Tissue Plasminogen Activator for Acute Ischemic Stroke: NINDS rt-PA Study Group

N Engl J Med. 1995 Dec 14; 333 (24): 1581-7

At the time of this study, there were no approved, acute treatment options for acute ischemic stroke (AIS), though it was clear that thrombolytic therapy was considered a viable option to reduce the extent of neurologic injury. In addition, two other open-label, dose-escalation studies had been completed using early (90-180 min) administration of recombinant human tissue plasminogen activator (t-PA) for AIS, to maximize recovery from AIS while also reducing hemorrhage risk. With this in mind, the goal of this study was to confirm the efficacy and safety of IV t-PA for use in AIS, when administered within 90-180min of stroke onset, in a larger, randomized, placebo-controlled trial.

Experimental Design and Statistics: Part 1 of this study tested the hypothesis that IV t-PA would yield early improvement, defined as deficit resolution/improvement by $\geq$4 pts on the NIHSS, at 24hrs post-treatment. Part 2, considered as the more important assessment in the study, tested the hypothesis that IV t-PA would yield a ***consistent benefit*** in terms of functional outcome at 3 months post-stroke. Though the hypotheses differed for each part of the study, and separate groups of patients were enrolled into each part, the protocols and analyses used were identical for all patients enrolled into each part. For patients enrolled into part 2, their 24hr data was analyzed only after their 3-month data was analyzed, to avoid premature data extrapolation.

Inclusion criteria included 1) a clearly defined onset of stroke, 2) a measurable deficit on the NIHSS, and 3) a baseline CTH without evidence for an ICH. Patients were excluded from randomization using our typical t-PA exclusion criteria, as below[1]. An SBP of >185mmHg or a DBP of >110mmHg required treatment before t-PA could be given. Overall, with this criteria, 624 patients were randomized to receive either IV t-PA (0.9mg/kg) or placebo. Statistically, in part 1, the proportions of patients achieving the primary efficacy outcome of early improvement at 24hrs was compared between the treatment groups using a proportional analysis. Data was individually analyzed in those who obtained t-PA vs. placebo within 90min or within 91-180min of symptom onset. In part 2, the primary efficacy outcome of minimal no deficit at 3 months was assessed via scores on the Barthel Index, MRS, GCS, and the NIHSS. A favorable outcome was collectively defined as a score of 95-100 on the Barthel, <1 on the NIHSS and MRS, and 1 on the GCS. Statistically, rates of a favorable outcome were compared between the treatment groups using a global test statistic, yielding an odds ratio for the favorable outcome. Safety outcomes included 3-month mortality, symptomatic ICH, systemic bleeding, and new strokes.

Results: In Part 1, there were no differences in terms of early (24hrs) improvement between the 2 treatment groups, regardless of when t-PA was given (e.g., 90 vs. 180min). 47% of the t-PA and 39% of placebo group achieved early improvement (**Table 3**). Notably, when the 24hr data from patients enrolled into part 2 of the study (analyzed post-hoc as a secondary analysis) was combined with that of part 1 patients, it appeared as though t-PA did yield a higher proportion of patients with early improvement vs. placebo. More noteworthy, however, was data from part 2, in which t-PA yielded a significantly higher proportion of patients with a favorable outcome at 3 months post treatment vs. placebo (**Table 4 and Figure 2**). The OR for a favorable outcome was 1.7 in the t-PA group (p = 0.008).

[1] Prior stroke or head trauma w/in the preceding 3 months, major surgery within 14d, prior h/o intracranial hemorrhage, rapidly improving or minor symptoms, evidence for subarachnoid hemorrhage, GI or GU hemorrhage w/in preceding 21d, arterial puncture at a non-compressible site w/in preceding 7s, seizure at stroke onset, full dose A/C or heparin w/in preceding 48hrs, elevated PTT, PT>15s, platelet < 100, glucose < 50 or > 400.

When this 3-month data was also analyzed in part 1 patients (considered as a secondary analysis), the results were the same. Notably, the positive effects of t-PA were relevant to all stroke subtypes/etiologies identified (**Table 5**). Finally, regarding safety outcomes, there were no group differences in terms of mortality at 3 months (17% for t-PA vs. 21% placebo), but symptomatic ICH was more common and with statistical significance in the t-PA vs. placebo group (~6% vs. 1%, $p < 0.001$). The other safety outcomes analyzed were similar between t-PA and placebo groups, in both parts 1 and 2.

Conclusions: In conclusion, this study was the first to definitively show that appropriate use of IV t-PA for AIS, when initiated within 3hrs of symptom onset, improves functional outcomes at 3 months post-treatment. By using 4 different scales of global and functional outcome, the study authors identified the true, long-term benefit of t-PA, given that a favorable outcome necessitated high scores on all 4 tests. Other smaller and larger scale t-PA studies conducted prior to this study did not show a benefit of t-PA and/or showed excess harm of t-PA, though the dosing regimens and time to treatment were variable then as opposed to this study. Despite the noted increase in ICH risk with t-PA in this study (reported as the 6% as used today), the ICH risk was much lower than that previously reported, owing to proper t-PA dosing, timing of t-PA use, and stricter control of blood pressure parameters here. Essentially, this study created the guidelines that we now follow for appropriate IV t-PA use. Later, the time window for TPA was extended to 4.5hrs after stroke onset, via the ECASS trial in 2008.

Associated reading, if interested:

Hacke, Werner et. al., Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke, NEJM. 2008 Sept 25; 359 (13): 1317-29.

Summary created by Elaine Sinclair, D.O.