole • clinical trial • North American Clinical Trials Network

Abbreviations used in this paper: ALS = amyotrophic lateral sclerosis; ASIA = American Spinal Injury Association; NACTN = North American Clinical Trials Network for Treatment of Spinal Cord Injury; SCI = spinal cord injury.
of the current Phase I trial, and outline potential options for future investigation.

**Pathophysiology and Existing Preclinical/Clinical Evidence**

Initiated by the primary spinal cord trauma, the evolution of secondary injury mechanisms begins within seconds and continues for several weeks. An important occurrence early on within this secondary injury cascade is the development of neuronal ionic imbalance, particularly increased intracellular sodium concentration, as a result of trauma-induced activation of voltage-sensitive sodium channels. The increased intracellular sodium concentration leads to a concomitant rise in intracellular calcium levels and also acts to stimulate intracellular acidosis and the development of cytotoxic edema. A calcium channel–blocking compound, and a control compound in a study by the Fehlings group, the effects of riluzole were examined.20,30 One approach investigated to attenuate these excitotoxicity-mediated secondary injury and local cell death.20,30 Given its documented efficacy in preclinical SCI studies, as well as its safety in a human ALS population, riluzole appears an attractive candidate for evaluation in human patients with SCI. Before proceeding with a comparative effectiveness study, however, it was felt prudent to first evaluate the safety and pharmacokinetic profile of this medication within an SCI-specific population.

**Phase I Clinical Trial for Riluzole in Traumatic SCI**

*Study Objectives and Design*

Beginning in the spring of 2010, a Phase I study was undertaken with the goal of developing the safety and pharmacokinetic profile of riluzole in patients with traumatic SCI. Secondary objectives were to compare neurological, functional, and pain outcomes of the enrolled participants to outcomes of patients from the NACTN prospective SCI registry, matched for injury and demographic characteristics. This trial was designed as a prospective, single-arm, open-label multicenter study with a target enrollment of 36 participants. The sample size was based on NACTN registry incidence rates of adverse events ranging from 0.15 to 0.30. Using a 1-sided exact binomial test with a Type I error rate of 5%, a case series of 36 is expected to have at least 80% power to detect a doubling of a complication rate.

The safety end point follow-up period for the study is 6 months. However, neurological, functional, and pain outcomes will continue to be assessed at 12 months postinjury.

*Study Setting*

The trial was undertaken by the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury. NACTN is a collaborative network of 8 North American university-affiliated departments of neurosurgery, a data management center, and a pharmacological center (Table I).

The study protocol was reviewed and approved by the institutional review board of each participating site and by the US Army Medical Research and Materiel Command Office of Research Protections, Human Protection Office. This study is also listed in ClinicalTrials.gov, a service of the US National Institutes of Health.

*Eligibility Criteria*

Assessment of an individual's study eligibility was made at hospital presentation by the site-specific princi-
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![Flow diagram summarizing the putative neuroprotective mechanisms of riluzole in SCI.](image)

**Fig. 1.** Flow diagram summarizing the putative neuroprotective mechanisms of riluzole in SCI.

**Intervention Details**

Participants received riluzole 50 mg every 12 hours for a total of 14 days, with treatment initiated within 12 hours of injury. The 12-hour drug window, as well as the 2-week duration of therapy, was chosen based on a desire to match the period of drug administration to the known period of sodium- and glutamate-induced secondary injury after SCI (several minutes after injury until 2 weeks after injury). Riluzole was administered either orally or enterally through a nasogastric tube. When given orally, a single 50-mg tablet was given; however, if a nasogastric route was required, the 50-mg tablet was crushed and then dispersed in water prior to administration. Although riluzole is well absorbed in the stomach and proximal intestine, coadministration of the drug with food can reduce absorption up to 20%. As a result, feeding, whether via an oral or nasogastric route, was not permitted within 2 hours before and was delayed until at least 1 hour after riluzole was given. Since riluzole undergoes hepatic metabolism, primarily by cytochrome P450 1A2, coadministration with other pharmacological agents metabolized by this enzyme (such as quinolone antibiotics, amitriptyline, or omeprazole) was prohibited to prevent variations in serum drug concentration.

**Baseline Assessment**

On patient admission to a study center, the site prin-
Adverse Events. Throughout the course of this study, adverse events were carefully monitored for each participant. Particular care was made to track adverse events previously associated with riluzole administration in the ALS literature, particularly hepatotoxicity. Baseline blood work included alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, and bilirubin levels as well as prothrombin time and international normalized ratio. Liver enzyme tests were repeated on Days 3 and 14 after the start of riluzole. Data were recorded on a wide range of adverse events including infections, respiratory complications, cardiovascular events, deep vein thrombosis/pulmonary embolus, skin breakdown, and neuropathic pain. All serious adverse events were reported to the coordinating center and to the central medical monitor. There were no deaths among the 36 patients enrolled in the study.

Neurological, Functional, and Pain Outcome Assessment. The ASIA Impairment Scale grade, ASIA motor score, and ASIA sensory score are the primary neurological outcome measures used in this study. The Spinal Cord Independence Measure and Brief Pain Inventory short form were used to assess functional status and pain outcomes, respectively.\textsuperscript{8,12} Outcome measures are assessed at 6 weeks, 3 months, 6 months, and 1 year postinjury.

Follow-up data on adverse events as well as neurological, functional, and pain outcomes will be compared between enrolled riluzole-treated patients and non–riluzole-treated patients enrolled in the NACTN prospective SCI registry in the final study analysis.

Collection of Pharmacological Data. Blood samples for determining the peak and trough serum riluzole concentrations were drawn on Day 3 and Day 14 of riluzole administration for all participants. Complete details of pharmacological data collection and analysis can be

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**TABLE 1: Summary of participating centers in NACTN Phase I riluzole trial**

<table>
<thead>
<tr>
<th>Center</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>The Methodist Hospital*</td>
<td>Houston</td>
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<tr>
<td>University of Toronto</td>
<td>Toronto</td>
</tr>
<tr>
<td>University of Texas Health Science</td>
<td>Houston</td>
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<tr>
<td>University of Virginia Health System</td>
<td>Charlottesville</td>
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<td>University of Louisville</td>
<td>Louisville</td>
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<td>Baltimore</td>
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<tr>
<td>University of Miami</td>
<td>Miami</td>
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<tr>
<td>Thomas Jefferson University</td>
<td>Philadelphia</td>
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</tbody>
</table>

**data management center**

| University of Texas School of Public Health | Houston |

**pharmacologic center**

| University of Houston College of Pharmacy | Houston |

\* Coordinating center.

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**TABLE 2: Summary of objectives and inclusion and exclusion criteria for Phase I riluzole trial**

<table>
<thead>
<tr>
<th>Study Objectives</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
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<tbody>
<tr>
<td>primary objective: to evaluate the safety &amp; pharmacokinetic profile of riluzole in patients w/ traumatic SCI</td>
<td>traumatic SCI &amp; an ASIA Impairment Scale grade of A, B, or C neurological level of injury from C-4 to T-12</td>
<td>preexistent liver or kidney disease injuries arising from penetrating mechanisms moderate or severe traumatic brain injury pregnant or nursing women preexistent neurologic or mental disorder that would preclude accurate evaluation and follow-up (e.g., Alzheimer disease, Parkinson disease, or schizophrenia) life-threatening injuries, the management of which would delay drug administration past 12 hrs postinjury unable to receive medication via an oral or nasogastric route recent history of illicit drug or alcohol abuse</td>
</tr>
<tr>
<td>secondary objective: compare neurological, functional, &amp; pain outcomes of enrolled participants w/ outcomes of matched patients from the NACTN SCI registry</td>
<td>btwn the ages of 18 &amp; 70 yrs able to receive riluzole w/in 12 hrs of injury able to cooperate in completion of informed consent</td>
<td></td>
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</tbody>
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found in the pharmacological review by Chow et al. in this supplement.

Progress Made to Date and Future Directions

As of January 2012, the target enrollment of 36 participants has been achieved. Complete analysis of the trial data is underway, and we anticipate that the final results will be available in the summer of 2012. Assuming that the safety profile of riluzole in SCI patients is confirmed, we will use the findings of this study to plan a Phase II trial evaluating the effects of riluzole on long-term neurological and functional outcomes. To this end, data from the current Phase I trial will be used to determine an appropriate treatment effect size for future sample size calculations.

Conclusions

Initiated by the primary spinal cord trauma, a host of secondary pathological processes combine to expand the area of neurological tissue injury after SCI. As part of this process, posttraumatic constitutive activation of neuronal voltage-gated sodium channels leads to increased intracellular sodium and calcium concentrations with concomitant cellular swelling and increased release of excitotoxic glutamate. Riluzole, a sodium channel–blocking anticonvulsant drug, has shown efficacy in preclinical SCI studies and has proven safe and effective in the treatment of human patients with ALS. To initiate the translation of this therapy to the clinic for SCI patients, we have undertaken an open-label Phase I trial to define the safety and pharmacokinetic profile of riluzole in this population. We look forward to publishing the final results of this study later this year.

Disclosure

Dr. Shaffrey reports a consultant relationship with Medtronic, NuVasive, and Biomet; being a patent holder with Medtronic and Biomet; receiving clinical or research support for the study described from the National Institutes of Health, the Department of Defense, NACTN, and AOSSpine; and receiving honoraria from Globus. Author contributions to the study and manuscript preparation include the following. Conception and design: Fehlings. Drafting the article: Wilson. Critically revising the article: Fehlings, Wilson, Frankowski, Toups, Aarabi, Harrop, Shaffrey, Guest, Grossman. Reviewed submitted version of manuscript: Fehlings, Wilson, Toups, Aarabi, Harrop, Shaffrey, Harkema, Guest, Tator, Burau, Johnson, Grossman. Statistical analysis: Tator, Burau, Johnson.

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