Published in final edited form as:
J Stroke Cerebrovasc Dis. 2014 ; 23(5): e313–e315. doi:10.1016/j.jstrokecerebrovasdis.2013.12.012.

A matched comparison of eptifibatide plus rt-PA versus rt-PA alone in acute ischemic stroke

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Abstract

Background—The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke-Enhanced Regimen (CLEAR-ER) trial found that IV rt-PA plus eptifibatide (combination arm) in acute ischemic stroke (AIS) was safe, and had a direction of effect that would justify a phase III trial. CLEAR-ER had unanticipated imbalances between treatment groups. We compared the rates of sICH and good outcomes for combination therapy patients in the CLEAR-ER trial to a matched cohort of rt-PA patients from the NINDS trial.

Methods—CLEAR-ER was a multi-center, double-blind, randomized study. rt-PA eligible AIS patients were randomized to 0.6mg/kg rt-PA plus eptifibatide (135mcg/kg bolus and 0.75mcg/kg/min two-hour infusion) versus standard rt-PA (0.9mg/kg). For this analysis, we matched 1:1 CLEAR-ER combination therapy patients with rt-PA arm NINDS trial patients.

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Conflicts-of-Interest/Disclosures
Arthur M. Pancioli MD – study drugs provided by Merck and Genentech for the CLEAR-ER trial
Opeolu Adeoye MD MS – none
Pamela A. Schmit RN BSN – none
Jane Khoury PhD – none
Heidi Sucharew PhD – none
William A. Knight MD - Genentech, Speaker's Bureau; Roche - Advisory Board
Joseph P. Broderick MD - Principal Investigator of NINDS-funded IMS III Trial, UC SPOTRIAS Center (includes NINDS-funded CLEARER and STOP-IT Clinical Trials) Genentech Inc. (Supplier of alteplase for NINDS-funded CLEARER, IMS III trials)

Patients were matched by age, gender, race, baseline modified Rankin Score, baseline NIH stroke scale score, and stroke onset to rt-PA time.

Results—Fifty four matches were made. One (1.8%) sICH occurred in each group (odds ratio 1.00, 95%CI 0.01–78.50). At 90 days, 51.8% of the CLEAR-ER group had good outcomes versus 46.3% in the NINDS rt-PA group (odds ratio 1.30, 95%CI 0.57–2.96). For subjects with baseline NIHSSS>12 (CLEAR-ER median NIHSSS), 38.5% of the CLEAR-ER group had good outcomes versus 23.1% in the NINDS group (odds ratio 2.33, 95%CI 0.60–9.02).

Conclusion—The safety and direction of effect of eptifibatide plus rt-PA was confirmed. A phase III trial is needed to determine the efficacy of eptifibatide plus rt-PA for improving long-term outcomes after AIS.

Keywords

ischemic stroke; tissue plasminogen activator; eptifibatide; clinical trial

Introduction

Recombinant tissue plasminogen activator (rt-PA) administered within hours of symptom onset remains the only proven therapy for improving outcomes after acute ischemic stroke (AIS). In the randomized Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke - Enhanced Regimen (CLEAR-ER) stroke trial,(1) we found that the combination of rt-PA with eptifibatide, a platelet glycoprotein IIb/IIIa inhibitor, was safe and had a direction of effect that justifies moving forward with a phase III trial to determine the efficacy of the combination for improving outcomes after AIS. However, there were imbalances in age, stroke severity and baseline disability in favor of the combination therapy group compared with the rt-PA group in CLEAR-ER trial. In this report, we matched a cohort of CLEAR-ER patients with patients in the original NINDS stroke trial(2) to compare symptomatic intracranial hemorrhage (sICH) rates and the proportions of good outcome.

Methods

This was a secondary post-hoc analysis of data from two previously published randomized clinical trials. Briefly, the NINDS trial was a multicenter double-blind randomized clinical trial of rt-PA (n=312) versus placebo (n=312) in AIS patients.(2) The CLEAR-ER trial was a multi-center, double-blind, randomized safety study. Ischemic stroke patients were randomized to 0.6mg/kg rt-PA plus eptifibatide (135mcg/kg bolus and a two-hour infusion at 0.75mcg/kg/min) (combination arm, n=101) versus standard rt-PA (0.9mg/kg) (n=25).(1) In both trials, rt-PA was administered within 3 hours of symptom onset.

For this analysis, we matched combination arm CLEAR-ER patients to rt-PA arm patients in the NINDS trial. The NINDS dataset was initially restricted to subjects with baseline NIH stroke scale score >5. The “greedy” matching algorithm was then used to match 1:1 by: gender (exact match), race/ethnicity (exact match), baseline modified Rankin score (mRS) (exact match), age (± 6 years), baseline NIH stroke scale score (± 4), and stoke onset to rt-PA minutes (± 30 minutes).

The primary safety endpoint was the incidence of sICH within 36 hours. The primary efficacy outcome measure was the mRS score ≤1 OR return to baseline mRS at 90 days. Analysis of the safety and efficacy outcome variables was done with multiple logistic regression. When low frequency of outcome was encountered (≤5), an exact logistic regression was used.

Results

All 101 combination therapy patients in the CLEAR-ER trial had baseline NIH stroke scale score >5 versus 269/312 in rt-PA arm of the NINDS trial. Of these, 54 matches were made. Characteristics of the matched patients are presented in Table 1. Stroke onset to IV rt-PA time was longer in the CLEAR-ER combination patients compared with the rt-PA NINDS patients (116 vs. 111 minutes, P=0.002). Safety and outcome data are presented in Table 2. One sICH occurred in each group within 36 hours. At 90 days, 52% of patients in the CLEAR-ER combination group had an mRS of 0 or 1 or a return to baseline compared with 46% of NINDS rt-PA patients (OR, 95% CI 1.30, 0.57–2.96).

Outcome was also assessed with stratification by NIH stroke scale score <12 or ≥12 (the median NIH stroke scale in the CLEAR-ER trial). In patients with NIH stroke scale <12, 64% of the combination group versus 68% of the rt-PA group had mRS 0 or 1 or return to baseline at 90 days (OR 0.86, 0.29–2.55). In patients with NIH stroke scale ≥12, 38% of the combination group had mRS 0 or 1 or return to baseline at 90 days versus 23% of the rt-PA group (OR 2.33, 0.60–9.02).

Discussion

In this matched comparison, we confirmed a direction of effect on good outcomes that was in favor of rt-PA plus eptifibatide over rt-PA alone in AIS patients. While the observed effect was not statistically significant and the study was underpowered to detect differences in efficacy, the six percent difference in proportion of good outcome suggests a clinically meaningful benefit may be observed in a well-designed, adequately powered phase III trial. We also observed identical sICH rates and no difference in mortality at 90 days. Overall, these findings are congruent with the previously published findings from the CLEAR-ER trial.(1)

We found that the direction of effect was stronger in patients with higher NIH stroke scale scores. The non-significant increased odds of good outcome was primarily mediated by treatment effect in patients with NIH stroke scale score ≥12. In acute myocardial infarction, adding glycoprotein IIb/IIIa antagonists to fibrinolytic regimens increases the speed of arterial recanalization and the percentage of patients with open arteries.(3) Patients with higher stroke scale scores are most likely to have a large vessel occlusion(4) and as such likely to gain the most should the vessel recanalize. Unfortunately, since vascular imaging was not required for either trial, we do not know if the observed effect was due to improved recanalization rates in the CLEAR-ER patients compared with the NINDS patients.

We acknowledge the limitation of historical comparisons. Functional outcomes of IV rt-PA patients in contemporaneous clinical trials have not been different from that observed in the

NINDS trial.(5, 6) We did randomize patients to rt-PA only in the CLEAR-ER trial but imbalances occurred despite adaptive randomization.(1) In this post hoc analysis, the goal was to conduct comparisons between treatment groups after minimizing imbalances. As such, we identified a group of patients from the NINDS trial who were similar to the combination group in CLEAR-ER. The similarity of findings in this analysis to the original results from the CLEAR-ER trial reinforce the need for a phase III trial to determine the efficacy of eptifibatide plus rt-PA for improving long-term outcomes after AIS.

Acknowledgments

Funding Source

NIH/NINDS P50 NS044283

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Table 1

Patient Characteristics

	CLEAR-ER rt-PA + Eptifibatide (n=54)	**NINDS rt-PA only (n=54)**	**p-value**
Age, mean (SD)	68.3 (11.8)	67.8 (11.1)	0.19
Female, n (%)	25 (46.3%)	25 (46.3%)	--
Black, n (%)	9 (16.7%)	9 (16.7%)	--
Baseline NIHSSS, mean (SD)	13.7 (6.6)	13.9 (6.5)	0.41
Baseline mRS 0, n (%)	52 (96.3%)	52 (96.3%)	--
Stroke onset to IV rt-PA (min), mean (SD)	116 (29)	111 (30)	0.002

Table 2

Safety and 90-day efficacy outcomes

	CLEAR-ER rt-PA + Eptifibatide (n=54)	**NINDS rt-PA only (n=54)**	**Odds ratio (95% CI)**
Safety			
sICH in 36 hours, n (%)	1 (1.8%)	1 (1.8%)	1.00 (0.01, 78.50)*
90-day efficacy			
mRS 0–1 or return to baseline, n (%)	28 (51.8%)	25 (46.3%)	1.30 (0.57, 2.96)
mRS 0–1, n (%)	28 (51.8%)	24 (44.4%)	1.44 (0.62, 3.38)
Barthel Index ≥ 95, n (%)	34 (63.0%)	30 (55.6%)	1.50 (0.61, 3.67)
Glasgow Outcome Score=1, n(%)	32 (59.3%)	27 (50.0%)	1.62 (0.67, 3.92)
Survival, n (%)	46 (85.2%)	46 (85.2%)	1.00 (0.32, 3.10)

* conditional exact logistic and CI