A Hopeful Sign in the Treatment of Stroke

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The SAINT I trial published in the February 9, 2006 issue of the New England Journal of Medicine represents the first “positive” neuroprotective trial in stroke.¹ This breaks a long string of “neuroprotective” failures and indicates some hope for stroke treatment.² Is NXY-059 a better drug than previous failed agents or was the trial just better designed? Probably both.

NXY-059 is the first agent that fulfilled all the Stroke Therapy Academic Industry Roundtable (STAIR) recommendations regarding preclinical development before it entered a large phase-III clinical trial in stroke.³ The preclinical data with NXY-059 were robust and impressive. NXY-059 was effective at both reducing infarct size and improving functional outcome in both temporary and permanent rodent middle cerebral artery (MCA) occlusion models.⁴,⁵ There was a clear dose response and the therapeutic window extended out to 4 hours.⁶ Next, NXY-059 was tested in a nonhuman primate model, albeit the lissencephalic marmoset.⁶,⁷ Again, NXY-059 both reduced infarct size and improved long-term (10-week) functional outcome (reduced neglect and improved arm function) with a 4-hour window in a permanent MCA occlusion model.⁷ The reduction in infarct size and functional improvement was better than that observed with other neuroprotective agents (the GABA mimetic agent, clomethiazole and the NMDA antagonist, AR-R15896AR) in the same primate model.⁸ Importantly, the neuroprotective NXY-059 plasma levels in primates (200 μmol/L) are achievable and safe in humans and even below the target concentrations of 260 μmol/L in SAINT I.⁷

The trial design was also improved over past neuroprotective trials. First, the primary outcome measure, a “shift” in the modified Rankin Scale, was appropriate for a neuroprotective agent and one that matched what was observed in the preclinical studies—a consistent modest improvement but not a “Lazarus” response. If the primary outcome chosen had been an excellent neurological outcome as defined by a National Institutes of Health Stroke Scale (NIHSS) score of 0 or 1, this would not have met statistical significance (33.1% for NXY-059 versus 30.9% for placebo; odds ratio 1.13; P=0.028) and the trial would have been considered “negative”. This illustrates the importance of choosing a primary outcome that is realistic and reflects the mechanism of action of the drug. Second, the time window in SAINT I was 6 hours, but forced stratification ensured that each site had to maintain an average time from the onset of symptoms to treatment of no more than 4 hours, matching the effective time window in the preclinical models. Although the window in humans may be longer than it is in rodents, it is wise to be conservative with respect to the time window. Third, the doses in the SAINT I study achieved target plasma concentrations of unbound drug that were known to be effective in permanent MCA occlusion models in rodents and primates.

NXY-059 is remarkably safe. Fewer NXY-059 than placebo-treated patients discontinued treatment because of adverse events. Hypokalemia during infusion was the only notable adverse event. NXY-059 is a bit cumbersome to use, requiring a 72-hour infusion when some of our milder stroke patients no longer stay in the hospital that long. Duration of treatment is seldom studied well in preclinical trials because long duration infusions in animals are costly and inconvenient. For example, in the preclinical primate studies with NXY-059, the infusion was administered for only 48 hours.⁷ It is not clear why 72 hours was chosen other than the belief that the “longer the better,” but one wonders if one could get by with 2 days of infusion.

Perhaps the most remarkable finding was in the post hoc safety analysis of symptomatic intracerebral hemorrhage (ICH). Approximately 29% of patients received tissue plasminogen activator (tPA), and the NXY-059 group had a significantly reduced rate of symptomatic ICH from 6.4% to 2.5%. This alone if confirmed in SAINT II would provide a strong rationale to use NXY-059 with tPA routinely, concurrently, or even before tPA. Why would NXY-059 have this effect? It is doubtful that the NXY-059 inactivated the tPA because an in vitro clot assay showed no interaction between NXY-059 and tPA. ICH related to tPA is associated with upregulation and activation of matrix metalloproteinase 9 (MMP-9).⁹,¹⁰ There is no data available of the effect of...
NXY-059 on MMP-9 levels or activity. MMP-9 has the redox-sensitive transcription factor NF-kB in its promotor, so conceivably trapping of free radicals at the endothelial-blood interface might reduce transcription and thereby activation of MMP-9.

One would have been more comfortable had the coprimary outcome and the secondary outcomes also been positive in SAINT I. However, these were NIH scale–based and apparently more in response to European regulators than a scientific rationale. The bimodal distribution of NIH scores and the assignment of the highest score of 42 to the patients who died made this outcome analysis less likely to be positive. Also, one wonders why there was no interaction with the time-to-treatment because the preclinical data showed a diminishing benefit with longer times to treatment. This may be related to a clustering of time-to-treatments around 4 hours and a limited number of patients treated under 2 hours. The authors are therefore right to await a confirmatory study (SAINT II) to conclude whether NXY-059 will be of benefit in stroke. Hopefully, the combined data with the SAINT II trial may be able to address these issues further.

Finally, what is the mechanism of action of the protective effect of NXY-059? In the earliest studies, NXY-059, a water-soluble drug, was found to penetrate the blood-brain barrier, poorly leading to the suggestion that it was primarily working at the blood-endothelial interface. Reactive oxygen species generated by endothelial cells and neutrophils lead to endothelial dysfunction and tissue injury. NXY-059 may be more properly viewed as a “vasculoprotective” drug acting primarily on the vascular part of the neurovascular unit.

If SAINT II replicates the findings of SAINT I, then we have a major advance in the treatment of stroke—a very safe drug that improves most patients a little bit and that reduces the feared complication of tPA-related ICH. We may finally have a drug that could be given to the majority of ischemic stroke patients. NXY-050 will likely increase the usage of tPA by relieving the fear factor that prevents many Emergency Room physicians from administering tPA. Moreover, there remains the future possibility, based on preclinical studies, that NXY-059 may extend the therapeutic window of a thrombolytic agent like tPA to beyond 3 hours.

Disclosures
D.C.H. has served on an Advisory Board for AstraZeneca.

References
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