Is Tenecteplase a Viable Alternative to Alteplase in the Treatment of Acute Ischemic Stroke?

In 1995, the publication of the National Institute of Neurological Disorders and Stroke (NINDS) Study using the recombinant tissue plasminogen activator (t-PA) Alteplase for the treatment of Acute Ischemic Stroke (AIS) was the beginning of a paradigm shift in the field of AIS.[1] Significant progress was made since the original NINDS t-PA study over the next two decades in the treatment of AIS and presently IV alteplase is recommended for selected AIS patients who can be treated within 4.5 hours of ischemic stroke symptom onset.[2] Besides, Mechanical Thrombectomy (MT) has now become the standard of care in the management of selected Large Vessel Occlusion (LVO) AIS patients when MT can be initiated within 6 hours from symptoms onset and in a very few select AIS patients where MT can be initiated within 24 hours of stroke onset.[2] However, some challenges remain in the management of AIS and much more so in infrastructure and resource poor regions of the world.

Two major concerns remain with IV alteplase. Efficacy in LVO remains a major concern with low recanalization rates and poor reperfusion. Besides, alteplase has a short half life thus requiring to be given as a one-hour infusion. This one-hour infusion of alteplase while not a big issue for well-established Stroke Centers or Stroke Systems, it is a major challenge for small hospitals and countries without organized stroke networks and/or well-established Emergency Medical Systems. On a similar note, MT as a standard of care for LVO AIS patients is beyond a generalizable reach in not so well-established centers/systems of stroke care.

Could we have a drug easier to administer? Possibly more efficacious? This is where tenecteplase comes into the picture.

Tenecteplase is a genetically modified variant of alteplase. It has a longer half-life than alteplase thus just requiring a bolus to administer. It also has greater fibrin specificity as compared to alteplase which may potentially increase its efficacy.[3] Besides, tenecteplase is an established treatment for acute myocardial infarction and in Acute Coronary Syndrome, it is associated with a reduced risk of major bleeding compared to alteplase without evidence of reduced efficacy.[4] Moving beyond pharmacokinetics and pharmacodynamics, the use of tenecteplase as a single bolus is a major advantage in resource deprived smaller centers where nursing and monitoring of infusion resources may be limited. Similar advantage exists for tenecteplase in drip and ship thrombolysis patients where a more dedicated skilled nurse-staffed ambulance is not required while being transported from a smaller hospital to a major medical/thrombectomy center. Technically, risk of early hemorrhage right after tenecteplase bolus remains but the advantage of bolus and quick transfer far outweighs the small likelihood of a very early hemorrhage right after the bolus.

Several clinical trials have compared tenecteplase to alteplase in the treatment of AIS. A meta-analysis of five published trials showed that there was strong evidence that tenecteplase is noninferior to alteplase in the treatment of AIS and a reasonable alternative to alteplase. However, dose of tenecteplase varied among those trials (0.1 mg/kg to 0.4 mg/kg of tenecteplase) and patients with severe presenting deficits were under-represented in the analyzed trials.[5] Published AIS trials involving tenecteplase since the aforementioned meta-analysis have addressed some of those concerns. Three trials need special mention: EXTEND IA TNK 2, NOR-TEST 2A , and ACT trial. The EXTEND-IA TNK 2 reported that in patients with LVO AIS, dose of 0.4 mg/kg did not significantly improve cerebral perfusion prior to MT as compared to the dose of 0.25 mg/kg thus suggesting that that the 0.4 mg/kg dose of tenecteplase does not confer an advantage over the 0.25 mg/kg dose in patients with LVO ischemic stroke in whom endovascular thrombectomy is planned.[6] The prematurely terminated NOR-TEST 2A trial comparing tenecteplase at the dose of 0.4 mg/kg to alteplase yielded worse safety and functional outcomes compared with alteplase while the lower tenecteplase dose (0.25 mg/kg) ACT trial clearly showed noninferiority of tenecteplase to alteplase for functional outcomes and with no major safety concerns.[7,8]

In this issue of the journal, Dhar *et al.*[9] present their retrospective data on 42 AIS patients treated with either alteplase or tenecteplase (0.2 mg/kg dose) at a tertiary care hospital in Northern Part of India, with the aim to compare safety and efficacy of alteplase versus tenecteplase. Tenecteplase dose of 0.2 mg/kg was based on the guidelines by the Indian approval body.[10] There were no major baseline differences in the two treated groups in terms of their demographic characteristics, National Institutes of Health Stroke Scale (NIHSS) or Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Patients who received tenecteplase had a slightly higher number of LVO AIS patients than those who received alteplase but it was not significantly different. Results did not show any significant difference in the mRS at 90 days, and there were no major safety concerns nor mortality differences between the two groups. One small caveat in their study was that whether patient received tenecteplase or alteplase was based on affordability and availability. That does lead to a bias but probably is a ground reality in smaller and/or resource restricted Stroke Centers. Their hospital did not have MT capability and thus no patients were offered MT. Thus, this study reveals a comparable efficacy and safety between alteplase and tenecteplase and results are comparable to the

above-mentioned meta-analysis and the recently published ACT study.[5,8] Their median NIHSS was also similar to the ACT study. What is even more relevant in the Indian setting, is that tenecteplase is cheaper than alteplase and in a resource challenged environment, easier to administer. Besides, were the patient to be transferred to a Thrombectomy Center, monitoring of one-hour infusion of alteplase would not be required enroute since tenecteplase has a distinct advantage of being given as a bolus.

Is tenecteplase a viable alternative to alteplase in the treatment of AIS? Picture is getting clearer. Repeated studies have provided evidence for tenecteplase as a reasonable alternative to alteplase with a significant added advantage of a one-time single bolus. The two recently published ACT and the NOR-TEST 2A trials comparing alteplase to two different doses of tenecteplase (0.25 mg/kg in the ACT trial dose and 0.4 mg/kg in the NOR-TEST 2A trial) suggest that 0.25 mg/kg of tenecteplase is probably equivalent to alteplase and that 0.4 mg/kg is harmful.[7,8] The authors in this issue's study used 0.2 mg/kg based on the Indian Stroke Guidelines and the dose may need to be relooked at after the publication of ACT and the EXTEND IA TNK2 study.

To conclude, tenecteplase seems to be now a very viable alternative to alteplase in the treatment of AIS within the 4.5-hour window and in setting of a single bolus administration, appears to have a distinct advantage in a resource challenged environment. Tenecteplase dose of 0.25 mg/kg seems to be the most pragmatic choice as far as dose is concerned.

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References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. New Engl J Med 1995;333:1581-7.
2. 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:e440-1.
3. Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. Clin Pharmacokinet 2002;41:1229-45.
4. Guillermin A, Yan DJ, Perrier A, Marti C. Safety and efficacy of tenecteplase versus alteplase in acute coronary syndrome: A systematic review and meta-analysis of randomized trials. Arch Med Sci 2016;12:1181-7.
5. Burgos AM, Saver JL. Evidence that tenecteplase is noninferior to alteplase for acute ischemic stroke: Meta-analysis of 5 randomized trials. Stroke 2019;50:2156-62.
6. Campbell BC, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, *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;323:1257-65.
7. Kvistad CE, Næss H, Helleberg BH, Idicula T, Hagberg G, Nordby LM, *et al.* Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): A phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. Lancet Neurol 2022;21:511-9.
8. Menon BK, Buck BH, Singh N, Deschaintre Y, Almekhalafi MA, Coutts SB, *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;400:161-9.
9. Dhar N, Kumar M, Tiwari A, Desai I, Madhaw G, Kumar N. Tenecteplase and alteplase for thrombolysis of acute ischemic stroke within 4.5 hours: An efficacy and safety study. Ann Indian Acad Neurol. doi: 10.4103/aian.aian_1127_21.
10. Guidelines for Prevention and Management of Stroke published by NPCDCS, Ministry of Health and Family Welfare, Govt. of India, 2019. Available from: https://main.mohfw.gov.in/Major- programmes/non-communicable-diseases-injury-trauma/Non-Communicable-Disease-II/National-Programme-for-Prevention-and-Control-of-Cancer-Diabetes-Cardiovascular-diseases-and-Stroke-NPCDCS.

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