Recombinant tissue plasminogen activator for acute ischemic stroke

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ABSTRACT

Stroke is a leading cause of serious and long-term disability and death worlwide, with approximately 750,000 strokes occuring annually in the United States of America. The risk of stroke doubles each decade for people over 55 years. Cerebral angiography conducted soon after the onset of stroke demonstrates arterial occlusion in 70%-80% of cases. Recanalization of an occluded cerebral artery may assist in the recovery of reversibly ischemic tissue and limit the neurological disability. In June 1996, the recombinant tissue plasminogen activator was approved as a safe and an effective intravenous treatment for acute ischemic stroke, especially if given within 3 hours of onset of symptoms. Since approval, less than 5% of all stroke patients are receiving recombinant tissue plasminogen activator. In this review we try to answer the question of whether recombinant tissue plasminogen activator therapy should be the first-line treatment for acute ischemic stroke. The result of major recombinant tissue plasminogen activator trials will be summarized and reviewed critically.

Keywords: Recombinant tissue plasminogen activator, stroke, infarction.

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Stroke is a leading cause of serious and long-term disability worldwide. In the United States of America (USA) where it ranks the 3rd leading cause of death and disability, approximately 750,000 strokes occur annually, with an annual mortality rate exceeding 150,000.[1] According to the Framingham Heart study, 28% of the people who suffer from stroke are under the age of 65 years and the risk of stroke doubles each decade for people over the age of 55.[1] Fourteen percent of persons who survived a first stroke or transient ischemic attact (TIA) will have recurrence within one year. Cerebral angiography conducted soon after the onset of stroke demonstrates arterial occlusion in 70%-80% of acute infarctions.[2,3] Recanalization of an occluded cerebral artery may assist in the recovery of reversibly ischemic tissue and limit the neurological disability.[4,5] In June 1996, the Food and Drug Administration (FDA) approved recombinant tissue plasminogen activator (rt-PA) as a safe and effective intravenous treatment for acute ischemic stroke especially if it is given within 3 hours of stroke onset.[6] This was based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) trial.[7] The guidelines for thrombolytic therapy for acute ischemic stroke treatment were subsequently published.[8,9] Since its approval, less than 5% of all the stroke patients are receiving rt-PA.[10-12]

Should rt-PA therapy be the first-line treatment for acute ischemic stroke? To be able to answer this question and reach a conclusion, we will critically review the 4 major trials carried out on intravenous rt-PA for the treatment of acute ischemic stroke. These include; 1. The National Institute of Neurological Disorders and Stroke (NINDS) trial,[7] 2. The European Cooperative Acute Stroke Study (ECASS),[13] 3. The European Cooperative Acute Stroke Study II (ECASS II),[14] 4. The Alteplase Thrombolysis for Acute Noninterventional Therapy

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in Ischemic Stroke (ATLANTIS) study.[15] Each study will be summarized first followed by critical analysis and conclusions. We will also review the current guideline for rt-PA therapy for acute ischemic stroke published by the American Heart Association,[8] and the Canadian Stoke Consortium.[9]

The National Institute of Neurological Disorders (NINDS) trial.[7] From January 1991 to October 1994, 624 patients underwent randomization in 2 parts, prospective, multicenter, double blind, and placebo-controlled trial. To assess the efficacy and safety of intravenous rt-PA (0.9 mg/kg, maximum dose 90mg, 10% bolus followed by a 60 minute infusion) in patients with acute ischemic stroke treated within 3 hours from well-defined stroke onset. Part one (291 patients) tested whether rt-PA had clinical activity, as indicated by an improvement of 4 points over the baseline on the National Institute of Health Stroke Scale (NIHSS),[16] or resolution of neurological deficit within 24 hours of stroke onset. Part 2 (333 patients) used a global test statistic to assess clinical outcome at 3 months according to scores on the Barthel Index (BI),[17] modified Rankin Scale (mRS),[18] Glasgow Outcome Scale (GOS),[19] and NIHSS. Subsequently, the results of the 2 parts were combined and stratified according to time from onset of stroke to initiation of treatment (0-90 and 91-180 minutes). The distribution of demographic variables was similar among the rt-PA and placebo treatment arms. The eligible patients were those with acute ischemic stroke and a clearly defined time of onset (<3 hours of treatment), in absence of a contraindication for rt-PA. Patients were excluded from the trial if they had any of the following: computed tomography (CT) evidence of intracranial hemorrhage (ICH) or infarction involving more than one 3rd of the middle cerebral artery territory, stroke or head injury during the preceding 3 months, major surgery during the preceding 2 weeks, history of ICH, systolic blood pressure>185 or diastolic>110, minor or rapidly improving symptoms of stroke, symptoms suggestive of subarachnoid hemorrhage, gastrointestinal or genitourinary bleeding during the preceding 3 weeks, arterial puncture of non-compressible site within 7 days, seizures at onset, anticoagulants use (prothrombin time> 15 seconds or international normalized ration (INR) >1.7), use of heparin in the previous 48 hours (or prolonged partial thromboplastin time), or platelet count <100,000 and glucose <2.7 or 22.2. There was a trend towards neurological recovery at 24 hours in the rt-PA treated group (47% versus 39%, P= 0.21) as shown in **Table 1**. AT 3 months, 50% of the rt-PA treated patients d none or minimal disability (BI score = 95-100) compared with 38% of controls, and 12% with absolute (32% relative) increase in number of patients with favorable outcome. A similar magnitude of effect was seen using the other scales. As evaluated by Global test statistic, the odds ratio for favorable outcome in the rt-PA group was 1.7 (95% confidence interval, 1.2-2.6; P=0.008). The rate of symptomatic brain hemorrhage (within 36 hours of treatment) was small in the placebo group (0.6%), but was increased 10 fold with rt-PA (6.4%), P<0.001. Despite this, there was no increase in mortality at 3 months of treatment of the rt-PA treated patients as compared with the placebo group (17% versus 21%, P=0.3).

The European Cooperative Acute Stoke Study (ECASS).[13] During the study period, 620 patients with moderate to severe acute ischemic stroke were randomized in a prospective, double blind, placebo controlled study to placebo or intravenous rt-PA (<6 hours post stroke). The rt-PA dose was 1.1 mg/kg (maximum 100 mg), 10% given as a bolus followed by 60 minutes infusion. Computed tomography

Table 1 - Neurological recovery at 24 hours from stroke onset, after treatment with rt-PA in the NINDS trial using NIHSS.

Time to treatment	rt- PA		Placebo		P-Value
	N of patients	N with improvement (%)	N of patients	N with improvement (%)	
Part 1					
0-90 minutes	71	36 (51)	68	31 (46)	0.56
91-180 minutes	73	31 (42)	79	26 (33)	0.23
0-180 minutes	144	67 (47)	147	57 (39)	0.21
Part 2					
0-90 minutes	86	51 (59)	77	30 (39)	0.02
91-180 minutes	82	29 (35)	88	35 (40)	0.52
0-180 minutes	168	80 (48)	165	65 (39)	0.19

rt-PA- recombinant tissue plasminogen activator, NINDS - National Institute of Neurological Disorder and Stroke, NIHSS - National Institute of Health Stroke Scale, N-number

Table 2 - Median outcome measures in the ECASS.

Outcome measure	Intention to treat pop.		P-Value	Target pop.		P-Value
	rt-PA	Placebo		rt-PA	Placebo	
Primary endpoint						
BI	85	75	0.99	90	80	0.16
mRS	3	3	0.41	2	3	0.035
Secondary endpoint						
SSS at 3 months	39	36	0.54	43	37	0.04
Combined BI, mRS at 3 months	97.5	90	0.003	90	100	<0.001
Mortality at 30 days	17.9	12.7	0.08	14.6	11.7	0.36
In-hospital stay in days	17	21	0.002	17	21	0.004

ECASS - European Cooperative Acute Stroke Study, BI - Barthel index; mRS - modified Rankin Scale, pop. - population, rt-PA - recombinant tissue plasminogen activator, SSS - stroke severity score

exclusion criteria were early signs of a major infarction (>1/3 of the middle cerebral artery territory), which included diffuse sulcal effacement, poor differentiation between gray-white matter and diffuse hypodensity. One hundred and 9 patients were excluded from the target population (TP) analysis due to major protocol violation (major early infarction, primary hemorrhage, unavailability of CT, or intravenous heparin within 24 hours or other prohibited drugs). At 3 months, the primary endpoint (15 points difference on the BI and one point difference on the mRS) showed no significant difference between rt-PA and placebo treated patients on BI (both intention to treat (ITT) an TP analysis), but was significantly in favor of rt-PA on mRS (TP analysis only). The secondary endpoint analysis (combined BI and mRS at 3 months) showed a difference in favor of the rt-PA treated patients in both ITT and TP analyses (P<0.001). Recombinant tissue plasminogen activator was also associated with increased rate of recovery and shorter hospital stay (**Table 2**). Mortality rates in the rt-PA group were higher than the placebo group at 30 days in ITT analysis (17.9% versus 12.7%, P=0.08) and significantly higher at 3 months (22.4% versus 15.8%, P=0.04). However, this difference was not significant in the TP analysis (14.6% versus 11.7%, P=0.36) and (19.4% versus 14.8%, P=0.17) at 30 days and 3 months. Although the development of cerebral hemorrhage was common in the placebo group (36.8%) in both ITT and TP analysis, large parynchymal hemorrhages increased 3-fold with rt-PA (19.8% versus 6.5%, P<0.001). This led to significant increase in brain hemorrhage associated death in the rt-PA group (6.3% versus 2.4%, P=0.02) in TP analysis (**Table 3**).

The European Cooperative Acute Stroke Study II (ECASS II).[14] Between October 1996 and January 1998, 800 patients were randomized to placebo or rt-PA (<6hours post stoke) at a dose of 0.9 mg/kg (maximum 90 mg, 10% as a bolus followed by 60 minutes infusion). Treatment groups were stratified according to the treatment time from stroke onset (0-3 and 3-6 hours). Computed tomography scan was carried out to rule out early signs of major infarction such as involvement of more than one 3rd of the area supplied by middle cerebral artery. To improve CT scan assessments by investigators, a training course was taken prior to patient's enrollment. In the primary endpoint (mRS at 90 days), a favorable

Table 3 - Brain hemorrhage in the 2 groups of patients in the ECASS.

Event	Intention to treat N (%; 95% CI)		Target population N (%; 95% CI)	
	rt-PA	Placebo	rt-PA	Placebo
Hemorrhagic infarction	72 (23; 18.5-28)	93 (30; 25-36)	60 (24; 19-30)	79 (30; 24.5-36)
Parenchymal hematoma	62 (20; 15.6-25)	20 (6.5; 4-10)	48 (19; 15-25)	18 (7; 4.2-11)
Total	**134 (42.8; 38-48)**	**113 (37; 31-42)**	**108 (44; 38-50)**	**97 (37; 31-43)**

ECASS - European Cooperative Acute Stroke Study, N- number, rt-PA - recombinant tissue plasminogen activator, CI - confidence interval

Table 4 - Endpoint analyses of patients in the ECASS II.

Endpoint	rt- PA	Placebo	P-Value
mRs at day 90 (0-1)	165 (40.3; 35.6-45)	143 (37; 31.8-42)	0.28
Median mRS and BI at day 90	90	90	0.15
Median change in NIHSS (baseline to day 30)	-6	-5	0.04
Further endpoints			
BI at day 90	204 (50%; 45-55)	179 (46%; 41-51)	0.30
Median SSS at day 90	42	41	0.10
Median hospital stay (days)	13 (N=364)	15 (N=342)	0.50

ECASS II- European Cooperative Acute Stroke Study II; rt-PA - recombinant tissue plasminogen activator; mRS - modified Rankin Scale; BI - Barthel index; NIHSS - National Institute of Health Stroke Scale; SSS - stroke severity score, N - number

outcome was seen in rt-PA treated patients (40.3% versus 36.6%, P=0.27). Of the secondary endpoint (change from baseline to day 30 on NIHSS scale and the combination of BI and mRS at day 90), only the median change in NIHSS score showed significant difference between the 2 groups (P=0.035) as shown in **Table 4**. There was no significant difference in the primary or secondary endpoints in the stratified analysis according to the time to treatment. The mortality rate was higher in the rt-PA group in patients treated within 3 hours, which was not seen in patients treated between 3-6 hours of stroke onset. This may reflect the small number of patients in the first subgroup. The overall frequency of intracranial hemorrhage was higher in the rt-PA than the placebo group (48.4% versus 40.2%). Parenchymal hemorrhage was 4 times more common in the rt-PA group, and large confluent, space occupying intracranial hemorrhage was 10 times more common in the rt-PA group as compared to placebo.

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ishemic Stroke (ATLANTIS) study.[15] The sutdy was initiated in August 1991 and was initially designed to assess the efficacy and safety of intravenous rt-PA given within 0-6 hours of stroke onset. In December 1993, enrollment was halted and the time window was changed due to the safety committee's concern regarding the 5-6 hours group (Part A). The study was restarted (Part B) with a new time window (<5 hours) and new study endpoints. The ATLANTIS Part B study was further modified in February 1996 to 3-5 hours window after stroke onset in light of the results of the NINDS trial. Of the 613 patients

Table 5 - Results of the ATLANTIS outcome measures.

Endpoint	ITT (%)		P-Value	TP (%)		P-Value
	rt-PA (N=307)	Placebo (N=306)		rt-PA (N=227)	Placebo (N=275)	
Day 30						
NIHSS score (0-1)	32.8	26.2	0.08	32.1	24.6	0.06
BI>95	47.2	47.0	0.96	46.6	46.8	0.96
mRS (0-1)	36.2	31.9	0.26	36.5	31.2	0.20
GOS scale=1	42.3	38.0	0.29	41.1	36.9	0.32
BI / mRS score	32.2	28.9	0.37	32.0	28.3	0.35
NIHSS score (>11 improvement)	41.1	32.2	0.02	40.4	30.6	0.02
Infarct volume, mean (SD) in cm^3	47 (66)	47 (71)	0.98	46 (66)	47 (74)	0.95
Day 90						
NIHSS score (0-1)	34.5	34.0	0.89	33.8	32.0	0.65
BI>95	54.1	54.6	0.90	53.7	53.5	0.96
mRS (0-1)	41.7	40.5	0.77	42.3	38.9	0.42
GOS score=1	46.3	46.1	0.97	46.3	44.0	0.59
BI / mRS score	37.5	36.6	0.83	37.9	34.5	0.42
NIHSS score (>11 improvement)	45.1	39.0	0.13	44.9	36.0	0.03

ATLANTIS - Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke study, rt-PA - recombinant tissue plasminogen activator, N - number, BI - Barthel index, NIHSS - National Institute of Health Stroke Scale, GOS - Glasgow Outcome Scale, mRS - modified Rankin Scale, SD - standard deviation, TP - Target population, ITT - intention to treat

Table 6 - Safety results in target population analysis of the ATLANTIS.

Serious Adverse Events	rt-PA (N=272)	Placebo (N=275)	P-Value
Asymptomatic ICH	11.4	4.7	0.004
Symptomatic ICH	7.0	1.1	<0.001
Fatal ICH	3.0	0.3	<0.001
Death within 90 days	11.0	6.9	0.09
Death within 30 days	7.0	4.4	0.18

ATLANTIS - Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke study, rt-PA - recombinant tissue plasminogen activator, N - number, ICH - intracranial hemorrhage

enrolled in the study, 31 (7%) received treatment within 3 hours, who were included in the intention to treat but not in the target population (547 patients) analysis. The patients were randomized in a placebo controlled, double blind study to placebo or rt-PA (0.9 mg/kg dose,maximum 90mg) given as 10% bolus followed by 60 minutes infusion. For the primary endpoint (NIHSS score <1 at day 90), 32% of placebo patients and 34% of rt-PA patients had an excellent recovery at 90 days (P=0.65) in the TP. No treatment benefit was seen on any of the secondary endpoints in the TP (excellent recovery on functional outcome measure BI, mRS and GOS at day 30 and 90). However, the treatment with rt-PA did produce significant increase in the percentage of patients in the TP with major neurological recovery (defined as an 11-point improvement or complete recovery on the NIHSS at day 30 and 90) on day 30 (31% placebo versus 40% rt-PA, P=0,02), and on day 90 (36% placebo versus 45% rt-PA, P=0.03) as shown in **Table 5**. The results of outcome measures were similar in the ITT population. In the first 10 days, treatment with rt-PA significantly increased the rate of symptomatic ICH (1.1% versus 7%, P=0.001), asymptomatic ICH (4.7% versus 11.4%, P=0.004), and fatal ICH (0.3% versus 3.0, P<0.001). Mortality at 90 days was 6.9% with placebo and 11% with rt-PA (P=0.09) as shown in **Table 6**.

Summary. The NINDS trial was the only positive study supporting the use of rt-PA for acute ischemic stroke in patients who met certain eligibility criteria within 3 hours of stroke onset. The improvement in outcome was seen in all stroke subtypes. The most recognizable difference between this study and the others (ECASS I, II, and ATLANTIS) is time to treatment (namely, therapeutic window). Patients evaluation, CT scan, laboratory studies, informed consent and randomization were accomplished within 90 minutes of stroke onset. Because the treatment was started so early, some patients with transient ischemic stroke could have been enrolled despite the exclusion of patients with rapidly improving symptoms. Since so few patients who were given placebo (2%) were free of symptoms at 24 hours on the basis of NIHSS, it is unlikely that the benefit seen with rt-PA was due to spontaneous resolution of stoke symptoms and in fact was related to rt-PA.

The ECASS findings did not support the use of rt-PA >3 hours after the stroke onset, however, it must be emphasized that 17.6% of randomized patients were specified protocol violators (mainly due to signs of major infarction on baseline CT scan). As well, 2/3 of these protocol violators were randomized to the rt-PA arm, with case fatality rate of up to 32%. The protocol was planned in ITT and TP analyses, whereas the ITT analysis focuses on the applicability of rt-PA in daily life, and the TP analysis demonstrates the effect of an active and potentially dangerous compound in patients who were considered candidates for therapy. With the negative results of the ECASS, smaller rt-PA dose and better patients selection were considered for the subsequent ECASS II.

In the ECASS II, there was no statistically significant difference between rt-PA and placebo, but the findings were consistent with the positive trend and benefit seen in the previous trial. The benefit of the treatment may have been undetected due to high spontaneous recovery rate in the placebo group secondary to mild baseline stroke severity. The overall mortality rates at day 90 were much lower in ECASS II than in ECASS I (rt-PA 22.4% versus placebo 15.8%), or the NINDS trial (rt-PA 17% versus placebo 21%). The most likely reason for the lower mortality rates is selection bias. The ECASS II patients had less severe neurological deficit at study entry and fewer signs of major infarction on the baseline CT scan, presumably as a result of better CT scan surveillance.

Regarding the ATLANTIS study (Part B), it was the 3rd large randomized stroke trial evaluating intravenous rt-PA with the majority of the patients being treated more than 3 hours of stroke onset that

has failed to find a treatment benefit in the ITT population. A comparison of the ATLANTIS and ECASS II suggests that the 2 trials were quite similar, the baseline median NIHSS scores were 10 and 11. The rate of spontaneous symptomatic ICH in the placebo group was lower in ATLANTIS than ECASS II (1.1% versus 3.4%), which could not be explained with the baseline similarity between the 2 trials.

Guidelines for intravenous rt-PA in acute ischemic stroke. Restricted use of rt-PA by an experienced physician in stroke management and in patients who fall within the strict guidelines by the stroke council of American Heart Association[8] and the Canadian Stroke Consortium[9] was recommended. The following is a summary of these recommendations. 1. Recombinant tissue plasminogen activator must be administered in an acute care setting by a physician with expertise in the management of stroke and in most cases a neurologist in a tertiary care or major hospital setting will give rt-PA with the use of a hospital-approved protocol is recommended. 2. Computed tomography scan must be available on a 24 hour basis with personnel experienced in detection of early CT signs of significant infarction and intracranial hemorrhage as CT evidence of cerebral hemorrhage or significant mass effect, are absolute contraindication to rt-PA. 3. The informed consent should be obtained from all patients or family prior to treatment with rt-PA. 4. Recombinant tissue plasminogen activator should be administered intravenously in a dose of 0.9 mg/kg to maximum of 90 mg, with an initial 10% given as a bolus followed by 60 minutes infusion, within 3 hours of a certain stroke onset. 5. The exclusion criteria are those shown in **Table 2** (NINDS trial) and myocardial infarction within 3 weeks is an additional exclusion criterion. 6. No aspirin, heparin, warfarrin, ticlopidine or other antiplatelets drugs must be given for at least 24 hours after rt-Pa, however, aspirin treatment prior to rt-PA infusion is not a contraindication. 7. The facilities must be readily availabe on a 24-hour basis to manage hemorrhagic complications and the infusion should be discontinued immediately and emergency CT scan obtainted. 8. The vital signs should be taken every 15 minutes during the drug infusion, then every 30 minutes for the next 12 hours, then according to patient's condition. 9. If the patient is hypertensive (BP>180/110), 10 mg labetalol should be infused over 1-2 minutes and repeated every 10-20 minutes up to a maximum dose of 150 mg.

Current status of rt-PA in treatment of acute ischemic stroke. It is difficult to determine which patients are most like to benefit from intravenous rt-PA and which patients are at risk, even after using the proposed guidelines. Several factors may be critical in selecting patients who will have the best risk-benefit ratio. Time window is critical in view of the results of the rt-PA trials. The data from functional imaging such as diffusion-weighted magnetic resonance suggests that the therapeutic time window may extend well beyond 3 hours in some patients, while in others it may already be closed within one hour.[20] A simple tool to detect ischemic but viable tissue may be useful to select candidates for rt-PA. Identifying predictive factors for recovery and brain hemorrhage may also help in better patient selection.[21] The factors with a favorable outcome include yougner age, absence of cardiac disease, lower blood pressure on admission, better neurological score, absence of early ischemic parenchymal changes, large artery thrombus visible on baseline CT, and well develped collateral circulation.[22,23] Several risk factors have been identified for brain hemorrahge such as time to treatment, rt-PA dose, blood pressure level, severity of neurological deficit, and severity of ischemia.[24]

In conclusion, rt-Pa is an important, effective and relatively safe treatment for selected patients with acute ischemic infarction. Recombinant tissue plasminogen activator therapy results in improved neurological outcome when initiated within 3 hours of stroke symptoms (narrow therapeutic window). Recombinant tissue plasminogen activator should be restricted to tertiary care centers or major hospitals with well-established intensive care units and available neurological, radiological, and neurosurgical services.

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