Low-Dose Intravenous Recombinant Tissue-Type Plasminogen Activator Therapy for Patients With Stroke Outside European Indications

Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry

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Background and Purpose — The purpose of this study was to determine the safety and efficacy of intravenous recombinant tissue-type plasminogen activator (0.6 mg/kg alteplase) within 3 hours of stroke onset in Japanese patients outside the indications in the European license.

Methods — Of the 600 patients who were treated with recombinant tissue-type plasminogen activator, 422 met the inclusion criteria of the European license (IN group) and 178 did not (OUT group).

Results — The OUT group was inversely associated with any intracerebral hemorrhage (adjusted OR, 0.50; 95% CI, 0.29–0.84), positively associated with an unfavorable outcome (2.48; 1.55–3.94) and mortality (2.04; 1.02–4.04), and not associated with symptomatic intracerebral hemorrhage (0.53; 0.11–1.79) or complete independency (0.65; 0.40–1.03) after multivariate adjustment.

Conclusions — Functional and vital outcomes 3 months after low-dose recombinant tissue-type plasminogen activator in patients outside the European indications were less favorable compared with those included in the indications; however, the risk of intracerebral hemorrhage was not. (Stroke. 2012;43:253-255.)

Key Words: acute stroke ▪ diabetes mellitus ▪ elderly patients ▪ intracerebral hemorrhage ▪ outcomes ▪ thrombolysis

Patients with severe stroke as indicated by a baseline National Institutes of Health Stroke Scale (NIHSS) score of ≥25, those >80 years old, and those with any history of prior stroke and concomitant diabetes were excluded from a European postmarketing monitoring study for intravenous recombinant tissue-type plasminogen activator (rtPA) therapy (the Safe Implementation of Thrombolysis in Stroke-Monitoring STudy [SITS-MOST] registry) without sufficient rationale.1 European regulatory agencies do not advocate rtPA therapy for patients having such exclusion items. Using our multicenter registry,2 this study documented the safety and efficacy of low-dose intravenous rtPA (0.6 mg/kg) in patients with stroke outside the European indications as compared with those who fulfilled the SITS-MOST criteria.

Patients and Methods

Patients were derived from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry.3 Patient eligibility for alteplase was determined based on the Japanese guideline4 stating that patients >75 years old, those with NIHSS score ≥23, those with a history of prior stroke, and those with poorly controlled diabetes are to be carefully considered but not excluded. Other exclusion criteria are almost identical between the European and Japanese indications. Each patient received alteplase (0.6 mg/kg) intravenously with 10% given as a bolus within 3 hours of stroke onset and the remainder delivered through continuous intravenous infusion over 1 hour. Patients not meeting the inclusion criteria of the European license were categorized into the OUT group and those who did were categorized into the IN group.

Outcomes included: any and symptomatic intracerebral hemorrhage (ICH) within the initial 36 hours, complete independence...
Symptomatic ICH was defined as that associated with neurological deterioration corresponding to an increase of 4 points from the baseline NIHSS score.

To evaluate the independent effect of the OUT group and each exclusion criterion on the clinical outcomes, a multivariate logistic regression model was estimated adjusting for sex, hypertension, dyslipidemia, atrial fibrillation, onset-to-treatment time, Alberta Stroke Programme Early CT Score, and internal carotid artery occlusion. The model was adjusted for: patients 80 years using NIHSS score, prior stroke, and diabetes; patients with NIHSS score ≥25, using age, prior stroke, and diabetes; and patients with prior stroke plus diabetes using age and NIHSS score.

Results

Of the 600 patients, 178 (85 men; age, 81.7±8.6 years) were categorized into the OUT group and the remaining 422 (292 men; 67.7±10.5 years) into the IN group. A higher percentage of patients in the OUT group were female, older, hypertensive, diabetic, and had higher initial NIHSS scores and internal carotid artery occlusion compared with the IN group (Supplemental Table I; http://stroke.ahajournals.org). Of the OUT group, 129 patients were 80 years old, 40 had severe stroke with an NIHSS score ≥25, and 25 had prior stroke plus diabetes.

Table. Safety and Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>IN Group (N=422)</th>
<th>OUT Group (N=178)</th>
<th>≤80 Y (N=471)</th>
<th>&gt;80 Y (N=129)</th>
<th>≤25 (N=560)</th>
<th>≥25 (N=40)</th>
<th>Absent (N=575)</th>
<th>Present (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ICH within 36 h, no. (%)</td>
<td>93 (22.0)</td>
<td>26 (14.6)</td>
<td>96 (20.4)</td>
<td>23 (17.8)</td>
<td>113 (20.2)</td>
<td>6 (15.0)</td>
<td>116 (20.2)</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1 0.50 (0.29–0.84)*</td>
<td>1 0.83 (0.46–1.46)</td>
<td>1 0.62 (0.22–1.46)</td>
<td>1 0.32 (0.05–1.16)</td>
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<tr>
<td>Symptomatic ICH, no. (%)</td>
<td>13 (3.1)</td>
<td>3 (1.7)</td>
<td>15 (3.2)</td>
<td>1 (0.8)</td>
<td>15 (2.7)</td>
<td>1 (2.5)</td>
<td>15 (2.6)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1 0.53 (0.11–1.79)</td>
<td>1 0.27 (0.01–1.47)</td>
<td>1 1.17 (0.06–6.88)</td>
<td>1 1.32 (0.07–7.70)</td>
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<tr>
<td>mRS 0–1, no. (%) (N=532)</td>
<td>161 (40.5)</td>
<td>35 (26.1)</td>
<td>173 (39.4)</td>
<td>23 (24.7)</td>
<td>191 (38.2)</td>
<td>5 (15.6)</td>
<td>189 (38.8)</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1 0.65 (0.40–1.03)</td>
<td>1 0.58 (0.31–1.04)</td>
<td>1 0.40 (0.13–1.05)</td>
<td>1 0.97 (0.32–2.91)</td>
<td></td>
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<tr>
<td>mRS 5–6, no. (%)</td>
<td>68 (16.1)</td>
<td>69 (38.8)</td>
<td>86 (18.3)</td>
<td>51 (39.5)</td>
<td>117 (20.9)</td>
<td>20 (50.0)</td>
<td>128 (22.3)</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1 2.48 (1.55–3.94)†</td>
<td>1 2.36 (1.36–4.09)†</td>
<td>1 3.23 (1.51–6.97)†</td>
<td>1 2.35 (0.81–6.44)</td>
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<tr>
<td>Mortality, no. (%)</td>
<td>20 (4.7)</td>
<td>23 (12.9)</td>
<td>25 (5.3)</td>
<td>18 (14.0)</td>
<td>34 (6.1)</td>
<td>9 (22.5)</td>
<td>41 (7.1)</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1 2.04 (1.02–4.04)*</td>
<td>1 2.00 (0.93–4.24)</td>
<td>1 3.75 (1.45–9.09)†</td>
<td>1 1.54 (0.23–6.24)</td>
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</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; CI, confidence interval; OR, odds ratio.

*P<0.05.
†P<0.01.
‡P<0.001.
§Assessed for patients who had premorbid mRS 0–1.
After multivariate adjustment, any ICH was less common in patients in the OUT group than those in the IN group, but the frequency of symptomatic ICH did not differ significantly between the groups. Unfavorable outcome and death were more common in the OUT group than in the IN group and in patients with a NIHSS score ≥25 compared with those <25. Unfavorable outcome was also more common in patients >80 years than those ≤80 years (Table). The Figure shows the distribution of patients and their modified Rankin Scale scores at 3 months.

Discussion

More than 25% of ischemic strokes occur in patients ≥80 years old in Japan. Advanced age was reported to be a strong predictor of poor outcomes and mortality independent of other clinical characteristics. Randomized trials on rTPA did not include a sufficient number of patients with advanced age. In the National Institute of Neurological Disorders and Stroke trial, rtPA treatment was associated with increased likelihood of favorable outcome 3 months after stroke even in 49 patients aged >75 years with a NIHSS score >20 as compared with the placebo group. Risk of symptomatic ICH after thrombolysis did not increase, although clinical outcomes were worse in patients >80 years old as compared with younger patients in several studies. An adjusted, controlled comparison based on 3472 patients >80 years old showed a better distribution of the modified Rankin Scale in thrombolysis patients than nonthrombolysis patients. In this study, 0.6 mg/kg of alteplase may have caused the relatively small number of symptomatic ICH both in patients older than and ≤80 years old.

Diabetes mellitus was independently associated with symptomatic ICH after standard-dose rtPA therapy. In frequent development of ICH in our cohort and exclusion of patients with premorbid modified Rankin Scale ≥2 from the outcome analysis might weaken the impact of prior stroke plus diabetes on outcomes in this study. The small number of patients with prior stroke plus diabetes might also affect the statistical power. This was not a randomized controlled study, subgroups were small, and physicians used judgment in selecting patients, all of which limit this study and introduce potential for error. In addition, data for patients with stroke who did not undergo thrombolysis were not collected and a comparison of patients with and without thrombolysis was not done.

In conclusion, 3-month outcomes after low-dose rtPA in patients outside the European indications were less favorable compared with those included in the indications. Low-dose intravenous rtPA therapy may be safely administered to patients outside the European indications without an increase of ICH by careful selection of patients. Patients with prior stroke and concomitant diabetes seem to be appropriate candidates for rtPA therapy.

Sources of Funding

This study was supported in part by Grants-in-Aid (H20-Junkanki-Ippan-019, H23-Junkanki-Ippan-010) from the Ministry of Health, Labor, and Welfare, Japan (MHLW-Japan) and a Grant from the Japan Cardiovascular Research Foundation (Bayer Scholarship for Cardiovascular Research).

Disclosures


References

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*Stroke*. 2012;43:253-255; originally published online September 29, 2011; doi: 10.1161/STROKEAHA.111.631176

*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:
http://stroke.ahajournals.org/content/43/1/253

Data Supplement (unedited) at:
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## Online Supplement Table

Baseline characteristics of patients within and outside the European indications

<table>
<thead>
<tr>
<th></th>
<th>OUT-group</th>
<th>IN-group</th>
<th>&gt;80 years</th>
<th>NIHSS ≥25</th>
<th>Prior stroke + diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 178)</td>
<td>(N = 422)</td>
<td>(N = 129)</td>
<td>(N = 40)</td>
<td>(N = 25)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>85 (47.8)</td>
<td>292 (69.2)‡</td>
<td>50 (38.8)‡</td>
<td>20 (50.0)</td>
<td>18 (82.0)</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>81.7 ± 8.6</td>
<td>67.7 ± 10.5‡</td>
<td>85.8 ± 4.1‡</td>
<td>75.9 ± 10.0*</td>
<td>71.9 ± 7.7</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension, n (%)</td>
<td>121 (68.0)</td>
<td>245 (58.6)*</td>
<td>86 (66.7)</td>
<td>24 (60.0)</td>
<td>21 (84.0)*</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>42 (23.6)</td>
<td>68 (16.2)*</td>
<td>17 (13.2)</td>
<td>2 (5.0)*</td>
<td>25 (100)‡</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>30 (17.0)</td>
<td>95 (22.8)</td>
<td>16 (12.5)†</td>
<td>4 (10.0)</td>
<td>12 (48.0)‡</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>93 (52.8)</td>
<td>165 (39.9)</td>
<td>71 (55.9)‡</td>
<td>23 (57.5)</td>
<td>10 (40.0)</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolism, n (%)</td>
<td>126 (70.8)</td>
<td>254 (60.2)</td>
<td>95 (73.6)</td>
<td>33 (82.5)</td>
<td>13 (52.0)</td>
</tr>
<tr>
<td>Large-artery atherosclerosis, n (%)</td>
<td>19 (10.7)</td>
<td>72 (17.1)</td>
<td>11 (8.5)</td>
<td>2 (5.0)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Small-vessel occlusion, n (%)</td>
<td>7 (3.9)</td>
<td>22 (5.2)</td>
<td>4 (3.1)</td>
<td>0 (0)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>26 (14.6)</td>
<td>74 (17.5)</td>
<td>19 (14.7)</td>
<td>5 (12.5)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Onset-to-treatment time [min, median (IQR)]</td>
<td>150 (125-170)</td>
<td>145 (120-165)</td>
<td>145 (123-165)</td>
<td>151 (129-171)</td>
<td>155 (140-169)</td>
</tr>
<tr>
<td>Initial NIH Stroke Scale [median (IQR)]</td>
<td>16 (10-23.25)</td>
<td>11 (7-17)‡</td>
<td>15 (10-21)‡</td>
<td>27 (26-32.5)‡</td>
<td>11 (7-16.5)</td>
</tr>
<tr>
<td>ASPECTS [median (IQR)]</td>
<td>9 (8-10)</td>
<td>9 (8-10)</td>
<td>10 (8-10)</td>
<td>10 (7-10)</td>
<td>10 (8.25-10)</td>
</tr>
<tr>
<td>Internal carotid artery occlusion, n (%)</td>
<td>41 (23.2)</td>
<td>50 (12.0)‡</td>
<td>29 (22.7)†</td>
<td>10 (25.0)</td>
<td>5 (20.0)</td>
</tr>
</tbody>
</table>

NIHSS = National Institute of Health Stroke Score; SD = Standard deviation; IQR = interquartile range; ASPECTS = Alberta Stroke Programme Early CT Score

* p <0.05, † p <0.01, ‡ p <0.001 vs. each opposite group