The Shifting Landscape of Thrombolytic Therapy for Acute Ischemic Stroke

Menon BJ, Buck BH, Singh N, et al. 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;400(10347):161-169. doi:10.1016/S0140-6736(22)01054-6

Wang Y, Li S, Pan Y, et al. Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial. Lancet. 2023;401(10377):645-654. doi:10.1016/S0140-6736(22)02600-9

Study 1 Overview (Menon et al)

Objective: To determine whether a 0.25 mg/kg dose of intravenous tenecteplase is noninferior to intravenous alteplase 0.9 mg/kg for patients with acute ischemic stroke eligible for thrombolytic therapy.

Design: Multicenter, parallel-group, open-label randomized controlled trial.

Setting and participants: The trial was conducted at 22 primary and comprehensive stroke centers across Canada. A *primary stroke center* was defined as a hospital capable of offering intravenous thrombolysis to patients with acute ischemic stroke, while a *comprehensive stroke center* was able to offer thrombectomy services in addition. The involved centers also participated in Canadian quality improvement registries (either Quality Improvement and Clinical Research [QuiCR] or Optimizing Patient Treatment in Major Ischemic Stroke with EVT [OPTIMISE]) that track patient outcomes. Patients were eligible for inclusion if they were aged 18 years or older, had a diagnosis of acute ischemic stroke, presented within 4.5 hours of symptom onset, and were eligible for thrombolysis according to Canadian guidelines.

Patients were randomized in a 1:1 fashion to either intravenous tenecteplase (0.25 mg/kg single dose, maximum of 25 mg) or intravenous alteplase (0.9 mg/kg total dose to a maximum of 90 mg, delivered as a bolus followed by a continuous infusion). A total of 1600 patients were enrolled, with 816 randomly assigned to the tenecteplase arm and 784 to the alteplase arm; 1577 patients were included in the intention-to-treat (ITT) analysis (n = 806 tenecteplase; n = 771 alteplase). The median age of enrollees was 74 years, and 52.1% of the ITT population were men.

Main outcome measures: In the ITT population, the primary outcome measure was a modified Rankin score (mRS) of 0 or 1 at 90 to 120 days post treatment. Safety outcomes included symptomatic intracerebral hemorrhage, orolingual angioedema, extracranial bleeding that required blood transfusion (all within 24 hours of thrombolytic administration), and all-cause mortality at 90 days. The noninferiority threshold for intravenous tenecteplase was set as the lower 95% CI of the difference between the tenecteplase and alteplase groups in the proportion of patients who met the primary outcome exceeding –5%.

Main results: The primary outcome of mRS of either 0 or 1 at 90 to 120 days of treatment occurred in 296 (36.9%) of the 802 patients assigned to tenecteplase and 266 (34.8%) of the 765 patients assigned to alteplase (unadjusted risk difference, 2.1%; 95% CI, –2.6 to 6.9). The prespecified noninferiority threshold was met. There were no significant

differences between the groups in rates of intracerebral hemorrhage at 24 hours or 90-day all-cause mortality.

Conclusion: Intravenous tenecteplase is a reasonable alternative to alteplase for patients eligible for thrombolytic therapy.

Study 2 Overview (Wang et al)

Objective: To determine whether tenecteplase (dose 0.25 mg/kg) is noninferior to alteplase in patients with acute ischemic stroke who are within 4.5 hours of symptom onset and eligible for thrombolytic therapy but either refused or were ineligible for endovascular thrombectomy.

Design: Multicenter, prospective, open-label, randomized, controlled noninferiority trial.

Setting and participants: This trial was conducted at 53 centers across China and included patients 18 years of age or older who were within 4.5 hours of symptom onset and were thrombolytic eligible, had a mRS ≤ 1 at enrollment, and had a National Institutes of Health Stroke Scale score between 5 and 25. Eligible participants were randomized 1:1 to either tenecteplase 0.25 mg/kg (maximum dose 25 mg) or alteplase 0.9 mg/kg (maximum dose 90 mg, administered as a bolus followed by infusion). During the enrollment period (June 12, 2021, to May 29, 2022), a total of 1430 participants were enrolled, and, of those, 716 were randomly assigned to tenecteplase and 714 to alteplase. Six patients assigned to tenecteplase and 7 assigned to alteplase did not receive drugs. At 90 days, 5 in the tenecteplase group and 11 in the alteplase group were lost to follow up.

Main outcome measures: The primary efficacy outcome was a mRS of 0 or 1 at 90 days. The primary safety outcome was intracranial hemorrhage within 36 hours. Safety outcomes included parenchymal hematoma 2, as defined by the European Cooperative Acute Stroke Study III; any intracranial or significant hemorrhage, as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria; and death from all causes at 90 days. Noninferiority for tenecteplase would be declared if the lower 97.5% 1-sided CI for the relative risk (RR) for the primary outcome did not cross 0.937.

Main results: In the modified ITT population, the primary outcome occurred in 439 (62%) of the tenecteplase group and 405 (68%) of the alteplase group (RR, 1.07; 95% CI, 0.98-1.16). This met the prespecified margin for noninferiority. Intracranial hemorrhage within 36 hours was experienced by 15 (2%) patients in the tenecteplase group and 13 (2%) in the alteplase group (RR, 1.18; 95% CI, 0.56-2.50). Death at 90 days occurred in 46 (7%) patients in the tenecteplase group and 35 (5%) in the alteplase group (RR, 1.31; 95% CI, 0.86-2.01).

Conclusion: Tenecteplase was noninferior to alteplase in patients with acute ischemic stroke who met criteria for thrombolysis and either refused or were ineligible for endovascular thrombectomy.

Commentary

Alteplase has been FDA-approved for managing acute ischemic stroke since 1996 and has demonstrated positive effects on functional outcomes. Drawbacks of alteplase therapy, however, include bleeding risk as well as cumbersome administration of a bolus dose followed by a 60-minute infusion. In recent years, the question of whether or not tenecteplase could replace alteplase as the preferred thrombolytic for acute ischemic stroke has garnered much attention. Several features of tenecteplase make it an attractive option, including increased fibrin specificity, a longer half-life, and ease of administration as a single, rapid bolus dose. In phase 2 trials that compared tenecteplase 0.25 mg/kg with alteplase, findings suggested the potential for early neurological improvement as well as improved outcomes at 90 days. While the role of tenecteplase in acute myocardial infarction has been well established due to ease of use and a favorable adverse-effect profile,[1] there is much less evidence from phase 3 randomized controlled clinical trials to secure the role of tenecteplase in acute ischemic stroke.[2]

Menon et al attempted to close this gap in the literature by conducting a randomized controlled clinical trial (AcT) comparing tenecteplase to alteplase in a Canadian patient population. The trial's patient population mirrors that of real-world data from global registries in terms of age, sex, and baseline stroke severity. In addition, the eligibility window of 4.5 hours from symptom onset as well as the inclusion and exclusion criteria for therapy are common to those utilized in other countries, making the findings generalizable. There were some limitations to the study, however,

including the impact of COVID-19 on recruitment efforts as well as limitations of research infrastructure and staffing, which may have limited enrollment efforts at primary stroke centers. Nonetheless, the authors concluded that their results provide evidence that tenecteplase is comparable to alteplase, with similar functional and safety outcomes.

TRACE-2 focused on an Asian patient population and provided follow up to the dose-ranging TRACE-1 phase 2 trial. TRACE-1 showed that tenecteplase 0.25 mg/kg had a similar safety profile to alteplase 0.9 mg/kg in Chinese patients presenting with acute ischemic stroke. TRACE-2 sought to establish noninferiority of tenecteplase and excluded patients who were ineligible for or refused thrombectomy. Interestingly, the tenecteplase arm, as the authors point out, had numerically greater mortality as well as intracranial hemorrhage, but these differences were not statistically significant between the treatment groups at 90 days. The TRACE-2 results parallel those of AcT, and although there were differences in ethnicity between the 2 trials, the authors cite this as evidence that the results are consistent and provide evidence for the role of tenecteplase in the management of acute ischemic stroke. Limitations of this trial include potential bias from its open-label design, as well as exclusion of patients with more severe strokes eligible for thrombectomy, which may limit generalizability to patients with more disabling strokes who could have a higher risk of intracranial hemorrhage.

Application for Clinical Practice and System Implementation

Across the country, many organizations have adopted the off-label use of tenecteplase for managing fibrinolytic-eligible acute ischemic stroke patients. In most cases, the impetus for change is the ease of dosing and administration of tenecteplase compared to alteplase, while the inclusion and exclusion criteria and overall management remain the same. Timely administration of therapy in stroke is critical. This, along with other time constraints in stroke workflows, the weight-based calculation of alteplase doses, and alteplase's administration method may lead to medication errors when using this agent to treat patients with acute stroke. The rapid, single-dose administration of tenecteplase removes many barriers that hospitals face when patients may need to be treated and then transferred to another site for further care. Without the worry to "drip and ship," the completion of administration may allow for timely patient transfer and eliminate the need for monitoring of an infusion during transfer. For some organizations, there may be a potential for drug cost-savings as well as improved metrics, such as door-to-needle time, but the overall effects of switching from alteplase to tenecteplase remain to be seen. Currently, tenecteplase is included in stroke guidelines as a "reasonable choice," though with a low level of evidence.[3] However, these 2 studies support the role of tenecteplase in acute ischemic stroke treatment and may provide a foundation for further studies to establish the role of tenecteplase in the acute ischemic stroke population.

Practice Points

- Tenecteplase may be considered as an alternative to alteplase for acute ischemic stroke for patients who meet eligibility criteria for thrombolytics; this recommendation is included in the most recent stroke guidelines, although tenecteplase has not been demonstrated to be superior to alteplase.
- The ease of administration of tenecteplase as a single intravenous bolus dose represents a benefit compared to alteplase; it is an off-label use, however, and further studies are needed to establish the superiority of tenecteplase in terms of functional and safety outcomes.

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