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Developing Acute Stroke Therapy

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ÖZET

Akut iskemik inme için tedavi geliştirilmesi hem zordur hem de uğraş gerektirir. Uzun yıllardan beri akut inme tedavisine iki ana yoldan yaklaşabileceği düşünülmüştür; perfüzyonu yeniden sağlamak ve iskeminin etkilerini hücresel seviyede önlemeye çalışarak, iskemik hasarın dokudaki sonuçlarını iyileştirmek. Akut iskemik inmede birçok klinik çalışma yürütülmüş ve bu yıkıcı bozukluk için tedavi yöntem ve araçlarımızı genişletecek olan geleceğe yönelik çabaları etkilemesi gereken birçok önemli dersler çıkarılmıştır. Ek olarak, akut iskemik beyin hasarının patofizyolojisiyle ilgili, tedaviye yaklaşım konusunda kavrama gücümüzü geliştiren önemli ilerlemeler kaydedilmiştir. Halihazırda, inmenin başlangıcından sonraki 3 saat içinde başlanan t-pa, kanıtlanmış etkinliği olan, resmi olarak onaylanmış tek tedavidir. Birçok t-pa çalışmasının son dönemde yapılan kombine analizi, tedavinin inmenin başlangıcından sonraki 90 dakika içinde başlaması halinde, olumlu bir sonuç elde etmek için tedavi edilmesi gereken hasta sayısı yaklaşık 6'dır ve orkaya çıkan potansiyel faydalar oldukça doğrudur.

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INTRODUCTION

The development of therapies for acute ischemic stroke remains difficult and challenging. It has been appreciated for many years that acute stroke therapy can be approached from two primary directions, establishing reperfusion and ameliorating the tissue consequences of ischemic injury by attempting to impede the effects of ischemia at a cellular level. Many clinical trials in acute ischemic stroke have been conducted and many important lessons have been learned that should impact upon future efforts to expand our armamentarium for this devastating disorder[1]. Additionally, substantial advances have occurred regarding the pathophysiology of acute ischemic brain injury, providing an enhanced comprehension of how to approach treatment.

Currently, t-pa initiated within 3 hours after stroke onset remains the only treatment with proven efficacy and regulatory approval[2]. A recent combined analysis of several t-pa trials demonstrated that when treatment is initiated within 90 minutes of stroke onset, the potential benefits

are quite robust with a number needed to treat for one favorable outcome of approximately 6[3]. A significant treatment effect is also present for treatment initiated between 90-180 minutes and even for treatment started between 180-270 minutes after stroke onset, but the magnitude of the benefit is much reduced at these later times with the number needed to treat being slightly less and more than 20 during the two time epochs. The combined analysis reinforces the contention that as time passes after stroke onset less potentially salvageable ischemic tissue persists and the likelihood of improving outcome is reduced. However, in clinical practice t-pa is rarely initiated within 90 minutes after stroke onset, so efforts must be made to enhance treatment effects at later time points.

In the four t-pa trials incorporated in the combined analysis, the NINDS trial, ECASS I&II and the ATLANTIS trial patients were included based upon clinical criteria and exclusion of hemorrhage on CT or extensive early infarcts in the ECASS trials. The identification of patients with potentially salvageable ischemic tissue, i.e. the ischemic penumbra could help in extending the therapeutic time window for successful i.v. thrombolysis and to provide a more robust treatment effect. Currently, the most advanced methodology for approximating the ischemic penumbra is diffusion MRI (DWI) and perfusion MRI (PWI)[4]. Early after stroke onset a large percentage of ischemic stroke patients will demonstrate a mismatch of the abnormal PWI and DWI volumes and it is thought that the region of abnormal PWI where DWI is normal approximates the ischemic penumbra[5]. Several case series demonstrated that patients with a DWI/PWI mismatch treated with t-pa are more likely to have a favorable outcome even when therapy is initiated more than 3 hours after stroke onset[6,7]. As might be expected, patients demonstrating early reductions in the volume of PWI abnormality are more likely to benefit from t-pa therapy[8]. The utility of DWI and PWI for identifying suitable patients for thrombolytic therapy beyond 3 hours and also assessing a therapeutic response is now beginning to be tested in clinical trials. In the Desmoteplase in Acute Stroke trial (DIAS), a t-pa variant derived from bat saliva was given to stroke patients between 3-9 hours after stroke onset, if they had a DWI/PWI mismatch. In the initial part of the study that employed fixed and relatively high doses of desmoteplase, an unacceptably high rate of intracerebral hemorrhage occurred. However, when weight-adjusted dosing was used in a dose escalation paradigm, it was observed that desmoteplase induced a significant reduction in the abnormal perfusion volume at the highest dose employed with an effect on the evolution of ischemic lesion volume and clinical outcome[9]. The sample size of 15 patients per group for the dose escalation study was quite small, but the study is now being replicated and expansion to a larger group is being planned. Separate Australian and American studies of t-pa up to 6 hours after stroke onset are ongoing also exploring the utility of a DWI/PWI mismatch for identifying patients more likely to respond to delayed thrombolysis.

The DWI/PWI mismatch concept must be viewed as an approximation of the ischemic penumbra for several reasons[10]. First, it is now abundantly clear from animal and human observations that abnormalities of the apparent diffusion coefficient (ADC) that lead to the appearance of hyperintense regions on DWI are potentially reversible and not synonymous with irreversible ischemic injury. In animal stroke models, early reperfusion can reverse ADC abnormalities, but secondary declines occur later on even with sustained reperfusion[11]. Similarly in stroke patients, ADC reversals were observed after intra-arterial (i.a.) and intravenous reperfusion with the potential for delayed ADC abnormalities[12]. In one series, the development of late ADC abnormalities after normalization tended to predict a worse clinical outcome[13]. This observation will need to be confirmed in a larger series of patients. Predicting where ADC normalization is most likely to occur will play an important role in expanding the DWI/PWI mismatch concept for identifying the ischemic penumbra. Preliminary animal experiments suggest that the severity of initial ADC decline and reduction of cerebral blood flow (CBF) can begin to classify the propensity of ADC declines to reverse with reperfusion[14]. Further experiments in animals and then humans will be needed to develop probability maps for the potential of ADC abnormalities to reverse at a particular time point. A second limitation of the DWI/PWI mismatch concept is that some portions of the perfusion abnormality are only mildly affected and will not develop infarction, the oligemic region[15]. The oligemc region can likely be identified by quantifying CBF with more advanced perfusion MRI techniques such as with arterial spin-labeling perfusion MRI. Quantitative CBF maps will also enhance the capability to distinguish potentially reversible and irreversibly injured ADC declines and to identify abnormal perfusion regions with normal ADC at greater risk for infarction. In the future we can anticipate that quantitative

ADC and CBF maps will reliably identify ischemic tissue that is likely still salvageable at a particular time point after stroke onset when the patient presents for clinical and imaging assessment. Additionally, the use of susceptibility-weighted imaging can reliably detect evidence of acute intracerebral bleeding and serve as an exclusion for the use of thrombolytic therapy[16]. The presence of old microhemorrhages on susceptibility-weighted MRI may identify patients at increased risk for t-pa-related acute hemorrhages and be a relative contraindication for the use of t-pa.

A major problem with advanced MRI techniques is the relative lack of availability. CT scanning is much more widely available and with ultrafast CT machines perfusion CT and CT angiography can be used to potentially assess patients who might benefit from delayed thrombolysis. With CT angiography large and medium sized vessels can be seen readily and vascular occlusions identified[17]. Such patients are the apparent target for thrombolytic therapy designed to induce reperfusion. CT perfusion after the injection of an i.v. contrast agent can provide information about the existence of the ischemic penumbra. Preliminary information suggests that when cerebral blood volume (CBV) collapses below a critical threshold irreversible ischemic injury has occurred[18]. Relative CBF can be derived from contrast perfusion CT and combining the CBF and CBV maps can generate a mismatch of region where CBF values are below a critical threshold of abnormality but CBV values have not yet collapsed[19]. This mismatch region may represent in part the ischemic penumbra, but further validation is needed to confirm this hypothesis. One recent study performed both perfusion CT and DWI/PWI in close temporal relationship[20]. The study demonstrated that both techniques could be used to predict the fate of ischemic tissue with comparable reliability. The source images for CT angiography can also provide information about CBV and its collapse, but not with the same precision as perfusion CT. With the validation of CT techniques for approximating the ischemic penumbra, a widely available tool for designing future thrombolytic trials and extending the therapeutic time window will become available.

In addition to imaging-guided identification of patients likely to benefit from delayed thrombolysis, another important advance for the future of brain reperfusion therapy is procedure-related reperfusion. Intra-arterial thrombolysis is presumed by many clinicians and interventionalists to be an effective stroke therapy. Unfortunately, robust evidence to support this perception is not available. One trial of i.a. thrombolysis, the PROACT II study, does provide a modicum of supportive evidence[21]. In this study, ProUrokinase, a recombinant molecule related to the widely used Urokinase was compared to placebo therapy in 180 patients (2:1 randomization) with an angiographically confirmed middle cerebral artery occlusion. Therapy was initiated within 6 hours in quite severely affected stroke patients and follow up angiography performed to document recanalization effects. Two hours after therapy began, the partial or complete recanalization rate was 67% in the treated group and 18% in the placebo group. At 3 months, 40% of the ProUrokinase patients had a favorable outcome, prespecified as Rankin 0-2, while only 25% of the placebo patients achieved this outcome ($p=0.043$). The symptomatic intracerebral hemorrhage rate was 10.2% in the ProUrokinase group and 1.8% in the placebo group, a concerning difference that did not achieve statistical significance because of the small patient numbers. Regulatory approval in the United States was not granted based upon this small trial and a required further study was never performed. Currently, i.a. t-pa is used by some groups for treating stroke patients beyond 3 hours based upon variable criteria for initiating treatment and with doses based upon local preference. Standardization of i.a. t-pa therapy based upon clinical trial data would be useful, but apparently no such trials are ongoing. One approach to i.a. t-pa therapy is being evaluated in clinical trial, combining early i.v. t-pa with i.a. therapy later on in patients who do not respond to the initial therapy and who have a persistent, angiographically confirmed arterial occlusion[22]. A preliminary study suggested that the combination was relatively safe but did not appear to confer additional benefit over i.v. t-pa alone.

The use of mechanical devices to establish reperfusion is being explored by several companies and investigators. A noncontrolled study with a corkscrew device in patients treated up to 8 hours after stroke onset was reported recently and demonstrated that adequate reperfusion could be established in approximately 50% of the treated patients[23]. In two patients, the device punctured an artery. The clinical benefits could not truly be assessed without a control group and such a trial is being initiated. For both i.a. thrombolysis and mechanical clot retrieval devices identifying patients more likely to respond to reperfusion at delayed time points with MRI or CT techniques will be critical because just establishing reperfusion that is not nourishing is unlikely to confer clinical benefit.

Neuroprotection as an acute stroke therapy remains an unfilled concept. Despite numerous phase II and phase III trials of a plethora of neuroprotective agents directed at many aspects of the ischemic cascade no neuroprotective has demonstrated clear evidence of clinical efficacy[24]. There are numerous reasons why the neuroprotective drugs have failed, as outlined in the table. A major reason for these failed neuroprotective trials is likely the late time window for patient inclusion, as the trials typically had a 6-hour time window for inclusion. This time window led to inclusion of many patients between 5 and 6 hours after stroke onset when potential treatment effects appear to be minimal at best in patients selected upon clinical criteria alone based on the combined t-pa analysis. Many of the previous neuroprotective trials were underpowered for detecting modest, absolute treatment effects of 3-5%. Based upon these two considerations and the others outlined in the table, it may be reasonable to conclude that the neuroprotection hypothesis has not been adequately tested and that some of the drugs evaluated previously might actually have modest benefits that could be identified in adequately designed and conducted clinical trials. Currently, there are several neuroprotective drugs in advanced clinical trials and the designs of these trials have implemented many of the lessons learned from the prior neuroprotection trials, especially the early enrollment of patients and adjusting the anticipated day 90 outcome to the baseline stroke severity.

What might be anticipated for the future of neuroprotection? It is clear that the cascade of ischemic injury is complex and multifaceted[25]. Therefore, impeding one aspect of the cascade is likely to have only modest benefit. Interrupting several components of the ischemic cascade simultaneously, preferably upstream and downstream mechanisms, could optimize potential reductions of ischemic injury[26]. This can be accomplished by employing two or more drugs, but the development of two unproven drugs will be complex from both a pharmacological and regulatory perspective. Another approach to targeting multiple aspects of the ischemic cascade is to use a single drug with several mechanisms of action. Drugs such as FK-506 and nicotinamide have these multiple effects and the attraction of a single agent with multiple effects is that drug interaction issues can be avoided. Ultimately, combining neuroprotection with reperfusion could maximize potential treatment effects. One approach to combination therapy would be to initiate neuroprotection first to impede the progression of the ischemic penumbra to irreversible injury and extend the potential time window when reperfusion therapy might be effective. The initiation of neuroprotective therapy prehospital is feasible and is being explored in the FASTMAG trial that is starting i.v. magnesium therapy in the ambulance within 2 hours after stroke onset[27]. Another approach to combining neuroprotective and reperfusion would be to give an agent targeted at reperfusion injury after successful mechanical or drug-induced reperfusion. With the employment of an intra-arterial device for mechanical or i.a. reperfusion, the neuroprotective agent could be instilled in the arterial territory of interest. The design of these combination neuroprotective and reperfusion trials will be complex and require extensive discussions among the sponsor, investigators and regulatory authorities.

Table 1. Potential reasons for failure of neuroprotective drug trials.

1. The drug does not have robust neuroprotective effects.
2. The time window of efficacy is too short to have clinical relevance.
3. The side effect profile precludes giving adequate doses
4. The trial was not adequately powered to detect modest treatment effects.
5. The time window for enrolling patients was too long.
6. Patients were included in the trial with stroke subtypes not likely to respond to the treatment being tested.
7. The trial included too many mild or severely affected patients, diluting signals of efficacy.
8. The drug tested does not work without initial reperfusion.

The development of acute stroke therapies has seen few successes and many failures. Much has been learned and the future appears bright, if careful attention is paid to the lessons from past trials and recent imaging and basic science advances. Hopefully, within the next few years several additional acute stroke therapies will become available.

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