Novel Therapies For Acute Ischemic Stroke

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Abstract

Acute ischemic stroke is one of the leading causes of mortality and chronic disability in the western world. Yet, despite the enormous socioeconomic burden that it imposes, therapies to combat AIS are not widely available. Moreover, revascularization of the ischemic tissue with tissue plasminogen activator, the only FDA-approved therapy for AIS, is hampered by a very narrow therapeutic time window and is only used in a minority of patients. Cerebral ischemia leads to brain damage caused by several pathologic mechanisms that can potentially be blocked by neuroprotective drugs that aim to salvage the ischemic penumbra. However, despite numerous clinical trials, no single drug candidate has proved efficacious in AIS. The current situation calls for novel therapeutic strategies to be used in acute ischemic stroke. This review surveys some of these novel and promising cutting edge therapies.

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The revolution in stroke therapy in recent years has changed the face of Neurology, and raised consciousness for the necessity of neurologic intensive care stroke units. With 750,000 new strokes per year in the United States and 15,000 in Israel, acute ischemic stroke is the third leading cause of mortality and the leading cause of chronic disability in the western world. Cerebral ischemia may result from a variety of causes that impair cerebral blood flow and lead to deprivation of both oxygen and glucose. When persistent and critical, such impairment in blood flow may eventually lead to neuronal death [1]. Cells at the center of the ischemic focus, the ischemic core, are especially vulnerable and may die within minutes of ischemic onset. The ischemic penumbra surrounding the core is an area of reduced perfusion in which cells are still viable [2]. Spontaneous reperfusion usually occurs in the set-up of cerebral ischemia [3]. While this process may reverse the ischemic damage when occurring early enough (e.g., transient ischemic attacks), it usually takes place much later when most penumbral cells have died.

Specific therapeutic options for acute stroke include reperfusion of the ischemic area in order to open occluded arteries, and neuroprotective drugs to protect cells in the ischemic penumbra from dying until the return of normal cerebral blood flow with spontaneous reperfusion. To date, thrombolysis with tissue plasminogen activator is the only therapy for acute stroke that is approved by the U.S. Food and Drug Administration [4]. tPA therapy is limited by a narrow therapeutic window of up to 4.5 hours from stroke onset, according to one recent meta-analysis [5]. Thus, tPA use is limited to less than 5% of stroke patients. Furthermore, while reperfusion of the occluded brain is associated with better outcome [5], systemically administered tPA achieves this goal in only about 30% of patients with success rates lower in large arteries than in smaller vessels [6]. Furthermore, neuroprotective therapy has been unsuccessful in clinical trials thus far and no drug is currently approved by the FDA for standard use in stroke patients [for review see ref. 7].

Clearly, this situation necessitates the implementation of novel therapeutic strategies in stroke and indeed a number of such therapies are being studied, as detailed below. This review presents some novel approaches to improve patient selection, increase the rate of recanalization, and increase the therapeutic time window of existing stroke therapies.

Improvement of patient selection for tPA

Several studies now explore whether improved patient selection by using magnetic resonance imaging-based criteria can reduce the risk of symptomatic intracranial hemorrhage and increase the therapeutic time window for tPA. MRI-based techniques such as diffusion-weighted and perfusion-weighted imaging have been advocated for penumbral demonstration in both animals and humans [8-10]. DWI MRI may be especially sensitive for detecting irreversible tissue damage, while PWI MRI reflects the perfusion deficits [10]. Most early scans in ischemia show a mismatch between the two methods with a larger PWI lesion and a smaller DWI lesion. By subtracting the DWI lesion volume from the PWI volume it is possible to predict penumbral volume [10]. Demonstrating the actual presence of a penumbra is suggested to be of the utmost importance since it may be used as a guide to whether thrombolytic or neuroprotective therapy should be used in a given patient [10-12]. Thus, if a penumbra cannot be demonstrated (i.e., the PWI lesion volume is smaller or equal to the DWI volume), then no salvageable tissue is thought to be present and no thrombolytic or neuroprotective agents should be given. Diffusion-perfusion mismatch on MRI delineates the ischemic penumbra and it is presumed that patients with such a mismatch would benefit from lytic drugs even beyond the accepted thera-

AIS = acute ischemic stroke
tPA = tissue plasminogen activator
FDA = Food and Drug Administration
DWI = diffusion weighted imaging
PWI = perfusion weighted imaging

peutic window of 4.5 hours. Preliminary reports from the DEFUSE study presented at the International Stroke Meeting in Orlando in February 2006 suggest that this is indeed the case in patients in which tPA is given up to 6 hours from symptom onset. MRI selection criteria are now also being studied for patient selection even when symptom onset is unclear, e.g., in people who awake from sleep with neurologic deficits and in whom the time of falling asleep was considered until very recently as the time of stroke onset (Kang DW, personal communication). Moreover, MRI criteria for patient selection can also be used for various stroke types, including arterial dissection where the presence of a persisting perfusion deficit is used to guide placement of endovascular stents to improve perfusion [13]. In conclusion, the use of MRI-based criteria can be utilized for tailoring the most appropriate therapy for individual patients.

Successful therapy in acute ischemic stroke depends on effective revascularization and on protecting penumbral brain tissue from death

Development of novel thrombolytic drugs for systemic use

Novel drugs with greater clot specificity may serve to reduce the complication rate associated with tPA and increase the therapeutic time window. Desmoteplase, which is manufactured from bat saliva, is one such agent. This drug is 1000 times more specific than tPA for fibrin binding [14,15]. The DIAS and DEDAS studies have shown that desmoteplase is safe in patients with acute ischemic stroke even when given at up to 9 hours after stroke onset [11,16]. Furthermore, these studies, which used MRI criteria of DWI-PWI mismatch for recruiting patients, show that the efficacy of achieving reperfusion is at least comparable to that of tPA. In the phase 2 dose-finding safety DIAS study [11], patients were recruited in two phases. In the earlier phase all 47 patients were given fixed doses of desmoteplase (up to 50 mg) vs. placebo. This stage was stopped after excessive symptomatic bleeds in the active therapy group (26.7%). In the second part of this study 57 patients were treated with a weight-adjusted dose at 62.5, 90 or 125 µg/kg. In this part the rate of sICH was only 6.7% (vs. 0% in placebo patients) and that of asymptomatic intracranial hemorrhage 25.3% (vs. 12.5% in the placebo group). Recruited patients in both groups had comparable National Institutes of Health Stroke Scale scores at baseline (median 12 in all groups) but placebo patients had insignificantly larger DWI lesions on their admission scan. Reperfusion rates at 4–8 hours from stroke onset in the higher dose tier of desmoteplase were 71.4% compared with 19.2% in the placebo group. Favorable outcome (modified Rankin Scale < 2) was found in 22% of placebo patients and in 60% of the higher dose desmoteplase patients. In the DEDAS phase 2 safety study [16], 37 patients were included between 3 and 9 hours from stroke onset. Patients had a median NIHSS score of 11 (12 in the placebo group and 9 in the desmoteplase group) and were treated at comparable time intervals from stroke onset but placebo patients had slightly larger DWI lesion volumes although there were no statistically significant differences between the groups. Reperfusion at 4–8 hours was observed in 37.5% of patients given placebo and in 53.3% of patients treated with desmoteplase at a dose of 125 µg/kg. Importantly, 60% of the desmoteplase patients achieved a good clinical outcome (mRS < 2) 90 days after stroke onset compared with only 25% of the placebo group. Moreover, no sICH was noted in either group but 12.5% of the placebo patients and 37.5% of the desmoteplase patients were noted to have small asymptomatic brain hemorrhages. No differences in allergic anaphylactic reactions or mortality rates were observed between the groups.

Taken together, the results of these promising phase 2 studies provide hope that an ongoing phase 3 randomized double-blind study will also be positive, providing a much needed solution for patients presenting at the emergency room at a time window that is beyond that of tPA.

Applying lytic drugs locally into the clot

Intraarterial application of thrombolytic drugs can minimize the total use of drugs used and can thus reduce side effects while increasing the chances of achieving reperfusion. In the randomized PROACT II study [17], 180 patients with middle cerebral artery occlusions on angiography 3–6 hours from stroke onset were recruited to receive either intraarterial heparin alone (n=59) or intraarterial heparin and pro-urokinase (n=121). The results show that 40% of the pro-urokinase patients had good outcomes (mRS < 2) 90 days post-stroke compared with only 25% of the controls (P = 0.04). Importantly, intraarterial administration of pro-urokinase 3–6 hours after the onset of stroke resulted in a reperfusion rate of 66% compared with only 18% in the placebo group (P < 0.001). Mortality rates were similar and sICH with neurologic deterioration within 24 hours occurred in 10% of pro-urokinase patients and 2% of control patients (P = 0.06) [17]. The authors concluded that despite an increased frequency of early sICH, the treatment still significantly improved clinical outcome at 90 days. However, the FDA did not approve the drug for routine use in clinical practice based on the results of this study. Despite this, intraarterial thrombolysis is currently widely used in tertiary centers with intraarterial capability for patients with acute proximal MCA, distal internal carotid artery or basilar occlusion when these patients present outside of the therapeutic time window for intravenous tPA. This practice is supported by evidence from non-randomized case series [18-22] and is increasingly being used all over the world. Furthermore, the PROACT

sICH = symptomatic intracranial hemorrhage

NIHSS = National Institutes of Health Stroke Scale
mRS = modified Rankin Scale
MCA = middle cerebral artery

trial only allowed for patients to be treated with pro-urokinase without any adjunct therapy such as mechanical clot lysis or administration of IIbIIIa antagonists. These therapies are used in practice and probably increase patency rates even further.

In conclusion, intraarterial thrombolysis seems to be appropriate mainly for severe hemispheric and basilar events that present after the 3 hour time window

Identification in real time of a significant penumbra by perfusion and diffusion MR imaging can increase the therapeutic window in acute ischemic stroke

Potentiating the lytic effects of tPA

Use of ultrasound energy has shown promise in increasing the chances of achieving reperfusion after tPA administration. The CLOTBUST study [6] recruited 126 patients with acute MCA occlusion within 3 hours of stroke onset and randomized to receive either tPA alone (n=63) or tPA with continuous insonation of the occluded vessel with a 2MHz transcranial Doppler probe (n=63). The results show that concomitant TCD increases the chances of reperfusion at 2 hours from 30% to 49%. This increase was associated with a greater likelihood of reaching independence (mRS < 1) 3 months after the index stroke (42% vs. 29%). The rates of sICH were 3% in both groups and there was no difference in mortality. A more recent study has shown that the addition of ultrasonographic contrast material potentiates these effects even further. Agitation of the contrast bubbles probably increases clot lysis [23]. Of the 111 patients in this study 80 (72%) had a proximal and 31 (28%) a distal MCA occlusion on TCD. The median NIHSS score was 18, denoting moderate to severe stroke. Patients received tPA alone, tPA with TCD alone, or tPA with TCD and microbubbles. Baseline parameters including stroke severity, time to treatment, and location of vessel occlusion were similar among groups. Recanalization rates at 2 hours were highest in the group treated with the bubbles (71% compared with 39% in the group that received only tPA), as were the rates for complete recanalization. The time to recanalization after tPA bolus was 26 ± 18 minutes in the tPA-TCD group and 19 ± 12 minutes in the tPA-TCD-bubbles group (P = 0.12). One of the patients receiving the bubbles had sICH (2.6%) compared with two of the patients treated with tPA alone (5.5%). More patients in the bubbles group improved more than 4 points on their NIHSS score 24 hours post-injury (55% vs. 31% and 41% respectively). Taken together, these two studies provide evidence that TCD-assisted clot fragmentation may improve patency rates after administration of tPA, hasten clot disintegration and improve outcome.

Ultrasound energy also appears to improve clot lysis when given together with intraarterial lytics directly into the artery using the EKOS system [24], as preliminary data from the ongoing IMS-2 trial show a higher and more rapid reperfusion rate associated with this treatment.

Boosting the lytic effects with ultrasound energy appears promising but this method is currently being studied in larger confirmatory trials and its routine use will await the results of such studies.

Development of novel devices for mechanical thrombectomy/ embolectomy

In recent years several new devices that allow for mechanical retrieval of the occluding thrombus/embolus have been introduced into clinical practice [25-28]. For instance, in the MERCI study [25] a corkscrew-like retrieval device was used in stroke patients presenting to the ER within 8 hours of stroke onset. This multicenter non-randomized study recruited 151 patients with a baseline NIH stroke scale of 20.1 ± 6.6. These patients were ineligible for thrombolysis and their condition was more severe than that of the usual patients entered in thrombolysis trials, with most patients having either proximal MCA or distal internal carotid artery lesions. Reperfusion was achieved in 48% of treated patients as compared with a projected rate of observed 18% in historical controls. sICH rates observed in the study were 7.8%, and 13% of patients had procedure-related complications. Only 28% of treated patients reached an excellent outcome of mRS < 2, with lower NIHSS scores, younger age, shorter procedure duration and successful recanalization identified as predictors of good outcome. While the percentage of patients achieving good outcome may seem somewhat low, it certainly is expected considering the stroke severity of patients in the study. The ongoing multi-MERCI study allows for treatment of patients with adjunctive therapy such as addition of IIbIIIa antagonists and stents. If this confirmatory study has a good outcome, it will provide neurologists with a valid alternative for reperfusion in patients who cannot receive thrombolytics.

In summary, these mechanical devices can be used in selected patients who are unable to receive lytic drugs and arrive at the hospital beyond the therapeutic window of 6 hours.

The use of desmoteplase, intraarterial thrombolysis, ultrasound energy, and endovascular mechanical devices may help to increase the rate of revascularization during acute stroke

Development of new methods for mechanical revascularization

Surprisingly, in great contrast to the cardiology field where percutaneous cardiac interventions became the mainstay of therapy in acute myocardial infarction, only a few studies [26,29-32] explored

TCD = transcranial Doppler

ER = emergency room

the use of mechanical balloon and stent-assisted reperfusion in the setting of acute stroke (percutaneous brain intervention). The most obvious reason is that the standard equipment for these brain procedures is still undergoing modification as optimal requirements are being studied. Brain arteries are not similar to coronary arteries in many parameters, including the absence of an external elastic lamina, the presence of a very thin muscular media layer, the absence of tissue support, and their greater fragility. Furthermore, cerebral arteries are often tortuous, curved and tapered, making endovascular approach technically difficult. This necessitates the design of new equipment – a process that will take time. Furthermore, most neurologists have no adequate training in brain catheterization and have to rely on the rarely available invasive neuroradiologists for the performance of these procedures. Despite these limitations, preliminary randomized studies and case series have proved that percutaneous brain intervention may indeed be effective in acute stroke. For example, the Wingspan multicenter study showed that all 44 treated lesions, of which half were in the anterior territory and half in the vertebrobasilar system, were successfully dilated with the stent. Mean stenosis rates improved from 75% before stent deployment to 28% 6 months later. The rates for stroke or death within 6 months of the procedure were only 7% with no vessel dissections, stent migration or symptomatic restenosis. Similar results were also reported for single-center case series [29-33].

While various glutamate receptor antagonists previously failed to improve the outcome of acute stroke patients, a free radical scavenger has shown promise as a neuroprotective agent

Development of novel therapies for neuroprotection

Neuroprotective therapies aim to prevent cell death in the ischemic penumbra until spontaneous reperfusion occurs [7]. Penumbral cells die as a result of multiple pathologic mechanisms that are activated immediately upon ischemic onset but cause cell death at different time points following the ischemia. These mechanisms include excitotoxicity, apoptosis, damage due to inflammatory changes, and free radicals injury secondary to energy depletion and recurrent depolarizations [7]. Survival of penumbral cells is generally believed to last around 6 hours [34]. This may hold true for only some cases, as it became clearer that different brain areas have different susceptibilities to ischemia [35]. For example, brain stem neurons are more resilient to ischemic changes and may survive for up to 24 hours before reperfusion occurs, while cortical neurons appear to be more vulnerable. Furthermore, even within the same penumbral zones different cell types have different susceptibilities to ischemia. These differences may be explained by differences in membranal receptor subtypes, cell connections, neurochemical properties and by exposure to growth factors. Different therapies aimed at counteracting these deleterious mechanisms have been proposed, but despite the overwhelming number of clinical studies none had a positive outcome until recently [7]. The SAINT-1 study explored the potential protective effects of the free radical scavenger NXY-059 vs. placebo administered within 6 hours of stroke onset in 1699 subjects with acute stroke [36]. This double-blind randomized study showed a modest beneficial effect of NXY-059 on the mRS scores compared with placebo ($P = 0.038$) but failed to improve NIHSS or Barthel Index scores. Mortality and rates of adverse events were similar in the two groups. Recruitment into the confirmatory SAINT-2 study has just ended, and if these promising results will be confirmed this would be the first proof that neuroprotection can indeed work in acute ischemic stroke.

Combined therapies

Since the main goal of acute stroke therapy is to minimize the amount of dead cells in the brain it is conceivable that combinations of the above-mentioned therapies will result in better overall survival of brain cells. Combinations of several strategies to achieve reperfusion are gaining wide acceptability in recent years. Thus, combinations of thrombolytic drugs with mechanical devices may offer rescue reperfusion of the ischemic tissue in patients who failed to reperfuse on tPA alone [26,37]. Multimodal strategies also include combinations of intravenous and intra-arterial lytics [38], and stenting with lytics [26,37].

The combination of reperfusion with thrombolytic agents and neuroprotectants may offer significant advantages to the singular use of each strategy [39]. Thus, reperfusion may be associated with excessive production of free radicals in the previously ischemic areas and this may contribute to further tissue damage. The adjuvant neuroprotective agents may be able to reduce such damage and, therefore, increase the therapeutic gain of reperfusion [39,40]. Furthermore, reperfusion may enhance the therapeutic effect of neuroprotective agents due to better delivery into the ischemic region. Indeed, the SAINT study has shown that patients treated with both tPA and NXY-059 had a better outcome compared with those treated with the neuroprotectant alone [36].

Conclusions

Multiple novel strategies to reduce ischemic stroke burden are currently being investigated. It is expected that many of these strategies will be incorporated into our growing arsenal of stroke therapies and will allow us to reduce stroke-related mortality and morbidity. Multimodal combinations of novel lytic agents with mechanical reperfusion devices and stents and their further combinations with newer effective neuroprotectants may increase the therapeutic effects even further.

Another approach to improve stroke outcome is to enhance late healing processes in the brain by cell and growth factor therapy. This approach is still in basic research and will probably be discussed in future reviews detailing novel methods of stroke therapy.

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