Emerging Therapies for Acute Ischemic Stroke
New Therapies on Trial
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The development of additional effective therapies for acute ischemic stroke remains a challenging but critical endeavor. Intravenous recombinant tissue plasminogen activator (rtPA) initiated within 3 hours of stroke onset remains the only approved and validated therapy for acute ischemic stroke, and regulatory approval has expanded recently. Many other therapies have been evaluated, and these trials have either been inconclusive or negative. These acute stroke trials do provide valuable information concerning how to implement future trials and some glimmers of hope about existing data. Some of the lessons learned from prior acute stroke trials that will help to guide future trials are outlined below. The two fundamental approaches to the development of acute stroke therapy remain reperfusion and neuroprotection. This short review will focus on the current status of both approaches and how they might be combined, hopefully in the near future.

Negative acute stroke treatment trials may be explained by the following:

1. The agents evaluated in clinical trials may not have been adequately tested in preclinical studies to provide robust confirmation of efficacy in appropriate animal models.
2. Side effects precluded adequate drug assessment or did not allow use of adequate drug concentrations.
3. Because of macro-occlusions and, perhaps, micro-occlusions, the drug did not penetrate into or beyond the penumbral tissue in adequate concentrations.
4. Trials included patients not appropriate for the purported mechanism of action of the drug being tested.
5. Patients were included too late after stroke onset to allow for adequate assessment of the drug’s efficacy, and imaging studies were not done to identify patients with appropriate tissue for treatment.
6. Trials have been inadequately powered to detect modest treatment effects.
7. Trials included too many patients with mild or very severe deficits in whom treatment effects are likely difficult to assess with currently used outcome measures.
8. The single primary outcome measure chosen to assess drug efficacy may not be sensitive enough to detect modest treatment effects.

Currently, intravenous rtPA within 3 hours of stroke onset is used in only a very small percentage of acute ischemic stroke patients at most centers, although in a few locations, 5% to 10% of such patients receive this intervention. From published reports, the efficacy and safety of intravenous rtPA when used in routine clinical practice seems to be comparable to that reported in controlled clinical trials. An important challenge remains how to increase the percentage of patients treated within the 3-hour window. This will require additional physician and patient educational efforts, as well as enhancement of healthcare delivery systems. Not only does the percentage of patients treated with intravenous rtPA needs to be maximized within 3 hours from stroke onset, it is also critical that physicians try to initiate treatment as soon as possible and not wait until the end of 3-hour window. A reanalysis of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA study data confirmed that treatment earlier in the 3-hour window is clearly more beneficial than treatment later. A combined analysis of the NINDS, European Cooperative Acute Stroke Study (ECASS), and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trials emphasized this point. This combined analysis demonstrated that patients treated within 90 minutes of stroke onset had an odds ratio of 2.83 (95% confidence interval, 1.77 to 4.53) of achieving a modified Rankin outcome of 0 to 1, whereas patients treated from 91 to 180 minutes had an odds ratio of 1.53 (95% CI, 1.11 to 2.11). Interestingly, even patients treated from 181 to 270 minutes from stroke onset were shown to benefit from intravenous rtPA (odds ratio, 1.40; 95% confidence interval, 1.06 to 1.85). It is clear, however, that the absolute benefit with intravenous rtPA initiated beyond 90 minutes is relatively modest, with an absolute treatment effect of 5% to 6% and a number needed to treat for one beneficial outcome approaching 20.

Additional goals for the expanded use of thrombolysis in acute stroke will be to establish reperfusion more rapidly and to extend the therapeutic time window for effective reperfusion therapy. Several approaches to result in more rapid reperfusion are under investigation. One approach is to use endovascular methodologies such as mechanical clot retrieval devices, devices to dissolve rapidly and suction intravascular clots, and intra-arterial ultrasound devices in conjunction with intra-arterial thrombolysis. Another approach under preliminary investigation is to combine transcranial ultrasound with intravenous rtPA, because preliminary data suggest that this combination may lead to more rapid reperfusion. Combining initial intravenous rtPA with intra-arterial rtPA given later is also being investigated to determine if delayed intra-arterial therapy after initial lower-dose intravenous rtPA can be used...
safely and effectively if the initial intravenous therapy does not induce successful reperfusion. Enhancing reperfusion by combining intravenous or intra-arterial thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor abciximab is also under study. The rationale is that platelet activation may be enhanced by plasminogen activators, but platelet aggregation, which is critical for clot formation, can be effectively inhibited by blocking the IIb/IIIa receptor. Abciximab, a long-acting IIb/IIIa inhibitor, was investigated in preliminary studies primarily focused on safety in combination with intravenous reteplase. Eptifibatide, a shorter acting agent, has been studied in combination with intra-arterial thrombolysis, and a dose-escalation study of eptifibatide and low-dose intravenous rtPA is underway (A. Pancioli, MD, unpublished data, 2002). Interestingly, abciximab has also been studied alone in acute ischemic stroke. Two safety studies demonstrated a reasonable safety profile, and the second study provided a hint of efficacy. A larger efficacy trial is apparently being designed.

A potentially promising approach to extending the therapeutic time window for both thrombolytic and neuroprotective drugs is the use of imaging techniques to identify patients with potentially salvageable ischemic tissue hours after stroke onset. Currently, diffusion-perfusion MRI is the imaging technology most widely employed for identifying potentially salvageable ischemic tissue. Early after stroke onset, the volume of the perfusion MRI (PWI) abnormality depicting reduced perfusion in the brain’s microvasculature is typically substantially larger than the region of diffusion MRI (DWI) abnormality, which depicts ischemic brain regions of high energy metabolism failure where ion homeostasis has been lost. The region of PWI abnormality with a normal DWI is termed the diffusion-perfusion mismatch and seems to provide an approximation of the potentially salvageable ischemic zone, ie, the ischemic penumbra. The DWI-PWI mismatch is clearly only an approximation of the ischemic penumbra because some of the abnormal PWI region is only oligemic and will not go onto infarction, and shortly after stroke onset some of the DWI abnormality is potentially reversible. Nevertheless, the presence of a DWI-PWI mismatch in open-label studies seems to identify stroke patients up to 6 hours after onset who are more likely to improve with intravenous rtPA than patients without a mismatch. The use of DWI-PWI to identify patients for inclusion/exclusion in intravenous thrombolysis trials has begun. In Australia, the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) is underway to determine if patients with a DWI/PWI mismatch treated with intravenous rtPA 3 to 6 hours after stroke onset have a reduction of final infarct size and improved clinical outcome compared with placebo-treated group. The desmoplastic in acute stroke (DIAS) trial is using the presence of a DWI/PWI mismatch up to 9 hours after stroke onset to randomize patients in a Phase II B dose-escalation safety study of bat rtPA (W. Soehngen, MD, unpublished data, 2002). Another imaging modality that may be potentially useful for detecting the presence of potentially salvageable ischemic tissue shortly after stroke onset is perfusion computed tomography. A preliminary study demonstrated that determining cerebral blood flow and cerebral blood volume levels with perfusion computed tomography early after ischemic stroke onset seemed to distinguish potentially salvageable ischemic tissue from tissue already irreversibly damaged. This observation will have to be validated in a larger sample size and be related to delayed infarct volume and clinical outcome before clinical trials can be implemented.

The development of neuroprotective therapies for acute ischemic stroke is based on the concept of impeding the cascade of ischemic injury induced by focal disruption of blood flow to the brain. Animal studies have shown convincingly that neuroprotective drugs given after stroke onset can reduce infarct size and improve functional outcome measures. Unfortunately, modeling has not been ideal. Initiation of pharmacotherapy has, in most experiments, not been sufficiently delayed to mimic the clinical setting. Experimental drug administration has often followed early effective reperfusion, which is rare clinically. Penetration and measurement of drug concentrations within the ischemic region have, in most cases, not been measured rigorously. The animal data have not yet been translated into clinical trials demonstrating significant treatment efficacy.

Most prior neuroprotection trials had serious flaws that precluded adequate assessment of the drug being studied, and the lessons learned from these trials reflect many of the problems with prior neuroprotection trials. The concept of neuroprotection should not be abandoned, but refined. Monotherapy neuroprotection drug development might be proven to be effective for selected acute ischemic stroke patients. The drugs to be evaluated in clinical trials will need to be rigorously tested in preclinical stroke models designed to investigate dose ranges, time window of treatment effect, histological and functional outcomes, sustained treatment effects, and toxicology.

Failure to provide evidence of safety, efficacy, and a prolonged treatment effect in animals will likely predict failure in clinical trials. Unfortunately, the converse observation of efficacy in animals may not predict success in patients. Human neuroprotection trials need to be well designed and performed to have a reasonable chance for success. The studies should be adequately powered to detect modest absolute benefits in comparison with placebo, enroll patients as soon as possible after stroke onset, target patients of moderate severity, and use outcome measures with the broadest chance to detect meaningful treatment effects.

A number of new neuroprotection trials are now underway or will begin shortly. These include studies of the antioxidant, Ebselen, the spin trap agent, NXY-059, magnesium, a noncompetitive NMDA antagonist, the AMPA antagonist, YM872, the serotonin antagonists, Repinotan and SUN N4057, and the astrocye inhibitor, ONO-2506. Hopefully, one or more of these drugs or others will demonstrate treatment efficacy.

The basic pathophysiology of acute ischemic stroke can be summarized simplistically as localized vascular occlusion inducing a complex array of cellular consequences, leading to irreversible tissue injury and ultimately clinically measurable impairment. It is therefore logical to conclude that maximizing therapy will require combinations of different therapies. The benefits of early reperfusion are clear, and combined reperfusion strategies such as the use of intravenous thrombolysis, intra-arterial thrombolysis, mechanical thrombolysis, and platelet glycoprotein IIb/IIIa antagonists to maximize reperfusion are potentially attractive approaches. Combining thrombolysis with neuroprotection to target both the vascular and cellular consequences of focal brain ische-
mia theoretically should provide greater benefits than either approach alone.\textsuperscript{30} Neuroprotection initiated before or concomitant with thrombolysis might extend the time window and extent of therapeutic effects of thrombolysis by delaying the evolution of salvageable ischemic tissue toward irreversible injury. Perhaps more importantly, thrombolysis given before or with neuroprotection will likely enhance the delivery of neuroprotective drugs to ischemic brain, presumably enhancing the likelihood of tissue salvage by the neuroprotective drug. Endovascular reperfusion techniques could even allow bypassing occlusions to administer neuroprotective agents. Penetration into and beyond major arterial trunk occlusions with the guide catheter is an initial step in most current intra-arterial protocols. A neuroprotective drug could be injected beyond the occlusion at that time to maximize drug concentrations within the entire ischemic region.\textsuperscript{31}

Another potential synergistic effect of thrombolysis and neuroprotection would be the use of neuroprotectants designed to ameliorate reperfusion injury after successful thrombolysis-induced reperfusion. An initial pilot study combining Lubeluzole with rtPA demonstrated the feasibility of combining the intravenous thrombolysis and neuroprotection approach.\textsuperscript{32} Currently, the AMPA antagonist YM872 is being studied in conjunction with intravenous rtPA initiated within 3 hours of stroke onset.\textsuperscript{25} Other combination trials combining neuroprotective drugs that affect different components of the ischemic cascade or that combine neuroprotection and/or thrombolysis with manipulation of physiological variables such as temperature need to be considered. The future of acute stroke therapy trials will be to move increasingly in the direction of more sophisticated and complex multimodality trials. The move to multimodality trials will require careful planning and cooperation among industry, investigators, centralized granting agencies, and regulatory bodies.

References


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