Alteplase at 0.6 mg/kg for Acute Ischemic Stroke Within 3 Hours of Onset
Japan Alteplase Clinical Trial (J-ACT)

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Background and Purpose—Based on previous studies comparing different recombinant tissue plasminogen activator (rt-PA) doses, we performed a clinical trial with 0.6 mg/kg, which is lower than the internationally approved dosage of 0.9 mg/kg, aiming to assess the efficacy and safety of alteplase in acute ischemic stroke for the Japanese.

Methods—Our prospective, multicenter, single-arm, open-label trial was designed with a target sample size of 100 patients. The primary end points were the proportion of patients with a modified Rankin Scale (mRS) score of 0 to 1 at 3 months and the incidence of symptomatic intracranial hemorrhage (sICH) within 36 hours. Thresholds for these end points were determined by calculating 90% CIs of weighted averages derived from published reports. The protocol was defined according to the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke study with slight modifications.

Results—Among the 103 patients enrolled, 38 had an mRS of 0 to 1 at 3 months; this proportion (36.9%) exceeded the predetermined threshold of 33.9%. sICH within 36 hours occurred in 6 patients; this incidence (5.8%) was lower than the threshold of 9.6%.

Conclusions—In patients receiving 0.6 mg/kg alteplase, the outcome and the incidence of sICH were comparable to published data for 0.9 mg/kg. These findings indicate that alteplase, when administered at 0.6 mg/kg to Japanese patients, might offer a clinical efficacy and safety that are compatible with data reported in North America and the European Union for a 0.9 mg/kg dose. (Stroke. 2006;37:1810-1815.)

Key Words: stroke, acute ■ thrombolytic therapy ■ tissue plasminogen activator

The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (rt-PA) stroke study1 demonstrated that alteplase treatment within 3 hours of onset improved functional outcome. On that basis, alteplase has been approved and recommended for treating acute ischemic stroke in 40 countries. In Japan, the regimen has not yet been approved but is used clinically.2 Although randomized controlled clinical trials of rt-PA (duteplase) in Japan have demonstrated that intravenous duteplase was beneficial for acute embolic stroke patients within 6 hours of onset,3–5 development of duteplase was aborted because of the patent issue. A pressing need exists to demonstrate that alteplase within 3 hours of onset is beneficial in the Japanese population. However, because randomized controlled trials, in which the alteplase arm is compared with the placebo arm, are impracticable under such circumstances, the regimen should be tested with another study design.

To assess the efficacy and safety in the Japanese population, a prospective, single-arm, open-label study was conducted. Although the internationally recommended dosage is 0.9 mg/kg, a 0.6 mg/kg dose was selected based on previous data for rt-PA in Japan.1–5 The primary outcome measures were the proportion of patients without functional deficits at 3 months and the incidence of symptomatic intracranial hemorrhage (ICH) within 36 hours. These outcomes were compared with the results of a systematic review and meta-analysis based on data from the literature.

Materials and Methods

The trial was conducted between April 2002 and September 2003 at 22 centers in Japan under good clinical practice regulations. The protocol was approved by each institutional review board. An independent review committee monitored the study for safety.

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1810
Inclusion and Exclusion Criteria
The inclusion and exclusion criteria were as in the NINDS study.\(^1\) We also excluded patients with a National Institutes of Health Stroke Scale (NIHSS) score of \(\leq 4\) at baseline, computed tomography (CT) evidence of significant early ischemic change (affecting more than one third of the middle cerebral artery territory), a comatose state, or a modified Rankin Scale (mRS) score of \(\geq 2\) before stroke onset.

Rationale for Dose Selection
In Japan, 3 randomized double-blind trials\(^3\)–\(^5\) of duteplase, an rt-PA very similar to alteplase, have been conducted on embolic stroke patients within 6 hours of onset. After a pilot study,\(^7\) 20 million international units (MIU) of duteplase proved to be superior to placebo based on the angiographical recanalization rate.\(^8\) Twenty MIU did not differ from 30 MIU in either the recanalization rate or clinical improvement.\(^9\) However, massive brain hematoma/hemorrhagic transformation occurred in 2 of 56 patients given 20 MIU and 9 of 65 patients given 30 MIU.\(^5\) Therefore, we considered that the optimal test dose of alteplase for the Japanese population was 20 MIU per person or 0.33 MIU/kg at a mean body weight of 60 kg and selected 0.6 mg/kg for the present trial, which is equivalent to 0.33 MIU/kg, as the appropriate alteplase dose, instead of the 0.9 mg/kg in the NINDS trial. Details of the properties and other relevant data for duteplase and alteplase are given in the supplemental Appendix 2, available online at http://stroke.ahajournals.org.

Intervention and Evaluation
A single alteplase dose of 0.6 mg/kg (not exceeding 60 mg) was administered intravenously, with 10% given as a bolus, followed by continuous infusion of the remainder over 1 hour. The NIHSS, mRS, and Barthel Index (BI) were evaluated at the same time points as in the NINDS study.\(^1\) CT scans were repeated before treatment and at 24 hours, 7 to 10 days, and 3 months or at discharge.

Symptomatic ICH (sICH) was defined prospectively in the protocol, as CT evidence of new ICH with apparent neurological deterioration, which was defined as documented objective evidence of neurological decline or an increase of 4 points from the most recent NIHSS score. The protocol required CT scans and NIHSS evaluations whenever neurological deterioration was identified.

As in the NINDS study, use of antithrombotic agents was prohibited for 24 hours after onset, blood pressure was maintained at \(180/105\) mm Hg, and neurological symptoms were frequently monitored.

According to the prospective definition, CT evidence of hemorrhage was classified into 4 grades by the CT Film Reading Panel blinded to clinical information: (0) no hemorrhage; (1) hemorrhagic infarction without hematoma; (2) hematoma without shift of the midline structures; and (3) hematoma with shifts of the midline structures.

Primary End Points
The primary efficacy end point was the proportion of patients with favorable outcomes (mRS score of 0 to 1) at 3 months. The primary safety end point was the incidence of sICH within 36 hours after starting treatment. These primary end points were evaluated in comparison with a meta-analysis of published data on alteplase. To make response assessments in 100 patients, threshold values were predetermined as follows. We performed a Medline search in June 2001 with key words “ischemic or ischaemic/stroke/tissue plasminogen activator or alteplase,” identifying all studies published after the NINDS report in which \(\geq 50\) patients were involved and the mRS data at 3 months\(^6\)–\(^7\) and incidence of sICH\(^8\)–\(^14\) were available. When reports contained overlapping patients, defined from the institutions and periods, those treating more patients were selected and assessed. Such overlapping occurred in reports from Cologne, Calgary, and Houston. As shown in the Figure, there is some possible heterogeneity (Katzan et al\(^11\) and Lopez-Yunez et al\(^13\)) among these studies visually. However, because we wished to embrace the actual medical conditions involving all of these studies, we used them for calculation of the combined statistics, weighted by study size, in the meta-analysis. These valid reports in combination with the NINDS study\(^1,15\) revealed a weighted average proportion of mRS score of 0 to 1 at 3 months of 42.0%, with a 90% CI (95% for 1 tailed) in 100 patients of 33.9% to 50.1%; the lower confidence limit was used as the threshold. The weighted average incidence of sICH was 5.8%, with a 90% CI in 100 patients of 2.0% to 9.6%; the upper confidence limit was used as the threshold. The targets for our study were thus set at >33.9% as the proportion of patients with an mRS score of 0 to 1 at 3 months and <9.6% as the incidence of sICH within 36 hours. As other secondary analyses, including the BI at 3 months and NIHSS, comparisons with values from applicable published reports, such as the NINDS study, were undertaken.

Results
The baseline characteristics of the 103 patients enrolled were comparable to those in the NINDS study, except for body
TABLE 1. Demographic and Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>J-ACT</th>
<th>rt-PA n=168</th>
<th>Placebo n=165</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.9±9.8</td>
<td>69±12</td>
<td>66±13</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>39 (37.9%)</td>
<td>(43%)</td>
<td>(42%)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.6±11.0</td>
<td>76±16</td>
<td>80±21</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>15</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Range</td>
<td>5–30</td>
<td>2–37</td>
<td>2–33</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>80 (77.7%)</td>
<td>(45%)</td>
<td>(44%)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>12 (11.7%)</td>
<td>(39%)</td>
<td>(45%)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>2 (1.9%)</td>
<td>(14%)</td>
<td>(9%)</td>
</tr>
<tr>
<td>Other/not differentiated</td>
<td>9 (8.7%)</td>
<td>(2%)</td>
<td>(3%)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>151.0±19.0</td>
<td>153±22</td>
<td>152±21</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>82.3±11.9</td>
<td>85±14</td>
<td>86±15</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>141.3±48.3</td>
<td>149±66</td>
<td>149±78</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>21 (20.4%)</td>
<td>(12%)</td>
<td>(9%)</td>
</tr>
<tr>
<td>No pre-existing disability</td>
<td>85 (82.5%)</td>
<td>(95%)</td>
<td>(93%)</td>
</tr>
<tr>
<td>Previous use of antiplatelet drugs</td>
<td>30 (29.1%)</td>
<td>(40%)</td>
<td>(26%)</td>
</tr>
<tr>
<td>Concomitant disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>55 (53.4%)</td>
<td>(67%)</td>
<td>(67%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (18.4%)</td>
<td>(20%)</td>
<td>(20%)</td>
</tr>
<tr>
<td>Mean time from onset to treatment (min)</td>
<td>150.5</td>
<td>119.7*</td>
<td></td>
</tr>
</tbody>
</table>

*In the NINDS study, the mean time from onset to treatment is reported as the combined value of all rt-PA, placebo, and parts 1 and 2.1,6

J-ACT indicates Japan Alteplase Clinical Trial.

TABLE 2. Results of J-ACT and NINDS Studies

<table>
<thead>
<tr>
<th></th>
<th>J-ACT</th>
<th>NINDS Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rt-PA n=165</td>
<td>Placebo n=165</td>
</tr>
<tr>
<td>mRS score 0–1 at 3 months</td>
<td>36.9%</td>
<td>39%</td>
</tr>
<tr>
<td>BI 95–100 at 3 months</td>
<td>48.5%</td>
<td>50%</td>
</tr>
<tr>
<td>NIHSS improvement by ≥4 points or decreased to 0 at 24 hours</td>
<td>49.5%</td>
<td>47%</td>
</tr>
<tr>
<td>sICH within 36 hours</td>
<td>5.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Death within 3 months</td>
<td>9.7%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*As the NINDS study values, the mRS and BI from part 2, NIHSS improvement from part 1, and sICH from parts 1 and 2 are presented because these were treated as the primary end points in the trial.1

J-ACT indicates Japan Alteplase Clinical Trial.

NINDS study (part 2).1 Fifty-one patients (49.5%) experienced improvement by ≥4 points or a decrease to 0 points on the NIHSS at 24 hours after stroke onset compared with 47% of the rt-PA arm and 39% of the placebo arm in the NINDS study (part 1).1 The median NIHSS scores were 15 points at baseline and 10.5 points at 24 hours in this trial (ie, close to the median NIHSS change [5 to 6 points] of the rt-PA arm and larger than that of the placebo arm [1 to 2 points] in the NINDS study).1 All efficacy end points in our trial were closely comparable to those of the rt-PA arm in the NINDS study.

Six patients (5.8%) had sICH within 36 hours (Table 3). This incidence was lower than the predetermined threshold of 9.6%, and similar to that of the rt-PA arm in the NINDS study. Four of the 6 cases of sICH revealed hematoma on CT, which corresponded to parenchymal hematoma-2 on the European Cooperative Acute Stroke Study (ECASS) criteria;6 the other 2 cases were of hemorrhagic infarction. Two patients with sICH died, 1 within 24 hours after stroke onset and the other on day 3. Within 10 days, the CT Film Reading Panel identified 26 patients (25.2%) with hemorrhagic infarction and 12 patients (11.7%) with hematoma, of whom 9 also exhibited shifts of the midline structures. Asymptomatic ICH was detected in 17% and 31% of patients within the initial 36 hours and 10 days of treatment, respectively.

Ten patients (9.7%) died within 90 days after onset. This mortality was somewhat lower than that reported in rt-PA–treated patients (10% to 17%).1,6,7,12,13

**Discussion**

The primary efficacy and safety end points were within the predetermined thresholds, based on a meta-analysis of published studies, and approximated to those of the rt-PA arm in the NINDS trial. All secondary end points were also similar to those of the rt-PA arm. The baseline factors known to affect outcome, including age, severity of stroke, diabetes, and hypertension, were comparable to those in the NINDS study. The age and stroke severity of the study population were similar to or slightly higher than those in previous reports. None of the baseline characteristics appeared to affect outcomes favorably in this study. Before inferring that 0.6 mg/kg intravenous alteplase for Japanese patients is consistent with the 0.9 mg/kg used in North America and the
TABLE 3. Six Cases With sICH

<table>
<thead>
<tr>
<th>Age</th>
<th>Onset to Treatment Time (min)</th>
<th>Baseline NIHSS score</th>
<th>Baseline Blood Pressure (mm Hg)</th>
<th>Treatment to Hemorrhage (CT)</th>
<th>3 Months mRS</th>
<th>CT Findings*</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>170</td>
<td>7</td>
<td>142/82</td>
<td>21 hours, 29 minutes</td>
<td>4</td>
<td>(3)</td>
</tr>
<tr>
<td>80</td>
<td>171</td>
<td>20</td>
<td>166/76</td>
<td>20 hours, 29 minutes</td>
<td>5</td>
<td>(3)</td>
</tr>
<tr>
<td>70</td>
<td>148</td>
<td>24</td>
<td>164/82</td>
<td>1 hour, 12 minutes</td>
<td>Death</td>
<td>(3)</td>
</tr>
<tr>
<td>77</td>
<td>115</td>
<td>24</td>
<td>185/71</td>
<td>22 hours, 25 minutes</td>
<td>5</td>
<td>(1)</td>
</tr>
<tr>
<td>81</td>
<td>134</td>
<td>19</td>
<td>176/96</td>
<td>21 hours, 9 minutes</td>
<td>4</td>
<td>(2)</td>
</tr>
<tr>
<td>72</td>
<td>179</td>
<td>20</td>
<td>150/64</td>
<td>18 hours, 20 minutes</td>
<td>Death</td>
<td>(1)</td>
</tr>
</tbody>
</table>

*Findings according to the CT Film Reading Panel assessment.  
(1) Hemorrhagic infarction without hematoma.  
(2) Hematoma without shift of the midline structures.  
(3) Hematoma with shifts of the midline structures.

European Union (EU) with regard to efficacy and safety, we need to consider the issue of dose rate and limitations of the present study.

The rationale for our decision to use 0.6 mg/kg instead of 0.9 mg/kg was based on dose-rate findings of duteplase trials for acute stroke completed in Japan a decade ago. This lower dose is considered optimal for longer-elapsing patients up to 6 hours after onset because of the risk of intracerebral hemorrhage may arise. Assuming that lower-dose rt-PA is associated with a better risk/benefit ratio in patients beyond 3 hours of stroke onset, a pilot study of 0.6 mg/kg intravenous alteplase has been conducted. Nevertheless, the optimal dosage for acute ischemic stroke might need reassessment because the optimal dose has not been fully explored. Even pilot dose-escalation studies for the NINDS rt-PA trial did not yield any conclusive findings. Another reason behind our preference for a lower dose is racial differences in blood coagulation–fibrinolysis factors, such as fibrinogen and factor XIII. Comparing the dose-rate findings of alteplase studies for acute myocardial infarction between Japan and North America/EU may point to racial differences in dose rate. The optimal dose to attain a coronary patency rate of 65% to 80% was estimated at 0.5 to 0.75 mg/kg in Japan, which was lower than the recommended dose (≈1.25 mg/kg) in North America/EU. Data analysis in the acute myocardial infarction studies demonstrated differences in response between blacks and whites after thrombolytic therapy with rt-PA; black patients revealed a greater thrombolytic efficacy and more hemorrhagic events. For US/EU stroke patients within 8 hours of onset, duteplase between 0.29 MU/kg and 0.75 MU/kg achieved a recanalization rate of almost 40%, which is comparable to the results of the Japanese duteplase trials at 0.33 to 0.5 MU/kg. Because of the limited sample sizes, no apparent dose rate was evident. Differences in the efficacy and safety of duteplase and alteplase for ischemic stroke among different races remain to be explored.

The present trial design was a prospective open-label cohort study without controls. The disadvantages and limitations of such a design are self-evident. The lack of a control group is the most critical issue. However, it would be impracticable to conduct a randomized placebo-controlled trial under the present circumstances. Because intravenous duteplase trials had already indicated benefits, intravenous alteplase had been approved and used worldwide, and a substantial proportion (3%) of patients with acute ischemic stroke in Japan had received thrombolytic therapy. Given that the development of duteplase was aborted by a patent suit despite appropriate placebo-controlled trials showing benefits, the usual acceptable standard of trial design could not be conducted, and the use of thrombolytic agents for ischemic stroke was abruptly halted in Japan a decade ago. Although the present design uses “historical controls,” there is no other way to perform this trial in the current climate ethically. Where treatments affect survival or irreversible morbidity, placebo-controlled trials cannot be conducted ethically. Equivalence study design may be an alternative choice. In the present study, similarity of safety and efficacy outcomes was assessed by comparison with those available from a meta-analysis of the literature. Although our study lacked a control group, the efficacy and safety results are consistent with the data of the systematically reviewed studies. The point estimate in this study was within the CI in 100 patients calculated through the meta-analysis. This fact indicates that, assuming the efficacy and safety of alteplase are equivalent to the published experience, this point estimate can be considered to be within the expected range for a study involving 100 patients. Furthermore, another systematic review conducted in December 2003 confirmed the consistency of the original meta-analysis (see bottom part of Figure, where PostStudy means reports that are newly picked up in the same manner as for the PreStudy, at the end of this study). The weighted average of the proportion of mRS score of 0 to 1 at 3 months was 39.0% (among 1140 patients; 90% CI, 36.7% to 41.4%) in total from 9 reports providing information on the mRS score of 0 to 1 at 3 months. The weighted average of the incidence of sICH was 5.4% (among 2927 patients; 90% CI, 4.7% to 6.1%) from 16 reports containing information on sICH. These ranges of CI values should contain the almost true mRS 0 to 1 proportion and sICH incidence with the respective 90% CI values in the present trial of 29.1% to 44.7% for the mRS 0 to 1 proportion and 2.0% to 9.6% for sICH.

Another possible problem with this trial was detection bias because outcome measurement was not blinded. Although detection bias effects cannot be ruled out, the outcomes were...
comparable to those obtained in open-label studies as well as those of blinded trials.

Our trial included more patients with cardioembolic stroke than other studies, probably because of the exclusion of those of mild severity (NIHSS ≤4). It has been reported that more than half of patients with lacunar stroke exhibit mild deficits with an NIHSS score ≤4. Moreover, cardioembolic strokes generally arrive at hospital much earlier than other subtypes, which could influence the distribution of stroke subtypes. In any event, the present high proportion of cardioembolic stroke is unlikely to favor the present trial because stroke subtype is not associated with outcome of thrombolysis when adjusted for severity. Comparisons of data from different countries, with different medical, social, and racial backgrounds, should be interpreted cautiously. Nontreated historical controls were available in a Japanese stroke registration study involving 312 ischemic stroke patients referred to ical controls were available in a Japanese stroke registration study. This clinical trial was supported by Kyowa Hakko Kogyo Co., Ltd. and Mitsubishi Pharma Corporation.

In conclusion, 0.6 mg/kg intravenous alteplase in Japanese patients with acute ischemic stroke is likely comparable to data reported for patients in North America and the EU at a 0.9 mg/kg dose. Further studies are needed to confirm these results.

Appendix

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Disclosures
None.

References
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