Expanding Footprints of Biosimilar Tenecteplase

The introduction of intravenous recombinant tissue plasminogen activator (rTPA) at the turn of the last century was a momentous step forward in the management of acute ischemic stroke.[1] However, the narrow therapeutic window of 4.5 hours, the potential for hemorrhagic complications, and most importantly the high cost have always necessitated the development and testing of alternatives to rTPA. In the last few years, much interest has focused on tenecteplase (TNK), a genetically modified variant of rTPA, with higher fibrin specificity and longer half-life, thereby allowing it to be administered as a bolus rather than one-hour infusion with at least theoretically less chances of intracranial and systemic bleeding besides being significantly less expensive.[2]

The initial studies on tenecteplase by Haley *et al*. from Virginia, USA (2010), Parson *et al.* from Melbourne, Australia (2012), and Huang *et al*. from Glasgow, UK (2015), though small, were promising in suggesting TNK as an alternative to rTPA.[3-5] Subsequently, a large multicentric study, The Norwegian tenecteplase stroke trial (NORTEST), conducted by Nicola Logello on 1100 patients of milder strokes in Norway showed similar efficacy and safety outcome compared with the rTPA group.[6] This was followed by the Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA) TNK study by Bruce CV Campbell *et al*.[7] from Australia, which clearly showed the superiority of TNK in achieving higher reperfusion and better functional outcome. Based on these two studies, TNK was featured in both American and European stroke guidelines for acute stroke treatment, although the recommendation was weak.[8,9] More recently, driven by efforts to minimize the administration time of intravenous thrombolytic agent during the coronavirus disease 2019 (COVID-19) pandemic, Bijoy Menon *et al*.[10] from Canada demonstrated TNK to be as effective as rTPA in a pragmatic, multicentric, open-label, registry-linked, randomized, noninferiority trial (AcT) in patients with acute ischemic stroke within 4.5 hours of symptom onset, thereby further strengthening TNK as an alternative to rTPA in acute ischemic stroke.

The story of TNK in India is somewhat different as TNK in India is available as a biosimilar, and whether the Western data on TNK are applicable to biosimilar TNK available in India has always been a question. Because of the low price, biosimilar agents at present are attractive options, accepted universally provided they are approved by the regulatory drug control authority. In fact, the Drug Controller General of India (DCGI) was the earliest in the world to approve TNK for acute ischemic stroke in 2017. The approval was based on a 2-part study carried out in multiple centers in India in 2015, which compared TNK at a dose of 0.2 mg/kg versus historical controls of the original National Institute of Neurological Disorders and Stroke (NINDS) rTPA trial and showed clear superiority of TNK over rTPA in 3-month modified Rankin Scale (Mrs) outcome, Barthel Index scores, and mortality. The limitation of this study was that it tested a now suboptimal dose of. 2 mg/kg within a now suboptimal therapeutic window of 3 hours, against controls of different ethnicity, clinical severity, and time period.[11] Therefore, the study by Mohan *et al*.[12] in AIIMS, Delhi, during the COVID-19 period on biosimilar TNK, published in the January–February 2023 issue of the Annals of Indian Academy of Neurology is timely and appropriate. A total of 160 eligible patients received rTPA or TNK during the study period. The numbers in both the study groups were unequal: TNK arm (n = 57) and rTPA group (n = 103) possibly reflecting the treating physicians' bias. The baseline characteristics, including the frequency of stroke subtypes, were generally balanced between the groups except showing more males and more patients with a history of hypertension in the TNK group.

The mean National Institutes of Health Stroke Scale (NIHSS) in the rTPA group was 9 and in the TNK group was 8, suggesting that the trial results are applicable to mild-to-moderate strokes, as opposed to only mild strokes as in the NORTEST trial.[6] The dose of TNK in various studies of acute ischemic stroke has ranged from 0.2 to 0.4 mg per kg body weight, but most studies have shown 0.2 5 mg per kg body weight to be the most effective dose, which was also used in the study.[7,12] The door to needle (DTN) time was longer in the TNK arm as compared to the rTPA arm, possibly because TNK was mainly used during the COVID-19 pandemic when much time was taken in ensuring safety measures.

The functional outcome measured by median mRS at 3 months among the two groups (two (IQR 1–4) in the rTPA group and three (IQR 1–4) in the TNK group)) was similar. Unlike the results of EXTEND-IA study, 70% of large artery occlusions in rTPA showed recanalization as compared to 33% in the TNK group on subsequent vascular imaging, but the difference was not statistically significant. A higher proportion of patients in the TNK arm (8.77%) underwent decompressive hemicraniectomy as compared to the rTPA arm (1.94%), balanced by a higher prevalence of intracerebral hemorrhage and systemic complications in rTPA arm, none of which reached statistical significance. The inherent limitations of the study are as follows: It has a retrospective nature and small sample size. Nevertheless, this study provides a peek into the use of TNK in acute ischemic stroke in a real-world setting in India and clearly demonstrates the noninferiority of biosimilar tenecteplase to rtTPA. The ease of administration and lower cost make it an attractive and welcome option in the armamentarium of intravenous thrombolytic agents for acute ischemic stroke in India.

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