Tenecteplase for Adult Acute Ischemic Stroke

IU Health Status Update

On September 1, 2022, IU Health will convert from alteplase to tenecteplase for the management of acute ischemic strokes (AIS) requiring thrombolytics in adult patients. The primary benefits of this change are ease of dosing (0.25 mg/kg, maximum 25 mg), ease of administration with tenecteplase (IV Push vs 1 hour infusion), and reduced cost (~$2,000/ dose).

Mechanism

Tenecteplase is a genetically modified form of alteplase, a tissue plasminogen activator (tPA), with greater fibrin specificity, longer half-life, and greater resistance to inhibition by plasminogen activator inhibitor type 1. The long half-life allows for single-bolus administration compared with alteplase which requires a single bolus plus infusion. Alteplase is a naturally occurring tPA produced by recombinant DNA technology while tenecteplase is a deletion mutant with two single amino acid substitutions in the kringle-1 domain and substitution of four amino acids in the catalytic domain. The basic mechanism of these drugs is catalyzing the formation of plasmin from plasminogen, which leads to fibrinolysis.[1]

Dosing

Based on the available data for efficacy and safety, IU Health has decided to administer tenecteplase as a 0.25 mg/kg (maximum 25 mg) IV Push x1 over 3-5 seconds.

****CAUTION** Dosing for stroke is ½ of the dose for myocardial infarction!**

Pharmacokinetics

A biphasic disposition from the plasma is described after single-bolus administration. Initially cleared from plasma at 20-24 minutes, the terminal half-life is 90-130 minutes. Alteplase for comparison purposes has a half-life of 3-5 minutes. The volume of distribution is weight related and approximately plasma volume. Hepatic metabolism is the major clearance mechanism.

Brief Review of Evidence[1]

- The Phase 3 AcT trial assessed for non-inferiority between tenecteplase 0.25 mg/kg and alteplase 0.9 mg/kg in adult AIS patients presenting within 4.5 hours of stroke onset. The primary endpoint was the proportion of patients with a modified Rankin Scale (mRS) 0-1 at 90 days. In total, 36.9% of tenecteplase-treated patients and 34.8% of alteplase-treated patients achieved an mRS 0-1; the non-inferiority threshold was met. Symptomatic intracranial hemorrhage (SICH) rates were 3.4% and 3.1% in the tenecteplase and alteplase groups, respectively.[2]

- In the Phase 3 NOR-TEST trial, tenecteplase 0.4 mg/kg was evaluated for superiority over alteplase 0.9 mg/kg for treatment of AIS patients treated within 4.5 hours of stroke onset. The primary endpoint was favorable functional outcome as defined by achieving mRS 0-1 at 90 days. Tenecteplase did not show superiority vs alteplase. Overall, 3% and 2% of patients in the tenecteplase and alteplase groups, respectively, experienced SICH.[3,4]

    - Since NOR-TEST patients had a median baseline National Institute of Health Stroke Scale (NIHSS) score of 4, NOR-TEST 2A evaluated AIS patients treated with tenecteplase 0.4 mg/kg vs alteplase with admission NIHSS scores ≥ 6. In total, 32% of patients in the tenecteplase arm and 51% in the alteplase arm had mRS 0-1 at 90 days ($p = 0.0064$). Non-inferiority was not demonstrated. Mortality within 3 months was higher in the tenecteplase group (16%) vs the alteplase group (5%), $p = 0.013$. Overall, SICH rates were 6% and 1% in the tenecteplase and alteplase groups, respectively.[5]

    - Increased rate of ICH hypothesized to be related to higher tenecteplase dose.

- The Phase 2 EXTEND-IA TNK trial compared IV tenecteplase 0.25 mg/kg with IV alteplase 0.9 mg/kg for non-inferiority in patients with acute anterior ischemic stroke and plans for subsequent mechanical thrombectomy. Overall, 22% of tenecteplase-treated and 10% of alteplase-treated patients achieved the primary outcome of modified Treatment in Cerebral Infarction (mTICI) 2b/3 or non-retrievable thrombus at initial angiogram (odds ratio 2.6 [95% CI 1.1-5.9], $p = 0.002$). Both groups reported similar rates of SICH and death.[6]

    - Part 2 of the EXTEND-IA TNK trial compared 2 doses of IV tenecteplase, 0.4 mg/kg (up to 40 mg) and 0.25 mg/kg (up to 25 mg). Substantial reperfusion was reported in 19.3% of each group. Rates of death and SICH were similar in both arms.[7]

Treatment Guidelines

The 2019 update to the 2018 guidelines for the early management of AIS in adults, developed by the American Stroke Association (ASA) which is a division of the American Heart Association (AHA), offers the following recommendations on the use of IV tenecteplase for the management of AIS:[8]

- "It may be reasonable to choose tenecteplase (single IV bolus of 0.25 mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy." (**Class IIb; Level of Evidence B-Randomized**)

- "Tenecteplase administered as a 0.4 mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion." (**Class IIb; Level of Evidence B-Randomized**)

Key Take-Aways

- On September 1st all IU Health facilities will convert to tenecteplase as the preferred thrombolytic for the acute treatment of strokes in adult patients.
- Stroke order sets will be updated to tenecteplase 0.25 mg/kg (maximum 25 mg) IV Push.
- Treatment of a hemorrhagic conversion post thrombolytic will remain the same.

References

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