Pilot Randomized Trial of Tissue Plasminogen Activator in Acute Ischemic Stroke

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Background and Purpose: Early thrombolytic therapy with recombinant tissue-type plasminogen activator is a theoretically attractive approach to the treatment of acute focal cerebral ischemia. In preparation for a larger multicenter trial, three centers piloted a protocol for a randomized, double-blind, placebo-controlled trial of intravenous recombinant tissue plasminogen activator begun within 3 hours of the onset of symptoms of acute stroke to test its feasibility and to explore trends.

Methods: Eligible patients had pretreatment computed tomographic scanning, gave informed consent, and began treatment with either 0.85 mg/kg recombinant tissue-type plasminogen activator or placebo as soon as possible, but no later than 180 minutes after stroke onset. Patients were stratified by whether treatment was begun within 90 minutes or 91 to 180 minutes from onset. The primary end point was the proportion of patients in each group who improved by 4 or more points on the National Institutes of Health Stroke Scale at 24 hours, as determined by a separate blinded evaluator.

Results: Twenty-seven patients were randomized: 20 (10 recombinant tissue-type plasminogen activator, 10 placebo) within 90 minutes, and 7 (4 recombinant tissue-type plasminogen activator, 3 placebo) from 91 to 180 minutes. Median baseline Stroke Scale scores were 16 (minimum=5, maximum=26) for the recombinant tissue-type plasminogen activator–treated group and 11 (minimum=3, maximum=21) for the control subjects in the group treated within 90 minutes. Six patients treated with recombinant tissue-type plasminogen activator within 90 minutes improved by 4 or more points at 24 hours compared with 1 patient in the placebo group (P<.05, Fisher’s Exact Test). Two patients in each group in the 91- to 180-minute arm improved. One fatal intracerebral hemorrhage occurred in the placebo group.

Conclusions: A randomized, double-blind, placebo-controlled trial of recombinant tissue-type plasminogen activator very early in acute stroke is feasible. Preliminary observations suggest that recombinant tissue-type plasminogen activator treatment within 90 minutes may be associated with early neurological improvement. Larger studies are needed so that the potentially serious short-term risks of this treatment can be assessed in relation to meaningful long-term benefit. (Stroke 1993;24:1000-1004)

Key Words • cerebral infarction • cerebral ischemia • plasminogen activator, tissue type • thrombolytic therapy

T

reatment of ischemic stroke with thrombolytic therapy has received renewed interest, particularly in conjunction with emergency medical systems designed to expedite the identification, transport, evaluation, and rapid initiation of treatment as soon as possible after the onset of symptoms. 1 Two dose-escalation safety studies of intravenous human recombinant tissue plasminogen activator (rt-PA) in patients treated within 90 minutes and from 91 to 180 minutes from stroke onset were recently completed. 2,3 The experience from these open-label studies suggested that intravenous rt-PA, at doses lower than 0.95 mg/kg administered over 1 hour, was associated with a low risk of serious bleeding complications in ischemic stroke patients. However, since no information was available on the natural history of ischemic stroke patients observed so early in their course, few conclusions could be derived regarding efficacy.

For this reason, plans were formulated for a larger trial of rt-PA in early ischemic stroke. This trial was to be a randomized, double-blind, placebo-controlled study looking at the comparative frequency of neurological improvement at 24 hours after stroke onset as the major end point. Accrual to this study, the NINDS (National Institute of Neurological Disorders and Stroke) TPA Stroke Trial, began in February 1991. To test the feasibility of such a study, three centers that participated in the dose-escalation study organized in January 1990 to pilot a preliminary version of the
protocol for the NINDS trial. The results of this feasibility study are the subject of this report.

The major goal of this study was to test the feasibility of procedures proposed for use in a larger, randomized, placebo-controlled trial of intravenous rt-PA administered within 3 hours of onset of acute ischemic stroke. Secondary goals of the study were to develop preliminary information on the natural history of ischemic infarction beginning within 180 minutes from onset and to explore preliminary trends for early benefit from rt-PA therapy.

Subjects and Methods

Patients for this study were recruited from all patients with acute ischemic stroke who were admitted to 13 hospitals in three areas: Cincinnati, Ohio; Charlottesville, Va; and Winchester, Va. Methods for rapid patient identification, transport, and evaluation have been described previously. The protocol and consent form used for this trial were approved by each participating hospital’s Institutional Review Board. Eligible patients were stratified into two groups by time from onset of symptoms to time treatment began: those treated within 90 minutes from onset, and those treated from 91 to 180 minutes from onset. Other eligibility criteria included age 18 to 80 years and clinical diagnosis of ischemic stroke causing a serious neurological deficit measurable on the National Institutes of Health (NIH) Stroke Scale. Exclusion criteria included the following: stroke symptoms consisting only of sensory loss or only of ataxia; evidence of intracranial hemorrhage on a pretreatment computed tomographic (CT) scan; clinical presentation suggesting subarachnoid hemorrhage; patients whose deficits were rapidly improving; women who were lactating or known or suspected to be pregnant; platelet count less than 100,000/mm³, prothrombin time greater than 15 seconds, or patients who had received heparin and had an elevated partial thromboplastin time; major surgery or serious trauma in the previous 14 days; history of gastrointestinal or urinary tract hemorrhage in the previous 21 days; arterial puncture at a noncompressible site in the previous 7 days; calculated mean blood pressure of 135 mm Hg or greater at the time treatment was to begin; history of intracerebral hemorrhage or brain infarction in the previous 3 months; or serious medical illness that was likely to interfere with this trial.

After informed consent was obtained, eligible patients were randomly assigned to receive either rt-PA (Alteplase, Genentech Corp, S San Francisco, Calif), 0.85 mg/kg, or an identically appearing placebo by continuous intravenous infusion over 60 minutes. Ten percent of the total dose was administered as a bolus at the initiation of treatment. Patients were allocated to treatment groups, rt-PA or placebo, using a stratified, blocked randomization. Treatments were randomly chosen within the strata of time periods (ie, 0 to 90 minutes and 91 to 180 minutes) and participating center. A blocking factor of 4 was used within each stratum. Each center received sealed envelopes indicating rt-PA or placebo ordered in sequential number. The center pharmacist opened the envelope and prepared the study infusion when an eligible patient was admitted. The patient and all other study personnel remained blinded to the identity of the study drug throughout the course of the trial. Verification of the randomization was sent to the Coordinating Center at the University of Virginia.

Patients were carefully monitored for neurological changes or evidence of bleeding in an acute care area. Intravenous heparin was prohibited until at least 30 minutes after the infusion was complete, and even then only after a posttreatment CT scan showed no evidence of bleeding.

Neurological status was measured using the NIH Stroke Scale at baseline, 30 minutes, and 1 and 2 hours after the infusion began, and at 24 hours±30 minutes after the stroke onset. The 24-hour evaluation was performed by a blinded examiner not involved in the acute treatment of the patient. Additional NIH Stroke Scale examinations were performed at 2 days, 7 to 10 days, and 3 months after the entry stroke. Functional status was rated qualitatively and classified by the treating investigator as no, mild, moderate, or severe limitations before stroke onset (using historical information), at 7 to 10 days, and at 3 months. An assessment of ischemic stroke type was made by the investigators at 7 to 10 days using standard criteria. Large-vessel atherosclerotic and atheroembolic infarcts were generally distinguished angiographically and by CT topography; cardioembolic strokes were associated with well-known cardiac sources; and lacunar strokes were diagnosed using classic clinical criteria combined with documentation of a small deep infarct on follow-up CT scanning.

Follow-up CT scanning was performed at 1 day, 7 to 10 days, and 3 months after stroke. The volume of new cerebral infarction was measured using planimetric techniques, and any evidence of hemorrhage was recorded. Intracerebral hemorrhagic change was classified as either intraparenchymal hematoma or hemorrhagic conversion of the infarction.

The primary end point for the study was the proportion of patients in each of the four treatment groups who improved by 4 or more points or attained a perfect score of zero on the NIH Stroke Scale at 24 hours after stroke onset. Improvement of 4 or more points was chosen as an easily clinically recognizable neurological change based on the experience from the pilot dose-escalation studies. In a patient with a moderate hemiparesis of face, arm, and leg (NIH Score=6), a 4-point improvement might leave the patient with only a minor facial droop and arm drift.

Group rank comparisons of the baseline NIH Stroke Scale scores were made using a Kruskal-Wallis test; normally distributed, parametric data were compared using a t test; comparisons of the proportion of patients who improved by 4 or more points were made using Fisher’s Exact Test. Additional end points included neurological status at 2 hours, 7 to 10 days, and 3 months; functional status at 3 months; and volume of cerebral infarction at 7 to 10 days. Patients dying before the 7- to 10-day follow-up had their last CT scan used for the infarct volume measurement. Group rank comparisons of the infarct volumes were made using a Kruskal-Wallis test.

Safety measures examined included the incidence of symptomatic and asymptomatic intracerebral hemorrhage and other major (life-threatening or requiring transfusion) or minor bleeding.
TABLE 1. Comparability of Groups Treated Within 90 Minutes

<table>
<thead>
<tr>
<th></th>
<th>rt-PA (n=10)</th>
<th>Placebo (n=10)</th>
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<td>Age (y) (mean±SD)</td>
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<td>11, 5, 16</td>
<td>.25</td>
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<td>Baseline blood pressure (mm Hg)</td>
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</table>

rt-PA, recombinant tissue-type plasminogen activator.

Results

From March 1, 1990, through February 28, 1991, 27 patients were randomized into the study. Detailed data on excluded patients were not kept for this trial, but all patients who were eligible during the recruitment period were offered entry. Twenty patients (10 rt-PA, 10 placebo) were treated within 90 minutes, and 7 (4 rt-PA, 3 placebo) were treated from 91 to 180 minutes from onset of stroke symptoms.

Tables 1 and 2 detail the baseline characteristics of the four groups. For the patients treated within 90 minutes (Table 1), the mean age and baseline systolic and diastolic blood pressures were similar between the rt-PA- and placebo-treated groups. The median baseline NIH Stroke Scale score in the rt-PA group was 16 (range, 5 to 26) compared with 11 (range, 3 to 21) in the placebo group. The difference was not statistically significant. Most of the strokes in both groups were judged clinically to be caused by large-vessel occlusions. By chance, all of the entry strokes were in the carotid territory except for one (patient 1, Table 3), which was in a posterior cerebral artery distribution. For the small numbers of patients accrued in the 91- to 180-minute group (Table 2), statistical comparisons were not performed. A large imbalance in baseline NIH Stroke Scale scores in the 91- to 180-minute group is apparent.

Table 3 details the NIH Stroke Scale scores in both groups of patients treated within 90 minutes. At 2 hours after treatment was begun, two patients treated with rt-PA had improved by 4 or more points on the NIH Stroke Scale compared with one in the placebo group. At 24 hours after stroke onset, six patients treated with rt-PA had improved by 4 or more points versus one in the placebo group (P=.03). One patient in the rt-PA-treated group had untestable items on the NIH Stroke Scale at 24 hours and was judged by the investigator as not improved. By 7 to 10 days, two patients in the placebo group had died of stroke complications, and one patient in the rt-PA group died. Four of the survivors in the placebo group were now improved by 4 or more points compared with the same six patients in the rt-PA group. The difference was not statistically significant.

An analysis of the change in NIH Stroke Scale scores from baseline was also performed using a comparison of rank scores. The direction of the difference from baseline to the posttreatment assessments favored the rt-PA group in all comparisons, but only the 24-hour assessment nearly statistical significance (P=.057, Kruskal-Wallis test).

By 3 months, no further deaths had occurred, but three patients failed to return for follow-up examinations, two in the placebo group and one in the rt-PA group. Survivors in both groups who had 3-month follow-up showed further improvement in the NIH Stroke Scale scores. Five patients in each group were rated as having no or mild limitations at 3 months.

There were no symptomatic or asymptomatic intracerebral hemorrhages noted in either the rt-PA or placebo groups in the patients treated within 90 minutes. Minor bleeding (such as oozing at venipuncture sites or gingival bleeding) was noted in three patients treated with rt-PA and in one treated with placebo.

Infarct volumes at 7 to 10 days in patients treated within 90 minutes demonstrated exceptional variability in both the treated and placebo groups, ranging from 0 to over 300 cm³. The median infarct volume in the rt-PA group was 28.3 cm³ (minimum=0, maximum=317) compared with 59.9 cm³ (minimum=0, maximum=301) in the placebo group. The difference in infarct volumes at 7 to 10 days was not statistically significant (P=.60). Because of the very small sample and the imbalance in baseline neurological deficits, infarction volumes in the 91- to 180-minute arm were not compared.

Table 4 details the serial NIH Stroke Scale scores for the patients treated from 91 to 180 minutes from onset. Two patients treated with placebo improved by 4 or more points on the NIH Stroke Scale within 2 hours versus none in the rt-PA group. However, by 24 hours, two patients in the rt-PA group had improved, while one of the placebo-treated patients had worsened and died, and another had improved. Patients who were improved at 24 hours maintained their improvement at 7 to 10 days and 3 months.

One patient in the placebo group, a 63-year-old woman with atrial fibrillation and acute left hemisphere deficits, had marked improvement in both her speech and right hemiparesis beginning within 30 minutes of starting the study infusion. However, at 3 hours after beginning treatment she suddenly worsened, and an emergency CT scan showed a large intracerebral hem-
or hemorrhage into the affected hemisphere. She became comatose, herniated, and died. Careful review of her pharmacy records disclosed no medication errors, and it was confirmed that she had received placebo. No anticoagulants had been administered; she had not previously been taking aspirin. All coagulation studies, including a posttreatment screen for fibrinogen and fibrin degradation products, were normal.

No patients treated with study drug from 91 to 180 minutes from onset received intravenous heparin during their hospitalizations. In patients treated within 90 minutes, five patients (patients 12, 15, 16, 17, and 19) in the rt-PA group received heparin by continuous intravenous infusion beginning 0 to 3 days after study drug treatment. Reasons for heparin administration included potential cardiac source of embolism (patients 12, 16, and 17), unstable angina (patient 15), and fluctuating neurological deficit (patient 19).

**Discussion**

The experience from this pilot study suggests that a randomized, double-blind, placebo-controlled clinical trial of rt-PA in patients with very early cerebral infarction is feasible. Problems encountered in this trial, which were subsequently addressed before beginning the NINDS TPA Stroke Trial, included difficulties conferred by the finding of untestable items in the NIH Stroke Scale score (eg, aphasia testing in an intubated patient). This becomes particularly important when the total Stroke Scale score is used to derive one of the primary end points. Another problem was the large number (nearly 15%) of patients who failed to return for 3-month follow-up. Major logistic problems were encountered, including cross-country moves and inability of severely disabled stroke victims to travel. Future efficacy studies should consider simplifying all late follow-up procedures and providing resources and incentives for patients and investigative personnel to fully complete all protocol procedures. Additionally, standardization of ancillary therapies, particularly the use of heparin, is important because the impact of these treatments on clinical outcome, with or without thrombolytic therapy, remains unknown. Three of the five

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</table>

NIH, National Institutes of Health; rt-PA, recombinant tissue-type plasminogen activator; LTF, lost to follow-up.

**Table 3. Total NIH Stroke Scale Score in Patients Treated Within 90 Minutes**

**Table 4. Total NIH Stroke Scale Score in Patients Treated Within 91 to 180 Minutes**

NIH, National Institutes of Health; rt-PA, recombinant tissue-type plasminogen activator; LTF, lost to follow-up.
patients treated with heparin in the rt-PA group had improved by 4 or more points on the NIH Stroke Scale. Whether the adjunctive heparin therapy contributed to the improvement in these patients is uncertain.

This was a double-blind clinical trial with a clinical measurement as the primary end point. Individual packaging of the study drug to blind the participating pharmacists was not feasible for this small pilot study. However, every attempt was made to preserve blinding of the patients and study personnel in this trial, including using an examiner uninvolved in the patient’s acute care as the evaluator of the primary end point. These measures make it unlikely that bias has influenced the results of the primary end point. Because rt-PA administration may be associated with minor gum bleeding or oozing from puncture sites, careful blinded evaluation of clinical end points in subsequent studies is strongly recommended.

The results from this trial provide impetus for the further study of intravenous rt-PA in acute cerebral infarction. Despite the small numbers of patients randomized, the data suggest that in patients treated within 90 minutes from onset, rt-PA therapy may be associated with early neurological improvement. Caution is urged, however, because the power of this observation is quite low (1 − β = 0.38) because of the small numbers, the baseline stroke scale scores are potentially different (the rt-PA group had worse scores), and there was an imbalance in the use of heparin. Nevertheless, these findings are consistent with the observations of Mori et al. who, in a randomized, placebo-controlled trial of rt-PA in acute carotid territory stroke, found significantly greater improvement in Hemispheric Stroke Scale scores in the two rt-PA–treated groups, although the differences were not statistically different until day 2.

An important issue regarding ultra-early thrombolytic treatment of acute stroke is the risk of treating patients who would have spontaneously improved, i.e., those with transient ischemic attacks. However, in this trial, only 1 of 10 patients treated with placebo within 90 minutes from stroke onset had an improvement of 4 or more points in NIH Stroke Scale Score within 24 hours. Only 2 (both treated with rt-PA) of the total 27 patients randomized had NIH Stroke Scale scores of 0 at 24 hours, suggesting that few patients eligible for emergent treatment of acute ischemic neurological deficits within 180 minutes actually have transient ischemic attacks.

Although the results of this trial are promising, they should not be construed as implying that rt-PA is efficacious in acute ischemic stroke. The benefit of therapy was no longer apparent clinically by 7 to 10 days in this small sample, and the cerebral infarct volumes were not significantly different. A type 2 statistical error (that is, asserting that no difference exists when it really does) cannot be excluded, however. Moreover, whether or not the observed clinical improvements were, in fact, due to recanalization of occluded cerebral arteries cannot be ascertained from these data. Finally, experience with larger numbers of patients treated with this dose of rt-PA suggests that there is a small but serious risk of possibly fatal intracranial hemorrhage.2,3,7 The fatal hemorrhage observed in the placebo group in this trial, however, suggests that the risk of intracranial hemorrhage with rt-PA therapy must be balanced against the risk of hemorrhage complicating acute cerebral infarction spontaneously. Clearly, additional larger, placebo-controlled trials of rt-PA therapy in early acute stroke are needed.

Appendix

Participants in the TPA Bridging Study Group

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Winchester Medical Center: George L. Sheppard, MD; David Zontine, MD; Katherine Gustin, MD; Neil Crowe, MD; Sandra Massey, RN
NIH-NINDS Division of Stroke and Trauma: John R. Marler, MD
Genentech: David Stump, MD; Stephen Peroutka, MD, PhD

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