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Reteplase versus alteplase for acute ischaemic stroke within 4.5 hours (RAISE): rationale and design of a multicentre, prospective, randomised, open-label, blinded-endpoint, controlled phase 3 non-inferiority trial

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ABSTRACT

Background and purpose Reteplase is the third generation of alternative thrombolytic agent. We hypothesis that reteplase will be non-inferior to alteplase in achieving excellent functional outcome at 90 days among eligible patients with acute ischaemic stroke.

Methods and design Reteplase versus alteplase for acute ischaemic stroke within 4.5 hours (RAISE) trial is a multicentre, prospective, randomised, open-label, blinded endpoint (PROBE), controlled phase 3 non-inferiority trial. A total of 1412 eligible patients will be randomly assigned to receive either reteplase at a dose of 18 mg+ 18 mg or alteplase 0.9 mg/kg at a ratio of 1:1. An independent data monitoring committee will review the trail's progress and safety data.

Study outcomes The primary efficacy outcome of this study is proportion of individuals attaining an excellent functional outcome, defined as modified Rankin Scale (mRS) 0–1 at 90 days. The secondary efficacy outcomes encompass favourable functional outcome defined as mRS 0–2, major neurological improvement on the National Institutes of Health Stroke Scale, ordinal distribution of mRS and Barthel Index score of at least 95 points at 90 days. The primary safety outcomes are symptomatic intracranial haemorrhage at 36 hours within 90 days.

Discussion The RAISE trial will provide crucial insights into the selection of thrombolytic agents for stroke thrombolysis.

Trial registration number NCT05295173.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Reperfusion therapy is an evidence-based intervention intended to reduce the global burden of ischaemic stroke. While there has been a great increase in the rate of intravenous thrombolysis recently, challenges persist in terms of underutilisation and suboptimal prognosis reteplase is a non-glycosylated variant of alteplase, characterised by a longer half-life that facilitates double-bolus administration with a fixed dosage and reinforced thrombolytic effect.

WHAT THIS STUDY ADDS

⇒ RAISE trial is a multicentre, prospective, randomised, open-label, blinded endpoint (PROBE), controlled phase 3 non-inferiority trial. RAISE trial aims to test the hypothesis that recombinant plasminogen activator, reteplase, 18 mg+ 18 mg will be non-inferior to standard recombinant tissue plasminogen activator, alteplase, in achieving excellent functional outcome at 90 days post-stroke in patients within 4.5 hours from symptoms onset.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The RAISE trial will provide crucial insights into the selection of thrombolytic agents for stroke thrombolysis.

INTRODUCTION AND RATIONALE

Intravenous thrombolysis with alteplase (a recombinant tissue plasminogen activator, rt-PA) represents the primary reperfusion therapy for early recanalisation of acute ischaemic stroke, preserving the cerebral ischaemic penumbra and enhancing clinical outcomes.[1–5] The widespread utilisation of thrombolytics continues to be in high clinical demand. Reteplase (r-PA) and tenecteplase are third generation of alternative thrombolytic agents for acute myocardial infarction.[6–10] Tenecteplase was non-inferior to rt-PA in patients with acute ischaemic stroke within 4.5 hours of onset.[11–13] To date, there is a lack of definitive clinical trials comparing r-PA with rt-PA in patients with acute ischaemic stroke.[14–16]

Reteplase is a non-glycosylated variant of rt-PA, characterised by a longer half-life that facilitates double-bolus administration with a fixed dosage instead of infusion based on body weight in kilogram.[17–19] Theoretically, the reduction in fibrin specificity can enhance thrombolysis, meanwhile, it may also increase

the risk of bleeding. Thus, it is crucial to determine the appropriate dosage of r-PA for patients with acute ischaemic stroke in order to achieve an optimal benefit-risk ratio.

A multi-centre, prospective, randomised controlled, open-label, blinded-endpoint, dose-finding, phase 2 clinical trial of r-PA has suggested that the rate of death and symptomatic intracranial haemorrhage (sICH) among 12 mg+12 mg of r-PA, 18 mg+18 mg of r-PA and 0.9 mg/kg of rt-PA were similar in patients with acute ischaemic stroke within 4.5 hours of onset in China. Although there was a slightly higher incidence of extracranial bleeding (without statistically significant differences) in patients treated with 18 mg+18 mg of r-PA compared to those treated with 12 mg+12 mg of r-PA and 0.9 mg/kg of rt-PA, the group receiving 18 mg+18 mg of r-PA had a numerically superior proportion of excellent functional outcome (defined as modified Rankin Scale 0–1) when compared with the groups receiving 12 mg+ 12 mg of r-PA and 0.9 mg/kg of rt-PA. The recommended dosage of r-PA for patients with acute myocardial infarction is 18mg+18 mg.

In this study, we aim to test the hypothesis that r-PA 18 mg+18 mg will be non-inferior to rt-PA 0.9 mg/kg in achieving excellent functional outcome at 90 days post-stroke in patients within 4.5 hours of symptoms onset.

METHODS AND DESIGN

RAISE is a multicentre, prospective, randomised, open-label, blinded endpoint (PROBE), controlled phase 3 non-inferiority trial that evaluates the efficacy and safety of reteplase versus alteplase in 1:1 ratio in patients with acute ischaemic stroke who are eligible for intravenous thrombolysis within 4.5 hours from symptom onset. The trial was prospectively registered with ClinicalTrials.gov, and the assessment flowchart is shown in table 1.

PATIENT POPULATION

Participants were eligible if they were 18–80 years, suffered an acute ischaemic stroke within 4.5 hours of symptoms onset and had a score on baseline National Institutes of Health Stroke Scale (NIHSS) 4–25 (inclusive) judged by the investigator. Patients are excluded with a modified Rankin Scale (mRS) score of no more than 1 before the onset of the current stroke, a history of haemorrhage and severe head trauma in the last 3 months, etc. The inclusion

Table 1 Trial assessment flow chart

	Baseline	Treatment				Follow-up	
Visit	V1	V2	V3	V4	V5	V6	V7
Day-visit	D1 (–4.5 h to 0 h)	D1 (0 h)	D2 (24 h ±2 h)	D4 (72 h ±6 h)	D8±l d	D31±3 d	D91±7 d
Informed consent	X						
Demographic data	X						
Weight	X						
Medical history	X						
Inclusion/exclusion criteria	X						
Vital signs	X		X	X	X	X	X
Physical examination	X				X		
Brain CT/MRI	X		X				
Pregnancy tests	X						
Haematology	X		X		X		
Urinalysis			X		X		
Stool routine test			X				
Blood chemistry	X		X		X		
Coagulation test	X		X	X			
Finger blood glucose Test[m]	X						
ECG	X		X		X		
NIHSS	X		X		X		
mRS	X (prestroke)					X	X
Barthel Index						X	X
Randomisation	X						
Administration		X					
Concomitant medications	X						
Procedure	D1 (–4.5 h ±0 h)	D1 (0 h)	D2 (24 h ±2 h)	D4 (72 h ±6 h)	D8±l d	D31±3 d	D91±7 d
Adverse events	X						

CT, computed tomographic; D, day/days; h, hour/hours; MRI, Magnetic Resonance Imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

and exclusion criteria are comprehensively outlined in box 1 and box 2. The participants or their legal representatives provided written informed consent prior to their enrolment.

Randomisation and intervention

The eligible patients were allocated to experimental (r-PA) or control (rt-PA) groups randomly at a 1:1 ratio by an interactive web response system (Randomisation and Trial Supply Management eBalance V.5.3, Zhejiang Taimei Medical Technology, China). Block randomisation was performed on the system without stratification and with a random block length of two, four or six. The random codes were obtained by the local investigators through the system, and the treatment assignment was completed based on the random codes. The standard of care for ischaemic stroke guided all other treatments. r-PA was administered as a double, intravenous bolus (bolus over 2 min) at 18 mg + 18 mg with 30-min intervals. rt-PA was administered at a dose of 0.9 mg/kg (maximum dose 90 mg), with 10% of the dose given as a bolus within 1 min and the remaining dose administered over the subsequent 60 min. The intravenous thrombolytic treatment was open label. Clinical investigators responsible for assessing efficacy endpoints were blinded to treatment allocation. Following initial evaluation by the local investigators, important clinical events, including sICH, other significant haemorrhage events and all-cause death, will be further evaluated by the independent clinical-event adjudication committee.

PRIMARY OUTCOMES

The primary outcome of this study is proportion of patients with mRS 0–1 at 90 days (excellent functional outcome).

Secondary efficacy outcomes

1. Proportion of patients with NIHSS score decrease of at least 4 points from baseline or no more than 1 at 24 hours, or at 7 days.

Box 1 Inclusion criteria

- ⇒ Aged 18–80 years at the time of signing the informed consent form, either males or females.
- ⇒ Within 4.5 hours after the onset of symptoms of neurological impairment due to acute ischaemic stroke according to the diagnosis criteria for stroke issued by the WHO. Onset time refers to the time the patient was last known to be well.
- ⇒ 4≤National Institutes of Health Stroke Scale score≤25 before thrombolysis
- ⇒ Fertile men and women of childbearing age who have no childbearing plan from the date of enrolment to 3 months after thrombolysis administration and are willing to take effective contraceptive measures.
- ⇒ Understand and follow the procedures of clinical trial, participate voluntarily and sign the informed consent (the informed consent can be signed voluntarily by the person or guardian).

Box 2 Exclusion criteria

- ⇒ Patients are known to be allergic to investigation drugs (recombinant human tissue-type plasminogen activator derivative for injection, alteplase) or similar components, or materials used for imaging examinations.
- ⇒ Body weight >120 kg or <45 kg.
- ⇒ The onset of stroke symptoms cannot be ascertained.
- ⇒ Modified Rankin Scale score ≥2 before the onset of the current stroke.
- ⇒ 1a (level of consciousness) of National Institutes of Health Stroke Scale consciousness score ≥2 at screening.
- ⇒ Intracranial haemorrhage history (including parenchymal/intraventricular/subarachnoid haemorrhage, subdural/external haematoma, etc).
- ⇒ CT/MRI imaging shows signs of intracranial haemorrhage or subarachnoid haemorrhage is suspected despite normal CT/MRI.
- ⇒ Severe head trauma, clinically symptomatic stroke history or other severe trauma in the last 3 months.
- ⇒ Patients with intracranial tumours, intracranial arteriovenous malformations or aneurysms before enrolment.
- ⇒ Intracranial surgery, or intraspinal surgery or other major surgery within 3 months before enrolment (based on the assessment of the investigators).
- ⇒ Gastrointestinal or urinary system haemorrhage within the past 3 weeks.
- ⇒ Patients with active visceral haemorrhage.
- ⇒ Aortic arch dissection confirmed by prestudy examination or medical history.
- ⇒ Arterial puncture at the site that is not easily compressed to stop bleeding within the last week.
- ⇒ Acute bleeding tendency, including but not limited to the following: (1) platelet count less than 100×10^9/L; (2) patients received low molecular weight heparin within 24 hours before onset; (3) use of thrombin inhibitor or factor Xa inhibitor within 48 hours before onset; (4) taking oral anticoagulants and international normalised ratio (INR) >1.7 or prothrombin time (PT) <15 s.
- ⇒ Actively treated but uncontrolled hypertension, defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg.
- ⇒ Blood glucose <50 mg/dL (equivalent to 2.78 mmol/L) or >400 mg/dL (equivalent to 22.2 mmol/L) during screening.
- ⇒ Large cerebral infarction on CT or MRI.
- ⇒ Severe liver dysfunction including liver failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis.
- ⇒ Patients with bacterial endocarditis, pericarditis or acute pancreatitis at enrolment.
- ⇒ History of gastrointestinal ulcer, oesophageal varices, aneurysm or arterial/venous malformation within 3 months before enrolment.
- ⇒ Unable or unwilling to cooperate due to epileptic seizures during stroke episodes or other mental illness.
- ⇒ Planned or received endovascular treatment after the onset of the current stroke.
- ⇒ Patients have to take or desire to continue to take the restrictive drugs specified in the protocol or any drug that may interfere with the test results.
- ⇒ With an expected survival time less than 1 year due to other diseases.
- ⇒ Have participated in other clinical studies within 30 days prior to randomisation, or are participating in other clinical trials.

Continued

Box 2 Continued

⇒ Women are in pregnancy or lactating or have a positive pregnancy test result.
⇒ Considered by the investigator to have other conditions that might affect compliance or preclude participation in the study.

2. The proportion of patients with mRS score 0–2 at 90 days (favourable functional outcome).
3. Ordinal distribution of mRS scores at 90 days.
4. Proportion of patients with a Barthel Index score of at least 95 points at 90 days.

Safety outcomes

1. sICH defined by Safe Implementation of Thrombolysis in Stroke and The European Cooperative Acute Stroke Study III.[5 20]
2. All-cause death within 7 days and 90 days.
3. Major bleeding events within 90 days defined by International Society on Thrombosis and Haemostasis.[21]
4. Clinically related non-massive haemorrhage within 90 days defined by International Society on Thrombosis and Haemostasis.[22]
5. The proportion of patients with adverse events and serious adverse events within 90 days.

Data monitoring body

An independent data monitoring committee (IDMC) will review the progress of the trial, and safety data. IDMC consists of two clinical experts specialising in stroke thrombolysis and one biostatistician with experience in statistical analysis of clinical trial data. To ensure objectivity, the Statistical Support Group, which operates independently from the sponsors, will provide assistance to the IDMC. Scheduled meetings will be conducted to review data when either a minimum of 18 patients with sICH (defined by the European Cooperative Acute Stroke Study [ECASS] III) are observed among a maximum of 600 patients or when the total number of patients with sICH (defined by ECASS III) reaches 42 out of 1412 patients.[5] A comprehensive elucidation regarding the composition, responsibilities and objectivity of the IDMC can be found in IDMC Charter (supplemental material 4).

Sample size estimates

The sample size was calculated based on the primary efficacy outcomes and non-inferiority research design. In the RAISE study, the non-inferiority criterion was set to preserve at least 50% of the alteplase efficacy effect, which was a somewhat conservative estimate. Since the lower limit of 95% CI of rt-PA relative ratio (RR) was 1.15 compared with placebo,[4 5] the non-inferiority margin of r-PA to rt-PA was set to be 0.93 (calculated as $-1/(\exp(\text{Log}(1.15))/2)$). With the assumed 62.5% proportion of the primary outcome for alteplase, the determined sample size of 1412 (706 in each treatment group) would provide 80% power, allowing for a 3% dropout rate at 90 days. The probability of at least one death or symptomatic intracranial haemorrhage occurrence was estimated to be >99% among 1412 patients based on the incidence of symptomatic intracranial haemorrhage and death among patients with acute ischaemic stroke (1% incidence for symptomatic intracranial haemorrhage[20] and 5% for death.[23]

STATISTICAL ANALYSES

Data will be presented as mean±SD or median (IQR) for continuous variables and counts (proportion) for categorical variables. When comparing the differences, t-test or rank sum test will be used for continuous variables, Wilcoxon rank-sum test for ordinal variables, and χ^2 test or Fisher's exact test for categorical variables, as appropriate.

Efficacy analyses will be conducted in the modified intention-to-treat population, comprising patients diagnosed with acute ischaemic stroke, who were randomly assigned and received thrombolytic treatment based on randomisation. For primary efficacy outcomes, proportions of patients with mRS 0–1 at 90 days, will be summarised separately for each group, and the RR of r-PA versus rt-PA will be calculated from log binomial regression (robust Poisson regression, if the model does not converge) based on complete case analysis, with trial centres set as a random effect. The r-PA would be declared non-inferior to rt-PA if the lower boundary of RR for the primary outcome is higher than the predetermined non-inferiority limit of 0.93. Superiority would be established if the lower boundary of RR is higher than 1. In sensitivity analyses, the influence of missing data, and concomitant therapy will be evaluated to test the robustness of the main findings. For the missing data, various multiple imputation techniques were applied. The secondary efficacy outcomes were subjected to comparable statistical analysis.

Safety analyses were conducted in the safety set, who have received drug treatment and subsequent safety evaluation at least once. Similar to the analysis of efficacy outcomes, safety outcomes will be summarised by each group, and RR will be calculated from robust Poisson regression, with trial centres set as a random effect.

All data analyses were conducted by SAS software V.9.4 (SAS Institute, Cary, North Carolina, USA). No interim analyses were planned in the RAISE study.

DISCUSSION

The RAISE trial will be one of the largest trials investigating r-PA treatment for acute ischaemic stroke conducted to date, providing crucial insights into the selection of thrombolytic agents for stroke thrombolysis.

Despite the pivotal role of intravenous thrombolysis in stroke management, its utilisation remains limited due to stringent time window and restricted drug options. Many innovative thrombolytic agents are undergoing clinical

trials. Based on the findings from the phase 2, dose finding trial assessing the safety and efficacy of r-PA in the management of acute ischaemic stroke, intriguing dose-response trends in efficacy outcome of r-PA have been observed. Compared with the groups receiving 12 mg + 12 mg of r-PA and 0.9 mg/kg of rt-PA, the group receiving 18 mg + 18 mg of r-PA achieved a numerically higher proportion of excellent functional outcome without an increased incidence of fatal bleeding. The results of this phase 2 trial are valuable in informing the design of pivotal phase 3 trials.

The RAISE trial is an industry-sponsored trial conducted to support the biological license application of r-PA for patients with acute ischaemic stroke. To fulfil the supervision requirements of the Center for Drug Evaluation of National Medical Products Administration, a statistical analysis plan (SAP) was developed in advance by an independent third-party statistical agency, following the statistical principles for clinical trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (ICH E9 (R1), May 2021). This updated version of E9 adopts five different strategies for handling intercurrent events, in contrast to the per-protocol analysis used in the previous version form since September 1998. Recognising that clinicians and academia are more accustomed to the analytical strategy of E9, another SAP consistent with the statistical method introduced in this protocol has been predeveloped for the RAISE trial by the statistical agency of the China National Clinical Research Center for Neurological Diseases. The original protocol and SAP for the biological license application are provided in the supplementary appendix (online supplemental file 1-3).

Reteplase's remarkable efficacy in the treatment of myocardial infarction has resulted in its approval for this indication.[7 9 24–26] Given the approval of r-PA for acute myocardial infarction and the supportive evidence from this phase 2 clinical trial in patients with acute ischaemic stroke, we are motivated to investigate its potential application in acute ischaemic stroke, thereby highlighting its therapeutic advantage.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The trial was done in accordance with the guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. The study protocol, patient consent form and all amendments were ethically approved by the institutional review board of the Beijing Tiantan Hospital and each clinical centre involved. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data sharing not applicable as no data sets generated and/or analysed for this study.

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