Alteplase: thrombolysis for acute ischemic stroke

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Alteplase is the only licensed thrombolytic agent for the treatment of acute ischemic stroke. The body of evidence to date suggests that it reduces the number of stroke patients who are dead or dependent at follow up, despite the risk of intracranial hemorrhage. However, in Europe, the license has only been granted for people aged under 80 years who fulfil specific criteria and who can be seen and treated within 3 h of symptom onset. There is a need for further data from randomized controlled trials to determine more precisely which patients are most likely to benefit and whether a wider variety of patients could be treated.

Stroke is a major cause of death and morbidity throughout the world. Currently, it is the third most common cause of death. By 2020 it is estimated that stroke will, not only account for 6.2% of the total burden of illness in the developed world [1], but will also be a significant problem in the developing world. The true global incidence of stroke is difficult to establish due to a lack of data from the developing world. As incidence rises steeply with age and as the number of people surviving to old age increases, stroke will remain a major health problem for the foreseeable future.

Over four fifths of strokes are ischemic and are due to the blockage of extra- or intracranial arteries by thrombus or embolic material. The remaining 15% of strokes are caused by hemorrhage, either primary intracerebral (~10%) or subarachnoid (~5%). This article will focus on acute ischemic stroke.

The most widely applicable medical treatment for the acute phase of ischemic stroke was aspirin, which has only modest benefits [2]. Admission to hospital and care within a stroke unit that offers comprehensive care and multidisciplinary rehabilitation has more substantial benefits (and benefits all stroke types) [3,4]. Intravenous thrombolytic therapy has been licensed for use in selected patients with acute ischemic stroke. The idea behind thrombolytic therapy is that, by dissolving the clot occluding the cerebral artery, ischemic brain tissue is reperfused quickly. Early reperfusion should decrease the volume of brain tissue damaged by ischemia and, hence, lead to less neurologic impairment and less disability. Thrombolysis for acute stroke is not new. The first trial of thrombolysis for acute stroke was published in 1958 [5] and the first 'positive' trial was reported 10 years ago [6]. However, even in countries such as the USA where it has been licensed since 1996, use in routine clinical practice is limited and variable [7,8]. Since then alteplase (Actilyse®, Boehringer Ingelheim) has been licensed for the treatment of acute ischemic stroke in Europe and many other parts of the world. The European license specifies that the drug is available for use by 'physicians trained and experienced in the use of thrombolytic treatments and with the facilities to monitor that use' [9].

Overview of the market

Currently, the only licensed thrombolytic regimen for acute ischemic stroke is intravenous alteplase. Although therapy is currently underused, it has the potential to benefit many more patients if ongoing trials show that alteplase can be administered to a wider variety of patients. One theoretic model of wider usage suggests that, in Europe, up to 14,000 ischemic stroke patients could avoid death or disability each year [10]. The main problem with therapy is that patients must be treated within 3 h of symptom onset. At present, this is a difficult target to achieve. There may be delays at every stage: recognition of symptoms as stroke; calling emergency services; getting to hospital; clinical examination; bedside investigations; and brain imaging (which is necessary to exclude intracranial hemorrhage and stroke mimics). Even in hospitals that have a large throughput of stroke patients and well-organized acute stroke services, this is a time-consuming process. Some centers do not have acute stroke experts on site and it is here that processes such as telemedicine are being introduced to try and ensure an equity of care across different regions [11]. Before alteplase drug can reach its full potential it is vital that hospitals have organized stroke unit care. This requires, not

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only the reorganisation of existing services, but also a large investment of time and money. In the USA, for example, alteplase has been licensed since 1996 but, despite this, less than 2% of ischemic stroke patients in US community hospitals [12,13] and only 6% in university hospitals receive thrombolysis [14]. Prompted by the need to deliver thrombolysis to more people, the US government is to pass a bill to spend US$165 million (£101m) to establish specialist stroke centers, with an annual funding of $125 million thereafter [15]. In the UK, one of the targets of the National Services Framework (NSF) for elderly people was to establish stroke units in all hospitals by 2004 [3].

There have been trials of a variety of neuroprotective agents in acute stroke but, to date, none have been licensed for use. Other medical treatments have also been tested, such as corticosteroids, anticoagulants, hemodilution and calcium channel antagonists, yet none have been shown to be clearly beneficial [16]. At present, there are a number of other thrombolytic agents being evaluated for the treatment of acute stroke. These include desmoteplase, which has been assessed in two Phase II studies, Desmoteplase In Acute ischaemic Stroke (DIAS) [17] and Dose Escalation study of Desmoteplase in Acute Ischemic Stroke (DEDAS) [18] and tenectaplase, for which a pilot dose-escalation safety study has recently been published [19]. Antithrombotics including the glycoprotein IIb/IIIa inhibitors abciximab and eptifibatide are undergoing trials (Abciximab in Emergent Stroke Treatment Trial–II, AbESSTT–II, and the Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke [CLEAR] trial) [101]. Physical methods for use either in combination with thrombolytics, or on their own, are also near clinical testing such as power Doppler ultrasound.

Introduction to the compound

Alteplase is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein consisting of 527 amino acids. It is synthesized using the complementary DNA for natural human tissue-type plasminogen activator obtained from a human melanoma cell line. The manufacturing process involves the secretion of the enzyme alteplase into the culture medium by an established mammalian cell line (Chinese hamster ovary cells) into which the complementary DNA for alteplase has been genetically inserted [9]. Alteplase works as a plasminogen activator, breaking down the fibrin polymers of an acute thrombosis by converting plasminogen to plasmin. This, in turn, breaks down fibrin, releasing fibrin degradation products. Therefore, in acute ischemic stroke, the beneficial effect of alteplase is to disperse the thrombus within an occluded vessel, therefore reducing the damage to the surrounding cerebral tissue. The hope is that this can limit a patient's subsequent neurologic deficit.

Pharmacodynamics, pharmacokinetics & metabolism

The plasma half-life of alteplase is 3 to 4 min, with metabolism mainly by the liver (plasma clearance 550–680 ml/min). Total plasma clearance therefore occurs in approximately 40 min. Due to its relative fibrin specificity, alteplase, at a dose of 100 mg, leads to a modest decrease of the circulating fibrinogen levels to about 60% at 4 h, which generally reverts to more than 80% after 24 h. Plasminogen and α2–antiplasmin decrease to approximately 20 and 35%, respectively after 4 h and increase again to more than 80% at 24 h. A marked and prolonged decrease of the circulating fibrinogen level is only seen in a few patients [9]. The product characteristics emphasize that, although alteplase is rapidly metabolized, its pharmacodynamic effects are prolonged and so administration of other inhibitory coagulation agents is not recommended for at least 24 h due to the increased risk of hemorrhage. The recommended dose of alteplase in acute ischemic stroke is 0.9 mg/kg to a maximum of 90 mg. Initially a 10% bolus is given over 1 to 2 min, followed by the remainder of the infusion (i.e., 90% of the dose) given over 1 h.

Clinical efficacy

Thrombolytic therapy has now been evaluated in several randomized trials in acute ischemic stroke. An up-to-date summary of the randomized trial evidence is provided by Wardlaw and colleagues in their Cochrane systematic review [20]. By 2003 there had been 18 randomized trials, including 5727 patients. The agents tested include urokinase, streptokinase and recombinat pro-urokinase. Approximately half the data relates to recombinant tissue plasminogen activator (rt-PA, alteplase) and, as mentioned previously, this is the only thrombolytic drug currently licensed for acute stroke treatment. In an analysis of 'any thrombolytic agent versus control' there was a significant reduction in death or dependency with thrombolysis; 53.3% of those allocated to thrombolytic therapy compared with 58% of

those allocated to control (odds ratio [OR]: 0.84; confidence interval [CI]: 0.75–0.95; p = 0.004). Clinically, this is the equivalent to 43 fewer dead or dependent (Rankin 3–6) patients/1000 treated [20]. The review permitted an indirect comparison of the effect of rt-PA with other thrombolytic agents. The authors stated that trials testing intravenous recombinant tissue plasminogen activator suggested that it may be associated with slightly less hazard and more benefit than other drugs when given up to 6 h after stroke but these are non-random comparisons (death within the first 10 days – OR: 1.24; 95% CI: 0.85–1.81. Death at the end of follow-up OR: 1.17; 95% CI: 0.95–1.45. Dead or dependent at the end of follow-up – OR: 0.80; 95% CI: 0.69–0.93). However, no trial has directly compared rt-PA with any other thrombolytic agent.

In 2003, a cumulative meta-analysis of all the rt-PA trials was published [21]. Data on 2830 patients from eight trials, since 1992, were included. The cumulative analysis confirmed that there were net benefits in treating patients with alteplase, despite the hazards. For every 1000 patients treated with rt-PA in up to 6 h, approximately 55 more patients will be independent at the end of follow-up, including the 'cost' of approximately 20 extra deaths [21].

Individual data on 2775 patients from six trials (National Institute of Neurological Disorders and Stroke [NINDS] part 1 and 2, European Cooperative Acute Stroke Study [ECASS]-I + II and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS] part A and B) were pooled by the rt-PA study group [22]. This analysis has the advantage of enabling the effect to be explored in specific subgroups. Multivariate analysis showed that the main factor associated with a favorable outcome (based on Rankin, Barthel and The National Institutes of Health Stroke Scale [NIHSS]) was early onset of treatment. The analyses were consistent with the Cochrane review and also suggested that there may be a worthwhile benefit from thrombolysis commenced up to 6 h from stroke onset. However, at all time points the CIs were wide and, hence, the estimates of effect were imprecise.

Overall, there is good evidence to support the use of alteplase in highly selected patients with ischemic stroke, aged under 80 years, treated in well-organized centers within 3 h of symptom onset. However, trial data suggests a wider variety of patients might benefit from thrombolysis, although this hypothesis needs to be tested in further larger-scale trials. The most notable group is the elderly. To date, the elderly have been under represented in trials of thrombolysis for stroke, despite the fact that stroke is a disease of the elderly. In the UK, for example, approximately 20,000 patients aged over 80 years have an acute stroke each year. As a consequence of many of the trials setting an upper age limit (only three of the recent trials have not had an upper age limit), only 42 patients aged over 80 have been included in randomized, controlled trials and, hence, alteplase is only licensed for acute stroke in those patients under the age of 80 years.

More needs to be known about which factors really influence the benefit from treatment, such as age, concomitant aspirin use, blood pressure, the presence on the pretreatment computed tomography (CT) scan of 'early infarct' signs, or the degree of diffusion/perfusion mismatch on magnetic resonance (MR) scanning, to name but a few. Once more is known about these factors, we will be better able to assess the balance of risk and benefit for each individual patient.

Another concern is the under utilization of rtPA within the license and the wide variation between centers and countries. In March 2005, the Safe Implementation of Thrombolysis in Stroke (SITS) registry reported a 50-fold variation between European countries in the use of rt-PA for stroke between Finland (about 50 treatments/million population) and France and Portugal (about 1/million) [103]. At least part of the explanation must be the lack of large-scale randomized trial evidence. The example of the implementation of thrombolytic therapy for acute myocardial infarction (MI) is illuminating. Before the late 1980s there was similar under utilization of the treatment, and enormous variation between centers. It was not until randomized trial data were available for over 60,000 patients that cardiologists finally accepted the benefits of in routine, clinical practice, which changed extremely rapidly after the publication of the large-scale trials (Second International Study of Infarct Survival [ISIS-2] and Gruppo Italiano per lo Studio della Streptochinasinellâ Infarto miocardico [GISSI]) [23,24]. In stroke, the evidence base for thrombolysis is much smaller (just 2800 patients), and the authors suggest that this lack of large-scale evidence must contribute to the poor uptake in routine practice. The ongoing randomized trials of alteplase in acute stroke should help to improve the situation, although none are of 'cardiologic' scale (Third International Stroke Trial [IST-3], ECASS-III, Echoplanar Imaging Thrombolysis Evaluation [EPITHET]) [101,102].

An economic analysis (based on the UK National Health Service [NHS]) of thrombolysis with alteplase for acute ischemic stroke, found that the estimates of effectiveness and cost effectiveness were imprecise. Although the benefits of treatment up to 6 h appeared promising, the data did not support the widespread use of thrombolytic therapy outside the terms of the current restricted license in routine clinical practice in the NHS [25].

Postmarketing surveillance

In the USA, there is an unconditional license for alteplase, but in Europe the licence is currently conditional on

- The completion of ECASS-III, a randomized controlled trial of intravenous alteplase, that seeks to recruit 800 patients between 3 h and 4 h, 30 min after symptom onset
- Satisfactory safety from the monitoring study, SITS: a Multinational multicenter study Of Safety and efficacy of Thrombolysis in stroke (SITS-MOST)

This registry assesses the outcome of patients treated in routine practice within the terms of the restricted license. Those centers in Europe that have the facilities to deliver thrombolyis must register all patients treated with alteplase in their center with SITS-MOST [103].

Safety & tolerability

The most serious side effect of alteplase is bleeding, with intracranial hemorrhage potentially the most serious. In trials using alteplase to treat acute ischemic stroke, there were 25 (95% CI 13–44) extra fatal intracranial hemorrhages/1000 patients treated (OR: 3.60; 95% CI: 2.28–5.68; $p < 0.00001$) [20]. Extracranial hemorrhage may occur, but is generally mild, resulting in superficial skin bruising, epistaxis and gingival bleeding. However, more serious extracranial hemorrhage does occur, such as from the gastrointestinal tract, with a frequency of approximately 1% [26]. The manufacturers of alteplase, Boehringer Ingelheim [9] suggest that, in potentially dangerous hemorrhage, in particular cerebral hemorrhage, fibrinolytic therapy must be discontinued. Their advice is that most patients can then be managed with volume replacement (if indicated). It is rarely necessary to replace the clotting factors due to the short half-life of the drug and the minimal effect on the systemic coagulation factors. In those who fail to respond, transfusion of cryoprecipitate, fresh-frozen plasma and platelets should be considered. Antifibrinolytics (e.g. tranexamic acid) are sometimes used, but the benefits are unclear. Clozel and colleagues examined the use of aprotinin as an antidote for rt-PA [27]. In their small animal study they found that aprotinin immediately stopped thrombolysis, but the duration of this effect was dose dependent. A study examining intracranial hemorrhage after coronary thrombolysis found that the exact mechanisms behind the hemorrhage were unclear [28]. Their patients had received rt-PA and heparin and it was suggested that excessive prolongation of the activited partial thromboplastin time (APTT) and elevated fibrin degradation products may have contributed to the occurrence of intracranial hemorrhage. Hypofibrinogenemia was not a uniform finding. The British Society of Haematology produced a consensus report in 1995 on guidelines for the use of thrombolysis. For severe life-threatening bleeding they suggest a fibrinolytic inhibitor such as aprotinin or tranexamic acid and replacement of clotting factors depending upon the results of a coagulation screen [29].

Anaphylactoid reactions with rt-PA are rare, but have been reported. Hypersensitvity is estimated to occur in less than 0.2% of patients who receive alteplase for the treatment of MI [30], but the risk in acute ischemic stroke patients may be higher. The reaction is usually mild, but in some instances can be life threatening. The speed of onset of symptoms and signs is related to the severity of the process, with life threatening reactions occurring within minutes of parenteral antigen exposure [31]. Most symptoms will occur within 30 min.

Hill and colleagues examined a series of patients given rt-PA for acute ischemic stroke. The group reported a possible increase in anaphylactoid reactions to rt-PA in patients treated for stroke, compared with those receiving the drug for MI [32]. In a more recent communication, Hill's group reported the occurrence of orolingual angioedema in 5% (95% CI: 2.3–9.5) of those treated with intravenous rt-PA [30]. The reaction was usually mild and contralateral to the ischemic hemisphere. In most cases it was noted to be transient, and the risk seemed to be more common among patients receiving angiotensin-converting enzyme (ACE) inhibitor therapy and patients with signs on the initial CT of ischemia in the insular and frontal cortex. *In vitro* studies have suggested that the angioedma associated with rt-PA treatment of ischemic stroke relates to plasmin-mediated release of bradykinin [33].

Box 1. General contraindications to alteplase part 1

- Known hemorrhagic diathesis
- Patients receiving oral anticoagulants, such as warfarin sodium
- Manifest or recent severe or dangerous bleeding
- Known history of or suspected intracranial hemorrhage
- Suspected subarachnoid hemorrhage or condition after subarachnoid hemorrhage from aneurysm
- Any history of central nervous system damage (i.e. neoplasm, aneurysm, in_tracranial or spinal surgery)
- Hemorrhagic retinopathy, such as in diabetes (vision disturbances may indicate hemorrhagic retinopathy).
- Recent (<10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood vessel (e.g. subclavian or jugular vein puncture)
- Severe uncontrolled arterial hypertension
- Bacterial endocarditis, pericarditis
- Acute pancreatitis
- Documented ulcerative gastrointestinal disease during the last 3 months, esophageal varices, arterial-aneurysm, arterial/venous malformations.
- Neoplasm with increased bleeding risk
- Severe liver disease, including hepatic failure, cirrhosis, portal hypertension (esophageal varices) and active hepatitis
- Major surgery or significant trauma in past 3 months

As expected there are a number of contraindications and precautions defined for alteplase, mainly related to the risk of hemorrhage, which are summarized in **Box 1** and **Box 2**.

At present, the license in Europe only covers those patients between the ages of 18 and 80. The risk of hemorrhage is increased if coumarin derivatives, oral anticoagulants, platelet aggregation inhibitors, unfractionated heparin or low molecular weight heparin (LMWH) or other agents inhibiting coagulation are administered (before, during or within the first 24 h of treatment with alteplase). There is very limited experience with the use of alteplase during pregnancy and lactation. In cases of an acute life-threatening disease the benefit has to be evaluated against the potential risk [9].

Box 2. General contraindications to alteplase part 2

- Symptoms of ischemic attack began more than 3 h prior to infusion start or when time of symptom onset is unknown
- Minor neurological deficit or symptoms rapidly improving before the start of infusion
- Severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by appropriate imaging techniques
- Seizure at onset of stroke
- Evidence of intracranial hemorrhage on the CT scan
- Symptoms suggestive of subarachnoid hemorrhage, even if CT scan is normal
- Administration of heparin within the previous 48 h and a thromboplastin time exceeding the upper limit of normal for laboratory
- Patients with any history of prior stroke and concomitant diabetes
- Prior stroke within the last 3 months
- Platelet count of below 100,000/mm^3
- Systolic BP > 185 or diastolic BP > 110 mmHg, or aggressive management (IV medication) necessary to reduce BP to these limits
- Blood glucose <50 or > 400 mg/dl (<2.8 or > 22.2 mmol/l)

BP: Blood pressure; CT: Computed Tomography; IV: Intravenous; NIHSS: National Institutes of Health Stroke Scale.

In pregnant animals, no teratogenic effects were observed after intravenous infusion of pharmacologically effective doses. In rabbits, embryotoxicity (embryolethality and growth retardation) was induced by more than 3 mg/kg/day. No effects on peripostnatal development or fertility parameters were observed in rats with doses up to 10 mg/kg/day [9].

Conclusion

In conclusion, randomized trial evidence for the use of intravenous alteplase for stroke, although limited (in comparison with the scale of the evidence supporting its use in MI), show that, in carefully selected patients with acute ischemic stroke, treatment within 3 h, of onset increases the numbers of patients who are alive and independent at follow-up, despite a 3% risk of fatal intracranial hemorrhage. Despite trial evidence showing benefit in selected patients who present within 3 h this treatment is still underused in the USA and Europe. However, trial evidence suggests a wider variety of patients might benefit, but this needs to be tested in further trials. Data on whether the therapeutic time window can be extended to make this a more widely practicable treatment and what clinical and radiological features identify the patients most likely to benefit from, or be harmed by, treatment are also needed.

Expert opinion

Alteplase is the most promising new treatment available for acute ischemic stroke but there is still a lot to learn about how to best use it in routine clinical practice. Before it is to be implemented more widely, we not only need more data from randomized trials but, more importantly, we need to ensure that more acute hospitals have well organized inpatient stroke care unit. This requires appropriately trained nurses and ancillary staff, led by a stroke physician [34]. Once this organized care is in place, thrombolysis can be considered with the development of a 'fast track' system appropriate to each individual hospital. This will enable timely recognition of acute stroke patients, clinical assessment and appropriate imaging so that treatment can be administered within the 3 h

time window of the current license. Patients that do not meet the license criteria can be considered for entry into ongoing trials of intravenous thrombolysis and this is vital if we are to determine the true role of thrombolysis in acute ischemic stroke.

Outlook

Research is continuing apace on evaluating existing revascularisation therapies and in developing new ones for use in acute ischemic stroke. In a few years the results of IST-3, ECASS III, EPITHET and DIAS-2 [101] will be available and these will inform better patient selection for thrombolysis. These and other trials and observational studies are assessing which imaging modalities and what imaging appearances best identify the patient most likely to benefit from thrombolysis (e.g. Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution [DEFUSE]) [101]. There is also much interest in the use of transcranial ultrasound with or without microbubble administration to enhance the effects of systemic thrombolytic drugs (Microbubbles and Ultrasound in Stroke Trial [MUST], Combined Lysis Of Thrombus in Brain ischemia using 2 MHz transcranial Ultrasound and Systemic T-PA [CLOTBUST] and CLOTBUST-2) [101]. A large number of methods of mechanical clot retrieval or dispersal are also being developed and tested as alternatives to, or adjuncts to, intravenous and intra-arterial therapy (Mechanical Embolus Removal in Cerebral Ischemia [MERCI] and MULTIMERCI) [101].

Highlights

- Intravenous alteplase given within 3 h of symptom onset is the only licensed thrombolytic treatment for acute ischemic stroke. If given to appropriately selected patients within 3 h of onset, it increases the number of patients alive and independent after at follow-up, despite the 3% excess of early fatal intracranial hemorrhages.
- Despite the evidence showing the net benefits, the treatment is still underused, and there is variation between countries and within countries, an issue that needs to be addressed worldwide.
- Well-organized acute stroke services with a multidisciplinary team approach are essential in the management of stroke patients. Without this basic infrastructure it is difficult to deliver treatment efficiently and safely.
- More randomized controlled evidence is required to identify all those groups who may benefit from (or be harmed by) thrombolysis.

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