EDITORIALS

Paving the Way for Improved Treatment of Acute Stroke with Tenecteplase

Alison E. Baird, M.B., B.S., Ph.D., M.P.H.

The treatment of acute ischemic stroke is changing rapidly. Three years ago, endovascular thrombectomy was added to thrombolysis with intravenous recombinant tissue plasminogen activator (alteplase) as a cornerstone of treatment of acute stroke. Currently, patients are treated with intravenous alteplase during the first 3 to 4.5 hours after stroke onset, and until recently, those with large-vessel occlusion were eligible to undergo thrombectomy within the first 6 hours. In the past few months, the benefits of thrombectomy have been shown to extend to 16 to 24 hours if there is remaining ischemic but not yet infarcted tissue.[1,2] Eligibility to undergo thrombolysis and thrombectomy depends on the time between the onset of the first symptoms and arrival at an emergency department. Not all stroke centers have the capability to perform thrombectomy, which makes it critical that treatment delays be minimized.[3]

Patients with clots located in the major intracranial arteries, such as the distal internal carotid artery or the proximal middle cerebral artery, undergo bridging therapy with intravenous alteplase, followed by thrombectomy. Because alteplase restores perfusion in only a small proportion of patients with large clots, there is also a premium on reducing the time between thrombolysis and thrombectomy.[3,4] There has even been consideration of proceeding directly to thrombectomy, bypassing thrombolysis altogether, but the efficacy of this approach has not been proved.[5] Campbell et al.[6] have taken a different approach in these patients by studying an alternative thrombolytic agent, as reported in this issue of the *Journal*.

Tenecteplase is a genetically engineered variant of alteplase with superior fibrin specificity that could provide greater thrombolytic activity than alteplase, potentially averting the need for thrombectomy. Hemorrhagic complications may also be less frequent with tenecteplase than with alteplase. Tenecteplase has a long half-life and can be administered as a bolus, in contrast to alteplase, which is infused over a period of 1 hour; this difference could have the desirable effect of reducing the time between the onset of stroke and thrombectomy. In this trial, Campbell et al. compared intravenous tenecteplase with alteplase with regard to recanalization rates during the first 4.5 hours after stroke among patients who had proven large-vessel occlusion and for whom there was a plan to proceed to thrombectomy. Tenecteplase at a dose of 0.25 mg per kilogram of body weight (maximum, 25 mg) was associated with an approximate doubling of the rate of arterial recanalization before the commencement of the thrombectomy procedure: 22% of the patients treated with tenecteplase had substantially recanalized vessels or had no thrombus, as compared with 10% of those treated with alteplase ($P=0.002$ for noninferiority, $P=0.03$ for superiority). On secondary-outcome measures, there were significantly improved functional outcomes in tenecteplase-treated patients at 3 months but no significant between-group differences in the proportions of patients with functional independence, excellent outcome, or with early neurologic improvement.

This is the second phase 2 trial to show greater reperfusion with tenecteplase than with alteplase in patients potentially eligible for throm-

bectomy.[7] The additional thrombectomy procedures that were averted with tenecteplase in the present trial highlight the benefit and convenience of this therapy as compared with alteplase. However, to put this in perspective, in absolute terms, less than 25% of the tenecteplase-treated patients had substantial recanalization, whereas recanalization rates with stent-retriever thrombectomy are 80% or higher.[8] A dose of tenecteplase of 0.4 mg per kilogram (maximum, 40 mg) could result in higher recanalization rates than the dose of 0.25 mg per kilogram that was used in this trial. This higher dose is currently being investigated in a trial by the authors (Determining the Optimal Dose of Tenecteplase before Endovascular Therapy for Ischemic Stroke [EXTEND-IA TNK Part 2]; ClinicalTrials.gov number, NCT03340493), and it is hoped that higher rates of recanalization will occur without an increased incidence of intracerebral hemorrhage.

The secondary outcomes in the present trial provide an indication that higher rates of recanalization with tenecteplase than with alteplase may translate to noninferior, or even superior, clinical outcomes. Before these findings can be applied, however, noninferiority or superiority needs to be shown in a phase 3 trial with clinically relevant primary-outcome measures, not just with higher rates of recanalization. Ideally, such a trial would involve patients who are eligible for thrombectomy and are undergoing bridging therapy. Insights could also come from trials involving patients who are not eligible to undergo thrombectomy but who have similar stroke severity and type as the patients in the trial conducted by Campbell et al. In a phase 3 trial that enrolled mainly patients with mild stroke who were not expected to proceed to thrombectomy,[9] the superiority of tenecteplase was not shown at a dose of 0.4 mg per kilogram, as compared with conventional doses of alteplase.[9] Ongoing trials involving patients with stroke who are not expected to proceed to thrombectomy include TASTE (Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation; Australian New Zealand Clinical Trials Registry number, ACTRN12613000243718) and ATTEST2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; ClinicalTrials.gov number, NCT02814409).

Campbell et al. found no savings with tenecteplase with regard to the time between the initiation of thrombolysis and thrombectomy, possibly owing to transport delays within and between hospitals. Mobile stroke units, mobile interventional stroke teams, and innovative diagnostic scales are approaches that may improve stroke treatment and avoid delays.

The trial conducted by Campbell et al. has paved the way for tenecteplase to provide an alternative or replacement for alteplase in patients undergoing bridging therapy for acute stroke and to avoid thrombectomy procedures in some patients. Changes to practice would require not only further demonstration that tenecteplase is noninferior or superior in clinical efficacy to alteplase but also evidence of convenience, accessibility, affordability, and practicality. Tenecteplase could tick all these boxes.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From SUNY Downstate Medical Center, Brooklyn, NY.

1. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11-21.
2. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018;378:708-18.
3. Gerschenfeld G, Muresan IP, Blanc R, et al. Two paradigms for endovascular thrombectomy after intravenous thrombolysis for acute ischemic stroke. JAMA Neurol 2017;74:549-56.
4. Wei D, Oxley TJ, Nistal DA, et al. Mobile interventional stroke teams lead to faster treatment times for thrombectomy in large vessel occlusion. Stroke 2017;48:3295-300.
5. Fischer U, Kaesmacher J, Mendes Pereira V, et al. Direct mechanical thrombectomy versus combined intravenous and mechanical thrombectomy in large-artery anterior circulation stroke: a topical review. Stroke 2017;48:2912-8.
6. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med 2018;378:1573-82.
7. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med 2012;366:1099-107.
8. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285-95.
9. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol 2017;16:781-8.

DOI: 10.1056/NEJMe1801978