Topical Review

Section Editors: Mayank Goyal, MD, FRCPC, and Laurent Pierot, MD, PhD

Combining Neuroprotection With Endovascular Treatment of Acute Stroke

Is There Hope?

Michael Tymianski, MD, PhD

The goal of any clinical trial is to operationalize a paradigm in which the study enrolls the greatest proportion of responders in a setting that maximizes that study intervention's treatment effect. Such a trial would have the most power to detect the therapeutic benefit it seeks to evaluate. Importantly, the trial should be grounded in—and consistent with—the preclinical science of the test intervention. Based on this, an acute ischemic stroke (AIS) trial must overcome the following 4 challenges: to have a design that conforms to that of animal studies that support the intervention, to minimize subject heterogeneity, to ensure that the treatment effect size is maximized, and to enroll subjects in the correct therapeutic window. Recent trials of endovascular thrombectomy (EVT)[1–5] have decisively risen to this challenge for each of these aforementioned criteria: EVT recapitulates a wealth of animal studies demonstrating that stroke outcomes from temporary ischemia (eg, temporary middle cerebral artery occlusion [MCAO]) are better than in analogous animal models in which the MCAO is permanent. Subject heterogeneity in the recent EVT trials was reduced by selecting only those subjects who, on medical imaging, exhibit a large vessel occlusion (LVO). Selecting subjects with LVO also maximized the treatment effect size because untreated patients with LVO have a poorer prognosis even with tissue-type plasminogen activator (tPA) therapy,[6–8] thus expanding the opportunity for EVT to provide a clinical benefit. Enrollment in the correct therapeutic window was achieved by optimizing the speed from diagnosis to reperfusion[9] and, in some instances,[1–3] by imaging criteria ensuring that enrolled patients still exhibited a penumbra. The success of recent EVT trials teaches that studies designed with the deliberate strategy of meeting these criteria may provide a better opportunity to demonstrate a clinical benefit than those that do not. Thus, the learnings from EVT provide an unprecedented opportunity to design AIS neuroprotection trials along similar lines and perhaps to combine the 2 to further enhance the potential benefits of both.

Neuroprotection as a Stand-Alone Treatment

Pre-clinical studies suggest that neuroprotection may be a valid treatment for AIS either as a stand-alone therapy or in combination with reperfusion. A neuroprotectant that provides clinical benefits in a wide range of scenarios is perhaps the ideal goal but one that has proven difficult to attain in clinical trials. A wide range of scenarios implies heterogeneity, which is introduced when the subject population varies too much in demographics, medical comorbidities, clinical stroke severity, degree of completed ischemic damage, rate of stroke progression, the presence of a collateral circulation, or site of vessel occlusion. A study that purposefully enrolls patients exhibiting the full spectrum of such prognostic variables or that does not explicitly narrow them down risks being underpowered to show a treatment effect of a neuroprotectant because of noise inherent in the study design.

In the case of neuroprotection trials for AIS, all to date have failed to demonstrate a clinical benefit of the study agent. Our review of studies since the year 2000[10] shows that none conformed to the 4 key elements espoused above. Many were not conducted in accordance with the animal studies that supported efficacy. They enrolled a heterogeneous subject population with varying (small and large) vessel occlusions and without knowledge of the degree of completed infarctions. Most had not implemented a strategy to ensure that the treatment effect size was maximized, and all in-hospital trials enrolled in treatment windows that exceeded 4 hours, at which an important proportion of enrolled subjects cannot respond to treatment because they no longer have salvageable brain.[10]

In addition, in all stand-alone neuroprotection trials to date, only a small proportion of subjects also received successful recanalization. Recanalization arrests or markedly inhibits stroke progression[11,12] and is strongly associated with improved functional outcomes and reduced mortality.[13] In a meta-analysis of recanalization rates and stroke outcomes, Rha and Saver[13] showed that, on average, only 25% of patients with stroke enrolled in various trials spontaneously recanalized by 24 hours. Numbers for earlier spontaneous recanalization times are less clear but may be as low as 15% in the first 6 hours.[14] Thus, most patients enrolled in past neuroprotection trials did not experience recanalization. For example, only 44% of 3306 subjects enrolled in the SAINT-II

Received February 14, 2017; final revision received March 28, 2017; accepted April 3, 2017.

From the Division of Neurosurgery (M.T.) and Krembil Research Institute (M.T.), Toronto Western Hospital, University Health Network, Ontario, Canada; and Department of Surgery, University of Toronto, Ontario, Canada (M.T.).

Correspondence to Michael Tymianski, MD, PhD, Krembil Research Institute, Toronto Western Hospital, 4W-435, 399 Bathurst St, M5T 2S8, Toronto, Ontario, Canada. E-mail mike.tymianski@uhn.ca

(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.117.017040.)

trial (Stroke–Acute Ischemic NXY Treatment) received tPA.[15] Because recanalization within 6 hours of stroke onset occurs in 40% to 50% of patients who receive tPA,[16,17] ≈80% of subjects in SAINT-II received study agent without recanalization.

Some of the difficulties associated with stand-alone neuroprotection trials may be correctible. For example, in the FAST-MAG trial (Field Administration of Stroke Therapy–Magnesium),[18] study drug was administered in the prehospital setting with a median interval from stroke onset to treatment is of 45 minutes. This short interval ensured that the vast majority of enrolled subjects who received the study agent had salvageable brain at the time that intervention was given. This approach resolved uncertainty about therapeutic window. However, FAST-MAG came at the cost of increased subject heterogeneity, enrolling a broad range of ischemic strokes who subsequently had low rates of recanalization, as well as subjects with hemorrhagic strokes, transient ischemic attacks, and stroke-mimicking conditions.

Another approach to stand-alone neuroprotection trials is to use imaging to identify potential responders. An appealing strategy is to image the ischemic penumbra—that portion of the ischemic territory that is still salvageable if an appropriate treatment is given.[19] Although the concept has existed for >30 years,[20] penumbra imaging in a neuroprotection trial is uncommon. However, lessons from stroke reperfusion studies support this approach. For example, the DEFUSE[16] and DEFUSE-2[21] trials (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) showed that a diffusion/perfusion mismatch on magnetic resonance imaging predicts a benefit from reperfusion. This philosophy was successfully implemented in the EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial) EVT trial that used perfusion imaging.[2] However, penumbra imaging could also select patients with better rates of spontaneous recovery because of collateral circulation, thereby reducing the power to detect a therapeutic benefit of a neuroprotectant.

The heterogeneity of strokes, speed of stroke progression, uncertainty about remaining salvageable brain, enrollment windows, and the low rates of recanalization are formidable challenges to overcome in stand-alone AIS neuroprotection trials. A large number of subjects may be needed to achieve the necessary power to discern a treatment effect. Because of the global health importance of AIS, such studies remain worthwhile but may not be the most efficient way to test the neuroprotection hypothesis.

Is Neuroprotection Without Recanalization Possible?

A clinical trial risks failure if it is underpowered or if its underlying assumptions are incorrect. For example, as stated by Saver (2012)[22]: "Among the several deficiencies identified in neuroprotective clinical trials, the most important, in my view, is that patients were being treated too late." This expert statement accurately summarizes the failure of all past in-hospital trials to enroll in the correct therapeutic window. However, it does not resolve the uncertainty of whether correcting this single factor is sufficient. As also stated by Saver[22]: "While neuroprotection is intrinsically a temporizing therapy, enabling brain cells to tolerate an ischemic episode longer, reperfusion is intrinsically a definitive therapy, finally resolving the ischemic episode." Thus, even if neuroprotection was administered in the correct window, a clinical benefit may not be realized without reperfusion.

Animal studies have addressed this on multiple occasions. Pre-clinical models of permanent cerebral ischemia exist[23,24] and are used to evaluate putative neuroprotectants. Although often criticized for methodological quality,[25,26] an overwhelming number of permanent ischemia studies indicate that tissue sparing by neuroprotectants is achievable in rats and mice. However, the treatment effect is smaller than in transient ischemia.[27] For example, NA-1/Tat-NR2B9c is a promising agent that acts by inhibiting the interactions of the synaptic scaffolding protein PSD95 with N-methyl-D-aspartate glutamate receptors,[28] thereby interfering with pro-death signaling pathways.[29] NA-1 reduced ischemic brain infarction in rats subjected to permanent pial vessel occlusion[30,31] or permanent MCAO.[30,32] NA-1 also reduced stroke damage in primates subjected to multiple, permanent, embolic small vessel occlusions induced by intracarotid injections of polystyrene beads[33] and in humans subjected to iatrogenic embolic small vessel strokes induced during endovascular brain aneurysm repair.[34] Thus, evidence exists across species, including primates and humans, that neuroprotection can reduce ischemic tissue damage without reperfusion. However, translation of these findings to human AIS relies on the assumption that these data apply to larger stroke volumes. It is concerning that no animal studies have ever addressed the mechanism by which neuroprotection in permanent ischemia is possible in animals and yet remains a failed strategy in so many AIS trials. Experience with NA-1 rules out that differences in biology across species are the cause. Rather, an important observation is that all encouraging data in permanent ischemia studies were derived from small volume strokes. By sheer geometry, smaller strokes have larger surface-to-volume ratios. A plausible hypothesis is that neuroprotection, by slowing tissue decay, enables oxygenation from vascularized tissue to penetrate a small distance into adjacent ischemic brain because of augmented autoregulation and diffusion. In considering infarct volumes typical of permanent MCAO models in rats,[30] survival of just the most peripheral 1 mm rim of tissue in a 216-mm^3 infarct would reduce the volume by >40%. This same effect is unlikely to be meaningful in the larger infarcts seen in human AIS and that are measured in the tens of cubic centimeters. Simple geometry could explain the absence of any reliable reports in support of neuroprotection in the setting of permanent vessel occlusions that produce large strokes.

Given these considerations, neuroprotection in permanent ischemia is at best less effective than in ischemia–reperfusion. At worst, the modest efficacy observed in pre-clinical studies is not scalable to the clinical situation. Under either circumstance, the lack of reperfusion reduces substantially the power of a stand-alone neuroprotection trial to detect a treatment effect and enhances its risks.

Studies in Support of Neuroprotection With EVT

The acceptance of EVT for appropriately selected patients provides an unprecedented opportunity to evaluate neuroprotection as an adjunct, thereby recapitulating the pre-clinical

scenario of ischemia–reperfusion in which neuroprotection is maximally effective. If neuroprotection is a temporizing therapy that slows ischemic core growth,[22] it could enhance the clinical benefit of reperfusion. Under this scenario, the entire volume of ischemic tissue, not just tissue in the periphery, is the target of neuroprotection provided that treatment is administered before infarction is complete.

We posit that the failure of past trials was because of enrollment in the incorrect therapeutic window and to a lack of reperfusion, rather than to as yet undiscovered interspecies differences in biological response to stroke. If so, then the success of neuroprotection with EVT should be anticipated from carefully conducted animal studies. Many neuroprotectant studies in rats and mice report efficacy in temporary MCAO akin to EVT but not in permanent MCAO,[27] suggesting that EVT outcomes are bolstered by neuroprotectants. However, if stroke size matters, then relying solely on evidence from small animal studies increases the risk of a corresponding clinical trial.

To mitigate this risk in the case of NA-1/Tat-NR2B9c and to bridge as much as possible any potential for a biological gap, we conducted experiments in cynomolgus macaques.[35] These nonhuman primates possess higher order brains anatomically similar to humans and a rich behavioral repertoire amenable to assessments using standardized tests.[36,37] They are also amenable to imaging to quantify the ischemic penumbra, which we operationally defined similarly to the DEFUSE study[16,21] as that brain region in which the perfusion-weighted and diffusion-weighted magnetic resonance images are mismatched. To replicate the human trial scenario, we conducted experiments in which LVO was induced by MCAO such that, after 3 hours, the animals exhibited a small core with a collateral circulation that maintained an ischemic penumbra—an inclusion requirement in successful EVT trials.[1–3] As in humans, this penumbra evolved to a completed stroke in the absence of treatment.[35]

Using this nonhuman primate model, we replicated a practical clinical scenario for testing neuroprotection as an adjunct to EVT: in the clinic, subjects would be enrolled if their AIS met the criteria of a small core, presence of a collateral circulation, and a decision to pursue EVT. Enrollment would be followed by randomization to and administration of active drug or placebo followed by EVT for all subjects. To model this, nonhuman primates undergoing MCAO as described were administered NA-1/Tat-NR2B9c or placebo 3 hours after MCAO, followed by reperfusion at 3.5 hours. These time lines corresponded well to process times reported subsequently in the ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) EVT trial,[1] whereby the median time from onset to the randomization decision to pursue EVT was ≈3 hours and the time from onset to recanalization was 4 hours. In the nonhuman primate study, drug-treated animals exhibited significant reductions in infarct volumes as compared with placebo and exhibited improved neurological scores throughout a 14-day observation period.[35] Thus, neuroprotection in high-order gyrencephalic primates with LVO, a small core, good collaterals, and in timelines mimicking the ESCAPE trial is effective. Such results may derisk a clinical trial aimed at evaluating the benefits of neuroprotection as an adjunct to EVT.

Some early human data provide further support for neuroprotection in combination with reperfusion therapy in the presence of a good collateral circulation. The URICO-ICTUS study (Safety and Efficacy of Uric Acid in Patients With Acute Stroke) evaluated combined treatment with uric acid and rtPA administered intravenously in patients with AIS within the first 4.5 hours of onset of symptoms.[38] In a tertiary analysis, the effect of uric acid on reducing early worsening after ischemia was most pronounced in patients with good collaterals,[38] suggesting that either collaterals provide access of the neuroprotectant to the ischemic core or that they identify patients with slower stroke progression and thus more salvageable brain by the time that treatment is given.

Outcomes From EVT: There Is Still Much Potential for Improvement

AIS trials evaluating neuroprotection in combination with EVT can overcome deficiencies inherent in stand-alone neuroprotection studies. They can be designed in accordance with pre-clinical animal data that support an incremental benefit of neuroprotection over that of reperfusion alone. They can reduce heterogeneity through imaging selection of subjects with LVO, a small ischemic core, and good collaterals. Neuroprotection in the setting of ischemia–reperfusion ensures that the treatment effect size is maximized, thereby enhancing a study's power. Adherence to the enrollment criteria of successful EVT trials also ensures that subjects are enrolled in the correct therapeutic window.

A study of neuroprotection in the setting of EVT is as yet unprecedented, and all aspects of its design must be approached with caution. An important consideration is the choice of primary outcome. We think that currently the primary outcome should be a measure that clearly reflects a clinical benefit of the intervention as measured by a validated outcome scale. An alternative is to consider a surrogate outcome. However, there is a paucity of validated surrogate measures in the field of stroke. For example, surrogates, such as computerized tomography or magnetic resonance imaging measurements of infarct volumes, show no or modest correlations between infarct volume and outcomes using conventional clinical scales[19–21] because a small infarct can produce severe clinical disability. Among the recent EVT trials, MR-CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) demonstrated that subjects in the intervention group exhibited both improved outcomes and smaller infarct volumes at 3 to 9 days.[5] In EXTEND-IA, reperfusion led to a reduction in infarct growth, suggesting that penumbra salvage reflects the clinical benefit of reperfusion.[2] However intuitive, it is unclear whether such surrogates can substitute for conventional outcome scales for the purpose of drug approval. The US Food and Drug Administration recognizes stroke as a serious and life-threatening condition, making stroke drugs eligible for accelerated approval using data from validated surrogate markers.[39] However, to date, no surrogate marker has been accepted in lieu of a clinical outcome scale as reasonably likely to predict clinical benefit as required under the accelerated approval process. Surrogates, such as stroke volume, core progression, or penumbra preservation, may be useful for

proof-of-concept studies. But because of their inherent variability, they may not be necessarily more robust than clinical assessments for detecting treatment effects. Consequently, reliance on surrogate measures may not decrease the sample size needed to properly power a neuroprotection trial. Imaging outcomes that are obtainable in the initial hours or days after the stroke may simplify some aspects of trial conduct if they are substituted for long-term clinical follow-up. However, until they are validated, the risk of conducting a large trial based solely on a surrogate outcome is too great.

A further consideration is whether EVT is so effective that the incremental benefit of neuroprotection could be missed. In the recent MR-CLEAN, ESCAPE, REVASCAT (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset), SWIFT PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment), and EXTEND-IA trials,[1–5] many patients enrolled with severe strokes were restored to functional independence. However, a meta-analysis of these studies with 1287 participants (634 EVT and 653 controls)[40] indicated that overall only 46% of subjects receiving EVT were functionally independent at 90 days as defined by a modified Rankin Scale (mRS) score of 0 to 2. Only 10% were neurologically normal (mRS=0), suggesting that even with EVT, 90% of AIS victims exhibit a meaningful deterioration of functional status. The mechanisms of this deterioration remain a topic of intense study and may include excessive oxidative stress–related reperfusion injury, blood–brain barrier damage, mechanical vascular injury, and irreversible neuronal damage. Neuroprotectants may mitigate such mechanisms, providing a further rationale for their use in an ischemia–reperfusion setting. Given this, there remains a major unmet medical need to improve the outcomes of stroke victims treated with EVT, as well as ample room to detect a clinical benefit of neuroprotection as an EVT adjunct in a clinical trial.

Maximizing the Treatment Effect of Neuroprotection in Patients With EVT

Ideally, a neuroprotectant should be administered as early as possible in the stroke evolution. The only scenario in which such agents would be futile is in patients who are reperfused so rapidly after LVO that ischemic damage could not set in. However, in the recent EVT trials, the time from symptom onset to reperfusion was a median of 285 minutes with an interquartile range of 210 to 362 minutes,[40] during which the penumbra was presumably shrinking as the ischemic core expanded. An agent that can freeze the penumbra[32] or reduce the rate of core expansion[35] may thus offer significant benefit if administered before ischemic damage is complete. A trial protocol should thus ensure that the study drug is given as early as possible after the subject is enrolled and that EVT be conducted with modern devices that achieve high reperfusion rates and with low complications.

The ESCAPE-NA-1 Trial

The Extension of Stroke Care by Adding neuroProtection to Endovascular treatment trial (ESCAPE-NA-1; clinicaltrials.gov, NCT02930018) is a recently launched study of NA-1/Tat-NR2B9c aimed at integrating the principles that overcome deficiencies of prior stand-alone trials. Its design corresponds to pre-clinical primate studies.[33] It minimizes heterogeneity through imaging-based selection, ensures that the neuroprotective effect is amplified through reperfusion, and enrolls subjects in a therapeutic window and with criteria that are validated by its predecessor, the ESCAPE trial.[1] The primary objective of ESCAPE-NA-1 is to determine the efficacy of NA-1 in reducing global disability in subjects with AIS harboring a small established infarct core and with good collateral circulation and who are selected for rapid endovascular revascularization. This is a phase-3 randomized, multicentre, blinded, placebo-controlled study with a parallel group, single-dose design. A single 2.6 mg/kg IV dose of NA-1 or placebo is initiated in subjects with AIS who are selected for EVT using criteria substantially similar to those in ESCAPE[1] and within 30 minutes of randomization. A key enrollment is a confirmed LVO at ≥1 of the intracranial carotid T/L or M1 middle cerebral artery. Patients with evidence of a large core of established infarction defined as ASPECTS (The Alberta Stroke Program Early CT Score) 0 to 4 or with absent collateral circulation on computed tomography angiography will be excluded. The use of tPA, but not any other thrombolytic agent, is permitted. Up to 1120 subjects will be enrolled in ≈35 sites globally. All subjects undergo attempted endovascular recanalization therapy with a stent retriever or clot aspiration device and receive best medical care throughout a 90-day observation period according to modern acute stroke care guidelines.

The primary variable for the pivotal assessment of efficacy is the overall proportion of subjects having an mRS score of 0 to 2 at 90 days after randomization. Assuming the 52% overall responder rate expected for the placebo group based on ESCAPE,[1] there will be 80% power to detect an 8.7% absolute effect difference between response rate with NA-1 and placebo, at α level 0.025, 1-sided with a planned sample size of 1076 evaluable subjects, randomized 1:1, per group, accounting for a single interim analysis when 600 subjects have completed their 90-day follow-up visit. All analyses will be conducted on the intent-to-treat population, defined as all subjects randomized into the trial with grouping by randomized treatment, regardless of treatment actually received.

A key secondary analysis will evaluate a shift of ≥1 categories to reduced functional dependence across the whole distribution of mRS scores at day 90 or the last rating. This will be an adjusted analysis using a proportional odds model to derive the common odds of improvement (shift) along the mRS scale. Additional secondary outcomes are the proportion of subjects on day 90 or the last rating with good neurological outcome as defined by a score of 0 to 2 on the National Institutes of Health Stroke Scale; functional independence in activities of daily living as defined by a score of ≥95 on the Barthel Index; a reduction in mortality rate, as defined by event rate (%) for mortality during the 90-day study period; and infarct volumes as determined by computerized tomography or magnetic resonance imaging.

Beyond ESCAPE-NA-1

ESCAPE-NA-1 opens the opportunity to enable more stroke victims to benefit from reperfusion. A neuroprotectant could be administered at a referring hospital to enable more patients

who are transported to comprehensive stroke centers to benefit from EVT on arrival. This becomes increasingly important as stroke services globally adopt spoke-and-hub systems, with or without telestroke,[41,42] to enhance access. Neuroprotectants administered at spoke hospitals, or by first responders in the ambulance,[18] could dramatically increase access to EVT.

A trial to test this scenario might involve identifying candidates for EVT at the referring (spoke) hospital using criteria substantially similar to those in ESCAPE-NA-1. Randomization to receive drug or placebo followed by initiation of study drug infusion would occur at the spoke hospital just before patient transfer. On arrival at the comprehensive stroke center, imaging could be repeated to determine any of several parameters, including the size or rate of growth of the infarct core or the change in the ischemic penumbra. In a pivotal trial, the primary outcome would be a comparison of clinical outcomes between the drug and placebo groups, similar to that of conventional stroke trials. However, because the effectiveness of EVT is already established for appropriately selected patients, a proof-of-concept study could be conducted more easily by comparing the impact of neuroprotection on imaging parameters or on the fraction of transported patients in each treatment group who still qualify for thrombectomy on arrival to the stroke center. This type of comparison is already planned in the currently ongoing Field Randomization of NA-1 Therapy in Early Responders trial (FRONTIER; clinicaltrials.gov, NCT02315443). FRONTIER is a randomized, double-blind, placebo-controlled study to determine the efficacy and safety of intravenous NA-1 initiated by paramedics in the field for acute cerebral ischemia within 3 hours of symptom onset. Subjects in FRONTIER are enrolled in the ambulance using criteria substantially similar to those of the FAST-MAG trial.[18] The primary outcome of FRONTIER is the degree of functional recovery as measured by the mRS at 90 days. However, a key secondary efficacy end point is the proportion of subjects who are deemed to be candidates for endovascular recanalization therapy, as determined by computerized tomography/computed tomography angiography, on arrival at the stroke center.

More than half of subjects enrolled in FRONTIER to date have received tPA or EVT (M. Tymianski, unpublished observataions, 2017). This preserves the possibility that the trial will detect a treatment benefit of NA-1 even with the caveats raised in connection with stand-alone neuroprotection trials. Of equal importance is that FRONTIER will provide a safety database for NA-1 in a wide range of stroke subtypes, including AIS, hemorrhagic strokes, transient ischemic attacks, and stroke-mimicking conditions. This safety information will be useful for justifying subsequent studies in which NA-1 is planned for use in a stroke population broader than that defined by the strict criteria of ESCAPE-NA-1.

Conclusions

The recent success of EVT provides an unprecedented opportunity for neuroprotection trial design. For the first time, neuroprotection can be evaluated in a clinical setting of ischemia–reperfusion in which neuroprotection has the largest treatment effect. Subject heterogeneity can be minimized using imaging-based selection to enroll only subjects with LVO, small core infarcts, and good collaterals. The effectiveness of modern EVT devices ensures that the majority of subjects will be successfully recanalized, ensuring that neuroprotection is relevant to the entire volume of brain-at-risk. Adherence to the enrollment criteria of EVT studies ensures that subjects are enrolled while they have salvageable brain. Ultimately, neuroprotection may be the mainstay of initial stroke therapy, being administered by first responders in the ambulance or in the emergency department. The impact of neuroprotection, at least initially, is closely tied to EVT and may significantly increase the number of patients who can benefit from recanalization. Thanks to recent advances, the future of neuroprotection has never been brighter.

Sources of Funding

Work in this review was funded by grants to Dr Tymianski from the Canadian Stroke Networks, the Canadian Institutes for Health Research, and by NoNO Inc. Dr Tymianski is a Canada Research Chair (tier 1) in translational stroke research.

Disclosures

Dr Tymianski is president of NoNO Inc, a biotechnology company founded to develop PSD95 inhibitors discovered in his research laboratory. NoNO Inc, in collaboration with academic partners, is the regulatory sponsor of the FRONTIER and ESCAPE-NA-1 trials.

References

1. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905.
2. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792.
3. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061.
4. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780.
5. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587.
6. De Silva DA, Brekenfeld C, Ebinger M, Christensen S, Barber PA, Butcher KS, et al; Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) Investigators. The benefits of intravenous thrombolysis relate to the site of baseline arterial occlusion in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). *Stroke*. 2010;41:295–299. doi: 10.1161/STROKEAHA.109.562827.
7. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al; CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38:948–954. doi: 10.1161/01.STR.0000257304.21967.ba.
8. Nakashima T, Toyoda K, Koga M, Matsuoka H, Nagatsuka K, Takada T, et al. Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. *Int J Stroke*. 2009;4:425–431. doi: 10.1111/j.1747-4949.2009.00347.x.
9. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288. doi: 10.1001/jama.2016.13647.

10. Tymianski M. Novel approaches to neuroprotection trials in acute ischemic stroke. *Stroke*. 2013;44:2942–2950. doi: 10.1161/STROKEAHA.113.000731.
11. Seitz RJ, Oberstrass H, Ringelstein A, Wittsack HJ, Siebler M. Failed recovery from thrombolysis is predicted by the initial diffusion weighted imaging lesion. *Cerebrovasc Dis*. 2011;31:580–587. doi: 10.1159/000324947.
12. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, et al; EPITHET Investigators. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol*. 2008;7:299–309. doi: 10.1016/S1474-4422(08)70044-9.
13. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. 2007;38:967–973. doi: 10.1161/01.STR.0000258112.14918.24.
14. Molina CA, Montaner J, Abilleira S, Arenillas JF, Ribó M, Huertas R, et al. Time course of tissue plasminogen activator-induced recanalization in acute cardioembolic stroke: a case-control study. *Stroke*. 2001;32:2821–2827.
15. Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, et al; SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. *N Engl J Med*. 2007;357:562–571. doi: 10.1056/NEJMoa070240.
16. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, et al; DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol*. 2006;60:508–517. doi: 10.1002/ana.20976.
17. Molina CA, Alvarez-Sabín J, Montaner J, Abilleira S, Arenillas JF, Coscojuela P, et al. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. *Stroke*. 2002;33:1551–1556.
18. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, et al; FAST-MAG Investigators and Coordinators. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *N Engl J Med*. 2015;372:528–536. doi: 10.1056/NEJMoa1408827.
19. Fisher M. The ischemic penumbra: identification, evolution and treatment concepts. *Cerebrovasc Dis*. 2004;17(suppl 1):1–6. doi: 10.1159/000074790.
20. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia—the ischemic penumbra. *Stroke*. 1981;12:723–725.
21. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, et al; DEFUSE 2 Study Investigators. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. *Lancet Neurol*. 2012;11:860–867. doi: 10.1016/S1474-4422(12)70203-X.
22. Saver JL. The 2012 Feinberg Lecture: treatment swift and treatment sure. *Stroke*. 2013;44:270–277. doi: 10.1161/STROKEAHA.112.671354.
23. Casals JB, Pieri NC, Feitosa ML, Ercolin AC, Roballo KC, Barreto RS, et al. The use of animal models for stroke research: a review. *Comp Med*. 2011;61:305–313.
24. Howells DW, Porritt MJ, Rewell SS, O'Collins V, Sena ES, van der Worp HB, et al. Different strokes for different folks: the rich diversity of animal models of focal cerebral ischemia. *J Cereb Blood Flow Metab*. 2010;30:1412–1431. doi: 10.1038/jcbfm.2010.66.
25. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. *Ann Neurol*. 2006;59:467–477. doi: 10.1002/ana.20741.
26. Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, Bradley EW, et al. A call for transparent reporting to optimize the predictive value of preclinical research. *Nature*. 2012;490:187–191. doi: 10.1038/nature11556.
27. Weng YC, Kriz J. Differential neuroprotective effects of a minocycline-based drug cocktail in transient and permanent focal cerebral ischemia. *Exp Neurol*. 2007;204:433–442. doi: 10.1016/j.expneurol.2006.12.003.
28. Aarts M, Liu Y, Liu L, Besshoh S, Arundine M, Gurd JW, et al. Treatment of ischemic brain damage by perturbing NMDA receptor- PSD-95 protein interactions. *Science*. 2002;298:846–850. doi: 10.1126/science.1072873.
29. Sattler R, Xiong Z, Lu WY, Hafner M, MacDonald JF, Tymianski M. Specific coupling of NMDA receptor activation to nitric oxide neurotoxicity by PSD-95 protein. *Science*. 1999;284:1845–1848.
30. Sun HS, Doucette TA, Liu Y, Fang Y, Teves L, Aarts M, et al. Effectiveness of PSD95 inhibitors in permanent and transient focal ischemia in the rat. *Stroke*. 2008;39:2544–2553. doi: 10.1161/STROKEAHA.107.506048.
31. Soriano FX, Martel MA, Papadia S, Vaslin A, Baxter P, Rickman C, et al. Specific targeting of pro-death NMDA receptor signals with differing reliance on the NR2B PDZ ligand. *J Neurosci*. 2008;28:10696–10710. doi: 10.1523/JNEUROSCI.1207-08.2008.
32. Bråtane BT, Cui H, Cook DJ, Bouley J, Tymianski M, Fisher M. Neuroprotection by freezing ischemic penumbra evolution without cerebral blood flow augmentation with a postsynaptic density-95 protein inhibitor. *Stroke*. 2011;42:3265–3270. doi: 10.1161/STROKEAHA.111.618801.
33. Cook DJ, Teves L, Tymianski M. A translational paradigm for the preclinical evaluation of the stroke neuroprotectant Tat-NR2B9c in gyrencephalic nonhuman primates. *Sci Transl Med*. 2012;4:154ra133. doi: 10.1126/scitranslmed.3003824.
34. Hill MD, Martin RH, Mikulis D, Wong JH, Silver FL, Terbrugge KG, et al; ENACT Trial Investigators. Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2012;11:942–950. doi: 10.1016/S1474-4422(12)70225-9.
35. Cook DJ, Teves L, Tymianski M. Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain. *Nature*. 2012;483:213–217. doi: 10.1038/nature10841.
36. Cook DJ, Tymianski M. Nonhuman primate models of stroke for translational neuroprotection research. *Neurotherapeutics*. 2012;9:371–379. doi: 10.1007/s13311-012-0115-z.
37. Roitberg B, Khan N, Tuccar E, Kompoliti K, Chu Y, Alperin N, et al. Chronic ischemic stroke model in cynomolgus monkeys: behavioral, neuroimaging and anatomical study. *Neurol Res*. 2003;25:68–78. doi: 10.1179/016164103101200950.
38. Amaro S, Laredo C, Renú A, Llull L, Rudilosso S, Obach V, et al; URICO-ICTUS Investigators. Uric acid therapy prevents early ischemic stroke progression: a tertiary analysis of the URICO-ICTUS Trial (efficacy study of combined treatment with uric acid and r-tPA in acute ischemic stroke). *Stroke*. 2016;47:2874–2876. doi: 10.1161/STROKEAHA.116.014672.
39. New drug, antibiotic, and biological drug product regulations; accelerated approval—FDA. Final rule. *Fed Regist*. 1992;57:58942–58960.
40. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X.
41. Morris S, Hunter RM, Ramsay AI, Boaden R, McKevitt C, Perry C, et al. Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *BMJ*. 2014;349:g4757. doi: 10.1136/bmj.g4757.
42. Switzer JA, Demaerschalk BM, Xie J, Fan L, Villa KF, Wu EQ. Cost-effectiveness of hub-and-spoke telestroke networks for the management of acute ischemic stroke from the hospitals' perspectives. *Circ Cardiovasc Qual Outcomes*. 2013;6:18–26. doi: 10.1161/CIRCOUTCOMES.112.967125.

KEY WORDS: brain ischemia ■ neuroprotection ■ prognosis ■ reperfusion ■ stroke

Stroke
Journal of the American Heart Association

Combining Neuroprotection With Endovascular Treatment of Acute Stroke: Is There Hope?

Michael Tymianski

Stroke. published online May 9, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628