Update on intravenous tissue plasminogen activator for acute stroke: from clinical trials to clinical practice

Review

Synthèse

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Abstract

TISSUE PLASMINOGEN ACTIVATOR (tPA) INJECTED INTRAVENOUSLY within 3 hours of symptom onset has emerged as a treatment option for acute ischemic stroke. Although controversial and not universally accepted, its use in carefully selected patients is supported by evidence from randomized controlled trials and by mounting community experience. In this paper we review the literature published in the past 5 years regarding the safety, clinical trial efficacy and real-world effectiveness of intravenous tPA for stroke. First we review data from the phase III clinical trials on which approval for tPA is based. Then we summarize a growing literature of postmarketing phase IV studies and discuss the limitations and challenges that lie ahead. Our aim is to provide clinicians with an overview of this evolving therapy.

Every 60 seconds, someone in North America experiences a stroke.[1] This condition is the leading cause of adult neurologic disability and the fourth leading cause of death in Canada.[2] Most strokes are due to sudden blockage of blood flow in the brain by a thrombus. The aim of thrombolytic therapy is to limit the size of the infarct by dissolving clots and restoring blood flow to ischemic tissue.

Intravenous tissue plasminogen activator (tPA) was recently approved for use in acute stroke in the United States (1996) and Canada (1999), and national treatment guidelines have been published.[3–5] However, the benefits and risks of tPA are still the subject of intense debate worldwide, and the drug has not yet been approved for use in Europe.[6-8] Apparently conflicting results from various thrombolytic trials and differences in methods and outcome measures among the trials have made interpretation of the literature difficult. Many physicians are reluctant to offer this therapy and few have had experience with stroke thrombolysis. This paper is intended to assist clinicians by providing an up-to-date analysis focusing on new information from recently published and ongoing postmarketing studies.

Methods

We conducted a MEDLINE search to identify completed large-scale multicentre, double-blind, randomized controlled trials of intravenous tPA for stroke, which would qualify as level I evidence, as well as published postmarketing reports of tPA use.

Phase III clinical trials: tPA in the experimental setting

National Institute of Neurological Disorders and Stroke rtPA Stroke Study

The National Institute of Neurological Disorders and Stroke (NINDS) study, published in 1995,[9] provided valid evidence[10,11] that patients treated with tPA within 3 hours of symptom onset achieved greater neurologic recovery and experienced less disability than patients who received placebo. The tPA dose was 0.9 mg/kg (maximum 90 mg), and half of the patients were treated within 90 minutes of stroke onset. The patients had moderately severe strokes, as indicated by the median base-

line scores on the National Institutes of Health stroke scale (NIHSS): 14 for the tPA-treated patients and 15 for the placebo group. There was a strict protocol for managing hypertension, and all patients were admitted to the intensive care unit for 24 hours. At 24 hours neurologic improvement was greater for the tPA-treated patients than the placebo group (median NIHSS score 8 v. 12, $p < 0.01$). At 3 months, each of 4 primary outcome scales and a combined global test statistic for "favourable outcome" showed statistically and clinically significant[6] benefits of tPA ($p = 0.02$): according to these measures, 31% to 50% of tPA-treated patients but only 20% to 38% of placebo-treated patients had achieved complete or near-complete recovery. Similarly, 42% of the tPA-treated patients but only 26% of placebo-treated patients had regained functional independence at 3 months. In this study, 6 patients (95% confidence interval [CI] 5–11) had to be treated for 1 additional patient to recover self-care independence, and 9 patients (95% CI 5–25) had to be treated for 1 additional patient to achieve full neurologic recovery.[9,12] The beneficial effects occurred in patients with all subtypes of stroke, including suspected lacunar infarction, and were sustained at 1 year.[9,13,14]

The most feared complication, symptomatic intracranial hemorrhage, occurred in 6.4% of the tPA-treated patients and 0.6% of placebo-treated patients ($p < 0.001$). Most tPA-related hemorrhages occurred within the first 24 hours, and nearly half of these were fatal. Despite this 10-fold difference in rate of symptomatic intracranial hemorrhage, there was no increase in mortality attributable to tPA within the first week, the first month or the first 3 months (3-month all-cause mortality rate 17% v. 21%, $p = 0.3$).[9,15] The improvement in outcome among tPA-treated patients was not associated with an increase in the number of patients surviving with severe disability.[9,15] Most of the patients with symptomatic intracranial hemorrhage had experienced a severe stroke (median NIHSS 20, range 3–29). In subgroup analysis, stroke severity and baseline CT findings of brain edema (hypodensity) or mass effect emerged as independent predictors of symptomatic intracranial hemorrhage[15] (Table 1). Nonetheless, even in these high-risk patients, tPA was more likely than placebo to be associated with a favourable outcome.

European Cooperative Acute Stroke Studies

The methods and analysis of the European Cooperative Acute Stroke Studies (ECASS I and II)[16,17] differed significantly from those of the NINDS trial. In the first ECASS trial (in 1995),[16] the tPA dose was higher — 1.1 mg/kg (maximum 100 mg) — and the allowable time of administration after symptom onset was longer — 6 hours (median time to treatment was 4 hours). There was an unacceptably high incidence of intracranial hemorrhage in the tPA-treated patients (20% v. 6.5%), probably related to the greater tPA dose, the longer treatment window and the inclusion of a large number of patients (17%) with protocol violations (mainly unrecognized abnormalities on pretreatment CT that should have excluded them from the study). No statistically significant differences in primary outcome were detected in the intention-to-treat analysis. However, when the data were reanalyzed without the patients who should have been excluded from the study, the proportion of patients with minimal or no disability (modified Rankin scale [mRS] score 0 or 1)[18] at 3 months was significantly greater in the treatment group than in the control group (41% v. 29%, $p < 0.05$) (median mRS score at 3 months 2 v. 3, $p = 0.035$).

In the second ECASS trial (in 1998),[17] the dose was reduced to 0.9 mg/kg (the same dose as in the NINDS trial), the investigators were trained to recognize CT abnormalities that would exclude patients from the study, and strict blood pressure control was implemented to reduce the risk of intracranial hemorrhage. The results of this study stimulated much debate. According to the predefined primary endpoint — the proportion of patients with a favourable outcome (mRS score 0 or 1) at 3 months — there was no significant difference between treatment and placebo. However, the distribution of the mRS scores revealed a benefit in favour of treatment. In a single post-hoc analysis, patients' outcomes were classified as either independence in self-care (mRS score 0–2) or death or dependence (mRS score 3–6). A significantly greater proportion of the treated patients achieved independence at 3 months (54% v. 46%, $p = 0.024$). According to this analysis, 12 patients had to be treated to achieve 1 additional independent survivor. Intracranial hemorrhage was more common in the treated patients (9% v. 3%), but there was no difference in mortality rate between the groups. These results strengthened the case for tPA by showing that, even within a 6-hour time window, the drug reduced disability without increasing the mortality rate. In this particular trial, it was a change in the definition of "favourable outcome" that made the difference between a statistically negative result and a statistically positive one; nonetheless, meta-analysis of all of the randomized trials of stroke thrombolysis has clearly shown an overall benefit from tPA treatment, regardless of the defini-

Table 1: Risk of symptomatic intracranial hemorrhage related to administration of tissue plasminogen activator in the NINDS Stroke Study[15]

Pretreatment variable	Risk of symptomatic intracranial hemorrhage, %
NIHSS score	
> 20 (most severe)	17
11–20	4–5
< 10 (least severe)	2–3
Edema or mass effect on CT	
Present	31
Absent	6

NINDS = National Institute of Neurological Disorders and Stroke, NIHSS = National Institutes of Health stroke scale (an indicator of stroke severity).

tion of "favourable outcome" (i.e., mRS 0 or 1, or 0–2).[19,20] Combined data from ECASS I and ECASS II for patients treated within 3 hours of symptom onset further supports the efficacy of tPA.[21]

Phase IV studies: tPA in the real world

Summary of postmarketing studies

The main question that has arisen since tPA was approved as a treatment for stroke is whether the beneficial results observed in clinical trials can be extended to "real world" practice. An increasing number of postmarketing studies are now available from the United States,[22–29] Canada[12,30–36] and Germany[37,38] that describe the feasibility, safety and effectiveness of tPA in clinical practice (see Table 2).

The largest published postapproval experience from the United States is the Standard Treatment with Alteplase to Reverse Stroke (STARS) study,[22] which prospectively documented the outcomes of 389 patients treated with tPA in 24 academic and 33 community centres. In the study cohort, baseline demographic characteristics and stroke severity were comparable to those of the NINDS study, and the incidence of symptomatic intracranial hemorrhage was low (3.3%; fatal intracranial hemorrhage 1.5%). One-month outcomes were favourable (35% had minimal or no disability, and 43% were independent).

In Canada, as of February 2001, more than 800 patients had been treated with tPA, and the initial results have been encouraging.[33–35] The Canadian Activase for Stroke Effectiveness Study (CASES), coordinated at the University of Calgary, is the national registry collecting data prospectively from academic and community hospitals across the country, in compliance with the regulatory conditions for approval of tPA.[34] Canadian patients receiving tPA are older than those in the NINDS cohort, but their initial stroke severity is similar to that in the earlier study. Preliminary results indicate a low rate of symptomatic intracranial hemorrhage (4.4%) and favourable 3-month outcomes[33,35] (comparable to the NINDS results). The University of Calgary group has also reported favourable results for 68 consecutive patients treated by neurologists at a regional stroke centre; for these patients, mean time to treatment has been 100 minutes.[12] Similarly, initial experiences in Vancouver, Halifax and London have been encouraging.[30–32,36]

In Cologne, Germany, 150 consecutive patients were treated, and the incidence of symptomatic intracranial hemorrhage was low (4%).[37] The authors confirmed that long-lasting benefits can be achieved with tPA in clinical practice: at 1 year 41% of the patients had recovered with minimal or no disability and 52% were functionally independent.[38] The study population consisted of younger patients with lower stroke severity (median NIHSS 11) than in the NINDS cohort. In other surveys, such as the OSF Stroke Network experience involving 20 mostly rural hospitals in Illinois,[28] and in the Houston experience,[23] initial stroke severity was comparable to that in the NINDS cohort and rates of symptomatic intracranial hemorrhage were 5% to 7%.

Several reports have highlighted the dangers of protocol violation (the treatment of patients who do not meet the eligibility criteria or treatment that deviates from published guidelines). For example, in the Calgary cohort, 10 of 11 patients with protocol violations had a poor outcome (symptomatic intracranial hemorrhage, dependence or death).[12] Similarly, the t-PA Stroke Survey,[24] involving 189 consecutive patients from 13 stroke centres in several US cities, reported an overall rate of symptomatic intracranial hemorrhage of 6%, the same as in the NINDS study; however, the rate was 4% among patients treated according to protocol but 11% among those with protocol violations. In Indianapolis, tPA-related intracranial hemorrhage occurred in 38% of patients with protocol violations but in only 2% of those without violations.[29] Thus, as summarized succinctly by Buchan and colleagues, it is becoming apparent that "outcome relates to appropriateness" of treatment for the particular patient and that strict adherence to protocol is therefore critical.[12]

A report from Cleveland stands out as the only published postmarketing study to date to show unusually high rates of complication,[27] and it has raised concerns about the community use of tPA.[39] In this cohort of 70 patients from 29 hospitals, the rate of both symptomatic intracranial hemorrhage and in-hospital mortality was 15.7%. This cohort also had the highest reported rate of protocol violations: for 50% of the patients there were deviations from national treatment guidelines. Although no statistical association between protocol violations and intracranial hemorrhage was found, unrecognized differences between those with and without protocol violations may have been present. The patients with symptomatic intracranial hemorrhage were older than those who did not experience this complication (78 v. 67 years) and had higher glucose levels; furthermore, recommended blood pressure control was followed in only 27% of the patients in the study, NIHSS scores were documented for only 27%, and neurologic and functional outcomes were not reported. The lack of initial NIHSS data makes it difficult to know whether differences in stroke severity contributed to the high hemorrhage rate.

Overall, community experience has been instructive, and clinical outcomes and (when treatment guidelines have been followed) complication rates have been reassuringly close to those observed in the NINDS trial. Variations may relate to regional differences (academic v. community centre), patient characteristics, stroke severity, deviations from protocol, and the experience of staff at the centre and the treating physicians (most reports have come from centres with experience in acute stroke management). A lack of uniformity in outcome measures, length of follow-up, definition of recovery and reporting of protocol deviations makes it difficult to compare studies. For future studies,

standardization in the study design and reporting of stroke outcomes is needed.[40]

Limitations and challenges

Intravenous tPA is not approved for administration beyond 3 hours after stroke onset, and this narrow time window constitutes the main barrier limiting its widespread application. It is estimated that tPA treatment currently reaches only 2% to 3% of the North American stroke population.[41] For example, in the NINDS trial, 17 324 patients were screened but only 624 eligible subjects were recruited; most of those excluded were ineligible because of the time elapsed since stroke onset. The efficacy of tPA rapidly diminishes as the time from stroke onset to drug administration increases.[42] One study that has attempted to extend this

Table 2: Summary of published postmarketing reports of IV tPA given within 3 hours of symptom onset compared with the NINDS study

					Outcome; % of patients					
Study	Setting	No. of patients	Baseline median NIHSS score	Follow-up, mo	Minimal or no disability (mRS 0 or 1)	Functional independence (mRS 0–2)	Neurologic recovery (NIHSS score 0–1)	Symptomatic intracranial hemorrage	Death	Protocol violations, % of patients
Randomized controlled trial										
NINDS[9]										
Placebo		312	15	3	26	27	20	0.6	21	NR
Treatment		312	14	3	39	43	31	6.4	17	NR
Prospective										
STARS[22]	57 US hospitals (24 academic, 33 community)	389	13	1	35	43	NR	3.3	13	33
CASES[33]*	49 Canadian hospitals	645	14	3	NR	NR	31	5	NR	10
Cologne experience[37,38]	1 academic hospital	150	11	12	41	52	NR	4	15	NR
Calgary experience[12]	1 academic hospital	68	15	3	NR	57	38	9	16	16
OSF Stroke Network (Illinois)[28]	20 urban and rural hospitals	57	15	To discharge	47	NR	44	5	9	9
London (ON) experience[36]	1 academic centre	30	14	3	37	NR	37	0	13	7
Oregon experience[26]	6 hospitals	33	17 (mean)	3	36	NR	NR	9	18	NR
Houston experience[23]	1 academic, 2 community hospitals	30	14 (mean)	5	30	NR	NR	7	23	10
Historical prospective cohort										
Cleveland experience[27]	29 hospitals	70	12	To discharge	NR	NR	NR	16	16	50
Prospective and retrospective										
Vancouver experience[30]	1 academic hospital	46	14	13	43	NR	NR	2	22	17
Retrospective										
t-PA Stroke Survey[24]	13 urban US hospitals	189	NR	To discharge	34	NR	NR	6	10	30
Indianapolis experience[29]	10 hospitals	50	11	To discharge	NR	NR	NR	10	10	16

Note: IV tPA = intravenous tissue-type plasminogen activator, mRS = modified Rankin scale,[18] NR = not reported, STARS = Standard Treatment with Alteplase to Reverse Stroke, CASES = Canadian Activase for Stroke Effectiveness Study.
*Interim results from CASES.

treatment window by investigating the administration of intravenous tPA between 3 and 5 hours after stroke onset was terminated prematurely because of lack of efficacy.[43] Safety and efficacy of intra-arterial administration of thrombolytic agents up to 6 hours after stroke onset have been demonstrated; this treatment is being used in selected centres, and a second trial is underway.[44,45] Neuroprotective drugs that protect the brain from ischemic cell death are being investigated in clinical trials and may become a future strategy for extending the treatment window for thrombolysis.[45,46]

Adopting tPA in clinical practice presents many challenges for the health care system.[1,12,41,47,48] There must be continuous efforts to raise public awareness of the symptoms of stroke and of the need to act quickly[1] — at present, one-third of the general public cannot name a single warning sign of stroke.[47] Improvements in prehospital screening methods are needed,[49–51] and hospitals must be better equipped with resources and personnel for rapid assessment and treatment of acute stroke. The University of Calgary approach to acute stroke care — rapid prehospital transfer to a regional stroke centre and an organized "brain attack" team — could be a model for stroke centres throughout the country.[52] A recent report from the Heart and Stroke Foundation of Ontario and the Ontario Ministry of Health and Long-Term Care recommended that stroke care be reorganized, such that care would be provided through designated community hospitals and district and regional stroke centres; these recommendations were based in part on the success of demonstration projects in London, Kingston, Hamilton and west Toronto.[47]

tPA should be administered by physicians with expertise in acute stroke and with strict adherence to published treatment guidelines.[3–5,53] This is in keeping with the position taking by the Canadian Association of Emergency Physicians, who recommend giving tPA only in a closely monitored clinical practice setting with adherence to the NINDS protocol.[54] Treating physicians should also have expertise in recognizing the signs of early infarction on brain CT and familiarity with the NIHSS as a tool for rapid assessment and risk stratification. The initial NIHSS score has prognostic value that may help to guide treatment decisions[13,55–57] (Table 3). Candidates for thrombolysis should have a nonresolving neurologic deficit that can be measured with the NIHSS and that is significant enough to warrant the risks of treatment. It is not yet clear what level of neurologic deficit justifies treatment, but some clinicians are reluctant to give tPA if the NIHSS is not greater than 4. The London group excludes patients in whom more than one-third of the middle cerebral artery territory is involved.[32] The Calgary group also emphasizes the importance of prespecified criteria for CT interpretation and has developed a CT rating scale (called ASPECTS) to assist in selecting patients for acute therapy.[58] A set of practical guidelines for stroke thrombolysis, encompassing suggested inclusion criteria, contraindications and warnings, has recently been published,[52] and an updated version of the guidelines from the Canadian Stroke Consortium will be available soon.

Ongoing studies aim to identify specific patient subgroups most likely to benefit and those at particular risk from thrombolysis.[59] For example, in a recent retrospective study, elevated pretreatment serum glucose (greater than 11.1 mmol/L) or diabetes were predictors of tPA-related hemorrhage; in patients with and without these risk factors, the rates of intracranial hemorrhage were 25% and 9% respectively.[60] In the future, the use of prognostic scales (e.g., ASPECTS) and improvements in brain and vascular imaging technologies may enhance our ability to select the best candidates for treatment. Diffusion- and perfusion-weighted MRI and CT perfusion imaging aim to rapidly distinguish patients with reversible ischemia around the infarct core (who may benefit from reperfusion therapy) from those with irreversible ischemic injury (who may not benefit from thrombolysis).[61]

Conclusions

The approach to treating patients with acute stroke has evolved dramatically in the past 5 years. Intravenous tPA (at 0.9 mg/kg) has proven efficacious when administered to appropriate patients within the first 3 hours of ischemic stroke. The value of this treatment after 3 hours is still uncertain.[16,17,43] Despite the limitations and skepticism, community experience with tPA is growing. It appears that favourable results, similar to those obtained in the NINDS trial, can be achieved in the community in suitably selected patients, and some centres have reported even lower rates

Table 3: Prognostic value of NIHSS score in patients not treated with tPA[13,55–57]

NIHSS score	Prognosis
> 20 plus age > 75 yr	Mortality rate 45%*
> 17 plus atrial fibrillation	Positive predictive value for poor outcome 96% (mRS > 3)
≥ 16	High probability of death or severe disability
> 7	Only 2.5% of patients functionally normal at 48 h
≤ 7	45% of patients functionally normal at 48 h
≤ 6	Good spontaneous recovery

Note: mRS = modified Rankin scale.[18]
*Mortality rate 48% with tPA.

of symptomatic intracranial hemorrhage than were observed in the NINDS trial. Higher complication rates have occurred in only a few studies, and these were usually related to protocol violations.

With the approval of tPA, stroke has finally become a treatable disorder in the acute stage. Yet if this treatment is to realize its full potential, physicians and patients alike need to recognize and react to stroke as a medical emergency. To ensure continued safe and effective implementation of this therapy, tPA should be administered by physicians with expertise in acute stroke and published treatment guidelines should be followed.[3–5,53] Ongoing education of both physicians and patients is needed and postmarketing surveillance should continue.

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