

Study Protocol

Official Title of the study: Effectiveness and safety of Chinese herbal medicine for hepatitis B virus-related acute-on-chronic liver failure: A multi-center, randomized and controlled trial

NCT number: not yet assigned

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This prospective, multi-center, parallel, centrally randomized controlled trial was designed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline, which is led by the principal investigator from 302 military hospital in Beijing, will be carried out from September 2018 and December 2020 among 16 tertiary academic hospitals in China. Patients with hepatitis B virus (HBV) related Acute-on-chronic liver failure (ACLF) will be randomly allocated to the Chinese herbal medicine (CHM) group or the standard medical treatment (SMT) group in a 1:1 ratio. The last patient will be enrolled before August 2019 to make sure the availability of 48 week's survival status by the end of this study. We will decide whether to expand additional institutions to guarantee adequate enrolments after interim assessment of effective participant numbers around December 2018. Patients in the SMT group will receive the standard medical treatment, and patients in the CHM group will receive rhubarb decoction enema for 1 week and CHM for 8 weeks additionally. All patients will be followed at pre-designed time points after 8 weeks' observational period until August 30, 2020 for the primary outcome and secondary outcomes.

The study is consistent with Good Clinical Practice(GCP) guidelines and has been approved by 302 military hospital ethics review committee (2018007D). Written informed consent is requisite to be signed by the patients or the authorized person under the willingness. The privacy and data of all participants will be protected carefully before, during and after the trial.

Patients will be consented and enrolled by co-principal investigators at each institution and managed by care providers including residents, attending physicians and nurses according to the protocol. Most of the patients will be treated in hospital for 8 weeks so clinicians can supervise the administration of CHM, in addition, the policy of reimbursement filed by the lab results at determined time points will boost the regular follow-up of this study.

Diagnostic criteria

The diagnosis of HBV-ACLF refers to the guideline of liver failure issued by Chinese Group on the Study of Severe Hepatitis B (COSSH) in 2012. In this guideline, HBV-ACLF was described as acute decompensation of liver function within short time (28 days usually) in patients with previously diagnosed or undiagnosed chronic liver disease, reaching the following obligatory criteria: (1) asthenia combined with obvious symptoms of digestive tract, (2) quick progress of jaundice defined as total bilirubin (TBIL) greater than 10 mg/dl or increase 1mg/dl daily, (3) coagulopathy with prothrombin activity less than or equal to 40% or international normalized ratio (INR) greater or equal to 1.5 except other extrahepatic reasons and another dispensable item of decompensated ascites and/or hepatic encephalopathy. There are three grades classified by the degree of coagulopathy and liver complications.

The TCM syndrome was judged by two qualified senior TCM physicians simultaneously based on the published criteria to decide what CHM will be given, and the discrepancy will be solved by consulting another senior physician.

Inclusion criteria

(1) In-patients with ACLF. (2) Patients with chronic hepatitis B or compensated cirrhosis caused by HBV. (3) Patients who are willing to sign the informed consent. (4) Patients aged from 16 to 65 years old.

Exclusion criteria

(1) Acute liver failure, sub-acute liver failure, or chronic liver failure. (2) ACLF caused by another disease such as autoimmune disorder, drug, alcohol, toxin, parasites other than HBV. (3) Pregnant or lactating women. (4) Primary liver cancer. (5) Combined with other severe systemic diseases or mental disease. (6) Anti-HIV positive or combined with infection of hepatitis A, C, D, E virus or cytomegalovirus, Epstein-Barr virus. (7) Patients participating in other clinical trials three months back. (8) Patients unwilling to cooperate. (9) Poor compliance, unable to guarantee to complete the protocol. (10) Complicated by severe cerebral edema, severe infection, type I hepatorenal syndrome (HRS), and gastrointestinal hemorrhage. (11) Patients allergic to one of the Chinese herbs in this protocol.

Criteria for discontinuing or modifying allocated interventions

The study will end at once if severe adverse events associated with CHM occurs or sufficient evidence indicates that adding CHM is not superior to the SMT group. Besides, CHM will discontinue and the final status will be censored in the condition of liver transplantation or the onset of liver cancer. Allocated interventions can be changed upon participant's request. All these changes will be recorded and analyzed based on intention-to-treat (ITT).

Intervention

Standard medical treatment

The SMT include a high-calorie diet; nucleoside analogues for HBV DNA-positive patients; sodium restriction, diuretics and paracentesis combined with albumin infusion for ascites; lactulose and L-ornithine aspartate and lactulose for HE and hyper-ammonia; hemostatic treatment for gastrointestinal hemorrhage; antibiotics for infections and renal replacement for HRS and uremic symptoms. CHM formulas, whatever routes of administration, are prohibited in the SMT group.

Chinese herbal medicine formula

There are two kinds of CHM based on traditional Chinese Medicines (TCM) syndromes. The common components of the two CHM formulas include *Artemisiacapillaris* Thunb (30g), *Salvia miltiorrhiza* Bge (30g), *Rhizoma*

Atractylodis Macrocephalae (30g), Rubia cordifolia L (30g), Sieyesbeckiaorientalis L (30g). Additional four components of Paeoniae Radix Rubra (60g), Gardenia jasminoides Ellis (9g), Hedyotis diffusa Willd (30g), Bletilla striata (15g) are involved for excess syndrome, and five other components of Astragalus membranaceus (30g), Radix Pseudostellariae (15g), Radix Aconiti Lateralis Praeparata (10g), Galli Gigeriae Endothelium Corneum (20g), Polygonum cuspidatum Sieb.et Zucc (15g) are involved for deficiency syndrome. All ingredients are manufactured as a Chinese herbal granule in a specific weight ratio to the raw herb (Beijing Kang Rentang Pharmaceutical Co., Ltd, Beijing, China) in accordance with the quality criteria of Chinese pharmacopoeia in 2015. Patients will take one dosage of CHM granule per day for 8 weeks. For patients who cannot take oral medicine can be switched to colon route by the colonic therapy system (IMS-100A produced by Sunny Medical in Beijing China).

In addition, patients in the CHM group will also receive daily herbal enema of 100 microliter decoction composed by Radix et Rhizoma Rhei Palmati (Dahuang) 30g and Fructus Mume (Wumei) 30g for 7 days expect the following contraindications: (1) severe hemorrhoid, (2) female patients during menstruation, (3) anal stenosis, (4) artificial anal and (5) cardiac disease.

Outcome measurements

Primary outcome

The primary outcome is transplant-free survival at week 12.

Secondary outcomes

Secondary outcomes include (1) transplant-free survival at week 24, (2) the influence on liver function assessed by MELD score (involving levels of serum bilirubin, creatinine, INR and sodium) at week 12, (3) the influence on liver function assessed by Child-Pugh score (involving the serum bilirubin, coagulation function, albumin and the complication of hepatic encephalopathy and ascites) at week 12. (4) quality of life assessed by WHOQOL-BRIEF at week 12 and (5) the incidence of serious complications (including infections, encephalopathy, HRS, and gastrointestinal bleeding) from week 1 to week 24.

Safety outcomes

Primary vital signs, physical examinations, electrocardiogram and some laboratory tests such as routine blood test, urine test, renal function will be assessed before and after treatment to monitor the safety of this study. Furthermore, adverse events are also recorded in a predesigned case report form (CRF) through the whole study period. An independent safety committee will analyze the incidence and severity of adverse events to identify any unexpected adverse events or mortality in the CHM groups.

Other assessed parameters

Epidemiological characteristics, the details of nucleoside/nucleotide analog therapy, family history of liver disease were collected from patient medical record, the level of HBV DNA, endotoxin, and lymphocyte subsets were tested as well as CLIP-C-ACLF score were computed at week 24 and 48. The plasma level of HBV DNA, endotoxin, and cytokines were tested in ADICO clinical laboratories (Shanghai, China) which is blind to the allocation information. Remnant plasma will be stored at -80°C for ancillary studies. Women of childbearing age will undergo pregnancy test for the eligibility.

Sample size

The proposed -12% superiority margin of 8-week mortality rate was chosen based on our previous results of 30.87% in the SMT group. Considering a power of 0.80 and 10% of attrition rate, 255 subjects are needed for each group to achieve the significance level of 0.05 in assessing the difference between the two groups.

Randomization

The eligible patients will be randomly allocated to the SMT group and CHM group in a 1:1 ratio. The sealed numbers are generated by a computerized random number generator with statistical analysis system (SAS) software by an independent statistician from the center of clinical evaluation in China Academy of Chinese medical sciences (Beijing, China) and are concealed using opaque envelopes.

Trial monitoring

Trial monitoring is assumed by an independent Contract Research Organization so as to verify that: (1) The rights and well-being of human subjects are protected. (2) The reported trial data are accurate, complete, and verifiable from source documents. (3) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). Monitors should be appropriately trained and have the scientific and/or clinical knowledge needed to monitor the trial adequately. A risk-based monitoring strategy is developed in this trial, which includes on-site and centralized monitoring, which is more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality. On-site monitoring is an in-person evaluation carried out by the monitor at the sites at which the clinical investigation is being conducted. Centralized monitoring is a remote evaluation carried out at a location other than the sites at which the clinical investigation is being conducted. Key monitoring processes include subject inclusion process; implementation of the inclusion criteria; source data verification; data integrity, etc.

Data management and Statistical methods

Data entry will be conducted by two independent administrators using online electronic CRF for accuracy and consistency. At the end of the study, the database will be locked and analyzed under the agreement of principal investigator and statistician, who are privileged to access the final trial dataset.

The randomized subjects who take at least one dose of CHM or SMT constitute the full analysis set (FAS) and those who complete all the visits constitute the per-protocol set (PPS). An efficacy assessment will be analyzed using FAS and PPS based on the principle of ITT. Subjects who have taken the CHM and been evaluated the safety at least once constitute the safety set (SS), which is used for safety evaluation. The statistical analysis will be performed using SAS 9.0 software (SAS Institute, Cary, NC, USA) by independent data management committee who are blind to the interventions.

Comparison of the two groups is conducted for the continuous variables with *t*-test and the categorical variables or rates with the chi-square test. The Kaplan-Meier overall survival curves will be generated and tested by log-rank. Cox proportional hazards regression model will be adopted to determine the prognostic factors associated with transplant-free survival. Multivariate logistic regression analyses will be adopted to explore factors associated with the incidence of liver-related complications. Subgroup analyses will be done based on the diagnostic criteria of Asian Pacific Association for the Study of the Liver (APASL) and European Association for the Study of the Liver (EASL) guideline.

The last observation carried forward approach was used for missing values. The statistical significance is defined as a two-sided $P < 0.05$.