Critical Review Form
Therapy

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; 282: 2019-2026

Objective: "To assess the efficacy, as measured by improved clinical outcome, and relative safety of 0.9 mg/kg of rt-PA (alteplase) vs. placebo in acute ischemic stroke patients treated between 3 and 5 hours of stroke onset." (p. 2020)

Methods: From December 1993 thru July 1998 patients were enrolled from 140 sites into a randomized, double-blinded placebo controlled clinical trial. Inclusion criteria included age 18 through 79 years presenting with clinical diagnosis of ischemic stroke causing a measurable neurological deficit who received the study drug (or placebo) within 3 to 5 hours of definite symptom onset. Exclusion criteria included:

a. Coma, severe obtundation, fixed eye deviation, or complete hemiplegia.
b. Patient has only minor stroke symptoms (ie, <4 points on the National Institutes of Health Stroke Scale and normal speech and visual fields) or major symptoms that are rapidly improving by the time of randomization.
c. History of stroke within the previous 6 weeks.
d. Known active seizure disorder or a first seizure within the 6 hours immediately prior to administration of study drug.
e. Previous known intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, arteriovenous malformation, or aneurysm.
f. Clinical presentation suggestive of subarachnoid hemorrhage, even if initial computed tomographic scan is normal.
g. Hypertension, defined as systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg on repeated measures prior to study entry or requiring aggressive (eg, intravenous antihypertensive) treatment to reduce blood pressure to within these limits.
h. Presumed septic embolus.
i. Presumed pericarditis or presence of either ventricular thrombus or aneurysm related to recent acute myocardial infarction.
j. Recent (within 30 d) surgery or biopsy of a parenchymal organ.
k. Recent (within 30 d) trauma with internal injuries or ulcerative wounds.
l. Recent (within 90 d) head trauma.
m. Any active or recent (within 30 d) hemorrhage.
n. Known hereditary or acquired hemorrhagic diathesis, eg, activated partial thromboplastin time or prothrombin time greater than normal; unsupported coagulation factor deficiency; or oral anticoagulant therapy with prothrombrin time greater than normal.
o. Pregnancy, lactation, or parturition within the previous 30 days.
p. Baseline lab values: glucose, < 50 mg/dL (2.8 mmol/L) or > 400 mg/dL (22.2 mmol/L); platelet count, < 100,000/µL; hematocrit measurement < .25.
q. Other serious, advanced, or terminal illness.

r. Any other condition that the investigator feels would pose a significant hazard to the patient if recombinant tissue-type plasminogen activator therapy were initiated.
s. Current participation in another research drug treatment protocol.

CT scans to exclude intracranial hemorrhage (ICH) were obtained prior to randomization. Copies of all CT scans were sent to a central neuroradiologist blinded to the patient's treatment group. Nitropaste for blood pressure control was acceptable, but not aggressive BP management (nitroprusside). Antiplatelet agents were allowed as was Coumadin if the INR was normal. Following randomization subjects received either placebo or rt-PA 0.9 mg/kg (90 mg max dose) with 10% bolus over 1-2 minutes and the remainder over 60-minutes. Following rt-PA or placebo administration, antiplatelet agents, heparin, and Coumadin were prohibited for 24-hours.

The primary outcome was 90-day NIH Stroke Scale (NIHSS) of 0 or 1 (no disability). The trial had 80% power with 2-sided α level of 0.05 with placebo arm NIHSS 0 or 1 in 35% and rt-PA arm 44% if 968 patients were randomized. Unfortunately, the trial was stopped prematurely based upon interim safety board analysis since "treatment was unlikely to prove beneficial". Secondary outcome measures included NIHSS at 120-minutes, 24-hours, days 7, 30, and 90. In addition, Barthel index, mRS, and Glasgow Outcome Scale were obtained at days 30 and 90 with excellent functional recovery on these scales as secondary outcomes.

Safety parameters included overall mortality, asymptomatic ICH, symptomatic ICH, fatal ICH, and other serious adverse events in both treatment groups. CT was performed at baseline, 18-30 hours, and 23-37 days.

Analysis was performed with SAS on 2 populations. The entire cohort (including those with protocol violations < 3 hours or > 5 hours) and the target population treated within the 3- to 5-hour window.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "The patients were randomized following a central code using a blocked randomization, stratified by clinical center." (p. 2020)
2.	Was randomization concealed (blinded)?	Yes. "No one at the local site was aware of patient group assignment." (p. 2020)

3.	Were patients analyzed in the groups to which they were randomized?	"Analyses on 2 populations were performed: a target population that was treated within the 3- through 5-hour window and an ITT (intention-to-treat) analysis based on all patients randomized." (p. 2021).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	"The groups were well matched for baseline age and initial NIHSS score (mean 11 both groups). The target population had a higher percentage of men in the placebo group". "The groups were well matched for history of smoking hypertension, cardiac disease, and prior stroke. In the treatment population, the rt-PA group had a trend toward a higher incidence of diabetes and atrial fibrillation." (p. 2022)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	"No one at the local site was aware of patient group assignment". (p. 2020)
2.	Were clinicians aware of group allocation?	"All personnel at each study site and at Genentech involved in conducting and monitoring the trial were blinded to the study drug codes". (p. 2021)
3.	Were outcome assessors aware of group allocation?	"To avoid potential unblinding, the clinical examinations at 30 and 90 days were performed by an individual who was not present during study drug administration and did not see the patient in the first 24 hours." (p. 2021)
4.	Was follow-up complete?	No loss to follow-up or missing data were reported.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 613 patients enrolled including 31 between 0-3 hours from symptom onset (before protocol changed) and 32 protocol violations (8 less than 3 hours, 24 after 5 hours) and 3 subjects who did not receive any study medications. This left 547 who received rt-PA or placebo between 3- and 5-hours. • No difference noted in primary outcome (excellent recovery at 90 days): 32% placebo vs. 34% rt-PA. (p = 0.65). • No treatment effects were seen for any of the secondary outcomes. • No global treatment effect was seen when adjusted for baseline differences between DM and A-fib. • No treatment effect or early recovery (2-hour mean NIHSS 9.8 placebo vs. 10.0 rt-PA). • The only beneficial effect was in proportion of subjects with ≥ 11 point NIHSS improvement at 30 and 90 days (30 days placebo 31%, t-PA 40% p = .02; 90-days 36% vs. 45% p = 0.03). • <u>When stratified by time-to-drug for the primary outcome there was still no beneficial effect</u>: Between 3 and 4 hours (N=111; placebo 31%, rt-PA 34%; p = 0.92) and between 4 and 5 hours (N = 436; placebo 33%, rt-PA 34% p = 0.92). • <u>Treatment with rt-PA significantly increased the rate of both asymptomatic and symptomatic ICH</u> - asymptomatic 4.7% placebo vs. 11.4% rt-PA (p = 0.004) **NNH = 15** - symptomatic 1.1% placebo vs. 7% rt-PA (p = 0.001) - fatal ICH 0% placebo vs. 3% rt-PA (p = 0.005) **NNH = 33** • No significant difference in 90-day mortality although <u>trend for higher mortality in rt-PA</u> (6.9% vs. 11% rt-PA, p = 0.09)

2.	How precise was the estimate of the treatment effect?	No significant or near-significant treatment effects so precision less important and CI's not presented.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Probably although scant patient hospital, or protocol details provided.
2.	Were all clinically important outcomes considered?	Yes – functional improvement and adverse effects.
3.	Are the likely treatment benefits worth the potential harm and costs?	No – based upon this data the use of IV rt-PA beyond 3-hours of symptom onset cannot be supported.

Limitations

1) **Premature closure of study so underpowered and potential Type II error.**
2) **Poor description of study hospitals or thrombolytic protocol (BP management, Neurology vs. EM roles, EMS training, community education).**
3) **Patient profile differed from NINDS with milder strokes (baseline NIHSS 11 in ATLANTIS vs. 14 in NINDS) with better outcomes in the control group. Could this lesser illness severity (better baseline prognosis) difference account for the lack of benefit of rt-PA?**

Bottom Line

Even in select patient populations (see myriad exclusion criteria above) at academic medical centers with protocol-driven care in a regimented research setting, rt-PA for acute ischemic stroke beyond 3-hours after symptom onset cannot be supported since patients derive no benefit and still experience a substantially increased risk of symptomatic ICH.