

Transition to Tenecteplase From t-PA for Acute Ischemic Stroke at Walter Reed National Military Medical Center

CPT Cole P. Denkensohn, MD, MC, USA^a; CPT Javed L. Khanni, MD, MC, USA^a; John Y. Choi, MD, MPH^a

Background: Tissue plasminogen activator (t-PA) has been the standard IV thrombolytic drug used in acute ischemic stroke treatment since 1995. Tenecteplase has been available for use in acute myocardial infarction and has been endorsed by the American Heart Association stroke guidelines as an alternative to t-PA.

Observations: A systematic process to safely transition from t-PA to tenecteplase for acute ischemic stroke was undertaken at Walter Reed National Military Medical Center. The process to implement tenecteplase required extensive training and education for staff physicians, nurses, pharmacists,

radiologists, trainees, and the rapid response team. There are a variety of benefits and implementation challenges to consider when transitioning thrombolytic therapy for institutional use in acute ischemic stroke.

Conclusions: Evidence supports the transition from t-PA to tenecteplase for acute ischemic stroke. Successful transition required months of preparation involving multidisciplinary meetings that included neurology, nursing, pharmacy, radiology, rapid response teams, critical care, and emergency medicine. Safeguards must be implemented to avoid dosing errors that can lead to life-threatening adverse events.

Author affiliations can be found at the end of this article.

Correspondence:

Cole Denkensohn
(coledenkensohn@gmail.com)

Fed Pract. 2023;40(1):e0351.
Published online January 19.
doi:10.12788/tp.0351

Tissue plasminogen activator (t-PA) has been the standard IV thrombolytic used in acute ischemic stroke treatment since its US Food and Drug Administration (FDA) approval in 1995. Trials have established this drug's efficacy in the treatment of acute ischemic stroke and the appropriate patient population for therapy.¹⁻³ Published guidelines and experiences have made clear that a written protocol with extensive personnel training is important to deliver this care properly.⁴

Tenecteplase has been available for use in the treatment of acute myocardial infarction (MI) and studied in acute ischemic strokes since 2000. Recent large multicenter trials have suggested tenecteplase may work better than t-PA in the recanalization of large vessel occlusions (LVOs) and have provided guidance on proper dosing in acute ischemic stroke victims.⁵⁻⁸ Compared with t-PA, tenecteplase has a longer half-life, is more fibrin specific (causing less coagulopathy), and is more resistant to endogenous plasminogen activator inhibitor.^{9,10} Using tenecteplase for acute ischemic stroke is simpler as a single dose bolus rather than a bolus followed by a 1-hour infusion with t-PA. Immediate mechanical thrombectomy for LVO is less complicated without the 1-hour t-PA infusion.^{5,6} Tenecteplase use also allows for nonthrombectomy hospitals to accel-

erate transfer times for patients who need thrombectomy following thrombolysis by eliminating the need for critical care nurse-staffed ambulances for interfacility transfer.¹¹ Tenecteplase also is cheaper: Tenecteplase costs \$3748 per vial, whereas t-PA costs \$5800 per vial equating to roughly a \$2000 savings per patient.^{12,13} Finally, the pharmacy formulary is simplified by using a single thrombolytic agent for both cardiac and neurologic emergencies.

Tenecteplase does have some drawbacks to consider. Currently, tenecteplase is not approved by the FDA for the indication of acute ischemic stroke, though the drug is endorsed by the American Heart Association stroke guidelines of 2019 as an alternative to t-PA.¹⁴ There is no stroke-specific preparation of the drug, leading to potential dosing errors. Therefore, a systematic process to safely transition from t-PA to tenecteplase for acute ischemic stroke was undertaken at Walter Reed National Military Medical Center (WRNMMC) in Bethesda, Maryland. Here, we report the process required in making a complex switch in thrombolytic medication along with the potential benefits of making this transition.

OBSERVATIONS

The process to implement tenecteplase required extensive training and education for staff physicians, nurses, pharmacists,

TABLE Patients Transitioned to Tenecteplase (n = 10)

Characteristics	Results
Age, mean, y	72.4
Sex, No. (%)	
Male	6 (60)
Female	4 (40)
Comorbidities, No. (%)	
Hypertension	8 (80)
Hyperlipidemia	6 (60)
Diabetes mellitus	4 (40)
Atrial fibrillation	3 (30)
Active tobacco use, No.	0
National Institutes of Health Stroke Scale, mean	
At admission	8.6
At discharge	2.8
Modified Rankin Scale, mean	
At admission	1
At discharge	1.1
Time, mean (range), min	
To presentation	46.5 (0-90)
To computed tomography ^a	127
To tenecteplase ^a	189
Recanalization, No. (%)	
Complete	2 (22)
Partial	2 (22)
Completed stroke, No. (%)	3 (33)
Stroke mimic, No. (%)	2 (22)
Adverse events	0

^aOne outlier removed due to WAKE-UP trial use.

radiologists, trainees, and the rapid response team. Our institution administered IV thrombolytic drugs up to 25 times annually to acute ischemic stroke victims, meaning we had to train personnel extensively and repeatedly.

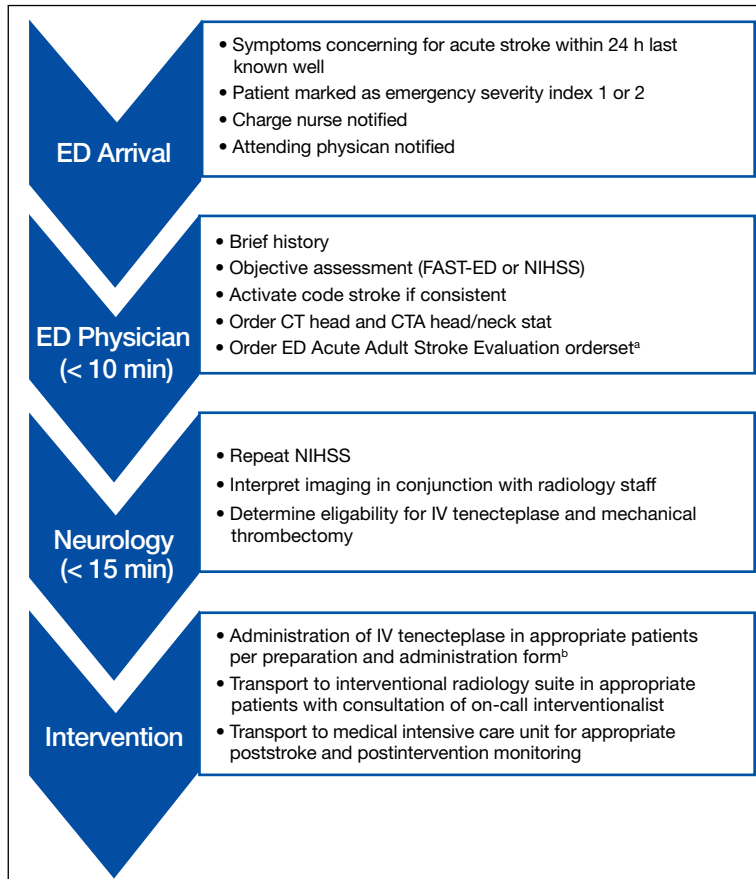
In preparation for the transition to tenecteplase, hospital leadership gathered staff for multidisciplinary administrative meetings that included neurology, emergency medicine, intensive care, pharmacy, radiology, and nursing departments. The purpose of these meetings was to establish a standard operating procedure (SOP) to ensure a safe transition. This process began in May 2020 and involved regular meetings to draft and revise our SOP. Additionally, several leadership and training sessions were held over a 6-month period. Stroke boxes were developed that

contained the required evaluation tools, consent forms, medications (tenecteplase and treatments for known complications), dosing cards, and instructions. Final approval of the updated acute ischemic stroke hospital policy was obtained in November 2020 and signed by the above departments.

All inclusion and exclusion criteria were determined to be the same for tenecteplase as they were for t-PA with the notable exception that the WAKE-UP trial protocol would not be supported until further evidence became available.⁹ The results of the WAKE-UP trial had previously been used at WRNMMC to justify administration of t-PA in patients who awoke with symptoms of acute ischemic stroke, the last known well was unclear or > 4.5 hours, and for whom a magnetic resonance imaging (MRI) of the brain could be obtained rapidly. Based on the WAKE-UP trial, if the MRI scan of the brain in these patients demonstrated restricted diffusion without fluid attenuated inversion recovery (FLAIR) signal changes (diffusion-weighted [DWI]-FLAIR mismatch sign), this indicated that the stroke had likely occurred recently, and it was safe to administer t-PA. This allowed for administration of t-PA outside the standard treatment window of 4.5 hours from last known well, especially in the cases of patients who awoke with symptoms.

Since safety data are not yet available for the use of tenecteplase in this fashion, the WAKE-UP trial protocol was not used as an inclusion criterion. The informed consent form was modified, and the following scenarios were outlined: (1) If the patient or surrogate is immediately available to consent, paper consent will be documented with the additional note that tenecteplase is being used off-label; and (2) If the patient cannot consent and a surrogate is not immediately available, the medicine will be used emergently as long as the neurology resident and attending physicians agree.¹⁵

Risk mitigation was considered carefully. The stroke box described above is stocked and maintained by the pharmacy as we have transitioned to using designated pharmacists for the storage and preparation of tenecteplase. We highly recommend the use of designated pharmacists or emergency department pharmacists in this manner to avoid dosing

FIGURE Protocol Flowsheet

Abbreviations: CT, computed tomography; CTA, computed tomography angiography; ED, emergency department; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; NIHSS, National Institutes of Health Stroke Scale.

^aED Acute Adult Stroke Evaluation order set includes placement of 2 peripheral IVs, body weight, 12-lead electrocardiogram, continuous telemetry, and standard laboratory evaluation (complete blood count, coagulation studies, basic metabolic panel, serum pregnancy test, troponin T, fingerstick glucose).

^bThe preparation and administration form for tenecteplase includes a dosing calculation formula, dosing chart (correlates weight with dose), maximum dose, and steps to reconstitution (including discarding 10 mL syringe before withdrawing final dose). Pharmacy will prepare the medication to further reduce dosing errors.

errors.^{7,16} Since the current pharmacy-provided tenecteplase bottle contains twice the maximum dose indicated for ischemic stroke, only a 5 mL syringe is included in the stroke box to ensure a maximum dose of 25 mg is drawn up after reconstitution. Dosing card charts were made like existing dosing card charts for t-PA to quickly calculate the 0.25 mg/kg dose. In training, the difference in dosing in ischemic stroke was emphasized. Finally, pharmacy has taken responsibility for dosing the medication during stroke codes.

Any medical personnel at WRNMMC can initiate a stroke code by sending a page

to the neurology consult service (Figure). A neurology resident or staff will then ensure that all the correct next steps are completed to properly triage the patient. This includes a physical examination, vital signs, laboratory workup, and computed tomography (CT)-based imaging. Treatment decision is based on a standard set of criteria. These include imaging findings on noncontrast head CT and CT angiography head and neck, disabling symptoms, presentation within standard treatment window, and lack of contraindications. Infusion of tenecteplase obviates the need for an IV pump and thus opens an IV site for alternate uses if needed. Removal of the infusion phase eliminates delays in mechanical thrombectomy in cases of LVO. Treatment with mechanical thrombectomy is based on evidence of LVO on CT angiography head and neck on arrival and discussion with the on-call interventionalist.

TRANSITION AND RESULTS

From November 2020 to December 2021, 10 patients have been treated in total at WRNMMC (Table). One case was treated under the WAKE-UP trial despite protocol and considered to be an outlier. All patients other than the 1 outlier were treated within the standard 4.5-hour window and underwent noncontrast head CT as the initial study. CT angiography head and neck was performed in 7 cases (70%). One case occurred periprocedurally and had a 0 minute time to presentation. One patient strongly believed to be related to ischemic stroke ultimately demonstrated no signal on DWI. Involved vascular territories included the middle cerebral artery (n = 4), pons (n = 2), and multifocal (n = 1). One treated case was determined to be LVO and had mechanical thrombectomy with complete recanalization before intervention. Two of the treated patients were later determined to be stroke mimics. While the number of patients treated thus far is small, these initial results support both the safety and efficacy of tenecteplase use for acute ischemic stroke and indicate a successful transition.

CONCLUSIONS

The available evidence supports the transition from t-PA to tenecteplase for acute ischemic stroke. The successful transition

required months of preparation involving multidisciplinary meetings between neurology, nursing, pharmacy, radiology, rapid response teams, critical care, and emergency medicine departments. Safeguards must be implemented to avoid a tenecteplase dosing error that can lead to potentially life-threatening adverse effects. The results at WRNMMC thus far are promising for safety and efficacy. Several process improvements are planned: a hospital-wide overhead page will accompany the direct page to neurology; other team members, including radiology and pharmacy, will be included on the acute stroke alert; and a stroke-specific paging application will be implemented to better track real-time stroke metrics and improve flow. These measures mirror processes that are occurring in institutions that treat acute stroke patients.

Author affiliations

^aDepartment of Neurology, Walter Reed National Military Medical Center, Bethesda, Maryland

Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner*, Frontline Medical Communications Inc., the US Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review the complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

Ethics and consent

Data were obtained through a quality improvement project, and no identifying information was used. Given this, institutional review board approval was not deemed necessary.

References

1. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375(9727):1695-1703. doi:10.1016/S0140-6736(10)60491-6
2. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581-1587. doi:10.1056/NEJM199512143332401
3. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363(9411):768-774. doi:10.1016/S0140-6736(04)15692-4
4. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(3):870-947. doi:10.1161/STR.0b013e318284056a
5. Campbell B, Mitchell P, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med*. 2018;378(17):1573-1582. doi:10.1056/nejmoa1716405
6. Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med*. 2020;382(21):1981-1993. doi:10.1056/NEJMoa2001123
7. Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischemic 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
8. Campbell BCV, Mitchell PJ, Churilov L, et al. Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: the EXTEND-IA TNK part 2 randomized clinical trial. *JAMA*. 2020;323(13):1257-1265. doi:10.1001/jama.2020.1511
9. Warach SJ, Dula AN, Milling TJ Jr. Tenecteplase thrombolysis for acute ischemic stroke. *Stroke*. 2020;51(11):3440-3451. doi:10.1161/STROKEAHA.120.029749
10. Huang X, Moreton FC, Kalladka D, et al. Coagulation and fibrinolytic activity of tenecteplase and alteplase in acute ischemic stroke. *Stroke*. 2015;46(12):3543-3546. doi:10.1161/STROKEAHA.115.011290
11. Burgos AM, Saver JL. Evidence that tenecteplase is non-inferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. *Stroke*. 2019;50(8):2156-2162. doi:10.1161/STROKEAHA.119.025080
12. Potla N, Ganti L. Tenecteplase vs. alteplase for acute ischemic stroke: a systematic review. *Int J Emerg Med*. 2022;15(1). doi:10.1186/s12245-021-00399-w
13. Warach SJ, Winegar A, Ottenbacher A, Miller C, Gibson D. Abstract WMP52: reduced hospital costs for ischemic stroke treated with tenecteplase. *Stroke*. 2022;53(suppl 1):AWMP52. doi:10.1161/str.53.suppl_1.WMP52
14. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/str.0000000000000211
15. Faris H, Dewar B, Dowlatshahi D, et al. Ethical justification for deferral of consent in the AcT trial for acute ischemic stroke. *Stroke*. 2022;53(7):2420-2423. doi:10.1161/strokeaha.122.038760
16. Kvistad CE, Næss H, Helleberg BH, et al. Tenecteplase versus alteplase for the management of acute ischemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. *Lancet Neurol*. 2022;21(6):511-519. doi:10.1016/S1474-4422(22)00124-7