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)

Jyoji Nakagawara, MD; Kazuo Minematsu, MD; Yasushi Okada, MD; Norio Tanahashi, MD; Shinji Nagahiro, MD; Etsuro Mori, MD; Yukito Shinohara, MD; Takenori Yamaguchi, MD; for J-MARS Investigators

**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;41:00-00.)

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

Since the recombinant tissue plasminogen activator (t-PA) 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 Japan.
Japan. After a pilot study, 20 million international units (MIU) of duteplase proved to be superior to placebo based on the angiographic recanalization rate. In a randomized, double-blind, dose-comparison study, partial recanalization and complete recanalization in 18 of 54 (33.3%) patients administered 20 MIU and in 25 of 59 (42.4%) patients administered 30 MIU, respectively, were not found to be statistically different. However, massive brain hematoma/hemorrhagic transformation occurred in 2 of 56 (3.6%) patients administered 20 MIU and 9 of 65 (13.8%) patients administered 30 MIU. Therefore, it was considered that the optimal dose of alteplase for J-ACT was 0.6 mg/kg, which was equivalent to 20 MIU per person or 0.33 MIU/kg at a mean body weight of 60 kg. The underlying rationale has been published on the Stroke web site (http://stroke.ahajournals.org/cgi/content/full/37/7/1810).

In J-ACT, 103 patients were treated with 0.6 mg/kg intravenous alteplase, and the proportion of modified Rankin Scale (mRS) score of 0 to 1 at 3 months was 36.9% (38/103; 90% confidence interval [CI], 29.1%–44.7%), and the incidence of symptomatic intracranial hemorrhage (sICH) within 36 hours was 5.8% (6/103; 90% CI, 2.0% to 9.6%). Consequently, alteplase at 0.6 mg/kg was approved and a license was granted in October 2005 by the Ministry of Health, Labor and Welfare (MHLW), Japan. At the time of approval, 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]). 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-to-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 in 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.

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 approved the protocol of this study and the sponsors instructed the investigators to perform the study according to Good Postmarketing Study Practice, which is the authorized standard for a postmarketing registration study. The ethics approval was obtained from institutional ethics committee when required. Thrombolysis with 0.6 mg/kg intravenous alteplase was applied for the patients in accordance with the existing labeling and guidelines for intravenous alteplase treatment in Japan.

Informed consent was obtained from the patient (or a relative if the patient could not understand the treatment). Recruitment of patients in J-MARS started in October 2005 and ended in October 2007.

Baseline and demographic characteristics, stroke severity, time intervals, risk factors, and medication history were collected. NIHSS score at 24 hours and mRS score at 3 months were requested as the outcome measures. The proportion of each mRS score at 3 months was also calculated. Any adverse events for patients in this study were reported via their case report forms (CRF) to the sponsors, who reported serious drug-related adverse reactions to MHLW.

All patients who were enrolled in this study underwent CT or MRI before and within 36 hours after treatment as a general rule. Further follow-up brain scans after that were optional; however, patients who presented neurological deterioration underwent additional scan. These scans were not reviewed centrally. sICH was defined as any intracranial hemorrhage with a neurological deterioration of NIHSS score ≥4 points from baseline, or from the lowest NIHSS score after baseline to 24 hours, or the intracranial hemorrhage leading to death. In addition, number of patients with sICH was stratified according to number of enrolled patients per center. Functional independence (mRS score, 0–1) was assessed at 3 months after stroke onset by face-to-face or telephone interview with the patient or the patient’s caregiver, or by letter reply form. Intracranial hemorrhage rates were calculated from any CT or MRI within 36 hours after alteplase treatment, and also from any additional scans.

Statistical Analysis

The proportion and 95% CI of patients with sICH, favorable outcome, and mortality rate were calculated. We used the statistical approach to calculate the upper and lower limits of the CI. Bar charts of proportions of patients were made to compare with the corresponding proportions of the NINDS study, the J-ACT, the SITS-MOST, the Standard Treatment with Alteplase to Reverse Stroke study (STARS), and the Canadian Alteplase for Stroke Effectiveness Study (CASES). All analyses were performed with SAS version 9.1.3.

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.

The median NIHSS score at baseline was 15 for J-MARS (n=3576) and 12 for SITS-MOST (Figure 2). The proportion of patients with NIHSS score ≥25 at baseline was 9.4% (463/4944) in J-MARS. The proportion of patients with alteplase treatment initiated later than 3 hours after symptom onset was 1.8% (91/4944).

In SITS-MOST, the subjects were restricted to those between ages 18 and 80 years with an NIHSS score <25.14 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.

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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.

### Discussion

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). 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%. 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). 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. 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 recan-alization 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 devises for patients with acute ischemic stroke.

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