Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke
Results of a Prematurely Terminated Randomized Clinical Trial

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Background and Purpose—Intravenous alteplase (rtPA) remains the only approved treatment for acute ischemic stroke, but its use remains limited. In a previous pilot dose-escalation study, intravenous tenecteplase showed promise as a potentially safer alternative. Therefore, a Phase IIB clinical trial was begun to (1) choose a best dose of tenecteplase to carry forward; and (2) to provide evidence for either promise or futility of further testing of tenecteplase versus rtPA. If promise was established, then the trial would continue as a Phase III efficacy trial comparing the selected tenecteplase dose to standard rtPA.

Methods—The trial began as a small, multicenter, randomized, double-blind, controlled clinical trial comparing 0.1, 0.25, and 0.4 mg/kg tenecteplase with standard 0.9 mg/kg rtPA in patients with acute stroke within 3 hours of onset. An adaptive sequential design used an early (24-hour) assessment of major neurological improvement balanced against occurrence of symptomatic intracranial hemorrhage to choose a “best” dose of tenecteplase to carry forward. Once a “best” dose was established, the trial was to continue until at least 100 pairs of the selected tenecteplase dose versus standard rtPA could be compared by 3-month outcome using the modified Rankin Scale in an interim analysis. Decision rules were devised to yield a clear recommendation to either stop for futility or to continue into Phase III.

Results—The trial was prematurely terminated for slow enrollment after only 112 patients had been randomized at 8 clinical centers between 2006 and 2008. The 0.4-mg/kg dose was discarded as inferior after only 73 patients were randomized, but the selection procedure was still unable to distinguish between 0.1 mg/kg and 0.25 mg/kg as a propitious dose at the time the trial was stopped. There were no statistically persuasive differences in 3-month outcomes between the remaining tenecteplase groups and rtPA. Symptomatic intracranial hemorrhage rates were highest in the discarded 0.4-mg/kg tenecteplase group and lowest (0 of 31) in the 0.1-mg/kg tenecteplase group. Neither promise nor futility could be established.

Conclusion—This prematurely terminated trial has demonstrated the potential efficiency of a novel design in selecting a propitious dose for future study of a new thrombolytic agent for acute stroke. Given the truncation of the trial, no convincing conclusions can be made about the promise of future study of tenecteplase in acute stroke. (Stroke. 2010;41:707-711.)

Key Words: acute ischemic stroke • tenecteplase • thrombolysis

To date, the only approved treatment for acute ischemic stroke is intravenous recombinant tissue plasminogen activator (alteplase, rtPA). Despite extensive efforts, implementation of this treatment has been limited, largely because of the narrow time limits within which treatment must be delivered, but also due to concerns regarding adverse bleeding risk. Development of an alternative thrombolytic therapy that might be easier and safer to administer could lead to wider acceptance and use of thrombolytic therapy for stroke. Tenecteplase is a modified version of rtPA that is more fibrin-specific and has a longer half-life and can thus be administered as an intravenous bolus. It has been approved for use in myocardial infarction, in which it is associated with fewer systemic bleeding complications than alteplase. A dose-escalation safety study of tenecteplase in patients with acute ischemic stroke observed no symptomatic intracranial hemorrhages (ICHs) among 75 patients treated with doses ranging from 0.1 mg/kg to 0.4 mg/kg. Although 3-month outcomes
were similar to patients treated with alteplase in the National Institute of Neurological Diseases and Stroke rtPA Stroke Trial, the results at 24 hours indicated that there may be important differences in the clinical activity of the tested doses. The proportion of patients with major neurological improvement at 24 hours was an absolute 20% higher in the 0.1-mg/kg group than at the highest safe dose tested, 0.4 mg/kg, suggesting the possibility of an inverse dose response. Further dose comparisons were considered prudent.

Based on these encouraging results, we designed an innovative, seamless, Phase IIb/III, randomized, multicenter, double-blind trial of intravenous tenecteplase versus standard-dose rtPA in patients with acute ischemic stroke within 3 hours of onset. We report here the results of the trial, which was prematurely terminated during Phase IIb due to slower than expected enrollment.

**Methods**

Phase IIb of the trial had 2 goals: (1) to use an efficient statistical strategy to select a “best” dose of tenecteplase for acute stroke using an early (24-hour) clinical outcome; and (2) to decide whether further comparison of these interventions was promising or futile by comparing the selected tenecteplase dose with standard-dose rtPA using safety and longer-term (3-month) efficacy outcomes. If tenecteplase proved promising, then Phase III provided for a pivotal randomized trial comparing the selected tenecteplase dose with rtPA for 3-month clinical outcome.

A complete description of the design will be published elsewhere. Summarizing the major features, the dose-selection component of Phase IIb compared 3 tenecteplase doses: 0.1 mg/kg, 0.25 mg/kg, and 0.4 mg/kg. A rapid-response outcome score was assigned at 24 hours as follows. Patient status was scored: 0 (worst), 1, or 2 (best) on a composite measure that balanced Major Neurological Improvement following. Patient status was scored: 0 (worst), 1, or 2 (best) on a modified Rankin Scale.6 Each hypothesis was to be tested at α = 0.025, 2-tailed, using the site-stratified Mantel-Haenszel 1 degree of freedom procedure with 1/2 continuity correction. The planned sample size was 1908 (954 per group). This provided 90% power to detect a ≥8% reduction in poor outcome without a reduction in good outcome or 89% power to detect an 8% increase in good outcome without an increase in poor outcome.

The premature termination of the trial precluded the planned comparisons of the selected dose of tenecteplase to rtPA for promise or futility as well as the full Phase III trial. A new “postspecified” analysis plan was developed by the investigators and approved by the trial Data and Safety Monitoring Board after the termination but before breaking the blind and before analysis of any efficacy data. The analysis plan compared the proportions of the 3 tenecteplase groups separately and combined with the rtPA group, first on the good outcome (Rankin 0 to 1) and then on the poor outcome (Rankin 4 to 6) using Mantel-Haenszel tests. Given the fact that the original analysis plan was not followed and that the presented analysis is exploratory, nominal probability values were calculated without taking into account the multiple comparisons; no prespecified level of significance was set. All outcome analyses are by treatment assignment (intent-to-treat).

For example, if the selected dose of tenecteplase showed a lower symptomatic ICH rate than rtPA, defined as at least 2 fewer symptomatic ICHs, we would declare it promising if the observed proportion of patients with poor 3-month outcome was less than or equal to that of rtPA (Scenario 1). In Scenario 2, if the rate of symptomatic ICH within 24 hours for tenecteplase was effectively the same (ie, ±1) as that for rtPA, then the proportion of poor outcomes on the 3-month Rankin Scale would have needed to be at least 8 percentage points lower than that of patients with rtPA for further study of tenecteplase to be declared promising. Additionally, if the proportion of good outcomes for tenecteplase was significantly less than the proportion of good outcomes with rtPA at the nominal 2-tailed 0.001 level in either scenario, then further study of tenecteplase would be declared futile. If the selected tenecteplase dose had ≥2 symptomatic ICHs than rtPA at the interim analysis, then the research would stop. Simulations showed that the operating characteristics of these decision rules, taken together, may be regarded as a second “selection procedure.” That is, there was a calculated ≥85% probability of correct selection (either continue or discontinue) using the design parameters.

If Phase IIb showed promise, Phase III would continue the trial with additional clinical sites to test 2 coprimary null hypotheses comparing tenecteplase and rtPA on the trichotomized 3-month Rankin: (1) the proportion of poor outcomes with tenecteplase treatment at the selected dose does not differ from the proportion of poor outcomes with rtPA treatment; and (2) the proportion of good outcomes with tenecteplase treatment at the selected dose does not differ from the proportion of good outcomes with rtPA treatment.

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The protocol and consent forms were reviewed and approved by the Institutional Review Board of each participating institution. Eligible patients were aged ≥18 years with serious neurological deficits believed to be on the basis of acute focal cerebral ischemia and who were otherwise suitable for treatment with intravenous rtPA within 3 hours of stroke onset using contemporary guidelines. After informed consent was obtained, a web-based randomization method provided a treatment assignment to an unblinded investigative pharmacist at the site, who then prepared 0.1 mg/kg, 0.25 mg/kg, or 0.4 mg/kg of tenecteplase to be administered in 10 mL of normal saline as a bolus followed by 90 mL of normal saline administered over 1 hour or 0.9 mg/kg of rtPA with 10% of the total dose administered in 10 mL as a bolus followed by the remaining 90% in 90 mL of normal saline administered over 1 hour. Treating physicians, staff, and investigators as well as trial patients remained blinded to the identity of the study drug throughout. A baseline National Institutes of Health Stroke Scale was performed immediately before initiation of the study drug in each patient to confirm continued eligibility in the trial. Patients whose deficits had cleared or who had become otherwise ineligible in the interval between treatment assignment and actual treatment were considered to be “enrolled” but were not “randomized” or included in the analyses.
Reasons for exclusion of enrolled but not randomized patients were recorded. Randomized patients were managed in an intensive care or acute stroke unit for 24 hours after treatment using standard guidelines for postthrombolytic stroke treatment. A follow-up National Institutes of Health Stroke Scale examination was performed at 24±2 hours after stroke onset, and a noncontrast head CT scan was performed at 48±6 hours after treatment to assess for asymptomatic intracranial bleeds. If neurological worsening occurred, then a head CT scan was performed and the primary and contributing causes of the neurological worsening were recorded. Neurological worsening was defined as any clinically significant neurological change (appearance of a new deficit or worsening of previous deficits) that persisted for >8 hours. All CT scans (both baseline and follow-up) were sent to the Clinical Coordinating Center for interpretation blinded to treatment assignment by a study neuroradiologist who independently judged whether the scan depicted ICH. If hemorrhage was present on any follow-up scan, the entire case was referred to an independent blinded clinical neurologist who adjudicated whether the hemorrhage was symptomatic or asymptomatic. A symptomatic ICH was defined as any clinically important neurological worsening (ie, meeting neurological worsening criteria, see previously) attributable to new hemorrhage seen on a follow-up head CT scan. Confluent hematoma occupying greater than one third of the infarct volume and exerting space-occupying effects and intraventricular or subarachnoid extension of blood were considered strongly, but the decisions of the neurological adjudicator were final. Symptomatic ICHs that became symptomatic within 24 hours of treatment were considered potentially attributable to the study drug.

Safety was overseen by an independent Medical Monitor and Data and Safety Monitoring Board. The Data and Safety Monitoring Board was also charged with reviewing the progress of the selection procedure, protecting the integrity of the trial, and reviewing the results of the analysis for promise or futility.

**Results**

From March 2006 through December 2008, 112 patients were randomized into the trial at 10 hospitals in 8 clinical centers (see the Appendix). One patient was randomized to rtPA but received 0.25 mg/kg tenecteplase, and 1 was randomized to 0.25 mg/kg tenecteplase but received 0.7 mg/kg tenecteplase. The remaining 110 patients received the assigned medication and dose. Seventeen additional patients received a provisional treatment assignment but were excluded before final eligibility determination. Seven became ineligible because of deficit resolution; drug was not available in time for 8; and 2 withdrew consent before treatment.

Table 1 shows the baseline characteristics and ischemic stroke subtypes (by TOAST criteria at 7 to 10 days following the entry stroke) by treatment group. The patients randomized to rtPA were older and had more severe stroke deficits at baseline than patients in the tenecteplase groups. Four patients (2 in the 0.1 mg/kg tenecteplase group, and 2 in the rtPA group) were determined to have had conversion disorders, hyperglycemia, or migraine as the cause of their acute neurological deficits. All 4 had complete resolution of their acute deficits.

The results of the tenecteplase dose selection procedure are depicted in the Figure. The 0.4-mg/kg dose fell 6 points behind the leading dose (0.25 mg/kg) after 14 triplets of patients on tenecteplase completed 24-hour follow-up. The 0.4-mg/kg dose was therefore eliminated and randomization to it discontinued. Randomization continued to 0.1 mg/kg tenecteplase, 0.25 mg/kg tenecteplase, or 0.9 mg/kg rtPA. When the trial was terminated after 112 patients had been randomized, the cumulative difference between the 2 remaining tenecteplase doses had, at times, reached as many as 4 points, but not the 6 needed to reach the dose selection criterion.

Data were collected for 5 additional patients on 0.4 mg/kg tenecteplase beyond the 14 used to eliminate that dose. Four were patients who had already been randomized to triplets that remained open, and therefore unanalyzed, when the 0.4-mg/kg dose was eliminated. The fifth was the only patient randomized at a site that was subsequently closed. The data from these patients did not contribute to the decision to eliminate the 0.4-mg/kg dose but are included in all subsequent analyses.

Table 2 shows the 3-month outcomes and 24-hour MNI rates for the patients by treatment group. Four patients were

| Table 1. Baseline Characteristics and Ischemic Stroke Subtypes by Treatment Group |
|-----------------------------------|-----------|-----------|-----------|-----------|
|                                  | TNK 0.1 mg/kg | TNK 0.25 mg/kg | TNK 0.4 mg/kg | rtPA 0.9 mg/kg |
| Age, years (mean±SD)             | 67 (19)     | 69 (15)    | 68 (16)    | 72 (16)    |
| Sex, no. (% male)                | 12 (39%)    | 16 (52%)   | 13 (68%)   | 17 (51%)   |
| Race, no. (% white)              | 24 (77%)    | 26 (84%)   | 12 (63%)   | 25 (81%)   |
| Baseline National Institutes of Health Stroke Scale score (median, interquartile range) |
| Systolic blood pressure, mm Hg (mean±SD) | 156 (21)    | 158 (31)   | 152 (27)   | 150 (23)   |
| Diastolic blood pressure, mm Hg (mean±SD) | 86 (15)     | 84 (14)    | 82 (17)    | 81 (13)    |
| Prestroke Rankin ≥2, no. (%)     | 7 (23%)     | 3 (10%)    | 0 (0%)     | 5 (16%)    |
| Medical history                   |             |            |            |            |
| Hypertension, no. (%)             | 25 (81%)    | 25 (81%)   | 17 (90%)   | 22 (71%)   |
| Diabetes, no. (%)                 | 6 (19%)     | 7 (23%)    | 4 (21%)    | 4 (13%)    |
| Prior stroke, no. (%)             | 6 (19%)     | 10 (32%)   | 5 (26%)    | 4 (13%)    |
| Heart disease, no. (%)            | 20 (65%)    | 14 (45%)   | 11 (58%)   | 24 (77%)   |
| Hypercholesterolemia, no. (%)     | 16 (52%)    | 15 (48%)   | 8 (42%)    | 17 (55%)   |
| Active smoker, no. (%)            | 2 (6.5%)    | 7 (23%)    | 0 (0%)     | 7 (23%)    |
| Ischemic stroke subtype           |             |            |            |            |
| Large vessel Atherothrombogenic, no. (%) | 3 (10%)     | 9 (29%)    | 5 (26%)    | 2 (7%)     |
| Cardioembolic, no. (%)            | 10 (32%)    | 11 (36%)   | 11 (58%)   | 13 (42%)   |
| Small vessel, no. (%)             | 9 (29%)     | 4 (13%)    | 2 (11%)    | 7 (23%)    |
| Other ischemic stroke cause, no. (%) | 1 (3%)      | 1 (3%)     | 0 (0%)     | 1 (3%)     |
| Unknown cause, no. (%)            | 6 (19%)     | 6 (19%)    | 1 (5%)     | 6 (19%)    |
| Not an ischemic stroke, no. (%)   | 2 (7%)      | 0 (0%)     | 0 (0%)     | 2 (7%)     |

TNK indicates tenecteplase.
either lost to follow-up or voluntarily withdrew from the trial. Their 3-month Rankin categories were imputed using the last observation carried forward or the last recorded National Institutes of Health Stroke Scale score using a prespecified algorithm. The 0.1-mg/kg tenecteplase group had the lowest proportion of poor outcomes (7 of 31 [22.6%]), whereas the rtPA group had 10 of 31 (32.3%) poor outcomes. In terms of good outcome, the 0.25-mg/kg tenecteplase group had the highest proportion (15 of 31 [48.4%]), but the 0.1-mg/kg tenecteplase group was similar (14 of 31 [45.2%]). By comparison, the rtPA group had 13 of 31 (41.9%) good outcomes. All probability values were >0.3.

Table 3 shows selected safety measures. There were a total of 6 symptomatic ICHs: 3 of 19 (15.8%) in the 0.4-mg/kg group, 2 of 31 (6.5%) in the 0.25-mg/kg tenecteplase group, and none (0 of 31) in the 0.1-mg/kg tenecteplase group. By comparison, there was 1 of 31 (3.2%) symptomatic ICH in the rtPA group. Additionally, there were 11 asymptomatic ICHs among the 4 treatment groups. There was 1 serious systemic hemorrhage in the 0.25-mg/kg group (a retroperitoneal hemorrhage) that resulted in life-threatening hypotension and neurological worsening.

**Discussion**

This randomized, controlled, Phase IIB trial used a number of novel design features in an attempt to answer efficiently several important clinical questions before escalating to a major Phase III efficacy trial. The first issue was to select an optimal dose of tenecteplase to carry forward into Phase III from among 3 doses that had appeared safe in a previous study in patients with acute stroke. We chose an adaptive, sequential dose selection procedure that used MNI at 24 hours balanced by risk, as measured by the incidence of symptomatic ICH, to choose among 3 different doses of tenecteplase. The selection procedure efficiently eliminated 0.4 mg/kg tenecteplase as “inferior” after only 73 patients had been randomized into the study (including patients concurrently randomized to rtPA). The trial was stopped before a propitious dose of tenecteplase could be selected. Based on the prespecified criteria, we could not distinguish between the 0.1-mg/kg and 0.25-mg/kg doses after 28 pairs had been compared. Because there may be as much as an absolute 10% true difference in 24-hour MNI rates between these 2 doses, further study would be required to make this distinction.

The second major purpose of the trial was to develop evidence for either promise or futility of further study of an optimal dose of tenecteplase compared with standard-dose intravenous rtPA. We planned to enroll at least 100 patients to either rtPA or the optimal dose of tenecteplase and then to compare their 3-month outcomes in an interim analysis. Unfortunately, the premature termination of the trial preempted the planned assessment. With only 31 patients in each of the remaining treatment groups, there were major imbalances in several important baseline prognostic factors for outcome, and the uncertainty associated with the outcome proportions was so broad as to make our prespecified decision rules for stopping or continuation substantially less reliable. The promising safety experience observed in the previous pilot dose-escalation study of tenecteplase was not duplicated in this trial. The observed symptomatic ICH rate in the 0.4-mg/kg tenecteplase dose group was 15.8% and contributed to its early relegation as an “inferior” tenecteplase.

Table 2. Outcomes at 3 Months (Rankin Good and Poor) and 24 Hours (MNI) by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>TNK 0.1 mg/kg</th>
<th>TNK 0.25 mg/kg</th>
<th>TNK 0.4 mg/kg</th>
<th>rtPA 0.9 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rankin good, no. (%) (N=31)</td>
<td>14 (45.2%, 27.3–64.0)</td>
<td>15 (48.4%, 30.2–66.9)</td>
<td>7 (21.1%, 6.1–45.6)</td>
<td>13 (41.9%, 24.6–60.9)</td>
</tr>
<tr>
<td>Rankin poor, no. (%) (N=31)</td>
<td>7 (22.6%, 9.6–41.1)</td>
<td>11 (35.5%, 19.2–54.6)</td>
<td>4 (16.1%, 5.5–33.7)</td>
<td>5 (16.1%, 5.5–33.7)</td>
</tr>
<tr>
<td>MNI, no. (%) (N=31)</td>
<td>7 (22.6%, 9.6–41.1)</td>
<td>11 (35.5%, 19.2–54.6)</td>
<td>4 (21.1%, 6.1–45.6)</td>
<td>5 (16.1%, 5.5–33.7)</td>
</tr>
</tbody>
</table>

TNK indicates tenecteplase.
dose. Only 1 of 31 (3.2%) symptomatic ICH was observed in the rtPA group, but the CIs include the widely reported 6% rate. The safest regimen appears to be the 0.1-mg/kg tenecteplase group in which no symptomatic intracranial hemorrhages were observed, and the point estimates suggest an absolute 9.7% reduction in poor outcomes and 3.2% increase in good outcomes in this group compared with rtPA. None of these differences is statistically persuasive, and as noted previously, the rtPA group was older and had more severe stroke deficits at baseline.

Finally, had the Phase IIB trial been completed, the plan was to continue seamlessly into a much larger Phase III efficacy trial comparing the 3-month outcomes between the selected dose of tenecteplase and standard rtPA. The inclusion of the Phase IIB patients in the larger Phase III study has traditionally raised questions among statisticians and clinical trialists of potential bias and lack of control for Type I statistical error. However, simulations demonstrated beyond any reasonable doubt that given the conservativeness of the tests for promise or futility, and other features, the Phase III trial as designed maintained excellent control of the Type 1 error rate below 5% overall (results to be reported separately). Despite this, as of this writing, the US Food and Drug Administration has not approved this plan, and had the Phase IIB trial been allowed to continue to completion, a separate, independent Phase III trial might have been required.

Recently, Parsons and colleagues reported the results of a prospective pilot study of 15 patients selected by CT or MRI diffusion/perfusion mismatch and treated with intravenous tenecteplase at a dose of 0.1 mg/kg between 3 and 6 hours from onset of acute ischemic stroke.9 Compared with a nonrandomized control group of 35 patients treated with standard rtPA within the 3-hour time window, more tenecteplase-treated patients had major neurological improvement at 24 hours (66.7% versus 20.0%) as well as improved reperfusion and large vessel recanalization compared with the rtPA-treated group. These observations, along with the results of our trial, suggest that further study of tenecteplase as an alternative treatment for acute ischemic stroke may be warranted.

Acknowledgments
We thank the patients and families who participated in this clinical trial.

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Disclosures
E.C.H. serves as a consultant to GlaxoSmithKline. J.C.G. holds a patent on the experimental compound, caffeinol, and served as a consultant for Lundbeck. P.D.L. received research support from Photothera; consultancies with Photothera, Mitsubishi Pharma, and Benechill; serves on an advisory board for CoAxia; and received honoraria from Mitsubishi Pharma. D.L.B. receives research support from CVR Global, Inc. C.F. serves on a Speaker’s Bureau for Genentech. R.H.L. receives research support from Diogenix. S.R.L. served on an advisory board for Astra Zeneca. K.C.J. serves as a consultant to Diffusion Pharmaceuticals Inc, Remedy Pharmaceutical, and OnoPharma USA; and serves on advisory boards for Astra Zeneca.

References

Table 3. Selected Safety Data by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>TNK 0.1 mg/kg (N=31)</th>
<th>TNK 0.25 mg/kg (N=31)</th>
<th>TNK 0.4 mg/kg (N=19)</th>
<th>rtPA 0.9 mg/kg (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ICH, no.</td>
<td>0 (0%, 0–11.2)</td>
<td>2* (6.5%, 0.8–21.4)</td>
<td>3 (15.8%, 3.4–39.6)</td>
<td>1 (3.2%, 0.1–16.7)</td>
</tr>
<tr>
<td>Asymptomatic ICH, no.</td>
<td>3 (9.7%, 2.0–25.8)</td>
<td>2 (6.5%, 0.8–21.4)</td>
<td>2 (10.5%, 1.3–33.1)</td>
<td>4 (12.9%, 3.6–29.8)</td>
</tr>
<tr>
<td>All ICH, no.</td>
<td>3 (9.7%, 2.0–25.8)</td>
<td>4 (12.9%, 3.6–29.8)</td>
<td>5 (26.3%, 9.2–51.2)</td>
<td>5 (16.1%, 5.5–33.7)</td>
</tr>
<tr>
<td>Major systemic bleeding</td>
<td>0 (0%, 0–11.2)</td>
<td>1 (3.2%, 0.1–16.7)</td>
<td>0 (0%, 0–17.6)</td>
<td>0 (0%, 0–11.2)</td>
</tr>
<tr>
<td>Death within 3 months,</td>
<td>2 (6.5%, 0.8–21.4)</td>
<td>7 (22.6%, 9.6–41.1)</td>
<td>3 (15.8%, 3.4–39.6)</td>
<td>8 (25.8%, 11.9–44.6)</td>
</tr>
<tr>
<td>all causes, no. (%)</td>
<td></td>
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</table>

*N.B.: Neither of these 2 ICHs is depicted in the Figure as a score of “0” because 1 also had MNI (see text) and the second was readjudicated from asymptomatic to symptomatic by the independent adjudicator after the sequential score had been recorded per protocol.

TNK indicates tenecteplase.

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一项提前终止的随机临床试验结果

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EE. Clarke Haley, Jr, MD; John L.P. Thompson, PhD; James C. Grotta, MD; Patrick D. Lyden, MD; Thomas G. Hemmen, MD; Devin L. Brown, MD, MS; Christopher Fanale, MD; Richard Libman, MD; Thomas G. Kwiatkowski, MD; Rafael H. Llinas, MD; Steven R. Levine, MD; Karen C. Johnston, MD, MSc; Richard Buchsbaum; Gilberto Levy, MD, MS; Bruce Levin, PhD; for the Tenecteplase in Stroke Investigators

**背景和目的:**

经静脉应用阿替普酶(rtPA)仍然是唯一被认可用于急性缺血性卒中治疗的方法，但是它的使用依然有局限。一项剂量递增的预研究初步证实，经静脉使用替奈普酶可能是一种更安全的溶栓治疗选择。因此，我们启动IIB期临床试验：1) 选择一个最佳剂量的替奈普酶继续研究；2) 进一步证实替奈普酶与rtPA相比是获益或无效。如果证实获益，则启动III期有效性实验：将选择的最佳剂量的替奈普酶与标准剂量的rtPA治疗进行对照研究。

**方法:** 该试验是一小型的、多中心、随机、双盲对照试验。在起病3小时内的急性缺血性卒中患者中，分别使用0.1, 0.25, 0.4 mg/kg的替奈普酶与标准0.9 mg/kg的rtPA进行对照。使用自适应序贯设计，权衡早期(24小时内)主要神经功能改善与症状性颅内出血的风险及效益，从而选择出替奈普酶治疗的“最佳剂量”。选择好“最佳剂量”后，试验继续进行，当至少入组100对研究对象时，进行一次中期分析，比较“最佳剂量”替奈普酶与标准剂量rtPA治疗后90天改良Rankin评分。根据决策规则决定该试验无效终止或可以继续进行IIB期试验。

**结果:** 在2006年至2008年期间，8个临床中心仅有112位患者随机入组，由于入组过慢，试验被迫提前终止。在只有73位患者随机入组的情况下，0.4 mg/kg替奈普酶组因不良结局被证实无效，但是在试验终止时，依然没有得出0.1 mg/kg, 0.25, 0.4 mg/kg哪个是最佳剂量。保留的替奈普酶剂量组与rtPA组3个月结局比较，未发现令人信服的统计学差异。症状性颅内出血发生率在0.4 mg/kg替奈普酶组最高，在0.1 mg/kg替奈普酶组最低(31例中有0例)，不能据此得出获益或无益的结论。

**结论:** 这个提前终止的试验提示：在将来的试验中，若选择合适剂量，该新型的溶栓药物有可能在急性卒中治疗中具有一定的潜力。因为本试验不完整(被中断)，所以无法为替奈普酶在将来的急性卒中研究中的有效性提供令人信服的结论。

**关键词:** 急性缺血性卒中，替奈普酶，溶栓

**(Stroke. 2010;41:707-711. 蒋智 孙欣 译 谭泽锋 校)**

迄今为止，经静脉应用rtPA仍然是唯一公认的急性缺血性卒中的治疗方法。尽管我们相当努力，但是rtPA的使用仍然有限制。其中大部分是由于有效治疗时间窗很短，同时也是因为考虑不良反应即出血风险 [1]。因此需要为临床工作者研究一种更简单、安全的溶栓治疗方法，从而使溶栓治疗可以被更广泛的认可和实施。替奈普酶是rtPA的改良型，它有更高的纤维蛋白特异性，更长的半衰期，并且可以经静脉推注使用。在急性心肌梗死的治疗中，替奈普酶已经被证实有效，并且与rtPA相比出血风险更小 [2]。一项应用替奈普酶治疗急性缺血性卒中的剂量递增安全 性研究表明：75例患者分别使用0.1 mg/kg 到 0.4 mg/kg替奈普酶，未观察到症状性颅内出血 [3]。虽
然该试验与使用阿替普酶治疗的 NINDS 研究 (The National Institute of Neurological Disorders and Stroke rtPA Stroke Trial) 结果相同，二者 90 天临床结局结果相同，但是若观察该试验 24 小时的临床结局则显示：不同剂量的替奈普酶治疗之间，存在有显著的临床效果差别，0.1 mg/kg 剂量组神经功能改善比例比 0.4 mg/kg 剂量组高 20%，这表明效果与剂量可能存在反函数关系。这提示我们在将来的关于替奈普酶的剂量相关研究应当相对谨慎一些。

基于这些令人鼓舞的结果，我们设计了一个新型的、无缝连接的 IIB/III 期，随机多中心双盲对照试验，比较起病 3 小小时内的急性缺血性卒中患者经静脉应用替奈普酶与标准剂量的 rtPA 治疗。我们在此次公布本试验结果，该试验在 IIIB 阶段由于入组比预期慢而提前终止。

方法

IIB 期试验有两个目标：(1) 应用有效的统计学方法，根据早期 (24 小时) 临床结局，选择急性卒中患者应用替奈普酶的 “最佳剂量”；(2) 比较已选的最佳剂量的替奈普酶与标准剂量 rtPA 治疗的安全性和有效性。试验 (90 天) 临床结局，观察替奈普酶治疗是否获益。如果替奈普酶被证明获益，则进行重要的 III 期随机对照试验，比较替奈普酶与 rtPA90 天临床结局。

关于这个设计的详细介绍，我们将在其他地方刊登。本试验设计主要特点概括为：IIB 试验期选择 3 个不同剂量的替奈普酶组 (分别为 0.1 mg/kg, 0.25 mg/kg, 0.4 mg/kg) 进行比较。24 小时临床结局评分如下：根据患者小的明显神经功能改善 (Major Neurological Improvement, MNI) 与症状性颅内出血 (symptomatic intracranial hemorrhage, SICH) 风险进行综合评分：0 分 (最差)，1 分，2 分 (最好)。SICH 记为 0 分。MNI 定义为：24 小时 NIHSS 评分与基线相比减少 8 分，或者 24 小时 NIHSS[5] 评分为 0 分，则 MNI 记为 2 分。患者既没有 SICH 也没有 MNI，或者两者都有，记 1 分。然后通过连续的选择程序，将临床结局较差剂量组的那种剂量剔除。患者在临床试验中心随机进入 4 组中的任何一组 (3 个不同剂量的替奈普酶组或 rtPA 组)，但只有替奈普酶组需要经过剂量选择程序 (rtPA 组将来也同时做为随机对照组与选择的最佳剂量的替奈普酶组进行 3 个月临床结局比较)。当三个替奈普酶剂量组中的任何一组完成 24 小时随访后，该剂量组的累积总分就将被计算出来。当某剂量组的累积得分比得分最高的剂量组低 6 分时，则该种剂量将被剔除。假设每组 SICH 发生率为 0.06，若该剂量组与其余 2 组在 MNI 上真正差别≥10%，那么通过这个判断标准挑选到的最佳剂量，至少有 80% 的准确度。因为这是个选择程序，所以 IIB 期试验所需样本量是个变量。所需样本量的区间相对较窄：均数为 278，标准差为 50。预先确定的 IIB 期试验所需最大样本量为 600。

一旦选择好最佳的替奈普酶剂量，则开始进行该种剂量组替奈普酶与标准剂量的 rtPA 组的随机对照研究，当每组至少入组 100 名患者后，才开始中期分析。为了避免每组 100 例患者时的假设检验效能过低，我们预先设定具有临床意义的决策规则，以确定初步结果是否充分支持继续试验。这个决策规则包括：24 小时 SICH 发生率及 3 个月不良临床结局发生率，其中不良临床结局的评定采用 III 期试验的主要临床结局的评估方法，即 mRS，将 mRS 分为三个等级：[0]: Rankin=0 或 1，定义为临床结局“好”；Rankin=2 或 3 定义为临床结局“中等”；Rankin=4，
5 或 6(死亡) 定义为临床结局“差”。例如，若选择剂量的替奈普酶组 SICH 发生率较 rtPA 组低（低的定义是：该组的 SICH 发生率较 rtPA 组至少低 2%），而且该选择剂量组的 3 个月临床结局差的发生率比 rtPA 组低或相等，我们则认为该选择剂量替奈普酶组是获益的，这就是方案 1。方案 2 是若选择剂量替奈普酶组 24 小时 SICH 发生率与 rtPA 组接近相同（如 ±1%），那么选择剂量替奈普酶组 3 个月临床结局差的发生率至少要低于 rtPA 组低 8%，我们才认为选择剂量替奈普酶组可能获益。此外若在任一情况下，如果选择剂量替奈普酶组的临床结局好的发生率都明显低于 rtPA 组，且双侧检验水平低于 0.001，这时我们认为选择剂量替奈普酶组未获益。如果在中期分析中，选择剂量替奈普酶组 SICH 发生率高于 rtPA 组 2 倍，那么这个研究将被停止。模拟结果显示综合以上这些临床决策规则可被认为是二次“选择程序”。这表明，使用这些设计参数，得出正确选择（连续或间断选择）的概率将大于 85%。

如果 IIB 期试验显示获益，那么我们将在其他的临床中心继续 III 期试验：比较替奈普酶与 rtPA 两组 3 个月临床结局（按照 mRS 三等级评估）来检验两个无效假设：（1）选择剂量替奈普酶组中临床结局差的发生率与 rtPA 组中无区别；（2）选择剂量替奈普酶组中临床结局好的发生率与 rtPA 组中无区别。每种假设都是在双侧检验水平 $\alpha = 0.025$ 下，应用分层的自由度为 1 的 Mantel-Haenszel 检验，1/2 连续性校正。计划需要的样本量为 1908 例（每组 954 例）。在这种情况下，当临床结局差的发病率下降幅度大于或等于 8%，而且临床结局好的发生率无下降时，则存在 90% 的检验力度；或者临床结局好的发生率增加 8%，而且临床结局差的发生率无增加时，则存在 89% 的检验力度。

由于试验被提前中止，使得之前计划好的选择剂量替奈普酶组与标准剂量 rtPA 组比较是否获益或无效的 III 期试验也被中止。试验被中止后，在破盲和任何疗效分析之前，试验研究者通过试验数据和安全监督委员会批准，进行一项新的“后期分析”计划。这个计划应用 Mantel-Haenszel 检验，先将 3 个不同剂量的替奈普酶组单独及联合起来分别与 rtPA 组进行比较，首先比较临床结局好（Rankin=0 或 1）的发生率，然后再比较临床结局差（Rankin=4-6）的发生率。考虑到最初设计好的计划没有如期执行，目前的分析只是探索性的，只计算特定的概率值，没有考虑多个对照，没有预先设定显著性水平。所有的结果分析都是意向性分析。

试验的操作规程和知情同意书均经审查委员会的每位成员的审查和批准。入选标准：年龄≥18 岁；急性局限性脑缺血所致的严重神经功能缺损；符合

### 表 2 各治疗组 3 个月 (Rankin 评分好和差) 和 24 小时 MNI

<table>
<thead>
<tr>
<th></th>
<th>TNK 0.1 mg/kg (N=31)</th>
<th>TNK 0.25 mg/kg (N=31)</th>
<th>TNK 0.4 mg/kg (N=19)</th>
<th>rtPA 0.9 mg/kg (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rankin 好，例数 (%，95% CI)</td>
<td>14 (45.2%，27.3–64.0)</td>
<td>15 (48.4%，30.2–66.9)</td>
<td>7 (36.8%，16.3–61.6)</td>
<td>13 (41.9%，24.6–60.9)</td>
</tr>
<tr>
<td>Rankin 差，例数 (%，95% CI)</td>
<td>7 (22.6%，9.6–41.1)</td>
<td>11 (35.5%，19.2–54.6)</td>
<td>6 (31.6%，12.6–56.6)</td>
<td>10 (32.3%，16.7–51.4)</td>
</tr>
<tr>
<td>MNI，例数 (%，95% CI)</td>
<td>7 (22.6%，9.6–41.1)</td>
<td>11 (35.5%，19.2–54.6)</td>
<td>4 (21.1%，6.1–45.6)</td>
<td>5 (16.1%，5.5–33.7)</td>
</tr>
</tbody>
</table>

TNK 代表替奈普酶。
目前的在起病3小时内使用静脉溶栓的治疗指南[7]。

取得患者知情同意后，采用网络随机化分组的方法，对试验中心参加试验的药师不设盲，药师根据不同剂量分组情况，将0.1 mg/kg或0.25 mg/kg或0.4 mg/kg的替奈普酶配以10 mL生理盐水静脉推注，然后接着静脉推注90 mL生理盐水(在1小时内滴完)或0.9 mg/kg的rtPA总量的10%配以10 mL生理盐水静脉推注，剩下90%的rtPA配以90 mL生理盐水静脉滴注1小时以上。从始至终对经治医生、研究者、调查人员和患者设盲。每位入选患者在使用研究药物之前都要求测基线NIHSS，以确保该患者仍然符合入选标准。若患者神经缺损症状消失或者患者在随机安排治疗和真正治疗开始之间发生变化而变得不符合入选标准，则仍然认为该患者“入选”，但是不属于“随机”同时也不纳入分析，并且需要记录排除这些患者(已经入选但未参加随机)的理由。

参与随机的患者在重症监护中心或卒中单元观察治疗24小时，溶栓后的治疗严格按照指南执行。卒中起病后24±2小时测NIHSS评分，溶栓治疗后48±6小时行头颅CT检查以评价非症状性颅内出血。如果出现神经功能恶化，行头颅CT检查，并记录神经功能恶化的主要原因及相关因素。神经功能恶化定义为：临床上显著的神经功能改变(出现新的神经功能缺损或原有的缺损症状加重)，症状持续超过8小时。所有的CT检查(基线CT或随访CT)送到临床协作中心(Clinical Coordinating Center)，由一位参与研究的神经影像学专家独立对CT影像进行解读，判定CT有无显示颅内出血。如果任何头颅CT判定存在颅内出血，则该病例就完全转交给另一位独立的临床神经科医生，由这位神经科医生对是否存在症状性颅内出血进行解读，并作出判定。SICH定义为：与头颅CT显示的新的出血灶相关的，临床上任何的重要神经功能的损害(符合神经功能恶化标准，见上)。血肿面积大于梗死面积的1/3，产生占位效应，脑室或蛛网膜下腔扩大一般都认为是占位效应的强烈指征，但是最终的评判以独立的临床神经科医生的观点为准。治疗24小时内出现的SICH认为系治疗药物所致。

安全性是由单独的医疗监测和数据与安全监测委员会负责监督。数据和安全监测委员会还负责审查选择程序的进展，保障试验的完整性，并对获益或无益的分析结果进行评审。

结果

2006年3月至2008年12月间，8个临床中心10家医院共随机入组了112例患者(参见附录)。其中有1例随机入组到rtPA组的患者接受的是0.25 mg/kg的替奈普酶，另1例入组到0.25 mg/kg替奈普酶组的患者接受的是0.7 mg/kg的替奈普酶；其余的110例患者均按照随机指定的药物和剂量给药。另外17例患者在最终决定入选之前接受了临时的治疗方法而被排除，7例患者入选前症状消失，8例患者没有及时的用药，另2例患者在治疗开始前退出试验。表1显示的是各治疗组所选择的安全性数据。

### 表1  各治疗组所选择的安全性数据

<table>
<thead>
<tr>
<th>处方</th>
<th>TNK 0.1 mg/kg (N=31)</th>
<th>TNK 0.25 mg/kg (N=31)</th>
<th>TNK 0.4 mg/kg (N=19)</th>
<th>rtPA 0.9 mg/kg (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>症状性颅内动脉出血例数(%, 95% CI)</td>
<td>0 (0%, 0–11.2)</td>
<td>2* (6.5%, 0.8–21.4)</td>
<td>3 (15.8%, 3.4–39.6)</td>
<td>1 (3.2%, 0.1–16.7)</td>
</tr>
<tr>
<td>无症状性颅内动脉出血例数(%, 95% CI)</td>
<td>3 (9.7%, 2.0–25.8)</td>
<td>2 (6.5%, 0.8–21.4)</td>
<td>2 (10.5%, 3.3–31.1)</td>
<td>4 (12.9%, 3.6–29.8)</td>
</tr>
<tr>
<td>所有颅内动脉出血例数(%, 95% CI)</td>
<td>3 (9.7%, 2.0–25.8)</td>
<td>4 (12.9%, 3.6–29.8)</td>
<td>5 (26.3%, 9.2–51.2)</td>
<td>5 (16.1%, 5.5–33.7)</td>
</tr>
<tr>
<td>主要系统出血例数(%, 95% CI)</td>
<td>0 (0%, 0–11.2)</td>
<td>1 (3.2%, 0.1–16.7)</td>
<td>0 (0%, 0–17.6)</td>
<td>0 (0%, 0–11.2)</td>
</tr>
<tr>
<td>3个月内所有原因引起的死亡例数(%, 95% CI)</td>
<td>2 (6.5%, 0.8–21.4)</td>
<td>7 (22.6%, 9.6–41.1)</td>
<td>3 (15.8%, 3.4–39.6)</td>
<td>8 (25.8%, 11.9–44.6)</td>
</tr>
</tbody>
</table>

* 这12例ICHs均未在图中作为评分为0而显示，因为1例有MNI(见文章)，另1例在程序化评分结束后被独立的评估者从非症状性重新判定为症状性颅内出血。TNK代表替奈普酶。
除了原来入组的 14 例患者外，我们另外收集了 5 例应用 0.4 mg/kg 剂量替奈普酶的患者。其中 4 名患者是在 0.4 mg/kg 剂量组被停止随机后，有些临床中心仍然开放而纳入的，因此并未纳入分析。第 5 名患者是一个临床试验中心的唯一的一名入选患者，后来该中心被剔除。这 5 名患者数据均未纳入之前的剔除 0.4 mg/kg 剂量的分析，仅纳入到后续分析当中。

表 2 显示的是各治疗组 3 个月预后及 24 小时的明显神经功能改善发生率。其中有 4 名患者或失访或自愿退出试验。他们 3 个月的 Rankin 分类评分来自于最后一次的 NIHSS 评分及观察记录。31 例入选患者中 0.1 mg/kg 的替奈普酶组临床结局差的发生率最低 (7 例预后不良, 22.6%), 而 rtPA 组临床结局差的发生率为 45.2%(14 例预后良好), 与之相当。rtPA 组良好预后率为 41.9%(13 例预后良好)。所有的概率值均大于 0.3。

表 3 显示的是治疗的安全性数据。共有 6 例 SICH：0.4 mg/kg 组的 19 例患者中有 3 例 (15.8%), 0.25 mg/kg 组的 31 例患者中有 2 例 (6.5%), 0.1 mg/kg 组无颅内出血病例，rtPA 组 31 例患者中有 1 例 (3.2%)。同时，4 个治疗组中还有 11 例非症状性颅内出血。0.25 mg/kg 的替奈普酶剂量组中有 1 例严重的系统性出血 (腹膜后出血), 导致最终危及生命的低血压及神经功能的恶化。

### 讨论

在开始 III 期有效性试验前，我们进行了一系列新颖设计的随机对照研究来回答一些重要的临床问题。第一个问题是：在以往急性卒中患者中应用过的 3 个安全剂量中选择一个最佳剂量应用于 III 期试验。我们选择自适应剂量选择程序，使用 24 小时主要神经功能改善，均衡 SICH 风险 (SICH 发生率)。从 3 种不同剂量的替奈普酶组中进行选择。剂量选择程序有效地剔除了 0.4 mg/kg 替奈普酶剂量组，因为仅随机入选了 73 例患者时 (包括同时随机入组到 rtPA 的患者)，该剂量就显示出其弊处。该试验还未选择出最佳有效剂量的替奈普酶即被停止。从预先确定的标准，仅通过比较 28 对患者我们无法区分 0.1 mg/kg 和 0.25 mg/kg 哪一种剂量更合适。因为这两种剂量组之间，24 小时 MINI 存在的绝对差异可能达到 10% 之多，因此这需要我们将来的进一步研究。

试验的第二个目的是将选择的合适剂量的替奈普酶与标准剂量的静脉 rtPA 比较是否获益或无效。我们计划 rtPA 组和选择剂量替奈普酶组至少各入组 100 名患者，然后在中期比较分析其 3 个月的预后。不幸的是，该试验在中期计划评估前被提前终止。每个治疗组仅有 31 例患者，而且其基线资料中几个重要的临床结局预后因子不平衡，其对最终结果产生的影响的相关程度也很不确定，使我们对下一步终止或是继续试验都缺乏依据。在之前的预试验中观察到的替奈普酶获益及安全性的结果并没有在本试验中出现。我们观察到 0.4 mg/kg 替奈普酶剂量组 SICH 发生率为 15.8%，也正因为此“劣势”而提前终止该剂量组的研究。虽然在 rtPA 组的 31 例患者中仅有 1 例 SICH(3.2%), 但是在其他的急性脑梗死治疗的研究中却显示 SICH 发生率一般在 6% 左右。最安全的方案似乎是 0.1 mg/kg 替奈普酶组，该组中没有观察到 SICH，与 rtPA 组相比其临床结局好的比例增加了 9.7%, 临床结局差的比例下降了 3.2%。但同时我们也看到以上的这些差异均无统计学意义，而且正如我们之前提到的，rtPA 组与 0.1 mg/kg 组基线资料比较，rtPA 组年龄更大，而且卒中严重程度更重。最后，IIb 期试验已经完成，我们的计划是直接无缝隙进入更大的 III 期有效性试验，比较选择剂量替奈普酶组与标准剂量 rtPA 组的 3 个月临床结局预后。更大的 III 期试验中包含有 IIb 期试验的患者，就这点很多统计学家和临床试验者提出质疑，他们认为这种方法会导致潜在的偏差，同时使试验设计缺乏对 I 型统计学错误的控制。尽管这些质疑使得我们对 III 期试验设计是否能真正用来判定替奈普酶获益或无效而持保守态度，但是模拟结果显示 III 期试验的设计可将统计学 I 型错误控制在 5% 以下，属于控制良好 (相关结果另外发表)。尽管如此，在撰写本文时，美国食品及药物监督局仍然没有批准这一计划，但是 IIb 期试验还是获准继续完成，并且可能已经被要求开展一个单独的，独立的 III 期试验。

最近，Parsons 和他的同事报告了一个前瞻性试验研究的结果，经 CT 或 MRI 弥散 / 灌注不匹配选择 15 例急性缺血性卒中患者，起病 3-6 小时内应用 0.1 mg/kg 替奈普酶静脉注射治疗[9]相较于非随机对照组的 35 例患者在 3 小时的时间窗内应用标准剂量的 rtPA，24 小时神经功能改善率为 (66.7% 比 20.0%)，而且缺血再灌注和大血管再通率均较 rtPA 组有显著改善。结合这个试验结果和我们的试验结果，提示替奈普酶作为急性缺血性卒中治疗的另外一种药物选择，有进一步研究的价值。

### 参考文献 (略)