Effects of 0.6 mg/kg Intravenous Alteplase on Vascular and Clinical Outcomes in Middle Cerebral Artery Occlusion
Japan Alteplase Clinical Trial II (J-ACT II)

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Background and Purpose—The purpose of this study was to evaluate further the efficacy of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in patients with middle cerebral artery occlusion in a postmarketing Phase IV trial of prospective cohort study design.

Methods—Alteplase was given intravenously at 0.6 mg/kg to patients with ischemic stroke within 3 hours of onset with MR angiography-documented middle cerebral artery occlusion. Vascular outcome was evaluated by MR angiography at 6 and 24 hours after symptom onset based on the modified Mori grade. The primary end points also included a favorable outcome (modified Rankin Scale 0 to 1 at 3 months after onset) and incidence of symptomatic intracranial hemorrhage within 36 hours after treatment. The impact of recanalization on clinical outcome was assessed by stepwise logistic regression analysis.

Results—Fifty-eight patients were enrolled. Recanalization was noted in 51.7% on 6-hour MR angiography and 69.0% on 24-hour MR angiography. A favorable clinical outcome was achieved in 46.6%. None had symptomatic intracranial hemorrhage. In logistic regression models, recanalization on either 6-hour or 24-hour MR angiography was an independent predictor for clinical outcome as well as the baseline National Institutes of Health Stroke Scale score.

Conclusions—Early recanalization of an occluded middle cerebral artery can be provoked by 0.6 mg/kg intravenous alteplase and may induce a favorable clinical outcome. The rates of recanalization and favorable outcome are comparable to that previously reported with the 0.9-mg/kg dose. (Stroke. 2010;41:461-465.)

Key Words: acute ischemic stroke ■ middle cerebral artery occlusion ■ magnetic resonance angiography ■ recanalization ■ tissue plasminogen activator

Based on the Japan Alteplase Clinical Trial (J-ACT) in 2002 to 2003, the Ministry of Health, Labor and Welfare of Japan approved alteplase at 0.6 mg/kg for treating acute ischemic stroke within 3 hours of symptom onset in October 2005. Although the internationally recommended dosage is 0.9 mg/kg, the 0.6-mg/kg dose had been selected according to previous tissue plasminogen activator data in Japan. The underlying rationale has been published on the Stroke web site (http://stroke.ahajournals.org/cgi/content/full/37/7/1810). In J-ACT, the efficacy and safety of 0.6 mg/kg intravenous alteplase for ischemic stroke were examined in a prospective cohort study and were compared with data reported for 0.9 mg/kg alteplase in North America and the European Union; the efficacy and safety profiles were compatible with those in the National Institute of Neurological Disorders and Stroke study and those in a meta-analysis of data for 0.9 mg/kg. One of the conditions required by the Ministry of Health, Labor and Welfare at the time of approval was that the dosage efficacy, including potential for occluded artery recanalization, should be documented in an angiography-based study. J-ACT II is thus a prospective cohort study, in which vascular outcome, that is, recanalization of an occluded middle cerebral artery, was documented by MR angiography (MRA) as well as clinical outcome. Recanalization of occluded arteries directly reflects the pharmacological effect of thrombolytics, and early recanalization after thrombolytic therapy represents a powerful factor affecting clinical outcome.

Methods
J-ACT II, a prospective, single-dose, open-label, multicenter, Phase IV trial, was performed at 15 centers in Japan between March 2007...
and July 2008. The protocol was approved by the Institutional Review Board at each center. Written informed consent was obtained from each patient or an appropriate family member before participation in this study. The patients with ischemic stroke within 3 hours of onset whose responsible arterial occlusion was identified in the middle cerebral artery (M1 or M2 segment) by MRA were given 0.6 mg/kg intravenous alteplase with 10% being administered as a bolus followed by continuous infusion of the remainder over 1 hour. Exclusion criteria were adopted from the National Institute of Neurological Disorders and Stroke rtPA Stroke Study5 and J-ACT.1

Exclusion criteria were adopted from the National Institute of Neurological Disorders and Stroke rtPA Stroke Study5 and J-ACT.1 Also excluded were patients whose National Institutes of Health Stroke Scale (NIHSS) score was ≥23, those contraindicated for MRI, those whose MRA demonstrated arterial occlusions other than of the middle cerebral artery, or whose Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was ≥6. Only CT and MRA were considered for subject selection, although diffusion-weighted images were also obtained to investigate their role in selecting patients (data to be reported elsewhere).

MRA Protocol

Before the study, the MRI conditions were standardized to unify the image quality among all participating sites. For MRI and MRA, a 1.5-T echoplanar imaging-equipped scanner was used. Three-dimensional time-of-flight MRA was performed under the following conditions: axial images parallel to the anterior commissure–posterior commissure plane; scanning range from the pontomedullary junction to the corpus callosum; slice thickness 1 to 1.5 mm; and field of view 200 to 240 mm. MRA images were processed by maximum intensity projection to create images of the axial projection and in rotation about the vertical axis (RL rotation, 15° to 18°). MRA was repeated at baseline, 6 hours, and 24 hours after symptom onset. The time allowance for 6-hour MRA was between the end of alteplase infusion and 8 hours from symptom onset and that for 24-hour MRA was between 24 and 36 hours after symptom onset. Arterial occlusion was assessed by 2 reviewers, one expert neurologist and one expert neuroradiologist (the image reading panel) blinded to information except the affected side. Recanalization was evaluated according to the modified Mori grade: Grade 0, no reperfusion; Grade 1, movement of thrombus not associated with any flow improvement; Grade 2, partial (branch) recanalization in <50% of the branches in the occluded arterial territory; and Grade 3, nearly complete recanalization with reperfusion in ≥50% of the branches in the occluded-arterial territory (Figure). Modifications were made to apply the original scheme,2 which was developed for conventional angiography, to MRA, because distal arterial branches are not visible on MRA. The recanalization rate was estimated by regarding Grades 2 and 3 as valid recanalization corresponding to Thrombolysis in Myocardial Infarction Grades 2 and 3.

Clinical Evaluations

As a primary outcome, the functional outcome after 3 months was assessed by the modified Rankin Scale (mRS). Symptomatic intracranial hemorrhage was designated as CT evidence of intracranial hemorrhage accompanied by apparent neurological deterioration defined as conditions that could be documented objectively or were increased by ≥4 points from the latest NIHSS score. CT images obtained at 24 to 36 hours were assessed by the image reading panel. According to the European Cooperative Acute Stroke Study CT criteria, the panel classified hemorrhagic transformation as none, hemorrhagic infarction (HI-1 and HI-2), or parenchymal hematoma (PH-1 and PH-2).

End Points

The primary end points were modified Mori Grade 2 and 3 recanalization on 6-hour MRA and 24-hour MRA and a favorable outcome of mRS 0 to 1 at 3 months. The safety primary end point was symptomatic intracranial hemorrhage within 36 hours. If data were missing at any follow-up time point, data were imputed using the “last observation carried forward.”

To test the hypothesis, we used a similar strategy to the one-arm trial, J-ACT: the incidences of the primary end points were compared with the results of a meta-analysis of published data on thrombolysis. First, we searched MEDLINE and Current Contents as of March 2006 using the following key words: (acute stroke OR ischemic stroke) AND tPA AND angiography. Publications incorporating information concerning the present primary end points were selected to determine the target reference values. Based on the 5 publications selected,2,3,7–9 we determined a target value for the recanalization rate on 6-hour MRA; the weighted average recanalization rate was 45.1% in 113 patients. The 90% CI of the recanalization rate in 50 patients (the target patient number for this study) was estimated to be 33.5% to 56.8% (normal approximation without sequential correction). In the present study, the treatment aim was thus for a recanalization rate of not <33.5%, the lower limit of the 90% CI. Similarly, we determined a target value for the recanalization rate on 24-hour MRA of not <57.7% based on one publication.10

Second, we repeated the database survey with a different search strategy: (acute stroke OR ischemic stroke) AND middle cerebral artery AND (tissue plasminogen activator OR urokinase OR prourokinase). Based on the 2 publications found in the literature search11,12 and unpublished data from the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT-J), which was published during this study,13 we estimated the weighted mean proportion of patients with a favorable outcome at 3 months to be 33.6% and the 90% CI in 50 patients to be 22.6% to 44.6%. From data in 3 publications9,14,15 and MELT-J,13 we estimated the
Table 1. Demographics and Baseline Characteristics of Patients (n=58)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.3 (11.5)</td>
</tr>
<tr>
<td>Sex, females</td>
<td>23 (39.7%)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>62.1 (11.7)</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>12 (5–22)</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>49 (84.5%)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>5 (8.6%)</td>
</tr>
<tr>
<td>Other/not differentiated</td>
<td>4 (6.9%)</td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>41 (70.7%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>148.5 (16.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.2 (12.1)</td>
</tr>
<tr>
<td>Blood glucose, mg/dL</td>
<td>132.9 (46.2)</td>
</tr>
<tr>
<td>Time elapsed, hours</td>
<td></td>
</tr>
<tr>
<td>Onset to treatment</td>
<td>2.2 (0.4)</td>
</tr>
<tr>
<td>Onset to 6-hour MRA</td>
<td>5.9 (1.4)</td>
</tr>
<tr>
<td>End of tPA infusion to 6-hour MRA</td>
<td>2.7 (1.3)</td>
</tr>
<tr>
<td>Onset to 24-hour MRA</td>
<td>27.1 (2.7)</td>
</tr>
<tr>
<td>End of tPA infusion to 24-hour MRA</td>
<td>23.9 (2.7)</td>
</tr>
</tbody>
</table>

Data show the mean (SD), median (range), or no. (%). tPA indicates tissue plasminogen activator.

Results

Fifty-eight patients were enrolled in this study and were included in the full analysis set both for primary safety and for primary efficacy. One patient had no occluded artery on baseline MRA according to the image reading panel and was excluded from further analysis. Table 1 summarizes the patients’ characteristics.

The recanalization rate on 6-hour MRA was 51.7% (Table 2). The recanalization rate did not differ significantly between M1 and M2 occlusions (48.8% versus 62.5%, respectively; P=0.391). In all except 2 patients who were withdrawn or had an obstacle for MRI, 24-hour MRA was available. The recanalization rate on 24-hour MRA was 69.0% (Table 2). Delayed recanalization was noted in 10 patients (17.5%). No patient had recanalization on 6-hour MRA that subsequently disappeared on 24-hour MRA.

Three-month clinical outcomes were unavailable in 2 patients; one withdrew consent and the other was discharged earlier with an mRS of 4. Both were categorized as having an “unfavorable outcome.” The proportion of a favorable outcome at 3 months was 46.6% (95% CI, 33.7% to 59.4%). Death within 3 months after onset occurred in one patient (1.7%), who died of septic shock at 50 days after entry. An alteplase-related serious adverse event occurred in one patient, who had an ischemic stroke on the side opposite to the original stroke 12 hours after alteplase infusion.

The proportion of a favorable outcome was significantly higher in patients with recanalization than in those without recanalization on either 6-hour or 24-hour MRA (Table 3). In a logistic regression model with 6-hour MRA entered as an independent variable, recanalization (OR, 6.030; 95% CI, 1.730 to 21.011) and baseline NIHSS (OR, 0.841; 95% CI, 0.719 to 0.983) emerged as independent predictors of a favorable outcome. In another model with 24-hour MRA entered, recanalization (OR, 21.231; 95% CI, 3.318 to 135.859) and baseline NIHSS (OR, 0.796; 95% CI, 0.672 to 0.943) were also independent predictors of a favorable outcome. The model with delayed recanalization revealed 6-hour recanalization (OR, 23.036; 95% CI, 3.474 to 135.859) and baseline NIHSS (OR, 0.796; 95% CI, 0.672 to 0.943) as independent predictors of a favorable outcome.

Statistical Analysis

The effect of recanalization on clinical outcome was assessed by comparing the proportion of a favorable outcome at 3 months between patients with and without recanalization using Fisher exact test, which was also expressed as the ORs and 95% CI. To examine the effects of baseline characteristics and recanalization on clinical outcome, disease-related factors, including time from onset, hypertension, diabetes mellitus, baseline NIHSS, occluded site (M1 or M2), and ASPECTS, and recanalization on either 6-hour MRA or 24-hour MRA were included in a stepwise regression analysis, in which age and sex were forcibly entered into the model to adjust for their possible confounding effects. To assess the possible interaction of recanalization with severity of disease/schema, interaction terms between recanalization and NIHSS, ASPECTS, or occlusion site were entered into the model. Furthermore, to examine the effect of delayed recanalization (ie, arterial occlusion unchanged on 6-hour MRA but recanalized on 24-hour MRA), a similar analysis was repeated, in which both delayed recanalization and early recanalization on 6-hour MRA were entered into the model. Significance was set at P<0.05 in all final models. The OR and 95% CI were also determined. SAS 9.1.3 was used for the statistical analyses.

Table 2. Vascular Conditions and Recanalization After Thrombolysis

<table>
<thead>
<tr>
<th>Time</th>
<th>Modified Mori Grade</th>
<th>Recanalization Rate (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-hour MRA</td>
<td>0</td>
<td>51.7 (38.9–64.6)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>21†</td>
</tr>
<tr>
<td></td>
<td>Percent</td>
<td>36.2</td>
</tr>
<tr>
<td></td>
<td>24-hour MRA</td>
<td>69.0 (57.1–80.9)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>12†</td>
</tr>
<tr>
<td></td>
<td>Percent</td>
<td>40.7</td>
</tr>
</tbody>
</table>

*Valid recanalization (Mori Grade 2 or 3) and 95% CI.
†Including one patient whom the image reading panel judged as having no occlusion on baseline MRA.
‡Including 2 patients in whom data were imputed using the “last observation carried forward” for missing 24-hour MRA.

Table 3. Relationship Between Vascular Outcome and Clinical Outcome at 3 Months

<table>
<thead>
<tr>
<th>Time</th>
<th>Favorable (mRS 0–1)</th>
<th>Unfavorable (mRS ≥2)</th>
<th>OR [95% CI] Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-hour MRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recanalized</td>
<td>20 (66.7%)</td>
<td>10 (33.3%)</td>
<td>5.714 [1.814–18.004] P=0.003</td>
</tr>
<tr>
<td>Not recanalized</td>
<td>7 (25.9%)</td>
<td>20 (74.1%)</td>
<td></td>
</tr>
<tr>
<td>24-hour MRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recanalized</td>
<td>25 (62.5%)</td>
<td>15 (37.5%)</td>
<td>12.500 [2.503–62.428] P&lt;0.001</td>
</tr>
<tr>
<td>Not recanalized</td>
<td>2 (11.8%)</td>
<td>15 (88.2%)</td>
<td></td>
</tr>
</tbody>
</table>
152.753), delayed recanalization (OR, 15.949; 95% CI, 1.710 to 148.762), and baseline NIHSS (OR, 0.801; 95% CI, 0.675 to 0.951) as independent predictors of a favorable outcome.

No patient had symptomatic intracranial hemorrhage within 36 hours. Asymptomatic intracranial hemorrhage was present in 19.0% of patients (11 of 58) on CTs at 24 to 36 hours, but no patient had parenchymal hematoma 2.

**Discussion**

This is the first prospective multicenter clinical trial to evaluate recanalization of occluded arteries by MRA shortly after tissue plasminogen activator administration and at 24 hours. The recanalization rates immediately (2.7 hours on average) after treatment and at 24 hours (23.9 hours on average) after treatment were 51.7% and 69.0%, respectively, exceeding the predetermined thresholds. A systematic review in May 2009 revealed that the weighted average of the recanalization rate in the placebo arm of randomized controlled trials of thrombolysis examined by conventional angiography or MRA was 19.8% up to 8 hours after onset.2,3,12,16 The recanalization rate in the present study was thus considered likely to be much higher than the rate of spontaneous recanalization.

Concerning clinical outcomes, the proportion of a favorable outcome at 3 months (46.6%) fairly well exceeded the predetermined threshold. The systematic review in May 2009 revealed that the weighted average of the proportion of a favorable outcome (mRS 0 or 1) for patients with middle cerebral artery occlusion in the placebo arm of randomized controlled trials of thrombolysis was 22.3%.11–13,16 The proportion of a favorable outcome in the present study was considered likely to be much higher than that in the natural course of patients with middle cerebral artery occlusion.

The present findings indicated that 0.6 mg/kg intravenous alteplase is, as expected, effective in terms of vascular and clinical outcomes. The most critical limitations of this study arise from the lack of a control group, a postmarketing clinical trial of open-label design, and comparison of results between vascular outcome and functional outcome as well as baseline stroke severity. Recanalization on either 6-hour or 24-hour MRA was an independent predictor for a favorable clinical outcome. Our data indicated that recanalization on 24-hour MRA was a much stronger predictor of clinical outcome than that on 6-hour MRA. These findings should be interpreted cautiously; they do not necessarily imply that delayed recanalization is far more effective than early recanalization, because recanalization on 24-hour MRA is a cumulative result. Nevertheless, delayed recanalization (recanalization occurring between 6 and 24 hours after treatment) was also a modest but independent predictor for a favorable outcome. The prognostic value of the 24-hour cumulative recanalization is supported by a transcranial Doppler study.19 Delayed as well as early recanalization may thus have a favorable impact on clinical outcome.

In conclusion, early recanalization of an occluded middle cerebral artery can be provoked by 0.6 mg/kg intravenous alteplase and may induce a favorable clinical outcome. The rates of recanalization and a favorable outcome are comparable to that previously reported with the 0.9-mg/kg dose.

**Appendix**

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