# Tenecteplase the Third Generation Thrombolysis for Treatment of Acute Ischemic Stroke

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***Abstract***
*Ischemic stroke is a focal neurological disorder that occurs as a result of insufficient or disconnected blood flow to the area of the brain, usually caused by clogged arteries. The sudden blockage of blood flow to the brain causes tissue hypoxia and triggers an inflammatory cascade. The point of ischemic can be seen from the irreversible tissue damage. Ischemic on penumbra represent tissue that functionally disturbed but structurally intact and therefore, potentially salvageable. Salvaging this tissue by restoring flow to non-ischemic levels is the goal of reperfusion therapy in acute stroke. One type of drug that is often used in ischemic stroke therapy such as thrombolysis. Tenecteplase is one of the third generation thrombolytics had their chemical structure slightly altered to increase fibrin specificity and to increase half-life. Tenecteplase was associated with significantly better reperfusion at 24 hr (TNK = 79,3%; t-PA = 55%) and clinical outcomes than alteplase in patients with stroke who were selected on the basis of CT perfusion imaging*
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## I. INTRODUCTION

Stroke, according to the World Health Organization (WHO) definitionis rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin. Classically stroke is characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH).[1,2] Stroke remains the leading cause of disability in the United States and is the country's fourth leading cause of death.[3] According to the latest data released by the American Heart Association, 87% of strokes are classified as ischemic stroke. Infarction occurs as a result of insufficient or disconnected blood flow to the area of the brain, usually caused by clogging of the arteries (although it can also be caused by a venous blockage of "venous infarction that can cause similar phenomena).[3] The pathophysiology of ischemic stroke is : a) occlusion of an intracranial vessel by an embolus that arises at distant site, b) in situ thrombosis of an Intracranial vessel, typically affecting the small penetrating artheries that arise from the major intracranial artheries, c) hypoperfusion cause by flow limiting stenosis of a major extracranial.[4] The presence of occlusion in the vessels is a major factor determining tissue outcomes in regional cerebral blood flow and the duration of occlusion of blood vessels. A decrease in CBF causes tissue perfusion decrease. In the persistent occlusion of large blood vessels, local perfusion pressure is a major factor affecting the outcome of the tissue.[5] The point of ischemic can be seen from the irreversible tissue damage. Ischemic on penumbra represent tissue that functionally disturbed but structurally intact and therefore, potentially salvageable. Salvaging this tissue by restoring flow to non-ischemic levels is the goal of reperfusion therapy in acute stroke.[5] Several types of drugs that are often used in ischemic stroke therapy include antiplatelet aspirin and thrombolysis, where trombolysis is used rt-PA.[6] Tenecteplase is the third generation thrombolytics had their chemical structure slightly altered to increase fibrin specificity and to increase half-life. It is an altered form of human tissue plasminogen activator (tPA) indicated for the reduction of mortality associated with acute ischemic stroke.[7,8,9]

## II. THROMBOLYTICS FOR ISCHEMIC STROKE

Thrombolytics is treatment to get rid of problems raised due to blood clot or thrombus to renovate function to the affected area, which is also known as clot buster, it has saved untold lives. The efficacy of the thrombolytic drug depends on several important factors: 1) the duration of the clot may reduce the efficacy of thrombolytics, and older clotting tends to have more crosslinked fibrin and is more resistant to thrombolytics; 2) The specificity of lltik or solvent of fibrin will determine its activity, and other determinants of that determine the efficacy of thrombolytics including the half-life and the duration of antibodies. Thrombolytics can be divided into two different categories 1) fibrin-specific thrombolytics, 2) nonfibrin specific thrombolytics. Some examples of fibrin-specific drugs are: alteplase, reteplase, and tenecteplase. Nonfibrinspecific drugs include streptokinase or stafilokinase. Thrombolytics can convert plasminogen into plasmin can be described directly or indirectly. The direct activator is the same as the one previously recorded for fibrin-specific. Indirect activators of plasminogen include streptokinase, stafilokinase, and desmoteplase. The direct activator which is all of the serine proteases will bind and break up a single amino acid (arginine-valine) to produce a plasmin. Indirect activators are not proteolytic, but rather form complexes with plasminogen which can then convert additional plasminogen to plasmin. [7,9]

**Table 1.** Classification of Thrombolytic Agent

| Generation of Thrombolytics | Fibrin specific | Non fibrin specific |
|---|---|---|
| First | ... | Urokinase |
| | ... | Streptokinase |
| Second | Recombinant tissue plasminogen activator (t-PA) | Prourokinase (scum-PA) Sk-plasminogen) activating complex |
| | Alteplase | |
| Third | Tenecteplase (TNK-tPA) | |
| | Reteplase | |
| | Monteplase | |
| | Lanoteplase | |
| | Pamiteplase | |

Until now the ideal thrombolytic drug has not been developed. While awaiting a better agent, efforts should be made to provide thrombolytic treatment as quickly as possible and to provide additional antithrombotic treatment without increasing the risk of bleeding.[8] The following table describes the characteristics of ideal thrombolytic agents for use.

**Table 2.** Characteristics of the Ideal Thrombolytic Agent

| **Characteristics of the Ideal Thrombolytic Agent** |
|---|
| Rapid, complete coronary flow and microcirculatory reperfusin in 100% of patients |
| Effective dissolving thrombi |
| Administration an intrvena bolus |
| Fibrin selective |
| Low risk for bleeding |
| No procoagulant effect |
| Low reocclusion rate |
| No effect on blood pressure |
| No antigenitocity |
| Reasonable cost |

## III. MECHANISM OF THROMBOLYTICS

The mechanism of action of thrombolytics is promotes thrombolysis by converting plasminogen to plasmin, and then plasmin degrades fibrin and fibrinogen.[4] Most thrombolytic drugs that have been tested or are being used to dissolve blood clots by activating plasminogen. Plasminogen after splitting will form plasmin, which is a proteolytic enzyme capable of breaking crosslinks between fibrin molecules. Because cross-links between fibrin provide structural integrity of thrombus, the breakdown of thrombus can be continued. Therefore, it is inaccurate to refer to this drug as a "plasminogen activator." Molecules that directly work on fibrin, such as plasmin or microplasmin are considered "Fibrinolytics that work directly". Since then, any drug that induces fibrinolysis (breaking the clot) will be referred to as thrombolytics. In this case it includes a drug that catalyzes the conversion of plasminogen into plasmin or works directly on fibrin as plasmin.[7] Other substances that play a role in the blood to inhibit fibrinolytic pathways, among which there are in principle four that inhibit this pathway include α2-anti-plasmin, α2-macroglobulin, plasminogen activator inhibitor, and thrombin. Although this inhibitor plays an important role, the use of thrombolytics at sufficient concentration will memepenagruhi desired fibrinolysis process in the treatment of acute ischemic stroke.[7]

## IV. TENECTEPLASE (TNK) IN ISCHEMIC STROKE THERAPY

Tenecteplase is derived from a cell line of Chinese hamster ovary cells; the polypeptide portion weighs approximately 58 742 daltons, and the molecular formula is $C_{2558}H_{3872}N_{738}S_{40.}$ Tenecteplase is an altered form of human tissue plasminogen activator (tPA).[10] Tenecteplase the third generation thrombolytics had their chemical structure slightly altered to increase fibrin specificity and to increase half-life. Changes in the position of amino acids in tenecteplase compared with alteplase occur in the following positions, among others at position 103 of the polypeptide the aminoacid threonine has been replaced by asparagine leading to a new glycosylation site. The carbohydrate chain that is linked to this site enlarges the molecule, thereby reducing its elimination and prolonging its plasma half life. At position 117 asparagine has been replaced by glutamine. By the exchange of this amino

acid the carbohydrate side chain that facilitates hepatic elimination has been removed. At position 296–299 the amino acids lysine, histidine, arginine, and arginine have been replaced by four amino acids alanine. Consequently, the inhibition by PAI-1 is reduced 80 times in comparison with alteplase.[11]

The modification of amino acid sequence changes in tenecteplase causes pharmacokinetic profile changes which can be seen in the table below.[11]

**Table 3**. Comparison of Pharmacokinetic Properties of Alteplase and Tenecteplase

| Agent | Fibrin specificity | Thrombolytic potency | PAI-I resistance | Fibrinogen depletion | PRT activity | Clearence (ml/kg/min |
|---|---|---|---|---|---|---|
| Alteplase | ++ | + | - | ++ | ++ | 16.1 |
| Tenecteplase | +++ | +++ | ++ | + | +++ | 1.9 |

*PAI-I* plasminogen activator inhibitor, *PRT* platelet-rich thrombus

Due to the modified structure, TNK has a longer half-life. The relatively long plasma half life of tenecteplase (approximately 17 minutes) allows for single bolus application in the thrombolytic treatment of acute myocardial infarction and proved to be as safe as the gold standard of thrombolytic therapy.[12] Tenecteplase for myocardial infarction (MI) has been approved, the safety profile of this drug can also be seen from the lower systemic bleeding complications. In addition to long half-lives, TNK has 14 times more specific effects on fibrin and is more resistant to degradation than plasminogen -1 activators compared with rt-PA. Theoretically, greater specificity for fibrin would provide a lower risk of bleeding in the treatment of MI .[7] Tenecteplase provides the benefit of a single-bolus dose compared to reteplase requiring two doses in which administration of the first dose and the second dose is made within 30 minute time difference. Because of the complicated doses of the regimen, potential treatment errors are common. Tenecteplase is much more expensive than streptokinase and is similar in price to alteplase and reteplase. Tenecteplase provides several benefits with respect to fewer noncerebral bleeding complications. The choice of thrombolytic agents between alteplase, reteplase, and tenecteplase for individual institutions can be made on the basis of cost without harming the patient.[10] The result of ATTEST 2015 showed that percentage of penumbra salvaged did not different significantly between the two treatment groups alteplase and tenecteplase; Incidence of symptomatic intracerebral haemorrhage, with either SITS-MOST definition or ECASS II definition, did not different between treatment groups.[13] Tenecteplase was associated with significantly better reperfusion at 24 hr (TNK = 79,3%; t-PA = 55%) and clinical outcomes than alteplase in patients with stroke who were selected on the basis of CT perfusion imaging.[14]

## V. CONCLUSION

Intravenous trombolystic or trombectomy is recommended medical management for Acute Ischemic Stroke (AIS) to get rid of problems raised due to blood clot or thrombus to renovate function to the affected area, which is also known as clot buster, has saved untold lives. Alteplase (t-PA) is the first thrombolytic agent for AIS is, but the use is limited by the short time periode (3-4,5h ). Alteplase is thrombolytic drug which has shorter plasma half life and lower fibrin selectivity than third generation trombolytic drugs. Tenecteplase is one of the third generation thrombolytics had their chemical structure slightly altered to increase fibrin specificity and to increase half-life. The relatively long plasma half-life of tenecteplase (approximately 17 minutes) allows for single bolus application in the thrombolytic treatment and proved to be as safe as the gold standard of thrombolytic therapy

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