Intravenous Recombinant Tissue Plasminogen Activator Therapy for Acute Ischemic Stroke: Initial Israeli Experience

Yvonne Schwammenthal MD[1,2], Michael J. Drescher MD[3], Oleg Merzeliak MD[1,2], Rakefet Tsabari MD[1], Bella Bruk MSc[2], Meir Feibel MD[4], Chen Hoffman MD[4], Mati Bakon MD[4], Zeev Rotstein MD[5], Joab Chapman MD[1] and David Tanne MD[1,2]

[1]Stroke Unit, Department of Neurology, [2]Neurovascular Laboratory, Department of Emergency Medicine[3], and Departments of [4]Radiology and [5]Medical Management, Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: ischemic stroke, tissue plasminogen activator, thrombolysis, reperfusion, transcranial Doppler

Abstract

Background: Intravenous recombinant tissue plasminogen activator therapy within 3 hours of stroke onset is a proven effective treatment for acute ischemic stroke.

Objective: To assess the feasibility and safety of rt-PA therapy for reperfusion in routine clinical practice in Israel, in the setting of a dedicated stroke unit.

Methods: Consecutive patients presenting within less than 3 hours of stroke onset were evaluated by an emergency physician and the neurology stroke team. After brain computerized tomography, eligible patients were treated with intravenous rt-PA (0.9 mg/kg, maximum dose 90 mg) according to an in-hospital protocol corresponding to recommended criteria. Patients were admitted to the acute stroke unit. Safety and clinical outcome were routinely assessed. Recanalization was assessed by serial transcranial Doppler.

Results: The study group comprised 16 patients, mean age 61 years (range 47–80 years), male to female ratio 10:6, whose median baseline National Institutes of Health stroke scale was 13 (range 6–24). They were treated within a mean door-to-CT time of 39 minutes (range 17–62 min), door-to-drug time 101 minutes (range 72–150), and stroke onset-to-drug time 151 minutes (range 90–180). There was an early improvement within 24 hours (of $\geqslant$ 4 points in the NIHSS score) in 7 patients (44%) and no early deteriorations. There were no protocol deviations, no symptomatic intracranial hemorrhages, and no major systemic hemorrhage within 36 hours of rt-PA treatment. Three asymptomatic hemorrhagic transformations of the infarct were noted on routine follow-up brain CT associated with neurologic improvement. Outcome data were comparable to the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study.

Conclusion: Intravenous rt-PA treatment within 3 hours of stroke onset in routine clinical practice in Israel is feasible and appears safe in the setting of a neurology stroke unit and team. Careful implementation of rt-PA therapy for selected patients in Israel is encouraged.

IMAJ 2004;6:70–74

For Editorial see page 95

rt-PA = recombinant tissue plasminogen activator
NIHSS = National Institutes of Health stroke scale

Stroke is the leading cause of severe neurologic disability and kills over 3,000 people in Israel annually [1]. Coping with the consequences of stroke presents a major emotional and financial challenge for the patient and family caregiver, and imposes a substantial economic burden on Israeli society. In the vast majority of cases the direct cause of ischemic stroke is an embolic occlusion of a brain artery by a blood clot. Reperfusion of the occluded brain artery using intravenous recombinant tissue-type plasminogen activator is a proven and efficacious therapy for acute ischemic stroke within the first 3 hours of stroke onset [2,3].

Intravenous rt-PA therapy was approved for use in the United States in June 1996, subsequently in Canada, and more recently in Europe. Experience in Israel, apart from anecdotal cases, is lacking partly because of concerns regarding safety and the feasibility of urgent treatment in a routine clinical setting in Israel.

In recent years we established a dedicated stroke unit based on accepted recommendations [4], and devised a collaborative approach for urgent triage and treatment of acute stroke supervised by a neurology stroke team. A written in-hospital protocol for intravenous rt-PA therapy was initiated and in-service education provided in order to: a) assess the feasibility, logistics and barriers of urgent triage and treatment of acute ischemic stroke with intravenous rt-PA in our setting, against the background of established recommendations (quality control); and b) assess the safety and clinical outcome of stroke patients treated with rt-PA.

Patients and Methods

Patients presenting to the emergency department of the Sheba Medical Center within less than 3 hours of stroke onset were evaluated. On arrival at the emergency department, patients were triaged by an emergency physician, routine blood tests were drawn and an urgent CT obtained. The patients and their CT scans were urgently reviewed by a neurologist or member of the stroke team. In patients eligible for treatment. After reviewing the history, neurologic examination, blood tests and brain CT of patients eligible for treatment, rt-PA therapy was initiated. The main protocol guidelines and selection criteria are summarized in the Appendix.

rt-PA 0.9 mg/kg (maximal dose 90 mg) was administered intravenously for 1 hour, with 10% of the total dose given as a bolus. Patients were admitted directly to the stroke unit and were closely monitored for vital signs according to the protocol and for neurologic deficits according to the NIH stroke scale score, a 42 point scale that quantifies neurologic deficits in 11 categories. For example, a mild facial paralysis is given a score of 1; a score of 25 is given to complete right hemiplegia with aphasia, gaze deviation, visual field deficit, dysarthria, and sensory loss. Normal function without neurologic deficit is scored as zero. (Details of stroke scales used for neurologic deficits and functional outcome can be found at: http://www.strokecenter.org/trials/scales/index.htm.) The NIHSS score was re-evaluated at 24 hours, at hospital discharge and at follow-up. Large vessel occlusion and re-canalization were assessed with transcranial Doppler using the Thrombolysis in Brain Ischemia (TIBI) classification [5]. Examinations were performed by a single experienced technician as soon as possible after stroke onset and with follow-up examinations thereafter. Standard brain CT (5 mm axial slices) was performed at baseline, during in-hospital follow-up, and upon clinical deterioration. Symptomatic intracerebral hemorrhage was defined as clinical deterioration accompanied by hemorrhage on brain CT. Functional outcome at discharge and follow-up was assessed by: a) the modified Rankin scale, a simplified overall assessment of function in which a score of 0 indicates the absence of symptoms and 5 indicates severe disability; and b) the Barthel index, a reliable and valid measure of the ability to perform activities of daily living such as eating, bathing, walking, and using the bathroom. Patients able to perform all activities with complete independence are given a score of 100.

Results

Between September 2002 and August 2003, intravenous rt-PA therapy was given to 16 patients with acute ischemic stroke, which represents 2.6% of patients with acute ischemic stroke admitted to the medical center in that period. Fourteen patients presented to the emergency department; in 2 patients the stroke occurred during hospitalization in another ward. Baseline characteristics are summarized in Table 1, and characteristics of patients included in the National Institute of Neurological Diseases and Stroke rt-PA Trial are shown for comparison. The mean age was 61 years (range 47–80) and the male to female ratio was 10:6. The median baseline NIHSS score was 13 (range 6–24), implying an overall moderate stroke severity. The stroke mechanism was assessed by the TOAST classification (cardioembolic in 7, small vessel occlusive in 3, large vessel atherothrombotic in 3, and undetermined origin in 3). Transcranial Doppler examination was performed in all patients. In two patients ultrasonographic temporal windows were lacking, in seven patients a relevant complete or partial occlusion was observed, and in seven patients occlusion of a large intracranial artery was not documented. Of note, occlusion of perforants and distal branches are not depicted by transcranial Doppler.

Table 1. Clinical baseline characteristics of the study population at Sheba Medical Center compared to the NINDS rt-PA Stroke study population

	Sheba Medical Center (n=16)	NINDS rt-PA Stroke Study [2]
Age (yrs)	61	69
Range	47–80	69
NIH stroke scale score	13	14
Range	6–24	1–37
Gender (female %)	38	43
Hypertension (%)	63	67
Diabetes mellitus (%)	6	20
Atrial fibrillation (%)	31	20

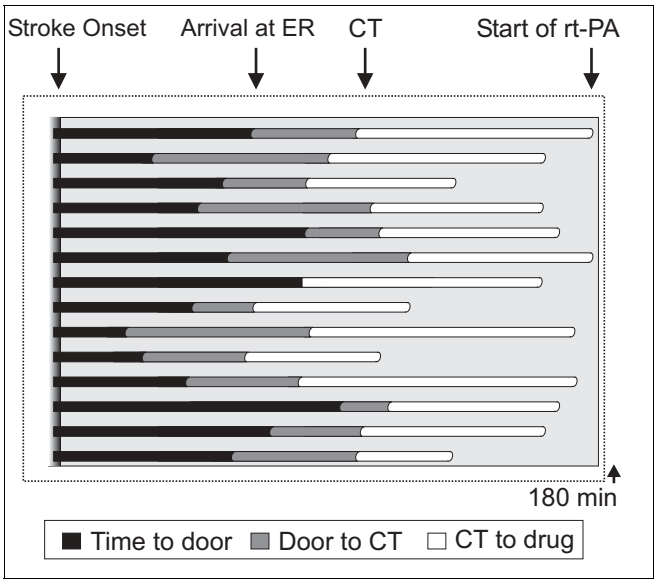

Figure 1. Timetable of out-of-hospital and in-hospital logistics, demonstrating for individual patients the time from stroke onset to emergency department arrival, brain CT and initiation of intravenous rt-PA

The detailed logistics and timing of triage and treatment are summarized in Figure 1. The mean onset-to-door time was 59 minutes (range 25–97 min), door-to-CT time 39 minutes (range 17–62), and door-to-drug time 101 minutes (range 72–150). The average stroke onset-to-drug time was 151 minutes (range 90–180).

The classification of patients based on the NIHSS revealed early improvement (defined by a decrease of $\geqslant$ 4 points within 24 hours) in seven patients (44%; a decrease up to 15 points or to no measurable neurologic deficit). The remaining patients remained stable (no change of > 3 points within 24 hours). No patient showed early deterioration (defined by an increase of $\geqslant$ 4 points within 24 hours). Stroke severity assessed by the NIHSS revealed a baseline median score of 13 and a 24 hour median score of 6. Functional outcome assessed at hospital discharge and at a mean follow-up of 65 $\pm$ 16 days revealed a modified Rankin scale score of 3 and a Barthel index of 51 and 60 respectively. For 4 of 16 patients follow-up data were not yet available.

There were no protocol deviations, and no patient had a symptomatic intracranial hemorrhage. Asymptomatic hemorrhagic transformation of the infarct was noted on routine repeat brain CT in three patients, and one patient had microhematuria. Figure 2 presents an example of an asymptomatic hemorrhage in a patient with successful re-canalization and an excellent clinical outcome.

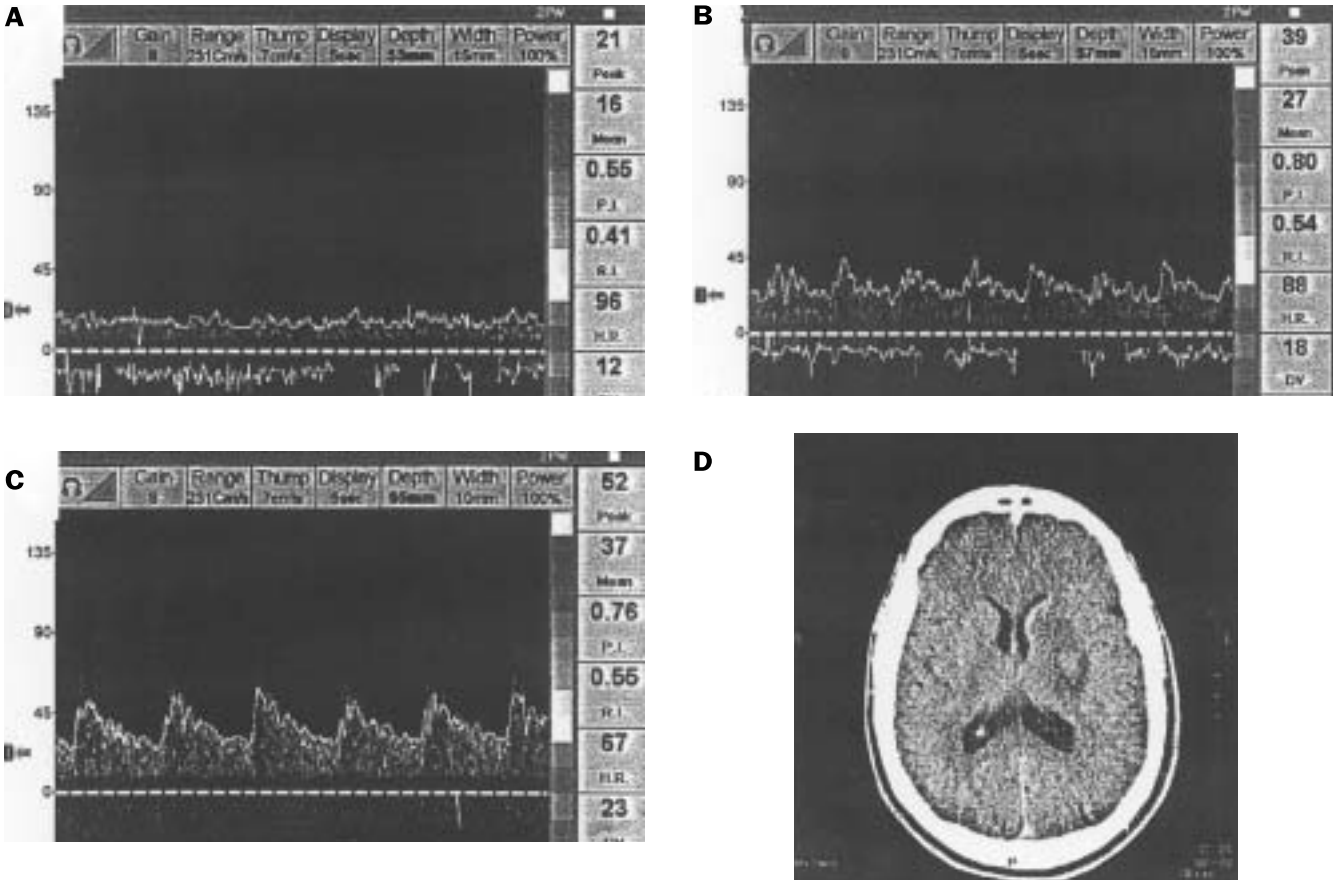

Figure 2. An asymptomatic hemorrhage after successful reperfusion. A 53 year old man presented with severe ischemic stroke in the distribution of the middle cerebral artery, with a baseline NIH stroke scale score of 16. He was treated after 2 hours and 5 minutes with intravenous rt-PA (total dose 75 mg). Transcranial Doppler at baseline demonstrated middle cerebral artery occlusion **[A].** Serial transcranial Doppler examinations after 2 hours **[B]** and 24 hours **[C]** revealed re-canalization of the occluded middle cerebral artery. NIH stroke scale after 2 hours was 10, after 24 hours 6 and after 7 days 2 (mild dysphasia and mild facial paralysis), implying marked neurologic improvement. Repeat brain CT after 24 hours revealed a striatocapsular infarct with some hemorrhagic transformation **[D]**.

Discussion

Our preliminary results demonstrate that intravenous rt-PA reperfusion treatment in routine clinical practice in Israel within 3 hours of stroke onset is feasible and appears safe when conducted by a neurology stroke unit and team adhering strictly to NINDS criteria.

The logistics of emergency department triage, brain imaging and a stroke unit can be effectively integrated to achieve delivery of rt-PA within the 180 minute time window. More detailed quality control of our early experience shows that despite a speedy diagnostic workup with an average door-to-CT time of 39 minutes (the NINDS benchmark is 45 minutes), door-to-drug time averaged 101 minutes, which is comparable to other early post-marketing data [6] but transgresses the NINDS benchmark set at 60 minutes [7]. This loss of time was due in part to the lack of sufficient neurology/stroke team expertise available for 24 hours, and in part to hesitation by patients/families and consultation with third-party advisors.

Even within the first 3 hours, the likelihood of an excellent outcome increases with earlier treatment and re-canalization [8,9]. Therefore, any undue delay of treatment, even within the 3 hour window, will reduce the likelihood of a good clinical outcome. Hence, the need to treat eligible patients as quickly as possible in order to preserve salvageable brain tissue. Indeed, rapid arterial re-canalization, as shown by transcranial Doppler, is associated with better short-term improvement [9]. In nearly half of our treated patients, significant early improvement was observed within the first 24 hours.

The major risk of rt-PA is bleeding into the damaged brain [10,11]. In the NINDS rt-PA Stroke Trial the rate of symptomatic intracerebral hemorrhage was 6%, while most major community-based studies later showed even lower rates [12–16]. In the Canadian Activase for Stroke Effectiveness Study (CASES) established to prospectively monitor the use of rt-PA in Canada, over 1,100 patients were treated in 60 medical centers and the risk of symptomatic intracerebral hemorrhage was 4.5%. Readily available predictors of ICH that may assist in bedside stratification of risk are known [11]. Deviations from the NINDS treatment protocol have

NINDS = National Institute of Neurological Disease and Stroke

ICH = intracerebral hemorrhage

been associated with higher rates of symptomatic ICH [12], which underscores the importance of adherence to the NINDS protocol. Quality improvement programs were found to decrease protocol deviations and subsequent risks [17]. In our series of patients there were no cases of symptomatic ICH and no protocol deviations. These results suggest that careful patient selection and strict adherence to the protocol increase safety. It is noteworthy that in our setting a dedicated stroke unit was first established, a written in-hospital protocol initiated, and in-service education provided. In all cases a member of the neurology stroke team evaluated the patient and his or her brain CT to determine eligibility for treatment, and most patients treated had moderate stroke severity. In patients with findings compatible with complete middle cerebral artery ischemia or basilar thrombosis, our preferred treatment strategy is intra-arterial thrombolytic therapy, if feasible [18]. Therefore, our results with rt-PA therapy cannot be generalized to clinical settings in which treatment is less meticulously implemented.

There were three cases of asymptomatic hemorrhagic transformation of the cerebral infarct in our series of patients. A large parenchymatous hematoma is, however, the only type of hemorrhagic transformation that alters the clinical course of ischemic stroke in the setting of rt-PA therapy [19], and petechial hemorrhagic transformation may be a marker of successful reperfusion and improved clinical outcome [20], as demonstrated also in the example shown in Figure 2. Both early and post-discharge follow-up results in our series compare favorably with standards set in large controlled trials [2].

Although stroke can occur in individuals of any age, it primarily affects the elderly. Intravenous rt-PA may also be safe in selected elderly patients over age 80 [21,22]. The oldest patient in the current series was 80 years old and had a favorable clinical outcome. Elderly patients, however, are more likely to have co-morbidities that may put them at higher risk; therefore, caution is advised in patient selection.

Conventional brain CT to rule out hemorrhage is the only imaging tool required prior to initiation of rt-PA therapy. Multi-modality neurovascular imaging is an evolving area in acute ischemic stroke management. Transcranial Doppler is readily available in most neurology departments in Israel and is an inexpensive bedside tool for serial assessment of vessel occlusion and re-canalization, as shown in our illustrative case. In acute ischemic stroke, transcranial Doppler may demonstrate the relevant intracranial large vessel occlusion, and monitor for re-canalization as well as for re-occlusion following re-canalization that may occur in up to a third of patients.

It is estimated that only about 2% of all ischemic stroke patients in the U.S. are currently treated with rt-PA. In our early experience the rate is comparable (2.6%). At selected centers with appropriate infrastructure, however, this rate may approach 10% or higher [15], requiring an effective stroke triage, cooperation with emergency medical services, and high public awareness. The performance of a stroke team can improve over time, thereby increasing the proportion of eligible patients and, consequently, the efficiency of the method [23], but a neurologist experienced in reperfusion therapy for acute stroke should be readily available to facilitate treatment within such a short time window. Experience with acute myocardial infarction in Israel has shown that with effective systems the proportion of patients eligible for urgent reperfusion therapy increases. With regard to the Israeli public, special efforts are necessary – once urgent therapy is more widely available – to educate about stroke symptoms and the potential benefits of speedy stroke therapy [24]. Based on our initial experience and that of others [24,25], we propose establishing comparable programs in several qualified medical centers sufficiently distributed across the country to allow quick access to potential stroke victims and close collaboration with local emergency medical services. Centers should first institute a written in-hospital protocol based on the NINDS criteria, and quality control should be monitored.

References

1. Causes of death 1996-1997. Jerusalem: Central Bureau of Statistics, 2000: publication no. 1124.
2. 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;333:1581–8.
3. Broderick JP, Hacke W. Treatment of acute ischemic stroke. Part I: Recanalization strategies. *Circulation* 2002;106:1563–9.
4. Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. Brain attack coalition. *JAMA* 2000;283:3102–9.
5. Demchuk AM, Burgin WS, Christou I, et al. Thrombolysis in Brain Ischemia (TIBI). Transcranial doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke* 2001;32:89–93.
6. Chiu D, Krieger D, Villar-Cordova C, et al. Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice. *Stroke* 1998;29:18–22.
7. National Institute of Neurological Disease and Stroke. Proceedings of a national symposium on rapid identification and treatment of acute stroke. Bethesda, MD: National Institutes of Health; 1997.
8. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology* 2000;55:1649–55.
9. Alexandrov AV, Burgin WS, Demchuk AM, El-Mitwalli A, Grotta JC. Speed of intracranial clot lysis with intravenous tissue plasminogen activator therapy: sonographic classification and short-term improvement. *Circulation* 2001;103:2897–902.
10. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA Stroke Study Group. *Stroke* 1997;28:2109–18.
11. Tanne D, Kasner SE, Demchuk AM, et al. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. *Circulation* 2002;105:1679–85.
12. Tanne D, Bates VE, Verro P, et al. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. The t-PA Stroke Survey Group. *Neurology* 1999;53:424–7.
13. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA* 2000;283:1145–50.
14. Hill MD, Buchan AM. Methodology for the Canadian Activase for Stroke Effectiveness Study (CASES). CASES Investigators. *Can J Neurol Sci* 2001;28:232–8.
15. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. *Arch Neurol* 2001;58:2009–13.

16. Tanne D, Demchuk AM, Kasner SE. Intravenous thrombolysis for acute ischemic stroke: the phase IV data. *Semin Cerebrovasc Dis Stroke* 2001;1:130–40.
17. Katzan IL, Hammer MD, Furlan AJ, Hixson ED, Nadzam DM. Quality improvement and tissue-type plasminogen activator for acute ischemic stroke: a Cleveland update. *Stroke* 2003;34:799–800.
18. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism [see comment]. *JAMA* 1999;282:2003–11.
19. Fiorelli M, Bastianello S, von Kummer R, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke* 1999;30:2280–4.
20. Berger C, Fiorelli M, Steiner T, et al. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke* 2001;32: 1330–5.
21. Tanne D, Gorman MJ, Bates VE, et al. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older: the tPA stroke survey experience. *Stroke* 2000;31:370–5.
22. Tanne D, Turgeman D, Adler Y. Management of acute ischaemic stroke in the elderly. Tolerability of thrombolytics. *Drugs* 2001;61:1439–53.
23. Koennecke H-C, Nohr R, Leistner S, Marx P. Intravenous tPA for ischemic stroke team performance over time, safety, and efficacy in a single-center, 2-year experience. *Stroke* 2001;32:1074–8.
24. Morgenstern LB, Staub L, Chan W, et al. Improving delivery of acute stroke therapy: the TLL Temple Foundation Stroke Project. *Stroke* 2002;33:160–6.
25. Lattimore SU, Chalela J, Davis L, et al. Impact of establishing a primary stroke center at a community hospital on the use of thrombolytic therapy: the NINDS Suburban Hospital Stroke Center Experience. *Stroke* 2003;34:55–7.

Correspondence: Dr. D. Tanne, Stroke Unit, Dept. of Neurology, Sheba Medical Center, Tel Hashomer 52621, Israel.
Phone: (972-3) 530-2069
Fax: (972-3) 530-5791
email: tanne@sheba.health.gov.il

Appendix:
Main guidelines for use of intravenous rt-PA in patients with acute ischemic stroke

Eligibility for intravenous treatment with rt-PA
Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
Time of symptom onset well established to be <180 minutes before treatment can begin
Final decision regarding eligibility determined by stroke team
Patient selection: contraindications
Evidence of intracranial hemorrhage on pretreatment CT*
Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT*
Active internal bleeding*
Platelet count less than 100,000/mm^3*
Patient has received heparin within 48 hours and has an elevated activated partial thromboplastin time*
Current use of oral anticoagulants (e.g., warfarin) with an elevated INR of 1.5 or more*
Within 3 months: any intracranial surgery, serious head trauma, or previous stroke*
On repeated blood pressure measurements, systolic >185 mmHg or diastolic >110 mmHg at the time treatment begins, or patient requires aggressive treatment to reduce BP to these limits*
History of intracranial hemorrhage*
Known arteriovenous malformation or aneurysm*
Seizures observed at onset of stroke symptoms**
History of gastrointestinal or urinary tract hemorrhage within 21 days**
Recent arterial puncture at a non-compressible site**
Recent lumbar puncture**
Abnormal blood glucose level (<50 or >400 mg/dl)**
Only minor or rapidly improving stroke symptoms**
Post-myocardial infarction pericarditis**
Caution advised for patients with extensive early infarct signs on CT, or severe stroke (NIHSS > 22)***
Drug infusion and monitoring
Infuse rt-PA at a dose of 0.9 mg/kg (maximum dose 90 mg) over a 60 minute period; first 10% of the total dose given as a bolus over 1 minute
Admit to stroke unit
Perform neurologic assessments every 15 minutes during infusion, every 30 minutes for the next 6 hours and every 60 minutes for the next 16 hours
If an intracranial hemorrhage is suspected, discontinue rt-PA infusion and obtain an emergency CT scan
Monitor BP every 15 minutes for 2 hours, every 30 minutes for 6 hours, and every 60 minutes for 16 hours; repeat measurements more frequently if systolic BP is >180 mmHg or diastolic BP >105 mmHg; administer antihypertensive drugs (such as intravenous labetolol) as needed to maintain BP $\leqslant$ those levels
No concomitant anticoagulants or antiplatelets during the first 24 hours
No central venous access or arterial puncture and, if possible, no insertion of nasogastric tube within 24 hours; no insertion of bladder catheter within drug infusion or 30 minutes after

* Contraindication
** Relative contraindications
*** Not part of the NINDS rt-PA Stroke Trial protocol. However, in patients with findings compatible with complete middle cerebral artery ischemia or basilar