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Extending tPA Use for Wake-up Stroke

Hebah Hefzy

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Extending tPA Use for Wake-up Stroke

Hebah Hefzy, MD
I have no disclosures
Where it all began

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TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

The National Institute of Neurological Disorders and Stroke t-PA Stroke Study Group

Abstract Background. Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over baseline values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo (P<0.001). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group (P = 0.30).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)
Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markus Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrieu, M.D., Kenneth R. Lees, M.D., Zafkaria Medeghi, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rödiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

ABSTRACT

BACKGROUND

Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke.

METHODS

After exclusion of patients with a brain hemorrhage or major infarction, as detected on a computed tomographic scan, we randomly assigned patients with acute ischemic stroke in a 1:1 double-blind fashion to receive treatment with intravenous alteplase (0.9 mg per kilogram of body weight) or placebo. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin scale), which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

RESULTS

We enrolled a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.14; 99% confidence interval, 1.02 to 1.27; P=0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.60; P=0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 3.7% vs. 1.7%; P=0.01; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; P=0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P=0.66). There was no significant difference in the rate of other serious adverse events.

CONCLUSIONS

As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage. (ClinicalTrials.gov number, NCT0015586.)

*The European Cooperative Acute Stroke Study (ECASS) investigators are listed in the Appendix.

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September 2008
Beyond 4.5 Hours?

TOO LATE

THIS IS THE END
The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

The IST-3 collaborative group*

Summary

Background: Thrombolysis in ischaemic stroke is not effective in patients with acute ischaemic stroke who are younger than 89 years of age and are treated within 4.5 h of onset. The third International Stroke Trial (IST-3) sought to determine whether a wider range of patients might benefit up to 6 h from stroke onset.

Methods: In this international, multicentre, randomised, open-treatment trial, patients were allocated to 0.9 mg/kg intravenous recombinant tissue plasminogen activator (rt-PA) or to control. The primary analysis was the proportion of patients alive and independent, as defined by an Oxford Handicap Score (OHS), of 0–2 at 6 months. The study was registered, ISRCTN185511.

Findings: 3835 patients were enrolled by 136 hospital sites in 12 countries. All of these patients were included in the analyses (3335 in the rt-PA group vs 1520 in the control group), of whom 1517 (53%) were older than 80 years of age. At 6 months, 554 (37%) patients in the rt-PA group versus 534 (35%) in the control group were alive and independent (OHS 0–2; adjusted odds ratio [OR] 1.33, 95% CI 0.95–1.85, p = 0.18): a non-significant absolute increase of 14/1000. 95% CI 1–7–1–7. An ordinal analysis showed a significant shift in OHS scores: common OR 1.27 (95% CI 1.10–1.47, p = 0.001). Fatal or non-fatal symptomatic intracranial haemorrhage within 7 days occurred in 104 (7%) patients in the rt-PA group versus 16 (1%) in the control group (adjusted OR 6.04, 95% CI 4.07–11.8; absolute excess 58/1000, 95% CI 4.4–7.2). More deaths occurred within 7 days in the rt-PA group (163 [11%] than in the control group (147 [7%]), adjusted OR 1.60, 95% CI 1.22–2.08, p = 0.001; absolute increase 37/1000, 95% CI 17–57), but between 7 days and 6 months there were fewer deaths in the rt-PA group than in the control group, so that by 6 months, similar numbers, in total, had died (408 [27%] in the rt-PA group vs 447 [27%] in the control group).

Interpretation: For these patients recruited in IST-3, despite the early hazards, thrombolysis within 6 h improved functional outcome. Benefit did not seem to be diminished in elderly patients.

Funding: UK Medical Research Council, Health Foundation UK, Stroke Association UK, Research Council of Norway, Arbeidsmarknadsens Partners FOrskningsbolag (AFA) Insurance Sweden, Swedish Heart Lung Fund, The Foundation of Marianne and Marcus Wallenberg, Polish Ministry of Science and Education, the Australian Heart Foundation, Swedish National Health and Medical Research Council (NIMRC), Swiss National Research Foundation, Swiss Heart Foundation, Asseccatorio alla Sanita, Regione dell’Umbria, Italy, and Dastube University.

*Members listed in the appendix.
IV Alteplase in MR-Selected Patients With Stroke of Unknown Onset is Safe and Feasible:

Results of the Multicenter MR WITNESS Trial (NCT01282242)

Lee H. Schwamm, MD
Stroke Service, Massachusetts General Hospital, Harvard Medical School

Presenting on behalf of my Co-PIs Drs. Wu, Warach, Latour, Song and all the MR WITNESS Trial Investigators
80 subjects – DWI positive, FLAIR negative
  • 71% symptoms discovered at wake-up
  • 59% white, 54% male, mean age 67
  • 14% had pre-stroke mRS >1

Median NIHSS 7.5 (IQR 4.3-13.8)

Results: tPA treatment started at median of 11.3 hr from LSW
  • Time from discovery to tPA: 3.85 hr (2.83-4.25)
  • Only 1 in 80 patients had sICH for a rate of 1.25%
MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset


BACKGROUND
Under current guidelines, intravenous thrombolysis is used to treat acute stroke only if the time since the onset of symptoms was less than 4.5 hours. We sought to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on magnetic resonance imaging (MRI) would benefit from thrombolysis with the use of intravenous alteplase.

METHODS
In a multicenter trial, we randomly assigned patients who had an unknown time of onset of stroke to receive either intravenous alteplase or placebo. All the patients...
• 503 patients randomized
• median interval between the time that the patient was last known to be well and treatment initiation was 10.3 hours

Efficacy and safety of MRI based thrombolysis in wakeup stroke: RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alleplase Group (N = 234)</th>
<th>Placebo Group (N = 249)</th>
<th>Effect Variable</th>
<th>Adjusted Value (95% CI)</th>
<th>P Value</th>
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<td><strong>Primary efficacy end point</strong></td>
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<tr>
<td>Favorable outcome at 90 days — no./total no. (%)</td>
<td>131/246 (53.3)</td>
<td>102/244 (41.8)</td>
<td>Odds ratio</td>
<td>1.61 (1.09 to 2.36)</td>
<td>0.02</td>
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<td><strong>Secondary efficacy end points</strong></td>
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<td>Median score on modified Rankin scale at 90 days (IQR)</td>
<td>1 (1–3)</td>
<td>2 (1–3)</td>
<td>Common odds ratio</td>
<td>1.62 (1.17 to 2.23)</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Correlation between treatment response at 90 days and deficit level at baseline — no./total no. (%)</td>
<td>72/246 (29.3)</td>
<td>44/244 (18.0)</td>
<td>Odds ratio</td>
<td>1.38 (1.22 to 2.89)</td>
<td>0.004¶</td>
</tr>
<tr>
<td>Global Outcome Score at 90 days**</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Odds ratio</td>
<td>1.47 (1.07 to 2.04)</td>
<td>0.02¶</td>
</tr>
<tr>
<td>Median score on Beck Depression Inventory at 90 days (IQR)**</td>
<td></td>
<td></td>
<td>Mean difference (log[2])</td>
<td>-0.04 (-0.22 to 0.15)</td>
<td>0.69</td>
</tr>
<tr>
<td>Total score on EQ-SD at 90 days††</td>
<td></td>
<td></td>
<td>Mean difference (log[2])</td>
<td>-0.52 (-0.88 to -0.16)</td>
<td>0.004¶</td>
</tr>
<tr>
<td>Score on visual analog scale on EQ-SD at 90 days§§</td>
<td>72.6 (19.7)</td>
<td>64.9 (23.8)</td>
<td>Mean difference (log[2])</td>
<td>7.64 (3.73 to 11.51)</td>
<td>&lt;0.001¶</td>
</tr>
<tr>
<td>Median infant volume at 22–36 hr (IQR) — m †††</td>
<td>3.0 (0.8–17.7)</td>
<td>3.3 (1.1–16.6)</td>
<td>Mean difference (log[2])</td>
<td>-0.16 (-0.47 to 0.15)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* EQ-SD denotes EuroQol-5 Dimensions.
† Odds ratios, common odds ratios, and differences are for the alteplase group, as compared with the placebo group. Odds ratios and common odds ratios were adjusted for stratification factors (i.e., age and symptom severity) at randomization but were not adjusted for multiple comparisons.
‡ A favorable outcome was defined as a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A total of 8 patients in the alteplase group and 5 in the placebo group were lost to follow-up.
¶ The between-group comparison of median scores on the modified Rankin scale was analyzed by means of a logistic-regression model.
P Values and confidence intervals for secondary outcomes have not been adjusted for multiple comparisons and cannot be used for hypothesis testing or inference. The values are shown for reference to a post hoc calculation of a P value adjusted for seven secondary outcome comparisons. Post hoc adjustment for multiple comparisons of secondary outcomes by means of the Bonferroni method required a significance level of P<0.007.
† A correlation between the treatment response at 90 days and the deficit level at baseline was defined as a score of 0 on the modified Rankin scale among patients with mild deficits at study entry (NIHSS score, ≤4), a score of 0 or 1 among patients with moderate deficits (NIHSS score, 5 to 14), and a score of 0 to 2 among patients with severe deficits (NIHSS score, ≥15).
‡‡ The Global Outcome Score is a multidimensional calculation of a favorable outcome that combines the estimation of treatment effect on four different scales into a single odds ratio, so there is no corresponding global numerator. The four measures are a score of 0 or 1 on the modified Rankin scale and on the NIHSS, a score of 95 to 100 on the Barthel Index (which assesses 10 categories of daily function and ranges from 0 to 100, with higher values indicating better independence), and a score of 5 on the Glasgow Outcome Scale (which ranges from 1 to 5, with higher values indicating better neurologic recovery).
†† Scores on the Beck Depression Inventory range from 0 to 63, with higher scores indicating more severe depressive symptoms.
††† Total scores on the EQ-SD scale range from 0 to 10, with higher values indicating more problems across the five dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.
§§ Scores on the EQ-SD visual analog scale range from 0 (indicating the worst imaginable health state) to 100 (indicating the best imaginable health state).
††† The infant volume was measured on diffusion-weighted imaging 22 to 36 hours after randomization. The final infant volume was missing for 27 patients in the alteplase group and 15 in the placebo group.
Protocol at HFH as of October 2018

Patient with suspected stroke

- ≤ 4.5 hours
  - CT/CTA
    - LVO absent
      - Chemical thrombolysis
    - LVO present
      - Chemical thrombolysis and mechanical thrombectomy
  - LVO present (and threshold core-perfusion mismatch if 6-24 hours)
- ≥ 4.5 hours
  - CT/CTA (and CTP if ≥ 6 hours)
    - LVO absent
      - MRI
        - DWI/FLAIR mismatch present
          - Chemical thrombolysis
    - LVO present
      - Mechanical thrombectomy
Tenecteplase Structure and Pharmacokinetics

Tenecteplase is a substitution variant of alteplase

<table>
<thead>
<tr>
<th>Table: Tenecteplase Characteristics</th>
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<tr>
<td><strong>Half-life</strong></td>
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<tr>
<td><strong>Circulating fibrinogen</strong></td>
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<td><strong>Clearance</strong></td>
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<tr>
<td><strong>Indication</strong></td>
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<td><strong>Administration</strong></td>
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Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial


Summary
Background Tenecteplase is a newer thrombolytic agent with some pharmacological advantages over alteplase. Previous phase 2 trials of tenecteplase in acute ischaemic stroke have shown promising results. We aimed to investigate the safety and efficacy of tenecteplase versus alteplase in patients with acute stroke who were eligible for intravenous thrombolysis.

Methods This phase 3, randomised, open-label, blinded endpoint, superiority trial was done in 13 stroke units in Norway. We enrolled adults with suspected acute ischaemic stroke who were eligible for thrombolysis and admitted within 4-5 h of symptom onset or within 4-5 h of awakening with symptoms, or who were eligible for bridging therapy before thrombectomy. Patients were randomly assigned (1:1) to receive intravenous tenecteplase 0.4 mg/kg...
A randomised-controlled trial of tenecteplase in patients who wake up with acute ischaemic stroke

Melinda B. Roaldsen MD Department of Neurology
International Trial Manager TWIST
University Hospital of North Norway

TNK vs. placebo 4.5-24 hours from last known well
TIMELESS – PHASE III trial

Ongoing since March 2019
Tenecteplase for acute stroke with LVO
4.5-24 hour time window
Post tPA intracranial hemorrhage
Blood-Brain Barrier Prediction of Symptomatic Hemorrhagic Transformation: A Sample Case

- Absolute permeability map (ml/min/100g) from perfusion-CT scan
- Post processed perfusion-CT image
- Non-contrast CT
- Follow-up non-contrast CT

Legend:
- Infarct
- Penumbra
- Permeability Hotspots

Admission Imaging (3 hours after onset of stroke symptoms)

Follow-up Imaging

23 hours later

Parenchymal hematoma type 2
Strategies to extend tPA time window

- BBB stabilizers – reduce tPA related ICH

Studied in humans

Cilostazol 100 mg

Studied in Animals

PROGESTERONE

MINOCYCLINE

ANTI-INFLAMMATORY

Bryostatin 1
I THANK YOU FOR YOUR ATTENTION

HOPE YOU ENJOYED IT