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Review

Tenecteplase utility in acute ischemic stroke patients: A clinical review of current evidence

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ABSTRACT

Introduction: Acute ischemic stroke is a leading cause of disability in the United States. Treatment is aimed at reducing impact of cerebral clot burden and life-long disability. Traditional fibrinolytic treatment with recombinant tissue plasminogen activator (tPA) has shown to be effective but at high risk of major bleeding. Multiple studies have evaluated tenecteplase as an alternative to tPA.
Objective: This review evaluates literature and utility of tenecteplase for treatment of acute ischemic stroke.
Discussion: Tenecteplase is modified, third generation fibrinolytic with greater specificity for fibrin bound clots. Current data in acute myocardial infarction suggest decreased bleeding events compared to alteplase. Multiple trials have investigated superiority of tenecteplase compared to tPA for treatment of acute ischemic stroke. Current guidelines designate tenecteplase as an alternative treatment for mild acute ischemic stroke patients based on recent literature.
Conclusion: Recent emerging literature and limited recommendation guidance from governing medical societies leave many emergency medicine providers to weigh benefit versus risk of fibrinolytic therapy and tenecteplase's place in therapy**.** This review evaluates the available literature regarding tenecteplase and its utility in the treatment of acute ischemic stroke patients.

1. Introduction

Acute ischemic stroke (AIS) affects roughly 700,000 patients annually, with a mortality rate of one in twenty patients [1]. AIS remains the leading cause of lifelong disability with a high negative impact on quality of life. The American Heart Association (AHA) and American Stroke Association (ASA) estimate $40 billion is spent annually for the overall treatment of AIS. $24 billion is spent for the acute treatment and $16 billion spent for the associated care of future loss of productivity and disability, respectively [1]. This estimated financial burden is expected to continue to rise significantly through year 2035 [1]. Treatment of AIS aims at minimizing neurologic injury by reducing clot burden and restoring adequate blood flow to the brain, ultimately reducing the likelihood of lifelong disability. Current standard of care for the treatment of AIS includes treatment with intravenous fibrinolytic therapy, directed intra-arterial fibrinolytic therapy, and/or mechanical thrombectomy [2]. Even so, only 5–10% of all AIS patients presenting to emergency departments are eligible for and receive thrombolytic therapy [2]. The decision to treat these patients with fibrinolytic therapy requires careful consideration of risks vs benefits of therapy, including: severity of symptoms, defining time of onset, and the presence or absence of contraindications to thrombolysis. This is often done under highly stressful, time sensitive pressures with the adage “time is brain” resonating in our minds.

Intravenous fibrinolytic therapy is recommended for select patients who present with acute debilitating stroke symptoms within the first 3–4.5 h of onset [2-4]. Recombinant tissue plasminogen activator (tPA), or alteplase, is the current FDA approved treatment of choice for AIS and has demonstrated to reduce clot burden and patient long-term disability [4,5]. However, a major adverse effect of tPA is intracerebral hemorrhage. The National Institute of Neurologic Disorders (NINDS) trial demonstrated a 6% absolute risk increase in symptomatic intracerebral hemorrhage rate of (6.0% vs 0.0%, $p < 0.0001$) with tPA compared to placebo [5]. Risk avoidance most notably includes ensuring appropriate patient eligibility using the manufacturer and guideline-based inclusion and exclusion criteria.

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Tenecteplase (TNK), another fibrinolytic agent, has recently gained attention for its possible use in AIS [7,8]. TNK is a modified tissue plasminogen activator with a more specific pharmacodynamic profile than tPA [9]. TNK is FDA approved for thrombolysis in acute myocardial infarction (MI) and has demonstrated decreased rates of symptomatic bleeding and decreased time to reperfusion of ischemic myocardial tissue [10,11]. Current AHA/ASA AIS treatment guidelines recommend TNK as an alternative treatment option to tPA for AIS patients [2]. With the improved safety profile of TNK, investigators have sought to test its potential benefit and superiority to tPA in AIS.

2. Methods

Given recent evidence and upcoming trials regarding TNK in AIS [7,8], we pursued to evaluate and review the current literature for emergency medicine physicians. Articles were obtained using search terms "tenecteplase" and "acute ischemic stroke" on MEDLINE database. Article search was restricted to human studies, published in English from 2005 to 2018. Articles were analyzed for inclusion using the PRISMA checklist and deemed appropriate by author consensus.

3. Discussion

3.1. Pharmacology of TNK

Tenecteplase is a third generation fibrinolytic with greater fibrin specificity than tPA. TNK was developed to overcome the known adverse effect of intracerebral bleeding and reduced reperfusion rate. TNK is a genetically modified version of tPA and targets clot-bound fibrin over circulating fibrin [6]. In the presence of clot-bound fibrin, TNK increases the rate of plasminogen to plasmin conversion, allowing for enhanced clot degradation. Additionally, through substitution of select amino acids, TNK has greater resistance to plasminogen activator inhibitor (PAI) (Table 2). This allows TNK to remain active for longer. TNK has a circulating half-life of 24 min with terminal half-life of 2 h, compared to tPA's half-life of 5 min and 1 h, respectively. Given its longer half-life, TNK can be given as a single intravenous bolus over seconds rather than a continuous intravenous infusion given over one hour. Based on its pharmacokinetic and pharmacodynamic design, TNK theoretically should have lower bleeding rates and systemic side effects compared to other thrombolytics.

Tenecteplase currently is only FDA approved for treatment of MI and is dosed based on weight, approximately 0.5 mg/kg to a max of 50 mg [6,9]. Based on current AIS evidence there is no defined superior dose of TNK. Phase II trials sought to determine the ideal weight-based dose of TNK in AIS patients. Haley and colleagues [12] performed a dose-finding study for treatment of acute ischemic stroke with TNK. Patients presenting with AIS were treated in four different dosing arms: 0.1 mg/kg, 0.25 mg/kg, 0.4 mg/kg, or 0.5 mg/kg. The study was terminated when two of the initial 13 patients developed symptomatic intracranial hemorrhage (sICH) conversion within 36 h of treatment in the 0.5 mg/kg TNK arm. No other sICH events occurred within 36 h of treatment, however there was an increased rate of asymptomatic ICH in the other dosing arms: 8% (0.1 mg/kg TNK), 32%(0.2 mg/kg TNK), and 28% (0.4 mg/kg TNK). Based on these results, further studies have investigated the optimal dose of TNK in patients presenting with AIS.

After this dose-finding study, Haley and colleagues [13] conducted a second phase IIB/III trial on TNK vs tPA in acute ischemic stroke patients. This multicenter, randomized, double blind, study aimed to establish the ideal dose of TNK to be used in a future phase III trial for test of efficacy. Patients were randomized to TNK 0.1 mg/kg, 0.25 mg/kg, or 0.4 mg/kg, or tPA 0.9 mg/kg. Study investigators utilized a response outcome score, Major Neurologic Improvement (MNI), which balanced neurologic improvement against risk of symptomatic ICH, to determine utility of each TNK dosing arm. The trial was designed to enroll 100 patients in each group prior to interim analysis. The primary outcome of good neurologic outcome, defined as modified Rankin Scale (mRS) 0–1 (Table 1), at 3 months was highest with 0.25 mg/kg of TNK but no different comparing 0.1 mg/kg TNK, 0.25 mg/kg TNK, 0.4 mg/kg TNK, or 0.9 mg/kg tPA groups: 14 (45.2%, 27–64) vs 15 (48.4%, 30.2–66.9) vs 7 (36.8%, 16.3–61.6) vs 13 (41.9%, 24.6–60.9) patients, respectively. The number of patients with symptomatic intracranial bleeding was no different between groups 0.1 mg/kg TNK, 0.25 mg/kg TNK, 0.4 mg/kg TNK, or 0.9 mg/kg tPA arms: 0 (0%, 0–11.2) vs 2 (6.5%, 0.8–21.4) vs 3 (15.8%, 3.4–39.6) vs 1 (3.2%, 0.1–16.7) patients; asymptomatic ICH: 3 (9.7%, 2.0–25.8) vs 2 (6.5%, 0.8–21.4) vs 2 (10.5%, 1.3–33.1) vs 4 (12.9%, 3.6–29.8) patients, respectively. At interim analysis the study investigators concluded the 0.4 mg/kg TNK arm to be inferior based on lower MNI score compared to other TNK arms 0.1 mg/kg TNK, 0.25 mg/kg TNK, 0.4 mg/kg TNK: 7 (22.6%, 9.6–41.1) vs 11 (35.5%, 19.2–54.6) vs 4 (21.1%, 6.1–45.6) respectively. But due to lack of enrollment, 112 total patients in all arms from 2006 to 2008, the study was discontinued early and did not go on to phase III testing.

3.2. Clinical trials of tenecteplase in AIS

In 2012 Parsons and colleagues [15] published the Australia-TNK study, a phase IIB multicenter trial, which randomized 75 patients to either 0.9 mg/kg of tPA or one of two doses of TNK: 0.1 mg/kg or 0.25 mg/kg. Patients within 6 h of symptom onset with a penumbra, defined as hypoperfused cerebral tissue that is potentially salvageable, of at least 20% the size of the infarct core as well as a vessel occlusion noted on computed tomographic (CT) perfusion and angiographic imaging were enrolled. Patients were evaluated for proportion of penumbra reperfusion on perfusion-weighted magnetic resonance imaging (MRI) and NIHSS score at 24 h. Baseline average NIHSS scores were similar between groups: 14.0 ± 2.3 (0.9 mg/kg tPA), 14.5 ± 2.3 (0.1 mg/kg TNK), and $14.6 + 2.3$ (0.25 mg/kg TNK). Improvement in penumbra reperfusion at 24 h was higher with the TNK groups compared to the tPA: $79.3\% \pm 28.8$ vs. $55.4\% \pm 38.7$ ($p = 0.004$). Patients who received TNK had greater improvement in NIHSS scores from baseline at 24 h: 8.0 ± 5.5 vs. 3.0 ± 6.3 ($p < 0.001$). Rate of intracranial bleeding were no different between TNK vs tPA: sICH 2 vs 3 patients ($p = 0.33$); parenchymal hematoma 3 vs 5 ($p = 0.11$). TNK patients had greater recovery at 90 days (mRS 0–2): 36 vs 11 ($p = 0.02$). The limitations of this phase IIB trial include the tPA group having a 62.5% larger infarct volume and smaller penumbra at baseline which predisposed patients in the tPA group to a worse outcome. Additionally, this study excluded 0.4 mg/kg dose which future trials have utilized.

Following the Australia-TNK trial, a larger phase II trial, ATTEST [16], was published in 2015 which was a single center study that randomized 104 patients to either 0.9 mg/kg of tPA or 0.25 mg/kg of TNK with maximum doses of 90 and 25 mg respectively. Patients with supratentorial ischemic stroke confirmed on CT, CT perfusion, and CTA who were eligible to receive thrombolytics within 4.5 h of symptom onset were eligible. Patients were assessed for percentage of penumbra salvaged at 24–48 h as well as 24-h NIHSS and 30-day mRS score. In contrast to the 2012 phase IIB trial, no significant differences were observed in

Table 1
Modified Rankin Scale (MRS): [14].

0 - No symptoms
1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3 - Moderate disability. Requires some help, but able to walk unassisted.
4 - Moderate severe disability. Unable to attend own bodily needs without assistance, and unable to walk unassisted.
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6 - Dead

Table 2
Pharmacology of TNK vs tPA [4,9].

	Tenecteplase [9]		Alteplase [4]	
FDA approved indications	Acute myocardial infarction		Acute ischemic stroke Acute myocardial infarction Acute massive pulmonary embolism	
Mechanism of action	Recombinant tissue plasminogen activator with substitution of three amino acids [threonine (T), asparagine (N), lysine (K)] to decrease plasminogen activator inhibitor (PAI) binding		Recombinant tissue plasminogen activator	
Binding affinity	Fibrin +++	PAI +	Fibrin +	PAI ++
Dosing (stroke)	Varies between trials, ranges from 0.1–0.4 mg/kg. Administered as single bolus over 5 s		0.9 mg/kg (max 90 mg). Administered as 10% of the dose administered as a bolus followed by 90% as an infusion over 1 h.	
Half-life	24 min		5 min	
Average wholesale price	$7034.24 (50 mg vial)		$10,560.43 (100 mg vial)	

any radiologic or neurologic outcomes between TNK and tPA. Rates of sICH were also no different between groups: 3 vs 4 patients ($p = 0.50$).

The NOR-TEST trial [7], a phase III randomized controlled trial published in 2017, evaluated TNK in patients eligible to receive thrombolysis within 4.5 h of stroke symptom onset. A total of 1100 patients were enrolled from 13 centers in Norway and were randomized to TNK 0.4 mg/kg or tPA 0.9 mg/kg with maximum doses of 40 and 90 mg respectively. Patients were assessed for NIHSS score at 24 h, mRS score at 3 months and mortality within 3 months. Significant differences were not observed in any of the study outcomes including the primary outcome defined as a mRS score at 0–1, at 3 months (64% vs. 63%, OR 1.08 [0.84 to 1.38]) and secondary outcome of sICH (3% vs 2%, OR 1.16 [0.51–2.68]). Several limitations exist to the findings of the NOR-TEST trial. The majority of patients enrolled (75%) had a baseline NIHSS score of 0–7 with a median NIHSS score of 4 (IQR 2–7) for the entire population. Given the overall low stroke severity, the efficacy of TNK seen in this trial cannot be accurately assessed in patients with a baseline NIHSS of 8–14 or >15 as only 16% and 9% of the study population fit those descriptions, respectively. Compounding the overall low stroke severity is the median time from onset of symptoms to thrombolytic of 114 min and the 17.3% of the patients that received thrombolytics for a stroke mimic, both of which further reduce the ability to assess the safety and efficacy of TNK in higher risk patients. Additionally, the tPA group included more patients with moderate and severe strokes, however not significantly different (23% vs 27%, $p = 0.06$), as well as patients with cardioembolic strokes, all of which may predispose patients in the tPA group to worse outcomes.

A meta-analysis by Bivard and colleagues [17] in 2016 pooled data of the ATTEST and Australia TNK trials to test superiority of 0.25 mg/kg TNK compared to 0.9 mg/kg tPA for AIS patients presenting within 4.5 h. Of note, Australia TNK study included a 0.1 mg/kg arm, however, these patients were excluded from pooled analysis to best match patients across both trials. 96 ATTEST patients and 50 Australia TNK patients were included and had demonstrated acute ischemic stroke on imaging. 75 patients received TNK and 71 received tPA. Patients who received TNK had greater initial improvement in stroke severity (median NIHSS change: 7 vs 2, p 0.018), greater vessel recanalization (87% vs 37%, $p < 0.001$), and improved imaging with less infarct growth (1.2 mL vs 18.3 mL, $p < 0.001$). Parenchymal hemorrhage was lower with TNK (3% vs 14%) but overall symptomatic intracerebral hemorrhage was no different between groups (1 patient vs 5 patients, p 0.12). Additionally, 90-day improvement to mRS score of 0–1 was no different (33 vs 22, p 0.102). Subgroup analysis of patients meeting target mismatch criteria also showed greater results with TNK treatment: greater immediate improvement (median NIHSS change 6 vs 1, $p < 0.001$), more patients with 90-day mRS score 0–1 (17 vs 8, p0.032), less parenchymal hematomas (0 vs 7, p 0.015), and less symptomatic intracerebral hemorrhage (0 vs 4, p 0.119). Differences between ATTEST and Australia TNK trials exist that should be considered. Timing of imaging was performed before study enrollment with Australia TNK which allowed for greater screening of patients. Additionally, ATTEST did not require target mismatch demonstration on imaging unlike Australia TNK. Targeted mismatch endpoint has not yet been validated as an optimal surrogate marker for stroke outcomes. The findings of the pooled analysis demonstrate there are improved outcomes with patients who received TNK; however, this may have been driven by patients with targeted mismatch.

The most recent study to date to investigate the use of TNK in AIS was the tenecteplase versus alteplase before endovascular therapy for ischemic stroke (EXTEND-IA TNK) trial [8]. Aim of the study was to establish noninferiority and superiority of TNK compared to tPA for acute ischemic stroke patients within 4.5 h of onset requiring endovascular thrombectomy. Patients enrolled had median baseline NIHSS scores of 17 (IQR, 12–22) and had image-demonstrated cerebral vascular occlusion of select major cerebral arteries (internal carotid, basilar, or middle cerebral artery). Patients were randomized to receive 0.25 mg/kg TNK or 0.9 mg/kg tPA and were assessed for reperfusion improvement at 1–2 h post fibrinolytic infusion by study personnel unaware of treatment arm. Reperfusion was defined as increase in blood flow rate >50% of involved tissue, or abscess of retrievable clot in the identified vessel.

A total of 202 patients were enrolled, with 101 patients in each group. Median time to treatment and time to reperfusion imaging was similar in both groups. Reperfusion of >50% restoration of blood flow was greater in the TNK group compared to the tPA group: 22 patients vs 10 patients (p 0.002). TNK patients had greater reduction in NIHSS scores at 24 h: 3 vs 6 (OR 1.4, CI 1.0–1.5, p 0.06). Overall mortality was decreased in patients who received TNK: 10% vs 18% (p 0.10). Of those who died, 9/10 TNK patients and 14/18 tPA patients, died related to progression of major stroke. Both groups had similar rate of symptomatic intracranial hemorrhage: 1 vs 1 patient. No patients in TNK group and 1 patient in tPA group died due to sICH. More patients in the TNK group had lower median modified rankin scores at 90 days: 2 vs 3 (p 0.04). Patients were 2.2 times more likely to have substantial reperfusion with TNK without an increased incidence of bleeding, and had lower degree of disability at 90 days.

3.3. Safety of tenecteplase

The outlined phase II and III trials suggest TNK is non-inferior to tPA in acute ischemic stroke. Given its demonstrated utility for AIS treatment, TNK seems to be an attractive alternative; however, the comparative safety of these high-risk medications deserves consideration.

The largest study investigating efficacy and safety of TNK was the ASSENT-2 trial [7], a MI trial which enrolled roughly 17,000 patients in over 1000 hospitals worldwide. The ASSENT-2 investigators showed a reduction in major bleeding and need for transfusions with TNK compared to tPA in acute MI patients. Reported intracranial hemorrhage was no different between two groups: 0.93% vs 0.94% (RR: 0.99, CI 0.73–1.35, p 1.0).

However, this associated reduction in bleeding risk with TNK has not been clearly defined for AIS patients. Rates of sICH vary significantly

Table 3
Safety outcomes in trials comparing tenecteplase to alteplase in ischemic stroke.

Trial	Baseline NIHSS	Tenecteplase dosing	All ICH Odds ratio[c] (95% CI)	sICH Odds ratio[c] (95% CI)	Mortality Odds ratio[c] (95% CI)
Haley et al. [13]	10[a]	0.1 mg/kg	0.6 (0.13 to 2.75)	0.32 (0.01 to 8.23)	0.20 (0.04 to 1.03)
		0.25 mg/kg	0.77 (0.19 to 3.19)	2.07 (0.18 to 24.08)	0.84 (0.26 to 2.69)
		0.4 mg/kg	1.86 (0.46 to 7.53)	5.63 (0.54 to 58.58)	0.54 (0.12 to 2.35)
Australia-TNK [15]	14.4[b]	0.1 mg/kg (max 10 mg) or 0.25 mg/kg (max 25 mg)	0.26[d] (0.06 to 1.17)	0.31[d] (0.05 to 1.96)	0.64[d] (0.13 to 3.10)
ATTEST [16]	11.5[a]	0.25 mg/kg	0.4 (0.2 to 1.2)	0.6 (0.1 to 3.2)	1.3 (0.4 to 3.7)
NOR-TEST [7]	4[a]	0.4 mg/kg	0.94 (0.60 to 1.45)	1.16 (0.51 to 2.68)	1.12 (0.63 to 2.02)
EXTEND-IA TNK [8]	17[a]	0.25 mg/kg	1.18 (0.38 to 3.64)	1.0 (0.1 to 15.9)	0.4 (0.2 to 1.1)

tPA: alteplase, sICH: symptomatic intracerebral hemorrhage, TNK: tenecteplase.
[a] Reported as median.
[b] Reported as mean.
[c] Comparing tenecteplase dose to alteplase 0.9 mg/kg.
[d] Comparing pooled tenecteplase doses to alteplase 0.9 mg/kg.

between trials, which may be explained by doses chosen to be investigated and baseline stroke severity (Table 3). Additionally, majority of TNK trials in AIS are limited to smaller studies with a higher-risk population.

3.4. Practicality/pearls

Currently, 2018 AHA/ASA acute ischemic stroke treatment guidelines designate TNK as an alternative to tPA and recommend dose of 0.4 mg/kg (maximum of 40 mg) TNK for treatment of acute AIS in patients who have minor neurological impairment (median NIHSS score 4) [7] and no major intracranial occlusions, a class IIb recommendation [2].

Outlined studies have demonstrated similar clinical applicability and safety of TNK for the treatment of AIS when compared to tPA. TNK use has additional practical applications that may offer advantages to its use for AIS including potential cost savings and ease of administration. Average wholesale price of one 50 mg vial of TNK is about $7000 compared to one 100 mg vial of tPA is about $10,000. Currently the manufacturer of TNK in the United States is Genentech®, who also manufactures tPA, offers a product replacement option for reconstituted but never used vials [18,19]. This program is available for both tPA and TNK for FDA approved indications only. Given TNK currently only holds FDA approval for acute myocardial infarction, this replacement program would not apply for its use in AIS patients as it currently stands which may outweigh any cost savings of TNK.

TNK is faster and easier to reconstitute and administer compared to tPA. Given its longer effective half-life and duration of effect, TNK is given as a bolus rather than continuous infusion. This has multiple practical implications including less chance for medication error with administration, faster time to reperfusion, as demonstrated in EXTEND-IA TNK, as well as possible impact on time to transfer between hospitals. While time to transfer to a higher level of care and time to interventional radiology procedure was no different between groups, this is likely attributable to study design and blinding efforts in the EXTEND-IA TNK trial. This has potential to impact the notion of 'time is brain' by reducing time from lytic administration to procedure or transfer.

3.5. Future studies & directions

Current published studies highlight benefit in moderate-severe AIS patients. However, the utility and optimal dose of TNK remains uncertain regarding other populations of stroke patients such as mild stroke, or those do not meet criteria for mechanical thrombectomy. Currently there are ongoing trials assessing efficacy and safety in these populations.

The TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion (TEMPO 2; ClinicalTrials.gov Identifier: NCT02398656) trial is evaluating the use of TNK 0.25 mg/kg bolus versus antiplatelet treatment in patients with minor stroke within 12 h of presentation. Optimal dosing of TNK is currently being evaluated by multiple studies. The EXTEND-IA TNK investigators are evaluating higher dose TNK 0.4 mg/kg vs 0.25 mg/kg prior to thrombectomy to determine optimal dose (EXTEND-IA TNK Part 2; ClinicalTrials.gov Identifier: NCT03340493). Additionally, The Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE; Australian New Zealand Clinical Trials REgistry number: ACTRN12613000243718) Trial is currently recruiting patients who have acute ischemic stroke and have a penumbra on perfusion CT or MRI within 4.5 h of symptom onset. Finally, the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (AT-TEST 2; ClinicalTrials.gov Identifier: NCT02814409) investigators are evaluating superiority of TNK compared to tPA in 90 day functional outcomes in patients with acute ischemic stroke eligible for intravenous (IV) thrombolysis.

4. Conclusion

Given current evidence, ideal pharmacokinetics, and ease of administration, TNK is an attractive alternative to tPA in the treatment of acute ischemic stroke. Its place in therapy has yet to be determined but current evidence suggests that moderate-severe stroke patients may benefit most from treatment with TNK. TNK improves time to reperfusion without an increase in symptomatic intracerebral hemorrhage. Until completion of future phase III trials result and/or until TNK is granted an FDA indication for AIS, TNK remains an acceptable alternative fibrinolytic to tPA for the treatment of acute ischemic stroke.

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None.

Conflicts of interest

None.

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