

MEMORANDUM

Date: June 12, 1996
From: Robert T. Brown, MD, PhD *Robert T. Brown*
Subject: Clinical Review of TTATTS for PLA 96-0350
Through: Marc Walton, MD, PhD *MW* 6/12/96
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To: PLA 96-0350 File

I. Overview:

Acute stroke is a thrombotic or thromboembolic event occurring in 75-80% of patients presenting with an acute neurological deficit. Thrombotic occlusion of a cerebral artery corresponding to the neurological deficit has been found in 85% of patients who present within 12 hours of onset of symptoms of stroke.

Tissue plasminogen activator (TPA), is an endogenous plasminogen activator with fibrin specificity based on a favorable plasminogen binding constant in the presence of fibrin. TPA can now be produced by recombinant DNA technology, and is currently approved for use in acute myocardial infarction, in which reperfusion of symptomatic coronary arteries has been demonstrated in response to infusion of TPA.

II. Objective

A. The primary objective was to evaluate the safety of IV Activase in patients with acute stroke secondary to angiographically documented cerebrovascular occlusion, and to evaluate the recanalization rate at 120 minutes.

B. The secondary objective was to compare baseline characteristics of Activase-treated patients who had evidence of recanalization with untreated subjects without complete occlusion at baseline.

III. Trial Design

This was an open-label, nonrandomized, multicenter (14 sites), dose-escalation trial of safety and efficacy of IV Activase in patients with acute thrombotic or thromboembolic stroke. Safety and efficacy parameters were to be determined in 20 patients at each of four doses (0.8-1.4 mg/kg). The study was to be terminated for safety if more than 3 of 20 patients deteriorated neurologically in association with any form of intracranial hemorrhage. Recanalization of at least 14 of 20 patients at 120 minutes would result in termination of the study for efficacy reasons.

Inclusion criteria:

- 18 to 79 years of age
- clinical diagnosis of ischemic stroke, defined as sudden onset of focal neurological

- deficit presumed to be ischemic after exclusion by CT scan (impairment of language, motor function, cognition, gaze, vision or neglect)
- onset of symptoms within 6 hours of treatment
- angiographic evidence of TIMI Grade 0 perfusion of the intracranial arterial territory appropriate to clinical presentation

Exclusion criteria:

- coma
- NIHSS score \leq 4, or major symptoms with rapid improvement at entry into the study
- history of stroke within 6 weeks
- seizure at onset of stroke
- clinical presentation suggesting SAH, even if no hemorrhage on CT scan
- history of ICH, neoplasm, SAH, AVM or aneurysm
- BP $>$ 185/110 on repeated measures, or requiring aggressive treatment to reduce BP
- presumed septic embolus
- presumed pericarditis due to recent MI
- surgery or biopsy of a parenchymal organ within 30 days
- trauma with internal injuries or ulcerative wounds within 30 days
- head trauma within 90 days
- known active inflammatory bowel disease
- hemorrhage within 30 days
- hereditary or acquired hemorrhagic diathesis
- glucose \leq 50 mg%, platelet count $<$ 100,000 or hematocrit $<$ 25%
- pregnant or lactating, or given birth within 30 days
- known serious sensitivity to contrast agents
- any serious, advanced or terminal illness
- any condition felt by the investigator to pose a significant hazard for therapy with Activase
- currently participating in another drug research study
- any condition for which angiography is contraindicated
- evidence on CT scan of high density lesion consistent with hemorrhage, significant mass effect with midline shift, or SAH
- angiographic evidence of suspected carotid dissection, arterial stenosis in which a luminal defect is not the sole lesion, nonatherosclerotic arteriopathy, extracranial carotid occlusion without corresponding intracranial occlusion, AVM or aneurysm

Procedure:

Significant neurological impairment prior to the qualifying stroke was excluded by baseline neurological history. Eligible subjects underwent CT scans to exclude intracranial hemorrhage, followed by arterial angiography of the appropriate arterial territory. Patients with complete occlusion (TIMI flow Grade 0) were given IV Activase, while patients without complete occlusions were not treated, and were followed as control subjects . Activase dose

levels were 0.8, 1.0, 1.2 and 1.4 mg/kg, with the total dose not to exceed 100 mg. An IV bolus of 10% of the dose was followed by infusion of the remainder of the dose over 60 minutes. Treatment was to be within 6 hours of onset of symptoms. Patients with a prolonged PTT due to recent administration of heparin were excluded from the study. The administration of IV heparin, oral anticoagulants, antiplatelet agents, hemorrhheologic agents and volume expanders was prohibited for the first 24 hours after infusion of Activase. Enrollment was planned at 20 patients per dose tier, with early termination if more than 3 of 20 deteriorated neurologically with any type of intracranial hemorrhage, or if at least 14 of 20 demonstrated any degree of recanalization, as demonstrated by repeat arteriography at 120 minutes after treatment. This sample size and frequency of recanalization would result in statistical significance at the 0.05 level, with a power of 85%. Replacement subjects were added as needed to ensure that there were 20 evaluable subjects in each dose tier. Subjects who did not complete the infusion of Activase were followed for the entire 10 day duration of the protocol.

The governing body for the study was a Steering Committee consisting of several Principal Investigators and representatives of Genentech. An external Data and Safety Committee assigned causality after reviewing all cases of hemorrhagic transformation. Written informed consent was obtained from all patients or their representatives.

Evaluation:

NIHSS	Baseline, 120 minutes, 24 hours, 72 hours, 7-10 days
Barthel Index	7-10 days
CT scan	Baseline, 24 hours, 7-10 days, as needed for emergency
Blood glucose	Baseline
Hgb, Hct	Baseline, 24 hours
RBC, WBC, platelet	Baseline, 24 hours
PTT	Baseline, 120 minutes, 6 hours, 24 hours, as needed for monitoring anticoagulation
PT, TT	Baseline, 6 hours, 24 hours
Fibrinogen, FDP	Baseline, 6 hours, 24 hours
Angiography	Baseline, 120 minutes, as needed for emergency

Angiographic response was assigned by a blinded reader at a core facility:

- Complete Responders TIMI grade 3 in all previously occluded vessels
- Partial Responders TIMI grade 2 of a single previously occluded vessel, or TIMI grade 2 or 3 of some but not all vessels if multiple arteries were occluded
- Nonresponders TIMI grade 0 or 1 of all previously occluded vessels

Adverse events:

An adverse event was defined as any adverse experience occurring during the study period, including any side effect, injury, toxicity, sensitivity reaction or failure of expected pharmacologic action. An adverse event was considered serious if it was life threatening or permanently disabling, required inpatient hospitalization or prolonged existing hospitalization,

including death, congenital anomalies in offspring, cancer, overdose or lack of pharmacologic effect. Any adverse event not identified in the current Activase label was considered unexpected.

Statistical analysis:

An "intent-to-treat" analysis was performed on data from all patients. The primary endpoint, the proportion of subjects in each response category was compared between treatment groups with a chi-squared test. NIHSS scores and Barthel Index were compared across groups by ANOVA, and Barthel Index was additionally evaluated by median test. The primary safety endpoint, intracranial hemorrhage, was categorized as symptomatic or asymptomatic, and listed in tabular form. PT, PTT, TT and fibrinogen levels were compared by ANOVA.

IV. Results

A. Number of patients receiving each dose of Activase:

0.8 mg/kg	24 patients
	21 received full dose
	2 had infusion terminated early (one subject had an accidental injury during the infusion, and a second subject was found to have elevated PTT after the infusion was started)
	1 total dose is unknown
1.0 mg/kg	14 patients, all received full dose

The rate of symptomatic ICH in the 1 mg/kg group was 28.6% (4 of 14 subjects), which led to termination of the study early.

B. There were three protocol violations in the study (all in the 0.8 mg/kg group):

- 2 subjects were treated more than 6 hours after onset of symptoms (6 hours 30 minutes and 6 hours 4 minutes)
- 1 subject with only a 98% occlusion of the carotid bifurcation was given TPA

C. Baseline characteristics in the different groups were similar, except for:

- a greater incidence of hypertension in the 0.8 mg/kg group (83.3%), compared with either untreated patients (48.0%) or the 1.0 mg/kg group (28.6%)
- a preponderance of males in the untreated group (68%, compared to 50% in both treatment groups)
- subjects in the 0.8 mg/kg group received 1036 ± 755 IU of heparin to maintain catheter patency during angiography, compare with 707 ± 860 in the 1.0 mg/kg group
- mean time to angiography (3.8 hours) and treatment (4.7 hours) was shorter for the 1.0 mg/kg group than for the 0.8 mg/kg group (4.6 hours and 5.4 hours)

respectively)

D. Response

1. Recanalization Rate

<u>Response</u>	<u>0.8 mg/kg</u>	<u>1.0 mg/kg</u>	<u>Total</u>
Complete	8.3%	7.1%	9.7%
Partial	16.7%	14.3%	19.4%
Non-responder	50.0%	71.4%	71.0%

2. Clinical Response

The NIHSS scores at all timepoints and the Barthel Index at 7-10 days were similar among the three groups.

E. Adverse Events

1. Intracranial hemorrhage

	<u>0.8 mg/kg</u>	<u>1.0 mg/kg</u>	<u>Untreated</u>
Symptomatic	16.7%	28.6%	0%
Asymptomatic	25%	21.4%	20%

The prospective threshold of 15% symptomatic ICH for ending the study early was reached even at the 0.8 mg/kg dose, but the decision had already been made to escalate to the next higher dose when this threshold was exceeded by symptomatic ICH on day 4 in the final patient in the 0.8 mg/kg group.

2. Serious adverse events

0.8 mg/kg:

- 1 patient with aspiration pneumonia
- 1 patient with a second stroke on day 3
- 4 patients with symptomatic ICH (2 died)

1.0 mg/kg:

- 1 patient with sinus bradycardia, acute MI & pulmonary embolism
- 1 patient with severe pneumonia
- 1 patient with a cardiogenic embolus
- 4 patients with symptomatic ICH (2 died)
- 1 patient with intracranial hypertension, pneumonia & sepsis (died)

Untreated:

- 2 patients with intracranial hypertension
- 1 patient with severe global aphasia on day 2
- 1 patient with meningitis

- 1 patient with progressive brain edema (died)
- 1 patient with herniation, pneumonia & pulmonary edema (died)
- 1 patient with AF, pneumonia & brain edema (died)
- 1 patient with acute MI, CHF & pneumonia (died)

F. Laboratory Parameters

1. PTT at 6 hours and TT at 24 hours were significantly longer in untreated patients (41 sec & 47 sec) than in the 0.8 mg/kg group (27 sec & 15 sec) or 1 mg/kg group (28 sec & 22 sec).
2. PT at 6 hours was significantly longer in the 0.8 and 1.0 mg/kg groups (13 & 12 sec) than in the untreated group (11 sec).
3. Decreases in fibrinogen levels in the 0.8 and 1.0 mg/kg groups were significant at 6 hours (274 & 196) and 24 hours (325 & 251).

V. Sponsor's Conclusions

A. Initiation of intravenous Activase in acute ischemic stroke patients with angiographically documented complete occlusion of the stroke-related artery may carry an increased risk of symptomatic intracranial hemorrhage.

B. Pretreatment assessment of arterial flow using noninvasive measures or confining invasive measures to post-treatment timepoints may reduce the risk of intracranial hemorrhage to stroke patients.

VI. Reviewer's Comments

A. The following discrepancies were found in the submission:

1. In calculation of the rate of recanalization after TPA administration (Table 2, page 113, volume 26), the denominator used for the 0.8 mg/kg and 1.0 mg/kg values was the value of n listed in the table, thus the percentages don't sum to 100% because of missing angiography data. For calculation of the overall rate of recanalization, the denominator used was the total number of repeat angiograms available, not n=38, as listed in the table.

2. In calculation of infarct volume (Table 6, page 149, volume 26), infarct volume is given in cm³ (key at bottom of page). Many of the volumes given in the table, however, exceed not only the volume of a cerebral hemisphere, but even the volume of the entire cranial vault.

3. Patient _____ was described on page 199, volume 28 as having died of herniation without hemorrhage, but on page 117, volume 26 as having also experienced an asymptomatic intracranial hemorrhage.

B. The following factors were examined for a relationship with adverse events during the trial:

1. Medical history

Congestive heart failure (CHF). Four of 7 patients with CHF had serious adverse events, and three of them died, suggesting that this is a predictor of poor outcome. Of 8 patients with a history of myocardial infarction, 3 had serious adverse events, and the two mortalities were in patients who also had CHF. There was no relationship of either factor with TPA treatment.

Atrial fibrillation (AF). Of 16 patients with AF, 12 (75%) experienced serious adverse events. This suggests a predictive effect of this factor because only 27/63 patients in the study had serious adverse events (42%). Of the 9 deaths in the study, 6 were associated with AF, although only 42% of patients had AF. There was no apparent association with TPA treatment.

History of hypertension. A history of hypertension was present in 36/63 patients (57%), compared with 16/27 patients with serious adverse events (59%), and in patients experiencing ICH, 64% had a history of hypertension, suggesting that a history of hypertension does not have an adverse effect on outcome. In each treatment group, the frequency of this history was approximately the same regardless of whether a serious adverse event had occurred.

2. History of smoking. A history of smoking was essentially as common in patients overall (54%) as in patients who had suffered a serious adverse event (56%) or ICH (55%).

3. Medications: calcium channel blockers, beta blockers, antiplatelet agents and oral anticoagulants. The frequency of use of these drugs was essentially the same in patients with ICH as in all patients overall, and did not differ according to treatment.

4. Heparin therapy. The administration of heparin during hospitalization had no apparent effect on the rate of ICH.

5. NIHSS score. The baseline NIHSS score in TPA patients experiencing ICH was higher (15.1) than in treated patients without ICH (10.8). This effect was not as prominent in control patients, in whom the NIHSS was 12.9 in patients without ICH, compared with 14.0 for those with ICH. This would be consistent with an increased risk of ICH in patients with high NIHSS scores treated with TPA.

6. Admission CT scan. Presence of edema or old infarct on admission CT scan had no obvious predictive value for either ICH or death.

7. Admission blood glucose level. There was no apparent relationship between blood glucose on admission and death, ICH or serious adverse event.

8. Admission platelet count. Platelet counts were normal in all patients experiencing serious adverse events.

9. Coagulation parameters. PT was <13.0 seconds in all patients with a serious adverse event, except patient (17 sec). In this patient, the TPA infusion was begun before the lab result was available. Although the infusion was stopped before completion, the patient experienced an asymptomatic ICH. Baseline PT values for 7 patients in the 1.0 mg/kg group were missing, as were PTT for 1 patient in each of the TPA groups, as well as TT for 11 patients in the 0.8 mg/kg group and 6 patients in the 1.0 mg/kg group. This suggests that a large number of patients may have undergone TPA infusion without having been screened for a preexisting coagulopathy.

10. Fibrinogen levels. All baseline fibrinogen levels given in the submission were normal, although values were missing on 7 patients receiving TPA.

11. Baseline blood pressure. Admission BP in patients with ICH in any given treatment group was not consistently higher than the mean for that group. With respect to symptomatic ICH, however, BP was higher in patients who experienced ICH compared with the mean BP for that group, both for the 0.8 mg/kg group (163/88 compared with 151/86) and the 1.0 mg/kg group (158/91 compared with 150/82). This implies that increased BP during infusion of TPA may increase the risk of symptomatic ICH.

C. Conclusions

Administration of TPA to acute stroke patients with angiographically documented cerebrovascular occlusion resulted in only minimal recanalization. The rate of ICH, however, was higher, and increased with increasing TPA dose. ICH was also more frequent in patients with high NIH Stroke Scale Scores or elevated blood pressure at the time of infusion, although the number of patients was too small for meaningful analysis. In addition, a large number of patients underwent TPA treatment without adequate screening of blood coagulation parameters, and one of these patients experienced an asymptomatic ICH, thus emphasizing the importance of careful screening of patients before treatment.

Note:
although importance of coag. screening is underscored, asymptomatic
ICH can occur even if coags are nl.
Kwan 6/1/96