INPLASY PROTOCOL

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All authors declare no conflicts of interest.

Efficacy and safety of different doses of tenecteplase for the treatment of acute ischemic stroke: a protocol for a systematic review and network meta-analysis

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Review question / Objective: **We designed this study with network meta-analysis technique to investigate the comparative efficacies and safety of different doses of tenecteplase in treating AIS for the purpose of determining the optimal prescribed dose of tenecteplase in clinical practice.**
Condition being studied: **As one option of thrombolytic therapy, tenecteplase which is a genetically modified variant of alteplase, has been used to treat AIS in clinical practice. To date, several published studies reported the efficacy and safety of tenecteplase in treating AIS, and suggested that tenecteplase may be a potential agent for effectively treating AIS. Moreover, a meta-analysis which investigated the comparative efficacy and safety of tenecteplase versus alteplase also determined the value of tenecteplase for the treatment of AIS. However, practitioners prescribed various doses when they considered tenecteplase to treat AIS, and no study to further determine the optimal dose of tenecteplase currently in clinical studies. Therefore, it is imperative to design new study to answer this question.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 October 2020 and was last updated on 22 October 2020 (registration number INPLASY2020100086).

INTRODUCTION

Review question / Objective: **We designed this study with network meta-analysis technique to investigate the comparative efficacies and safety of different doses of tenecteplase in treating AIS for the purpose of determining the optimal prescribed dose of tenecteplase in clinical practice.**

Rationale: **Acute ischemic stroke (AIS) has became the major reason of causing death around the world. As a newer generation fibrinolytic agent, the potential of tenecteplase in treating AIS has been determined in clinical studies and meta-analysis. However, various doses have been prescribed for tenecteplase in clinical**

practice, and the optimal dose is not yet clear.

Condition being studied: As one option of thrombolytic therapy, tenecteplase which is a genetically modified variant of alteplase, has been used to treat AIS in clinical practice. To date, several published studies reported the efficacy and safety of tenecteplase in treating AIS, and suggested that tenecteplase may be a potential agent for effectively treating AIS. Moreover, a meta-analysis which investigated the comparative efficacy and safety of tenecteplase versus alteplase also determined the value of tenecteplase for the treatment of AIS. However, practitioners prescribed various doses when they considered tenecteplase to treat AIS, and no study to further determine the optimal dose of tenecteplase currently in clinical studies. Therefore, it is imperative to design new study to answer this question.

METHODS

Participant or population: Patients diagnosed with AIS.

Intervention: Tenecteplase.

Comparator: Tenecteplase or other comparators.

Study designs to be included: Only randomized controlled trials will be considered.

Eligibility criteria: According to our aims, we designed the following inclusion criteria: (1) randomized clinical trial; (2) patients enrolled with acute cerebral ischemia, with brain imaging performed before enrollment to exclude hemorrhage; (3) allocation to tenecteplase versus active comparator alteplas; and (4) treatment initiated acutely, within 6 hours after last known well time.

Information sources: We will customize literature search strategies to each database with the help of a research librarian, incorporating database-specific controlled vocabularies and text words. We will search PubMed, Embase, and the Cochrane Library. We will not restrict searches by publication date, publication status, or language to minimize risk of publication bias as data from trials. We will examine references of included RCTs and other pertinent publications to reduce the risk of failing to include a relevant RCT. We will rerun each of the database searches before submission of the final manuscript to capture any newly published RCTs.

Main outcome(s): The primary efficacy end point analyzed was disability-free outcome (modified Rankin Scale [mRS] score, 0–1) at 3 months poststroke. Additional efficacy outcomes were functional independence (mRS, 0–2) at 3 months and reduced level of disability overall 7 mRS levels (shift analysis) at 3 months. Safety outcomes were symptomatic intracranial hemorrhage (sICH) and mortality. Symptomatic hemorrhage events in individual trials were identified using the sICH definition employed in that trial. Two raters (Dr Burgos and Dr Saver) independently abstracted end point data, and any discrepancies were resolved by consensus review.

Quality assessment / Risk of bias analysis: Independent reviewers will judge risk of bias in individual RCTs in duplicate according to the following domains outlined in the Cochrane risk of bias tool for RCTs: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel and other potential threats to validity), detection bias (blinding of outcome assessment and other potential threats to validity), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting assessed by comparing outcomes reported in the protocol to those reported in the completed RCT whenever possible) and other sources of bias (e.g. for-profit funding). For a given domain, RCTs judged as definitely or probably being free of a given risk of bias will be considered low risk of bias, whereas RCTs judged as probably or definitely biased will be

considered high risk of bias to reduce reporting of unclear bias assessments. The review pair will resolve disagreements with the help of a third reviewer when necessary.

Strategy of data synthesis: We will synthesize direct evidence using traditional head-to-head meta-analyses when possible. Given the variety of antibiotic therapies available, we anticipate that not all will have been studied in head-to-head trials. Insufficient or total lack of direct evidence for possible antibiotic comparisons will warrant inclusion of indirect evidence to better approximate the value of an antibiotic regimen. Indirect evidence may also complement direct evidence when available and improve precision of an observed summary effect estimate. Therefore, direct, indirect, and a combination of direct and indirect evidence will inform each summary effect estimate reported whenever possible. Summary effect estimates will include odds ratio (OR) with corresponding 95% credible intervals (CrIs) for dichotomous outcomes and mean differences (MDs) with corresponding SDs for continuous outcomes. We will employ a random effects model for direct comparison meta-analyses and network meta-analyses within the Bayesian framework to account for expected within-study and between-study variability. We will conduct all analyses in R software for statistical computing. We will conduct NMAs provided the following assumptions are met. The transitivity (similarity) assumption gauges the appropriateness of combining evidence from individual trials of different treatments with a common comparator to enable analysis of indirect evidence. We will judge transitivity by comparing important clinical and methodological characteristics. The distribution of potential effect modifiers and the common comparator should be similar between trials; otherwise, in the presence of large dissimilarity, NMA may be invalid. The consistency (coherence) assumption gauges the appropriateness of combining direct and indirect evidence for a given treatment comparison and is the result of intransitivity. We will assess consistency conceptually for treatment comparisons with direct and indirect evidence (a loop within a network) by comparing the size of the summary effect estimates and overlap between corresponding 95% CrIs of the two types of evidence.

Subgroup analysis: We will also conduct some subgroup analyses according to the following criteria: (a) low and high risk of bias; (b) impact factors (≥5, 3-5, and ≤3); (c) usage of endovascular thrombectomy or not.

Sensibility analysis: Not designed.

Language: English.

Country(ies) involved: China.

Keywords: Ischemic stroke, tenecteplase, intravenous thrombolysis, systematic review, network meta-analysis, protocol.

Dissemination plans: We will disseminate the results from the current study through submitting it to conferences or peer-reviewed journal.

Contributions of each author:

Author 1 - Tin Shen - TS conceived and designed the current protocol. TS reviewed scoping searches and contributed to the methodologic development of the protocol. TS drafted the manuscript. TS reviewed and approved the final version for publication.

Author 2 - Jinjian Zhou - JJZ conceived and designed the current protocol. JJZ critically made a revision. JJZ reviewed and approved the final version for publication.

Author 3 - Yan Zhao - YZ conceived and designed the current protocol. YZ reviewed scoping searches and contributed to the methodologic development of the protocol. YZ critically made a revision. YZ reviewed and approved the final version for publication. YZ is the review guarantor.