Tenecteplase for Ischemic Stroke: A “New” Thrombolytic

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Disclosures

• Nothing to disclose
Objectives

• Identify a few differences between tenecteplase and alteplase in acute ischemic stroke
• Review current guideline recommendations for tenecteplase in acute ischemic stroke
• Appreciate some available evidence assessing tenecteplase safety and effectiveness versus alteplase in acute ischemic stroke
• Recognize how some institutions are using tenecteplase in acute ischemic stroke
Thrombolysis for Ischemic Stroke

• An acute ischemic stroke (AIS) is an arterial blockage that decreases blood flow in the brain

• Decreased blood flow causes cellular death by reducing oxygen and glucose delivery

• Restoring blood flow may prevent further cellular death

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Fibrin Clot Formation & Breakdown: Basic Mechanism

Vascular Endothelium

Fibrin (FIIα) → Thrombin (FIIa) → Fibrin (FIIα) → Fibrin Clot → Tissue Plasminogen Activator (tPA) → Plasminogen → Plasmin → Fibrin Degradation Products

Tissue Plasminogen Activator (tPA)

- Stimulated by fibrin formation
- Natural fibrinolytic peptide
- Catalyzes plasminogen to plasmin conversion
- Plasmin degrades fibrin clots
- Increasing tPA could increase fibrin degradation & restore blood flow in AIS

Commercially available tPA

Alteplase (Activase®) [ALT]

Tenecteplase (TNKase®) [TNK]

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What Evidence Lead to the Use of Commercially Available tPA in AIS?

Tissue Plasminogen Activator for Acute Ischemic Stroke
The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group

ECASS-3

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

NINDS-2

• Randomized, controlled trials (RCTs) comparing ALT 0.9 mg/kg up to 90 mg versus placebo in AIS with symptom onset of less than three hours or three to four and half hours

• Both studies found ALT associated with functional benefit at three months but with more frequent symptomatic intracranial hemorrhage (ICH)

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2013 Guidelines

- IV ALT is recommended in select AIS patients without contraindication that have symptom onset within 4.5 hours
- Usefulness of IV TNK in AIS is unclear, and its use should be reserved for clinical trial

2019 Guidelines

- IV ALT is recommended in select AIS patients without contraindication that have symptom onset within 4.5 hours
- IV TNK may be reasonable over ALT in AIS patients eligible for mechanical thrombectomy that do not have a thrombolytic contraindication
- IV TNK might be considered as an ALT alternative in minor AIS without major intracranial occlusion and contraindication to thrombolytic treatment

Why did the 2019 guidelines to decide to include TNK???

## Thrombolysis for Ischemic Stroke

### How are TNK and ALT Different???

<table>
<thead>
<tr>
<th></th>
<th>Cost per dose *</th>
<th>Half-life</th>
<th>Elimination time</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (Activase®)</td>
<td>$8,179</td>
<td>&lt; 5 minutes</td>
<td>&lt; 20 minutes</td>
</tr>
<tr>
<td>TNK (TNKase®)</td>
<td>$5,780</td>
<td>&gt;20 minutes</td>
<td>~ 80 minutes</td>
</tr>
<tr>
<td><strong>ALT vs. TNK</strong></td>
<td><strong>TNK costs ~ $2,400 less per dose</strong></td>
<td><strong>TNK has a longer half-life</strong></td>
<td><strong>TNK takes longer to eliminate</strong></td>
</tr>
</tbody>
</table>

* Costs from our wholesale pharmacy distributor

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Thrombolysis for Ischemic Stroke

How are TNK and ALT Different???

**tPA Elimination**

- Both ALT & TNK are hepatically metabolized
- ALT is recombinant tPA and is susceptible to PAI-1 inactivation
- TNK is genetically modified ALT and has more PAI-1 resistance
- TNK has a much longer half-life versus ALT, and it takes longer to eliminate

**ALT** → *Must be given as a bolus and infusion*

Recommended dose: 0.9 mg/kg up to 90 mg (10% bolus over one minute, 90% infusion over one hour)

**TNK** → *May be given as a bolus without infusion*

Studied doses: 0.1 - 0.4 mg/kg bolus over five seconds

TNK dosing strategy less complex versus ALT in AIS
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How are TNK and ALT Different??

**ALT**: Bolus and infusion preparation

Materials required for ALT Preparation & Administration

1. ALT 100 mg kit containing lyophilized powder & diluent
2. Needles & syringes
3. Alcohol swabs
4. Saline flush for ALT bolus
5. Intravenous infusion pump for ALT infusion
6. Infusion pump tubing for ALT infusion
7. Saline flush bag for ALT infusion

TNK: Bolus preparation only

Materials required for TNK Preparation & Administration

1. TNK 50 mg kit containing lyophilized powder, diluent, needle, syringe and alcohol swabs
2. Saline flush for TNK bolus

TNK requires fewer materials for preparation & administration

TNK preparation & administration is less complex versus ALT
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How are TNK and ALT Different???

Do these differences in preparation and administration impact administration times??

**Original Research**

Tenecteplase Improves Door-to-Needle Time in Real-World Acute Stroke Treatment

- Retrospective chart review including 113 patients given TNK or ALT for AIS

**Brief Report**

Switching to Tenecteplase for Stroke Thrombolysis

Real-World Experience and Outcomes in a Regional Stroke Network

- Retrospective chart review including 838 patients given TNK or ALT for AIS

TNK decreases door-to-thrombolytic time versus ALT and may be easier to prepare and administer in AIS

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How are TNK and ALT Different???

Summary

**TNK has a lower cost per dose versus ALT**
Pharmacy acquisition cost per dose is > $2,000 less for TNK versus ALT at our institution

**TNK is easier to prepare and administer versus ALT**
TNK has genetic mutations that prolong its elimination versus ALT
TNK can be given as a bolus alone while ALT requires a bolus and an infusion
TNK requires fewer materials for preparation and administration
Evidence suggests TNK decreases door-to-thrombolytic time versus ALT in AIS

How do ALT & TNK Compare in Terms of Safety and Effectiveness in AIS???
Thrombolysis for Ischemic Stroke

2013 Guidelines

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

• IV ALT is recommended in select AIS patients without contraindication that have symptom onset within 4.5 hours
• Usefulness of IV TNK in AIS is unclear, and its use should be reserved for clinical trial

2019 Guidelines

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• IV ALT is recommended in select AIS patients without contraindication that have symptom onset within 4.5 hours
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Why did the 2019 guidelines decide to include TNK???

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How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS??

**Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke**

**EXTEND-IA TNK**

- RCT including 202 AIS with large vessel occlusion (LVO) and planned endovascular thrombectomy
- Patients received ALT 0.9 mg/kg up to 90 mg or TNK 0.25 mg/kg up to 25 mg within 4.5 hours of symptom onset
- TNK patients had higher incidence of recanalization at angiographic assessment and better 90-day functional outcomes
- Symptomatic ICH rates were similar with ALT & TNK
- **Conclusion**: TNK before thrombectomy had higher recanalization and better functional outcomes

**2019 Guidelines**

- **AHA/ASA Guideline**

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  - IV TNK may be reasonable over ALT in AIS patients eligible for mechanical thrombectomy that do not have a thrombolytic contraindication

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How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

NOR-TEST

• RCT including 1100 suspected AIS patients
• Patients received ALT 0.9 mg/kg up to 90 mg or TNK 0.4 mg/kg up to 40 mg within 4.5 hours of symptom onset
• Most had minor stroke severity at initial assessment and < 20% had AIS or transient ischemic attack as a final diagnosis
• There were no statistical differences in the rates of good or excellent outcome or ICH
• **Conclusion:** TNK was not superior to ALT in AIS but had comparable safety

2019 Guidelines

**AHA/ASA Guideline**

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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Thrombolyis for Ischemic Stroke

How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

- Meta-analysis including 8 studies and > 2,000 patients given TNK or ALT for AIS
- Some studies utilized advanced imaging and/or mechanical thrombectomy
- Treatment window varied but was up to six hours after symptom onset
- ALT dosed 0.9 mg/kg and TNK dosed 0.1 mg/kg, 0.25 mg/kg or 0.4 mg/kg
- TNK had higher rates of early neurologic improvement
- No differences in good or excellent functional outcome, ICH and death

TNK & ALT appear to have similar effectiveness and safety in AIS

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How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

- Meta-analysis including four RCTs and > 400 AIS patients with LVO
- Three studies used a thrombolytic in combination with endovascular intervention
- ALT 0.9 mg/kg versus TNK 0.1 mg/kg, 0.25 mg/kg or 0.4 mg/kg
- TNK associated with increased odds for successful recanalization and functional improvement
- Similar rates of early neurologic improvement, functional independence, ICH, and all cause-mortality

TNK may have additional benefit with similar safety versus ALT in AIS with LVO

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How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

- Abstract presented at 2022 International Stroke Conference
- Registry study including 7,891 patients given IV TNK or ALT for AIS
- TNK had lower symptomatic ICH rates (ALT 3.71% vs. TNK 2.13%, p = 0.002)
- TNK had lower symptomatic ICH rates in non-thrombectomy patients
- TNK did not have lower symptomatic ICH rates in thrombectomy patients

TNK appears at least as safe versus ALT in AIS, and it may potentially have a safety benefit

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Summary

• TNK appears to be at least as effective versus ALT in AIS and it may have additional benefit with LVOs and those undergoing mechanical thrombectomy

• TNK appears to be at least as safe versus ALT in AIS and recent evidence suggests TNK may have a potential safety advantage versus ALT, as TNK was associated with less symptomatic ICH
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There are Some Unclear Considerations with TNK in AIS

TNK is not FDA Approved for AIS
- Unclear if FDA is considering approving TNK for AIS
- There are at least five studies recruiting patients to assess TNK in AIS

TNK is not the Guideline Preferred Thrombolytic for AIS
- ALT \rightarrow\text{ guideline preferred thrombolytic}
- ALT \rightarrow\text{ More experience and familiarity}
- Confusing TNK recommendations in 2019 guideline update
  - Maybe reasonable to use TNK over ALT in AIS eligible for thrombectomy
  - TNK might be considered in minor stroke without major intracranial occlusion

Optimal TNK Dosing in AIS Unclear
- Studies utilized TNK doses of 0.1 mg/kg, 0.25 mg/kg and 0.4 mg/kg in AIS
- All doses at least as effective versus ALT
- All doses similar safety versus ALT
- TNK 0.25 mg/kg may be more effective versus ALT with thrombectomy

TNK Treatment Window Unclear
- Unclear if treatment window same or different versus ALT
- Most clinical trials have used a treatment window of <3 – 6 hours from symptom onset
- TNK at least as safe and effective versus ALT at all time points
- Current 4.5-hour treatment window is most likely appropriate currently

Institutions should likely assess these considerations before using TNK in AIS

Are experts currently recommending TNK in AIS???

Some Experts are Now Recommending Clinicians Consider using TNK in AIS

Using Tenecteplase for Acute Ischemic Stroke: What Is the Hold Up?

Conclusion

Tenecteplase is at least as effective as alteplase with regards to neurologic improvement after treatment of acute ischemic stroke. Additionally, tenecteplase is less expensive, easier to administer, and may have less bleeding complications than alteplase. Thus, physicians should consider using tenecteplase rather than alteplase for thrombolysis of acute ischemic stroke. If used, the preferred dose of tenecteplase is 0.25 mg/kg (maximum 25 mg).

How are institutions using TNK in AIS???
How are Institutions Using TNK in AIS???

Complete transition from ALT to TNK

- Medical center adopted TNK over ALT in disabling AIS without contraindication and symptom onset within 4.5 hours
- Institution recognizes transition is neither FDA or guideline approved but felt the logistical benefits with TNK were worthwhile
- TNK was dosed 0.25 mg/kg up to 25 mg
- Advised against using multiple thrombolytics with different dosing profiles to prevent dosing errors
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How are Institutions Using TNK when treating AIS??

Both TNK and ALT Available

- Institutions using this approach develop protocols and they are sometimes complex
- Decision to utilize TNK versus ALT dependent on indication and provider discretion
- This approach has error potential, most notably confusing thrombolytics

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How are Institutions Using TNK when treating AIS??

Both TNK and ALT Available

• Additional safety measures likely required with this approach
• One institution created a ‘code stroke box’ with separately packaged thrombolytic agents
• Each compartment included all materials required for preparation
• Dosing and administration instructions for TNK and ALT were updated in the order set

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Summary – TNK for AIS

• TNK is an ALT alternative not currently FDA approved for AIS
• TNK is easier to prepare, easier to administer, less costly and it may decrease door-to-thrombolytic time versus ALT
• TNK appears to be at least as effective versus ALT in AIS and it maybe more effective with LVO and mechanical thrombectomy
• TNK appears to be at least as safe versus ALT in AIS and recent evidence suggests it may cause less symptomatic ICH
• ALT is still the guideline preferred thrombolytic with AIS, but the guidelines do state it maybe reasonable to use TNK over ALT with mechanical thrombectomy without thrombolytic contraindications and that TNK might be considered as an ALT alternative in minor strokes without LVO
• There are some unclear considerations on how to use TNK in AIS, but the evidence is strongly encouraging, and some institutions are now using the medication for this indication
Questions???