Thrombolysis With 0.6 mg/kg Intravenous Alteplase for Acute Ischemic Stroke in Routine Clinical Practice

The Japan post-Marketing Alteplase Registration Study (J-MARS)

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Background and Purpose—In Japan, alteplase at 0.6 mg/kg was approved in October 2005 for use within 3 hours of stroke onset by the Ministry of Health, Labor and Welfare (MHLW). The aim of the Japan post-Marketing Alteplase Registration Study (J-MARS), which was requested by MHLW at the time of approval, was to assess the safety and efficacy of 0.6 mg/kg alteplase in routine clinical practice for the Japanese.

Methods—A total of 7492 patients from 942 centers were enrolled in the J-MARS, an open-label, nonrandomized, observational study, from October 2005 to October 2007. Primary outcome measures were symptomatic intracranial hemorrhage (a deterioration in NIHSS score ≥4 from baseline) and favorable outcome (modified Rankin Scale score, 0–1) at 3 months after stroke onset.

Results—The proportion of patients with symptomatic intracranial hemorrhage in 7492 patients (safety analysis) was 3.5% (95% confidence interval [CI], 3.1%–3.9%) within 36 hours and 4.4% (95% CI, 3.9%–4.9%) at 3 months. The overall mortality rate was 13.1% (95% CI, 12.4%–13.9%) and the proportion of patients with fatal symptomatic intracranial hemorrhage was 0.9% (95% CI, 0.7%–1.2%). The outcomes at 3 months were available for 4944 patients and the proportion of favorable outcome (efficacy analysis) was 33.1% (95% CI, 31.8%–34.4%). The subgroup analysis in patients between 18 and 80 years with a baseline NIHSS score ≥25 demonstrated that favorable outcome at 3 months was 39.0% (95% CI, 37.4%–40.6%).

Conclusions—These data suggest that 0.6 mg/kg intravenous alteplase within 3 hours of stroke onset could be safe and effective in routine clinical practice for the Japanese. (Stroke. 2010;41:1984-1989.)

Key Words: acute ischemic stroke ■ alteplase ■ postmarketing registration ■ thrombolysis ■ tissue plasminogen activator

Since the recombinant tissue plasminogen activator stroke study organized by the National Institute of Neurological Disorders and Stroke (NINDS) demonstrated that intravenous alteplase treatment within 3 hours of stroke onset improved functional outcome in 1995, this treatment has been an approved medical therapy for patients with acute ischemic stroke and is recommended as the first-line treatment by most national and international guidelines. Intravenous alteplase treatment of ischemic stroke within the 3-hour time window has been shown to be safe and effective in previous randomized controlled trials. However, the safety and efficacy of thrombolysis with alteplase in routine clinical practice should be investigated in each country.

Alteplase was licensed for the treatment of acute ischemic stroke in the United States in 1996 and in the European Union in 2002 for selected patients treated within the 3-hour time window. In Japan, a prospective, single-arm, open-label study called the Japan Alteplase Clinical Trial (J-ACT) was conducted from April 2002 to September 2003. Although the internationally recommended dosage of intravenous alteplase was adjusted to 0.9 mg/kg, the challenging dose of 0.6 mg/kg was selected in J-ACT based on previous recombinant tissue plasminogen activator studies for Japanese patients. Randomized controlled trials of duteplase, a recombinant tissue plasminogen activator similar to alteplase, have been conducted for acute stroke patients within 6 hours of onset in...
 Implementation of Thrombolysis in Stroke-Monitoring Study (J-MARS) was to investigate whether thrombolysis with 0.6 mg/kg intravenous alteplase could be safe and effective routine clinical practice for the Japanese. Here, we compared the results of J-MARS with those of the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) performed as a postmarketing study in the European Union.14

**Patients and Methods**

J-MARS was an open-label, multicenter, nonrandomized, observational study including clinical centers practicing thrombolysis for acute stroke in Japan. Participation in this study was possible for any medical centers that committed to register all patients treated with alteplase for 2 years after its approval and to collaborate in the elucidation of causes of any treatment complications. Joining this registry was not compulsory. The primary outcome measures in the protocol were sICH within 36 hours and at 3 months and favorable outcome (mRS score, 0–1) at 3 months after stroke onset. The MHLW required the sponsors (Mitsubishi Tanabe Pharma Corporation and Kyowa Hakko Kirin Co, Ltd) to perform a large-scale postmarketing registry study to assess the safety profile of 0.6 mg/kg intravenous alteplase and a clinical study for documentation of the dosage efficacy (Japan Alteplase Clinical Trial II [J-ACT II]).13 The sponsors asked the centers practicing thrombolysis with alteplase for participation in the postmarketing registry. The results of both studies will contribute to a standard for the reassessment of the benefit-risk profile of intravenous alteplase treatment.

The aim of Japan post-Marketing Alteplase Registration Study (J-MARS) was to investigate whether thrombolysis with 0.6 mg/kg intravenous alteplase could be safe and effective routine clinical practice for the Japanese. Here, we compared the results of J-MARS with those of the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) performed as a postmarketing study in the European Union.14

**Results**

According to the logistics research, 8313 patients with acute ischemic stroke at 1100 centers were treated with intravenous alteplase from October 2005 to October 2007 all over Japan, and a total of 7692 patients from 959 centers were registered in J-MARS. However, 200 patients from 83 centers (2.6%; 200/7692) whose CRF were not collected because of nonfulfillment by the investigators were excluded. Finally, 7492 patients (90%; 7492/8313) with CRF from 942 centers (86%; 942/1100) were enrolled in the safety analysis (Figure 1). The proportion of patients with sICH, prestroke independence (mRS score, 0–1), and functional outcomes at 3 months were obtained from the CRF. The overall mortality rate was estimated from the fatal records in the CRF. The median participated time in the registry for these 942 centers was 17.9 months. Table 1 shows baseline characteristics in 7492 patients, including risk factors, presence of concomitant disease, degree of neurological severity, and blood pressure in J-MARS in comparison with SITS-MOST. Table 1 also shows stroke subtypes of the subjects and median time from stroke onset to alteplase treatment in both studies.

Table 2 demonstrates the rates of adverse events, drug-related adverse reactions, intracranial hemorrhages confirmed by brain scans, and overall mortality in 7492 patients. The proportion of patients with sICH was 3.5% (259/7492; 95% CI, 3.1%–3.9%) within 36 hours and 4.4% (329/7492; 3.9%–4.9%) at 3 months. The overall mortality rate within 3 months was 13.1% (985/7492; 12.4%–13.9%) and the proportion of patients with fatal sICH was 0.9% (70/7492; 0.7%–1.2%).
Regarding neurological outcome in J-MARS, the median NIHSS score was 15 (interquartile range, 9–20) at baseline and 10 (interquartile range, 4–18) at 24 hours from starting therapy. Of the total 7492 patients, 758 patients had no documentation for prestroke independence (mRS score, 0–1) in the CRF (Figure 1). In these 758 patients, prestroke disability states of 741 patients were reported as mRS score 2 to 5, and those of remaining 17 patients were not mentioned. They were included in the safety analysis but not in the efficacy analysis, because favorable outcome was defined as mRS score 0 to 1 in this study. Number of patients who confirmed prestroke independence (mRS score, 0–1) was 6734. Follow-up data at 3 months were available for 4944 of 6734 patients whose prestroke independence was confirmed (Figure 1); 1790 of 6734 patients were excluded from the efficacy analysis because their mRS scores at 3 months were not available. Functional outcomes at 3 months (90±14 days) were obtained in 4060 of 4944 patients (including virtually all deceased cases within 3 months). For the other 884 patients who were surviving at 3 months, their functional outcomes were unavailable in the CRF, but their mRS score were confirmed by attending physicians and records at hospital discharge. The proportion of favorable outcome at 3 months in J-MARS was 33.1% (1637/4944; 31.8%–34.4%). The functional outcome estimated by mRS score at 3 months was compared with data from relevant published studies in Figure 2.

In SITS-MOST, the subjects were restricted to those between ages 18 and 80 years with an NIHSS score ≥25. The subgroup analysis with selected conditions such as those of SITS-MOST showed that the proportion of favorable outcome at 3 months in J-MARS was 33.1% (1637/4944; 31.8%–34.4%). The functional outcome estimated by mRS score at 3 months was compared with data from relevant published studies in Figure 2.

We stratified number of patients with sICH according to number of enrolled patients per center (Figure 4). The percentage of sICH for centers with a small enrolled number (≤4) was 6.0% (4.7%–7.7%), and those for centers with a relatively larger enrolled number (20–29 and ≥30) were 3.2% (2.3%–4.4%) and 3.2% (2.4%–4.2%), respectively.

**Table 1. Baseline Characteristics of Patients Analyzed in J-MARS and SITS-MOST**

<table>
<thead>
<tr>
<th></th>
<th>J-MARS (n=7492)</th>
<th>SITS-MOST (n=6483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72 (65–79)</td>
<td>68 (59–75)</td>
</tr>
<tr>
<td>Gender, female</td>
<td>2836 (37.9%)</td>
<td>2581 (39.8%)</td>
</tr>
<tr>
<td>Prestroke independence, mRS score 0–1</td>
<td>6734 (89.9%)</td>
<td>5899/6337 (93.1%)</td>
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<tr>
<td>Concomitant disease</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>3852 (51.4%)</td>
<td>3710/6318 (58.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1272 (17.0%)</td>
<td>1020/6374 (16.0%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3331 (44.5%)</td>
<td>1507/6306 (23.9%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>679 (9.1%)</td>
<td>467/6339 (7.5%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1373 (18.3%)</td>
<td>643/6395 (10.1%)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>15 (9–20)</td>
<td>12 (8–17)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>15 (13–164)</td>
<td>150 (137–166)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81 (71–90)</td>
<td>81 (74–90)</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>4509 (60.2%)</td>
<td>2270 (35%)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>1838 (24.5%)</td>
<td>2279 (35.2%)*</td>
</tr>
<tr>
<td>Lacunar</td>
<td>316 (4.2%)</td>
<td>535 (8.3%)</td>
</tr>
<tr>
<td>Other/not differentiated</td>
<td>811 (10.8%)</td>
<td>1171 (18.1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (0.2%)</td>
<td>228 (3.5%)</td>
</tr>
<tr>
<td>Stroke onset to treatment time, min</td>
<td>133 (110–160)</td>
<td>140 (115–165)</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) or n (%).

*Large vessel disease with or other than substantial carotid stenosis.

J-MARS indicates Japan post-Marketing Alteplase Registration Study; mRS, modified Rankin scale; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study.

Table 2. N (%) of Patients With All Adverse Events, Drug-Related Adverse Reactions, Intracranial Hemorrhage, and Overall Mortality

<table>
<thead>
<tr>
<th>Total N of Patients</th>
<th>7492</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>2412 (32.2%)</td>
</tr>
<tr>
<td>Drug-related adverse reactions</td>
<td>1627 (21.7%)</td>
</tr>
<tr>
<td>Intracranial hemorrhages</td>
<td>1217 (16.2%)</td>
</tr>
<tr>
<td>sICH</td>
<td></td>
</tr>
<tr>
<td>Within 36 hr</td>
<td>259 (3.5%)</td>
</tr>
<tr>
<td>At 3 mo</td>
<td>329 (4.4%)</td>
</tr>
<tr>
<td>Fatal sICH</td>
<td>70 (0.9%)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>985 (13.1%)</td>
</tr>
</tbody>
</table>

sICH, symptomatic intracranial hemorrhages.

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Figure 1. Flow chart showing the disposition of patients. *Of 4944 patients, modified Rankin Scale (mRS) scores at 3 months for 4060 patients were documented in their case report forms, and those of 884 patients were confirmed by attending physicians and records at hospital discharge.

The results from J-MARS suggested that 0.6 mg/kg intravenous alteplase could be an effective treatment with satisfac-
tory safety profile when used in a 3-hour time window in routine clinical practice for the Japanese. For the first 2 years after the approval of intravenous alteplase treatment in Japan, most patients who received this treatment were registered in J-MARS. The main aim of J-MARS was to confirm whether the levels of safety recognized in published clinical studies could be reproduced in routine clinical practice, especially with regard to sICH.

In J-MARS, the proportion of patients with sICH was 4.4% (3.9%–4.9%) at 3 months. The definitions of sICH have been slightly different among published studies.1,9,14,17,18 These differences could restrict any direct comparison of the results from those studies. In SITS-MOST, the proportion of patients with sICH was 7.3% (6.7%–7.9%) according to the National Institute of Neurological Disorders and Stroke and Cochrane review definition19,20 (defined as any hemorrhage plus any neurological deterioration [NIHSS score ≥1] or that leads to death within 7 days) and 4.6% (4.1%–5.1%) according to the European Cooperative Acute Stroke Study (ECASS) definition21 (defined as any hemorrhage plus a neurological deterioration of NIHSS score ≥4 points from baseline, or from the lowest NIHSS score after baseline to 7 days or leading to death).14 Our results showed that the proportions of patients who had sICH in J-MARS and SITS-MOST were comparable when the ECASS definition was applied to those in SITS-MOST (4.4% vs 4.6%).

In J-MARS, we stratified number of patients with sICH according to number of enrolled patients from each participating center to investigate the correlation between the experience and the safety with stroke thrombolysis. The number of enrolled patients per center in J-MARS was small compared to that of SITS-MOST, but the percentage of sICH in centers with a relatively large number (>20 cases) of enrollment was lower than that in centers with relatively small number (<19 cases) of enrollment (Figure 4). This finding suggested that the experience of stroke thrombolysis was one important factor for safe clinical practice.

The proportion of favorable outcome at 3 months in J-MARS remained at 33.1%, which is nearly the same rate as that seen in CASES, in which favorable outcome was 32%.18 The modest data collection rate of functional outcome evaluations at 3 months (4944/7492) seems to be an inevitable limitation of this observational study and could be a possible source of detection and exclusion biases. Although mRS scores for surviving patients at 3 months were not always reported in the CRF, virtually all fatal cases within 3 months were identified in the fatal records in the CRF. Accordingly, the proportion of mRS score 6 at 3 months (17% in Figure 2)
was seemingly higher than the overall mortality rate (13.1% in Table 2). Certainly, mortality at 3 months in J-MARS was higher than that in J-ACT (10% in Figure 2).9 The median NIHSS score at baseline was 15 in J-MARS, which is the same value as in J-ACT (Figure 2). In J-ACT, patients with a comatose state at baseline were excluded, and the highest NIHSS score at baseline was actually 30. However, a considerable number of patients with the severe baseline condition of NIHSS score >30 or with a comatose state were included in J-MARS, and their outcomes were almost always unfavorable. In SITS-MOST, the proportion of favorable outcome at 3 months was 39%.14 Concerning the relatively higher favorable outcome in SITS-MOST, it could be a contributing factor that study recruitment was restricted to patients between ages 18 and 80 years with NIHSS score <25. In SITS-MOST, the median age was 68 years (vs 72 years in J-MARS), and the median NIHSS score was 12 (vs 15 in J-MARS).14 Thus, clinical severity could be less severe in SITS-MOST. Consequently, we tried the subgroup analysis of J-MARS in patients between ages 18 and 80 years with an NIHSS score <25, which demonstrated that the favorable outcome at 3 months was 39%, which is much the same as that in SITS-MOST (39%; Figure 3).

Recently, the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) study was conducted in 10 Japanese stroke centers with much experience in alteplase treatment from October 2005 to July 2008.22 Six hundred patients treated with 0.6 mg/kg intravenous alteplase were enrolled in SAMURAI study and they were partially overlapped with those in J-MARS. In SAMURAI study, the proportion of favorable outcome at 3 months was 33.2% (29.5%–37.0%) of the total 600 patients and 37.2% (33.2%–41.4%) when 65 patients with a prestroke mRS score 2 to 5 were excluded from the analysis. Analysis of 399 patients with a prestroke mRS score 0 to 1 who met the criteria of SITS-MOST showed that the proportion of favorable outcome at 3 months was 40.6% (35.9%–45.5%). Although SAMURAI study group was composed of stroke centers with much experience in alteplase treatment, the proportion of favorable outcome in SAMURAI study was not so superior to that of the present study. The results of J-MARS, the national postmarketing study in Japan, could be positively ranked with those of SITS-MOST.

Conclusion

In conclusion, the result of J-MARS demonstrated that 0.6 mg/kg intravenous alteplase achieved low rates of sICH and sufficient favorable outcome in clinical practice in Japan. In addition, the results from J-ACT II showed that early recanalization of an occluded middle cerebral artery was generated by 0.6 mg/kg intravenous alteplase and directly associated with favorable clinical outcome.13 The results of these Japanese studies suggest that thrombolysis with 0.6 mg/kg intravenous alteplase could be comparable to those with 0.9 mg/kg alteplase used in North America and the European Union. Hereafter, the safety and efficacy of thrombolysis with 0.6 mg/kg intravenous alteplase could contribute not only to routine clinical practice but also to occasional combined approach with thrombolysis and endovascular devides for patients with acute ischemic stroke.

Acknowledgments

The authors thank the investigators involved in this postmarketing registration study.

Sources of Funding

This study was supported by Mitsubishi Tanabe Pharma Corporation and Kyowa Hakko Kirin Co, Ltd.

Disclosure

Jyoji Nakagawara received honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck, received a consulting fee from Lundbeck. Kazuo Minematsu received research grants from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck, and received honoraria from Mitsubishi Tanabe Pharma and Kyowa Hakko Kirin. Yasushi Okada received an honorarium from Mitsubishi Tanabe Pharma and a consulting fee from Lundbeck, Norio Tanahashi received an honorarium from Mitsubishi Tanabe Pharma. Shinji Nagahiro received a research grant and honorarium from Mitsubishi Tanabe Pharma. Etsuro Mori received a research grant from Mitsubishi Tanabe Pharma, honorarium from Mitsubishi Tanabe Pharma and Kyowa Hakko Kirin, and consulting fees from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Yukito Shinohara received an honorarium from Mitsubishi Tanabe Pharma. Takenori Yamaguchi received honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck, and received consulting fees from Mitsubishi Tanabe Pharma and Lundbeck. All authors have disclosed the financial relationships with the companies relevant to alteplase and desmoteplase.

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*Stroke*. 2010;41:1984-1989; originally published online July 22, 2010; doi: 10.1161/STROKEAHA.110.589606

*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

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