Thrombolytic therapy with alteplase for ischaemic stroke

Stroke is very common, with, for example, around 110,000 people each year in England alone experiencing a first or recurrent episode.[1] Consequences of stroke can include disability and early death, and the condition costs the UK economy around £7billion annually.[2-4] Around 70–80% of first strokes are ischaemic (i.e. due to the thromboembolic or thrombotic occlusion of an intracranial artery), and so some patients with stroke may be suitable for thrombolytic therapy.[5] Here we review the evidence for such therapy in acute ischaemic stroke.

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About stroke

The incidence of stroke increases with age, reaching around 21 per 1,000 in those aged over 80 years.[6] Overall, about 10% of patients die within a month of a first ischaemic stroke, and by 6 months, up to around 20% are dead and 30% or more are dependent on others in day-to-day activities.[7]

Measuring stroke severity

Stroke severity can be measured using a scoring system. For example, the National Institutes of Health Stroke Scale (NIHSS) is a 15-item scale that includes assessment of sensory and motor function, level of consciousness and orientation. It ranges from 0 to 34; the higher the score, the greater the neurological deficit.[8]

Measuring outcomes after stroke

Outcomes in stroke may be measured using a variety of neurological and disability rating scales.

The modified Rankin scale is commonly used to assess outcomes following stroke. It ranges from 0 to 6, where 0 indicates no symptoms at all; 1 and 2 mild disability; 3 moderate disability; 4 and 5 moderate to severe disability; and 6 death.[9,10] This scale is often dichotomised into a "favourable outcome" (score 0–1) or an "unfavourable outcome" (score 2–6),[9] or, alternatively, into "functional independence" (score 0–2) or "dependent or dead" (score 3–6).[11,12]

Another commonly used rating scale is the Barthel Index, which consists of 10 items that measure independence of function in terms of activities of daily living and mobility; it ranges from 0 to 100; the higher the score, the less dependent the patient, with 100 representing independence.[13]

The Glasgow Outcome Scale allocates patients into broad categories: 1 = good recovery (resumption of normal activities; may be minor deficits); 2 = moderate disability (disabled but independent); 3 = severe disability (conscious but dependent on others for daily support); 4 = persistent vegetative state (no obvious cortical function); 5 = death.[14,15]

Prognostic factors in stroke

Age

Of patients who have a stroke, those aged 80 years or over are more likely to die or be disabled as a result than are younger patients. For example, the 90-day mortality rate for older patients who do not receive thrombolytic therapy is around 45%, compared with 21% in younger patients, partly due to greater pre-stroke disability and greater stroke severity.[6]

Stroke severity

Patients with very mild strokes or rapidly improving symptoms usually have a good prognosis. Evidence for this includes a study of 39 patients with acute ischaemic stroke who had symptoms that were either mild (NIHSS score 4 or less) or rapidly improving (NIHSS score 4 or less, having improved from a more severe deficit).[16] In all, 8 (21%) were discharged with a modified Rankin score of 3 or more (a poor outcome) and 31 (79%) were discharged with a good outcome.

Around 60–70% of patients with an acute ischaemic stroke and a baseline NIHSS score below 10 will have a favourable outcome after 1 year, compared with 4–16% of those with a score above 20.[8] Patients with major strokes (NIHSS score above 22) have a very poor prognosis.[8]

Principles of acute management of stroke

Stroke is a medical emergency, with estimates suggesting that 1.9 million neurones are lost to the brain each minute that an ischaemic stroke goes untreated.[17] The Department of Health National Stroke Strategy sets out recommendations for minimising the damage done by a stroke, through prompt action in the early hours and days.[1] These include the following recommendations:

- A pre-hospital assessment tool should be used to recognise stroke features, such as the Face Arm Speech Test (FAST: **f**acial weakness; **a**rm weakness; **s**peech problems; **t**est these symptoms).

- People with an acute stroke need to be transferred directly by ambulance to a hospital able to provide "hyper-acute" stroke care, and to spend most of their time in hospital on a dedicated stroke unit with high-quality stroke specialist care.

- On arrival in hospital, patients should receive an immediate structured clinical assessment to determine the likely diagnosis and whether urgent brain imaging is required, such as the Recognition of Stroke in the Emergency Room (ROSIER) scale, a seven-item instrument based on clinical history (loss of consciousness, convulsive seizures) and neurological signs (face, arm or leg weakness, speech disturbance, visual field defect).[18] The score ranges from -2 to +5 and a score greater than zero predicts stroke.

• All patients with suspected stroke should have brain imaging as rapidly as possible with skilled radiological and clinical interpretation available.

Rationale for thrombolytic therapy

In ischaemic stroke, the occlusion of an intracranial artery leads to ischaemia and then infarction of brain tissue supplied by that vessel. In theory, prompt administration of drugs that can break down a thrombus could restore the arterial supply, thereby limiting reducing the potential damage to the brain. The thrombolytic drugs that have been tried in the treatment of patients with acute ischaemic stroke include streptokinase, urokinase, desmoteplase and alteplase.[12] Most of these drugs have been given intravenously; intra-arterial therapy has also been tried, but there are few data on this route.[12,19] Trials of streptokinase, urokinase and desmoteplase found an increased risk of fatal intracranial haemorrhage and no convincing evidence of clinical benefit in terms of death or disability.[12] Therefore, the focus of interest and research effort has become alteplase (also known as recombinant tissue plasminogen activator; Actilyse– Boehringer Ingelheim), for which data have been more promising.

Key initial data on alteplase

Clinical effectiveness

A systematic review identified eight randomised placebo-controlled trials of alteplase, involving a total of 2,955 patients with ischaemic stroke started on treatment up to 6 hours after stroke onset.[12] Based on data from 2,830 patients in a total of six trials, the risk of death or dependency at the end of follow-up was reduced with alteplase treatment (odds ratio [OR] compared with placebo 0.80, 95% CI 0.69 to 0.93; number needed to treat [NNT] to prevent 1 death or dependency around 18).[20] These data were from four large trials of over 600 patients each, including the key National Institute for Neurological Diseases and Stroke (NINDS) trial.[5]

The review found that of the 930 patients randomised within 3 hours of stroke onset, those given alteplase had a reduced risk of death or dependency at the end of follow-up compared with those on placebo (OR 0.64, 95% CI 0.50 to 0.83; NNT 10).[12] However, in those randomised 3–6 hours after symptom onset, alteplase did not reduce the risk of death or dependency (OR 0.88, 95% CI 0.73 to 1.06), and in fact increased the risk of death (OR 1.38, 95% CI 1.05 to 1.82).[12]

Unwanted effects

In the systematic review, patients treated with alteplase had an increased risk of symptomatic intracranial haemorrhage (associated with either deterioration in neurological state or death within 7–10 days) of around 62 (95% CI 40 to 90) added events per 1,000 patients treated.[12] Those given alteplase also had an increased risk of fatal intracranial haemorrhage within 7–10 days of around 25 (95% CI 13 to 44) added events per 1,000 patients treated.[12]

Problems with the trials

None of the above trials of alteplase started within 3 hours of stroke onset recorded patient details centrally prior to randomisation, but instead treatment allocation was determined by the selection of numbered treatment packs held at each participating hospital. So the trials did not stratify the randomisation according to key baseline variables like stroke severity: this could have confounded the results.[12,21]

The 930 patients providing evidence for benefit from starting alteplase within 3 hours of stroke onset came from five trials. Of these, the NINDS trial alone contributed 624 patients.[12] The overall results are therefore more reliant on the findings from the NINDS trial, and may therefore be more sensitive to error if that study had methodological problems. Particular concerns raised about the design and conduct of the NINDS trial include those relating to an imbalance in stroke severity between the two treatment groups, and the fact that the published account of this study reported the results of an 'as treated' analysis rather than an 'intention to treat' analysis.[5,21,22] Also, two of the other trials[23,24] were stopped early due to concerns about efficacy and safety of the intervention, a move that reduced the power of these studies.

How have these problems been addressed?

Data from the NINDS trial have been re-analysed with adjustment for the potential confounding factors (age, stroke severity, prior aspirin use, weight, smoking, blood pressure, baseline prothrombin time) and using an intention-to-treat approach;[21] neither changed the results appreciably. In addition, an independent re-analysis of the trial adjusting for differences in baseline stroke severity still found significant net benefit (OR of a favourable outcome with alteplase of 2.1, 95% CI 1.5 to 2.9).[22]

Another analysis adjusting the results for variables that might affect prognosis or treatment response (i.e. age, gender, diabetes, hypertension, smoking, pre-existing disability, mean arterial pressure, serum glucose, stroke sub-type, baseline CT characteristics, NIHSS score) also indicated a benefit from treatment with alteplase in the study (adjusted OR for a good outcome 1.75, 95% CI 1.20 to 2.57).[25] Furthermore, longer follow-up of the patients from the NINDS study showed that the benefits found at 3 months were sustained at 1 year (OR of a favourable outcome at 12 months 1.7, 95% CI 1.2 to 2.3).[26]

Meta-analyses based on data from individual patients in the six randomised placebo-controlled trials of alteplase found similar results to those of the systematic review.[27]

Cost of alteplase

Alteplase is licensed for the treatment of patients with acute ischaemic stroke, at a dose of 0.9mg/kg body weight (maximum dose 90mg).[28] The drug is available at a net price of £120 for 10mg, £180 for 20mg and £300 for 50mg.

The cost of treatment for a person whose weight is 75kg, for example, would be £480.

Who is eligible for alteplase?

Guidelines addressing practice in the UK, Europe and the USA recommend alteplase for treating certain adults with acute ischaemic stroke, as defined by strict criteria.[2,29-33] Similarly, the European Union summary of product characteristics (SPC) for alteplase advises restricting use of the drug in ischaemic stroke to a highly select subgroup of patients: those who are aged 18–80 years; whose symptoms began within the last 3 hours; and who have had intracerebral haemorrhage excluded by brain imaging.[28] The SPC also includes several contraindications (see box):

Contraindications for alteplase in stroke

- a high risk of haemorrhage (e.g. recent severe bleeding, major surgery or significant trauma in the past 3 months);
- symptoms beginning over 3 hours before the start of treatment or when the time of symptom onset was unknown;
- minor neurological deficit or symptoms rapidly improving before treatment [terms not defined in SPC];
- severe stroke assessed clinically (e.g. NIHSS score above 25) and/or by appropriate imaging;
- seizure at onset of stroke;
- intracranial haemorrhage on CT scan;
- symptoms suggesting subarachnoid haemorrhage;
- heparin in the previous 48 hours and a thromboplastin time exceeding the upper limit of normal;
- a history of prior stroke and concomitant diabetes;
- a prior stroke in last 3 months;
- a platelet count below 100,000/mm^3;
- a systolic blood pressure above 185mmHg or diastolic blood pressure above 110mmHg or intravenous pharmacotherapy necessary to reduce blood pressure to these limits;
- a blood glucose concentration below 50mg/dL [2.7mmol/L] or above 400mg/dL [22.2mmol/L].[28]

Use of alteplase in practice

Post-licensing safety studies

A condition for the granting of the licence (marketing authorisation) for intravenous alteplase for acute ischaemic stroke in Europe was that patients receiving thrombolytic therapy had to be registered in an observational study, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST). The intention was to assess the safety of alteplase in routine clinical practice when started within 3 hours of the onset of stroke symptoms. Data from this study showed that the baseline characteristics of the 6,483 patients registered were similar to those of the patients in the randomised controlled trials of alteplase that were used for comparison.[11] In all, 54.8% of patients in SITS-MOST were functionally independent (modified Rankin score 0–2) at 3 months (compared with 49.0% allocated to alteplase in the pooled randomised controlled trials); 7.3% in SITS-MOST (vs. 8.6% in the trials) had symptomatic intracerebral haemorrhage and 11.3% in SITS-MOST (vs. 17.3% in the trials) had died at 3 months.

A similar post-licensing study was mandated by the US Food and Drug Administration as a condition of licensing the drug in the USA.[10,21] It involved 389 patients treated with alteplase for stroke in clinical practice.[10] The study reported that at 30 days, 43% of patients were functionally independent (modified Rankin score 0–2; including 35% who had a favourable outcome i.e. score 0–1); 12% had moderate disability (score 3); 31% had moderate-to-severe disability (score 4–5) and 13% of patients had died. A total of 3.3% had had symptomatic intracerebral haemorrhage within 3 days of alteplase treatment and 8.2% had had asymptomatic intracerebral haemorrhage.

Another national prospective cohort study was carried out in Canada as a condition of licensing of alteplase in that country.[34] It included 1,135 patients treated with alteplase (started within 3 hours in 88.4%) and found that 36.8% returned to their pre-stroke level of functioning; symptomatic intracranial haemorrhage occurred in 4.6% of patients and 90-day mortality was 22.3%.

The authors of each of these safety studies concluded that alteplase was safe and effective when used within the 3-hour window in clinical practice as well as in a trial setting.[10,11,34]

How many patients receive thrombolytic therapy?

The Royal College of Physicians National Sentinel Stroke Audit stated that 870 patients received thrombolytic therapy in England, Wales and Northern Ireland in the year to April 2008, which is unlikely to represent all the patients potentially eligible.[35]

Who else might benefit?

Since the licensing of alteplase, debate has continued among specialists about whether certain patients currently excluded from treatment with alteplase might in fact benefit from such therapy. The main categories of these patients are those presenting outside the 3-hour treatment window; those with minor or rapidly improving symptoms; those with severe symptoms; and those aged over 80 years.[6,9,36-38]

Is the 3-hour treatment window justified?

Evidence from the initial studies

Meta-analysis based on data from individual patients in the six randomised placebo-controlled trials of alteplase given within 6 hours of stroke onset found that the odds of a favourable outcome (modified Rankin score 0–1, Barthel score 95–100 and NIHSS 0–1) increased as the time between stroke onset and treatment decreased (OR for benefit of alteplase compared with placebo: 2.8 [95% CI 1.8 to 4.5] for treatment starting 0–90 minutes after stroke onset; 1.6 [95% CI 1.1 to 2.2] for 91–180 minutes; 1.4 [95% CI 1.1 to 1.9] for 181–270 minutes and 1.2 [95% CI 0.9 to 1.5] for 271–360 minutes).[27] This suggested that the beneficial effect of alteplase might extend beyond 3 hours; however there seemed to be no clear benefit from treatment over 270 minutes (4.5 hours) after symptom onset.[27,39]

Additional studies

In a trial involving 101 patients who received alteplase or placebo 3–6 hours after onset of ischaemic stroke, mean infarct growth as assessed by MRI scanning (the primary outcome measure) did not differ significantly between groups (geometric mean growth at day 90 relative to baseline: 1.24 with alteplase vs. 1.78 with placebo, p=0.239).[36] Among the secondary outcome measures, reperfusion (a reduction of at least 90% between baseline and day 3 perfusion-weighted MRI) occurred in more patients on alteplase than on placebo (56% vs. 26%, p=0.01). However, there was no difference between the alteplase and placebo groups in the incidence of a good neurological outcome (NIHSS of 0–1, or improvements of 8 or more from baseline to day 90; 50% on alteplase vs. 37% on placebo, p=0.278); a good functional outcome (modified Rankin score of 0–2 at day 90; 45% vs. 40%, p=0.663); or death (25% vs. 14%, p=0.161). The trial was not specifically powered to assess these outcomes. The incidence of symptomatic intracerebral haemorrhage was 7.7% (95% CI 2.1 to 18.5) with alteplase compared with 0% on placebo (number needed to harm [NNH] 13).

In another trial, 821 patients with acute ischaemic stroke received alteplase or placebo 3–4.5 hours after stroke onset.[9] At 90 days, more patients on alteplase than placebo had a favourable outcome (modified Rankin score 0–1, the primary outcome measure; 52.4% vs. 45.2%, p=0.04; NNT 14). A secondary outcome measure was a global outcome analysis of four neurological and disability scores combined; on this measure, patients on alteplase had a higher chance of a good outcome than those on placebo (OR 1.28, 95% CI 1.00 to 1.65, p<0.05). The incidence of intracranial haemorrhage was higher with alteplase than with placebo (27.0% vs. 17.6%, p=0.001; NNH 11) but the two groups did not differ significantly in their mortality rates (7.7% vs. 8.4%). It should be noted that the NNH in this study was smaller than the NNT, suggesting an unfavourable risk-benefit ratio.

In addition, data from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Registry have been used to compare patients treated within either 3 hours or 3–4.5 hours after stroke onset.[40] There were no significant differences between these patient groups on the rate of symptomatic intracerebral haemorrhage (adjusted OR for those in whom treatment was started after 3 hours compared with under 3 hours 1.32, 95% CI 1.00 to 1.75, p=0.052); independence at 3 months (adjusted OR 0.93, 95% CI 0.84 to 1.03) or mortality at 3 months (adjusted OR 1.15, 95% CI 1.00 to 1.33, p=0.053). Overall, therefore, the evidence suggests that there may be a benefit for patients starting treatment with alteplase 3–4.5 hours after symptom onset, although this is likely to be less than for those treated earlier.

Minor or rapidly improving stroke

Using data from the NINDS trial, the NINDS study group published an analysis of the effect of alteplase on patients with minor stroke (defined as a score of 0 or 1 on every baseline pre-treatment NIHSS item, except level of consciousness, which had to be 0).[37] The odds ratio of a favourable outcome (a summary global statistic incorporating a score on the Barthel Index of 95 or above, modified Rankin Scale below 2, Glasgow Outcome Scale equal to 1 and NIHSS 0–1 at 3 months) for patients on alteplase compared with placebo was 2.0 (95% CI 1.4 to 2.7). No patients with this definition of minor stroke on alteplase or placebo had symptomatic intracerebral haemorrhage. The NINDS group also found that the odds ratio for a favourable outcome with alteplase was around 2 when four other definitions of minor stroke were used in the analysis.

In an uncontrolled observational study of 19 patients with rapid early improvement of neurological symptoms who were treated with thrombolysis, one died by the 3-month follow-up (of recurrent ischaemic strokes); none of the rest had neurological worsening and the NIHSS score was a median of 0.[41] The authors suggested that these data provided evidence against withholding alteplase on the grounds of spontaneous early regression of symptoms, but also stated that further evidence was needed.

Severe stroke

Patients with severe strokes (NIHSS score above 20) in the NINDS trial had an absolute benefit of around 4–5% in independent survival when they received alteplase within 3 hours; this is less than the benefit experienced by patients with strokes of moderate severity but still thought by some specialists to be worthwhile.[22,38]

Patients over 80 years of age

Data on thrombolytic therapy for patients aged over 80 years are mainly derived from cohort studies, since most of the randomised controlled trials deliberately excluded such patients.[6] Two reviews have concluded that there appears to be no increased risk of symptomatic intracranial haemorrhage following alteplase therapy in patients aged 80 years or above, compared to younger patients.[6,42] Although older patients have a higher mortality than younger ones and are less likely to achieve a favourable outcome after a stroke, this parallels the known poor outcome in older patients without alteplase therapy and does not appear to reflect an increased danger of alteplase use.[6,42] However, at present, there are insufficient data to recommend alteplase for these patients.

Conclusion

Alteplase was licensed for the treatment of patients with acute ischaemic stroke on the basis of evidence from initial randomised trials that showed a reduction in death and dependency when it is administered within 3 hours of onset of stroke symptoms. This benefit is partially offset by the fact that thrombolytic therapy can increase the likelihood of intracranial haemorrhage and, potentially, of early death. The summary of product characteristcs (SPC) for alteplase therefore states that in stroke, the drug should only be given to patients fulfilling strict criteria: those under the age of 80 years; whose stroke onset was within the last 3 hours; whose symptoms are neither severe nor minor nor rapidly recovering; who have had intracerebral haemorrhage excluded by

brain imaging; who do not have severe hypertension (blood pressure above 185/110mmHg); and who have no contraindications to thrombolytic therapy. At present, not all patients eligible for thrombolytic therapy actually receive it in the UK. The National Stroke Strategy aims to minimise the damage done by stroke by emphasising the importance of rapid diagnosis, transfer to hospital and assessment for eligibility for thrombolytic therapy, including rapid access to imaging and specialist services.

More recent studies have suggested that the eligibility criteria for use of thrombolytic therapy might be too conservative and that additional patients may also benefit from such treatment (e.g. those started on treatment 3–4.5 hours after the onset of symptoms; those with minor, rapidly recovering, or severe symptoms; and those aged over 80 years). However, data specifically on these groups are limited and are not sufficient to recommend treatment for them. Until further data are available, any administration of alteplase for acute ischaemic stroke outside the restricted criteria in the SPC should generally only be done within the context of a randomised clinical trial.

[R=randomised controlled trial; M=meta-analysis]

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