Intravenous thrombolysis for acute stroke*

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In 1996, the US Food and Drug Administration (FDA) approved the use of recombinant tissue-plasminogen activator (t-PA), a thrombolytic agent, for selected patients with ischemic stroke if treatment is begun within 3 hours of stroke onset. This marked the beginning of a new era of acute stroke therapy. While intravenous t-PA remains the only scientifically proven and FDA-approved pharmacologic or mechanical treatment for acute ischemic stroke, it is important to understand the scientific basis for its approval, its practical use and limitations, the experience with other intravenous thrombolytic agents, and the future of thrombolytic agents for acute stroke.

INTRAVENOUS t-PA FOR ACUTE ISCHEMIC STROKE

The evidence base

The two critical studies that formed the basis for approval of t-PA were funded by the National Institute of Neurological Disorders and Stroke (NINDS) and reported as the NINDS t-PA Stroke Trial.[1–7] Patients in these studies had to have t-PA administered within 3 hours of stroke onset, and nearly half of patients had t-PA started within 90 minutes of onset.

The dose of t-PA used in the NINDS studies was 0.9 mg/kg given intravenously over 1 hour, with 10% of the total dose given as a bolus. The maximum dose was 90 mg. This dose was determined by an NINDS-funded pilot dose-escalation study[8] in the late 1980s in which four of the five symptomatic intracerebral hemorrhages occurred at a dose of 0.95 mg/kg or higher, one at dose of 0.89 mg/kg, and none at lower dose tiers ($P < .02$.). No difference in favorable outcome was detected between lower and higher dose tiers in this small nonrandomized study.

In the subsequent randomized NINDS t-PA Stroke Trial, patients treated with t-PA were more likely to have an excellent functional outcome at 3 months as determined by one of four neurologic or functional rating scales (absolute difference of 11% to 13% vs placebo group).[2] A subsequent report from the NINDS t-PA Stroke Trial showed that the benefit seen among patients treated with t-PA was maintained at 1 year.[7] t-PA was also cost-effective overall since patients treated with t-PA were likely to be discharged earlier and to home, and were less likely to require nursing home care or extensive rehabilitation.[6]

The major risk of t-PA is bleeding into the damaged brain. Symptomatic intracerebral hemorrhage within 36 hours after stroke onset occurred in 6.4% of patients given t-PA in the NINDS t-PA Stroke Trial and in 0.6% of the placebo group ($P < .001$), but there was no significant difference in overall 90-day mortality between the t-PA (17%) and placebo groups (21%; $P = .30$).[5]

A subsequent report from the NINDS t-PA Stroke Trial indicated that the beneficial effect of t-PA is time-dependent, even within the first 3 hours of onset.[9] t-PA appears to be effective for all ischemic stroke subtypes and patient subgroups, provided that patients meet all of the inclusion and exclusion criteria of the NINDS t-PA Stroke Trial.[1]

There have been three other major randomized trials of intravenous t-PA for acute ischemic stroke. Two of these trials evaluated the safety and efficacy of t-PA in stroke patients treated within 0 to 6 hours: the European Cooperative Acute Stroke Study (ECASS and ECASS II).[10,11] The Atlantis Trials (Part A, time window of 0 to 6 hours; Part B, time window of 0 to 5 hours) focused primarily on patients treated within 3 to 5 hours of stroke onset.[12]

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Except for the fact that ECASS I used a slightly higher dose of t-PA (1.1 mg/kg), these studies were similar to the NINDS t-PA Stroke Trial in design and endpoints, and differed primarily in the time from stroke onset to start of t-PA adminstration.

None of these other t-PA studies was positive, as defined by a statistically significant difference between t-PA and placebo, with regard to the a priori primary clinical endpoint, although the direction of benefit was in favor of t-PA. Several predefined secondary analyses and post hoc analyses, including those using the defined primary endpoint from the NINDS t-PA Stroke Trial, did indicate a positive benefit for patients treated with t-PA in the two ECASS trials. The risk of symptomatic intracerebral hemorrhage in the three trials was similar to, but nonsignificantly higher than, that reported for the NINDS t-PA Stroke Trial.

A recent pooled analysis of the six larger randomized studies of intravenous t-PA (*Lancet*, in press) indicates that time to treatment is extremely critical, with the greatest likelihood of an excellent outcome when t-PA is given within the first 90 minutes to 2 hours after stroke onset. This analysis also indicates that t-PA given beyond 3 hours—and maybe up to 4 to 5 hours—may provide benefit. This hypothesis is currently being tested in the ECASS III and IST 2 studies.

Community experience

Community use of t-PA since 1996 has resulted in a similar percentage of successful outcomes and a similar rate of symptomatic intracerebral hemorrhage when the NINDS treatment protocol has been followed. Deviations from the NINDS treatment protocol have been associated with higher rates of symptomatic intracerebral hemorrhage. Currently only 1% to 2% of all ischemic stroke patients in the United States are estimated to be treated with intravenous t-PA within 3 hours of onset, although the recent experience of the first four Coverdell State Stroke Registries suggests an overall rate of about 3% to 4%.[13] The rate may be slightly higher at selected tertiary-care centers. The major reason for failure to treat is that most patients arrive beyond the 3-hour window.[14]

An excellent summary of the NINDS protocol for treatment with intravenous t-PA, including inclusion and exclusion criteria, management of blood pressure, and treatment of complications, is found in a recent book chapter by Marler and Lyden.[15]

Response and genotype

One unique observation in the past several years is that the response to intravenous t-PA may depend on the genotype of the patient.[16] In the NINDS t-PA Stroke Trial, persons with an Apo E2 phenotype were much more likely to have an excellent response to t-PA than were persons with an Apo E4 or Apo E3 genotype, even though these latter patient groups also had a beneficial response. This finding is currently being explored in in vivo clot models.

■ OTHER THROMBOLYTIC AGENTS

Streptokinase

Three randomized trials of intravenous streptokinase for acute ischemic stroke have been reported.[17–19] All studies were stopped prematurely because of excess mortality and intracranial hemorrhage. The Australian Streptokinase Trial did find a trend toward benefit in patients treated within 3 hours of stroke onset.[17] The reasons for streptokinase failure included a much later time to treatment in the streptokinase studies as compared with the NINDS t-PA Stroke Trial, as well the use of the full cardiac dose of streptokinase as compared with about two thirds of the cardiac dose of t-PA in the NINDS t-PA Stroke Trial.

Newer therapies and strategies

Pilot studies of newer thrombolytic agents and platelet-receptor antagonists are ongoing. Tenecteplase (TNK), a molecule derived from the t-PA molecule, is currently being tested for use within 3 hours of stroke onset in an NINDS-funded phase 1 pilot study, and results are encouraging.[20] Reteplase has also been used in small series of patients with acute stroke but has yet to be evaluated in a controlled trial.[21] Desmoteplase is currently under investigation in a study using MRI to select appropriate patients beyond 3 hours of stroke onset. Phase 1 and phase 2 studies of abciximab, a glycoprotein (GP) IIb/IIIa receptor antagonist, have been completed and a randomized phase 3 study is beginning.[22] Small series of patients treated with the combination of a GPIIb/IIIa receptor antagonist and t-PA or reteplase have been reported, and larger pilot studies are beginning, one of which (the CLEAR trial) is a subject for another presentation at this conference.

Finally, the combination of low-dose intravenous t-PA followed by intra-arterial t-PA and clot manip-

ulation (the EMS and IMS trials) is currently being tested in pilot studies.[23]

SUMMARY

Intravenous t-PA is effective if given to appropriate patients within 3 hours of stroke onset, and its effectiveness increases even within the first 3 hours when given as soon as possible. t-PA is reasonably safe if used in a carefully defined manner that ensures close attention to blood pressure, careful patient monitoring, no use of heparin and aspirin during first 24 hours, and appropriate patient selection.[13] It is still unclear whether a lower dose of t-PA given with 3 hours could be as effective as but safer than the currently approved intravenous dose of 0.9 mg/kg over 1 hour.

The effectiveness and safety of intravenous t-PA when given beyond 3 hours after stroke onset has yet to be conclusively demonstrated. One attractive development is the potential use of imaging, such as diffusion/perfusion MRI to determine if salvageable brain remains and if t-PA should be given in patients who are beyond the 3-hour time window. The drawback to MRI is the additional time required before the start of recanalization therapy.

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