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China Tongxinluo Study for myocardial protection in patients with Acute Myocardial Infarction (CTS-AMI): Rationale and design of a randomized, double-blind, placebo-controlled, multicenter clinical trial

Yi Xu, BM,[a] Xiangdong Li, MD, PhD,[a] Haitao Zhang, MD, PhD,[a] Yuan Wu, MD, PhD,[a] Jun Zhang, MD, PhD,[a] Jia Li, MD, PhD,[a] Kefei Dou, MD, PhD,[a] Hongbing Yan, MD, PhD,[a] Shijie You, MD, PhD,[a] Yanmin Yang, MD, PhD,[a] Yan Liang, MD, PhD,[a] Lianjun Xu, MD, PhD,[a] Xiaojin Gao, MD, PhD,[a] Chen Liu, MD, PhD,[a] Qiuting Dong, MD, PhD,[a] Wenjia Zhang, MD, PhD,[a] Guangyuan Song, MD, PhD,[a] Tao Zhang, MD, PhD,[a] Lin Jiang, MD, PhD,[a] Guihao Chen, MD,[a] Ruijie Tang, MD,[a] Chen Jin, MD, MSc,[a] Jingang Yang, MD, PhD,[a] Chen Yao, PhD,[b] Ying Xian, MD, PhD,[c] Eric D. Peterson, MD,[c] Runlin Gao, MD,[a] and Yuejin Yang, MD, PhD[a] *Beijing, China and Durham, USA*

Background Acute ST-segment elevation myocardial infarction (STEMI) remains a serious life-threatening event. Despite coronary revascularization, patients might still suffer from poor outcomes caused by myocardial no-reflow and ischemic/reperfusion injury. Tongxinluo (TXL), a traditional Chinese medicine, has been preliminarily demonstrated to reduce myocardial no-reflow and ischemic/reperfusion injury. We further hypothesize that TXL treatment is also effective in reducing clinical end points for the patients with STEMI.

Methods and results The CTS-AMI trial is a prospective, randomized, double-blind, placebo-controlled, multicenter clinical study in China. An estimated 3,796 eligible patients with STEMI from about 120 centers are randomized 1:1 ratio to TXL or placebo groups. All enrolled patients are orally administrated a loading dose of 8 capsules of TXL or placebo together with dual antiplatelet agents on admission followed by 4 capsules 3 times a day until 12 months. The primary end point is 30-day major adverse cardiovascular and cerebrovascular events, a composite of cardiac death, myocardial reinfarction, emergency coronary revascularization, and stroke. Secondary end points include each component of the primary end point, 1-year major adverse cardiovascular and cerebrovascular events, and other efficacy and safety parameters.

Conclusions Results of CTS-AMI trial will determine the clinical efficacy and safety of traditional Chinese medicine TXL capsule in the treatment of STEMI patients in the reperfusion era. (Am Heart J 2020;227:47-55.)

Acute ST-segment elevation myocardial infarction (STEMI) is a major life-threatening disease. Timely revascularization of the infarct-related artery with reperfusion therapy, such as percutaneous coronary intervention (PCI) or thrombolysis, has been demonstrated to improve outcomes for STEMI patients.[1,2] However, restoration of blood flow in the occluded infarct-related artery does not always equal to the recovery of myocardial reperfusion. Paradoxically, it can cause myocardial no-reflow and ischemic/reperfusion (I/R) injury.[3]

Myocardial no-reflow phenomenon is mainly due to the damage of microvascular endothelial cells and the injury of the integrity of microvascular structure, function, and barrier, which will then result in the obstruction of microvasculature and the extravasation of both white and red blood cells into myocardium.[4] Besides, it is also clinically acknowledged to be associated with the embolisms of microthrombi and plaque debris, microthrombogenesis, compression of myocardial edema, and

From the [a]Fuwai Hospital, National Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [b]Peking University Clinical Research Institute, Peking University, Beijing, China, and [c]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov/. Unique Identifier: NCT03792035

Gervasio A. Lamas, MD, served as guest editor for this article.

Submitted March 6, 2020; accepted June 8, 2020.

Reprint requests: Yuejin Yang, MD, PhD, Fuwai Hospital, National Center of Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Rd, Beijing, 100037, China.

E-mail: yangyjfw@126.com

0002-8703

https://doi.org/10.1016/j.ahj.2020.06.011

Table I. List of inclusion and exclusion criteria

Inclusion criteria
1. Age>18 year
2. Within 24 h of infarctional chest pain onset
3. ECG shows ST-segment elevation ≥0.2 mV in more than 2 adjacent leads or new left bundle-branch block
4. Voluntary participation in the study with consent forms signed

Exclusion criteria
1. Critically ill and dying
2. CPR >20 min
3. Suspected aortic dissection or acute pulmonary embolism
4. Explicit mechanical complications, including interventricular septum perforation, rupture of papillary muscles and chordae tendineae, or ongoing or ruptured left ventricular free walls
5. Serious cardiogenic shock and not responding to hypertensive agents
6. Uncontrolled acute left heart failure or pulmonary edema
7. Malignant arrhythmias uncontrolled by antiarrhythmia agents
8. Bleeding history of cerebral vessels, gastrointestinal tract, respiratory tract, urinary tract, or other organs within 1 m
9. Presence of active hemorrhage at any part of the body (including menstruation)
10. Known hemorrhagic constitution or serious hemostasis and blood coagulation disorders
11. Current use of anticoagulants
12. Allergy to the ingredients of this investigational drug
13. Women who are in pregnancy or nursery
14. Participation in clinical trial of other traditional Chinese medicine
15. Serious hepatic dysfunction (ALT ≥5 ULN)
16. Serious renal dysfunction (Cr >134 μmol/L [2 mg/dL] or eGFR <45 mL/min/1.73 m^2)
17. Serious COPD or respiratory failure
18. Severe infection
19. Very weak or frail
20. Neuropsychiatric system diseases
21. Malignancies
22. Other pathophysiological conditions with expected survival time <1
23. Unsuitability to participate in this study due to other diseases

CPR, cardiopulmonary resuscitation; *ALT*, alanine aminotransferase; *ULN*, upper limit of normal; *eGFR*, estimated glomerular filtration rate; *COPD*, chronic obstructive pulmonary disease.

spasm of microvessels.[5-8] Although several medications and devices have been studied in preventing myocardial no-reflow,[9-17] their effects are still controversial.

Myocardial I/R injury is traditionally considered to be associated with myocardial inflammation, oxidative stress, calcium overload, and mitochondrial dysfunction.[18-22] Decades of studies have pinpointed several pathways[23] that can be targeted to blunt myocardial I/R injury by inhibiting the opening of mitochondrial permeability transition pore, namely, the common reperfusion injury salvage kinase pathway of phosphatidylinositol 3-kinase-Akt, mitogen-activated protein kinase 1/2 –extracellular signal-regulated kinase 1/2,[24] the Survivor Activator Factor Enhancement[25] pathway, and the endothelial nitric oxide (eNOS)/protein kinase G pathway.[26] The translation of these findings to clinical setting is mostly unsuccessful.[23] For example, the CIRCUS trial, which evaluated the mitochondrial permeability transition pore antagonist cyclosporine-A in the clinical prevention and treatment of myocardial I/R, had negative results.[27] So was the study of remote ischemic conditioning.[28] No medicine has yet been recommended for the prevention and treatment of myocardial no-reflow and reperfusion injury by international guidelines so far.[1,29]

Tongxinluo (TXL) is a traditional Chinese medicine (TCM) compound composed of medicinal materials including *Radix ginseng, Buthus martensi, Hirudo, Eupolyphaga seusteleophaga, Scolopendra subspinipes, Periostracum cicadae, Radix paeoniae rubra, Semen ziziphi spinosae, Ligum dalbergiae odoriferae, Ligum Santali albi,* and *Borneolum syntheticum*. Its basic pharmacological effect is to protect endothelial cells, which has promise for the alleviation of myocardial no-reflow and I/R injury. In a porcine model, we have demonstrated that pretreatment with middle- (equal to the conventional dose for human) and high-dose TXL 3 days, 3 hours, and 1 hour prior to ligation of coronary artery was able to protect the structure, function, and barrier of the endothelium; maintain the integrity of myocardial microvessels[30,31]; and minimize the myocardial no-reflow and infarction area by 60%-80% and 19%-32%, respectively,[32-36] with the beneficial effects of anti-inflammatory, antioxidative stress, antiapoptotic, anti–myocardial hemorrhage, and anti–myocardial cellular edema in myocardium through the PKA-eNOS pathway[35,37] and mitogen-activated protein kinase/extracellular signal-regulated kinase pathway.[38] TXL could also protect human cardiomyocytes from I/R injury by enhancing the phosphorylation of p70s6k1, an upstream protein of eNOS.[39] Furthermore, the ENLEAT study, a randomized, double-blind placebo-controlled multicenter clinical trial in STEMI patients undergoing primary PCI, has also found that TXL could

facilitate myocardial reperfusion, with the incidence of myocardial no-reflow significantly reduced by 36.6% (34.3% vs 54.1%) and the infarct size minimized.[40,41] We further hypothesize that TXL treatment is also effective in reducing the clinical end points for patients with STEMI.

Therefore, we designed this randomized multicenter clinical trial to evaluate the clinical efficacy and safety of TXL in STEMI patients in China.

Methods

The CTS-AMI trial is a prospective, randomized, double-blind, placebo-controlled, multicenter clinical study. Its objective is to evaluate the efficacy and safety of TXL capsules in Chinese patients with STEMI.

A total of 120 centers (including the principal site) are expected to participate in the present study. The inclusion and exclusion criteria are listed in Table I. Patients with STEMI are enrolled after preliminary screening to meet all the inclusion criteria and none of the exclusion criteria.

A computer-based central randomization system (Bioknow Randomization and Trial Supply Management System) is used and maintained in the present study by a third-party unit of the Institute of Clinical Research, Peking University. After signing the informed consent forms, the eligible patients' information is entered into the central randomization system to double-blindingly generate a randomizing number with the grouping of TXL or placebo at a 1:1 ratio for each enrolled patient. Each patient's randomizing number is automatically linked with the package number of research drugs (TXL or placebo) by the system. For drug distribution, investigators should apply for the package number via the system according to the enrolled patient's randomizing number.

The research drugs of TXL and placebo are almost identical in look, taste, and odor. After randomization and grouping, all patients are orally administrated a loading dose of 2.08 g (8 capsules, double the usual dose) of the research drug (TXL or placebo) together with loading doses of dual antiplatelet therapy (DAPT) agents (aspirin, clopidogrel or ticagrelor) followed by 1.04 g (4 capsules, the usual dose) 3 times a day with conventional doses of DAPT agents until 12 months (Figure 1).

A package of 3-month amount of TXL or placebo is distributed to each enrolled patient. At every scheduled 3-month follow-up, the residual drugs will be brought back by the patient, and another package of 3-month of the research drugs will then be given by investigators. All residual drugs will be retrieved and destroyed at the end of the study by the sponsor. Distribution and retrieval of research drugs will be recorded accurately and in a timely manner in the case report form (CRF).

All patients are receiving standard treatment for STEMI based on guideline recommendations, including coronary reperfusion (primary PCI or thrombolysis except for the contraindications and other exceptions from patients and physicians) and medical therapies.[1,29] Use of thrombus aspiration catheter, distal protective devices, platelet GPIIb/IIIa receptor antagonist, and stent implantation during primary PCI is at the interventionalist's discretion. Administration of other TCM or Chinese patent medicine similar in function and indications with the research drug is prohibited during the entire study period.

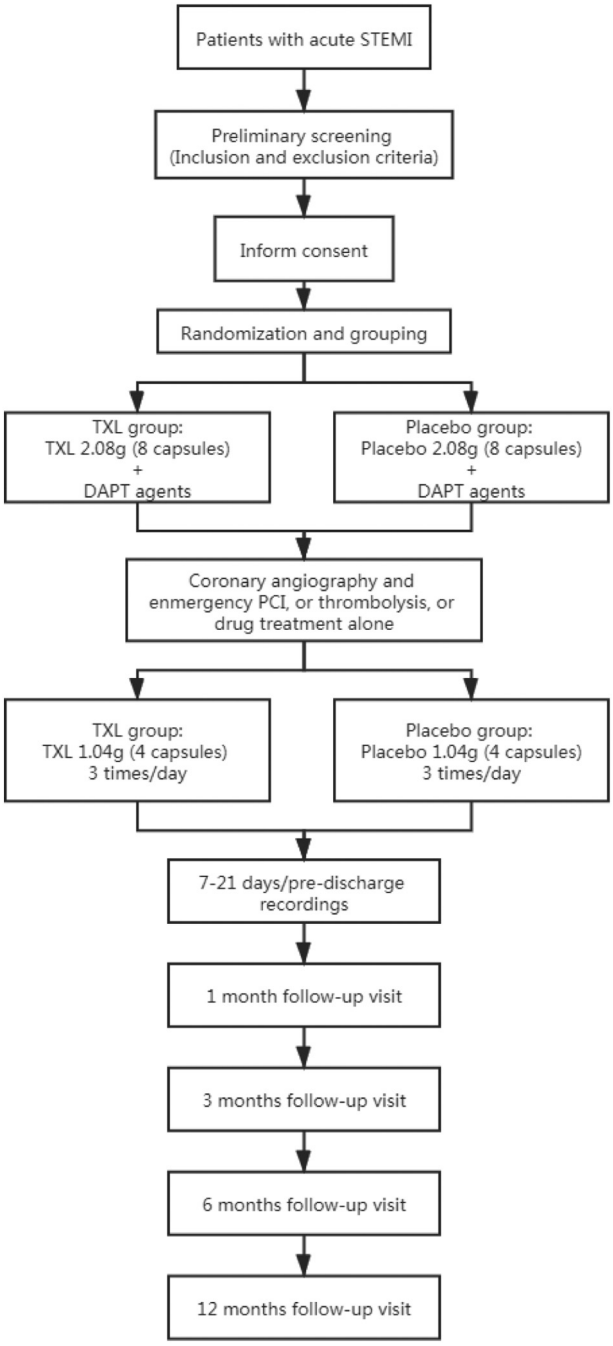
Each patient's medical history and baseline results of physical examination, electrocardiogram (ECG), and laboratory tests are collected on admission according to Table II. ECG will also be taken 2, 12, 24, and 72 hours after admission. Laboratory tests, echocardiogram, and 24-hour dynamic ECG (Holter monitor) are scheduled to be performed on the seventh day of hospitalization or before discharge (Table II). All surviving patients are followed up until 1 year regardless of reaching end point or not. Outpatient follow-up visits are scheduled at 1 month (30 ± 3 days), 3 months (± 7 days), 6 months (± 7 days), and 12 months (1 year ±7 days) after randomization (Figure 1). ECG and laboratory tests will be performed at 1, 6, and 12 months. Echocardiogram and Holter will be conducted at the last follow-up visit (Table II).

The primary end point of the present study is 30-day major adverse cardiovascular and cerebrovascular events (MACCE), a composite of cardiac death, myocardial reinfarction, emergency coronary revascularization, and stroke. Secondary end points include the following: each component of the primary end point, 30-day severe STEMI complications (including cardiogenic shock, heart failure, mechanical complications, and malignant arrhythmias), major bleeding (Bleeding Academic Research Consortium [BARC] type III and V[42]), 1-year MACCE, rehospitalization due to heart failure, all-cause death, and in-stent thrombosis. Besides, myocardial reperfusion and no-reflow rate (ST-segment resolution and occurrence of no-reflow) in ECG will be evaluated at 2 hours, 24 hours, and 7 days after revascularization therapy (Table III).

Adverse events (AEs) refer to any adverse medical event that occurs during the study period, regardless of its relation with the research drug. AE that meets any of the following criteria is defined as a severe adverse event (SAE): (1) death, (2) life-threatening situation, (3) temporary or permanent disabilities, or (4) rehospitalization or prolonged hospital stay. All AEs will be assessed about their relation with the research drug, recorded in CRF, and be followed up until recovery or stabilized. Any SAEs that occur during the study period will be reported to the sponsor, principal study site, clinical research organization, ethics committee, China Food and Drug Administration, and health administrative departments within 24 hours.

Sample size of the present study was calculated using PASS13 software (NCSS, Kaysville, UT) based on previous reports.[43,44] The assumptions included a 30-day MACCE rate of 9% in placebo group and 6.3% in TXL group. Based

Figure 1



Study flowchart.

on these, an estimated sample size of 1,518 patients in each group would give 80% (2-sided α = .05 and β = .20) statistical power to detect a significant difference. Accounting for a 20% dropout rate increased the sample size to 1,898 for each arm, leading to a total target enrollment of 3,796.

Continuous variables are described as mean and SD and compared using paired *t* test or Wilcoxon rank test, as appropriate. Categorical variables are described using frequencies and percentages and compared using χ^2 test or Fisher exact test, as appropriate. Statistical analyses will be carried out using SAS 9.4 (or higher version; SAS

Table II. Diagram of data acquisition

Item	Baseline	Hospitalized treatment period					Follow-up time point				
		2 h	12 h	24 h	72 h	7 d/discharge	1 m	3 m	6 m	9 m	12 m
History	○						○	○	○		○
Inclusion/exclusion criteria	○										
Informed consent	○										
Drug distribution	○							○	○	○	
ECG	○	○	○	○	○		○		○		○
cTNI and CKMB	○			○							
NT-ProBNP	○					○	○		○		○
Hematology	○					○	○		○		○
Urinalysis	○					○	○		○		○
Stool occult blood test	○					○	○		○		○
Echocardiogram						○	○				○
Holter						○	○				○
Evaluate clinical end point events						○	○				○
Outpatient follow-up							○	○	○		○

cTNI, cardiac troponin I; *CKMB*, creatine kinase–muscle/brain; *NT-ProBNP*, N-terminal pro–B-type natriuretic peptide.

Institute, Cary, NC), and a 2-tailed $P < .05$ is considered statistically significant. Efficacy analysis in 2 groups will be statistically described respectively, and the intergroup comparison will be performed with the statistical method mentioned above.

In accordance with the requirements of adverse drug reaction relation, the AEs and adverse drug reactions (including the number of cases with various AEs, the number of cases with "normal results to abnormal results" or "aggravation of abnormal results" of laboratory test indicators before and after testing, and the abnormal conversion rate) in 2 groups will be tabulated, and the relevant causes and explanations will be listed. The incidence of AEs will be comparatively analyzed between 2 groups.

The Steering Committee is chaired by Yuejin Yang, MD, FACC, FESC, professor of cardiology, Fuwai Hospital, Beijing, China. The Steering Committee is responsible for the scientific content of the protocol, oversees the trial operations, and will prepare the primary manuscript and other publications arising from the CTS-AMI trial.

Each participating center has a senior investigator with clinical trial experience, as well as their own study group. The core laboratories at Fuwai Hospital, Beijing, China, are responsible for the establishing of standard operating procedures for the measurements and analyses of key examinations including ECG, Holter, echocardiogram, and coronary angiography and intervention. Each participating center strictly follows the standard operating procedures to measure and analyze the results of trial-related examinations. Furthermore, the core laboratories are also responsible for 33% random sampling review of all enrolled cases in each participating site.

The Clinical Investigation Center is located at the National Center for Cardiovascular Disease, Fuwai Hospital, Beijing, China. Monitoring of all center sites is performed by an independent clinical research organization, the Beijing Longleding Medical Technology Co, Ltd. The Data Monitoring Board is responsible for data quality supervision. A third-party statistical unit (the Institute of Clinical Research, Peking University) is in charge of data analysis.

The authors are solely responsible for the design and conduct of the study, all study analyses, the drafting and editing of the manuscript, and its final contents.

The present study gained approval of institutional board review by the ethics committee of the principal site on August 8, 2018 (Approval No. 2018-1085). The approved study protocol, informed consent forms, CRF, and other relevant materials are sent to other participating sites. All sites should gain approval from their own ethics committee before starting patient enrollment and randomization. The study protocol was registered on ClinicalTrials.gov (no. NCT03792035) on January 3, 2019.

The first patient of CTS-AMI trial was randomized on May 23, 2019. A total of 1,266 patients have been enrolled up to the time of this submission. The entire enrollment is scheduled to be completed by September 2021 because of the epidemic of COVID-19 in China. Follow-up visits are planned to be completed by September 2022. The main results will be reported by December 2022.

Discussion

Despite the rapid progresses in cardiology and pharmacology, acute STEMI remains a dangerous life-threatening disease. Reperfusion therapy including primary PCI or thrombolysis has been considered the international standard treatment for STEMI patients,[2] although myocardial no-reflow and reperfusion injury may occur following

Table III. Detailed end point definition

Primary end points
30-d MACCE:
Cardiac death
Myocardial re-infarction
Emergency coronary revascularization, including PCI, thrombolysis, and CABG
Stroke
Secondary end points
1. Each component of the primary end point
2. 30-d severe STEMI complications:
Cardiogenic shock (Killip IV)
Acute left heart failure (Killip II, III)
Mechanical complications: including interventricular septum perforation, papillary muscle dysfunction, ruptured left ventricular free walls
Malignant arrhythmia: including ventricular fibrillation, ventricular flutter, ventricular tachycardia, ventricular premature contraction (frequent, polymorphic, multifocal, or R on T)
3. BARC type III and V major bleeding:
BARC IIIa: overt bleeding with hemoglobin drop of 3 to <5 g/dL or any transfusion with overt bleeding
BARC IIIb: overt bleeding with hemoglobin drop >5 g/dL, cardiac tamponade, bleeding that requires surgical intervention to control (excluding dental, nasal, skin, or hemorrhoid), or bleeding that requires intravenous vasoactive agents
BARC IIIc: intracranial hemorrhage (including intraspinal bleeding, excluding microbleeds or hemorrhagic transformation), subcategories confirmed by autopsy/imaging/lumbar puncture, or intraocular bleeding comprising vision
BARC V: fatal bleeding
4. 1-y MACCE
Cardiac death
Myocardial reinfarction
Emergency coronary revascularization, including PCI, thrombolysis, and CABG
Stroke
5. 1-y rehospitalization due to heart failure
6. 1-y all-cause death
7. In-stent thrombosis:
Acute: <24 h
Subacute: 1-30 d
Late: 1-12 m
8. ECG evaluation of myocardial reperfusion and no-reflow: ST-segment resolution and occurrence of no-reflow in ECG at 2 h, 24 h, and 7 d after revascularization therapy

CABG, coronary artery bypass grafting.

reperfusion therapy. Although rapid progress in experimental studies for myocardial protection has been made lately,[19,20] there is still no breakthrough in clinical use in this field so far.[45] Moreover, a large number of "reperfusion therapy missing" patients exist in China, particularly at primary hospitals in rural areas.

As a TCM compound, TXL was developed according to its theory of "main and collateral channels" and approved for clinical use in China in 1996. It has been proposed to treat coronary artery diseases across China for more than 20 years.[46-48] In accordance with the TCM theory, myocardial no-reflow phenomenon and I/R injury after reperfusion therapy of STEMI patients are considered a kind of "main and collateral channels" disease which is equivalent to microvascular dysfunction and obstruction occurring in the infarcted region. Then, we hypothesized that TXL was able to protect and even "dredge these channels," promote myocardial reperfusion, and to be expected for the prevention and treatment of myocardial no-reflow and I/R injury in STEMI patients.

Our series of animal studies[30-39] have demonstrated that TXL can reduce myocardial no-reflow and reperfusion injury by protecting the structural, functional, and barrier integrity of myocardial microvasculature with the effects of anti-inflammation, antioxidative stress, antiapoptosis, and antihemorrhage of the myocardium.[30-37] Furthermore, TXL was verified to directly protect cardiovascular endothelial cells against apoptosis by facilitating autophagy in our latest in vitro experiments.[38] Moreover, a recent study demonstrated that TXL could also have potent angiogenesis effect in addition to the abovementioned effects even in rat hearts after permanent ligation of coronary artery for 4 weeks.[49]

The clinical efficacy of TXL in the treatment of myocardial infarction has been studied by several clinical studies in China,[40,50-58] and a few of them have also demonstrated its beneficial effects in STEMI patients.[40,50,59] However, most of them had unclear randomization or blinding methods, which make these results less solid in methodology.[60] The previous ENLEAT clinical study found that TXL can promote myocardial reperfusion, reduce the incidence of no-reflow and infarct size, and improve cardiac function,[40] although it is a relatively small clinical trial with the primary end point of only surrogates instead of hard clinical cardiovascular events.

The CTS-AMI clinical trial is a prospective, randomized, double-blind, placebo-controlled, multicenter clinical study with a sample size of 3,796 patients in about 120

participating sites across China. It is the first time in cardiovascular medicine to examine the efficacy and safety of a compound of TCM in the treatment of STEMI patients in the reperfusion era. Of particular importance, the primary end point is clinical hard point of 30-day MACCE, which will provide solid data, rigorous evidence, and even novel treatment option for myocardial no-reflow phenomenon and I/R injury after reperfusion therapy in patients with STEMI probably including those who have missed the opportunity of reperfusion therapy in China.

The main expected obstacle during the 12-month study period is the drug compliance of patients, which might lead to inaccurate and misguiding results. To avoid this, patient compliance will be assessed during the whole study period. The residual amount of research drugs from each patient will be retrieved and accounted for before drug distribution at each follow-up visit. Drug compliance will then be quantitatively assessed and recorded in the CRF (compliance = actual/estimated amount of research drug taken during the follow-up period × 100%). A compliance >80% is considered consistent with study requirements. Moreover, investigators should thoroughly inform participating patients about the study and drug dosage to ensure satisfying compliance.

In conclusion, the CTS-AMI trial is a prospective, randomized, double-blind, placebo controlled, multicenter clinical study to evaluate the clinical efficacy of oral TXL capsule and its safety with clinical hard end point in the treatment of STEMI patients with reperfusion therapy or for the reperfusion-missing patients. The results will be expected to verify and provide novel evidence-based treatment options for myocardial no-reflow and reperfusion injury and probably further improve the outcomes of STEMI patients in the reperfusion era.

Funding

The present study is financially supported by the National Key Research and Development Program of China (2017YFC1700503).

Disclosure

The authors have declared no conflicts of interest.

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