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TENECTEPLASE VS. ALTEPLASE IN ACUTE ISCHEMIC STROKE: A SUPERIOR ALTERNATIVE BACKED BY EVIDENCE

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ABSTRACT

Background: Intravenous thrombolysis is a cornerstone of acute ischemic stroke (AIS) management. Alteplase (tPA) has long been the standard of care; however, tenecteplase (TNK), a genetically modified variant with greater fibrin specificity and a longer half-life, is emerging as a potential alternative. **Objective:** To compare the efficacy, safety, and practicality of tenecteplase versus alteplase in treating acute ischemic stroke. **Methods:** A comprehensive review of randomized controlled trials, observational studies, and meta-analyses published over the past decade was conducted to evaluate clinical outcomes, including recanalization rates, functional independence at 90 days (measured by modified Rankin Scale), symptomatic intracranial hemorrhage (sICH), and overall mortality. Administration protocols and pharmacokinetic properties were also examined. **Results:** Several recent trials (e.g., EXTEND-IA TNK, NOR-TEST) suggest that tenecteplase is at least non-inferior and potentially superior to alteplase in terms of early recanalization and neurological improvement. Tenecteplase has shown a favorable safety profile with similar or lower rates of sICH. Its single-bolus administration simplifies logistics, especially in pre-hospital and resource-limited settings. **Conclusion:** Tenecteplase represents a promising alternative to alteplase for intravenous thrombolysis in AIS, offering comparable or improved clinical outcomes with enhanced ease of use. Ongoing large-scale trials are expected to solidify its role in future stroke protocols and potentially redefine standard care practices.

KEYWORDS: Tenecteplase, Alteplase, Acute ishemic stroke, Superiority, Myocardial infarction.

INTRODUCTION

Stroke is one of the most commonly occurring diseases and a widely fatal ailment. Defined as the damage in the brain tissues due to a lack of adequate blood supply, stroke falls under one of the critical illnesses that require care at the earliest. Poor blood supply to brain tissues may be due to blockage in the blood vessels, which clots, bursts, or ruptures could cause.

Significant differences have been found in the two tissue plasminogen activators employed as antifibrinolytics in terms of their superiority in the management of stroke. Various areas of clinical studies have demonstrated the precedence of TNK over alteplase.

Alteplase and tenecteplase are recombinant tissue plasminogen activators (rtPAs) widely utilized in the management of thrombotic conditions, most notably acute ischemic stroke (AIS). Alteplase, a genetically engineered form of the naturally occurring tPA, was the first thrombolytic agent approved for AIS and remains the current standard of care. Tenecteplase, a newer generation thrombolytic, is a bioengineered variant of alteplase designed to overcome its limitations. Structurally, tenecteplase differs from alteplase by three point mutations (T103N, N117Q, and a tetra-alanine substitution at amino acids 296–299), which confer increased fibrin specificity, greater resistance to plasminogen activator inhibitor-1 (PAI-1), and a longer half-life, allowing for single bolus administration compared to the continuous infusion required for alteplase. These modifications not only simplify administration but may also enhance therapeutic efficacy and safety, making tenecteplase a promising alternative in clinical settings.

I. Advantages in Dose, Delivery and Dynamics: Why tenecteplase stands out

Onset to Arrival (OAT) and Door to Needle (DTN) time

Onset to arrival time is defined as the time the patient takes to arrive at the hospital after first notice of the stroke symptoms. The calculated amount of time from the onset of a stroke attack in a patient to the

administration of the appropriate therapy is Door to Needle (DTN) time in the management of Acute Ischemic Stroke (AIS). And the amount of time from the patient's arrival at the hospital to tissue plasminogen activator (rt-PA) drug therapy. According to the American Heart Association/American Stroke Association (AHA/ASA) updated protocols and recommendations for the management of stroke suggest that the pre-hospital onset to arrival time (OAT) and the intra-hospital door-to-needle time (DNT) should not exceed 35 and 60 min, respectively. From a study conducted by Nikita Dhar, on the efficacy and safety study of TNK and alteplase in AIS, it has been reported that the median onset to door time for both the alteplase and TNK groups was similar, with values of 120 minutes (range: 20 to 210 minutes) versus 120 minutes (range: 30 to 210 minutes), respectively (P = 0.823). Median onset to needle time was also comparable, with 150 minutes (range: 60 to 255 minutes) in the alteplase group and 160 minutes (range: 50 to 240 minutes) in the TNK group (P = 0.779). Supporting the previous statement, Ayush Mohan reported that although the OTN time was similar among the two groups; the DTN time was shorter among the patients treated with TNK.[1]

A retrospective cohort analysis conducted by Vilhem Sjogren suggests that the preparation of TNK is quicker, therefore improving door-to-needle time and offering other advantages such as streamlined administration and improved patient convenience and the median DNT of 19 minutes is significantly of higher value in comparison to that of 35 minutes of alteplase.[2] The upper hand in reduced DTN of TNK can be very crucial to a patient's life by significantly increasing their chances of improvement on early treatment as time is one of the critical factors in the management of AIS.

Administration

Administration of both TNK and alteplase is via the IV bolus route in AIS cases. The calculation of doses depends on an individual patient's body weight. TNK has an advantage in terms of easier administration compared to alteplase as it is administered as a single intravenous (IV) bolus of 0.25 mg/kg (with a maximum dose of 25 mg) over a short duration of 5 seconds. On the other hand, alteplase requires a more complex administration process. It involves giving 10% of the weight-based dose as a bolus, followed by an intravenous infusion of the remaining 90% over 60 minutes. This difference in administration methods makes TNK a more straightforward and efficient option for treatment.

TNK has shown promise in the concept of "drip and ship" thrombolysis for stroke patients who need to be transferred from a smaller hospital to a larger medical center or a thrombectomy facility. In this approach, the administration of TNK begins at the smaller hospital before transferring the patient to the specialized facility for further management or thrombectomy if necessary. The approach is particularly beneficial in areas where a more dedicated skilled nurse-staffed ambulance is not readily available or practical for transportation. The advantages of using Tenecteplase in "drip and ship" scenarios are faster treatment initiation, improved outcomes, and the safety profile of TNK which has demonstrated a favorable safety profile, making it a suitable thrombolytic for "drip and ship" cases.[3]

Due to the changes in administration pattern, TNK is administered as a single-bolus injection, which is much simpler, while alteplase is usually given as an intravenous infusion over a specific period, TNK provides favorable management therapy**.**

Dose

The initiation of thrombolytic therapy must be done under 4.5 hours of the first onset of stroke symptoms, according to the American Heart Association or American Stroke Association (AHA/ASA). The general dose of alteplase is 0.9mg/kg, however, it differs among patients based on the time of stroke onset. Certainly, contraindications (recent major surgeries, bleeding disorders, or recent major bleeding events may need a lower dose or may not be eligible for alteplase treatment), age of the patient, co-morbidities and clinical assessment like the severity of the stroke, and the presence of other neurologic deficits may be considered when determining the dose.

Several trials have been conducted on the dose optimization of TNK use in hospital settings for patient use. Guangsho Li reported that according to the American Heart Association/America n Stroke Association Guidelines20, 0.4mg/kg TNK can be used as an alternative to 0.9mg/kg of alteplase with no major intracranial occlusion in patients.[4] The most tested doses of TNK include 0.25mg/kg; 0.4mg/kg and higher doses, amongst which 0.25mg/kg of TNK is found to show improved clinical outcomes with fewer adverse events.

Norwegian tenecteplase stroke trial NOR-TEST (Study of Tenecteplase Versus Alteplase for Thrombolysis in Acute Ischemic Stroke) was the largest trial (n=1,100) conducted to test TNK superiority with a dose of 0.4mg/kg over 0.9mg/kg of Alteplase. The NOR-TEST trial, comparing Tenecteplase (0.4 mg/kg) to alteplase (0.9 mg/kg) in patients with mild strokes, showed equivalent safety and efficacy.[5] The NOR-TEST 2 trial revealed that the higher dose of Tenecteplase (0.4 mg/kg) led to increased rates of intracranial hemorrhage (ICH), higher mortality at three months, and worse functional outcomes compared to the standard dosing of alteplase (0.9 mg/kg).[6] Hence, concluding that an even lower dose of TNK must be tested in future trials, as the dose tested in these trials is unsafe in moderate and severe stroke patients. A probability of an increase in the risk of death and intracranial hemorrhage might be observed at the dose of 0.4mg/kg.[7]As a result, the study has been continued in a Part B format, using a lower dose of (0.25

mg/kg) to further investigate its safety and efficacy in this patient population. This trial highlights the importance of dose optimization and tailoring thrombolytic therapy to the specific characteristics of patients with moderate to severe ischemic stroke. The findings underscore the need for cautious consideration of dosing regimens in acute stroke care to maximize benefits while minimizing the risk of complications.

According to TRACE: A multicenter, randomized, open-label, blinded endpoint (PROBE) studies performed by Shuya Li, which compared the three tiers of 0.1, 0.25, 0.32 mg/kg rhTNK-tPA (recombinant human TNK) to 0.9mg/kg of atleplase. The results concluded that the 0.25mg/kg dose tier stipulates higher measures of improvement on neurological deficit, lower proportion of death, and no Symptomatic intracranial hemorrhage (sICH) events.[8] Frequently occurring dosing errors in the weight-based calculations with alteplase may also result in its improper activity. Lower mortality rates improved neurological deficit, sICH, and safety profile while employing a lesser dose of TNK offers more advantages compared to the usually practiced alteplase dose proving its superiority.

Pharmacokinetics

A series of events occurs in the body upon the administration of a drug to attain a desirable therapeutic effect. Factors such as absorption, distribution, mechanism, and excretion of a drug are very crucially learned before its release onto the market to predict its potential benefit in the patients. Despite sharing the same hepatic metabolism, TNK and alteplase differ in other pharmacokinetic properties, overriding one drug above another.

Being one of the key determinants of drug dosing, plasma half-life is also an important factor in determining the excretion rates of the drug in the body. The higher the absorption half-life of a drug, the better is its efficacy and requirement of lesser frequency of administrations. When the drug has a smaller half-life, it acts very rapidly but wears off quickly to show the effect for a longer period, therefore requiring a higher frequency of drug administration. Whilst TNK provides an initial half-life of 20 to 24 minutes and a terminal half-life of 90 to 130minutes (about 2 hours), on the other hand, the initial half-life of alteplase is only 5 minutes or less with the terminal half-life of 72 minutes, resulting in better therapeutic outcome in the patients treated with TNK. Tenecteplase exhibits an extended half-life and an increased fibrin affinity, which may enable more adaptable dosing options.[9]

The ability of the body to clear the drug over time is known as plasma clearance. Plasma clearance between 380 and 570 mL/min is shown in the patients on alteplase therapy, while the patients administered with TNK have reported plasma clearance ranging from 99 to 119 mL/min. TNK was developed to reduce plasma clearance propensity compared to alteplase, which is more favorable to patients requiring fibrinolytic therapy.[10]

Fibrin specificity

Fibrinolytic agents bind to the fibrin-bound plasminogen and cleave it to generate plasmin, further degrading the body's fibrin clots. To attain this mechanism of the drug, they have a certain level of fibrin specificity to bind to the fibrin-bound plasminogen. The higher the drug's fibrin binding potential, the more efficacious its outcome. Conversely, TNK has presented with higher fibrin specificity than Alteplase. The higher binding affinity of TNK (15-fold higher fibrin specificity than alteplase) allows it to show a more targeted and effective clot lysis in the cerebral blood vessels in stroke conditions.[11]

II. But did the TNK developed as a Viable and Superior alternative to alteplase successfully fit its role?

Therapeutic efficacy

Thrombolytic therapy in stroke aims to dissolve the clot in the cerebral arteries and reduce the extent of brain damage. Expected outcomes include reperfusion (opening of the blocked artery), improving neurological functions (reduced deficits), reduced disability (brain damage), reduced mortality, and enhancement of quality of life. Alteplase has been showing promising results in stroke therapy over the past few years. Since the introduction of TNK, growing evidence has consistently demonstrated its superiority over alteplase.

SVO/LVO Treatment - The treatment strategy for a stroke largely depends on the type of stroke occurring in an individual based on the type of artery that shows the clot manifestation. The interruption of blood to the brain occurring due to an occlusion in smaller arteries or larger arteries is called small vessel occlusion or large vessel occlusion respectively. The percentage of cases of large vessel occlusions is higher than small vessel occlusions in the case of acute ischemic stroke. Large vessel occlusions (LVO) occur in about 24% to 46% of the AIS cases and about 20% to 25% of small vessel occlusions have been reported.

Fibrinolytic therapy in small and large vessel occlusions has reportedly concluded that the effect of both TNK and alteplase is similar in small vessel occlusions. However, in the cases reported with large vessel occlusions, it has been noted that the effect of TNK is better in comparison with alteplase, concerning the drug's high fibrin binding affinity.[12] Several studies have shown that TNK is as effective and safe as alteplase for treating acute ischemic stroke (AIS), with some evidence suggesting it may offer advantages in certain patient groups, particularly those with acute large vessel occlusion (LVO).[13] A drug with a short duration of action is advantageous in therapies with a narrow treatment window, as it allows for precise dosing control, rapid onset, and quick elimination,

minimizing prolonged exposure and reducing the risk of complications, Hence, the short window therapy of TNK provides an advantage over alteplase[14] Tenecteplase (0.25 mg/kg) may offer superior clinical efficacy over alteplase for AIS patients with large-vessel occlusion (LVO) when given before EVT. It improves reperfusion rates and enhances functional outcomes without raising safety concerns.[15]

Recanalization and Reperfusion rates

According to Angel Estella, the chances of recanalization in the patients treated with TNK showed no difference than those with alteplase. However, reviews from various trials have reported the effectiveness of TNK in recanalization rates[12,16] EXTEND-IA (Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke trial) TNK trials have reported better reperfusion in TNK-treated patients.[17] TASTE-A (Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance) studies reported superiority of TNK in the setting of mobile stroke units (MSU). It shows that the patients treated with TNK in MSU were treated faster[12] 0.25mg/kg of TNK has shown more measure of improvement of neurological deficit.[8]

TNK demonstrates greater effectiveness than alteplase (ALT) in achieving early recanalization and is linked to lower 90-day mortality in acute ischemic stroke (AIS) patients undergoing mechanical thrombectomy (MT). However, there is no significant difference between TNK and ALT in terms of 90-day functional independence, symptomatic intracerebral hemorrhage, or overall intracerebral hemorrhage rates.[18] A study assessing the reperfusion rates when fibrinolytic was given before thrombectomy showed that administering TNK before thrombectomy in ischemic stroke patients treated within 4.5 hours of symptom onset led to a higher incidence of reperfusion and improved functional outcomes compared to alteplase. However, the rate of recovery to independent function and the incidence of cerebral hemorrhage did not differ significantly between the two treatments.[19] In stroke patients selected using CT perfusion imaging, TNK was linked to significantly improved reperfusion and better clinical outcomes compared to alteplase.[20]

Neurological improvements

The TAAIS (Tenecteplase versus Alteplase for Acute Ischemic Stroke) trial showed that the treated group showed a reduced NIHSS score (National Institutes of Health stroke scale- that measures stroke severity) than the alteplase group. The scale gives a reading from 0-5, wherein 0 indicates normal patients and 5 refers to life-threat situations it is also used to assess and quantify the neurological deficits in stroke patients as well.[4]

Ziyi Shen performed a systematic review of this study and this meta-analysis included 16 randomized controlled trials (RCTs) published after 2015, with a total of 7508 acute ischemic stroke (AIS) patients—3940 treated with alteplase and 3568 with TNK. TNK demonstrated superior outcomes in early neurological improvement (RR 0.10, P = 0.04), blood vessel recanalization (RR 0.24, P = 0.01), and 90-day excellent neurological recovery (RR 0.12, P = 0.04), with no significant differences in other efficacy and safety outcomes. The study concludes that TNK is non-inferior to alteplase and may offer some advantages.[21]

Patients who received TNK showed greater early neurological improvement and improved functional outcomes at 90 days, as reflected in modified Rankin Scale (mRS) scores of 5. This indicates that TNK could contribute to better long-term recovery than alteplase.[13] A pilot study on Real-world comparative safety and efficacy of TNK versus alteplase in acute ischemic stroke patients with large vessel occlusion suggests that AIS patients with large vessel occlusion (LVO) who received a 0.25 mg/kg bolus of TNK were more likely to experience early neurological improvement compared to those treated with alteplase. However, this association weakened after adjusting for potential confounding factors.[22] Results from a randomized control trial show that TNK demonstrated greater early neurological improvement compared to alteplase, with the 0.25 mg/kg dose showing particularly better outcomes and a lower tendency for any intracerebral hemorrhage (ICH). Additionally, in patients with severe stroke at baseline, TNK was associated with a reduced risk of ICH.[23]

III. Reinforcing the Shift: Safety, Efficacy and the Clinical Value of Tenecteplase

Efficacy and Safety

In the efficacy and safety study performed by Nikita Dhar, it was reported that the patients presented with large vessel occlusion showed good recovery, and functionality in 3 months in 50% alteplase-administered patients and 43.8% TNK-administered patients. Reportedly, this phase also noted that the requirements of mechanical ventilation were more in TNK-employed patients, 8 more than those treated with alteplase. (Alteplase: 2 (10.5%) v/s TNK: 10 (43.5%); P = 0.019). This phase 3 trial failed to report the superiority of TNK over alteplase in terms of recovery at 3 months.[24] A similar study conducted by Angel Estella, where the in vitro studies proved the higher thrombi-dissolving power of TNK and its resistance to plasminogen activator inhibitors enumerated with other factors listed above proved superiority of TNK over alteplase in theoretical terms. This results in worse neurological outcomes (e.g., after fibrinolysis, TNK is 30% vs. rtPA is 55% (p = 0.008). It has been concluded that there are no major differences between the two fibrinolytic agents concerning neurological progress.[17] A network meta-analysis of randomized controlled trials on different doses of tenecteplase vs. alteplase for acute ischemic stroke within 4.5 hours of symptom onset indicates that TNK (0.25 mg/kg) and alteplase (0.9 mg/kg) are both safe and effectively improve clinical outcomes in AIS patients treated within 4.5 hours of symptom onset.

Additionally, TNK (0.25 mg/kg) offers greater benefits and has the potential to replace alteplase (0.9 mg/kg) in AIS management.[25]

Therefore, proving that despite TNK showing no dissimilarities with alteplase in certain areas of anticipated clinical outcomes, it has proved its worth in the other outcomes like recanalization and reperfusion, additionally, various parameters like administration, dosing, PK, and PD specifications owing to its overall favorable selection in stroke treatment than alteplase.

Adverse events

Complex health issues may arise that further threaten one's life. The most reported adverse events upon therapy with fibrinolytic agents are bleeding risk, intracranial hemorrhage (bleeding in the brain), anaphylaxis, reperfusion injury (damage to the brain tissue), arrhythmias, fever, and other bleeding-associated complications.

Frequently associated adverse events with alteplase are the risk of bleeding and a dose exceeding 0.9mg/kg raises the incidences of intracranial hemorrhages. Likewise, a higher dose of TNK is associated with greater chances of occurrence of adverse events, especially causing symptomatic intracranial hemorrhage**.** Symptomatic hemorrhagic transformation manifested after AIS is a complication leading to mortality in many cases. Penumbral imaging-based thrombolysis studies show 0%, 6.5%, and 15.8% occurrence rates at 0.1, 0.25, and 0.4 mg/kg doses.[26] However, the popularly accepted dose of TNK is 0.25mg/kg, which shows no development of symptomatic intracranial hemorrhage. The high fibrin specificity of TNK raises a lower risk of bleeding than alteplase.[12] Lower fractions of death have been noted with the 0.25mg/kg of TNK, proving this dose tier to be most beneficial with the least anticipated adverse events[8] No significant difference in the risk of treatment complications between acute ischemic stroke patients treated with tenecteplase or alteplase. While higher doses of tenecteplase showed a numerically increased risk of symptomatic intracerebral hemorrhage (sICH), no significant dose-related subgroup interactions were observed, likely due to the low overall event rates.[27]

Exceptions in thrombolytic therapy are made when the patient's conditions may aggravate the patient's worsening condition. In patients with active internal bleeding, a history of cerebrovascular accidents, severe uncontrolled hypertension, aneurysm, intracranial trauma, pregnancy, etc., Initiation of thrombolytic therapy upon ignorance of these conditions may set off into a severe health situation leading to mortality. Although some studies suggest that TNK can be used in patients with alteplase contraindications, it is the physician's responsibility to make a wise therapeutic decision that outweighs the benefits of therapy rather than the associated risks.

Beyond stroke: Exploring the expanding therapeutic potential of tenecteplase

The other diseased conditions that may benefit from thrombolytic therapy are acute myocardial infarction (MI) with chief indication in STEMI wherein the patients are known to have prolonged lives with encouraging safety and patency profiles,[28] Deep vein thrombosis (DVT); Pulmonary embolism and peripheral artery occlusions. Drugs like alteplase and TNK can be of value in these conditions as well. A case report from a hospital in Malaysia presents an AIS patient with STEMI, wherein the immediate decision to administer patient with intravenous TNK was taken at the dose of 0.4mg/kg rather than alteplase which is usually suggested in case of simultaneous effect in brain and myocardium. This multidisciplinary action resulted in improved clinical outcomes for the patient.[29]

DISCUSSION

The study of various research and literature reviews draws one popular conclusion that highly suggests exceptional outcomes of using TNK over alteplase in the medical attention of stroke. In a review on stroke thrombolytics, Andrew Bivard underscores the critical importance of early therapeutic intervention, advocating for the optimization of thrombolytic delivery systems and the evaluation of more efficacious agents such as TNK to enhance clinical outcomes.[30] The repeating conclusions of TNK showing higher rates of mRS rates (0-2) in various studies along with comparable angiographic reperfusion rates and safety outcomes lead to a deeper understanding of using TNK as an interesting option over alteplase. According to the results from a study by Fouzi Bala, findings provide evidence supporting TNK as a viable alternative to alteplase in the management of stroke patients presenting with carotid tandem lesions.[31] A U.S. multicenter real-world clinical study demonstrated that switching from alteplase (tPA) to TNK prior to endovascular therapy (EVT) for large vessel occlusion (LVO) stroke resulted in comparable endovascular reperfusion rates, safety profiles, and functional outcomes.[32]

Even though some studies direct the results toward showing comparable clinical outcomes, TNK is considered the supreme alternative to alteplase in the management of acute ischemic stroke given the relatively low cost and ease of administration.[33] Available evidence suggests that tenecteplase may be a superior thrombolytic agent compared to alteplase for the treatment of acute ischemic stroke (AIS). This systematic review includes six randomized clinical trials comprising a total of 1,675 patients with AIS. While no single study compared tenecteplase and alteplase across all three major outcomes following AIS, this review synthesizes findings from multiple studies to evaluate whether tenecteplase offers better overall efficacy and safety compared to alteplase.[34] Even if TNK demonstrates comparable efficacy to alteplase, its simpler administration may confer a practical advantage, as

delays between bolus and alteplase are common and may reduce treatment effectiveness. Thus, further investigation of TNK in acute ischaemic stroke is warranted.[35]

In comparison, a lesser number of studies account for the observations that TNK is not a suitable substitute for alteplase in the context of their safety profiles. According to the first randomized controlled phase 3 trials, investigating the safety and efficacy of both drugs in acute ischaemic stroke, TNK showed a similar profile to alteplase with no superiority proof.[36,37] No differences in the functional outcomes, mortality, and sICH, were observed between the drugs in patients in another study.[38]

CONCLUSION

The detailed study of the comparison between alteplase and TNK at every step of the AIS management suggests that applying TNK would yield better outcomes with the least adverse events. From the availability of TNK in OTN & DTN to the discharge of patients from the hospital, superior results have been noted in the patients treated with TNK. The development of TNK to make it available in cost-effective terms to the patients to provide better clinical outcomes than alteplase has been fulfilled as suggested by various clinical trials. Therefore, it is safe to conclude that TNK is a viable alternative to alteplase in the management of Acute Ischemic Stroke (AIS).

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