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JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Marc Fisher

Stroke 2006;37;2651-2652; originally published online Aug 31, 2006;

DOI: 10.1161/01.STR.0000242800.29490.a1

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
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ISSN: 1524-4628

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Section Editors: Marc Fisher, MD, and Kennedy Lees, MD

NXY-059 for Acute Ischemic Stroke The Promise of Neuroprotection Is Finally Realized?

Marc Fisher, MD

The SAINT I article reports the results of a phase III trial of the free-radical-spin trap, neuroprotective agent, NXY-059 in acute ischemic stroke. The study had a statistically significant effect on the primary outcome measure, the range of 90-day outcomes on the modified Rankin Scale (mRS), a measure of functional outcome after stroke. The change in National Institutes of Health Stroke Scale (NIHSS) scores from baseline, the principal secondary outcome variable, was not effected by treatment with NXY-059. The primary outcome measure used in this trial is novel and has not to my knowledge been used in prior acute stroke trials. The observation in a post hoc analysis of a significant reduction of symptomatic and asymptomatic hemorrhage with NXY-059 in patients who were treated with IV tissue plasminogen activator (t-PA) is also encouraging. It suggests that NXY-059 could be a useful adjunct in stroke patients treated with IV recombinant t-PA to reduce hemorrhagic risk, if reproduced.

The primary outcome measure of a shift in the mRS in a favorable direction achieved statistical significance, and this observation substantiates the importance of this clinical trial. It is the first neuroprotective trial in acute ischemic stroke to achieve a significant treatment effect on its primary outcome measure.¹ Using a shift of the mRS across the entire spectrum of mRS scores is an important innovation. In prior acute stroke therapy trials, the mRS was typically dichotomized and occasionally trichotomized. When the mRS is dichotomized with a cut point at 1 or 2 and the primary end point is a comparison of the percentage of patients achieving an mRS of 0 to 1 or 0 to 2 in the active treatment group versus placebo, the trial is essentially looking for “cures”. The mRS shift approach is designed to look for a broadly defined treatment effect and not only patients with little or no deficit.² Certainly for neuroprotective drugs and likely also for thrombolytics, this mRS shift assessment across the entire range of the scale is more appropriate than looking for a “cure”. In animal studies of both types of therapies, a treatment is considered successful if infarct size is reduced by a reasonable

percentage and the goal is not to reduce infarct size to a small percentage of the involved hemisphere or zero.³

The authors report that the number-needed-to-treat to improve by 1 point on the mRS is 7.8. This is the best-case scenario. In fact, the most likely scenario is that some percentage of patients improved by 2 points and perhaps a few by 3 or 4 points. The number-needed-to-treat for mRS improvement in this study was likely somewhere between 9 to 12 between the estimate of 7.8 for a 1-point improvement and 15.5 for a 2-point improvement. If the approach of improving by 1 point on the mRS is used, the authors state that this “represents a clinically meaningful shift”. This statement is clearly true for a shift from 4 to 3 or 3 to 2, but a shift from 2 to 1 or even 1 to 0 is less obviously clinically meaningful. The mRS is burdened to some degree by semantics and subtlety.⁴ The impact on patients of being classified 0 versus 1 or 1 versus 2 is not always obvious to patients, care givers or physicians.

The observation that NXY-059 significantly reduced the rate of symptomatic and asymptomatic hemorrhages associated with IV t-PA use within the approved 3-hour window is intriguing. It suggests that this spin-trap agent may indeed be protective regarding t-PA-related hemorrhagic transformation of ischemic stroke, potentially by reducing endothelial cell injury. If this observation is confirmed in the larger SAINT II trial, then combination therapy will likely become standard when t-PA is used for acute ischemic stroke. Future studies with later initiation of t-PA therapy beyond the current 3-hour window could then be performed with NXY-059 to determine whether pretreatment with the neuroprotectant has even greater effects on hemorrhagic transformation and possibly extends the time window for the successful use of IV t-PA. The observation of a reduced rate of hemorrhage with NXY-059 in combination with IV t-PA does raise the question of how much of the overall benefit observed in the SAINT I trial is related to a reduced number of hemorrhages associated with t-PA use. Although most of the hemorrhagic reduction was termed asymptomatic, be-

Received and accepted April 19, 2006.

From the Department of Neurology, University of Massachusetts Medical School, Worcester, Mass.

Correspondence to Marc Fisher, MD, University of Massachusetts/Memorial Health Care, 119 Belmont Street, Worcester, MA 01605-2982. E-mail fisherm@ummhc.org

(*Stroke*. 2006;37:2651-2652.)

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000242800.29490.a1

cause a 4-point or greater decline in the NIHSS score was not seen within 36 hours, it is possible that more subtle early clinical declines could be associated with effects on the day-90 mRS outcome. Unfortunately, the article does not address directly the treatment effect ascribable to this reduction of t-PA-related hemorrhagic transformation.

The SAINT I trial is an important and timely step forward for the arena of acute stroke therapy development. The trial incorporated many lessons learned from prior unsuccessful neuroprotection trials and also innovated the use of a reasonable, clinically meaningful end point to evaluate therapeutic response. Hopefully, the results of the ongoing SAINT II trial will corroborate the results of SAINT I and lead to regulatory approval. This modest but clinically meaningful advance should then serve as a springboard for many future trials to enhance acute stroke therapy that will lead to maximizing clinical benefits.

Disclosures

Dr Fisher has served on an advisory board for AstraZeneca.

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KEY WORD: neuroprotectants