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Recombinant Tissue-Type Plasminogen Activator (Alteplase) for Ischemic Stroke 3 to 5 Hours After Symptom Onset

The ATLANTIS Study: A Randomized Controlled Trial

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THE FOOD AND DRUG ADMINISTRATION (FDA) approval in June 1996 of intravenous recombinant tissue-type plasminogen activator (rt-PA) for patients with acute ischemic stroke treated within 3 hours of symptom onset marked a historic first step in treating this devastating disease. This approval was primarily based on the results of the National Institute of Neurologic Disorders (NINDS) trials (1 and 2).¹ In the NINDS trials, patients with ischemic stroke were treated within 3 hours of symptom onset with either 0.9 mg/kg of rt-PA (alteplase) (maximum dose <90 mg) or placebo. A significant 11% to 15% absolute benefit was found favoring rt-PA despite a significant increase in the symptomatic intracerebral hemorrhage (ICH) rate (6.4% vs 0.6%; $P < .001$) at 36 hours. The current approved use of rt-PA is limited to otherwise eligible patients in whom treatment can be initiated within 3 hours after the onset of stroke symptoms. This greatly restricts the number of patients who could potentially be treated, because most stroke patients present more than 3 hours after symp-

Context Recombinant tissue-type plasminogen activator (rt-PA) improves outcomes for patients with acute ischemic stroke, but current approved use is limited to within 3 hours of symptom onset. This restricts the number of patients who can be treated, since most stroke patients present more than 3 hours after symptom onset.

Objective To test the efficacy and safety of rt-PA in patients with acute ischemic stroke when administered between 3 and 5 hours after symptom onset.

Design The Alteplase Thrombolysis for Acute Noninterventive Therapy in Ischemic Stroke (ATLANTIS) study is a phase 3, placebo-controlled, double-blind randomized study conducted between December 1993 and July 1998, with up to 90 days of follow-up.

Setting One hundred forty university and community hospitals in North America.

Patients An intent-to-treat population of 613 acute ischemic stroke patients was enrolled, with 547 of these treated as assigned within 3 to 5 hours of symptom onset. A total of 39 others were treated within 3 hours of symptom onset, 24 were treated more than 5 hours after symptom onset, and 3 never received any study drug.

Intervention Administration of 0.9 mg/kg of rt-PA ($n = 272$) or placebo ($n = 275$) intravenously over 1 hour.

Main Outcome Measures Primary efficacy was an excellent neurologic recovery at day 90 (National Institutes of Health Stroke Scale [NIHSS] score of ≤ 1); secondary end points included excellent recovery on functional outcome measures (Barthel index, modified Rankin scale, and Glasgow Outcome Scale) at days 30 and 90. Serious adverse events were also assessed.

Results In the target population, 32% of the placebo and 34% of rt-PA patients had an excellent recovery at 90 days ($P = .65$). There were no differences on any of the secondary functional outcome measures. In the first 10 days treatment with rt-PA significantly increased the rate of symptomatic intracerebral hemorrhage (ICH) (1.1% vs 7.0% [$P < .001$]), a symptomatic ICH (4.7% vs 11.4% [$P = .004$]), and fatal ICH (0.3% vs 3.0% [$P < .001$]). Mortality at 90 days was 6.9% with placebo and 11.0% with rt-PA ($P = .09$). Results in the intent-to-treat population were similar.

Conclusions This study found no significant rt-PA benefit on the 90-day efficacy end points in patients treated between 3 and 5 hours. The risk of symptomatic ICH increased with rt-PA treatment. These results do not support the use of intravenous rt-PA for stroke treatment beyond 3 hours.

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tom onset.² This time limitation is reflected in the finding that, since approval, less than 5% of all stroke patients are receiving rt-PA.³⁻⁵ This raises the question of whether intravenous rt-PA is still relatively safe and effective if given beyond 3 hours after stroke. This question is particularly important in light of a recent phase 4 trial in North America finding that more than 15% of patients receiving rt-PA are actually being treated after 3 hours from symptom onset even at experienced stroke centers.⁶

The objective of this phase 3 study, Alteplase ThromboLysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS), was to assess the efficacy, as measured by improved clinical outcome, and relative safety of 0.9 mg/kg of rt-PA vs placebo in acute ischemic stroke patients treated between 3 and 5 hours of stroke onset.

METHODS

The ATLANTIS study first began in August 1991 and was initially designed to assess the efficacy and safety of intravenous rt-PA in patients with acute ischemic stroke administered from 0 to 6 hours after symptom onset. This company-sponsored trial (Genentech Inc, South San Francisco, Calif) was designed to run concurrently with the NINDS trials in an effort to obtain more information on the use of rt-PA in stroke treatment. In December 1993, enrollment was halted and the time window was changed because of safety committee (data monitoring safety board) concerns in the 5- to 6-hour group. It was decided to restart the trial as "part B," reflecting a new time window (0-5 hours after symptom onset) and new study end points, with patients enrolled in "part A" to be considered a separate trial for analysis and reporting purposes. The company and investigators remained blinded to results from patients in part A. Data from part A will be reported in a separate publication.⁷ The ATLANTIS part B study was further modified in February 1996 to a 3- to 5-hour window after stroke onset in light of the results of the NINDS rt-PA study. At that time,

100 new study sites were added. Thirty-one patients were enrolled within 0 to 3 hours of stroke onset per protocol in part B of the trial before the change was made to the 3- to 5-hour window. Although data for all part B intent-to-treat (ITT) patients are presented here, this article focuses primarily on the patients enrolled in the 3- to 5-hour window who are the target population for the ATLANTIS part B trial.

This was a randomized, double-blind, multicenter, placebo-controlled clinical trial. Enrollment was based on clinical and computed tomography (CT) criteria; angiography was not required. The study was conducted at 140 centers in North America. All investigators were required to be certified in the National Institutes of Health Stroke Scale (NIHSS)⁸ according to National Institutes of Health (NIH) guidelines by means of a standard training videotape.⁹ Patients were randomized (1:1) and treated with either rt-PA (0.9 mg/kg) or matched placebo. All patients or their legal representatives signed an informed consent approved by the institutional review board of each study site.

Patients

The target population for part B of the study was defined as patients aged 18 through 79 years who presented with a clinical diagnosis of ischemic stroke causing a measurable neurologic deficit and received the study drug within 3 to 5 hours of definite symptom onset (TABLE 1). A CT scan excluding ICH was required before randomization. In addition, patients were excluded if signs of cerebral ischemia were seen in more than one third of the territory of the middle cerebral artery. This criterion was included in the February 1996 protocol amendment following the results of the European Cooperative Acute Stroke Study (ECASS) I trial¹⁰ that suggested that the risk of ICH is higher in this subgroup of patients. Copies of all CT scans were sent to a central neuroradiologist who was blinded to the patients' treatment group.

Primary exclusion criteria for this study are shown in Table 1. Simple

measures (eg, use of nitropaste) were allowed to lower blood pressure to less than 185/110 mm Hg prior to treatment but aggressive treatment (eg, nitroprusside intravenous infusion) was not. Patients taking coumadin were allowed only if their prothrombin time was normal. Patients taking antiplatelet agents were allowed.

The patients were randomized following a central code using a blocked randomization, stratified by clinical center. The study used an interactive voice system for randomization and drug supply management. No one at the local site was aware of patient group assignment. The study drug consisted of white lyophilized powder, indistinguishable between groups, that was reconstituted with sterile water. The reconstituted study drug, 0.9 mg/kg (no more than 90 mg total), was given as a 10% (of total dose) intravenous bolus over 1 to 2 minutes through a dedicated line, followed immediately by a 60-minute infusion of the remaining dose. Administration of heparin, oral anticoagulants, antiplatelet agents, or other hemorrhagic agents was prohibited during the initial 24 hours after completion of the infusion. After 24 hours, the use of intravenous heparin or other antithrombotic agents was at the local investigators' discretion.

The sample size estimate for part B using an NIHSS score of 0 or 1 as the primary end point was based on a 2-sided χ^2 test. The placebo group was assumed to have a 35% primary end point rate. Based on this assumption, 968 patients would be required to detect a primary end point rate of 44% or higher in the rt-PA group with an α level of .05 and power of 80%. The trial was stopped prematurely in July 1998 based on an interim analysis by the data monitoring safety board indicating that "treatment was unlikely to prove beneficial." Although the timing of this interim analysis was preplanned, the study did not meet any of the prespecified safety criteria for stopping.

Patients were monitored closely for the development of any neurologic symptoms or bleeding complications. An

NIHSS and general physical examination were completed by certified investigators at baseline; 120 minutes; 24 hours; and 7, 30, and 90 days following initiation of study drug, while Barthel index, modified Rankin scale, and Glasgow Outcome Scale assessments were performed at days 30 and 90. Vital signs were determined hourly for the first 24 hours. After initiation of study drug, the patient's blood pressure was maintained at less than 185/110 mm Hg in accordance with a treatment algorithm that included aggressive measures, if needed. Clinical laboratory tests, including complete blood cell counts, coagulation tests, and fibrinogen and fibrin degradation products (study personnel blinded to results), were performed at baseline, 6, and 24 hours. A noncontrast cerebral CT scan was performed at baseline, 18 to 30 hours (or sooner if clinical deterioration occurred), and 23 to 37 days after study drug infusion for assessment of ICH, infarct signs, and infarct size. 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.

Outcome Measures

The sponsor conducted data management and analysis. All personnel at each study site and at Genentech involved in conducting and monitoring the trial were blinded to the study drug codes. The primary efficacy outcome variable was the percentage of patients at 90 days with an excellent neurologic recovery defined as a score of 0 or 1 on the NIHSS. Secondary end points included excellent functional recovery at days 30 and 90 on the modified Rankin scale,¹¹ the Barthel index,¹² and the Glasgow Outcome Scale.¹³ A full list of the outcome variables for the trial is given in TABLE 2.

Safety parameters included overall mortality, asymptomatic ICH, symptomatic ICH, fatal ICH, and other serious adverse events in both treatment groups. An ICH was defined as the presence of any blood seen on a brain CT scan. The local investigator assessed cause of death. The records of all pa-

tients who died and who had any type of ICH were reviewed by the blinded independent data safety monitoring board on an ongoing basis.

Statistical Analysis

Data were double entered and verified using the Informix database management system. Statistical Analysis Software 6.12 (SAS Institute Inc, Cary, NC) was used to perform the statistical analysis. All tests of significance were 2-sided and conducted at the $P = .05$ level of significance. Analyses on 2 populations were performed: a target population that was treated within the 3- through 5-hour

window and an ITT analysis based on all patients randomized, including the 39 patients enrolled less than 3 hours after stroke onset prior to the protocol amendment. For both analyses, results are based on the last observation carried forward method with death given the worst outcome score on all of the measures. Differences in baseline characteristics were determined using t tests for continuous variables and χ^2 tests for categorical variables. Efficacy end points were tested using a 2-sample binomial test. Differences in ICH and serious adverse events between groups were compared with the Fisher exact test.

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria

- Age, 18 through 79 years (ie, candidates are at least 18 years old but not yet 80).
- Clinical diagnosis of ischemic stroke, causing a measurable neurological deficit (defined as impairment of language, motor function, cognition, gaze, or vision, or as neglect). Ischemic stroke is defined as an event characterized by the sudden onset of an acute focal neurological deficit presumed to be due to cerebral ischemia after exclusion of hemorrhage by computed tomographic scan.
- Onset of symptoms of ischemic stroke within 3-5 hours of initiation of treatment with the study drug: "time of onset" of stroke is defined as that point at which a change in the baseline neurological function occurred. If that time is not known, eg, the patient awakens from sleep with new symptoms, the last time the patient was observed to be neurologically intact must be considered the time of onset.

Exclusion Criteria

Clinical

- Coma, severe obtundation, fixed eye deviation, or complete hemiplegia.
- 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.
- History of stroke within the previous 6 weeks.
- Known active seizure disorder or a first seizure within the 6 hours immediately prior to administration of study drug.
- Previous known intracranial hemorrhage, neoplasm, subarachnoid hemorrhage, arteriovenous malformation, or aneurysm.
- Clinical presentation suggestive of subarachnoid hemorrhage, even if initial computed tomographic scan is normal.
- 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.
- Presumed septic embolus.
- Presumed pericarditis or presence of either ventricular thrombus or aneurysm related to recent acute myocardial infarction.
- Recent (within 30 d) surgery or biopsy of a parenchymal organ.
- Recent (within 30 d) trauma with internal injuries or ulcerative wounds.
- Recent (within 90 d) head trauma.
- Any active or recent (within 30 d) hemorrhage.
- 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 prothrombin time greater than normal.
- Pregnancy, lactation, or parturition within the previous 30 days.
- Baseline lab values: glucose, <50 mg/dL (2.8 mmol/L) or >400 mg/dL (22.2 mmol/L); platelet count, <100 000/ μ L; hematocrit measurement <.25.
- Other serious, advanced, or terminal illness.
- Any other condition that the investigator feels would pose a significant hazard to the patient if recombinant tissue-type plasminogen activator therapy were initiated.
- Current participation in another research drug treatment protocol.

Cerebral Computed Tomographic Scan Exclusions

- High-density lesion consistent with hemorrhage of any degree.
- Evidence of significant mass effect with midline shift.
- Subarachnoid hemorrhage.
- Parenchymal hypodensity, loss of gray/white matter distinction, and/or effacement of cerebral sulci in >33% of the middle cerebral artery territory.

RESULTS

From December 1993 through July 1998, a total of 613 patients were enrolled (ITT) at 140 sites into part B; this includes 31 patients appropriately enrolled at 0 to 3 hours of stroke onset prior to the protocol modification and 32 protocol violators enrolled after the modification within 3 hours (n = 8) or after 5 hours (n = 24) of stroke onset. An additional 3 patients

were excluded because they did not receive any study medication. Thus, 547 patients received study medication between 3 and 5 hours of symptom onset. Because of randomization errors, 9 patients were assigned rt-PA but actually received placebo and 4 patients were assigned placebo but actually received rt-PA. The final target population consisted of 547 patients (FIGURE 1). All ran-

domized patients were included in the ITT analysis (grouped by assigned randomization). For both populations, the groups were well matched for baseline age and initial NIHSS score (mean, 11 for both groups). The target population had a higher percentage of men in the placebo group (TABLE 3).

In the target population, mean time to treatment was 4 hours, 24 minutes from symptom onset in the placebo group and 4 hours, 28 minutes in the rt-PA 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.

Table 2. Study Outcome Measures

Primary Hypothesis

For patients treated within a 3-5 hour window, there is a significant difference between the recombinant tissue-type plasminogen activator (rt-PA) and placebo-treated groups in complete recovery, defined as a National Institutes of Health Stroke Scale (NIHSS) score of ≤ 1 at 90 days.

Secondary Hypotheses

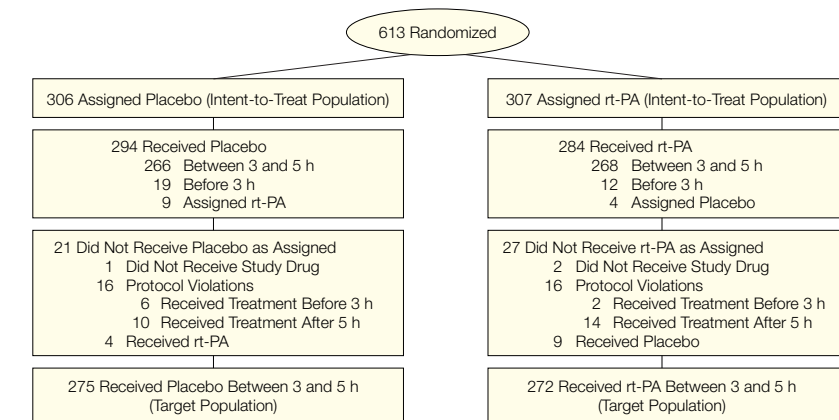
The following hypotheses deal with patients treated within a 3-5 hour window.

1. Using a global outcome assessment, there is a significant difference between the rt-PA- and placebo-treated groups in the proportion of patients with an NIHSS score of ≤ 1 , Barthel index score of ≥ 95 , modified Rankin scale score of ≤ 1 (no significant disease or symptoms), and Glasgow Outcome Scale score of 1 (good recovery) at 90 days.
2. There is a significant difference between the rt-PA- and placebo-treated groups in the proportion of patients with a Barthel index score of ≥ 95 , a modified Rankin scale score of ≤ 1 , and a Glasgow Outcome Scale score of 1 at 90 days, considered as separate variables.
3. There is a significant difference between the rt-PA- and placebo-treated groups in the distribution of outcome as assessed by NIHSS, Barthel index, modified Rankin scale, and Glasgow Outcome Scale scores at 90 days.

Additional Hypotheses

1. There is a significant difference between the rt-PA- and placebo-treated groups in clinical improvement, defined as a decrease in the NIHSS score of 11 or more points from baseline to 90 days, or complete recovery, defined as an NIHSS score of 0 at 90 days.
2. This end point will measure the same outcomes as 1-3 at 30 days.
3. There is a significant difference between the rt-PA- and placebo-treated groups in early clinical improvement in the mean of the NIHSS score at 120 minutes, at 24 hours, and at 7 days.
4. There is a significant difference between the rt-PA- and placebo-treated groups in complete functional recovery, defined as a score of 105 in the combined Barthel index/modified Rankin scale.
5. There is a significant difference between the rt-PA- and placebo-treated groups in the median change in the modified Rankin scale score from prestroke to 30 days and from prestroke to 90 days.
6. There is a significant difference between the rt-PA- and placebo-treated groups in the volume of cerebral infarction as measured by cerebral computed tomographic scanning at 30 days.

Figure 1. Patient Randomization



rt-PA indicates recombinant tissue-type plasminogen activator.

Efficacy Results

Results of the efficacy analysis are shown in TABLE 4. For the primary end point in the target population, 32% of placebo patients and 34% of rt-PA patients had an excellent recovery at 90 days ($P = .65$). No treatment benefits were seen on any of the secondary functional outcomes, including a composite "global outcome statistic" modeled after the method used in the NINDS rt-PA study,¹ and no global treatment effect was seen even when adjustments were made for baseline differences in diabetes and atrial fibrillation. The overall distribution of the NIHSS, modified Rankin scale, Barthel index, and Glasgow Outcome Scale scores in the target population is shown in FIGURE 2. There appeared to be no treatment effect on very early recovery. The mean (SD) NIHSS scores at 2 hours were 9.8 (5.7) in the placebo group vs 10.0 (6.4) in the rt-PA group ($P = .91$); at 24 hours, 9.0 (6.6) vs 9.0 (8.6) ($P = .34$); and at 7 days, 8.34 (8.3) vs 8.72 (10.1) ($P = .36$). However, treatment with rt-PA did produce a significant increase in the percentage of patients in the target population with major neurologic recovery, defined as an 11-point improvement or complete recovery on the NIHSS at days 30 and 90 (day 30: placebo, 31%; rt-PA, 40% [$P = .02$]; day 90: placebo, 36%; rt-PA, 45% [$P = .03$]). In a post hoc analysis, the percentage of patients with "independent" recovery defined as a modified Rankin

scale score of 0, 1, or 2 also showed no treatment effect (placebo, 56%; rt-PA, 54%; $P = .75$). For the primary outcome measure (NIHSS score, 0 or 1), an analysis of variance that accounted for differences in baseline variables was performed. These parameters did not affect the results significantly. Finally, in an additional post hoc analysis using 90-day NIHSS scores of 0 and 1, we found an equal lack of efficacy in patients treated between 3 and 4 hours of stroke onset ($n = 111$; placebo, 31%; rt-PA, 28%; $P = .84$) and patients treated between 4 and 5 hours ($n = 436$; placebo, 33%; rt-PA, 34%; $P = .92$).

No treatment benefit was seen on day 30; CT scan infarct volumes in both groups showed large variations (Table 4). A detailed analysis of the CT scan findings in this study will be addressed in a separate publication. There were no planned pharmacoeconomic analyses in this study; however, there was no significant difference in the mean (SD) length of hospital stay between groups: placebo, 13 (22) days; rt-PA, 11 (24) days.

Serious Adverse Events

Serious adverse events are shown in TABLE 5. The occurrence of ICH was determined by CT scan at 18 to 30 hours. Determination of whether the ICH was asymptomatic or symptomatic was made by the local principal investigator. In the target population, treatment with rt-PA significantly increased the rate of both asymptomatic and symptomatic ICH: asymptomatic in comparison with placebo, 4.7% placebo vs 11.4% rt-PA ($P = .004$); symptomatic, 1.1% placebo vs 7.0% rt-PA ($P < .001$) (fatal symptomatic, 0% vs 3%; $P = .005$). Safety results for the entire ITT population were similar. These ICH rates represent the incidence of ICH on any CT scan performed in the first 10 days. Although for most cases, this only involves the CT scan at 18 to 30 hours, any cases in which an ICH was observed on a repeat CT scan in the first 10 days were also included. No significant difference in the mortality rate at 90 days between groups was found in either population, although mortality rates tended to be higher with

rt-PA (placebo, 6.9%; rt-PA, 11.0%; $P = .09$) (Table 5). Other than ICH, the incidence of serious systemic bleeding was less than 0.2% in both the placebo and rt-PA groups.

COMMENT

The ATLANTIS part B trial did not find a benefit to intravenous rt-PA therapy for patients with ischemic stroke when treatment was initiated within 3 to 5 hours

Table 3. Baseline Demographics*

Group	Intent-to-Treat Population			Target Population†		
	Placebo (n = 306)	rt-PA (n = 307)	P Value	Placebo (n = 275)	rt-PA (n = 272)	P Value
Age, y, mean (SD)	65 (11)	66 (11)	.23	65 (11)	66 (12)	.05
Male sex	62	57	.19	63.6	54.8	.04
White race	83	84	.80	83.6	84.6	.33
Weight, kg, mean (SD)	80 (18)	78 (19)	.13	81 (18)	78 (19)	.07
Time to treatment, h (Median)	4:30	4:36		4:34	4:36	
<3	8.5	4.2	.21	0	0	.84
3-4	18.0	19.3		20.7	20.6	
>4-5	70.3	72.2		79.3	79.4	
>5	3.3	4.2		0	0	
Baseline NIHSS Mean (SD)	11 (5)	11 (6)	.36	11 (5)	11 (6)	.29
Median	10	10		10	10	
<10, %	58	53		58	53	
>20, %	7	8		7	9	
Smoker	44	46	.62	44	44	.93
Cardiac disease	72	74	.59	73	75	.61
Atrial fibrillation	14	19	.10	14	19	.09
Hypertension	60	60	.95	62	61	.79
Diabetes	18	25	.03	19	25	.07

*rt-PA indicates recombinant tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale. Data are presented as percentages unless otherwise indicated.

†The target population received treatment as assigned between 3 and 5 hours after symptom onset.

Table 4. Efficacy Results*

End Point	Intent-to-Treat Population			Target Population†		
	Placebo (n = 306)	rt-PA (n = 307)	P Value	Placebo (n = 275)	rt-PA (n = 272)	P Value
Day 90						
NIHSS score, 0 or 1	34.0	34.5	.89	32.0	33.8	.65
Barthel index, >95	54.6	54.1	.90	53.5	53.7	.96
Modified Rankin scale, 0 or 1	40.5	41.7	.77	38.9	42.3	.42
Glasgow Outcome Scale, 1	46.1	46.3	.97	44.0	46.3	.59
Barthel/Rankin‡	36.6	37.5	.83	34.5	37.9	.42
NIHSS score, >11 improvement	39.0	45.1	.13	36.0	44.9	.03
Day 30						
NIHSS score, 0 or 1	26.2	32.8	.08	24.6	32.1	.06
Barthel index, >95	47.0	47.2	.96	46.8	46.6	.96
Modified Rankin scale, 0 or 1	31.9	36.2	.26	31.2	36.5	.20
Glasgow Outcome Scale, 1	38.0	42.3	.29	36.9	41.1	.32
Barthel/Rankin‡	28.9	32.2	.37	28.3	32.0	.35
NIHSS score, >11 improvement	32.2	41.1	.02	30.6	40.4	.02
Infarct volume, cm ³ , mean (SD)	47 (71)	47 (66)	.98	47 (74)	46 (66)	.95

*rt-PA indicates recombinant tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale. Data are presented as percentages unless otherwise indicated.

†The target population received treatment as assigned between 3 and 5 hours after symptom onset.

‡Barthel/Rankin indicates patients who met criteria for both of the scales.

of symptom onset. No beneficial effects were seen on the day 90 evaluations in either the target population, those patients strictly enrolled between 3 and 5 hours of stroke onset, or in the ITT analysis group. The demographic data show that the groups were well matched. Although there was a larger number of women in the rt-PA group, this is unlikely to have influenced stroke recovery. Patients treated with rt-PA were on average 1 year older and although age does impact recovery, it is unlikely that

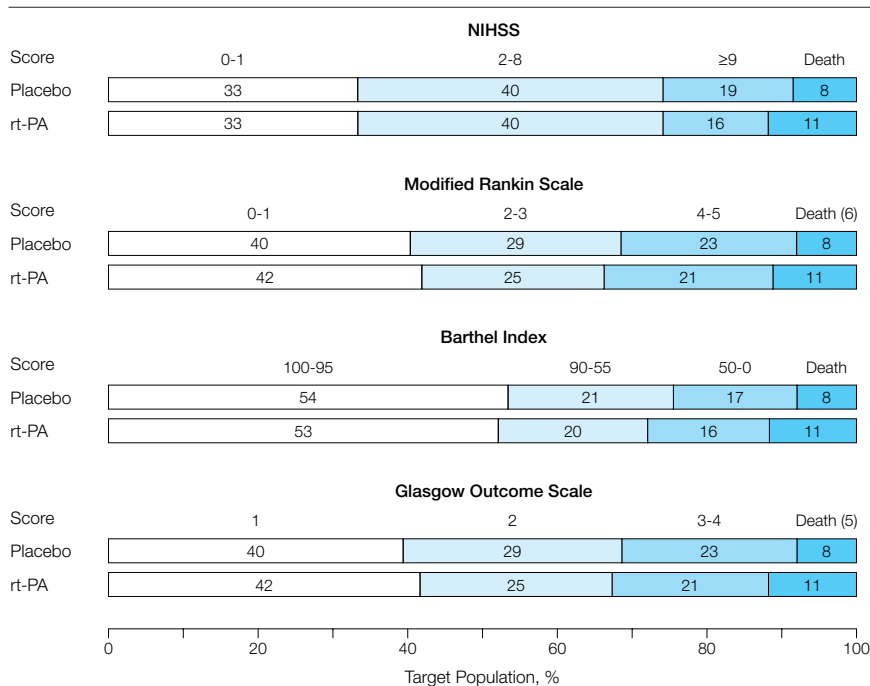
such a minor difference would affect the results. In this trial, 31 of the patients were appropriately treated less than 3 hours after the onset of symptoms before the protocol was modified to the 3- to 5-hour target window. Despite this, less than 7% of the patients were actually treated in less than 3 hours from onset of symptoms in the ITT population. Therefore, even the ITT population was primarily an evaluation of rt-PA treatment given within 3 to 5 hours of stroke onset. The percentage of patients who ex-

perienced at least an 11-point change in the NIHSS score was significantly higher at day 30 with rt-PA treatment. However, although this subgroup of patients with “dramatic responses” on the NIHSS was higher with rt-PA treatment, this effect did not lead to a difference in excellent overall recovery between the 2 groups. In addition, since this was the only positive finding out of 25 efficacy variables, the apparent effect may represent a chance finding due to the multiple comparisons. All of the other planned study end points failed to demonstrate any beneficial effect. In addition, a post hoc analysis evaluating the percentage of patients with independent recovery at day 90 (modified Rankin scale score, 0-2) also failed to document any significant treatment effect.

Treatment with rt-PA within 3 to 5 hours of symptom onset did significantly increase the rate of ICH. However, a comparison of the rate of symptomatic ICH in our trial, 7%, with that in the NINDS study, 6%, suggests that delaying therapy with rt-PA did not further increase the rate of ICH over that observed in the population treated within 3 hours from symptom onset. In this study, there was no significant difference in mortality between groups, although the trend toward improved 90-day mortality seen in the NINDS trial was not seen. Therefore, it appears that although the increased rate of symptomatic ICH remains when rt-PA therapy is delayed to 3 to 5 hours after symptom onset, the beneficial clinical effects that outweigh this risk in patients treated under 3 hours were not observed in this study. Finally, the fact that our trial involved patients with milder stroke and used different CT scan criteria may be confounding these results: if we had enrolled patients with more severe stroke, our symptomatic ICH rate may have been higher.

In the target population in this trial, 80% of patients were enrolled between 4 and 5 hours of symptom onset. One explanation for this is that patients who could be treated just after the 3-hour window may have been treated with rt-PA rather than enrolled in this study.

Figure 2. Outcome Scores in the Target Population



The target population is defined as patients aged 18 through 79 years who presented with a clinical diagnosis of ischemic stroke causing a measurable neurologic deficit and who received the study drug between 3 and 5 hours of definite symptom onset. NIHSS indicates National Institutes of Health Stroke Scale (scores range from 0 to 42); rt-PA, recombinant tissue-type plasminogen activator. Not all sums equal 100% due to rounding. Barthel index scores are given in 5-point increments.

Table 5. Safety Results*

Serious Adverse Event	Intent-to-Treat Population			Target Population†		
	Placebo (n = 306)	rt-PA (n = 307)	P Value	Placebo (n = 275)	rt-PA (n = 272)	P Value
Asymptomatic ICH	4.2	11.3	.001	4.7	11.4	.004
Symptomatic ICH	1.3	6.7	<.001	1.1	7.0	<.001
Fatal ICH	0.3	2.6	<.001	0.3	3.0	<.001
Death within 90 d	6.9	10.9	.08	6.9	11.0	.09
Death within 30 d	4.2	7.6	.08	4.4	7.0	.18

*rt-PA indicates recombinant tissue-type plasminogen activator; ICH, intracerebral hemorrhage. Data are presented as percentages unless otherwise indicated.
 †The target population received treatment as assigned between 3 and 5 hours after symptom onset.

Although the study failed to find a benefit for rt-PA in patients treated between 3 and 4 hours from symptom onset, the study is underpowered to evaluate the actual safety and efficacy for patients enrolled between 3 and 4 hours from symptom onset.

In comparison to the NINDS trials, patients in our trial had milder strokes with a median NIHSS score of 10 compared with 14. This may explain why the spontaneous recovery rates in the placebo group of our trial were higher. That patients in our trial had milder strokes is also a likely explanation for the lower mortality rate (7%) seen in the placebo group in our study vs that in the NINDS trials (21%). The stringent cerebral CT scan exclusion criteria in our study may also have excluded some patients with severe stroke. The spontaneous recovery rate in our study on the NIHSS primary end point (34%) was actually very close to the predicted value on which the original 968 sample size was calculated (35%). However, because of the relatively mild stroke in this population, if the study had used 1 of the functional end points that had a 50% spontaneous recovery rate, it would have been difficult for any therapy to obtain statistically significant effects (type II error) in a sample size of 900 patients. The conclusion that enrollment criteria should be an NIHSS score higher than 4 has also been supported by other clinical stroke trials.¹⁴

The ATLANTIS study is the third large randomized stroke trial evaluating intravenous rt-PA with the majority of patients being treated more than 3 hours after symptom onset that has failed to find a treatment benefit in the ITT population. In 1995, ECASS I was published, which evaluated the safety and effectiveness of 1.1 mg/kg of intravenous rt-PA in patients treated within 6 hours of ischemic stroke.¹⁰ More than 80% of the patients were enrolled after 3 hours, with an average time to treatment of 4.3 hours, nearly identical to that in the ATLANTIS trial. The ECASS I study failed to find a significant treatment benefit in the ITT population for the primary end points, the

Barthel index, or the modified Rankin scale score. The incidence of large intracerebral parenchymal hemorrhages was significantly more frequent in the rt-PA-treated patients. In the ECASS I study, the most frequent protocol violation was the inclusion of patients with early infarct signs of more than one third of the middle cerebral artery territory. By more effectively excluding these patients, the ECASS investigators hoped that a repeat study could find significant benefit in the ITT analysis.

The study was therefore repeated as the ECASS II study, with results reported in 1998.¹⁵ This trial enrolled 800 patients in Europe, Australia, and New Zealand, and treated them with rt-PA, 0.9 mg/kg, or placebo within 6 hours of symptom onset. The investigators were more successful in excluding patients with early infarct signs, with only 4.6% of the patients having significant changes in more than one third of the middle cerebral artery territory. In this trial, 80% of the patients were enrolled between 3 and 6 hours of symptom onset. No significant treatment benefit was seen in the primary end point (a 90-day modified Rankin scale score of 0-1): 40% of the patients in the rt-PA group had a good outcome compared with 37% in the placebo group ($P = .28$). The ECASS II study also failed to find a significant treatment benefit for any of the planned secondary end points. However, in a post hoc analysis using independent recovery (modified Rankin scale scores of 0, 1, or 2), a significant benefit was seen with 54% of the rt-PA-treated patients vs 46% of placebo-treated patients being independent at day 90 ($P = .02$). In this trial, 8.8% of the rt-PA-treated patients had a symptomatic ICH vs 3.4% of placebo-treated patients ($P < .05$).

In the ECASS II Study, treatment benefits may have been undetectable due to a high rate of spontaneous recovery in the placebo group secondary to mild baseline stroke severity. A comparison of the ATLANTIS trial with the ECASS II trial suggests that the 2 trial populations were quite similar. The median NIHSS score was 10 in the ATLANTIS study vs 11 in the ECASS II trial. The

incidence of excellent spontaneous recovery on the modified Rankin scale score (0,1) was similar, with approximately 40% of placebo patients showing an excellent recovery in both trials. However, unlike the ECASS II trial, the ATLANTIS study did not find a benefit on the outcome of achieving a modified Rankin scale score of 0, 1, or 2 in our post hoc testing. In addition, the rate of spontaneous symptomatic ICH in the placebo group of the ECASS II trial, 3.4%, was much higher than the 1.1% seen in the ATLANTIS study. This is somewhat puzzling in that the populations seemed to be very similar in age and initial stroke severity and both used similar CT criteria. The low spontaneous symptomatic hemorrhage rate seen in ATLANTIS is virtually identical to that seen in the NINDS trials. However, these are the only reported large randomized trials that have found placebo group hemorrhage rates this low; other trials report rates in the 2% to 3% range.^{10,15}

CONCLUSION

The results of the ATLANTIS trial part B failed to find a treatment benefit for rt-PA given 3 to 5 hours after symptom onset. Although the risk of symptomatic ICH did not appear to be higher than in patients treated within 3 hours (NINDS study), the beneficial effects of rt-PA seen in patients treated within 3 hours of symptom onset were not apparent among patients treated within 3 to 5 hours of symptom onset. These results, along with the results of the ECASS I and II trials, do not support the use of intravenous rt-PA in a general population of stroke patients presenting beyond 3 hours after symptom onset. These negative results apply only to patients treated with rt-PA after 3 hours of symptom onset. Further investigations using new imaging techniques and other methods to identify subgroups of patients who may still benefit from thrombolysis after 3 hours are needed.

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REFERENCES

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587.
2. Alberts MJ, Brass LM, Perry A, Webb D, Dawson DV. Evaluation times for patients with in-hospital strokes. *Stroke*. 1993;24:1817-1822.
3. Chiu D, Krieger D, Villar-Cordova C. Intravenous tissue plasminogen activator for acute ischemic stroke. *Stroke*. 1997;29:18-22.
4. Tanne D, Macsback H, Verro P, for the rt-PA in Clinical Practice Stroke Survey Group. Intravenous rt-PA therapy for stroke in clinical practice: a multi-center evaluation of outcome [abstract]. *Stroke*. 1998;29:288.
5. Hanson S, Brauer D, Anderson D, et al. Stroke treatment in the community: intravenous rt-PA in clinical practice. *Neurology*. 1998;50(suppl 4):A155-A156.
6. Albers G. Prospective, monitored, multi-center, post-approval experience with intravenous rt-PA for treatment of acute stroke [abstract]. *Stroke*. 1999;30:244.
7. Clark W, Albers G, Madden K, Hamilton S. The rt-pPA (Alteplase) 0-6 hour acute stroke trial part A (A0276g). *Stroke*. In press.
8. Brott T, Adams H, Olinger C, et al. Measurements of acute cerebral infarction. *Stroke*. 1989;20:864-870.
9. Lyden P, Brott T, Tilley B, et al. Improved reliability of NIH Stroke Scale using video training. *Stroke*. 1990;25:2220-2226.
10. Hacke W, Kaste M, Fieschi C, et al, for the ECASS Study Group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA*. 1995;274:1017-1025.
11. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HA. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1998;14:61-65.
12. Mahoney F, Barthel D. Functional evaluation: Barthel index. *MD State Med J*. 1965;14:61-65.
13. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480-484.
14. Clark W, Williams B, Selzer K, Zweifler R, Saboinjan L, for the Citicoline Stroke Study Group. Randomized efficacy trial of Citicoline in acute ischemic stroke. *Stroke*. In press.
15. Hacke W, Kaste M, Fieschi C, et al, for the Second European-Australasian Acute Stroke Study Investigators. Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous Alteplase in acute ischemic stroke (ECASS II). *Lancet*. 1998;352:1245-1251.