Effect of Intravenous Recombinant Tissue-Type Plasminogen Activator in Patients With Mild Stroke in the Third International Stroke Trial-3
Post Hoc Analysis

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Background and Purpose—Randomized trial evidence on the risk/benefit ratio of thrombolysis for mild stroke is limited. We sought to determine the efficacy of intravenous recombinant tissue-type plasminogen activator (IV r-tPA) in a subset of patients with mild deficit in the third International Stroke Trial (IST-3).

Methods—IST-3 compared IV r-tPA with control within 6 hours of onset in patients for whom IV r-tPA was considered promising but unproven. Analysis was restricted to subjects randomized within 3 hours of onset with a baseline National Institutes of Health Stroke Scale ≤5, pretreatment blood pressure <185/110, and no other r-tPA exclusion criteria. We compared r-tPA and control arms for primary (Oxfordshire Handicap Score [OHS] 0–2) and secondary (ordinal OHS and OHS 0–1) outcomes at 6 months.

Results—Among 3035 IST-3 subjects, 612 (20.2%) had a National Institutes of Health Stroke Scale ≤5; of these 106 (17.6%) met the restricted criteria. Allocation to r-tPA was associated with an increase in OHS 0 to 2 (84% r-tPA versus 65% control; adjusted odds ratio, 3.31; 95% confidence interval, 1.24–8.79) and a favorable shift in OHS distribution (adjusted odds ratio, 2.38; 95% confidence interval, 1.17–4.85). There was no significant effect of r-tPA on OHS 0 to 1 (60% versus 51%; adjusted odds ratio, 1.92; 95% confidence interval, 0.83–4.43).

Conclusions—This post hoc analysis in a highly selected sample of IST-3 supports the rationale of A Study of the Efficacy and Safety of Activase (Alteplase) in Patients With Mild Stroke (PRISMS) trial—a randomized, phase IIIb study to evaluate IV r-tPA in mild ischemic stroke. (Stroke. 2015;46:2325-2327. DOI: 10.1161/STROKEAHA.115.009951.)

Key Words: clinical trials ■ stroke ■ thrombolytic therapy

Over half of ischemic strokes in the US are mild in severity (National Institutes of Health Stroke Scale [NIHSS] ≤5).1 Single-center, prospective cohorts suggest that 30% will have significant disability at 3 months after mild stroke.2 However, the optimal acute treatment of patients with mild deficits, who are otherwise eligible for intravenous recombinant tissue-type plasminogen activator (IV r-tPA), remains unestablished. Initial randomized-controlled trials of IV r-tPA explicitly excluded mild strokes.3

The more recent third International Stroke Trial (IST-3)4 was designed to determine whether a wider range of patients with ischemic stroke, including mild strokes (NIHSS ≤5), might benefit from IV r-tPA. However, among mild stroke patients enrolled in this randomized trial, 221 of 304 (72.7%) r-tPA versus 232 of 308 (75.3%) control subjects were alive and independent (Oxfordshire Handicap Score [OHS] 0–2) at 6 months.

We sought to determine whether a further, randomized trial in patients with mild stroke was justified. We, therefore, examined the effect of r-tPA in the subset of IST-3 patients who met the eligibility criteria for our planned trial.5

Methods

IST-3 was a pragmatic, international, randomized-controlled, open-treatment trial with broad entry criteria comparing IV r-tPA with control within 6 hours of onset in 3035 subjects conducted in 12 countries outside the United States between May 2000 and July 2011. The primary results4 are published.

We restricted analysis to subjects randomized within 3 hours of onset with a baseline NIHSS ≤5, pretreatment blood pressure <185/110, and no other r-tPA exclusion criteria.
1. Randomized within 3 hours of last known well
2. Pretreatment blood pressure <185/110
3. Met all other standard IV r-tPA eligibility criteri\a

Consistent with the parent trial, the primary outcome for this analysis was the proportion alive and independent (OHS, 0–2) at 6 months, and secondary outcomes were the ordinal analysis of OHS and the proportion alive and with favorable outcome (OHS, 0–1) at 6 months, adjusted for age, time to randomization, and presence of ischemic change on baseline scan.

**Results**

Among 3035 subjects enrolled in IST-3, 612 (20%) subjects had an NIHSS ≤5. Among 612 subjects with low NIHSS score, 106 (18%) had mild stroke as the sole reason for uncertainty. Specifically, 487 were excluded for randomization beyond 3 hours from last known well, 87 for blood pressure ≥185/110 (including 68 with both exclusions); none were excluded for other standard IV r-tPA exclusion criteria.

Among these 106 subjects, 55 were treated with IV r-tPA and 51 received standard medical management. Patients in each treatment arm were relatively well matched for baseline demographics and comorbidities (Table 1).

Comparing IV r-tPA and control patients, we found a nominally significant increase in the proportion alive and independent (84% versus 65%; unadjusted odds ratio [OR], 2.79; 95% confidence interval [CI], 1.03–7.91; \( P = 0.03 \)); adjusted OR, 3.31; 95% CI, 1.24–8.79; \( P = 0.02 \)), and a favorable shift in distribution of OHS grades (unadjusted OR, 1.98; 95% CI, 0.99–3.96; \( P = 0.05 \)); adjusted OR, 2.38; 95% CI, 1.14–4.85; \( P = 0.02 \)) as demonstrated in the Figure. There was no significant effect on favorable outcome (60% versus 51%; unadjusted OR, 1.44; 95% CI, 0.62–3.34; \( P = 0.35 \)); adjusted OR, 1.92; 95% CI, 0.83–4.43; \( P = 0.13 \).

There were no symptomatic intracranial hemorrhages in the r-tPA–treated group (0/55; 95% CI, 0%–8%), as per the IST-3 trial definition of significant neurological deterioration.4 This post hoc analysis supports further testing of IV r-tPA in patients with mild ischemic strokes. A nominally significant effect was observed for the prespecified primary outcome of the parent IST-3, and the direction of effect was supportive for secondary outcomes as well.

This analysis approach allowed us to estimate the effect of r-tPA in the type of mild stroke patient likely to be included in our planned trial because the majority (82%) of the overall IST-3 cohort with NIHSS 0 to 5 had other relative contraindications to r-tPA. Chiefly, 80% were treated beyond 3 hours of stroke onset, and the potential benefit of reperfusion therapies is known to be highly time-dependent.7 In addition, 14% had the contraindication to IV r-tPA of elevated baseline blood pressure.6

Previous randomized trials of IV r-tPA had excluded patients with milder strokes based on varied exclusion criteria (Table 2).1 Pooled analysis of the few subjects with NIHSS 0 to 4 enrolled in these major completed trials has demonstrated encouraging results of potential IV r-tPA efficacy in mild stroke despite a 0.9% risk of fatal intracranial hemorrhage.4 However, recent exploratory data from IST-3 have suggested an adverse effect of r-tPA within 6 hours of stroke onset on long-term survival among strokes with better predicted prognosis (>50% with functional recovery).9

Limitations of this analysis include its post hoc design and small sample size. Randomized, prospective data are needed to confirm this finding. This is particularly relevant to estimating the risk of fatal or disabling intracranial hemorrhage.

Our analysis of this highly selected sample of IST-3 supports the rationale of A Study of the Efficacy and Safety of Activase (Alteplase) in Patients With Mild Stroke (PRISMS) trial,5 an ongoing, randomized, placebo-controlled, phase IIIb, 948-subject, 75-center, study evaluating the efficacy and particularly the safety of IV r-tPA in mild ischemic strokes. Mild stroke is defined as NIHSS ≤5 and not clearly disabling.

**Discussion**

This post hoc analysis supports further testing of IV r-tPA in patients with mild ischemic strokes. A nominally significant effect was observed for the prespecified primary outcome of the parent IST-3, and the direction of effect was supportive for secondary outcomes as well.

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**Table 1. Demographics of IST-3 Mild Stroke Subcohort**

<table>
<thead>
<tr>
<th>Median Value</th>
<th>IV r-tPA (n=55)</th>
<th>Control (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median yr)</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>43.6%</td>
<td>37.3%</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>18.1%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Baseline NIHSS (median)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>SBP at randomization (median mm Hg)</td>
<td>152</td>
<td>156</td>
</tr>
<tr>
<td>Baseline glucose (median mmol/L)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Baseline ischemic change on CT (%)</td>
<td>25.5%</td>
<td>15.7%</td>
</tr>
<tr>
<td>Time to randomization (median h)</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Table 2. Exclusion Criteria for Mild Deficits in Previous Randomized, Intravenous Thrombolysis Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Exclusion Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS parts 1 and 2</td>
<td>Rapidly improving or minor symptoms (including 4 prespecified syndromes)</td>
</tr>
<tr>
<td>ECASS I and II</td>
<td>Scandinavian Stroke Scale score ≤50</td>
</tr>
<tr>
<td>ATLANTIS A and B</td>
<td>NIHSS ≤4 and normal speech and visual fields</td>
</tr>
<tr>
<td>ECASS III</td>
<td>Symptoms rapidly improving or only minor before start of infusion</td>
</tr>
<tr>
<td>EPISTHET</td>
<td>NIHSS &lt;5</td>
</tr>
</tbody>
</table>

ATLANTIS indicates Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS, European Cooperative Acute Stroke Study; EPISTHET, Echoplanar Imaging Thrombolytic Evaluation Trial; NIHSS, National Institutes of Health Stroke Scale; and NINDS, National Institute of Neurological Disorders and Stroke.
Sources of Funding

Third International Stroke Trial was supported Medical Research Council, Stroke Association, The Health Foundation, The Research Council of Norway, Arbetsmarknadens försäkringsbolag Insurances (Sweden), the Swedish Heart Lung Fund, Chest Heart Stroke Scotland, UK Medical Research Council, UK Age UK, UK Row Fogo Charitable Trust, The Scottish Funding Council, The Foundation of Marianne and Marcus Wallenberg, Karolinska Institute, the Government of Poland, the Australian Heart Foundation, Australian National Health and Medical Research Council (NHMRC), the Swiss National Research Foundation, the Swiss Heart Foundation, the Foundation for health and cardio-/neurovascular research, Basel, Switzerland and the Assessorato alla Sanita, Regione dell’Umbria. The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336. PRISMS Trial was supported by Genentech, Inc.

Disclosures

Financial support to Dr Khatri department for her research roles from Genentech (PRISMS Trial PI), Penumbra (THERAPY Trial Neuro PI), and Biogen (DSMB member). Dr Tayama is an employee of Genentech and a shareholder of Roche. Genentech is the manufacturer and distributor of Activase, a biopharmaceutical used in the treatment of patients with acute ischemic stroke. Dr Wardlaw is a IST-3 Steering Committee member; coordinates Cochrane Database of Systematic Reviews review of thrombolysis in acute ischemic stroke; her institution received academic funding from Govt sources to undertake IST-3. Dr Yeatts is a statistician for National Institute of Neurological Disorders and Stroke-funded Interventional Management of Stroke (IMS) III trial; receives consultant fees from Genentech for PRISMS Steering Committee. Dr Broderick received research monies to his department from Genentech for PRISMS Steering Committee; travel to Australian conference paid by Boehringer Ingelheim; study medication from Genentech and catheters from Concentric, EKOS, and Cordis for IMS III. Dr Sandercock is a co-chief investigator of the IST-3; his institution received academic funding from Government sources to undertake IST-3; drug/placebo donated by Boehringer Ingelheim; honoraria from Boehringer Ingelheim for Scientific Committee member, Coviden for 2 lectures, and Pfizer for a project.

References

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Stroke. 2015;46:2325-2327; originally published online June 23, 2015;
doi: 10.1161/STROKEAHA.115.009951

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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