Thymosin alpha 1 in the prevention of infected pancreatic necrosis following acute necrotizing pancreatitis (TRACE trial): protocol of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial

Jing Zhou[1, a], Wenjian Mao[2, a], Lu Ke[1*], Tao Chen[3], Wenhua He[4], Xinting Pan[5], Miao Chen[6], Chengjian He[7], Weili Gu[8], Jingyi Wu[9], Jingchun Song[10], Haibin Ni[11], Jianfeng Tu[12], Junli Sun[13], Guoxiu Zhang[14], Weiwei Chen[15], Bing Xue[16], Xiangyang Zhao[17], Ming Shao[18], Yuxiu Liu[19], Zhihui Tong[1*], Weiqin Li[1], for the Chinese Acute Pancreatitis Clinical Trials Group(CAPCTG)

1 Department of General Surgery, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, Jiangsu Province, China

2 Department of General Surgery, Jinling Hospital, Nanjing Medical University School of Medicine, Nanjing 210002, Jiangsu Province, China

3 Tropical Clinical Trials Unit, Department of Clinical Sciences, Liverpool School of Tropical Medicine. Liverpool, L3 5QA, UK

4 Department of Gastroenterology, Medical College of Nanchang University, Nanchang 330006, Jiangxi Province, China.

5 Department of Emergency Intensive Care Unit, The Affiliated Hospital of Qingdao University, Qingdao, 266000, Shandong Province, China

6 Department of Intensive Care Unit, Affiliated Hospital of Zunyi Medical College, Zunyi 63000, Guizhou Province, China.

7 Department of Intensive Care Unit of the Affiliated Nanhua Hospital, University of South China, Hengyang 421001, Hunan Province, China.

8 Department of Intensive care Unit of the Second Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Province, China

9 Department of Intensive Care Unit of the Yijishan Hospital of Wannan Medical College, Wuhu 241000, Anhui Province, China.

10 Department of Intensive Care Unit, the 908th Hospital of Chinese People's Liberation Army Joint Logistic Support Force, Nanchang 330006, Jiangxi Province, China

11 Department of Emergency, Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing 210010, Jiangsu Province, China

12Department of Emergency Medicine, Zhejiang Provincial People's Hospital, Hangzhou Medical College, Hangzhou 310014, Zhejiang Province, China

13 Department of Intensive Care Unit, Luoyang Central Hospital, Luoyan 471100, Henan Province, China

14 Department of Intensive Care Unit, The Affiliated Hospital of Henan University of Science and Technology, Luoyan 471100, Henan Province, China

15 Department of Gastroenterology, Clinical Medical College of Yangzhou University, Yangzhou225009, Jiangsu Province, China

16 Department of Emergency Intensive Care Unit, The First People's Hospital of Shangqiu, Shangqiu 476100, Henan Province, China

17 Department of Intensive Care Unit, Qilu Hospital of Shandong University, Qingdao 266000, Shandong Province, China

18 Department of Intensive Care Unit, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui Province, China

19 Department of Medical Statistics, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, Jiangsu Province，China

*Correspondence to: Lu Ke & Zhihui Tong, Department of General Surgery, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, Jiangsu Province，China

Telephone: +8613182810702 Fax: +86-25-84803956

E-mail: kkb9832@gmail.com

a These authors contributed equally to this work

Abstract

Introduction: Infected pancreatic necrosis (IPN) and its related septic complications are the major causes of death in patients with acute necrotizing pancreatitis (ANP). Therefore, the prevention of IPN is of great clinical value, and immunomodulatory therapy with Thymosin Alpha 1 may be beneficial. This study was designed to test the hypothesis that the administration of Thymosin Alpha 1 during the acute phase of ANP will result in a reduced incidence of IPN.

Methods and analysis: This is a randomized, multicenter, double-blind, placebo-controlled study. 520 eligible ANP patients will be randomized in a 1:1 ratio to receive either the Thymosin alpha 1 or the placebo using the same mode of administration. The primary endpoint is the incidence of IPN during the index admission. Most of the secondary endpoints will be registered within the index admission including in-hospital mortality, the incidence of new-onset organ failure and new-onset persistent organ failure (respiration, cardiovascular and renal), receipt of new organ support therapy, requirement for drainage or necrosectomy, bleeding requiring intervention, HLA-DR on day0, day7, and day14, etc., and adverse events. Considering the possibility of readmission, an additional follow-up will be arranged 90 days after enrollment, and IPN and death at Day90 will also be served as secondary outcomes.

Ethics and dissemination: This study was approved by the ethics committee of Jinling Hospital, Nanjing University (No. 2015NZKY-004-02). The TRACE trial was designed to test the effect of a new therapy focusing on the immune system in preventing secondary infection following ANP. The results of this trial will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration： The trial has been registered at the ClinicalTrials.gov registry (NCT02473406)

Strengths and limitations of this study

Strength 1：This is a randomized, multicenter, double-blind, placebo-controlled trial providing top-class evidence concerning the efficacy and safety of thymosin alpha 1 for patients with acute necrotizing pancreatitis.

Strength 2: The data will be handled by an independent data safety monitoring board

(DSMB) to ensure the safety of the participants.

Strength 3: Thymosin alpha 1 is a well-studied drug with a favorable safety profile in previous trials.

Limitation 1: A sample size of 520 is required to detect the efficacy of Thymosin Alpha 1 in preventing infected pancreatic necrosis, which will take years before the conclusion could be drawn.

Limitation 2: Continuous immune function assessment is not applied in this study.

Background

Infected pancreatic necrosis (IPN) and its related septic complications contribute substantially to deaths in patients with acute necrotizing pancreatitis(ANP)[1]. Compared with patients with sterile necrosis, those with IPN suffered a significant increase in mortality ranging from 14% to 69%, despite advances in critical care, surgical and endoscopic interventions, and antibiotics[2]. Therefore, the prevention of IPN is of great clinical value in the treatment of ANP. Over the past years, numerous attempts had been made to prevent or delay the development of IPN, including antibiotic prophylaxis, early enteral nutritional, selective gut decontamination, and probiotics. Still, none of them had been proved to improve patient-centered outcomes with high-quality evidence [3-6]. More promising treatment aiming at reducing infectious complications of ANP is in need.

Immunosuppression and disorders characterized by decreased HLA-DR expression and unbalanced CD3/CD4+/CD8+ T cells of peripheral blood mononuclear cell are reported to be associated with IPN[7, 8], especially in those with a more severe type of disease, whose suppressed immune function occurs early and strongly[8, 9]. Our previous observational study found that early enteral nutrition could moderate the excessive immune response during the acute phase of severe acute pancreatitis without leading to subsequent immunosuppression, and ultimately reduce the incidence of infection and ICU stay [10]. Thus, immunomodulatory treatment could potentially intervene in the development of IPN, resulting in better outcomes. Efforts had been made in this field using drugs like lexipafant and octreotide. Still, the hitherto existing evidence failed to show robust clinical benefits of immunomodulation with regard to key clinical outcomes [11].

Thymosin alpha 1 had been shown to have immunomodulatory properties and was reported to be clinically beneficial in patients with sepsis[12, 13], majorly through the involvement of distinct Toll-like receptors acting on different dendritic cells subsets and involving the MyD88-dependent signaling pathway. However, for acute pancreatitis (AP), the only randomized controlled study was the pilot one conducted by our group years ago, suggesting that the use of Thymosin alpha 1 was associated with improved

cellular immunity and reduced infection rate in a group of 24 patients[14]. Due to the single-center set and small sample size, the clinical implication and generalizability of this study are thought to be limited. Therefore, we designed this multicenter trial, the Thymosin Alpha 1 in the Prevention of Infected Pancreatic Necrosis Following Acute Necrotizing Pancreatitis (TRACE), with sufficient power to test the hypothesis that the administration of Thymosin Alpha 1 during the acute phase of ANP will result in a reduced incidence of IPN.

Study objectives

The primary objective of the TRACE trial is to determine whether Thymosin Alpha 1 is superior to placebo in reducing the incidence of IPN in patients with ANP. Secondary objectives are to determine the safety and the impact on the immune function of Thymosin Alpha 1 among patients with ANP.

Study Design

The present study is an investigator-initiated, multicenter, individually-randomized, double-blind, placebo-controlled, parallel-group study. This trial was registered on June 16th, 2015, in the CT.gov registry (NCT02473406, https://www.clinicaltrials.gov/) and was approved by the ethics committee of Jinling Hospital, Nanjing University (No. 2015NZKY-004-02). Local ethics approval was also obtained before enrollment in each participating center. The TRACE trial was designed and coordinated by the Center of Severe Acute Pancreatitis at Nanjing University and the coordinating and data management center of the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG). The trial steering committee (TSC) was formed to oversee the implementation of the study, and a data safety monitoring board (DSMB) will regularly (every six months) review the safety report prepared by the trial statistician from the accumulating data of this trial.

Study population

This trial is performed in 16 hospitals from China. All adult patients with AP admitted to the participating centers will be assessed for eligibility after admission. The inclusion

and exclusion criteria are as follows:

Inclusion criteria

1. Symptoms and signs of AP based on abdominal pain suggestive of AP, serum amylase at least three times the upper limit of normal, and/or characteristic findings of AP on computed tomography or less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography according to the Revised Atlanta Criteria[15];
2. Less than one week from the onset of abdominal pain;
3. Age between 18 to 70 years old;
4. Acute Physiology and Chronic Health Evaluation(APACHE II) score ≥eight during the last 24 hours before enrollment
5. Balthazar CT score ≥5 (presence of pancreatic necrosis)[16].
6. Written informed consent obtained

Exclusion criteria

1. Pregnant pancreatitis;
2. History of chronic pancreatitis；
3. Malignancy related acute pancreatitis
4. Receiving early intervention or surgery due to abdominal compartment syndrome or other reasons before admission；
5. Patients with a known history of severe cardiovascular, respiratory, renal or hepatic diseases defined as (1) greater than New York Heart Association Class II heart failure(Class II not included), (2) active myocardial ischemia or (3) cardiovascular intervention within previous 60 days, (4) history of cirrhosis or (5) chronic kidney disease with creatinine clearance< 40 mL/min, or (6) chronic obstructive pulmonary disease with the requirement for home oxygen;
6. Patients with preexisting immune disorders such as AIDS.

A patient will be considered eligible if he/she meets the inclusion criteria and does not meet any of the exclusion criteria. Allocation will be performed after signed consent is obtained. The study protocol flow of participants is outlined in Figure 1.

Randomization and blinding methods

After the completion of screening measurements and the acquisition of written informed consent, eligible participants will be randomized in a 1:1 ratio to either the treatment group or the placebo group. The randomization code was computer-generated with a block size of 4, and the randomization was stratified by sites.

Participants, clinical investigators, and investigators assessing outcome data will be blinded to the treatment allocation to minimize potential sources of bias. The trial statistician will also be blinded regarding the treatment code when developing the statistical programs, which will be validated and completed using dummy randomization codes. The actual allocation will only be provided to the study team after locking of the database and approval of the statistical analysis plan.

Trial drugs

After randomization, the participant will receive:

1. Thymosin Alpha 1 1.6mg I.H q12h for the first seven days and 1.6mg I.H, qd for the following seven days. The administration will be terminated any day during the treatment when the patient is deemed as qualified for hospital discharge, or dead.
2. Matching placebo(normal saline) using the same mode of administration as the above mentioned.

As shown in Figure 1, the recruited patients will start to receive randomized drugs subcutaneously from the day after the allocation day. Thymosin Alpha will be provided by SciClone Pharmaceuticals and the matching placebo by Chengdu Tongde Pharmaceuticals. All study drugs will be stored in a secure area with access limited to the investigators and authorized study site personnel, and under appropriate storage conditions.

General treatment regimen

All patients will receive standard treatment including fluid therapy, early enteral nutrition, routine medical treatment like proton pump inhibitor as indicated, mechanical

ventilation if needed, and continuous renal replacement therapy (CRRT) if needed in the light of recently published guidelines[17]. All participating centers are able to offer appropriate intensive care in case the patients require organ support or continuous monitoring. The necrotic collection will be intervened when infection is suspected or confirmed, preferably after four weeks from the onset of the disease when the patient could tolerate the symptoms as suggested by the guidelines[17].

When pancreatic infection occurs, either a surgical or endoscopic step-up approach considering the location of the necrotic collection and the technical availability in each participating center will be applied. Principally, either percutaneous catheter drainage or endoscopic transluminal placement of double pig-tail stents，rather than debridement, are the primary choices of treatment.

Endpoints

Primary outcome measure

The incidence of IPN during the index admission will be served as the primary outcome measure of the TRACE trial. The diagnosis of IPN will be based on the international guidelines when one or more of the following were present: gas bubbles within (peri) pancreatic necrosis on computed tomography; a positive culture of (peri) pancreatic necrosis obtained by image-guided fine-needle aspiration; a positive culture of (peri) pancreatic necrosis obtained during the first drainage and/or necrosectomy[15].

Secondary outcome measures

Part I：Secondary outcomes during the index admission

1. The occurrence of new-onset organ failure and new-onset persistent organ failure (SOFA score for respiration, cardiovascular, or renal system ≥2). New-onset is defined as events that occur after randomization and not present 24 hours before randomization;
2. In-hospital mortality;
3. Bleeding requiring intervention；
4. Gastrointestinal perforation or fistula requiring intervention;
5. Incidence of pancreatic fistula

6. New receipt of mechanical ventilation (not applied 24 hours before randomization);
7. New receipt of renal replacement therapy (not applied 24 hours before randomization);
8. New receipt of vasoactive agents (not applied 24 hours before randomization);
9. The requirement for catheter drainage (either percutaneous or endoscopic)
10. Number of drainage procedures required;
11. The requirement for minimally-invasive debridement;
12. Number of minimally invasive necrosectomy required;
13. The requirement for open surgery;
14. Number of open operations required;
15. Length of intensive care unit(ICU) stay;
16. Length of hospital stay;
17. SOFA score on day0, day7, and day14；
18. CRP level on day0, day7, and day14;
19. HLA-DR level on day0, day7, and day14;
20. Lymphocyte count on day0, day7 and day 14;
21. In-hospital cost.

Part II：Secondary outcomes within 90 days after enrollment

1. Incidence of infection within 90 days after enrollment；
2. Mortality within 90 days after enrollment.

Sample size estimation

The incidence of IPN during the index admission was reported to be around 25% in ANP episodes combined with an APACHE II score≥8 in our previous studies[18, 19]. To reduce the incidence of IPN from 25% to 15% on the basis of our pilot study [14], we projected a sample size of 500 participants with 80% power at a two-sided alpha level of 0.05 using the PASS software (PASS 11, NCSS software, Kaysville, USA). In our study, we planned to randomize 520 patients after considering 4% of lost follow up.

Statistical analysis

Primary analyses will be based on the intention-to-treat (ITT) population, and secondary supportive analyses will be done on the PP population. The safety analysis will be performed on the safety population. Missing data will be handled by multiple imputations to evaluate the robustness of the primary endpoint analyses[20]. The populations are defined as follows:

1. ITT population: This population consists of all randomized subjects, regardless of whether they are ineligible, prematurely discontinue treatment, or are otherwise protocol violators/deviators.
2. Per-protocol (PP) population: This population is a subset of the ITT population. Subjects with major protocol deviations will be excluded from the PP population. Major protocol deviations will be defined in the statistical analysis plan.
3. Safety population: This population will be the same as the ITT population, which consists of all randomized subjects, who receive at least one dose of study drug.

The normality of continuous variables was examined using skewness and kurtosis. Categorical data were expressed as number and percentage. A generalized linear model (GLM) will be employed to compare group differences in the primary outcome. No interim analysis was planned in our study. The detailed analysis strategies for secondary outcomes and subgroup analyses by the severity of AP(severe and non-severe), age(dichotomized at 60 years old), etiologies of AP (biliary and non-biliary) and extent of pancreatic necrosis(>50% and ≤50%), will be included in the statistical analysis plan. Statistical tests will be two-sided, and p values < 0.05 will be deemed as significant.

Adverse events

Adverse events (AEs) are defined in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events as any untoward medical occurrence in a patient, or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment.

It is recognized that the study patient population (ANP with relatively high APACHE II score) will experience a number of common aberrations in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgment. Thymosin alpha 1 is a well-studied drug with a favorable safety profile in previous trials [21]. The DSMB will review the safety report every six months.

Recruiting process

The trial was registered on June 16th, 2015, in the CT.gov registry(NCT02473406 https://www.clinicaltrials.gov). The first patient was randomized on March 22nd, 2017. So far, 426 patients had been randomized, and the enrollment keeps to the schedule.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data collection and management

A web-based electrical database (access through the website of the CAPCTG, https://capctg.medbit.cn/) will be used for data collection and storage. All data will be input by the primary investigator or nominated investigators (less than two for each participating center) approved by the primary investigator, and a double check will be done by the research coordinator. Training for data entry will be performed by the provider of the electrical database (Unimed Scientific Inc., Wuxi, China) and the coordinating and data management center of the CAPCTG. According to the schedule shown in Figure 2, the investigator will collect data during the index admission and on day 90 after enrollment. If a study subject wishes to discontinue the study drug or the treating physician believes a study subject should discontinue the study drug due to medical considerations, the investigator will communicate with the study subject and the treating physician to obtain the reasons. Further evaluation and follow-up will still

be performed unless the study subject withdraws consent for disclosure of information. The study blinding will only be broken in a medical emergency when the treating physician believes that the administration of the study drug is associated with the emergency.

Ethics approval and dissemination

This study was approved by the ethics committee of Jinling Hospital. The ethical approval document ID is 2015NZKY-004-02. Even when central ethical approval has been confirmed, we will not begin recruiting at other participating centers in the trial until the local ethics committee approved the study. Site ethical approvals were obtained from ethics committees of First Affiliated Hospital of Nanchang University, The Affiliated Hospital of Qingdao University, Affiliated Hospital of Zunyi Medical College, Nanhua Hospital, Second Affiliated Hospital of Nantong University, Yijishan Hospital of Wannan Medical College, 908th Hospital of Chinese People's Liberation Army, Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Zhejiang Provincial People's Hospital, Luoyang Central Hospital, The Affiliated Hospital of Henan University of Science and Technology, Northern Jiangsu People's Hospital, First People's Hospital of Shangqiu, Qilu Hospital of Shandong University, and First Affiliated Hospital of Anhui Medical University. The results of this trial will be reported in peer-reviewed journals and presented at scientific conferences.

Consent to participate

The consents for this study is obtained from each patient or his/her next of kin with full information regarding the possible adverse effects of the experimental drug and potential consequences. The translated patient consent form is attached as a supplemental file(Supplement Materials).

Discussion

The TRACE trial was designed to test the efficacy of a new therapy targeting the immune system in preventing IPN following ANP, which is a potentially lethal

complication causing substantial morbidity and mortality. We also aimed to investigate the efficacy of immunomodulatory treatment with thymosin alpha 1 in patients with different clinical characteristics using predefined subgroup analysis. The results of the TRACE trial would potentially provide a novel therapeutic option in the management of ANP and identify the patient population who may benefit most from the administration of thymosin alpha 1.

Immunomodulation is of significant clinical value in critically ill settings and the treatment of sepsis[12]. While, acute pancreatitis, which has a lot in common with sepsis like overwhelmed inflammation and infection related complications, might be another suitable target for immunomodulatory therapy. In general, previously studied drugs such as lexipafant and octreotide were aimed to control cytokines, which are thought to be the pivotal part in the early inflammatory response of AP, rather than preventing the development of IPN[11]. However, like what we learned in sepsis, immunosuppression quickly following the initial inflammatory cascades should be the target of treatment during the course of ANP, as well, especially in those with organ failure[8, 22]. A pilot study published by our group several years ago indicated that the administration of thymosin alpha 1 could improve compromised monocyte HLA-DR expression and reduce infection rate in a small group of patients (n=24) with severe acute pancreatitis defined by the original Atlanta Classification. The result of this study is encouraging which drive us to conduct this large multi-center RCT to obtain more reliable clinical evidences[14].

The TRACE trial was sponsored by the CSAP at Jinling Hospital, Nanjing University, which is the national referral center for acute pancreatitis (AP) admitting more than 600 cases of AP annually and coordinated by the CAPCTG coordinating and data management center, which could cover the whole country. The trial is performed in 16 centers across China and aims to recruit 520 patients. Due to the limitation of the budget and technical availability, we can not conduct a continuous immune assessment with multiple markers and more time points. Alternatively, we choose monocyte HLA-DR, which is a representative parameter of the immune system, majorly reflecting the antigen presentation capacity to assess the immunomodulatory effect of thymosin alpha

1. HLA-DR was widely used in previous studies regarding immune function in different diseases like sepsis[12, 23].

In conclusion, the TRACE trial aims to assess the efficacy of thymosin α1 administered early during the ANP on the incidence of IPN and other major clinical outcomes and thereby potentially offer a novel therapeutic option in the treatment of ANP patients.

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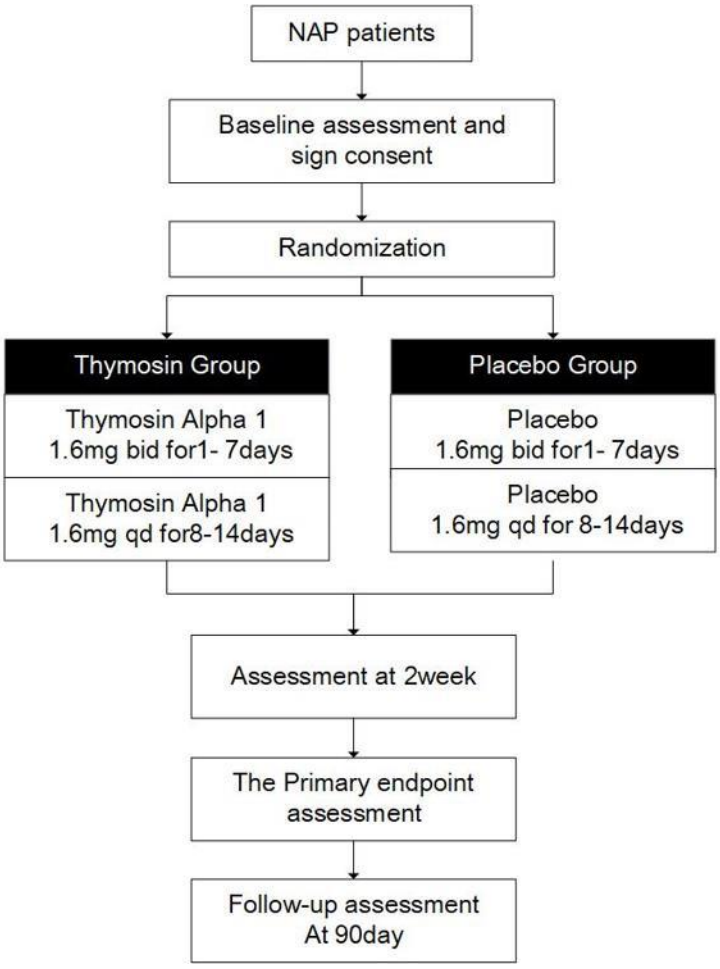

Figure 1：Trial flow chart.

	Study period							
	Enrollment	Allocation	Index admission					Follow-up
TIMEPOINT	< 24h	0	day1-6	day7	day8-13	day14	discharge/death	90 day
ENROLLMENT								
Eligibility screening	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Drug injection 1.6mg bid			X	X				
Drug injection 1.6mg qd					X	X		
ASSESSMENTS:								
Incidence of IPN			←	—	—	→		
Major complications			←	—	—	→		
Laboratory test	X			X		X		
Organ failure assessment	X			X		X		
Status of vitality and infection								X

Figure 2. Schedule for participants enrolment, drug administration, and data collection.

Declarations

Authors' contributions：

All authors were involved in the study design, and read and approved the final manuscript. During the study, J Z, W M and Y L are responsible for randomizing the patients and ensuring the blinding. J Z, W H, X P，M C，C H, W G, J W, J S, H N, J T, J S，G Z, W C, B X, X Z, M S are responsible for carrying out recruitment, managing the treatment of the patients and collecting data. W L,Z T,L K,J Z,TM and W H, X P，M C，C H, W G, J W, J S, H N, J T, J S，G Z, W C, B X, X Z, M S are members of the TSC. J Z , L K, Z T and T C drafted the manuscript.

Competing interests

This study is supported by SBE2016750187 of Science and technology project, Jiangsu Province, China. SciClone Pharmaceuticals provides the study drug for this investigator-initiated study but has no influence on the study design, data analysis, or report. The investigators take full responsibility for the integrity and content of this paper.

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Consent for publication

Not Applicable.