Review

Now that the door is open: an update on ischemic stroke pharmacotherapeutics for the neurointerventionalist

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SUMMARY

The last 10 years have seen a major shift in management of large vessel ischemic stroke with changes towards ever-expanding use of reperfusion therapies (intravenous thrombolysis and mechanical thrombectomy). These strategies ‘open the door’ to acute therapeutics for ischemic tissue, and we should investigate novel therapeutic approaches to enhance survival of recently reperfused brain. Key insights into new approaches have been provided through translational research models and preclinical paradigms, and through detailed research on ischemic mechanisms. Additional recent clinical trials offer exciting salves into this new strategy of pairing reperfusion with neuroprotective therapy. This pairing strategy can be employed using drugs that have shown neuroprotective efficacy; neurointerventionalists can administer these during or immediately after reperfusion therapy. This represents a crucial moment when we emphasize reperfusion, and have the technological capability along with the clinical trial experience to lead the way in multiprong approaches to stroke treatment.

INTRODUCTION

Acute ischemic stroke remains the fifth most common cause of death in the United States.1 Currently, the central aim of acute treatment is reperfusion via intravenous thrombolysis and mechanical thrombectomy. With significant limitations, only about 12% of patients receive treatment with tissue plasminogen activator,2 while about 15% are eligible for thrombectomy (though this number may be rising due to expanded eligibility criteria).3 Approximately half of patients receiving reperfusion treatments still have unfavorable outcomes with significant disability or death.4 Hence, there is a need for additional therapeutic strategies.

Neuroprotective/neuroreparative pharmacotherapies have aimed at preventing excitotoxicity, neutralizing free generation, and inhibiting apoptosis to efficacy at the bedside despite many in vitro and in vivo scientific successes.15 However, our understanding of the weaknesses of animal models in translational research has evolved significantly from these studies. Initially, efforts such as the Stroke Treatment Academic Industry Roundtable (STAIR) meetings were successful in providing evidence-based guidance on how to improve stroke therapeutic research.16 Despite, recommendations such as randomization, evaluation of both sexes, types of damage-impeding and injury-reversing therapeutics will only grow. In this setting, engagement of neurointerventionalists will be paramount.

Therefore, our aim in this review was to provide a primer for the clinical neurointerventionalist on current and upcoming neuroprotective therapeutic research. We will provide a brief overview of pathophysiology and research history, and describe recent developments in translational pathways for drugs. We will highlight one of the modern seminal clinical trials combining reperfusion and pharmacotherapy to demonstrate trial successes while highlighting design opportunities for future trials. Finally, we will provide a tailored update on the most ‘shovel-ready’ drugs currently in, or planned for, trials. Rather than provide a comprehensive summary of all neuroprotective agents under study, we aim to provide the clinical neurointerventionalist with the tools and knowledge needed to navigate this new frontier.

STROKE PATHOPHYSIOLOGY AND HISTORY OF THERAPEUTICS

Ischemia causes cell death by multiple mechanisms, including excitotoxicity, oxidative stress, glutathione loss, and mitochondrial damage.8 Furthermore, reperfusion itself can cause hemorrhagic transformation due to upregulation of lipid peroxidation, endothelial damage, cell organelle damage, autophagy and inflammatory mechanisms.9 With widespread use of thrombectomy, recent clot registry studies have reported an increase in proinflammatory molecules and helper T cells, with a decrease in neuroprotectant molecules.10–14 Understanding these pathways supports the role for neuroprotectant anti-inflammatory strategies to target multiple sites in the neurovascular unit. 'Neuroprotection for stroke' research was popularized with animal models beginning in the 1970s, but there has been little translational advancement to efficacy at the bedside despite many in vitro and in vivo scientific successes.15 However, our understanding of the weaknesses of animal models in translational research has evolved significantly from these studies. Initially, efforts such as the Stroke Treatment Academic Industry Roundtable (STAIR) meetings were successful in providing evidence-based guidance on how to improve stroke therapeutic research.16 Despite, recommendations such as randomization, evaluation of both sexes, types of
animal models and others, no drug is currently widely marketed to reverse or prevent ischemic injury. This represents a continued failure to move from the bench to the bedside.

TRANSLATIONAL RESEARCH IN NEUROPROTECTION

While clinicians may not routinely consider the basic science of ischemia, many are familiar with failed clinical trials in stroke therapeutics. Showing preclinical promise in animal studies, many drugs such as NXY-059 and magnesium failed in clinical trials. Reasons for poor bench-to-bedside translation have included varying routes of administration (intravenous, intraperitoneal, and intra-arterial), varying times of administration (from 4 hours to 10 days post-stroke), different preclinical animal stroke models (transient, embolic, photothrombotic, and permanent occlusion), and failure to recanalize the occluded vessel. Building on organized efforts to improve stroke research (such as the STAIR meetings), there have been efforts in both Europe and in the USA to apply the principles of human clinical trial design to preclinical research in order to improve rigor and translational success.

The European Commission gathered stroke researchers from across Europe and founded the Multi-Centre Preclinical Animal Research Team (Multi-PART), while no pharmacological compounds were tested to determine the efficacy of Multi-PART workflows across laboratories, Multi-PART did sponsor a multicenter evaluation of MRI protocols used in experimental stroke, finding significant variability between facility scanners and a need for improved standardization.

In the USA, the National Institutes of Health (NIH) and National Institute of Neurological Diseases (NINDS) established the Stroke Pre-clinical Assessment Network (SPAN). Similar to a clinical trial network, SPAN encompasses: six blinded testing sites, a steering committee, external advisory board, and a coordinating center. Using the CONSORT clinical trial as a model, the initial stage of SPAN examined the ability of all testing sites to successfully implement SPAN standard operating procedures for animal models across multiple institutions; they showed an ability to adhere to standardized operating procedures and to disseminate, receive, catalog, and report large volumes of data in a blinded fashion. Following successful completion of this initial stage, SPAN has identified potential targets, which will be tested further in SPAN to determine those with the greatest potential in early phase clinical trials. Their initial results were presented at the 2023 International Stroke Conference. In testing six potential therapies, only one, uric acid, showed a statistically significant positive effect. In such a way, these translational efforts can improve preclinical rigor to focus clinical trial efforts on treatments most likely to succeed.

LESSONS FROM RECENT CLINICAL TRIALS: OPTIMIZING DESIGN

Recent clinical trials have provided important insights into current and future designs for trials marrying thrombectomy with neuroprotection. One major obstacle to these types of trial is the conflict between standard of care based metrics and need for consent. The need for informed consent is paramount; however, the inability of patients with a stroke to consent due to neurologic impairment combined with difficulties finding family/legal representatives prior to the initiation of thrombectomy pose a mounting challenge. This has already affected a number of neuroprotection studies. Trialists should consider this when designing timing of medication. For example, can the patient be enrolled and can a drug be administered after thrombectomy is complete? Is ‘community consent’ with exception from informed consent an option for these trials? Such an ethical question should be considered by governmental bodies and professional societies as more of these trials are attempted.

Another design consideration is interactivity between a trial drug and current standard of care therapies. This issue arose in the ESCAPE-NA1 trial, which evaluated nerinetide as an adjuvant to thrombectomy. ESCAPE-NA1 was a landmark trial in neuroprotection because the study design was rigorous and it faithfully replicated the preclinical trials; the ‘usual suspects’ causing discordance between preclinical and human models of brain ischemia were ameliorated, including selection bias, assessment bias, power, reproducibility, time window, and heterogeneous inclusion criteria. The subjects were balanced for age, sex, site of arterial occlusion, baseline National Institutes of Health Stroke Scale and ASPECT scores, clinical site, and method of thrombectomy devices. The trial included patients undergoing both thrombolytic and thrombectomy treatments, which are the current standards of care.

Nerinetide is a synthetic eicosapeptide that interacts with postsynaptic density protein (PSD-95), disrupting the interactions between N-methyl-D-aspartate glutamate receptors and excitotoxic signaling proteins. The trial enrolled 1105 patients, who were randomly assigned to placebo versus nerinetide (2.6 mg/kg over 10 min) administered after thrombectomy, irrespective of whether the patient received alteplase. The trial found no significant difference in reducing disability; 61.4% of the patients in the nerinetide group (adjusted RR=1.04, 95% CI 0.96 to 1.14, P=0.35) and 59.2% of the patients in the placebo group achieved a modified Rankin Scale (mRS) score of 0–2 at 90 days. However, in the stratum of patients who received netinetide but no alteplase there was a 7.5% absolute risk reduction in mortality at 90 days and a halving of hazard ratio (adjusted RR=1.18, 95% CI 1.01 to 1.38). On pharmacokinetic analysis, this subgroup of patients also had higher netinetide plasma concentration than the patients who received alteplase. The putative mechanism of this effect is cleavage of amino acid sequences of nerinetide by plasmin, which is generated from plasminogen by alteplase, rendering the plasma concentration of nerinetide subtherapeutic. Alteplase was administered to 60.1% of the patients in the netinetide group. While the primary outcome results ‘failed’ overall, the drug–drug interaction was clearly evident, and has had an impact on the design of the upcoming ESCAPE-NEXT and FRONTIER trials.

ESCAPE-NEXT has a design like ESCAPE-NA1 except that nerinetide is administered only to patients who do not receive alteplase. The FRONTIER trial is also a randomized, double-blind, placebo-controlled trial designed to test the efficacy and safety of nerinetide in a prehospital setting. This knowledge gained is shaping these upcoming trials for nerinetide, and will also affect the design strategies for future combined thrombolysis/thrombectomy drug trials.

In parallel with our developing understanding of possible therapeutic agents and their interactions, we must also consider improvements in outcome monitoring. Traditional clinical stroke trials have used the mRS to assess clinical outcomes. While simple and easy to assess, this scale represents a relatively crude and undetailed assessment of functional outcomes. Future clinical trial design should include more in-depth analysis of cognitive outcomes, using a utility-weighted mRS, the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and Hachinski Ischemic Scale. Additionally, use of neuropsychological batteries and assessment of physical, social, and cognitive domains using quality of life measurement tools.
should also be incorporated into patient outcome analysis. These tools provide better sensitivity to identify improved patient outcomes, and they also more accurately assess outcomes and day-to-day neurocognitive functions that substantially affect patient quality of life. Finally, as reperfusion has shown such profound improvements in mRS scores, adjunctive pharmacotherapies may show more significant gains in cognitive and quality of life measurements.

COMBINING REPERFUSION AND REPARATIVE STRATEGIES: FRAMEWORK FOR THE FUTURE

Mechanical thrombectomy provides flow restoration, but can generate deleterious effects through the production of reactive oxygen species, furthering triggering apoptotic mechanisms and increasing cerebral edema. Therefore, continued efforts to pair reperfusion with neuroprotective drug administration are paramount. Currently, there are more than 100 trials listed on www.clinicaltrials.gov evaluating neuroprotection and stroke. Indeed, many of them use intra-arterial drug administration as part of their protocol. However, as stated, an exhaustive summary of all currently explored neuroprotective agents is beyond the scope of this review. Rather, we describe some of the most well-recognized and well-published therapies studied in combination with thrombectomy (figure 1). As mentioned, nerinetide remains one of the most promising adjuncts to reperfusion to-date, and its currently planned trials will be critical in showing more clear evidence of efficacy. In addition to nerinetide, magnesium sulfate has the potential to promote vasodilation, increase

Figure 1  Illustration profiling therapeutic adjuvants to reperfusion currently under study. These include vasodilators (such as verapamil (A) and magnesium (B)), hypothermia (C), 3K3A-APC (D), nerinetide (E), and ApTOLL (F).
cerebral blood flow, and inhibit excitatory and inflammatory mechanisms following ischemic stroke. While this has been trialed systemically, \(^{43}\) selective intra-arterial infusion has been proved to be effective in decreasing stroke size and improving outcomes in preclinical models. \(^{44}\) Unfortunately, recent clinical trials evaluating intra-arterial administration of magnesium sulfate in this setting have been beset by low recruitment (clinicaltrials.gov NCT01502761). Verapamil also acts as a vasodilator (enhancing cerebral blood flow) and a calcium channel blocker (decreased post-stroke excitotoxicity), and has also been shown to be efficacious in preclinical models, \(^{27}\) and safe during intra-arterial delivery at the time of thrombectomy. \(^{46}\) Efficacy in clinical trials has not yet been shown, but this study identifies another potential adjunctive intra-arterial treatment at the time of revascularization.

Hypothermia has long been discussed for its neuroprotective benefits, including a decrease in cerebral metabolic activity, inflammation, and apoptosis, but is frequently hampered by severe systemic side effects. Selective cerebral hypothermia, however, holds promise in local control of hypothermia delivered directly to the affected cerebral tissue, while limiting its systemic side effects. Early pilot studies have identified safety and feasibility in both preclinical \(^{47}\) and phase I clinical trials. \(^{48}\)

ApTOLL is a toll-like receptor 4 antagonist that interferes with innate immune response, and leads to tissue damage. It was initially studied as a therapeutic agent in acute ischemic stroke. \(^{49–51}\) Most recently, in a randomized double-blind, placebo-controlled phase IIa study, \(^{52}\) investigators determined two most effective doses of ApTOLL, and then compared them with placebo, finding that 0.2 mg/kg reduced mortality from 16.98% to 4.76%. These results were presented at the 2023 International Stroke Conference.

Finally, 3K3A-APC, a recombinant variant of human activated protein C, has been shown to reduce neurologic injury and to promote vascular integrity in preclinical models. \(^{52–53}\) The RHAPSODY trial, a randomized phase II dose–response study, demonstrated tolerable dosing with a trend toward improved post-reperfusion therapy hemorrhage rates. \(^{54}\) RHAPSODY-2, a multicenter phase III trial, is currently being planned, and will provide subgroup analyses on thrombectomy combined with drug-administration of 3K3A-APC. Although these represent only a small group of the many potential therapeutics currently planned for study, they are examples of the many different pathophysiologic ‘entry points’ for potential therapeutics. Furthermore, they exemplify that development of neuroprotective adjuncts to thrombectomy is not many years away, but truly ‘around the corner’.

CONCLUSIONS

Much of the latest clinical development in large vessel ischemic stroke has focused on the advancement of acute reperfusion as a gold standard. However, now that the ‘door is open’ we, as neurointerventionalists, should play a leading role in ‘what goes through it’. Having previously led trials in mechanical thrombectomy, neurointerventionalists must play a pivotal role in continued development of therapeutics for ischemic stroke by working with basic scientists in vital translational work, and by taking lead roles in trial design and execution. In addition, neurointerventionalists must not sacrifice incremental clinical success for an ‘all or nothing’ single drug approach. Given the complexity of the disease we battle, polypharmacotherapy is a likely end result. With such engagement and leadership, we can continue to move the goalposts in treatment of large vessel ischemic stroke.

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Contributors All authors (JF, SP, MI, MM, CM, MeM, KRP, DD) provided significant contribution to the research and drafting of this manuscript. Each author was responsible for drafting at least one section. All authors provided editing input for finalization of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

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