

Is tenecteplase ready to replace alteplase to treat acute ischaemic stroke? The knowns and unknowns

Yi Dong ¹, Yi Sui ^{2,3}, Xin Cheng ¹, David Z Wang⁴

To cite: Dong Y, Sui Y, Cheng X, *et al.* Is tenecteplase ready to replace alteplase to treat acute ischaemic stroke? The knowns and unknowns. *Stroke & Vascular Neurology* 2022;7:e001321. doi:10.1136/svn-2021-001321

Received 11 September 2021
Accepted 13 September 2021
Published Online First
19 October 2021



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Department of Neurology, Huashan Hospital Fudan University, Shanghai, China

²Department of Neurology, Shenyang Brain Hospital, Shenyang Medical College, Shenyang, China

³Department of Neurology, The First People's Hospital of Shenyang, Shenyang, China

⁴Department of Neurology, Barrow Neurological Institute, Phoenix, Arizona, USA

Correspondence to

Dr David Z Wang;
david.wang@dignityhealth.org

Tenecteplase (TNKase, TNK-tPA or TNK) is a thrombolytic agent derived from the tissue plasminogen activator (tPA). It is a 527-amino acid glycoprotein developed by replacing three amino acids at the T, N and K positions of the glycoprotein structure of tPA under genetic recombinant technology. After replacing threonine 103 with asparagine, asparagine 117 with glutamine and a tetra-alanine at amino acids 296–299, TNK is about eightfold more potent in dissolving clot, 80-fold higher resistance to plasminogen activator inhibitor-1 and 14-fold enhanced relative fibrin specificity, and with a longer half-life (20 min).¹ Hence, TNK is administered as a single intravenous bolus.

TNK 0.5 mg/kg intravenous bolus is the choice in treating acute myocardial infarction (MI),² and was approved by the United States Food and Drug Administration in 2000. In comparison, the optimal dosages of TNK used alone or as a part of the bridging therapy remain to be further defined. For Caucasians patients with acute ischaemic stroke (AIS), TNK was tested at doses of 0.1, 0.25, 0.4 or 0.5 mg/kg.^{3–7}

In the current issue of the journal, Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events (TRACE) trial tested three different doses of TNK versus standard dose of tPA in Chinese patients with AIS within 3 hours of onset.⁸ The trial is a dose selection phase II trial with a multicentre, prospective, randomised, open label, blinded-endpoint (PROBE) controlled design recruiting AIS patients with severity of National Institutes of Health Stroke Scale (NIHSS) 4–25. No difference in safety was revealed between different dose groups compared with tPA in terms of symptomatic intracerebral haemorrhage (sICH) events (5.0% in 0.1 mg/kg, 0.0% in 0.25 mg/kg, 3.3% in 0.32 mg/kg TNK and 1.7% in 0.9 mg/kg tPA; $p=0.52$). Also, no significant difference in any efficacy outcomes was observed. The study may be statistically underpowered due to a small sample size.

The Norwegian Tenecteplase Stroke Trial (NOR-TEST) showed a similar efficacy and safety profile between the TNK (0.4 mg/kg) and tPA in patients with mild AIS within 4.5 hours of onset.⁹ In its subgroup analysis, the distribution of favourable outcome and sICH were similar between treatment groups in patients with moderate and severe stroke. However, all-cause mortality in patients with severe strokes at 90 days was increased in the TNK group (26.3% vs 9.1%; $p=0.045$).¹⁰

Imaging assessment has been used as a surrogate marker to compare the efficacy of TNK to that of tPA. The Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) trial compared TNK 0.25 mg/kg to tPA 0.9 mg/kg in patients with AIS treated within 4.5 hours of onset. ATTEST failed to show a significant improvement of salvaged penumbra in the TNK group.¹¹ The Australian-TNK trial required a large vessel occlusion on baseline CT angiography and substantial mismatch on baseline CT perfusion imaging to select patient for either TNK 0.1 or 0.25 mg/kg versus standard dose of tPA within 3 hours of onset.⁵ The trial showed better early neurological improvement, reperfusion and higher rates of favourable 90-day outcome in patients treated with 0.25 mg/kg of TNK. The pooled analysis of ATTEST and Australian-TNK trials showed that TNK-treated patients with a TICI (Treatment in Cerebral Ischemia Score) 0/1 occlusion had higher rate of complete recanalisation at 24 hours (71% vs 43%, $p<0.001$) and had better early clinical improvement and favourable 90-day outcomes.¹² Further analysis stressed the importance of target perfusion mismatch.¹³ The EXTEND-IA TNK study showed that TNK (0.25 mg/kg) before thrombectomy was associated with a higher rate of reperfusion and better functional outcome than the standard dose of tPA in AIS patients with an large vessel occlusion (LVO), if treated within 4.5 hours of onset.¹⁴ EXTEND-IA TNK Part 2 showed that TNK doses of either 0.40 or 0.25 mg/kg had no

Table 1 Ongoing and planned clinical trials examining the efficacy and safety of TNK

Trial Type	Trial Name	Objectives	Study design	Primary outcome	Key safety outcome	Key eligibility criteria	Registration number
Within 4.5 hours of onset	AcT (Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke)	To test the real-world non-inferiority of TNK efficacy compared with tPA in patients with AIS eligible for IV thrombolysis	TNK 0.25 mg/kg vs tPA 0.9 mg/kg non-inferiority Pragmatic registry-based phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=1600	mRS at day 90–120	Mortality and sICH	Patients with AIS eligible for IV tPA or bridging therapy	NCT03889249
	ATTEST 2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis)	To test the superiority of TNK efficacy compared with tPA in patients with AIS eligible for IV thrombolysis	TNK 0.25 mg/kg vs tPA 0.9 mg/kg Phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=1870	mRS at day 90	Intracranial and extracranial haemorrhage, mortality, neurological deterioration	≥18 years old Thrombolysis initiated within 4.5 hours after onset Eligible for IV thrombolysis Premorbid mRS 0–1	NCT02814409
	NOR TEST 2 (The Norwegian Tenecteplase Stroke Trial 2)	To compare efficacy and safety of TNK vs tPA 0.9 mg/kg within 4.5 hours after onset, including wake-up stroke and before EVT	TNK 0.4 mg/kg vs tPA 0.9 mg/kg non-inferiority Phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=1342	% of mRS 0–1 at day 90	Cerebral haemorrhages on CT/MRI within 24–48 hours and mortality	≥18 years old Thrombolysis initiated within 4.5 hours after onset NIHSS >5 Premorbid mRS 0–2	NCT03854500
Large vessel occlusion	BRETIS-TNK (Boosting REcanalization of Thrombectomy for Ischemic Stroke by Intra-arterial TNK)	To explore whether a combination of IA TNK and EVT can increase recanalisation rate after the first attempt of device pass	IA TNK 4 mg bolus followed by infiltration (0.4 mg/min) for 30 min Single arm phase: Not applicable N=30	% of TICl 2b-3	sICH	≥18 years old LVO anterior circulation stroke eligible for EVT TOAST: LAA	NCT04202458
	TASTE (Tenecteplase vs Alteplase for Stroke Thrombolysis Evaluation)	To test TNK's efficacy in patients with demonstrated LVO and target penumbral pattern as opposed to tPA within 4.5 hours	TNK 0.25 mg/kg vs tPA 0.9 mg/kg non-inferiority Phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=1024	mRS 0–1 at day 90	sICH and all cause death	≥18 years old Thrombolysis initiated within 4.5 hours after onset Eligible for IV thrombolysis Premorbid mRS 0–1 Imaging selection criteria: Penumbra volume >15 mL; mismatch ratio >1.8; ischaemic core <70 mL; severely hypoperfused volume <100 mL	ACTRN12613000243718
	TEMPO 2 (TNK–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion)	To test TNK's efficacy compared with standard care, in patients of TIA or minor stroke with demonstrated LVO or near occlusion within 12 hours	TNK 0.25 mg/kg vs antiplatelets Phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=1274	mRS at day 90	Major bleeding	≥18 years old Treatment can be initiated within 12 hours after onset, and within 90 min of the start of CT/MRI TIA or minor stroke with NIHSS ≤5 Acute LVO or near occlusion (TICI 0 or 1) Premorbid mRS 0–2	NCT02398656

Continued

Table 1 Continued

Trial Type	Trial Name	Objectives	Study design	Primary outcome	Key safety outcome	Key eligibility criteria	Registration number
Late time window or wake-up strokes	CHABLIS-T (Chinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase)	Optimal dosage determination of TNK in AIS patients in extended time window.	TNK 0.25 mg/kg vs TNK 0.32 mg/kg Phase II randomisation: Yes Open-label: Yes Blinded outcome assessment: Yes N=86	For patients w/o EVT:>50% reperfusion at 4–6 hours and w/o sICH at 24–48 hours For patients with EVT: mTICI score $\geq 2b$ before EVT and w/o sICH at 24–48 hours	ICH, systemic bleeding and mRS 5–6	≥ 18 years old 4.5–24 hours after onset Anterior circulation AIS Premorbid mRS 0–2 Clinically significant neurological deficits Imaging selection criteria: Proven LVO or severe stenosis; mismatch ratio >1.2 ; ischaemic core <70 mL; absolute difference >10 mL	NCT04086147
	ETERNAL-LVO (Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion)	To evaluate the efficacy and safety of TNK in extended time window	TNK 0.25 mg/kg vs standard care (may include eligible IV tPA) Phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=740	mRS 0–1 or return to baseline mRS (if premorbid mRS=2) at day 90	ICH, all cause death, infarct growth, mRS 5–6	≥ 18 years Up to 24 hours after onset or last known well Anterior circulation AIS Premorbid mRS 0–2 Imaging selection criteria: Proven LVO or extracranial ICA stenosis; mismatch ratio >1.8 ; ischaemic core <70 mL; absolute difference >20 mL	NCT04454788
	ROSE-TNK (MRI-guided thrombolysis for Stroke beyond Time Window by TNK)	To examine the feasibility and outcome of TNK in 4.5–24 hours after stroke guided by a mismatch between DWI and FLAIR	TNK 0.25 mg/kg vs standard care Phase IV randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=80	mRS 0–1 at day 90	ICH, any bleeding events and death	18–80 years old 4.5–24 hours after onset NIHSS 6–25, or NIHSS ≤ 5 with culprit vessel occlusion or severe stenosis Premorbid mRS 0–1 Imaging selection criteria: DWI infarct $<1/3$ of MCA or $1/2$ of ACA or $1/2$ of PCA territory; infarct <70 mL; DWI/FLAIR mismatch	NCT04752631
	TIMELESS (Thrombolysis in Imaging-Eligible, Late-Window Patients to Assess the Efficacy and Safety of Tenecteplase)	To evaluate the efficacy and safety of TNK in extended time window	TNK 0.25 mg/kg vs placebo Phase III randomisation: Yes Blinded treatment: Yes Blinded outcome assessment: Yes N=456	mRS at day 90	ICH, adverse events, mortality	≥ 18 years old 4.5–24 hours after onset Anterior circulation AIS Premorbid mRS 0–2 NIHSS ≥ 5 prior to randomisation Imaging selection criteria: Proven LVO; mismatch ratio ≥ 1.8 ; ischaemic core <70 mL; absolute difference ≥ 15 mL	NCT03785678

Continued

Table 1 Continued

Trial Type	Trial Name	Objectives	Study design	Primary outcome	Key safety outcome	Key eligibility criteria	Registration number
	TWIST (Tenecteplase in Wake-Up Ischaemic Stroke Trial) ¹⁸	To test TNK's efficacy in stroke patients <4.5 hours of awakening	TNK 0.25 mg/kg+standard care vs no TNK +standard care Phase III randomisation: Yes Open label: Yes Blinded outcome assessment: Yes N=600	mRS at day 90	All-cause death and ICH	≥18 years old Wake-up stroke With limb weakness with NIHSS of 3–24, or dysphasia Treatment can be initiated <4.5 hours of awakening	NCT03181360

ACA, anterior cerebral artery; AIS, acute ischaemic stroke; DWI, diffusion-weighted imaging; EVT, endovascular therapy; FLAIR, fluid attenuation inversion recovery; IA, intra-arterial; ICA, internal carotid artery; ICH, intracerebral haemorrhage; IV, intravenous; LAA, large artery atherosclerosis; LVO, large vessel occlusion; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; mTICI score, Modified Treatment in Cerebral Ischemia Score; sICH, symptomatic intracerebral haemorrhage; TNK, tenecteplase; TOAST, Trial of Org 10172 in Acute Stroke Treatment; tPA, tissue plasminogen activator; tPA, tissue plasminogen activator;

difference in improving cerebral reperfusion prior to endovascular thrombectomy. However, sICH occurred in seven patients (4.7%) in the 0.40 mg/kg group compared with two patients (1.3%) in the 0.25 mg/kg group (risk ratio 3.50, 95% CI 0.74 to 16.62; $p=0.12$).⁶

With limited evidence, the 2019 AIS guideline of the American Heart/Stroke Association recommended TNK 0.4 mg/kg as an alternative to tPA in selected patients with AIS of minor neurological impairments and no major intracranial occlusion, while TNK 0.25 mg/kg for LVO patients prior to thrombectomy (both with level of evidence (LOE): B-R, and class of recommendation (COR): IIB).¹⁵

Current limited evidence supports no superiority of either dose over the other (0.25 mg/kg vs 0.4 mg/kg). Yet, dosage of 0.25 mg/kg is most frequently used in ongoing trials of TNK in AIS (table 1), with a support of its efficacy based on a recent network meta-analysis.¹⁶ In addition, TNK's efficacy when used in patient with LVO was only seen with imaging-based endpoints, while its safety is comparable to tPA. Therefore, its solid effects in treating AIS remain to be studied. TNK is likely to have its role to treat AIS, but more data are needed for it to completely replace tPA.

A series of ongoing phase III trials will further address the efficacy and safety of TNK either within early or late time windows, with or without LVO (table 1). Particularly in China, the ongoing TRACE II trial is testing the efficacy of TNK 0.25 mg/kg (single bolus, max 25 mg) as opposed to standard dose of tPA.¹⁷ TRACE III will study TNK in AIS due to LVO with perfusion mismatch up to 24 hours of symptom onset.

Acknowledgements We thank Dr XinZe Guo from The First People's Hospital of Shenyang for word processing and layout arrangement of the table.

Contributors YD and YS contributed equally. YD: Editorial conception, first draft of the manuscript and critical revisions. YS: Final draft of the manuscript, editorial conception and critical revisions. XC: Critical revisions. DZW: Editorial conception, critical revisions and approval of submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Yi Dong <http://orcid.org/0000-0001-6630-112X>

Yi Sui <http://orcid.org/0000-0002-2898-7877>

Xin Cheng <http://orcid.org/0000-0001-7816-0547>

REFERENCES

- Keyt BA, Paoni NF, Refino CJ, *et al*. A faster-acting and more potent form of tissue plasminogen activator. *Proc Natl Acad Sci U S A* 1994;91:3670–4.
- , Van De Werf F, Adgey J, *et al*. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the assent-2 double-blind randomised trial. *Lancet* 1999;354:716–22.
- Haley EC, Lyden PD, Johnston KC, *et al*. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. *Stroke* 2005;36:607–12.
- Thompson JLP, Thompson JLP, Grotta JC, *et al*. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke* 2010;41:707–11.
- 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.
- 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;323:1257–1265.
- Coutts SB, Dubuc V, Mandzia J, *et al*. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke* 2015;46:769–74.
- Li S, Pan Y, Wang Z, *et al*. Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (trace): a multicentre, randomised, open label, blinded-endpoint (probe) controlled phase II study. *Stroke Vasc Neurol* 2021;svn-2021-000978.
- 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.
- Kvistad CE, Novotny V, Kurz MW, *et al*. Safety and outcomes of tenecteplase in moderate and severe ischemic stroke. *Stroke* 2019;50:1279–81.
- Huang X, Cheripelli BK, Lloyd SM, *et al*. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (attest): a phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol* 2015;14:368–76.
- Bivard A, Huang X, Levi CR, *et al*. Tenecteplase in ischemic stroke offers improved recanalization: analysis of 2 trials. *Neurology* 2017;89:62–7.

- 13 Bivard A, Huang X, McElduff P, *et al.* Impact of computed tomography perfusion imaging on the response to tenecteplase in ischemic stroke: analysis of 2 randomized controlled trials. *Circulation* 2017;135:440–8.
- 14 Campbell BCV, Mitchell PJ, Churilov L, *et al.* Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573–82.
- 15 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:e344–418.
- 16 Kheiri B, Osman M, Abdalla A, *et al.* Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials. *J Thromb Thrombolysis* 2018;46:440–50.
- 17 Li S, Campbell BCV, Schwamm LH, *et al.* Tenecteplase reperfusion therapy in acute ischaemic cerebrovascular events-II (trace II): rationale and design. *Stroke Vasc Neurol* 2021. doi:10.1136/svn-2021-001074. [Epub ahead of print: 26 Aug 2021].
- 18 Roaldsen MB, Lindekleiv H, Eltoft A, *et al.* Tenecteplase in wake-up ischemic stroke trial: protocol for a randomized-controlled trial. *Int J Stroke* 2021;1747493020984073. doi:10.1177/1747493020984073