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Adjunctive medical therapies for acute stroke thrombolysis – is there a **CLEAR-ER** choice?

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Beyond intravenous tissue plasminogen activator (IV-tPA), the field of acute ischemic stroke suffers from a lack of safe and effective treatments aimed at both proximal thrombus dissolution and return of flow to the microcirculation. Larger thrombi have notoriously proven to be resistant to IV-tPA lysis with recanalization rates in the range of only 13–20%.^{1, 2} Even if endovascular treatment of ischemic stroke is proven to improve clinical outcomes, there will still be many patients with residual partial or complete occlusion after IV-tPA alone suffering ischemia while waiting for catheter rescue. The lag between endovascular team activation and groin puncture requires precious minutes-to-hours for team assembly. For example, in the IMS-3 clinical trial, the average time from tPA bolus to IA therapy was 2.2 hours.³

Therefore, development of combination therapies for acute ischemic stroke that can be delivered quickly in the emergency setting is crucial. Adjunctive therapies to IV-tPA can take many forms to include medical or mechanical, but any of these must be started early in order to augment the effect of IV-tPA.⁴ Ongoing strategies which are in either Phase II or III clinical trials include thrombin-inhibition, sonothrombolysis and platelet-inhibition.

In the _____ issue of *Stroke*, the results of the CLEAR-ER study (Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke - Enhanced Regimen) are published.⁵ This is a multicenter, double-blind, randomized phase II safety trial of 0.9mg/kg 0–3 hours IV-tPA versus 0.6mg/kg 0–3 hours IV-tPA + intravenous eptifibatide (bolus 135mcg/kg and 2-hour infusion at 0.75mcg/kg/min). CLEAR-ER sought to estimate the safety and efficacy of combination GP IIb/IIIa + reduced dose IV-tPA when delivered to hyperacute ischemic stroke. The trial was sponsored by the NIH/NINDS and enrolled 126 patients.

This study is important for many reasons. First, it builds on the data already known with regards to safety of combination therapy with tPA and GP IIb/IIIa inhibitors. The same group performed a similar safety study with lower doses of IV-tPA (0.3 and 0.45mg/kg) that was halted as no signal of increased intracranial hemorrhage could be identified after enrolling 94 patients.⁶ The CLEAR-ER study also demonstrates that emergent adjunctive therapies are feasible within the first few hours of stroke onset and need to be further pursued as a means to amplify the thrombolysis effect of IV-tPA.

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Conflicts of Interest/Disclosures:

None

CLEAR-ER randomized 5:1 into combination (n=101) and tPA alone (n=25) arms. Patients received their tPA bolus at an approximate median of 2 hours from symptom onset. Eptifibatide was bolused at a median of 40 minutes after tPA and continued for 2 hours. The median baseline NIHSS scores were lower in the combination group compared with the tPA alone group (12 vs. 17), but this was not statistically significant. Vessel imaging (CT or MR-angiogram or transcranial Doppler ultrasound) was not mandated by the protocol before or after treatment. The rate of symptomatic intracranial hemorrhage (sICH) was low in the combination group (2%) and unusually high in the tPA-alone group (12%). Further, the rate of PH-2 was also low in the combination group (1%). Other safety outcomes such as serious adverse events and death did not indicate any increased risk of combination therapy.

Efficacy estimates demonstrated higher rates of good clinical outcome (defined as mRS of 1 or return to baseline mRS) in the combination group versus tPA alone (49.5% versus 36%; OR 1.74 0.7–4.31, $p=0.23$). However, after controlling for baseline NIHSS, age and time to tPA treatment, the OR was blunted to 1.37 0.51–3.71, $p=0.53$). Caution must be exercised with regards to efficacy interpretation since the study was designed for testing safety of combination treatment. Nevertheless, the results should be used for hypothesis generation and suggest that the combination treatment warrants further investigation.

Strengths

The authors designed the study to employ a unique three month primary efficacy outcome: mRS 1 or return to baseline mRS. As a result, patients with pre-stroke disability were still eligible for enrollment. Determining the validity and timing of the baseline mRS probably warrants further study. Nevertheless, this method of outcome assessment is appealing, particularly if exception from informed consent (EFIC) were to be accepted by IRBs and the FDA for AIS stroke clinical trials. Then, stroke patients who are unable to provide traditional informed consent (e.g., due to aphasia or neglect) could be enrolled regardless of their baseline mRS.

Limitations

Despite the suggestion that more patients might have reached a good clinical outcome at 90 days, enthusiasm might be tempered due to the random allocation methods employed. First, having such a small number of control patients increases the chances of imbalance between groups, and in fact this is suggested by the higher baseline NIHSS score and very high rate of sICH in the control group. Also, although unequal allocation (5:1 in this trial) provides more safety information for the medication combination, it results in less power to detect differences compared with equal allocation.⁷ If the true proportions of good clinical outcome are indeed 49.5% in combination therapy and 36% in tPA alone, then utilizing 1:1 allocation (assuming 2-sided test and alpha of 0.05) would have increased the power by 70% (16% to 27%) and the unadjusted OR and 95% CI would have increased/narrowed to 1.8, 0.88–3.66, $p=0.13$ from 1.74, 0.7–4.31, $p=0.23$.

The authors admit that the tPA and eptifibatide dosing were chosen based upon data gathered from an *in vitro* clot model rather than stroke animal recanalization models or pilot data in stroke patients such as pre- and post-treatment CT-Angiograms. Therefore, one is still left with the question as to whether eptifibatide + full dose tPA (0.9mg/kg), the current standard of care for AIS, would also be safe and result in even greater rates of good clinical outcome. Early vascular recanalization with resultant rapid neurological recovery is a surrogate measure that can support the efficacy of thrombolysis and have been employed in other randomized Phase II trials.⁸ Despite a lack of recanalization data from the trial, the

percentage of NIHSS ≥ 5 at 2 hours was greater in the combination versus tPA alone arm (34.6% versus 24%, $p=0.31$).

Implications for future study design

Even if the study had used equal allocation the resulting p-value would still be deemed non-significant and more importantly would not address the question of interest to clinicians: given the observed data what is the probability that combination treatment is better than tPA alone? A Bayesian approach addresses this question by providing the likelihood of clinically relevant treatment effects, which cannot be obtained from conventional frequentist analyses.^{9, 10} A Bayesian analysis formally combines prior evidence with current evidence to update the likelihood of treatment benefit and/or harm. This updated likelihood is referred to as the posterior probability and is used to assess the strength of the evidence.^{10, 11} Using a prior probability that assumes no difference between combination therapy and tPA (OR=1; 95% credible interval: 0.14–6.0; dotted line on Figure using log OR scale), an unadjusted Bayesian analysis of the CLEAR-ER 90-day clinical outcomes results in a more conservative estimate of OR=1.6, but narrower 95% CI 0.70–3.3 (solid line on Figure), and an 84% posterior probability (area under the curve to the right of zero on Figure) that combination therapy is better than tPA alone (OR>1). Used in conjunction with any evidence (or lack) of harm, this information could guide researchers and clinicians on the future study and/or use of combination therapy.

Conclusion

We remain optimistic that combination medical therapies for acute ischemic thrombolysis represent a shift in future treatment paradigms. Due to the many promising cocktails of tPA-plus strategies, it seems logical that an adaptive, randomized trial which “drops the loser/ plays the winner” and employs more intuitive analyses might provide answers more rapidly with fewer required patients.

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Figure 1.

Prior and posterior probabilities of the log OR of combination therapy vs tPA alone. The prior probability assumes no difference between the two treatments with probability of $OR > 1$ of 50%. The posterior probability is a combination of the prior and the data from the CLEAR-ER study. Area under the curve to the right of zero corresponds to the probability of combination therapy being better than tPA alone.