Tenecteplase for Thrombectomy Thrombolysis

Every year an estimated 800 000 Americans suffer a stroke.1 Despite only accounting for an estimated 13% of these strokes, large vessel occlusions (LVOs) are responsible for the majority of stroke-related disability.2 Following the major stroke trials in 2015, mechanical thrombectomy with optimal medical management became the standard care for LVO strokes.3-6 While the procedural aspect of stroke treatment has rapidly progressed in the past decade, advancements in medical thrombolytics have been rather stagnant since the introduction of Alteplase (tissue plasminogen activator, tPA) in 1995.7 Tenecteplase is a genetically modified analog of Alteplase with higher fibrin binding specificity and a long half-life. While Alteplase is often given as a 1-h infusion, the pharmacology of Tenecteplase enables bolus administration. There has been growing evidence that Tenecteplase may be more effective than Alteplase with similar safety profiles.8,9

In the noninferiority study, “Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke” or EXTEND-IA TNK trial,” Campbell et al10 compared the reperfusion success of either Tenecteplase or Alteplase in patients suffering an LVO stroke. Patients from 13 medical centers in Australia and New Zealand, suffering from a LVO stroke located in the internal carotid artery, middle cerebral artery (M1 or M2), and basilar artery were studied. Patients were eligible for enrollment if they had prestroke functional independence and mechanical thrombectomy could be started within 6 h of symptom onset. Similar to the DAWN trial, inclusion criteria initially contained a perfusion-mismatch cutoff; however, this was removed following the release of pooled data from other trials that demonstrated benefit in patients with large ischemic cores.11 The primary outcome was restoration of at least 50% of the vascular territory or absence of thrombus on initial angiographic assessment. Secondary outcomes included 90-d functional status measured by the mRS score, early neurological improvement defined as an 8-point decrease on the NIHSS within 72 h, and hemorrhagic complications.

A total of 202 patients were enrolled. Following randomization and stratification by occlusion location, 101 received Alteplase and 101 received Tenecteplase prior to thrombectomy. Baseline characteristics between the 2 groups were similar. At initial angiographic assessment prior to thrombectomy, a total of 22 patients treated with Tenecteplase (22%) and 10 patients treated with Alteplase (10%) demonstrated over 50% reperfusion or absence of occlusion. While the trial was not designed for superiority, Tenecteplase was superior to Alteplase for the primary outcome (OR 2.6, \(P = .02\)). Most patients who achieved reperfusion with Tenecteplase had an MCA occlusion (20 of 22). There was no difference in thrombectomy reperfusion success (mTICI 2b/3) between the 2 groups. When 90-d mRS score was analyzed as an ordinal variable, separate levels from 0 to 6, the Tenecteplase group had significantly better 90-d functionality (OR 1.7, \(P = .04\)). However, significance did not hold when mRS was analyzed as a dichotomous variable describing functional independence (mRS 0-2, \(P = .06\)). There was no difference in early neurological improvement between the 2 groups (\(P = .053\)). There were more deaths observed in the Alteplase group (18 vs 10), although, this was not significant. Both treatment groups had 1 incidence of symptomatic intracerebral hemorrhage.

The EXTEND-IA TNK trial is the second published trial from the Australian Stroke Trials Network that investigates Alteplase vs Tenecteplase. The first trial, published in 2012, demonstrated that Tenecteplase was superior to Alteplase in CT perfusion-selected patients with small infarct volumes.9 The EXTEND-IA TNK trial expanded on this by demonstrating that Tenecteplase was superior to Alteplase for patients suffering LVO strokes and eligible for mechanical thrombectomy. The third trial, Tenecteplase vs Alteplase for Stroke Thrombolysis Evaluation (TASTE), is currently enrolling and compares the 2 treatments in patients who are not eligible for stroke thrombectomy.

The EXTEND-IA TNK trial takes another step towards demonstrating that Tenecteplase may be the superior thrombolytic agent for stroke patients; however, the trial has some major limitations. The trial was designed as noninferiority. Additionally, since functional outcome scores depend largely on thrombectomy reperfusion success, investigators made the primary outcome thrombolytic reperfusion rather than 90-d mRS. Both decisions were prudent and systematic, although, they reduce the external validity of the trial. To elaborate, a primary outcome of at least 50% reperfusion prior to thrombectomy isn’t generalizable if a clinical benefit is not observed as well. The 90-d functional outcomes favored the Tenecteplase group (\(P = .06\)). Perhaps if the trial was designed and powered to the 90-d mRS outcome it may have reached statistical significance. The better 90-d functional outcomes seen in the Tenecteplase group, despite similar thrombectomy mTICI scores, suggests that Tenecteplase may further reduce post-thrombectomy distal embolization or clot fragmentation that isn’t detectable in angiographic imaging.

The practical advantages of Tenecteplase are its single bolus administration and low cost. As the authors discuss, many patients are transferred between hospitals prior to receiving a mechanical thrombectomy. In many instances this transfer is delayed because the patient must finish the Alteplase infusion. A decreased transfer
time would decrease time to reperfusion and ultimately improve clinical outcomes. Additionally, the cost of Tenecteplase is fractions of the cost of Alteplase, which may make thrombolytic stroke treatment more accessible.

Disclosure
The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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