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 2003,1 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.2–4 The underlying rationale has been published on the Stroke web site (http://stroke.ahajournals.org/cgi/content/full/37/7/1810).1 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 study8 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.6

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 Study4 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 those for 24-hour MRA was between 24 and 36 hours after symptom onset. The time allowance for 6-hour MRA was between 18°). MRA was repeated at baseline, 6 hours, and 24 hours after injection and in rotation about the vertical axis (RL rotation, 15° to 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 neuroradiologist 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:1 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 publications2,7,14,15 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. (%).
IPa 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, 0.796; 95% CI, 0.672 to 0.943) were also independent predictors of a favorable outcome. In another model with 24-hour MRA entered, recanalization (OR, 21.231; 95% CI, 3.318 to 135.359) 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 135.359).

### Table 2. Vascular Conditions and Recanalization After Thrombolysis

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>Recanalization Rate (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-hour MRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>41</td>
<td>51.7 (38.9–64.6)</td>
</tr>
<tr>
<td>M2 occlusion</td>
<td>17</td>
<td>51.8 (34.2–69.4)</td>
</tr>
<tr>
<td>n</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Percent</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>24-hour MRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>41</td>
<td>69.0 (57.1–80.9)</td>
</tr>
<tr>
<td>M2 occlusion</td>
<td>17</td>
<td>69.2 (49.0–89.4)</td>
</tr>
<tr>
<td>n</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Percent</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

*Including delayed 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]</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-hour MRA</td>
<td></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]</td>
<td>$P=0.003$</td>
</tr>
<tr>
<td>Not recanalized</td>
<td>7 (25.9%)</td>
<td>20 (74.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour MRA</td>
<td></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]</td>
<td>$P&lt;0.001$</td>
</tr>
<tr>
<td>Not recanalized</td>
<td>2 (11.8%)</td>
<td>15 (88.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
size used. In the Phase III clinical study (J-ACT), symptom
than expected. However, this could reflect the small sample
clinical information, probably ensuring quality of image
sites, and 2 expert raters reviewed the images blinded to the
ing conditions were standardized among all participating
MRA images were interpreted cautiously; they do not necessarily imply that
delayed recanalization is far more effective than early recana-
ialization, because recanalization on 24-hour MRA is a
cumulative result. Nevertheless, delayed recanalization (re-
canalization occurring between 6 and 24 hours after treat-
ment) 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. Delayed as well as early recanalization may
thus have a favorable impact on clinical outcome.

Concerning clinical outcomes, the proportion of a favor-
able 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
trolled trials of thrombolysis examined by conventional
angiography or MRA was 19.8% up to 8 hours after on-
set. The recanalization rate in the present study was thus
considered likely to be much higher than the rate of
spontaneous recanalization.

Concerning safety, we did not encounter symptomatic
intracranial hemorrhage in this trial, which was much better
than expected. However, this could reflect the small sample
size used. In the Phase III clinical study (J-ACT), sympto-
amatic intracranial hemorrhage occurred in 5.8% of patients,
whose arterial occlusions were not documented. Asymptomatic
intracranial hemorrhage was noted in 19% of the present
subjects, which was comparable to that in the previous trial
(17%).

Recanalization immediately after any form of thrombolysis
has repeatedly been indicated to predict clinical outcome. A recent systematic review of cerebral artery recanalization
and clinical outcome in acute ischemic stroke. Several
investigations have also suggested that the baseline severity
of symptoms as measured by NIHSS represents an indepen-
dent predictor for clinical outcome in patients treated with
intravenous alteplase. Similar to previous thrombolysis
studies, the present results demonstrated a strong relationship
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 recana-
ization, because recanalization on 24-hour MRA is a
Cumulative result. Nevertheless, delayed recanalization (re-
canalization occurring between 6 and 24 hours after treat-
ment) 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. 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 compara-
table to that previously reported with the 0.9-mg/kg dose.

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Appendix

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