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Title Safety and outcomes of tenecteplase in moderate and severe ischemic stroke – Results from NOR-TEST

Cover Title TNK in moderate and severe ischemic stroke

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Abstract

Background: Tenecteplase represents a promising alternative to alteplase as thrombolytic treatment in acute ischemic stroke. There is limited data on tenecteplase 0.4 mg/kg in patients with increased stroke severity. We aimed to assess safety and efficacy of tenecteplase 0.4 mg/kg in patients with moderate and severe ischemic stroke.

Methods: NOR-TEST was a phase III trial designed to investigate safety and efficacy of tenecteplase 0.4 mg/kg versus alteplase 0.9 mg/kg in ischemic stroke. In this post-hoc analysis, moderate stroke was defined as admission NIHSS 6-14 and severe stroke as NIHSS ≥15. Rates of favorable outcome at 90 days, symptomatic intracerebral hemorrhage (sICH) and mortality after 7 and 90 days were assessed.

Results: In patients with moderate stroke (n=261), there were no differences in rates favorable outcome, sICH or mortality between tenecteplase and alteplase. In patients with severe stroke (n=87) there were no differences in outcome, frequency of sICH or mortality at 7 days, but all-cause mortality at 90 days was increased in patients treated with tenecteplase (10 [26.3%] vs. 4 [9.1%], p=0.045). One patient died of sICH in the tenecteplase group and two patients died of sICH in the alteplase group.

Conclusion: Rates of favorable outcome and sICH were similar between treatment groups in patients with moderate and severe stroke. Mortality after 90 days was increased in patients with severe stroke receiving tenecteplase. Future studies assessing tenecteplase 0.4 mg/kg should monitor safety parameters closely in patients with severe stroke.

Introduction

In acute ischemic stroke, several phase II trials have shown that tenecteplase 0.1, 0.25 and 0.4 mg/kg may be safe and associated with favorable outcome in selected patient populations.[1-4] Recently, The Norwegian Tenecteplase Stroke Trial (NOR-TEST) showed similar effect and safety outcomes of 0.4 mg/kg tenecteplase as compared to alteplase 0.9 mg/kg in a more general stroke population including 1100 patients.[5] However, a majority of patients had mild stroke.

We aimed to assess safety and efficacy of tenecteplase 0.4 mg/kg in patients with moderate and severe ischemic stroke included in NOR-TEST.

Methods

The data that support the findings of this study are available from the corresponding author on request. NOR-TEST was a multicenter, randomized, open-label, blinded endpoint, phase III trial designed to investigate safety and efficacy of tenecteplase 0.4 mg/kg versus alteplase 0.9 mg/kg in acute ischemic stroke.[5] Inclusion criteria comprised clinically suspected acute ischemic stroke eligible for thrombolytic treatment according to European guidelines in patients aged at least 18 years living independently pre-stroke and admitted within 4.5 hours of stroke onset with measurable deficits on NIHSS. Favorable outcome was defined as mRS 0-1. Clinical improvement was defined as an improvement of 4 NIHSS points within 24 hours as compared to admission NIHSS or NIHSS 0 at 24 hours. Cause of death was based on information from serious adverse event (SAE) registration forms completed by local investigators.

Patients with stroke mimics were excluded. Moderate stroke was defined as admission NIHSS 6-14 and severe stroke as admission NIHSS ≥15.

NOR-TEST was performed in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki and written informed consent was obtained from every patient or from close relatives if the patient was not able to sign.

Statistics

Univariate analyses were performed with student`s t-test or Mann-Whitney U test for continuous variables and Fisher`s exact test or chi-squared test for categorical variables as appropriate. Logistic regression analyses were performed with outcome variables as dependent variables and tenecteplase vs. alteplase as independent variable, in addition to confounders such as age, sex and variables with $p<0.1$ from univariate analyses.

Results

A total of 261 patients had moderate stroke of which 123 were treated with tenecteplase vs. 138 with alteplase and 87 patients had severe stroke of which 40 were treated with tenecteplase vs. 47 with alteplase (table 1).

In patients with moderate stroke, rates of favorable outcome (tenecteplase: 58 [49.2%] vs. alteplase: 61 [45.2%], p=0.528), sICH (5 [4.1%] vs. 3 [2.2%], (p=0.481) and mortality within 90 days (10 [8.5%] vs. 11 [8.3%], p=0.100) were similar in both treatment groups.

In patients with severe stroke, rates of favorable outcome (9 [23.7%] vs. 7 [15.6%], p=0.410) and sICH (4 [10.0%] vs. 3 [6.4], p=0.698) were also similar in both groups. Mortality within 90 days (10 [26.3%] vs. 4 [9.1%], p=0.045) was increased for patients treated with tenecteplase.

In patients with severe stroke who died within 90 days, there were no differences in median age, NIHSS on admission or minutes from stroke debut to thrombolytic treatment in patients who received tenecteplase as compared to alteplase.

There were no differences between tenecteplase vs. alteplase in rates of favorable outcome or clinical improvement in patients with occlusions of internal carotid artery (n=8), proximal (n=62) or distal (n=49) middle cerebral artery.

Of the ten patients treated with tenecteplase who were dead within 90 days, seven patients died during the hospital stay, five of which due to large ischemic stroke with no effect of thrombolytic treatment (two patients underwent unsuccessful thrombectomy), one due to sICH and one due to decreasing hemoglobin, renal insufficiency and pneumonia. Three patients died after hospital discharge and cause of death was unknown for these patients. Of the four deceased patients treated with alteplase, three patients died during hospital stay, two of which due to sICH and one due to large ischemic stroke with no effect of thrombolytic treatment. One patient with unknown cause of death died after hospital discharge.

In logistic regression analysis, tenecteplase was independently associated with death within 90 days (OR 6.0, 95% CI 1.2-29.4, p=0.027) after adjusting for age, sex, atherosclerotic stroke etiology and systolic BP on admission in patients with severe stroke.

Discussion

Our study showed that clinical outcomes were similar between tenecteplase 0.4 mg/kg vs. alteplase 0.9 mg/kg in patients with moderate and severe ischemic stroke. Crude frequencies of favorable outcomes were consistently higher in patients receiving tenecteplase, yet not significantly so. There were no significant differences between treatment groups in rates of cerebral hemorrhages, although frequencies of sICH were higher in patients with both moderate and severe stroke receiving tenecteplase. However, crude numbers were small in both groups and the results are thus vulnerable to influence by chance.

Our study showed increased all-cause mortality within 90 days in patients with severe stroke receiving tenecteplase. SAE-records showed that a majority of patients died due to severe stroke that did not respond to thrombolytic treatment. Two patients in both treatment groups died of causes that may be directly related as an adverse event of thrombolytic therapy: one patient due to sICH and decreasing hemoglobin, renal failure and pneumonia in the tenecteplase group and two due to sICH in the alteplase group. Consequently, there is no definitive reason to conclude that the increased mortality was directly related to tenecteplase. In addition, rates of mortality were relatively low in the alteplase group as compared to historical data.[6] Our findings of an increased mortality in patients with severe stroke treated with tenecteplase should, however, not be neglected.

There are some limitations to our study. First, cause of death was based on reports from SAE registration forms completed by local investigators and may thus be inaccurate as autopsy was not performed. Secondly, results should be interpreted with caution due to small numbers and the nature of post-hoc analyses.

In conclusion, we found similar rates of favorable outcome and sICH in patients with moderate and severe ischemic stroke treated with tenecteplase 0.4 mg/kg as compared to alteplase. Long-term mortality was increased in patients with severe stroke receiving tenecteplase. Future studies assessing tenecteplase 0.4 mg/kg should monitor safety parameters closely in patients with severe stroke.

Conflict of interest:

NL, UW-A, and LT reports grants from the Research Council of Norway to finance one study nurse at each recruiting centre during the study period. All other authors declare no competing interests.

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Table 1: Demographic data of patients with moderate and severe ischemic stroke included in NOR-TEST.

	Moderate stroke, NIHSS 6-14			**Severe stroke, NIHSS ≥15**		
	Tenecteplase n=123	**Alteplase n=138**	**P value**	**Tenecteplase n=40**	**Alteplase n=47**	**P value**
Age, mean (SD)	69.3 (15.3)	72.6 (13.6)	0.072	73.4 (13.1)	74.3 (13.4)	0.742
Female sex, (%)	50 (40.7)	62 (44.9)	0.486	23 (57.5)	18 (38.3)	0.088
Risk factors, (%)						
Hypertension	57 (46.3)	72 (52.2)	0.347	19 (47.5)	24 (51.1)	0.831
Atrial fibrillation	12 (9.8)	25 (18.1)	0.074	10 (25.0)	10 (21.3)	0.800
Diabetes mellitus	12 (9.8)	21 (15.2)	0.185	5 (12.5)	7 (14.9)	1.000
Clinical characteristics						
Minutes from stroke onset to treatment, mean (SD)	113.2 (59.8)	114.2 (50.8)	0.889	102.7 (54.9)	96.6 (44.4)	0.580
NIHSS on admission, median (IQR)	8 (7-10)	8 (7-11)	0.391	18.5 (17-22)	18 (17-21)	0.427
Systolic BP on admission, mean (SD)	155.4 (20.7)	152.2 (22.8)	0.233	153.7 (20.9)	146.2 (20.7)	0.098
Atherosclerotic aetiology (%)	27 (22.1)	41 (29.9)	0.155	14 (35.0)	8 (17.0)	0.082
Cardiac aetiology (%)	33 (27.1)	37 /27.0)	0.994	14 (35.0)	22 (46.8)	0.284
Intracranial arterial occlusion, (%)	25 (20.3)	34 (24.6)	0.406	25 (62.5)	29 (61.7)	1.000
Thrombectomy, (%)	7 (5.7)	7 (5.1)	0.825	8 (20.0)	12 (25.5)	0.615
Clinical outcomes, (%)						
mRS 0-1 at 90 days	58 (49.2)	61 (45.2)	0.528	9 (23.7)	7 (15.6)	0.410
Clinical improvement at 24 h	36 (29.3)	33 (23.9)	0.327	7 (17.5)	8 (17.0)	1.000
Any ICH	12 (9.8)	18 (13.0)	0.442	14 (35.0)	10 (21.3)	0.229
sICH	5 (4.1)	3 (2.2)	0.481	4 (10.0)	3 (6.4)	0.698
Mortality within 7 days	3 (2.4)	3 (2.2)	1.000	6 (15.0)	2 (4.3)	0.136
Mortality within 90 days	10 (8.5)	11 (8.3)	1.000	10 (26.3)	4 (9.1)	0.045

NIHSS; National Institutes of Health Stroke Scale, SD; Standard deviation, mRS; modified rankin scale, IQR; interquartal range, BP; blood pressure, ICH; intracranial hemorrhage, sICH; symptomatic intracranial haemorrhage