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A Narrative Review on Comparison of Tenecteplase and Alteplase in The Management of Acute Ischemic Stroke

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ABSTRACT
An acute ischemic stroke (AIS) is life-threatening. Blood flow to a brain region ceases abruptly, prompting the event. This disrupts oxygen and nutrient delivery. It leads to irreversible brain damage or cell death if not fixed soon. Blood clots in cerebral arteries are a common cause of AIS. The main goal of AIS management is to restore blood flow to the affected area quickly. This minimizes tissue loss and improves patient outcomes. Doctors use intravenous Alteplase (ALT), a clot buster. It is the standard treatment for a specific time window after stroke starts. This review looks at the safety and efficacy of Tenecteplase (TNK). It is an emerging clot-busting drug for the management of AIS. It analyses recent research on TNK. It looks at its potential to dissolve blood clots in AIS. It compares its impact on patient recovery to that of ALT. Current data suggests promise for TNK. It is great at unblocking arteries. It speeds recovery in some patient groups. TNK has several potential advantages over ALT, including a longer half-life, simpler administration, stronger clot affinity, slower clearance and possibly better cost-effectiveness. TNK shows promise as a new treatment for AIS. It offers benefits beyond ALT. Further research is necessary to understand its role in AIS management fully.

Keywords: (Acute Ischemic Stroke (AIS)), (Alteplase (ALT)), (Tenecteplase (TNK)), (tissue Plasminogen Activator (t-PA)).

INTRODUCTION

Ischemic stroke and hemorrhagic stroke are the 2 - forms of stroke, the most common type of stroke is Ischemic Stroke make up about 87% of all stroke cases, it occurs when blood flow to a part of the brain suddenly stops deprives the brain tissue of oxygen, nourishment and the reduced blood flow may be caused by a blood clot or plaque in a blood vessel supplying the brain this harms the brain cells in that location. Ischemic stroke has many intricate causes, including carotid artery blockage and brain tissue ischemia. Intravenous thrombolysis and endovascular therapy are common treatments for acute ischemic stroke (AIS) [1], [2]. Thrombolysis uses clot-busting drugs, such as tissue plasminogen activators (t-PAs) i.e., Alteplase (ALT) and Tenecteplase (TNK). They break the clot that blocks blood flow and restores it. Intravenous Thrombolysis (IVT) is commonly used in conjunction with endovascular treatment (EVT), a mechanical thrombectomy that physically removes the clot from the occluded blood artery when treating large vessel occlusions. The treatment plan also heavily incorporates telemedicine, neuroprotective medications, secondary prevention, and advanced neuroimaging [3]. To improve outcomes and lessen the burden of this crippling condition, ischemic stroke care often entails a multidisciplinary approach that incorporates acute interventions, secondary preventive initiatives, and continuous research. Thrombolytic therapy became the standard of care for AIS after the National Institute of Neurologic Disorders and Stroke's t-PA (NINDS t-PA trial) was published. Despite a high risk of bleeding, the trial showed that Intravenous (IV) t-PA therapy is effective, it works when given within 3 hours of symptoms onset due to its time limit. When there is insufficient history, such as in the case of aphasia or unpredictable symptoms, it may be challenging to assess eligibility in the acute situation. Patients without a last known well time are typically not given treatment [4]. The only approved medicine for AIS is ALT, which improves outcomes when given within the recommended window is often within 4.5 hours of symptom onset [3]. TNK is a genetically modified version of ALT, it has enhanced resistance to plasminogen activator inhibitor-1 (PAI-1), a longer half-life that allows for bolus delivery, and enhanced fibrin specificity which reduces the danger of systemic bleeding and fibrinogen depletion and it can act as an alternative to ALT. The US FDA has approved it for the treatment of ST-segment elevation myocardial infarction (STEMI) at a dose of 0.5 mg/kg after it was shown to have 30-day mortality that was comparable to alteplase but with fewer systemic haemorrhages [5].

A meta-analysis of five randomized controlled studies conducted by (Burgos A. M. and Saver JL., 2019) concluded that TNK is not inferior to ALT while treating AIS. The American Stroke Association (ASA) has updated its guidelines for the emergency care of AIS and transient ischemic attack (TIA), recommending using TNK as an alternative to ALT. Results from ongoing randomized trials investigating the use of TNK in combination with thrombectomy and during the delayed treatment window are greatly desired. In the evolving field of thrombolytics for AIS, TNK is becoming more and more evidence-based about its safety and effectiveness [6], [7].

MECHANISM OF ACTION OF TENECTEPLASE

Tenecteplase binds to fibrin in blood clots and converts plasminogen into plasmin (Fig 1), breaking the clots and restoring blood flow to the injured area [8]. Compared to alteplase, it has a better selectivity for fibrin. Tenecteplase's specificity allows it to more easily bind to fibrin within the thrombus, resulting in localized fibrinolysis and the disintegration of clots. Tenecteplase has been engineered to resist inhibition by plasminogen activator inhibitor 1 (PAI-1), a platelet surface expressed protein that prevents clots from breaking. This resistance enhances the ability of tenecteplase to promote clot lysis and enable thrombus dispersion [7].

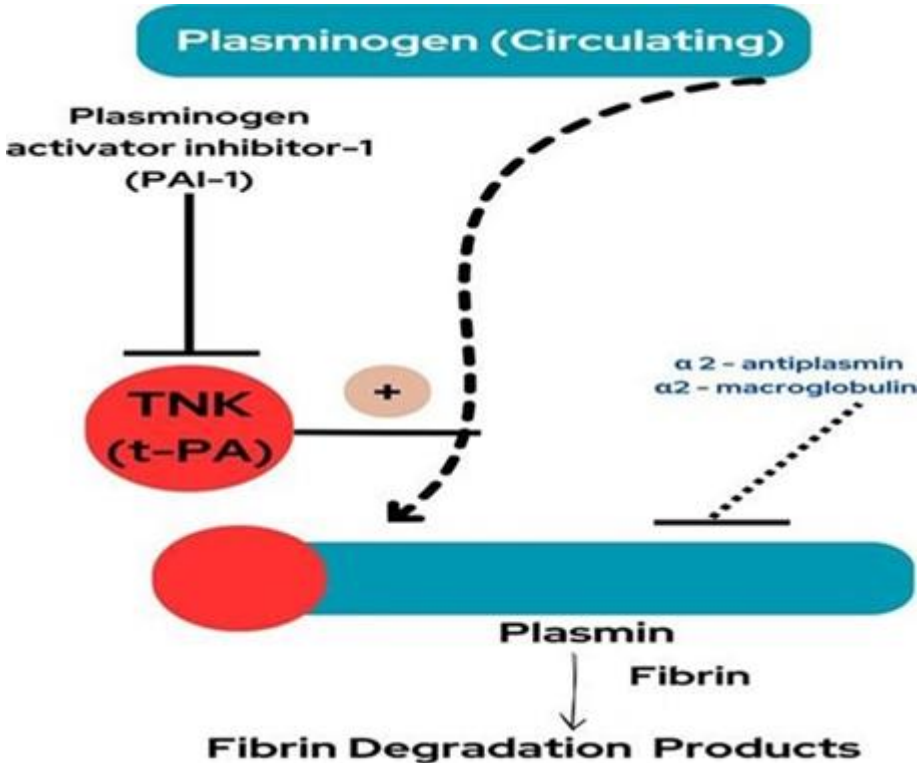

Figure 1 Mechanism of Action of Tenecteplase (tissue plasminogen activator)

DOSING

Several phase-2 trials assessed tenecteplase for treating acute ischemic stroke. One study found 0.1– 0.4 mg/kg safe, with 0.25 mg/kg showing better recanalization than 0.1 mg/kg. Another investigation in 2020 found similar outcomes for 0.25 mg/kg and 0.4 mg/kg. The standard dose for tenecteplase in acute ischemic stroke is 0.25 mg/kg over 4.5 hours, with a lower hemorrhage risk than alteplase
[9].

PHARMACOKINETICS

The pharmacokinetic profile of TNK has various benefits that enable the delivery of a single bolus. It is more resistant to being inactivated by PAI-1 because it has a longer half-life, a slower clearance rate, a stronger specificity for fibrin, and less binding to PAI-1 [10].

*Fibrin Selectivity: Tenecteplase is 14 times more selective for fibrin than alteplase [11]. It is more receptive to fibrin found in blood clots.

*Half-Life Time: Tenecteplase can stay active in the body for a longer period because it has a longer half-life than alteplase.

*Resistance to PAI-1: Tenecteplase's increased resistance to PAI-1, a protein that suppresses plasmin activity and increases its fibrin selectivity, is attributed to its plasminogen activator inhibitor-1 (PAI-1) [12].
*Lower Risk of Intracerebral Hemorrhage: Tenecteplase has a better pharmacokinetic profile than alteplase, which includes fibrin selectivity and a lessened effect on the coagulation process. These factors may help to explain the decreased risk of intracerebral haemorrhage. For patients suffering from ischemic stroke, tenecteplase provides a safer thrombolytic alternative by reducing the risk of systemic bleeding episodes and maintaining the integrity of the blood-brain barrier [13].

Tenecteplase is intended to be given as a bolus, in contrast to alteplase, which necessitates a continuous infusion. By exposing the clot to high enzyme concentrations quickly, this bolus administration promotes faster fibrinolysis, vascular recanalization, and reperfusion [7]. Large artery occlusion patients may benefit most from this administration's simplicity since it enables the start of following endovascular mechanical thrombectomy treatments more quickly [6].

VARIOUS INDICATIONS OF TENECTEPLASE

1. Acute Ischemic Stroke: Tenecteplase is used to help break blood clots and restore blood flow to the damaged brain area in cases of acute ischemic stroke. To enhance results and lessen impairment, it is given within a certain time frame following the onset of stroke symptoms [3].
2. Acute Myocardial Infarction: Although this condition is also referred to as a heart attack, it can also be treated with tenecteplase. To restore blood flow and stop additional damage to the heart, it is used to break blood clots in the coronary arteries, which feed blood to the heart muscle [14].
3. Pulmonary Embolism: Zhang Z et al. [15] carried out a comprehensive review and meta-analysis In some patient populations, tenecteplase is recommended for the treatment of pulmonary embolisms (PE), especially high-risk PE cases.

According to the systematic review and meta-analysis, Tenecteplase may help raise the 30-day survival rate in high-risk PE patients without raising the incidence of hemorrhagic episodes. It's crucial to remember, though, that because of the increased risk of bleeding, Tenecteplase is not advised for individuals with intermediate-risk PE. The trial demonstrated how low-dose Tenecteplase combined with catheter-directed thrombolysis may be advantageous for some patient categories.

TENECTEPLASE USE: OFF LABEL

The term "off-label" refers to the usage of tenecteplase for patient populations or indications that have not received regulatory agency approval. Tenecteplase is regarded as off-label in the setting of acute ischemic stroke (AIS) because alteplase is the only thrombolytic drug that regulatory bodies have approved for this indication [16]. Tenecteplase off-label use in AIS may entail the following situations:

- Tenecteplase is given to AIS patients who have large vascular occlusion (LVO) and are slated to undergo mechanical thrombectomy (MT).
- Using tenecteplase to shorten intravenous thrombolysis (IVT) workflow time metrics and speed up IVT and MT bridging, particularly in emergencies like the COVID-19 pandemic.
- Taking into account tenecteplase as an affordable substitute for alteplase before MT for AIS linked to lung cancer [17].

EFFICACY OF TENECTEPLASE

Studies like the EXTEND-IA TNK experiment have shown that tenecteplase enhances clinical outcomes and increases rates of early recanalization in major artery occlusion strokes planned for mechanical thrombectomy. Thus, tenecteplase might be useful in encouraging vascular recanalization and enhancing the prognosis of acute stroke patients [18]. The term "ischemic wakeup stroke" describes a particular kind of stroke in which the victim experiences stroke symptoms while they are asleep. Because the precise moment of stroke onset is unknown, people who experience symptoms upon awakening have historically been deemed ineligible for thrombolytic treatment. However, according to new research, thrombolytic therapy might be helpful for certain wake-up stroke victims if the attack started just before they awakened.
Clinical trials with Tenecteplase have been conducted, including the Tenecteplase in Wake-up Ischemic Stroke Trial (TWIST). Tenecteplase is being tested in wake-up stroke patients as part of the TWIST randomized controlled study to determine its safety and effectiveness.
As a possible substitute for alteplase in the thrombolytic therapy of acute ischemic stroke, including wake-up stroke cases, tenecteplase is now being studied. Research initiatives like TWIST are designed to yield important information on how well tenecteplase works to improve functional outcomes and lessen disability in wake-up stroke patients. Treatment of acute ischemic stroke, including wake-up stroke cases, appeared promising [19]. The more well-established of the two thrombolytic medicines, alteplase, was found to be non-inferior to tenecteplase inappropriate acute ischemic stroke patients by the ATTEST-2 trial [20].

SAFETY OF TENECTEPLASE

Research has shown that there is no discernible increase in the risk of a cerebral hemorrhage when using tenecteplase instead of alteplase for the treatment of AIS [16].

1. Symptomatic Intracerebral Hemorrhage (SICH): In certain trials, the rates of SICH for TNK and alteplase have been comparable, but larger TNK doses may be linked to a higher risk of SICH.
2. Mortality: In the majority of investigations, the mortality rates for TNK and alteplase are similar.
3. Bleeding Complications: Because TNK has a higher fibrin specificity than alteplase, it may have less unfavorable bleeding complications, potentially lowering the incidence of bleeding events.
4. Door-to-Needle Time (DNT): Compared to alteplase, TNK has been linked to a noticeably shorter

DNT, which may result in a quicker start to treatment and possibly better results [21].

ADVERSE DRUG REACTIONS

Tenecteplase-related adverse drug reactions (ADRs) might include both frequent and uncommon side effects. The following ADRs are linked to TNK:

1. Problems with Bleeding: The risk of bleeding, particularly cerebral hemorrhage, is the most important adverse drug reaction (ADR) linked to tenecteplase. Tenecteplase patients are regularly watched for bleeding symptoms, such as easy bruising, prolonged bleeding from small incisions, or blood in the stool or urine [22].
2. Allergic Reactions: Although they are uncommon, tenecteplase allergies can happen. An allergic reaction may cause a rash, itching, swelling, lightheadedness, or trouble breathing. If an allergic reaction is detected, immediate medical assistance is required.
3. Hypotension: When Tenecteplase is administered, blood pressure may drop, resulting in symptoms including lightheadedness, dizziness, or fainting. For patients to manage their hypotension both during and after therapy, supportive interventions could be required.
4. Fever: After using tenecteplase, some patients may develop a fever or flu-like symptoms. It could be required to keep an eye out for fever and administer the proper symptomatic treatment.
5. Nausea and Vomiting: Adverse drug reactions (ADRs) to tenecteplase may result in gastrointestinal symptoms as nausea and vomiting. Patients should be treated appropriately and kept an eye out for these signs.
6. Injection Site Reactions: After tenecteplase is administered, local reactions at the injection site, such as discomfort, redness, or swelling, may happen. Usually moderate, these symptoms go away on their own.
7. Effects on the Liver and Renal Systems: Tenecteplase may occasionally impact the liver's or kidneys' ability to function. Patients using tenecteplase may need to have their liver and kidney functions monitored, particularly if they have a history of hepatic or renal disease [19].

TOLERABILITY

A manageable degree of side effects is often observed in patients treated with tenecteplase. There is now less chance of brain hemorrhage. Apart from being aware of the possibility of tenecteplase allergies, medical practitioners also need to be prepared to manage any hypersensitive symptoms that can appear, including rash, itching, or difficulty breathing. Patients with liver or renal impairment should use tenecteplase with caution as these conditions may affect the metabolism and clearance of medications. It may be necessary in some circumstances to adjust the dosage or the frequency of administration. Tenecteplase therapy may not be appropriate for patients with bleeding problems, trauma, recent major surgery, or gastrointestinal bleeding. It is crucial to evaluate each patient's medical history and contraindications in detail before beginning treatment. Tenecteplase is generally well tolerated when administered as prescribed and monitored closely for any possible side effects [19].

ADMINISTRATION

For a 60-minute infusion of alteplase, an intravenous pump and bolus syringe need to be ready, but tenecteplase can be administered as a single, 5-second intravenous bolus injection with minimal setup time. The single-bolus administration can increase workflow efficiency and be helpful in emergencies. The likelihood of mistakes in the acute environment can be reduced by the

administration of tenecteplase [23,24]. In "drip and ship" situations, where patients are being transferred between institutions, the prompt delivery of tenecteplase can accelerate the start of following endovascular therapy [24]. Tenecteplase is a first-line thrombolytic medication that shows promise due to its superior pharmacological features and ease of administration [25].

COST

Both domestically and globally, Tenecteplase is routinely stated to be less expensive than Alteplase. When choosing thrombolytic therapy for acute ischemic stroke, cost considerations may be a major factor [26].

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ALTEPLASE Vs TENECTEPLASE

Results regarding early neurological improvement and complete recanalization are important markers of therapy efficacy and patient outcomes when comparing alteplase versus tenecteplase (Table 1) for acute ischemic stroke (AIS).

1. Complete Recanalization: To protect the brain tissue that has been ischemic and improve patient outcomes, this procedure involves reopening the blocked artery to blood flow. TNK significantly enhanced entire recanalization relative to alteplase, as demonstrated by the results of a meta-analysis conducted by Mohamed Aboulezam et al. [25] suggesting that TNK may be able to improve vascular patency and reperfusion in AIS patients. Higher rates of recanalization with TNK, particularly at specific dosages, imply that TNK might be superior to alteplase in terms of restoring blood flow and lessening ischemia damage in the brain.
2. Early Neurological Improvement: Showing the return of neurological function and maybe indicating long-term recovery, this is a crucial therapeutic result in AIS treatment. TNK may help AIS patients' neurological abnormalities improve more quickly than alteplase, according to research showing a higher rate of early neurological recovery with TNK. Early neurological improvement can affect patient outcomes and quality of life and is crucial to the effectiveness of thrombolytic therapy in AIS [28].

TABLE 1: DIFFERENCE BETWEEN ALTEPLASE AND TENECTEPLASE.

	ALTEPLASE	**TENECTEPLASE**
Type	Tissue Plasminogen Activator	Modified Tissue Plasminogen Activator
Administration	Intravenous infusion	Single Intravenous Bolus
Dose	0.9 mg/kg (max 90 mg)	0.25 mg/kg (max 25 mg)
Half-life	Shorter (4 min)	Longer (20 min)
Fibrin Specificity	Lower	Higher
Resistance to PAI -1	Lower	Higher
Efficacy	Similar to Tenecteplase	Non- inferior to Alteplase
Bleeding Risk	Higher risk of Intracranial Hemorrhage	Potentially lower risk of Intracranial hemorrhage
Mortality rate	Studies show mixed results	Potentially lower mortality
Cost	Higher	Lower

THE BENEFITS OF TENECTEPLASE

In comparison to more established drugs such as alteplase, tenecteplase has advantages in terms of safety, efficacy, convenience of administration, and pharmacokinetics, making it a viable alternative for thrombolytic therapy in acute ischemic stroke [23].

POSSIBLE OBSTACLES TO TENECTEPLASE IMPLEMENTATION IN EMERGENCY SITUATIONS

- Physician Awareness and Acceptance: Given the established use and familiarity with Alteplase, there may be a delay in Tenecteplase's general adoption, despite its potential benefits.
- Regulatory Approval: Tenecteplase has theoretical advantages over Alteplase, despite not having FDA approval for acute stroke. The regular use of this medication in emergencies may be hampered by its lack of special approval for stroke care.

CONCLUSION

TNK has demonstrated encouraging results in multiple trials regarding its safety, efficacy, ease of administration, and prolonged half-life. These factors make it a viable substitute for ALT in the treatment of AIS, although TNK is currently used off-label for this purpose. Beyond stroke treatment, TNK offers significant clinical benefits for AMI and PE. Currently, ALT is the only FDA-approved drug for AIS. However, it is less fibrin-specific and more expensive than TNK. Like ALT, TNK is approved for AIS treatment only after clinical trials assessing its safety and efficacy. Completed trials, systematic reviews, and meta-analyses have shown that TNK is not inferior to ALT in terms of safety, efficacy, pharmacological activity, cost-effectiveness, and convenience of administration. Future research should investigate the potential of TNK in combination with other treatments, as well as the drug's long-term safety and efficacy in larger and more diverse patient populations.

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