Curr Treat Options Cardio Med (2023) 25:15–28
DOI 10.1007/s11936-022-00973-2

Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Intravenous Thrombolytics in the Treatment of Acute Ischemic Stroke

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Published online: 2 January 2023

This article is part of the Topical Collection on *Cerebrovascular Disease and Stroke*

Keywords Tenecteplase · Ischemic stroke · Thrombolysis

Abstract

Purpose of Review To review the current evidence and ongoing clinical trials evaluating the efficacy and safety of tenecteplase (TNK), an alternative tissue plasminogen activator (tPA), in the acute management of arterial ischemic stroke (AIS). To date, alteplase is the only tPA approved by the United States FDA for use in AIS.

Recent Findings There have been multiple phase two and three trials investigating the safety and efficacy of TNK in AIS. In patients with AIS due to large vessel occlusion, one randomized controlled trial demonstrated superiority of TNK for vessel recanalization rates and long-term functional outcomes when compared to alteplase. A meta-analysis of all phase two and three trials evaluating TNK in AIS concluded that TNK has a comparable safety and efficacy profile to alteplase. The results of these trials prompted new recommendations in the Acute Stroke Guideline published by the AHA suggesting it may be reasonable to use as an alternative to alteplase. Furthermore, recent real-world data has also reported decreased door-to-needle time with TNK utilization.

Summary In patients with AIS, use of a thrombolytic agent is standard of care and has been shown to reduce neurological disability and improve functional outcome. Randomized controlled trials have demonstrated that TNK is non-inferior to alteplase from a clinical

outcome and safety standpoint. The existing data evaluating the efficacy of TNK compared to alteplase in acute AIS within 4.5 h from symptom onset showed no significant difference between these two agents with regard to functional outcome at 90 days but improved median time to treatment and large vessel recanalization in TNK-treated patients. The results from ongoing TNK trials in larger patient cohorts and in wake-up stroke populations will be instrumental to the wide-scale utilization of TNK in acute AIS management.

Introduction

Stroke is a leading cause of long-term disability and ranks fifth among all causes of death in the USA [1]. Stroke statistics published by the CDC reveal that approximately 87% of strokes are arterial ischemic strokes (AIS), and nearly one in four strokes are recurrent strokes [1]. Throughout the past three decades, alteplase is the only thrombolytic agent approved by the FDA for use in AIS to improve long-term outcomes. Alteplase, a recombinant tissue-type plasminogen activator (tPA), is a glycoprotein composed of 527 amino acids with five structural domains synthesized from the complementary DNA of the endogenous serine protease abundant in endothelial cells. Endogenous tPA and recombinant alteplase break down fibrin in thrombi by cleaving fibrin-bound plasminogen to plasmin, a proteolytic enzyme involved in fibrinolysis [2]. While revolutionizing standard acute stroke care, the use of alteplase comes with rare but serious complications and limitations in administration. Alteplase is associated with an increased risk of major bleeding and intracranial hemorrhage [3]. Regarding alteplase administration, the very short half-life (4–5 min) necessitates a bolus and infusion-based approach. Furthermore, there is risk of rapid inactivation of alteplase by the endogenous tPA antagonists like plasminogen activator inhibitor-1 (PAI-1).

The limitations of alteplase prompted a fervent search for newer, more favorable thrombolytic agents and subsequent studies and clinical trials to evaluate their efficacy and safety in comparison to alteplase. In this review, we will provide a background on the investigations into alternative thrombolytic agents and then discuss, in depth, the pre-clinical and clinical trial rationale for TNK in AIS.

Alternatives to alteplase

The search for alternatives to alteplase leads to the discovery of several thrombolytic agents, either by isolation of new naturally occurring thrombolytic enzymes or by further modifications of the recombinant tissue plasminogen activator. Desmoteplase and reteplase were two thrombolytic agents studied in the acute management of arterial ischemic stroke.

Desmoteplase, a thrombolytic enzyme derived from vampire bat saliva with noted high fibrin specificity, was one of the earliest alternative tPAs that was studied extensively in AIS and yielded conflicting data regarding efficacy [4]. Desmoteplase was selected due to its longer half-life and minimal neurotoxicity and was considered for extended window treatment of AIS: for patients presenting 3–9 h after onset of symptoms. Unfortunately, while early randomized controlled trials (RCTs) showed higher rates of reperfusion compared to placebo, a meta-analysis of RCT data failed to demonstrate any

improvement in neurological outcome at 90 days in patients treated with desmoteplase compared to placebo [4–6].

Reteplase, another recombinant thrombolytic agent modified from endogenous tPA that is fibrin specific and has a longer half-life [7], was tested in an early small clinical trial in patients who were not candidates for IV thrombolytics [8]. Reteplase was administered intra-arterially and reported to improve rates of recanalization compared to angioplasty alone. Subsequently, the ROSIE (Reo-pro Retevase Reperfusion of Stroke safety Imaging Evaluation) and ROSIE-CT trials evaluated intravenous reteplase in combination with abciximab in acute AIS. Preliminary analyses showed no increased risk of symptomatic ICH, but no published efficacy outcomes from these trials were available for review [9]. Further data on the intravenous use of reteplase remains sparse and conflicted, with some case series and review articles reporting no benefit compared to alteplase [10]. A relatively recent clinical trial that aimed to demonstrate the benefit of adding aspirin to a thrombolytic agent in hyperacute AIS included a sub-analysis of alteplase compared to reteplase administered as a two-dose IV bolus + infusion, and did not show a benefit for reteplase over alteplase with regard to mRS score and NIHSS score at 30 days post-treatment [11].

The search for alternative thrombolytic agents also produced tenecteplase (TNK), a protein derived from mutagen analyses performed on alteplase. Amino acid changes at three locations in the structure of alteplase created TNK: a substitution of threonine at site 103 (T) with asparagine, asparagine at 117 (N) replaced with glutamine (both in the kringle domain of the protein) and lysine (K), histidine and two arginines replaced with four alanines at sites 296–299 (in the protease domain) [12]. TNK exhibited favorable pharmacokinetic properties when compared to alteplase including tenfold greater thrombolytic potency, 6- to eightfold slower clearance, and an 80-fold increased resistance to PAI-1 [13, 14]. Initial trials for the use of TNK as a thrombolytic agent were in the management of acute ST elevation myocardial infarction (STEMI). When compared to alteplase, TNK had similar efficacy and significantly fewer extracranial bleeding complications in STEMI patients [15]. Ultimately, when percutaneous intervention (PCI) became standard of care for management of STEMI, with further studies showing that preceding PCI with thrombolysis with TNK had an unfavorable outcome, TNK became reserved for treatment of STEMI when PCI was not available or possible [14].

Pilot studies evaluating the use of TNK in the management of AIS were performed as early as 2005. In a pilot dose-escalation safety study, Haley et al. tested ascending doses of TNK for AIS patients within 3 h of stroke symptom onset. No symptomatic ICH was reported for the 0.1, 0.2, and 0.4 mg/kg TNK tiers (25 patients per tier) and enrollment into the 0.5 mg/kg tier was terminated after 2 of 13 patients had symptomatic ICH [16]. In 2009, Parsons et al. reported the results of a prospective, nonrandomized, pilot study of TNK (0.1 mg/kg) given 3 to 6 h after stroke onset compared to alteplase within 3 h of stroke onset [17]. Of 15 patients treated with TNK, rates of reperfusion (74% vs. 44%; $P = 0.01$) and major vessel recanalization (10/15 patients TNK vs. 7/29 patients alteplase; $P = 0.01$) were higher with TNK. Notable eligibility criteria for this study included an associated vessel occlusion and a perfusion lesion > 20% of the infarct core in the TNK arm, While the imaging selection

differences and nonrandomized study design limited definitive conclusions on the efficacy of TNK, this study provided further evidence of the need for subsequent randomized clinical trials comparing TNK to alteplase in AIS.

Between 2005 and 2017, three small randomized clinical trials of TNK for AIS thrombolysis had been reported [18–20] and will be discussed next. In summary, the search for alternatives to alteplase yielded several agents, with tenecteplase showing promise in early clinical trials.

Early randomized clinical trials for TNK in AIS

In 2010, Haley et al. continued their work and pursued an adaptive sequential design phase IIB/III dose-finding RCT comparing 0.1, 0.25, and 0.4 mg/kg TNK with 0.9 mg/kg alteplase [20]. The original intent was to use 24-h early neurological improvement and symptomatic ICH to identify a single TNK dose for the remainder of the trial and a goal of 100 participants in both arms. This trial, however, was prematurely terminated due to slow enrollment with only 112 patients enrolled over 2 years. The 0.4 mg/kg dose was discarded as inferior after 14 triplets of TNK patients completed the 24-h follow-up based on the pre-specified rapid response outcome, a composite score of sICH and NIHSS score improvement post-treatment. The cumulative difference between the 0.1 and 0.25 mg/kg TNK doses at 24 h did not achieve the pre-defined difference for the dose selection criterion. At 90 days, there was no statistically significant difference in good functional outcomes (mRS < 2) between groups (TNK 0.1 mg/kg: 45.2%, 95% CI 27.3–64; TNK 0.25 mg/kg: 48.4%, 95% CI 30.2–66.9; and alteplase 0.9 mg/kg: 41.9%, 95% CI 24.6–60.9; 31 participants per arm).

Following this trial, the Australian TNK trial by Parsons et al. enrolled 75 AIS patients randomized to TNK doses of 0.1 mg/kg and 0.25 mg/kg or alteplase 0.9 mg/kg up to 6 h after stroke onset as part of a phase IIB trial [19]. Notable inclusion criteria were a confirmed intracranial vessel occlusion on CT angiogram and a target mismatch > 20% on CT perfusion. Twenty-five AIS patients were enrolled in each arm. The primary outcomes were rates of reperfusion, defined as the change in perfusion lesion volume at 24 h compared to baseline, and a change in NIHSS score at 24 h post-treatment. The pooled TNK group ($N = 50$) had better reperfusion rates (TNK: 79.3%; alteplase: 55.4%; $P = 0.004$) and improvement in NIHSS score at 24 h (TNK: 8.0; alteplase 3.0; $P < 0.001$). Furthermore, the pooled TNK group had reduced infarct growth and a higher proportion of patients with mRS < 3 at 90 days compared to the alteplase group (TNK: 72%; alteplase: 44%, $P = 0.02$). The results of the Australian TNK trial demonstrated that in AIS patients with confirmed intracranial vessel occlusion and target mismatch, TNK is associated with better reperfusion and clinical outcomes compared to alteplase.

The third early trial looking at TNK thrombolysis in various AIS subgroups, the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST, NCT01472926), sought to investigate the safety and efficacy of TNK compared to alteplase in AIS patients within 4.5 h of stroke onset, notably, not predicated on the utilization of advanced neuroimaging [18].

As a single-center, phase 2, open-label RCT, ATTEST compared TNK 0.25 mg/kg with alteplase 0.9 mg/kg in supratentorial AIS patients within 4.5 h of stroke onset. The primary endpoint of ATTEST was percentage of penumbra salvaged, defined as CT perfusion-defined penumbra at baseline minus CT infarct volume at 24–48 h. One hundred four AIS patients were enrolled with 71 patients available for primary endpoint analysis. No difference was observed in the percentage of penumbra salvaged between the TNK and alteplase groups (TNK: 68%; alteplase 68%; $P = 0.81$). In addition, no difference in rates of symptomatic ICH was observed between groups. While ATTEST showed a comparable safety profile for TNK compared to alteplase, potential baseline imbalances were found between groups that may have impacted the results, including non-significant larger ischemic core volumes and higher rates of ICA/M1 occlusions in TNK patients (Table 1).

Building on these randomized trials, further studies to evaluate safety, dosing, and feasibility of TNK in AIS were performed. The TNK-Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke with Proven Occlusion (TEMPO-1, NCT01654445) trial investigated TNK in AIS patients within 12 h of stroke onset with minor stroke (NIHSS < 6) and intracranial arterial occlusion. TEMPO-1 was a multicenter, dose-escalation, phase II trial to demonstrate the safety and feasibility of TNK in minor stroke patients [21]. Of fifty patients enrolled, half were treated with 0.1 mg/kg and half with 0.25 mg/kg TNK. Median NIHSS score was 2.5. No patients in the 0.1 mg/kg group had symptomatic ICH and 1 out of 25 patients in the 0.25 mg/kg group had symptomatic ICH. Recanalization rates were high with TNK treatment (0.1 mg/kg, 39% complete; 0.25 mg/kg, 52% complete) and associated with excellent functional outcome (mRS < 2: RR 1.65; 95% CI 1.09–2.5; $P = 0.026$). The TEMPO 1 dose-escalation study showed safety and feasibility of TNK thrombolytic treatment for minor stroke with intracranial occlusion, a group often excluded from AIS RCTs [21].

Another study evaluated the safety and feasibility of extended window treatment with TNK; the penumbral-based novel Thrombolytic Therapy in Acute Ischemic Stroke Study was a prospective, nonrandomized phase II study of 0.25 mg/kg TNK in AIS patients 4.5–24 h from stroke onset with target mismatch on baseline CTP/MRP (NCT02101606) [22]. Of 16 AIS patients treated with TNK at a median 9.6 h from stroke onset, one symptomatic ICH occurred. The TNK treatment group also observed 48.3 mL penumbral salvage volume. The results of this pilot study suggest that TNK treatment of AIS patients 4.5–24 h from stroke onset is feasible. Overall, the results of the early-stage TNK trials suggest that TNK treatment of AIS patients is feasible and with comparable safety profiles to alteplase (Table 2).

Recent RCTs for TNK in AIS

Building on the results of the early TNK studies and phase IIB trials in AIS, subsequent RCTs were pursued investigating TNK efficacy in phase III AIS trials. The largest trial to date that examined the efficacy and safety of TNK in a head-to-head comparison with alteplase was the NOR-TEST trial: tenecteplase

Table 1 Randomized clinical trials

Study	ATTEST [18]	Australian TNK trial [19]	Haley et al. [20]	EXTEND-IA TNK [24•]	NOR-TEST [23]
Design	RCT phase II	RCT phase IIB	RCT Phase IIB/III	Phase III open-label blinded endpoint RCT	Phase III open-label blinded endpoint RCT
Inclusion criteria	Supratentorial AIS	CTP: penumbra ≥ 20% core+ CTA occlusion	AIS < 3 h	Evidence of proximal LVO on CTA + eligible for EVT	Clinically suspected AIS with measurable deficit on NIHSS + eligible for EVT
N	104	75	112	202	1100
TNK dose (mg/kg) (*n*)	0.25 (*n* = 52)	0.1 (*n* = 25) 0.25 (*n* = 25)	0.1 (*n* = 31) 0.25 (*n* = 31) 0.4 (*n* = 19)	0.25 mg/kg	0.4 mg/kg
Treatment window	4.5 h	6 h	3 h	< 4.5 h from LKW	< 4.5 h from LKW or from Awakening
Imaging selection	NCCT	CTP and CTA	NCCT	CTA/CTP: perfusion mismatch for anterior circulation strokes on CTP; ratio of > 1.2, absolute difference in volume > 10 ml, ischemic core volume < 70 ml *	NCCT for < 4.5 h from LKW MRI (DWI/FLAIR) mismatch for < 4.5 h from awakening
Primary outcome	**Salvaged penumbra** 68% TNK *p 0.81* 68% alteplase	**Reperfusion** 79.3% TNK *p 0.004* 55.4% alteplase **NIHSS improvement** 8 TNK *p < 0.001* 3 Alteplase	**90 Day mRS** mRS < 2 TNK 0.1 mg/kg: 45.2% TNK 0.25 mg/kg: 48.4% Alteplase 0.9 mg/kg: 41.9%	**Reperfusion > 50%** at time of angiogram **OR absence of retrievable thrombus** at time of the initial angiogram: **22% TNK vs. 10% Alteplase** *(P = 0.002 for non-inferiority; P = 0.03 for superiority)*	**Excellent functional outcome**: mRS score 0–1 at 90 days: **64% TNK vs. 63% Alteplase** *(P = 0.52)*
sICH	2% TNK *p 0.5* 4% alteplase	4% TNK *p 0.33* 12% alteplase	0% 0.1 mg/kg TNK 6.5% 0.25 mg/kg TNK 8% 0.4 mg/kg TNK 3.2% alteplase	1% in both groups	**Any ICH at 24–48 h:** 9% for both **sICH at 24–48 h:** 3% for TNK 2% for alteplase

Table 1 (continued)

Study	ATTEST [18]	Australian TNK trial [19]	Haley et al. [20]	EXTEND-IA TNK [24•]	NOR-TEST [23]
Conclusion	Outcomes did not differ between groups	TNK had better reperfusion rates and clinical outcomes	TNK 0.4 mg/kg was discarded as inferior	TNK associated with improved reperfusion and improved functional outcomes No significant difference in number of patients with no/minimal disability at 90 days (mRS < 2)	Further studies necessary to establish non-inferiority of TNK and safety/efficacy in moderate/severe strokes

*This criterion was removed after ~80 patients enrolled due to analysis from other trials demonstrating benefit in patients with larger ischemic core volumes

Table 2 Observational studies and nonrandomized trials

Study	Haley et al. [16]	Kate et al. [22]	TEMPO-1 [21]	Parsons et al. [17]
Design	Dose-finding	Single arm	Dose escalation	Prospective
Inclusion criteria	NINDS, 1995	CBV or ASPECTS > 6 + mismatch score > 2	TIA or minor stroke + CTA occlusion	Penumbra ≥ 20% core + CTA occlusion
n	88	16	50	50
TNK dose (mg/kg) (n)	0.1 ($n=25$) 0.2 ($n=25$) 0.4 ($n=25$) 0.5 ($n=13$)	0.25 ($n=16$)	0.1 ($n=25$) 0.25 ($n=25$)	0.1 ($n=15$)
Treatment window	3 h	4.5–24 h	12 h	3–6 h for TNK group < 3 h for alteplase group
Imaging selection	NCCT	CTP or PWI	CT and CTA	Perfusion/angiographic imaging with CT/MRI
Primary outcome	sICH	sICH	Drug-related serious adverse events	**Rates of reperfusion** 74% TNK vs. 44% Alteplase; $P=0.01$ **Major vessel recanalization:** 10/15 patients TNK vs. 7/29 Alteplase; $P=0.01$
sICH	0.1–0.4 mg/kg dose: **0%** 0.5 mg/kg dose: **15%**	1 (6.3%)	0% in both groups	0% TNK 11.4% Alteplase
Conclusion	TNK 0.1–0.4 mg/kg dose is safe in AIS	TNK is feasible in AIS patients with penumbra 4–24 h after stroke onset	TNK is feasible and safe for TIA or minor stroke with LVO	TNK may be efficacious in AIS within 3–6 h onset with advanced imaging selection

versus alteplase for management of acute ischemic stroke; a multicenter phase 3, randomized, open-label, blinded endpoint trial [23]. This study enrolled patients with AIS within 4.5 h of symptom onset or awakening with symptoms. Patients with wake-up stroke or unknown onset of symptoms underwent advanced neuroimaging selection (received TNK if mismatch on DWI/FLAIR MRI was present). Importantly, this trial administered a dose of TNK previously thought to be associated with higher rates of hemorrhagic complications (0.4 mg/kg up to a maximum of 40 mg). A total of 1100 patients were enrolled, with the median NIHSS at 4 points. Mild stroke among most participants was another key distinguishing feature of this trial. The primary outcome was the proportion of patients with excellent functional outcome (mRS 0–1) in each arm at 3 months. This was achieved by 354 (64%) patients in the tenecteplase group and 345 (63%) patients in the alteplase group (OR 1.08, 95% CI 0.84–1.38; $P = 0.52$). Mortality at 90 days and frequency of serious adverse events were similar in both arms. Notable limitations of NOR-TEST, however, were the aforementioned mild stroke severity, high rates of stroke mimics (17–18%), and protocol deviations (12%). While NOR-TEST again demonstrated that TNK has a similar safety profile to alteplase, including at the 0.4 mg/kg dose, further studies were necessary to establish TNK efficacy in AIS.

The most recently published RCT evaluating the efficacy of TNK in AIS is EXTEND-IA TNK, Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke [24•]. EXTEND-IA TNK examined whether there was any difference in achieving recanalization with TNK treatment within 4.5 h of symptom onset compared to alteplase, in patients with large vessel occlusions prior to receiving mechanical thrombectomy. A total of 202 patients were enrolled and randomized to TNK 0.25 mg/kg (maximum dose 25 mg) or alteplase 0.9 mg/kg (maximum dose, 90 mg). The primary outcome of reperfusion of more than 50% of the involved ischemic territory or an absence of intraluminal clot at the time of initial angiogram was achieved in 22% of the patients treated with TNK vs. 10% of those treated with alteplase (incidence difference: 12 percentage points; 95% CI). Furthermore, improved functional outcome was observed in the TNK group compared to the alteplase group: median mRS at 90 days was 2 vs. 3 (common odds ratio, 1.7; 95% CI, 1.0 to 2.8; $P = 0.04$). Major complications including intracranial hemorrhage occurred in 1% of each group. The results of EXTEND-IA TNK demonstrated that TNK 0.25 mg/kg was non-inferior to alteplase for reperfusion of the LVO territory and associated with better functional outcomes. While the results of EXTEND-IA TNK are encouraging for TNK efficacy, the generalizability of these findings is somewhat limited given that this was a trial of EVT eligible LVO patients treated with thrombolysis, an AIS subgroup that comprises approximately 13% of all AIS patients [24•]. Furthermore, a recently published follow-up pooled analysis of the EXTEND-IA TNK trials compared the treatment effect of TNK vs. alteplase stratifying for patient age (> 80 years). Interestingly, there were no differences between the treatment arms in younger patients in contrast to the group of older patients where TNK dosed at 0.25 mg/kg was associated with improved 90-day mRS with lower mortality rates in patients over 80 years of age [25].

A meta-analysis of the data presented in the five RCTs that investigated TNK versus alteplase in AIS pooled clinical information from 1585 patients with AIS [26••]. The main result from this meta-analysis showed cumulative rates of excellent functional outcome at 3 months (mRS 0–1) were similar between TNK- and alteplase-treated patients (TNK 57.9% versus alteplase 55.4%). Of note, the TNK analysis was based on pooled analysis of doses (0.1, 0.25, and 0.4 mg/kg) from the aforementioned trials with almost one third of patients having received either 0.1 mg/kg (6.8%) or 0.25 mg/kg (24.6%) doses. The overall conclusion of this meta-analysis was that TNK is non-inferior to alteplase for AIS functional outcomes and has a comparable safety profile.

The results of NOR-TEST and EXTEND-IA TNK additionally provided moderate quality evidence that supported the two new recommendations in the guideline for the management of AIS published by the American Heart Association/American Stroke Association in 2019 pertaining to the use of TNK: a single intravenous bolus of 0.25 mg/kg (maximum 25 mg) of TNK can be used as an alternative to intravenous alteplase in patients who can receive thrombolytic therapy and are eligible to undergo mechanical thrombectomy, and TNK given as a 0.4-mg/kg bolus can be used instead of alteplase in patients with minor neurological symptoms and no large vessel occlusion [27].

TNK implementation in clinical practice

On a practical level, the ease of administration of TNK, its cost effectiveness, and the growing body of evidence demonstrating the safety and efficacy of TNK have led many comprehensive stroke centers, such as our institution Massachusetts General Hospital, to recently switch to TNK from alteplase. As a result, safety and clinical outcome data are now available on the TNK experience in clinical practice.

In March of 2020, the Hyper-acute Stroke Network in New Zealand switched to TNK, and Mahawish et al. reported the following findings after TNK implementation: better functional outcomes (favorable mRS score 0–2) with TNK demonstrated by both shift analysis (adjusted OR, 1.60 [95% CI, 1.15–2.22]) and dichotomous analyses (modified adjusted OR, 2.17 [95% CI, 1.31–3.59]), and shorter median (IQR) door-to-needle time (median, 53 [38–73.5] vs. 61 min [45–85], $P = 0.0002$) when compared with alteplase [28]. Importantly, no increase in symptomatic intracranial hemorrhage was observed in patients treated with TNK. Zhong et al. also published outcomes from the New Zealand experience and performed a retrospective analysis of data acquired from 1 comprehensive and 2 regional stroke centers [29]. They found that TNK had a comparable safety profile to alteplase; sICH occurred in 1.8% of the TNK cohort vs. 2.7% of those patients treated with alteplase ($P = 0.75$), and rates of angioedema were similar in both groups. The percent of patients achieving functional independence at 90 days was also similar between the groups.

From Greece, a smaller prospective study reported on their experience with switching to TNK. They noted a higher rate of averted thrombectomies in addition to a higher rate of neurological improvement at 24 h in the TNK group. These observations did not reach statistical significance. They also noted a slightly increased rate of sICH in patients who received TNK (16% vs. 5% in the alteplase group, $P = 0.201$). Measures of functional outcomes were similar in both groups at all time points studied [30].

Hall et al. published their findings after switching to TNK at their comprehensive stroke center in New Jersey, USA. Their main finding was that patients receiving TNK had a significantly faster door-to-needle time when compared to alteplase patients (median time 41 min [IQR, 34–62 min] vs. 58 min [IQR 45–70 min]; $P < 0.01$) with no significant difference in symptomatic intracranial hemorrhage (2% vs. 7%; $P = 0.37$) [31]. The results of these real-world accounts of the impact of TNK on stroke quality measures are promising and potentially represent additional benefits for TNK in comparison to alteplase.

The recent strain placed on alteplase supply in the context of the global public health crisis produced by the COVID-19 pandemic induced an additional motivation to switch to the use of TNK for AIS, not only as an alternative to alteplase, but to also minimize time of exposure/interaction between health care providers and patients under contact precautions due to its much-simplified workflow [32]. As previously mentioned, TNK is given as a single intravenous bolus over 5 s and takes 2 min to prepare and administer [32].

Ongoing clinical trials and future directions

The current clinical trial landscape for TNK in AIS demonstrates a significant amount of momentum to clearly establish efficacy of TNK in AIS. Recent RCTs evaluating the efficacy of TNK were critiqued for issues with generalizability (recruitment of proximal LVO patients only in EXTEND-IA TNK), potential bias towards enrolment of patients with milder strokes (median NIHSS of 4 in the NOR-TEST trial), and small sample size not powered to demonstrate non-inferiority or superiority of TNK (e.g., ATTEST trial). The limitations of these earlier trials in combination with their results suggesting non-inferiority or possibly superiority of TNK over alteplase have prompted subsequent RCTs to further probe this question. The Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2/ NCT02814409) is currently underway in the UK and aims to enroll 1870 participants to assess whether TNK is superior in efficacy to alteplase, based on functional outcome (mRS at 90 days). The Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE, ACTRN12613000243718) trial aims to recruit 400 AIS patients not treated with endovascular thrombectomy across Australia and the UK with the same primary aim as ATTEST-2.

In light of recent data demonstrating improvement in clinical outcomes in carefully selected stroke patients treated with alteplase beyond 4.5 h from symptom onset including those with wake-up stroke [33], several trials are underway to examine whether a similar benefit is observed for these

stroke subgroups in patients treated with TNK. TIMELESS (NCT03785678) is a phase III, prospective, double-blind, randomized, placebo-controlled trial of thrombolysis in imaging-eligible, late-window patients to assess the efficacy and safety of tenecteplase. Recruitment is underway across 122 centers in the USA and Canada, and its primary aim is to compare the efficacy of TNK versus placebo (functional outcome at day 90) in AIS patients presenting between 4.5 and 24 h of symptom onset with a demonstrated proximal large vessel occlusion eligible for endovascular thrombectomy.

Extending the time window for tenecteplase by effective reperfusion in patients with large vessel occlusion (ETERNAL-LVO, NCT04454788) is another RCT that plans to enroll 700 patients with AIS and LVO, which are EVT candidates with demonstrated mismatch on CTP within 24 h of symptom onset, and will be randomized to receive standard of care (alteplase within 4.5 h of onset) or TNK regardless of symptom onset prior to EVT. Primary outcome is mRS at 90 days.

Finally, one study will examine the safety and efficacy of TNK exclusively in wake-up stroke patients: Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST/NCT03181360). No advanced neuroimaging will be employed in this trial that is underway in Norway and aims to recruit 600 patients randomized to standard of care versus thrombolysis with TNK 0.25 mg/kg. Non contrast head CT will be obtained to rule out contra-indications to thrombolytic therapy, but no perfusion imaging or brain MRI scans will be used in the selection process.

Conclusions

Tenecteplase has emerged as a safe, non-inferior, and potentially superior thrombolytic agent when compared to alteplase in the management of AIS. Real-world experience highlighting the additional advantages in cost, preparation, and administration leading to decreased door-to-needle times has prompted implementation of treatment protocols utilizing TNK at many comprehensive stroke centers across the USA and elsewhere. With pending clinical trials of TNK in other stroke patient populations such as extended window AIS and wake-up stroke, there is substantial momentum for TNK as the choice of thrombolytic agent for the majority of patients presenting with AIS.

Compliance with Ethical Standards

Conflict of Interest

Kenda Alhadid declares no competing interests. Lara Oliveira declares no competing interests. Mark R. Etherton declares no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
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