Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

THERAPEUTICS

Recombinant tissue-type plasminogen activator at 3 to 5 hours after ischemic acute stroke onset was not effective or safe

Clark WM, Wissman S, Albers GW, et al., for the ATLANTIS Study Investigators. **Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS study: a randomized controlled trial.** JAMA. 1999 Dec 1;282:2019-26.

QUESTION

In patients who are treated between 3 and 5 hours after acute ischemic stroke onset, does recombinant tissue-type plasminogen activator (rt-PA) improve clinical outcome?

DESIGN

Randomized (allocation concealed*), blinded (patients, clinicians, and outcome assessors),* placebo-controlled trial with 90-day follow-up (Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS]).

SETTING

140 centers in North America.

PATIENTS

613 patients who were 18 to 79 years of age (mean age 66 y, 59% men), had a clinical diagnosis of ischemic stroke with a measurable neurologic deficit, and received the study drug within 3 to 5 hours of symptom onset. Exclusion criteria included history or presence of other neurologic conditions, evidence of hemorrhage on computed tomography, history of stroke in previous 6 weeks, hypertension, recent trauma or hemorrhage, presumed septic embolism, conditions related to recent acute myocardial infarction, recent surgery or biopsy of a parenchymal organ, or other serious medical conditions. All patients were included in the analysis.

INTERVENTION

After stratification by clinical center, patients were allocated to rt-PA, 0.9 mg/kg of body weight (maximal dose 90 mg) ($n = 307$), or placebo ($n = 306$). rt-PA was given in a 1- to 2-minute intravenous bolus (10% of dose) and a 60-minute infusion (90% of dose).

MAIN OUTCOME MEASURES

Proportion of patients with excellent neurologic recovery (score ≤ 1 on the National Institutes of Health Stroke Scale). Serious adverse events were also assessed.

MAIN RESULTS

Analysis was by intention to treat. At 90 days, the groups did not differ for neurologic recovery ($P > 0.2$) or death ($P = 0.08$) (Table). rt-PA led to more asymptomatic ($P = 0.001$), symptomatic ($P < 0.001$), and fatal ($P < 0.001$) intracerebral hemorrhages than did placebo (Table).

CONCLUSION

Recombinant tissue-type plasminogen activator at 3 to 5 hours after acute ischemic stroke onset did not improve neurologic recovery and increased the risk for intracerebral hemorrhage.

Source of funding: Genentech Inc.

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*See Glossary.

Recombinant tissue-type plasminogen activator (rt-PA) vs placebo for acute ischemic stroke within 3 to 5 hours of onset†

Outcomes	rt-PA	Placebo	RBI (95% CI)	NNT (CI)
Excellent neurologic recovery at 90 d	34.5%	34.0%	1.6% (–18 to 27)	Not significant
			RRI (CI)	NNH (CI)
Asymptomatic ICH at 18 to 30 h	11%	4.2%	168% (47 to 394)	14 (9 to 34)
Symptomatic ICH at 18 to 30 h	6.8%	1.3%	423% (91 to 1346)	19 (12 to 39)
Fatal ICH at 18 to 30 h	2.6%	0.3%	697% (31 to 4798)	44 (21 to 208)
Death at 90 d	11%	6.9%	57% (–7 to 163)	Not significant

†ICH = intracerebral hemorrhage. Other abbreviations defined in Glossary; RBI, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

Although the findings appear contradictory, results from the studies by Clark and Furlan and their colleagues contribute substantially to our understanding of thrombolytic therapy for acute ischemic stroke. On the basis of results from the U.S. National Institute of Neurologic Disorders and Stroke (NINDS) study in 1995 (1), the only treatment for acute ischemic stroke that is currently approved by the U.S. Food and Drug Administration is intravenous rt-PA when given within 3 hours of symptom onset. The ATLANTIS study of intravenous rt-PA treatment between 3 and 5 hours after stroke onset along with 2 previous European studies of intravenous rt-PA given within 6 hours of symptom onset (2, 3) have all failed to show substantial benefit in patients receiving rt-PA beyond 3 hours.

Results from 2 recent studies of intravenous rt-PA used outside the clinical trial setting showed that approximately 13% of patients treated with intravenous rt-PA were treated beyond the 3-hour window (4, 5). Whereas the rate of symptomatic intracerebral hemorrhage was 3.3% in 1 report (one half of the rate seen in the NINDS trial), this study was done primarily at centers with substantial experience in administering thrombolytic therapy (4). In a community-based study of 29 hospitals in the Cleveland area (5), the rate of symptomatic intracerebral hemorrhage was a sobering 15.7%. Although symptomatic intracerebral hemorrhage was not significantly associated with protocol deviations in either study, these observations, when viewed in light of the findings from ATLANTIS, underscore the need for adherence to established guidelines for intravenous rt-PA treatment.

The PROACT II study included only patients with angiographically documented occlusion of the middle cerebral artery; the prognosis for these patients is much poorer than for those with most other causes of stroke. As expected, spontaneous recovery to functional independence occurred in only 25% of patients in the control group. Therefore, the study was able to show a significant benefit with treatment, despite a 10% rate of symptomatic intracerebral hemorrhage.

(continued on page 19)

Intra-arterial recombinant prourokinase improved neurologic recovery in acute middle cerebral artery ischemic stroke

Furlan A, Higashida R, Wechsler L, et al., for the PROACT Investigators. **Intra-arterial prourokinase for acute ischemic stroke. The PROACT II Study: a randomized controlled trial.** JAMA. 1999 Dec 1;282:2003-11.

QUESTION

In patients with ischemic stroke caused by middle cerebral artery occlusion, does intra-arterial recombinant prourokinase (r-proUK) given within 6 hours of stroke onset improve clinical outcome?

DESIGN

Randomized (allocation concealed*), blinded (outcome assessor),* controlled trial with 90-day follow-up (Prolyse in Acute Cerebral Thromboembolism II [PROACT II]).

SETTING

54 centers in North America.

PATIENTS

180 patients who were 18 to 85 years of age (mean age 64 y, 59% men) and had new focal neurologic signs in the middle cerebral artery distribution that allowed treatment to begin within 6 hours of symptom onset and a National Institutes of Health Stroke Scale (NIHSS) score ≥ 4 except for isolated aphasia or hemianopia. Exclusion criteria included intracerebral hemorrhage, an NIHSS score ≥ 30, coma, a history of stroke within the past 6 weeks, trauma, other previous or current neurologic conditions, surgery or biopsy of a parenchymal organ, or hypertension. Follow-up was 98% for neurologic recovery and death, 88% for recanalization rates, and 90% for intracranial hemorrhage.

INTERVENTION

After stratification for stroke severity, patients were allocated to intra-arterial r-proUK, 9 mg total over 2 hours, plus intravenous heparin (n = 121) or to intravenous heparin alone (n = 59). Heparin was given in a bolus, 2000 U, and an infusion for 4 hours, 500 U/h.

MAIN OUTCOME MEASURES

Proportion of patients with a modified Rankin score ≤ 2. Secondary outcomes included the proportion of patients with an NIHSS score ≤ 1, rate of recanalization, and adverse events.

MAIN RESULTS

After adjustment for stroke severity, intra-arterial r-proUK led to more patients scoring ≤ 2 on the modified Rankin scale at 90 days than did heparin alone (P < 0.04) (Table). Groups did not differ for NIHSS scores or death. More patients in the r-proUK group than in the control group had partial or complete recanalization on 2-hour angiography (66% vs 18%, P < 0.001). A trend existed toward more intracranial hemorrhages with neurologic deterioration by 36 hours in the r-proUK group than in the control group (10% vs 2%, P = 0.06).

CONCLUSION

In patients with ischemic stroke, intra-arterial recombinant prourokinase led to improved neurologic recovery.

Source of funding: Abbott Laboratories.

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*See Glossary.

Intra-arterial recombinant prourokinase (r-proUK) vs no r-proUK for ischemic stroke ≤ 6 hours in duration†

Outcome at 90 d	r-proUK	No r-proUK	RBI	NNT (95% CI)‡
Modified Rankin score ≤ 2	40%	25%	58%	7 (3 to 268)

†Abbreviations defined in Glossary. Data are adjusted for stroke severity.
‡NNT and CI calculated from odds ratio in article.

COMMENTARY *(continued from page 18)*

Because the administration of an intra-arterial thrombolytic agent requires substantial technological resources, its applicability in the general community may be limited at present. Identifying eligible patients requires recognition of the clinical signs of a large hemispheric infarction and probably a noninvasive imaging test that suggests occlusion of the middle cerebral artery. Previous concerns about the practical aspects of evaluating and treating patients with acute stroke within 3 hours with intravenous rt-PA were never validated, and safe, effective use of rt-PA has been shown.

Fewer than 5% of all patients who have a stroke in the United States each year are treated with thrombolytic therapy. The leading barrier to treatment is patient arrival beyond the time limit for intervention, and the results from the ATLANTIS study clearly discourage treatment with intravenous rt-PA beyond 3 hours.

Expanding the time frame for intervention by using alternative means of delivery may increase the number of patients with acute stroke who can be safely treated with thrombolytic therapy. Whereas the ATLANTIS study has reaffirmed the time limitations of intravenous thrombolysis, the PROACT II study has redefined the window of opportunity for alternative methods of thrombolysis, at least in some patients.

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