The Need for New Therapies for Acute Ischaemic Stroke

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Key Words

Acute ischaemic stroke · Tissue plasminogen activator · Neuroprotection

Abstract

Stroke creates the fourth highest burden of disease worldwide, and is the leading cause of adult long-term disability in developed countries. These factors mean that stroke has a high associated cost for healthcare systems, and a potentially devastating effect on family and carers. One of the main reasons why patients have such a poor prognosis is a lack of treatment options. Recombinant tissue plasminogen activator (rt-PA) is the only treatment currently licensed to treat selected patients with acute ischaemic stroke. However, only 1–8.5% of hospitalised patients receive treatment with rt-PA due to the short time window for administration (within 3 h of symptom onset), risk of intracerebral haemorrhage, need for a computed tomography scan, and exclusions due to other specific criteria. For acute ischaemic stroke, well-tolerated treatments that offer an extended therapeutic window are urgently needed to decrease disability, aid neurological recovery and improve patient prognosis. Neuroprotective agents potentially offer benefit to stroke patients without the associated haemorrhagic risk of thrombolytic therapy. Such agents target the ischaemic penumbra and aim to reduce the risk of brain injury and long-term disability by disrupting the cellular,

biochemical, and metabolic consequences of infarction following exposure to ischaemia. Future directions should involve developing a neuroprotective compound that is safe, well tolerated and effective in a broad range of patients.

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The Burden of Stroke

Worldwide, stroke accounts for the fourth highest burden of disease [1], and in developed countries, stroke is the second leading cause of mortality, and the leading cause of adult long-term disability [1]. Approximately 15 million people per year suffer a stroke, and of these, 5 million patients die and 5 million patients are left permanently disabled [1].

In addition to the impact on patients and their families, the cost of hospitalisation, treatment and rehabilitation is high. The total cost of stroke in 2006 is predicted to reach USD 57.9 billion in the US [2], and the global burden of stroke is forecast to rise from around 38 million disability-adjusted life years (DALYs) in 1990 to 61 million DALYs by 2020 [1]. In a prospective study of 435 consecutive patients, the direct cost of health care in the first year following stroke was EUR 17,799 per patient, of which hospitalisation, rehabilitation and ambulatory care accounted for 42, 29 and 8%, respectively, with level of disability (according to the modified Rankin scale

[mRS]) explaining 43% of the variance in costs ($p < 0.0001$) [3]. These figures highlight the currently unmet need for treatments that may potentially reduce disability and improve neurological recovery, leading to improving patient prognosis and reducing the burden on family, carers and society.

Thrombolytic Therapy for Acute Ischaemic Stroke: Recombinant Tissue Plasminogen Activator

There are various reasons why patients who experience an acute ischaemic stroke have such a poor prognosis, but these centre mainly on a lack of public awareness of stroke symptoms [4, 5], and the lack of treatment options. Recombinant tissue plasminogen activator (rt-PA) is the only pharmacological agent currently licensed to treat selected patients with acute ischaemic stroke when administered within 3 h of the onset of stroke symptoms and following a computer tomography (CT) scan to exclude intracerebral haemorrhage [6, 7]. rt-PA was granted FDA approval in 1996, based on data from the National Institute of Neurologic Disease and Stroke (NINDS) [6, 8] and in Europe, rt-PA has been approved since 2002 on the basis of a restricted licence to specialist centres [9].

Evidence from randomised controlled clinical trials has shown that systemic administration of rt-PA within 3 h of symptom onset is, in some patients, a highly effective treatment for acute ischaemic stroke. In the NINDS study, where half the patients were treated less than 90 min after the onset of stroke, rt-PA was found to prevent one death or dependency for every seven patients treated [8]. However, since only a small proportion of patients actually access treatment, the disease impact number (which comprises the number of patients with stroke who will have one event of poor outcome prevented by treatment with rt-PA) is 158, which is considerably higher than the seven patients of the need-to-treat population according to the NINDS study results [10].

A cumulative meta-analysis of randomised controlled trials has suggested that there may be benefit in receiving rt-PA up to 6 h after the onset of stroke [7, 11], although no trial has had positive results beyond a 3-hour threshold of symptom onset. A pooled analysis of data from randomised placebo-controlled rt-PA stroke trials (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS], European Cooperative Acute Stroke Study [ECASS], and NINDS), involving 2,775 patients who had initiated treatment within 6 h of

Table 1a. Odds ratio of favourable outcome at 3 months in patients treated with rt-PA in randomised controlled trials (ATLANTIS, ECASS, NINDS; $n = 2,775$) [12]

Interval, min	Odds ratio (95% CI)
0–90	2.81 (1.75, 4.50)
91–180	1.55 (1.12, 2.15)
181–270	1.40 (1.05, 1.85)
271–360	1.15 (0.90, 1.47)

Table 1b. Frequency of parenchymal haemorrhage by OTT in randomised controlled trials (ATLANTIS, ECASS, NINDS; $n = 2,775$) [12]

Interval min	Placebo		rt-PA	
	n	patients experiencing PH	n	patients experiencing PH
0–90	150	0 (0)	161	5 (3.1)
91–180	315	3 (1.0)	302	17 (5.6)
181–270	411	7 (1.7)	390	23 (5.9)
271–360	508	5 (1.0)	538	37 (6.9)

OTT = Interval from stroke onset to start of treatment; PH = parenchymal haemorrhage.

onset of stroke, was carried out to assess potential relationships between the interval from stroke onset to start of treatment (OTT) on favourable 3-month outcome, and on the occurrence of clinically relevant parenchymal haemorrhage [12]. The odds ratio of a favourable outcome at 3 months was found to decrease as the OTT increased, with greatest benefit being observed following initiation of treatment within 90 min of stroke onset (table 1a). In clinical practice, however, rt-PA is most often administered between 120 and 180 min, where the benefit of rt-PA use is smaller [13].

Overall results for patients receiving treatment with rt-PA showed that 5.9% (82/1,391) of patients experienced parenchymal haemorrhage compared with 1.1% (15/1,384) of patients receiving placebo ($p < 0.0001$). The frequencies of parenchymal haemorrhage associated with different OTT intervals are shown in table 1b. The occurrence of haemorrhage was significantly associated with rt-PA ($p = 0.0001$) and age ($p = 0.0002$), but not with either OTT ($p = 0.071$) or NIHSS score ($p = 0.10$). This meta-analysis suggested a potential benefit for patients

receiving rt-PA treatment more than 3 h after the onset of stroke symptoms. The reduced benefit of delayed treatment was not attributed to an increased rate of parenchymal haematoma, and so it may be explained by a progressive disappearance of the ischaemic penumbra [12].

The Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST), an observational safety monitoring study in Europe, was designed to investigate whether the efficacy and safety of rt-PA in routine clinical practice is similar to that observed in randomised controlled clinical trials [14]. SITS-MOST has strict entry criteria with a maximum of 3 h from symptom onset to treatment, in line with the European licence. Between January 2003 and February 2005, more than 2,200 patients from over 200 clinical centres were recruited. Preliminary data indicate that the rate for symptomatic intracranial haemorrhage was lower than in randomised trials.

Limitations of Treatment with Intravenous rt-PA

rt-PA can only be administered to patients presenting to the hospital within 3 h of the onset of stroke with no evidence of intracranial haemorrhage as detected by CT scan [12]. These limitations highlight a number of problems faced in the treatment of stroke in terms of the time taken to recognise the symptoms, reach a hospital and undergo a CT scan, as well as the availability of a physician specialised in neurological care to administer rt-PA.

Clinicians have expressed concern that there are limited criteria available to assist with identification of those patients who are most or least likely to benefit from treatment with rt-PA. This, together with the risk of intracerebral haemorrhage, means that many physicians, particularly non-neurologists, are concerned about using rt-PA in routine clinical practice. Indeed, a survey of the use of rt-PA outside clinical trials found that while 46.9% of responding neurologists administered rt-PA, 61.6% of respondents were 'very concerned' about the risk of intracerebral haemorrhage [15]. A recent study among emergency room physicians in the USA found that the most common reason cited by physicians who are unlikely to use rt-PA is the perceived risk of symptomatic intracerebral haemorrhage [16].

Some studies involving unselected community-based settings have shown that the safety and efficacy of rt-PA treatment in routine clinical practice may be different

from that observed during a randomised controlled trial. Firstly, mortality rates following stroke are higher in hospitals with limited experience of treating stroke [17–20]. A pooled analysis of four German stroke registers found that the number of treatments administered per year influenced the in-hospital mortality rate [18]. Among the 384 (3%) patients who received rt-PA, those patients treated in hospitals administering five or less thrombolytic therapies per year had an increased risk of in-hospital mortality (overall response [OR] 3.3; 95% confidence intervals [CI] 1.1, 9.9) compared with those patients who received treatment in hospitals administering more than five thrombolytic therapies per year (OR 1.3; 95% CI 0.8, 2.4). A further point of concern is that a meta-analysis of 15 published, open-label studies involving 2,639 nonselective patients who received rt-PA during routine clinical practice showed that mortality rate correlates with the number of protocol violations [17]. However, the symptomatic intracerebral haemorrhage rate of 5.2% was slightly lower than that of 6.4% observed in the NINDS trial [8] and similar results were obtained for both the mean total death rate and number of subjects achieving a favourable outcome when the patients were treated according to the accepted guidelines [17].

Although 22–50% of patients arrive at hospital within 3 h of the onset of stroke symptoms, only 1–8.5% of patients with acute ischaemic stroke receive treatment with rt-PA [9, 13, 21–23]. Two studies have tried to determine why these figures are so low [9, 21]. Fifteen of the 145 patients eligible for inclusion in the study by Cocho et al. received treatment with rt-PA, accounting for only 7% of patients with acute ischaemic stroke [9]. In the study conducted by Barber et al., only 84 (7.2%) patients from 1,168 eligible for treatment received rt-PA [21]. The most common reasons for exclusion from treatment in either study were deviation from protocol, neurological improvement or the stroke being too mild, and avoidable reasons such as delayed consultation, which may be partly explained by the fact that stroke is not always regarded as a medical emergency by pre-hospital and hospital-based emergency personnel (table 2) [9, 21].

For patients who receive rt-PA treatment, less than 40% achieve systematic reperfusion [24] or complete functional recovery (SITS-MOST; Wahlgren personal communication 2005). To date, there are no pharmacological treatment alternatives for patients who do not respond to treatment. However, in the near future, a series of potential interventions such as sonothrombolysis [25, 26], intraarterial [27] and mechanical thrombolysis [28] could increase the rate of recanalisation.

Fig. 1. Expanding the time-window for thrombolytic therapy with desmoteplase and a magnetic resonance imaging-based patient selection approach; results from the DIAS trial (reperfusion was assessed 4–8 h post-treatment and defined as either $\geq 30\%$ reduction of MTT volume of abnormality or ≥ 2 points improvement on the adapted Thrombolysis in Myocardial Infarction grading scheme using magnetic resonance angiography. Favourable outcome was based on the combined analysis of the National Institute of Health Stroke Scale [NIHSS], modified Rankin scale [mRS], and Barthel Index [BI]; defined as ≥ 8 points improvement or scoring 0 to 1 on the NIHSS, 0 to 2 on mRS, and a BI score of 75 to 100 at 90 days) [36].

Table 2. Reasons why patients arriving at hospital within 3 h of acute ischaemic stroke symptom onset do not receive treatment with rt-PA

Acute ischaemic stroke <3 h	Barber et al. [21] 2001, %	Cocho et al. [9] 2005, %
Protocol exclusion	13.6	21
Improvement	18.2	7.6
Too mild	13.1	22
Too elderly	1.3	10 ^a
Comorbidity	8.0	–
Avoidable reasons	18.7	27
Delayed consultation	8.9	16
Clinician doubt	1.9	8
Delay on CT	5.4	2
Refused consent	0.6	1
Other reasons	1.9	2 ^b

^a Age >80 years; ^b onset-to-door >150 min.

A further approach to improving the response to thrombolysis is to prevent the neurotoxic effects of rt-PA. In animal models, treatment with rt-PA has been found to activate N-methyl-D-aspartate (NMDA) receptors increasing excitotoxic damage, and also to upregulate matrix metalloproteinases (MMPs) such as MMP-9, which has a central role in the development of vascular damage in stroke [29–31]. Such activation may promote further disruption to the blood-brain barrier resulting in oedema and cerebral haemorrhage [32]. A further complication of treatment with rt-PA is that reperfusion after cerebral ischaemia may result in formation of free radicals [29], which can induce additional brain infarction and enhance accumulation of polymorphonuclear leukocytes.

Desmoteplase as an Alternative Approach to Achieve Reperfusion

The excitotoxic effects and ischaemic injury associated with rt-PA treatment have resulted in alternative reperfusion strategies being sought. Desmoteplase, a salivary plasminogen activator from the vampire bat, is thought to have fewer neurotoxic effects than rt-PA. In a study that compared the ability of desmoteplase and rt-PA to promote kainate- and NMDA-induced neurodegeneration in tPA $-/-$ mice and wild-type mice, respectively, desmoteplase was not shown to promote either kainate- or NMDA-mediated neurotoxicity in vivo [33]. In addition, desmoteplase has been shown to have high fibrin specificity and a long terminal half-life [34, 35]. The Phase II randomised double-blind, placebo-controlled Desmoteplase in Acute Ischemic Stroke (DIAS) trial investigated the safety and efficacy of several doses of desmoteplase administered within 3–9 h of ischaemic stroke onset to patients with a perfusion/diffusion mismatch as measured by magnetic resonance imaging (MRI) [36]. Dose-dependent reperfusion was shown to correlate with favourable outcome (fig. 1) and the symptomatic intracerebral haemorrhage (sICH) rate with desmoteplase was low using doses up to 125 µg/kg. The clinical outcome of patients treated with desmoteplase 6–9 h after stroke onset was found to be as favourable as for those treated within 3–6 h after stroke onset. This suggests that a longer time-to-treatment window may potentially be achievable when using a thrombolytic drug with an improved safety and efficacy profile, particularly in patients selected using MRI technology to identify ischaemic penumbra [36]. The US twin study Dose Escalation Study of Desmoteplase in Acute Ischemic Stroke (DEDAS) confirmed these

findings for the 125 µg/kg dose but not for the 90 µg/kg dose, mainly due to a number of MRI protocol violations. From a joint analysis of the DIAS and DEDAS studies, there was a low rate of sICH in the doses investigated, and significant improvement for 125 µg/kg compared with placebo for both reperfusion and clinical outcome. These findings suggest that a dose of 125 µg/kg is potentially safe and well tolerated, although further studies are needed to confirm these findings in a larger number of patients [37].

Rationale for Neuroprotection

Early reperfusion does not prevent either worsening or delayed injury in over a third of patients, suggesting that neuroprotection should be recommended even in optimal conditions [24, 38]. There are a number of clinical arguments for potential reperfusion injury and late secondary damage, providing further evidence to support a role for neuroprotection. Thirty-seven percent of patients with early recanalisation do not show an immediate clinical improvement [24], a small proportion of patients deteriorate following improvement through reasons not associated with re-occlusion or haemorrhagic transformation [39] and 28% show late secondary injury defined as initial resolution of diffusion weighted image (DWI) abnormality followed by partial or complete reappearance of the lesion on day 7 [40]. Therefore, other mechanisms such as reperfusion damage or progressive enlargement of the irreversibly damaged ischaemic core to incorporate penumbral regions that could be targeted by neuroprotection may explain this deterioration.

Cerebral ischaemia leads to neuronal cell injury in the penumbra, an area of brain surrounding the ischaemic core that is electrically quiescent but has the potential to either deteriorate or recover if blood flow is restored. However, it is unclear whether the penumbra is the only tissue at risk of infarction. To try to answer this, a descriptive study was undertaken involving 74 patients who had acute hemispheric infarction within the first 12 h of symptom onset [41]. Diffusion/perfusion weighted image (DWI/PWI) lesion volumes were measured on admission and at 72 h using MRI. DWI was considered to have extended to the peripenumbral zone if it had exceeded the initial PWI lesion volume by 20% or more at 72 h, and at this time 23 (31%) patients were found to have infarction in the peripenumbral zone. A significant correlation was found between the infarcted peripenumbral volume and plasma glutamate levels on admission and at 24 h ($r =$

0.80 [$p < 0.001$], and $r = 0.65$ [$p < 0.001$], respectively). This study highlights that tissue is still at risk beyond the penumbra, and that outward spreading glutamate excitotoxicity may play a role in DWI lesion growth in patients with acute ischaemic stroke.

Neuroprotective agents target the ischaemic penumbra, and aim to reduce the risk of brain injury and long-term disability by interrupting cellular, biochemical, and metabolic consequences of infarction following exposure to ischaemia. By limiting the area and impact of injury to neuronal cells within the ischaemic penumbra, neuroprotection may offer a viable strategy to treat patients experiencing acute ischaemic stroke as well as improve recovery. In addition, neuroprotection may offer a more favourable safety profile and a longer time window than thrombolytic therapy [38, 42, 43].

Where Do We Go from Here?

For acute ischaemic stroke, safe and effective treatments that offer an extended therapeutic window are urgently needed to decrease disability and aid neurological recovery. In particular, it would be beneficial if treatment could start immediately without the requirement for selection by a CT scan. In addition, availability of new treatments will raise the clinical management of stroke to a high priority medical emergency [4, 44].

Neuroprotective agents potentially offer benefit without the increased bleeding risk associated with thrombolytic therapy. However, the previous negative and equivocal results seen in trials of investigative compounds require that strict adherence to the conditions of preclinical models where these compounds were found to be effective are maintained when translating into clinical trial design. To offer new hope for the treatment of patients who experience an acute ischaemic stroke, future directions should concentrate on developing a neuroprotective compound that is safe and well tolerated, is effective in a broad range of patients, and can be used with or without rt-PA.

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