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PRE-ASSESSMENT

Recombinant Tissue Plasminogen Activator (rt-PA) in Acute Ischemic Stroke

Before CCOHTA decides to undertake a health technology assessment, a pre-assessment of the literature is performed. Pre-assessments are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided here as a quick guide to important, current assessment information on this topic. Readers are cautioned that the pre-assessments have not been externally peer reviewed.

Introduction

A stroke, which is also called a "brain attack," is defined as a sudden neurological deficit due to brain ischemia or hemorrhage. Ischemic stroke, which is the most frequent type, occurs in up to 80% of all acute stroke patients.[1] The causes of ischemic stroke are related to atherosclerosis, cardiac embolism and small-vessel arterial diseases.[2] These lead to focal cerebral vessel occlusion, resulting in the cessation of oxygen and glucose supply to the brain with subsequent neuronal cell death in the affected area within a few minutes. It is thought that the early re-canalization of occluded cerebral vessels improves the clinical outcomes for patients with acute ischemic strokes.[3]

Acute stroke is one of the leading factors that cause morbidity and mortality worldwide. Stroke is the fourth leading cause of death in Canada. Each year, about 16,000 Canadians die from stroke.[4] The incidence of new strokes is between 40,000 to 50,000 per year in Canada. About 300,000 Canadians are living with the effects of a stroke.[4] Over 71% of Canadians who have had a stroke need help with daily activities.[4] Its economic burden is among the highest when all diseases are compared.[4,5] Over the past decades, acute stroke has been recognized as a medical emergency.

Pharmacologic options for the treatment of acute ischemic stroke have been lacking and their development was slow despite the advances in the treatment of ischemic heart disease. Intravenous thrombolysis with recombinant human tissue-type plasminogen activator (rt-PA) is the only approved option for patients seen ≤3 hours after the onset of a stroke. The use of rt-PA is still debatable. The prevention of stroke recurrence (i.e., secondary prevention) by treatment with antiplatelet agents such as Aspirin[6] and to a lesser extent clopidogrel,[7] is an important factor for stroke patients. Other interventions include carotid endarterectomy,[8] warfarin (e.g., atrial fibrillation)[9] and perindopril, a blood-pressure lowering agent.[10] Neuroprotection with agents such as glutamate antagonists is still being investigated.[11] The benefit (avoidance of death and disability) of acute interventions is mostly related to their effect on patient management in stroke care units.[12,13] Furthermore, the primary prevention of stroke may produce a greater overall benefit than its treatment.[14]

rt-PA (alteplase; Genentech, Inc.) is the first and only licensed thrombolytic agent approved for use in acute ischemic stroke in the US (1996), Canada (1999) and the EU (2000) (Actilyse; Boehringer Ingelheim).[15] Administration of rt-PA at a recommended dose of 0.9 mg/kg (maximum 90 mg) infused over 60 minutes, with 10% of the dose given as an initial intravenous bolus, must be performed by a physician who is specialized in neurological care, ≤3 hours after the onset of symptoms and after exclusion of intracranial hemorrhage as determined using a computed tomography (CT) scan.

Recombinant Tissue Plasminogen Activator (Rt-PA) in Acute Ischemic Stroke

Research Questions

- What is the evidence regarding the effectiveness and cost-effectiveness of treatment with rt-PA (alteplase) in acute ischemic stroke?
- What are the potential harms associated with rt-PA use in acute ischemic stroke?

Assessment Process

Literature was identified by searching PubMed, The Cochrane Library and the University of York Centre for Reviews and Dissemination (CRD) databases (HTA, DARE and EED) for 1991 until October 2003. The web sites of major HTA agencies were also searched. Google™ was used to search for conference abstracts. Update searches were performed in July 2004.

Summary of Findings

Systematic reviews and meta-analyses

In a systematic review[16] of thrombolytic agents in acute ischemic stroke, about 50% of patients had been treated with rt-PA. The authors concluded that thrombolytic therapy may be associated with less hazard and more benefit. The review concluded, "The data are promising and may justify the use of thrombolytic therapy with intravenous [rt-PA] in experienced centres in highly selected patients where a licence exists. However, the data do not support the widespread use of thrombolytic therapy in routine clinical practice at this time, but suggest that further trials are needed to identify which patients are most likely to benefit from treatment and the environment in which it may best be given."

Hacke *et al*.[17] analyzed the combined data for patients enrolled in five trials. To confirm the importance of rapid treatment, the authors, using a multivariable logistic regression, assessed the relationship between the interval from stroke onset to the start of treatment (OTT) and the occurrence of 1=favourable outcome [defined as modified Rankin scale (mRS) score of 0 or 1], 2=death and 3=clinically relevant parenchymal hemorrhage, after three months. Their meta-analysis included 2,775 patients with a median age of 68 years, a median baseline National Institutes of Health Stroke scale score (NIHSS) of 11 and a median OTT of 243 minutes (4 hours).

Table 1 presents the outcomes of patients who are randomly allocated to receive rt-PA or placebo treatment starting ≤360 minutes (6 hours) after the onset of stroke.

The authors concluded that the sooner rt-PA is given to ischemic stroke patients, the greater the benefit, especially if it is started in 90 minutes. The results also suggested that there was a potential benefit beyond three hours, but this may come with additional risks for harm in some patients.[17]

Table 1: Effect of rt-PA in acute ischemic stroke[17]

Time (minutes)	N*	Minimal or No Disability (mRS 0 or 1)	Independence (mRS 0 to 2)	Moderate Disability (mRS = 3)	Severe Disability (mRS 4 to 5)	Death	Substantial Intracerebral Hemorrhage[$]
		Number of patients (%)					
0 to 90 Placebo Treatment	 150 161	 29 (19.3) 41 (25.5)	 42 (28) 49 (30.4)	 12 (8) 14 (8.9)	 26 (17.3) 18 (11.2)	 21 (14) 19 (11.8)	 0 (0) 5 (3.2)
91 to 180 Placebo Treatment	 315 302	 30 (9.5) 43 (14.2)	 40 (12.7) 50 (16.6)	 17 (5.4) 14 (4.6)	 29 (9.2) 19 (6.3)	 16 (5.1) 17 (5.6)	 3 (1) 17 (5.6)
181 to 270 Placebo Treatment	 411 390	 32 (7.8) 37 (9.5)	 43 (10.5) 49 (12.6)	 16 (3.9) 12 (3.1)	 30 (7.3) 26 (6.7)	 12 (2.9) 13 (3.3)	 7 (1.7) 23 (5.9)
271 to 360 Placebo Treatment	 508 538	 36 (7.1) 37 (6.9)	 49 (9.6) 49 (9.1)	 14 (2.8) 12 (2.2)	 27 (5.3) 24 (4.5)	 10 (2) 15 (2.8)	 5 (1) 37 (6.9)

mRS=modified Rankin scale (Table 2). N=number of patients. *Respectively 1, 8, 9 and 6 patients from NINDS part 1, ECASS I, ECASS II and Atlantis B were excluded from analyses as they were randomized after 360 minutes or OTT was not reported. [$]Substantial intracerebral hemorrhage (parenchymal hematoma type II) is defined as a dense blood clot exceeding 30% of the infarct volume with significant space-occupying effect. Reproduced with permission from Hacke *et al.*[17]

Table 2: Modified Rankin scale*

Level	Description
0	No symptoms
1	No significant disability despite symptoms: able to perform all usual duties and activities
2	Slight disability: unable to perform all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requires help, but able to walk without assistance
4	Moderately severe disability: unable to walk or attend to own bodily needs without assistance
5	Severe disability: bedridden and incontinent; requires constant nursing care

*Adapted from Foell *et al*.[18]

Randomized controlled trials

Among the five studies that were identified,[19-23] the National Institute of Neurological Disorders and Stroke (NINDS) study[19] yielded positive results (Table 3). Other studies either failed to find a benefit based on the primary outcome or found substantial harm.[22] This explains the controversy surrounding the use of rt-PA in acute ischemic stroke (Tables 4 and 5).[24-26]

Table 3: Randomized controlled trials assessing efficacy and safety of rt-PA use in acute ischemic stroke

Characteristics				Outcomes					
				Patient with Minimal or No Disability* (mRS 0 or 1)		Death (from all causes)		Symptomatic Intracranial Hemorrhage	
Trial, year Quality (Jadad score)	Dose, window of time	Number of patients	Baseline median NIHSS score	Number of patients (%)	RR (95% CI)	Number of patients (%)	RR (95% CI)	Number of patients (%)	RR (95% CI)
NINDS,[19] 1995 Placebo Treatment High quality (5)	0.9 mg/kg 0 to 3 hours	 312 312	 15 14	 83 (26.6) 133 (42.6)	 1.60 (1.28; 2.01)	 66 (21) 53 (17)	 0.80 (0.58; 1.11)	 2 (0.6) 20 (6.4)	 10.00 (2.36; 42.42)
ECASS-I,[22] 1995 Placebo Treatment High quality (4)	1.1 mg/kg 0 to 6 hours (mean 4.3 hours)	 307 313	 13 12	 90 (29.3) 112 (35.7)	 1.22 (0.97; 1.53)	 49 (15.8) 70 (22.4)	 1.40 (1.01; 1.95)	 NR	 ND
ECASS-II,[23] 1998 Placebo Treatment High quality (5)	0.9 mg/kg 0 to 6 hours (80%>3 hours)	 391 409	 11 11	 143 (36.6) 165 (40.3)	 1.10 0.93; 1.32)	 42 (10.7) 43 (10.5)	 0.98 (0.65; 1.46)	 13 (3.4) 36 (8.8)	 2.65 (1.43; 4.92)
ATLANTIS A,[21] 2000 Placebo Treatment High quality (4)	0.9 mg/kg 0 to 6 hours (85%=3 hours)	 71 71	 11 10	 Data with mRS NR	 ND	 5 (7) 16 (22.5)	 3.20 (1.24; 8.26)	 0 (0.0) 8 (11.3)	 17.00 (1.00; 289.05)
ATLANTIS B,[20] 1999 Placebo Treatment High quality (5)	0.9 mg/kg 3 to 5 hours	 306 307	 10 10	 124 (40.5) 127 (41.5)	 1.02 (0.84; 1.23)	 21 (6.9) 33 (10.9)	 1.57 (0.93; 2.64)	 4 (1.3) 21 (6.7)	 5.23 (1.82, 15.07)

*Favourable outcome as measured using modified Rankin scale (mRS≤1) (Table 2). RR=relative risk (the effect is not significant when the confidence interval includes one). NR=not reported. All studies had a follow-up period of three months. ND=not determined.

Table 4: Selection of patients for rt-PA use

Inclusion Criteria
1. Patient had an ischemic stroke with a defined time of onset of symptoms within 3 hours. 2. Patient had a measurable deficit on NIH stroke scale examination. 3. Patient's computed tomography (CT) scan at baseline showed no evidence of intracranial hemorrhage.
Exclusion Criteria
1. Patient has had another stroke or serious head trauma in past 3 months. 2. Patient had major surgery in last 14 days. 3. Patient has history of intracranial hemorrhage. 4. Patient has systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg. 5. Patient's symptoms are minor or rapidly improving. 6. Patient has symptoms suggestive of subarachnoid hemorrhage. 7. Patient has had gastrointestinal or urinary tract hemorrhage in previous 21 days. 8. Patient has had arterial puncture at non-compressible site in last 7 days. 9. Patient had seizure at onset of stroke. 10. Patient has received heparin in last 48 hours and has elevated PTT. 11. Patient's prothrombin time (PT) is >15 seconds. 12. Patient's platelet count is <100,000 uL. 13. Patient's serum glucose is <50 mg/dL (2.7 mmol/L) or >400 mg/dL (22.2 mmol/L). 14. Patient requires aggressive treatment to lower blood pressure.

Adapted from NINDS study.[19] PTT=partial thromboplastin time.

Table 5: Recommendations on thrombolytic therapy for acute ischemic stroke

The Canadian Association of Emergency Physicians has published a position statement stating that thrombolytic therapy for acute stroke should be restricted to use in formal research protocols or in closely monitored programs, until there is further evidence that the benefits of this therapy outweigh the risks. All outcome data should be collated and made available to the medical community. Studies of the safety and effectiveness of this therapy should be carried out in community hospitals. The following are key recommendations.
1. Only radiologists or neurologists with demonstrated expertise in neuroradiology should provide interpretation of CT scans of the head used for deciding whether to administer thrombolytic agents to stroke patients. 2. Stroke thrombolysis should be limited to centres with appropriate neurological and neuro-imaging resources that can administer this therapy within 3 hours. In such centres, emergency physicians should identify potential candidates, initiate low risk interventions and facilitate prompt CT scanning. They should not be the primary decision-makers concerning the administration of thrombolytic agents to stroke patients. Neurologists should be directly involved before the administration of thrombolytic therapy. 3. Administration of throbolytic agents to stroke patients should be carried out only in an approved research protocol or a formal clinical practice protocol. These protocols should adhere to the NINDS eligibility criteria. All data on adherence to protocols and patient outcomes should be collated in a central Canadian registry for the purposes of tracking the safety and efficacy of this intervention.

Adapted from CAEP Committee on Thrombolytic Therapy for Acute Ischemic Stroke.[24]

The NINDS study[19] was carried out in two parts to address early improvement (decrease in the NIHSS score by ≥4 points 24 hours after the onset of treatment) and determine the proportion of patients who recovered with minimal or no deficit three months after treatment, using different functional scales. Parts 1 and 2 had similar experimental designs. Both parts enrolled 624 patients ≤3 hours after stroke onset to receive either rt-PA (dose of 0.9 mg/kg) or a matching placebo (Table 3). After 24 hours, neurologic improvement was greater for the rt-PA-treated patients than for those in the placebo group (median NIHSS score 8 versus 12, $p<0.01$).[19] At three months, a pooled analysis of the two parts showed a significant increase in the proportion of patients with favourable outcomes (i.e., minimal or no disability: mRS score of 0 or 1) when rt-PA treatment was compared with placebo (42.6% versus 26.6%, Table 3). The odds for a favourable outcome in the rt-PA group were 2.05 [95% confidence interval (CI): 1.46 to 2.87]. Mortality (from all cases) was not changed (rt-PA 17% versus placebo 21%; RR: 0.80, 95% CI: 0.58 to 1.11). These results were obtained at the cost of a 10-fold increase in the rate of symptomatic intracranial hemorrhage (6.4% with rt-PA versus 0.6% with placebo; RR: 10, 95% CI: 2.36 to 42.42). Most rt-PA related hemorrhages occurred within 24 hours. Nearly half of these were fatal. No difference was observed between the two groups with regard to systemic hemorrhages.

It is suggested in a retrospective analysis of the NINDS trial that the benefit from rt-PA treatment may be higher when it is administered in the first 90 minutes compared with between 90 to 180 minutes.[27] In clinical practice, however, only a few patients are treated in the first 90 minutes.[28] The results of the NINDS study seem to be valid in showing that rt-PA is effective when given under optimum circumstances, but concerns exist regarding the generalization of these results in practice.[29] Another concern is that in the 91- to 180-minute group, more of the patients who received rt-PA had a mild stroke at baseline than those treated with placebo.[27,30] These differences may explain much of the benefit that has been attributed to rt-PA.[31]

ECASS I included 620 patients treated during a wider window of time (0 to 6 hours) from stroke onset, using a higher dose of rt-PA (1.1 mg/kg).[22] Primary outcome measures included the mRS at 90 days. In the intention to treat analysis, no significant differences in a favourable outcome (severity of deficit after stroke as measured with mRS) were detected between the treatment groups.[22] The mortality rate was higher in the rt-PA group (22.4% versus 15.8% with placebo; RR: 1.4, 95% CI: 1.01 to 1.95) (Table 3). The incidence of intracranial hemorrhage was also higher in the rt-PA-treated group (20% versus 6.5%).[22]

The factors to consider in interpreting these results include the higher dose of rt-PA and the significant number of protocol violations (17% of patients). In the target population (excluding the patients with protocol violations), an increase in the proportion of patients with a favourable outcome has been reported after rt-PA treatment, with no difference in mortality at 90 days.[22] A wider period for initiating treatment (most patients were enrolled after three hours and the average time to treatment was 4.3 hours) may have been a

contributing factor. A retrospective subgroup analysis of the ECASS I study subjects treated ≤3 hours after stroke onset shows similar outcomes to those of the NINDS study.[32,33]

The ECASS-II study included 800 patients treated with rt-PA (0.9 mg/kg; 0 to 6 hours after stroke onset) or placebo.[23] Patients were also stratified by time of presentation in two groups: zero to three and three to six hours after symptom onset. The main criterion was the percentage of patients having a favourable outcome (score on Rankin scale ≤1) after three months. This endpoint did not differ between the two groups: 40.3% with rt-PA and 36.6% with placebo (RR: 1.10, 95% CI: 0.93 to 1.32) (Table 3). As in ECASS I, subgroup analysis showed a trend toward improved outcome in the few patients treated ≤3 hours after stroke onset.[23] The mortality rate at three months was not different between the treatment groups (RR: 0.98, 95% CI: 0.65 to 1.46). On the other hand, cerebral hemorrhages were more frequent with rt-PA (8.8%) than placebo (3.4%) (RR: 2.65, 95% CI: 1.43; 4.92). In this study, 80% of patients were enrolled after three hours.

The ATLANTIS study was initially designed to assess treatment with rt-PA given at a dose of 0.9 mg/kg ≤6 hours after stroke onset. Because the safety committee had concerns about patients being enrolled at between five to six hours, the initiation of rt-PA treatment was changed to between zero to five hours. The study design was further modified to a three- to five-hour window after the results of the NINDS study were published. The results of this study was reported in parts A and B.[20] Part A evaluated the safety and efficacy of rt-PA given between zero to six hours after stroke onset in 142 patients.[21] There was no treatment difference seen on any functional outcomes (as measured with other functional scales; data with mRS not reported) at 30 and 90 days between rt-PA- and placebo-treated patients. Treatment with rt-PA significantly increased the rate of symptomatic intracranial hemorrhage (11.3% versus 0%, RR: 17, 95% CI: 1 to 289) and mortality at three months (22.5% versus 7%, RR: 3.20, 95% CI: 1.24 to 8.26) (Table 3). These results may have been driven by patients treated after three hours, as only 15% of the patients were enrolled within three hours.

Part B[20] enrolled 613 patients treated with rt-PA or a matching placebo. Treatment was initiated three to five hours after stroke onset and subjects were followed for three months. The primary outcome was neurological recovery at three months. The secondary outcome included functional recovery at one and three months. There was no difference between placebo and rt-PA-treated patients at three months for these outcomes. Treatment with rt-PA was associated with a rate of 6.7% of symptomatic hemorrhage versus 1.3% with placebo (RR: 5.23, 95% CI: 1.82 to 15.07) (Table 3). Mortality was 6.9% versus 10.9% with rt-PA and placebo respectively (RR: 1.57, 95% CI: 0.93 to 2.64) (Table 3). These results suggested that rt-PA may offer no benefit when administered >3 hours after the onset of acute stroke.

Observational Studies: rt-PA in practice

In a meta-analysis[34] of safety data derived from some observational studies included in Table 6 and based on 2,639 treated patients, the symptomatic intracerebral hemorrhage rate was 5.2% (95% CI: 4.3 to 6.0). The mean mortality rate was 13.4%. Protocol deviations occured in 19.8% and correlated with the mortality rate. The author concluded that post-approval data supported the safety of intravenous thrombolytic therapy with rt-PA for acute ischemic stroke, especially when established treatment guidelines were followed.

Table 6: Observational studies* using rt-PA in acute ischemic stroke

Characteristics							Outcome		
Author (year) (sorted by date)	**Setting (country)**	**N**	**NIHSS**	**Median Onset To Treatment Time (minutes)**	**Follow-up (months)**	**Protocol Violation (% of patients)**	**Minimal or No Disability (% of patients)**	**Death (% of patients)**	**SIH**
Chiu *et al*. (1998)[35]	Academic and community hospitals (US)	30	NR (mean =14)	157	5	10	30	23	7
Grond *et al*. (1998)[36,37]	University hospital (Germany)	150	11	NR	12	1.3	41	15	4
Tanne *et al*. (1999)[38]	Urban hospitals (US)	189	NR	NR	To discharge	30	34	10	6
Albers *et al*. (2000)[39] (STARS)	Academic and community hospitals (US)	389	13	164	1	32.6	35	13	3.3
Buchan *et al*. (2000)[40]	Academic Hospital (Canada)	68	15	NR	3	16	38	16	9
Chapman *et al*. (2000)[41]	Academic hospital (Canada)	46	14	165	13	17	43	22	2
Katzan *et al*. (2000)[29] (Cleveland study)	Hospitals (US)	70	12	NR	To discharge	50	NR	15.7	15.7
Wang *et al*. (2000)[42]	Urban and rural hospitals (US)	57	15	NR	To discharge	9	47	9	5
Hill *et al*. (2001)[43] (CASES)	Hospitals (Canada)	784	14	NR	3	10	29	NR	4.5
Lopez-Yunez *et al*. (2001)[44]	Hospitals (US)	50	11	141	To discharge	16	NR	10	10
Silver *et al*. (2001)[45]	Academic hospital (Canada)	30	14	NR	3	7	37	13	0

Bravata *et al.* (2002)[46]	Hospitals (US)	60	NR	NR	To discharge	67	NR	25	13
Heuschmann *et al.* (2003)[47]	Academic and community hospitals (Germany)	384	NR	NR	To discharge	NR	NR	11.7	NR
Lindsberg *et al.* (2003)[48]	University hospital (Finland)	75	NR	NR	3	NR	37	5	8
Szoeke *et al.* (2003)[49]	Tertiary-care hospital (Australia)	30	14	168	To discharge	23	37	10	7
Schwammenthal *et al.* (2004)[50]	Academic hospital (Israel)	16	13	151	24 hours	0	44	0	0
Wiegand *et al.* (2004)[51]	Academic hospital (Switzerland)	15	14	135	To discharge	NR	NR	6.7	0

*Some studies used a control group of patients (for the comparison with rt-PA-treated patients) recruited from the same study population, while other studies compared their outcomes with the results of the NINDS trial. Adapted from Gladstone & Black[52] and updated. Only results for the rt-PA-treated group are presented. SIH=symptomatic intracranial hemorrhage (% of patients); N=sample size or number of patients.

There is controversy about the safety of rt-PA when it is applied outside clinical trials.[30,53] Even if the efficacy results of the NINDS study are accepted at face value, given the potential risk with rt-PA use and the possible misuse by non-experts, the benefit from using rt-PA in practice is far from established[31] (see Tables 4 and 5 for patient inclusion criteria and recommendations).

Some phase IV studies reported increased mortality and a risk of symptomatic intracranial hemorrhage in the rt-PA treatment group when it was compared with a control group or responses seen in the NINDS trial.[29,46] These results may be partly related to protocol violations[46] or a lack of experience with rt-PA treatment as suggested in one study in which it was reported that rt-PA therapy in hospitals with limited experience in its use increased the risk of in-hospital mortality.[47] In the Cleveland study,[29] the 15.7% rate of symptomatic intracerebral hemorrhage was more than twice that in NINDS and half of these were fatal. Other studies focusing on the use of intravenous rt-PA in university and community hospitals demonstrated similar response and safety profiles to those of the NINDS study, particularly when the inclusion criteria were carefully followed.[38,42]

Cost-effectiveness analyses

In the US, when a Markov model was applied to the clinical results of a NINDS study, savings of US$4 million to US$5 million (1996 values) per 1,000 patients treated with alteplase were projected.[54] These savings were predicted to result from decreases in the length of hospital stay; decreased inpatient, rehabilitation and nursing home costs; and increases in the number of patients discharged directly to home. This occurred despite an initial increase in acute care costs of US$1.7 million. Moreover, a savings of 564 quality-adjusted life years (QALY) over 30 years was also found.[54]

In the UK, a systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic therapy for acute ischemic stroke found that there was a 77% probability of a gain in quality-adjusted survival during the first year at a cost of £13,581 per QALY gained.[55] Over a lifetime, rt-PA was associated with an incremental cost-effectiveness ratio of £96,565 per QALY.[55]

In Canada, Sinclair *et al*.[5] compared the clinical and economic outcomes of intravenous rt-PA therapy versus no rt-PA for acute ischemic stroke based on the outcomes achieved in the NINDS trial. A Markov model with a natural lifetime time horizon was used to compare no rt-PA with rt-PA in a hypothetical cohort of 1,000 patients with acute ischemic stroke in a Canadian health care system setting. Total acute stroke and post-stroke treatment costs and cumulative QALYs were evaluated. The estimated lifetime stroke costs were C$103,100 per patient (1999 values) in the rt-PA arm compared with C$106,900 per patient in the no-treatment arm, yielding a lifetime cost difference of C$3,800 per patient in favour of rt-PA versus no treatment.[5] Treatment with rt-PA resulted in a net benefit of 3,460 additional QALYs per 1,000 patients (3.46 QALYs per patient). No treatment, outcome or economic variables influenced the model outcome. The authors concluded that the treatment of acute ischemic stroke with intravenous rt-PA was an economically attractive strategy.[5]

These economic studies indicate that intravenous rt-PA is cost-effective when administered to treat acute ischemic stroke in appropriate patients. Two of these three studies, however, base their analyses solely on the results of the NINDS trial and consequently may have over-estimated the net cost savings resulting from rt-PA use. Moreover, starting therapy with alteplase in the narrow three-hour window after symptom onset poses a challenge for clinical response teams. Furthermore, only a minority of patients who have a stroke are eligible for thrombolysis.

Conclusion

Overall, it seems that rt-PA, when administered ≤3 hours after the onset of stroke symptoms in a tertiary care neurological centre (in a manner similar to that in the NINDS trial), can decrease the level of disability of acute stroke survivors. No significant mortality benefit, however, has been demonstrated. It is assumed that this may translate into a rehabilitation benefit. The use of outside specialized centres may result in more harm from intracranial hemorrhage than benefit, especially when treatment guidelines are not followed. The results of the Canadian Activase for Stroke Effectiveness study may clarify this matter (Table 7).

It is unclear whether a lower dose of rt-PA given ≤3 hours after the onset of symptoms can be as effective as and safer than the approved intravenous dose of 0.9 mg/kg. The efficacy and safety of intravenous rt-PA when given ≥3 hours after the onset of a stroke are yet to be conclusively demonstrated. Ongoing trials may clarify this matter (Table 7). Diffusion-perfusion magnetic resonance imaging is being proposed as a method to determine if

salvageable brain tissue remains and if rt-PA should be given to patients who are beyond the three-hour time window.[56] This new treatment scheme may involve additional time and lead to more costs.

Table 7: Ongoing or recently completed clinical trials of rt-PA in ischemic stroke

Clinical Trial Register	Project Status	Project Title	Purpose
Stroke Trials Directory http://www.strokecenter.org	Complete	CASES: Canadian Activase for Stroke Effectiveness Study; open label, multi-centre post-marketing study	To prospectively evaluate use of intravenous rt-PA in Canada
Stroke Trials Directory http://www.strokecenter.org	Ongoing: trial is scheduled to run from April 2003 to October 2005	ECASS-III: placebo controlled trial of alteplase (rt-PA) in acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4 hours after stroke onset; multi-centre, randomized, double-blind, placebo-controlled trial in 110 hospitals in 15 European countries	To evaluate efficacy and safety of rt-PA between 3 and 4 hours after stroke onset in European setting
Stroke Trials Directory http://www.strokecenter.org	Ongoing: as of November 2003, 159 randomized patients in 13 centres; three-year expansion phase (which will aim to include 300 patients from 50 centres) began in January 2003; if successful, will be followed by main phase (6,000 patients, 300 centres) in 2005	IST-3: Third International Stroke Trial; international, multi-centre, randomized, double-blind, controlled trial with a planned enrolment of 6,000 patients	To determine whether administration of rt-PA ≤6 hours after ischemic stroke increases proportion of independent survivors at 6 months
Stroke Trials Directory http://www.strokecenter.org	Ongoing: as of June 2002, 200 patients enrolled, with expected total enrolment of >1,000	SITS-ISTR: Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register: international register of rt-PA-treated stroke patients; data will be used in SITS-MOST trial	To generate database of clinical information regarding patients treated with rt-PA ≤3 hours after acute stroke
Stroke Trials Directory http://www.strokecenter.org	Ongoing: as of June of 2002, 200 patients enrolled, with expected total enrolment of >1,000	SITS-MOST: Safe Implementation of Thrombolysis in Stroke Monitoring Study; non-controlled, observational study comparing outcomes of non-study patients to those participating in controlled clinical trial	To compare safety and efficacy of tissue plasminogen activator (TPA) administered in controlled clinical trials to that of TPA prescribed in routine clinical practice
Stroke Trials Directory http://www.strokecenter.org	Ongoing: as of October 17, 2003, 3 patients enrolled	SYNTHESIS: thrombolytic therapy for acute ischemic stroke; randomized, controlled, multi-centre, open-label, blinded follow-up	To determine efficacy of intra-arterial compared to intravenous administration of rt-PA

Several questions regarding the influence of patient and stroke characteristics on the risk of intracranial hemorrhage and death remain to be answered.[16] Hence, estimates for key outcomes remain imprecise, as significant between-trial heterogeneity persists (e.g., regarding patient's age, severity of stroke).[16]

In summary, a high quality systematic review[16] and a recent meta-analysis of all major clinical rt-PA trials[17] provide the best available evidence to date on thrombolysis for acute ischemic stroke. Evidence from other controlled clinical trials of rt-PA is needed to better define the optimal stroke population and time-window for treatment initiation. This will help build a consensus regarding clinical use for ischemic stroke patients.[57]

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