Stroke

BRIEF REPORT

Routine Use of Tenecteplase for Thrombolysis in Acute Ischemic Stroke

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BACKGROUND AND PURPOSE: In ischemic stroke, intravenous tenecteplase is noninferior to alteplase in selected patients and has some practical advantages. Several stroke centers in New Zealand changed to routine off-label intravenous tenecteplase due to improved early recanalization in large vessel occlusion, inconsistent access to thrombectomy within stroke networks, and for consistency in treatment protocols between patients with and without large vessel occlusion. We report the feasibility and safety outcomes in tenecteplase-treated patients.

METHODS: We performed a retrospective analysis of consecutive patients thrombolyzed with intravenous tenecteplase at 1 comprehensive and 2 regional stroke centers from July 14, 2018, to February 29, 2020. We report the baseline clinical characteristics, rates of symptomatic intracranial hemorrhage, and angioedema. These were then compared with patient outcomes with those treated with intravenous alteplase at 2 other comprehensive stroke centers. Multivariable mixed-effects logistic regression models were performed assessing the association of tenecteplase with symptomatic intracranial hemorrhage and independent outcome (modified Rankin Scale score, 0–2) at day 90.

RESULTS: There were 165 patients treated with tenecteplase and 254 with alteplase. Age (75 versus 74 years), sex (56% versus 60% male), National Institutes of Health Stroke Scale scores (8 versus 10), median door-to-needle times (47 versus 48 minutes), or onset-to-needle time (129 versus 130 minutes) were similar between the groups. Symptomatic intracranial hemorrhage occurred in 3 (1.8% [95% CI, 0.4–5.3]) tenecteplase patients compared with 7 (2.7% [95% CI, 1.1–5.7]) alteplase patients (P=0.75). There were no differences between tenecteplase and alteplase in the rates of angioedema (4 [2.4%; 95% CI, 0.7–6.2] versus 1 [0.4%; 95% CI, 0.01–2.2], P=0.08) or 90-day functional independence (100 [61%] versus 140 [57%], P=0.47), respectively. In mixed-effects logistic regression models, there was no significant association between thrombolytic choice and symptomatic intracranial hemorrhage (odds ratio tenecteplase, 0.62 [95% CI, 0.14–2.80], P=0.53) or functional independence (odds ratio tenecteplase, 1.20 [95% CI, 0.74–1.95], P=0.46).

CONCLUSIONS: Routine use of tenecteplase for stroke thrombolysis was feasible and had comparable safety profile and outcome to alteplase.

Key Words: angioedema ■ intracranial hemorrhage ■ ischemic stroke ■ tenecteplase ■ thrombectomy

Intravenous alteplase is the standard thrombolytic treatment for acute ischemic stroke.[1] Tenecteplase is a genetically engineered version of alteplase, with faster onset of action and longer half-life.[2] Although randomized-controlled stroke trials are ongoing, there is evidence to indicate that tenecteplase is noninferior to alteplase,[3] with similar safety profile in patients with mild strokes.[2,4] In patients with large vessel occlusion (LVO), tenecteplase may be superior to alteplase. Randomized-controlled trials found tenecteplase increased

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Nonstandard Abbreviation and Acronyms

LVO	large vessel occlusion
NIHSS	National Institutes of Health Stroke Scale
sICH	symptomatic intracranial hemorrhage

early reperfusion of LVO before thrombectomy and was safe.[2,5,6] Tenecteplase is already being used either preferentially in patients with LVO[7] or off-label for routine stroke thrombolysis in some centers.[8]

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Off-label tenecteplase became the routine agent used for stroke thrombolysis at 3 South Island hospitals in New Zealand in July 2018. This change was driven by inconsistent regional endovascular thrombectomy coverage, evidence that tenecteplase improves rates of early recanalization in LVO,[2,6] and local imperatives to implement a thrombolytic protocol that was consistent for patients with and without LVO. The aim of this study is to assess the safety of tenecteplase in the real-world setting when compared with standard-dose alteplase.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. We included consecutive patients managed with intravenous tenecteplase from July 14, 2018, to February 29, 2020, at one comprehensive stroke center serving a local stroke catchment population of 530 000 and 2 primary stroke centers in the same South Island of New Zealand stroke network, each serving catchment populations of 50 000. We compared these patients with those contemporaneously treated with intravenous alteplase at 2 comprehensive stroke centers in the North Island serving a combined population of 900 000, with one center having limited after hours thrombectomy coverage. These 3 comprehensive stroke centers provide all thrombectomy in New Zealand. Three patients from one South Island center enrolled into the TASTE trial (Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation; URL: https://www.anzctr.org.au; Unique identifier: ACTRN12613000243718) during the study period were included in the alteplase cohort. The tenecteplase dose was 0.25 mg/kg with the exception of 7 patients who received 0.40 mg/kg dose at Christchurch Hospital as part of EXTEND-IA TNK part 2 trial (Tenecteplase Versus Atleplase Before Thrombectomy for Ischemic Stroke).[2] All centers perform routine CT angiogram in reperfusion eligible patients, and perfusion imaging is additionally available at the comprehensive stroke centers and one regional center. Perfusion imaging is not used to determine thrombolysis eligibility, which is administered to patients within 4.5 hours of symptom onset based on standard criteria. Perfusion imaging is also not used to determine thrombectomy eligibility during the time window relevant to thrombolysis in this study.

Baseline demographics, National Institutes of Health Stroke Scale (NIHSS), reperfusion time metrics, rates of symptomatic intracranial hemorrhage (sICH), and angioedema between alteplase and tenecteplase were compared. sICH was defined as NIHSS increase of ≥4 with associated with parenchymal hemorrhage type 2 or subarachnoid hemorrhage on repeat imaging within 48 hours. Functional independence was defined as modified Rankin Scale score 0 to 2 at 90 days. Patients with missing NIHSS or functional outcome were included in this report. The main data points were derived from local stroke reperfusion registries[9] and the New Zealand National Reperfusion Registry.[10]

We used standard descriptive statistics to describe baseline data and continuous variables were represented as median (interquartile range). χ^2 and Fisher exact test were used for categorical variables and Mann-Whitney *U* test for continuous variables. To account for clustering in individual institutes, we undertook mixed-effects logistic regression modeling for sICH and functional independence. Thrombolytic agent, age, and baseline NIHSS were treated as fixed effects and institutes as a random effect in the model for functional independence. The same covariates, excluding age, were used for the model assessing sICH. Statistical analyses were performed using Stata v.15 (StataCorp LP, College Station, TX). A 2-sided $P<0.05$ was considered statistically significant.

This study has approval from the New Zealand Health and Disability Ethics Committee. All data were collected as part of routine care, and additional patient consent was not required as per legislation.

RESULTS

During the study period, 165 patients received tenecteplase and 254 alteplase. Patient demographics (median age [75 versus 74 years, $P=0.48$], sex [male 56% versus 60%, $P=0.48$]), and vascular risk factors (Table in the Data Supplement) were similar except tenecteplase patients were less likely to have history of hypertension (56% versus 74%), hyperlipidemia (32% versus 48%), and smoking (10% versus 18%). Baseline NIHSS (8 versus 10, $P=0.17$), onset-to-needle time, (130 versus 129 minutes, $P=0.78$), door-to-needle times (47 versus 48 minutes, $P=0.93$) were similar between the 2 groups (Table). Rates of proximal intracranial LVO of the internal carotid, middle cerebral (M1 and M2 segments), and basilar artery were nonsignificantly higher in tenecteplase patients (53% versus 46%, $P=0.21$) with more tenecteplase-treated patients going on to thrombectomy (37% versus 24%, $P<0.01$).

sICH occurred in 3 (1.8% [95% CI, 0.4–5.3]) tenecteplase-treated patients compared with 7 (2.7% [95% CI, 1.1–5.7], $P=0.75$) alteplase-treated patients. Seven (4.2%) tenecteplase patients were treated at the primary stroke centers, none had intracranial hemorrhage. Although follow-up imaging was missing in 4

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Table. Demographics, Stroke Reperfusion Metrics, and Outcome

	Tenecteplase (n=165)	Alteplase (n=254)	*P* value
Male	93 (56%)	152 (60%)	0.48
Age, y	75 (64–84)	74 (62–83)	0.50
Onset-to-needle time, min	130 (97–183)	129 (100–175)	0.72
Door-to-needle time, min	47 (33–69)	48 (33–66)	0.93
Baseline NIHSS	8 (5–14)	10 (5–17)*	0.17
Large vessel occlusion	87 (53%)	118(46%)	0.21
Endovascular thrombectomy	61 (37%)	61 (24%)	0.004
Angioedema	4 (2.4% [95% CI, 0.7%–6.2%])	1 (0.4% [95% CI, 0.01%–2.2%])	0.08†
Symptomatic intracerebral hemorrhage	3 (1.8% [95% CI, 0.4%–5.3%])	7 (2.7% [95% CI, 1.1%–5.7%])	0.75†
90-day functional Independence‡	100 (61%)	140 (57%)	0.47

NIHSS indicates National Institutes of Health Stroke Scale.
*Two missing, n=252.
†Fisher exact test.
‡One missing for tenecteplase n=164, 10 missing for alteplase, n=244.

patients, precluding assessment of hemorrhagic transformation, none of these patients had an increase in NIHSS score and, therefore, could not have had sICH. Angioedema occurred in 4 (2.4% [95% CI, 0.7–6.2]) tenecteplase-treated patients compared with 1 (0.4% [95% CI, 0.01–2.2], *P*=0.08) alteplase-treated patient. There was no difference in the proportion of patients with functional independence at day 90 between the 2 groups (modified Rankin Scale score, 0–2; tenecteplase 100 [61%] versus alteplase 140 [57%], *P*=0.47).

In mixed-effects logistic regression, there was no association between thrombolytic agent used with sICH (tenecteplase odds ratio, 0.62 [95% CI, 0.14–2.80], *P*=0.53) or functional independence(tenecteplase odds ratio, 1.20 [95% CI, 0.74–1.95], *P*=0.46). The associations were similar after removing 25 patients enrolled in randomized-controlled trials, adjusting for presence of LVO or thrombectomy treatment, and adjusting for differences in baseline risk profiles between tenecteplase and alteplase groups(material in the Data Supplement).

DISCUSSION

This real-world observational study has found that the routine use of tenecteplase for stroke thrombolysis is feasible and has a comparable efficacy and safety profile to alteplase. Tenecteplase was also safely implemented in 2 small regional stroke centers less experienced in stroke reperfusion treatment.

The sICH rate in the tenecteplase (1.8%) patients was similar to the alteplase (2.7%) cohort and compares favorably with sICH rates for alteplase (3.7%)[11] reported in randomized trials. There were numerically more tenecteplase patients with angioedema but this was not significant.

There was no difference in the association between each thrombolytic agent and outcome in the present study. The increased utilization of thrombectomy in tenecteplase patients may present a bias towards improved outcome, but there was no change in the association with functional independence after adjusting for LVO or thrombectomy.

Tenecteplase has practical and pharmacological advantages over alteplase and improves early reperfusion in patients with intracranial LVO referred for thrombectomy. In the EXTEND-IA TNK trials, recanalization had occurred at the time of angiography in 20% of tenecteplase-treated patients compared with 9.9% with alteplase patients (adjusted RR, 1.90 [95% CI, 1.02–3.53], *P*=0.04)[2] without increased hemorrhagic risk.

The 2019 American Heart Association and American Stroke Association guidelines endorsed class IIB recommendations for tenecteplase for patients with LVO and in those with minor neurological symptoms.[1] The Australian Stroke guidelines support tenecteplase as a reasonable alternative to alteplase in LVO (strong recommendation) and non-LVO (weak recommendation) ischemic stroke patients who meet specific clinical and brain imaging eligibility criteria.[12] Although further randomized-controlled trials are ongoing, there is accumulating evidence that tenecteplase is at least noninferior to alteplase for ischemic stroke.[3]

This study has a number of limitations. The decision to implement off-label tenecteplase was driven mainly by limited access to endovascular therapy. While it is a regulatory requirement that all thrombolyzed patients are entered into the New Zealand National Reperfusion registry, data are not adjudicated by blinded assessors, thus exposing our results to ascertainment bias. The data are observational and, despite adjusting for baseline variables and clustering by institution, we cannot account for unmeasured confounders such as prethrombolysis glucose level. Our results also need to be considered in the context of the relatively small sample size.

In summary, our data found routine use of tenecteplase for stroke thrombolysis was feasible and had comparable efficacy and safety to alteplase. The results of large ongoing randomized trials comparing tenecteplase and alteplase in a broad range of patients will be critical to improve the precision of comparisons of safety and efficacy between agents, particularly in understudied subgroups.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Table
Additional outcome analyses

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