

AcT: Intravenous Tenecteplase Compared to Alteplase for Acute Ischaemic Stroke in Canada

The Alteplase compared to Tenecteplase (AcT) study was a multicenter randomized controlled trial¹ conducted in 22 primary and comprehensive stroke center hospitals across Canada. Findings from AcT are likely currently under review by the United States Food & Drug Administration (US-FDA), although presently it remains unknown whether study findings will change the American drug regulatory label for Tenecteplase (TNK). In this article, we detail the trial's design and important clinical findings.

The AcT study enrolled ischemic stroke patients that were at least 18 years in age and presented with disabling deficits within 4.5 hours of symptom onset. Patients had to meet current Canadian guideline criteria for thrombolysis; additionally, patients eligible for mechanical thrombectomy were eligible for enrollment in the study.¹ Once enrolled, patients were randomly assigned 1:1 by computer algorithm to receive either alteplase (0.9 mg/kg to a maximum of 90 mg [10% bolus; remaining 90% delivered over 60 minutes]) or TNK (0.25 mg/kg to a maximum of 25 mg).

The primary endpoint of the clinical trial was the proportion of patients that achieved a modified Rankin Scale (mRS) score of 0 or 1 at between 90 to 120 days after treatment.¹ Secondary endpoints examined mRS 0-2, differences on the EuroQol visual analog scale (EQ-VAS), return to baseline function, extended Thrombolysis in Cerebral Infarction (eTICI) recanalization score in

patients receiving thrombectomy, door to needle time, and numerous other outcomes; because the focus of this article is on the primary outcome (mRS 0-1), results of these additional secondary endpoint analyses are not detailed in this review. An intention-to-treat approach was utilized for the presentation of the definitive results, whereby all patients randomized that did not withdraw consent, were analyzed and reported even if they subsequently never received thrombolysis.

The AcT study was designed to determine whether TNK was non-inferior to alteplase. Non-inferiority trials aim to determine if a new treatment is capable of achieving similar outcomes to a gold standard treatment. These types of clinical trials set a non-inferiority margin; if results are better than this set threshold, the new treatment is deemed “non-inferior” to the gold standard. There is no set standard for what constitutes an acceptable non-inferiority margin, and because of this, margins vary substantially between trials. The larger the margin, the easier it is for the new treatment to be found non-inferior to the gold standard, whereas the smaller the margin, the more rigorous the non-inferiority standard. In considering acceptance of non-inferiority clinical trial results, reviewers should think about whether findings meet clinical acceptability. For example, a 20% inferiority margin would mean that the new treatment would be considered acceptable, even though 20% of subjects did not achieve the targeted outcome. In AcT, investigators set a 5% non-inferiority margin, meaning that



Stroke Clinician Research Corner

TNK would be considered non-inferior if the difference in mRS 0-1 endpoint attainment exceeded 5%.¹

Investigators also assessed safety differences between the TNK and alteplase groups. Symptomatic intracerebral hemorrhage (sICH) occurring within 24 hours of treatment was measured; sICH was defined in the trial as any intracerebral hemorrhage temporally related to treatment and directly responsible for worsening of neurologic status, that in the opinion of the local investigator was the most important factor causing neurological worsening. All cause death occurring after treatment was also measured.¹

All study hospitals were participants in stroke quality registries, namely the Quality Improvement and Clinical Research (QuiCR) registry, or the Optimizing Patient Treatment in Major Ischemic Stroke with EVT (OPTIMISE) registry. Data entry into these registries was overseen to ensure completeness, and both baseline patient characteristics and workflow process data were integrated into the trial database.¹

The trial was open-label, meaning that clinicians managing enrolled patients knew which drug was given to each of their subjects. Because of this knowledge, the mRS study endpoint was measured over telephone by an assessor blinded to treatment group at between 90 and 120 days from the date of enrollment.

AcT enrolled a total of 1600 patients between December 2019 and January 2022. Of these, 23 patients withdrew consent from the study so that 1577 patients were ultimately analyzed with 806 (51%) that received TNK and 771 (49%) that received alteplase. Baseline characteristics and workflow

processes were similar between groups, with the overall median age 74 (IQR 63-83) years, and 52.1% were male. Investigators reported that only 10 (0.6%) patients were lost to follow-up, reflecting excellent study quality.

Median time to measurement of the mRS 0-1 primary endpoint was 97 (IQR 91-111) days and did not differ between groups. A total of 296 out of 802 (36.9%) patients in the TNK group achieved an mRS 0-1, compared to 266 out of 765 (34.8%) patients in the alteplase group; the unadjusted risk difference was 2.1% (95% CI: -2.6 to 6.9). Since the lower bound 95% CI was -2.6% and greater than the threshold -5%, TNK was found to be non-inferior to alteplase. Further analyses showed that while TNK was non-inferior to alteplase, it was not found to be significantly superior to alteplase. Overall, there were no significant differences in sICH or any type of intracranial hemorrhage. Death within 90-days was also similar between the TNK and alteplase groups, and other adverse events (peripheral bleeding and orolingual angioedema) were rare in both groups.

While it remains unknown whether the US-FDA will change the regulatory label for TNK to include acute ischemic stroke treatment up to 4.5 hours from symptom onset, many other countries have already taken this step. Use of TNK offers the significant advantage of single bolus treatment due to its longer half-life, and some have suggested that there may be a cost advantage in hospitals that lack large buyer purchase agreements. Regardless of US-FDA regulatory approval, TNK is likely here to stay in the treatment of acute ischemic stroke, and the findings of this important clinical trial should help to reduce any remaining angst related to TNK adoption.



References

1. Menon BK, Buck BH, Singh N, et al.; AcT Trial Investigators. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *Lancet*. 2022 Jul 16;400(10347):161-169. doi: 10.1016/S0140-6736(22)01054-6. Epub 2022 Jun 29. PMID: 35779553.

