Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

WITHDRAWN: Efficacy and safety of He-He-Shu-Yang Particles plus Anluohuaxian Pills for early liver fibrosis in Chronic Hepatitis B patients: study protocol for a multicenter, randomized controlled trial

Meijie Shi
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Huanming Xiao
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Junmin Jiang
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Pengtao Zhao
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Shuduo Wu
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Chaozhen Zhang
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Yueqing Yang
Shaanxi Provincial Hospital of Traditional Chinese Medicine
Chunlan Zhang
Guangzhou Eighth People's Hospital
Rongzhen Zhang
First Affiliated Hospital Of Guangxi University of Traditional Chinese Medicine
Huabao Liu
Chongqing City Hospital of Traditional Chinese Medicine
Jing Wang
Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University

Guiqin Zhou
Beijing Tiantan Hospital
Jianmei Hao
Xi'an Hospital of Traditional Chinese Medicine
Junfeng Zhu
Shanghai municipal Hospital of Traditional Chinese Medicine
Huaizhang Li
Shanxi Provincial Hospital of Chinese Medicine
Hui Guo
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine
Sheng Li
2nd Clinical Hospital of Guangzhou Chinese Traditional Medicine College: Guangdong Provincial Hospital of Traditional Chinese Medicine
Yingxian Li
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Gaoshu Cai
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Baoyu Xie
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Jiezhen Chen
2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine
Huijun Chen
2nd Clinical Hospital of Guangzhou Chinese Traditional Medicine College: Guangdong Provincial Hospital of Traditional Chinese Medicine
Chanyuan Xu
2nd Clinical Hospital of Guangzhou Chinese Traditional Medicine College: Guangdong Provincial Hospital of Traditional Chinese Medicine
Zehuai Wen
2nd Clinical Hospital of Guangzhou Chinese Traditional Medicine College: Guangdong Provincial Hospital of Traditional Chinese Medicine
Xiao ling Chi
chixiaolingqh@163.com

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine https://orcid.org/0000-0003-3193-1943

Study protocol

Keywords: He-He-Shu-Yang Particles, Anluohuaxian pills, Multicenter randomized controlled trial, Early liver fibrosis, Efficacy

Posted Date: March 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-67829/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background: In recent years, more and more studies revealed that liver fibrosis progression could happen at early stage in chronic hepatitis B (CHB) patients. However, there is no anti-fibrotic agent available at present in modern medicine.He-He-Shu-YangParticles (HHSYP) and Anluohuaxian Pills (AHP)are two commonly used Traditional Chinese Medicine (TCM) agents for liver fibrosis, but there is no data of them for early liver fibrosis(F1 or F2) in multicenter, randomized controlled trial. Therefore, the aim of this study is to evaluate efficacy and safety ofHHSYP plus AHP for early liver fibrosis in CHB patients.

Methods/design: For the 72-week randomized controlled study, 480 CHB patients with early liver fibrosis are randomly assigned at a 2:1 ratio to two groups: the intervention group and the placebo group. The intervention group was treated with HHSYP plus AHP. The placebo group was treated with placebo of HHSYP and AHP. The primary end point is the histological change after 72-week treatment.

Discussion: Although previous studies have confirmed the anti-fibrosis efficacy of HHSYP and AHP in CHB patients, the efficacy and safety of their combination treatment for early liver fibrosis is still not clear.Therefore, this will be the first multicenter randomized trial to prove the efficacy and safety of combination TCM treatment of HHSYP and AHP for early liver fibrosis, which will use histological changes as the primary end point. This will provide reliable data for the TCM combination treatment of early liver fibrosis and might give a new direction for further international studies on liver fibrosis.

Ethics and dissemination: This study protocol was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (BF2018-175-01) and all other participating centers (Project number2018ZX10725506-003).The study findings will be published in peer-reviewed journals and presented at the national and international conferences.

Trial registration: Chinese Clinical Trial Registration: ChiCTR1900025897, Registered:13 September 2019, http://www.chictr.org.cn/edit.aspx?pid=40222&htm=4

Introduction

Nowadays, chronic hepatitis B (CHB) is still a serious public health problem worldwide. About 240 million people, 6 percent of the world's population, were diagnosed as CHB patients[1]. Liver fibrosis is an important pathological process of CHB, which could progress to cirrhosis, liver cancer and even greatly decrease CHB patients' survival rate. Dr. Hans Popper, a famous professor on liver diseases, once pointed out that "anyone who can stop or delay liver fibrosis would be able to cure most chronic liver diseases." Therefore, regression of liver fibrosis can greatly improve prognosis of CHB patients. However, there is no anti-fibrotic agent available at present in modern medicine.Although highly effective antiviral therapy might prevent liver fibrosis progression partly[2], there were still some patients showing fibrosis progression,even patients with fibrosis stageF2 at baseline. Due to side effects of antiviral agents, some patients, especially those with F2, are particularly eager to find other alternative therapy. More importantly, no treatment is recommended for patients with F1 in current guidelines. However, more and more

researchers believed that liver fibrosis progression could also happen at early stage of liver fibrosis. Results from a Korean study[3]revealed that 11% CHB patients with METAVIR fibrosis stage F0 or F1 at baseline developed cirrhosis after about 10-year follow-up. One of our previous studies[4] also showed that 35.3% CHB patients with F1 or F2 at baseline developed fibrosis progression of at least one Ishak fibrosis score after an average of 28.1 months. In view of this issue, finding a useful alternative therapy for early liver fibrosis (F1 or F2) is quite urgent. Over the past decade, Traditional Chinese Medicine (TCM) has been widely used as a useful complementary therapy for liver fibrosis in China. In recent years, many studies have confirmed the anti-fibrosis efficacy of TCM in CHB patients[5].

As for TCM theory, liver fibrosis is thought to be associated with several pathogenic factors, such as Qi stagnation, disorder of spleen transformation and transportation, internal accumulation of dampness, heat and blood stasis. Most TCM experts believe that blood stasis is the most important pathogenic factors during the development of liver fibrosis. The more serious the blood stasis, the more serious the liver fibrosis. Previous guidelines for liver fibrosis in China[6][7] also pointed out that the basic syndromes of liver fibrosis are deficiency of qi and yin and blockage of collaterals by blood stasis. TCM syndrome of liver depression and spleen deficiency is one of the main syndromes. In our previous study[8], we also find that TCM syndrome of liver depression, spleen deficiency and blood stasis can exist at any stage of liver fibrosis, especially often in CHB patients with early fibrosis. So, a useful alternative therapy for early fibrosis target at the TCM syndrome of liver depression, spleen deficiency and blood stasis.

AHP has been proved to be a widely used TCM patent for liver fibrosis in China[9][10][11], which was approved by CFDA (license numberZ20010098) and entered the market in 2001. The components of AHP included Radix Rehmanniae, Panax Notoginseng, Hirudo, Calculus Bovis, Lumbricus, Bighead AtractylodesRhizome, Cortex Moutan and Rhubarb etc. According to the theory of TCM, AHP can promote blood circulation and soften hard masses so that it is appropriate for liver fibrosis with TCM syndrome of blood stasis. In a multicenter randomized, placebo-controlled study[12] for early fibrosis, we find that 37.7% patients showed liver fibrosis improvement after 48-week AHP treatment, which was significantly higher than that in placebo group.However, there were still 17.0% patients showed liver fibrosis progression. Thus, we hypothesize that a more useful alternative therapy for early fibrosis might not only target at TCM syndrome of blood stasis but also target at TCM syndrome of liver depression and spleen deficiency. He-He-Shu-Yang Particles (HHSYP) is another commonly used TCMagents for liver fibrosis in Guangdong province of China for nearly 40 years, which is made by famous TCM doctor Chi Xiao-ling in Guangdong. This recipe (including Bupleurum chinense, Radix Paeoniae Alba and Codonopsispilosula, etc) aims for treating CHB-fibrosispatients with TCM syndrome of liver stagnation and spleen deficiency, which comes from the Golden mirror of medicine, a famous medical TCM book in Qing Dynasty. The previous studies[13][14] of HHSYP have proved its anti-fibrosis efficacy. Therefore, we hypothesize that the combination TCM treatment of HHSYP plus AHP might be a more useful alternative therapy for early fibrosis, which target at TCM syndrome of liver depression, spleen deficiency and blood stasis. Based on this hypothesis, we designed a standard multicenter, double-blind, randomized controlled clinical trial for evaluating the efficacy and safety of HHSYP plus AHP for early fibrosis by liver histomorphology before

and after treatment, which might help physicians make correct and reasonable decisions in the treatment of early liver fibrosis.

Methods

Study design

This is a large, prospective, multicenter, centrally randomized, double-blind, placebo-controlled trial. The study is being conducted in accordance with the Declaration of Helsinki[15] and has been approved by the ethics review committees of each participating institution. Meanwhile, this study has been registered with the Chinese Clinical Trial Registry (ChiCTR1900025897). Informed consents are being signed for all patients before enrollment. The treatment will be for 72 weeks. The study's flow chart is shown in Figure 1.

Patient population

In all, 480 eligible CHB patients is being enrolled and followed up in eleven institutions in China between September 2019 and December 2021. The eleven institutions are eleven academic hospital from eight different provinces in China, including Guangdong Hospital of Chinese Medicine, Shaanxi Provincial Hospital of Traditional Chinese Medicine, Guangzhou Eighth People's Hospital, First Affiliated Hospital of Guangxi University of Traditional Chinese Medicine, Chongqing Hospital of Traditional Chinese Medicine, Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Beijing Ditan Hospital, Xi'an Hospital of Traditional Chinese Medicine, Shanghai municipal Hospital of Traditional Chinese Medicine, Shanxi Provincial Hospital of Chinese Medicine, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine. All enrolled patients are randomly assigned at a 2:1 ratio into two groups: the intervention group treated with HHSYP plusAHP (n=320) and the placebo grouptreated with placebo of HHSYP and AHP (n=160).

Western medicine diagnostic criteria

The patients' western medicine diagnostic criteria are based on "The guideline of prevention and treatment for chronic hepatitis B (2015 version)"[16] and "Liver fibrosis: consensus recommendations of the Asian Pacific Association for the Study of the Liver"[17].

Diagnostic criteria for TCM syndrome differentiation

The diagnostic criteria of TCM syndrome of liver stagnation, spleen deficiency and blood stasis are based on the Standards of Traditional Chinese Medicine syndrome differentiation for liver fibrosis[7].

Inclusion criteria

The inclusion criteria of this study include: agreeing to participate in this clinical trial and signing the informed consent form; fulfilling the diagnosis criteria for CHB-fibrosis with TCM syndrome of liver

stagnation, spleen deficiency and blood stasis; age 18-65 years; patients with alanine aminotransferase (ALT)<two times upper limit of normal (ULN) and liver stiffness measurement (LSM) tested by Transient Elastography (TE)< 9.4 Kpa; patients with liver inflammation grade G≤2 and liver fibrosis stage F<2 at first liver biopsy, if patients with F2, who should sign an another informed consent of refusing antiviral treatment voluntarily; Female patients must fulfill: (a) menopause (defined as no menstruation for at least one year) or surgical sterilization, or (b) fertility and fulfilling: negative result of blood pregnancy examination at baseline, and consent to use of appropriate contraceptive measures and nobreast-feed during the treatment and follow up period.

Exclusion criteria

The exclusion criteria of this study include: patients with allergy to the constituents or excipients of the drug used in this experiment or allergic constitution; co-infection with another hepatitis virus (A, C, D or E) or human immunodeficiency virus; patients with metabolic or autoimmune liver disease, or drug-induced liver damage, or congenital liver disease; patients with a history of alcohol, drug or drug abuse; patients with renal creatinine >one upper limit of normal; patients with evidence of cirrhosis or liver cancer tested by upper abdomen ultrasonography/CT/MR; patients with evidence of decompensation of liver function, such as ascites, portal hypertensive related upper gastrointestinal bleeding, hepatic encephalopathy, primary spontaneous peritonitis, hepatorenal syndrome, etc;patients with serious primary diseases such as heart, lung, kidney and other important organs and hematopoietic system, such as heart failure classified as Grade II, III and IV by the New York Heart Association, heart pacemaker, chronic obstructive pulmonary disease, chronic kidney disease, type 2 diabetes mellitus, etc; patients with neurological or mental disorders who are unable to cooperate or unwilling to cooperate; patients with history of diseases of affecting drug absorption, distribution and metabolism (such as inflammatory bowel disease, gastrointestinal surgery, chronic pancreatitis, glutenin allergy, vagotomy, etc.); patients having participated in other clinical trials in the past three months.

Withdrawal criteria

Any enrolled patients will be withdrawn from this study if they have such conditions as follows: a) taking prohibited drugs or therapies, such as antiviral drugs, other anti-fibrosis TCM drugs, or drugs leading to liver fibrosis and so on; b) having serious adverse events (SAE), such as severe liver dysfunction (ALT>10ULN or PT>15s or TBIL>5ULN), cirrhosis or liver cancer, etc; c) having poor compliance, who do not take medicine for more than 4 weeks according to the protocol; d) lost to follow up; e) wanting to cease or withdrawing the consent. If patients showed ALT>2ULN during treatment, hepatoprotective drugs will be used. If patient receiving hepatoprotective drugs still shows ALT>2ULN level for more than two weeks, antiviral agents will be used. These patients will be dropped from this study too.

Recruitment methods

Patients are being recruited in the following ways: a) inpatients or outpatients in each participating institution, b) recruitment advertisement has been designed and posted to attract potential participants,

c) recruitment advertisements are also widely disseminated through WeChat's circle and hospital WeChat Subscription. All participants are being informed of the benefits and risks of participating in the clinical trial, especially the right to withdraw from the trial at any time.

Randomization and blinding

A center-stratified and permuted blockrandomization sequence is being generated by JMP 6.0 software (SAS Inc., Cary, NC) and was performed by Key Unit of Methodology in Clinical Research of Guangdong Provincial Hospital of Chinese Medicine. The research doctor will enroll and assign participantsrandomly to either intervention group or placebo group at a 2:1 ratio through the interactive web response system which was a verified online randomization facility established by the Key Unit of Methodology in Clinical Research. The randomization schedule has been kept confidential and treatment assignments are being blinded to patients, investigators, outcomes assessors and statistician until the completion of the entire study. Corresponding emergency letter has been designed for each coded trial drug. The emergency letter contains a note recording what the coded trial drug is. The emergency letters have been sealed and sent to each participating situation. Unblinding is only permissible in emergencies, such as SAE.

Interventions

All the enrolled patients are being randomized into two groups. The intervention group is beingtreated with HHSYP (23.6g, twice daily) and AHP (6g, twice daily), while the placebo groupis beingtreated with placebo of HHSYP dummy agent (23.6g, twice daily) and AHP dummy agent (6g, twice daily). The placebo of HHSYP and AHParesimilar in taste, shape and color to HHSYP and AHP, respectively and the main ingredients include pearl barley and grilled germinate barley. Treatment will be conducted over a period of 72 weeks and the follow-up visits last for 72 weeks after the treatment. The time points of treatment for the visits are at baseline, 12 weeks, 24 weeks, 36 weeks, 48 weeks, 60 weeks and 72 weeks post baseline. The time schedule of enrolment, interventions and assessments is shown detailly in Figure 2.

Concomitant care and interventions

Any drugs having good benefits for liver fibrosis, such as interferon, nucleoside (acid) antiviral drugs, colchicine, compound bovine fetal liver extract or anti-fibrosis TCM drugs, are not allowed throughout this trial. Hepatoprotective drugs except for Schisandra medication are permitted in theparticipants with ALT>2ULN during the treatment. However, all the concomitant drugs should be recorded detailly in the case report forms (CRF), which will be analyzed and reported at the end of the trial.Drinking, staying up late or being tiredness, which might aggravate the disease, are also not allowed throughout the trial.

Strategies to improve patients' compliance

a) Before enrollment, individual health education is being given to the participants by the project doctors. Therefore, participants could understand the necessity and importance of the treatment and adhere to intervention protocols strictly. b) Besides to face-to-face interview at regular visits, the project nurses are

also conducting another kind of follow-up via wechat every 2 weeks so as to supervise patients to taking drugs on time. c)At each regular visit, the unused drugs and the empty package of the used drugs must be returned. Meanwhile, compliance is being assessed at each regular visit. If poor compliance is found, the project doctor will conduct a face-to-face interview to find out the causes of low compliance and solve relevant problems.

Outcome measurements

Primary outcomes

Improvement or progression of liver fibrosis by histological assessment

Improvement or progression of fibrosis will be defined as at least 1 stage decrease or increase by METAVIR system, whereas no change or less than one stage change compared to that at baseline will be identified as the absence of improvement or progression.Liver fibrosis is assessed by the METAVIR system for fibrosis stage[18]. The fibrosis stages are as follows: no fibrosis (F0), mild fibrosis (F1), moderate fibrosis (F2), severe fibrosis (F3) and cirrhosis (F4). Liver fibrosis will be assessed before and after treatment (at baseline and week 72) based on patients' preferences. To ensure the quality of liver specimens, every liver specimenshould have a minimum of 15-mm length and at least ten portal tracts. Liver biopsies in all centers are being performed using 18G MAXCO needles (Bard Co., NJ,USA) and the tissue is being fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin, eosin and Masson. All the biopsy slides will be collected by the independent third-party and three pathologists will be invited to examine the biopsy slidestogether in double-blind manner.The final pathological result can be determined only when the results of two pathologists are consistent. If the results of three experts are inconsistent, discussion should be conducted to determine the final result.

Secondary outcomes

Liver stiffness changes assessed by Transient Elastography (TE)

Liver fibrosis progression assessed by Transient elastography will be reflected by an increase in LSMof at least one fibrosis stage. The relationship between LSM and liver fibrosis stage is as follows[19]: LSM≤7.4Kpa: F0-F1; 7.4≤LSM 9.4: F2; 9.4≤LSM 12.4:F2-F3; 12.4≤LSM 17.5: F3-F4; LSM ≥17.5: F4. Measurements of LSM using TEare being performed by a single trained operator at each participating institution according to the standard operating procedures of TE in "clinical application of transient elastography"[19]. And TE will be performed every 12 weeks for each patient.

Other secondary outcomes include changes of the cumulative TCM symptom score, changes in the scores of the Chronic Liver Disease Questionnaireand the short form healthsurvey SF-36, the occurrence of liver cirrhosis and hepatocellular carcinoma.

Safety outcomes

Safety indicators will be monitored regularly and timely to ensure the safety of each enrolled patients, including routine urine test, routine stool test, routine blood test, liver and renal function test and so on. Safety outcomes include results of. These biological indicators are monitored at baseline, 24 weeks, 48 weeksand 72 weeks post baseline.

Data collection, data and safety monitoring board

The CRF are being completed by the investigators and submitted to submitted to the inspector for verification. The CRF data will be double entered into Electronic Data Capture and checked by the data manager. After the data of each center is confirmed to be correct, blind audit and data locking will be carried out. In order to ensure the consistency of the study implementation at each participating center, the trial progress will be supervised by independent monitoring visits so that the trial will be conducted strictly in accordance with the protocol and standard operating procedures. The data in this study will be collected and entered at each site. The data quality will be checked regularly by investigators and monitors. The data and safety monitoring board consists of three independent investigators. The monitoring board will protectthe ethical interests and safety of each enrolled patients by reviewing safety data. Based on the safety concerns, the board also has the power to recommend termination of the study. Any adverse effects or other unintended effects will be collected, assessed and reported truthfully and detailly through out the trial.

Ethics, consent, confidentiality and dissemination

This current trial has been approved by Guangdong Provincial Hospital of Chinese Medicine Ethics Review Committee (BF2018-175-01) and accepted by the ethics review committees at each participating center. The investigators are responsible for obtaining informed consents from trial participants, who should inform the participants about the objectives, treatment regimens, risks, benefits of the trial clearly, including provisions for collection and use of participant data and biological specimens. Though the results of current trial will be published in peer-reviewed journals or presented in academic conference, the patient's information will be kept confidentially according to the legal requirements, which can be disclosed only through legal proceedings. If any harm is confirmed to come from the trial participation, medical expenses and corresponding economic compensation will be paid according to the laws and regulations.

Modification of the protocol

When the clinical started, the protocol is not allowed to be modified arbitrarily. If the protocol was modified a lot, such as changes of study design, patient population, sample sizes, study procedures and so on, a formal amendment should be agreed upon by the sponsor's delegates and the researchers. This amendment should be also approved by each institutional review board before implementation.

Sample size and statistical methods

Based on results from our previous study, it is expected that the rate of liver fibrosis improvement in intervention group will be increased to 45%, while it will be about 20% in placebo group. Using Pass11.0 (package for encyclopedia of medical statistics), we calculated that the sample size needs to be 164 cases in all and 240 cases if there is a dropout rate of 20%. Moreover, it is estimated that 50% of all enrolled patients will agree to have a second liver biopsy after 72-week treatment. Therefore, a total of 480 patients (360 in intervention group and 120 in placebo group) are needed to achieve a significance level of 0.05 and a power level of 0.90.

SAS 9.2 software (SAS Institute, Cary, NC, USA) will be used to perform the statistical analysis for this study. The adverse events and the number of lost cases will be recorded and calculated. Missing data were imputed by the last observation carried-forward method. At baseline, the demographic data and other essential information will be compared between the intervention group and the placebo group. The intention-to-treat (ITT) analysis set included all participants who received at least one dose of the study drug, while per-protocol (PP) analysis was done in a population who completed the whole study without a main violation of protocol. The primary outcomes will be analyzed in both the per-protocol (PP) population and the intention-to-treat (ITT) population. Categorical variables were presented as counts and percentages. Chi-square test or Fisher's exact test will be used to compare the rate of liver fibrosis improvement or progression between the two groups or subgroups of patients with different ALT stratification (patients with normal ALT vs patients with abnormal ALT at baseline). Since this study is a multicenter clinical trial, the influence of central effect on primary outcomes should be considered in the analysis. Improvement or progression of liver fibrosis by histological assessment (METAVIR score) will be compared by the Cochran–Mantel–Haenszel test between the two groups. In addition to LSM analyzed in the ITT and PP population, the other secondary outcomes were analyzed on a PP analysis principle. LSM were expressed as the mean and standard deviation, or median and interquartile range. Group t test or nonparametric test (Wilcoxon) will be used for comparison between the two groups, while paired t test or signed rank sum test will be used for intra group comparison. The covariance model will be chosen to evaluate the change in LSM between the two groups with an adjustment for baseline. Statistically significant is being defined as a P-value of less than 0.05 and all P values are two-tailed.

Discussion

Liver fibrosis is a quite important and complex pathological stage during the process of CHB, which should be stopped before progressed to cirrhosis. However, long term antiviral treatment, the etiological treatment, could not stopped liver fibrosis progression completely[20]. Therefore, antifibrosis treatment became quite important for CHB patients. But antifibrotic drugs are still only effective in clinical trials in western medicine[21]. In this case, CHB patients with early liver fibrosis are often ignored due to lack of effective antifibrotic drugs. In recent years, increasing studies proved that TCM can be used as a useful complementary medicine strategy for liver fibrosis [8]. However, there are still few standard multicenter, randomized controlled clinical trials for evaluating the efficacy of TCM treatment for liver fibrosis by liver histomorphology. Therefore, we design this study to explore whether the combination TCM treatment of HHSYP plus AHP could manage liver fibrosis progression in CHB patients with early liver fibrosis.

This will be the first multicenter randomized trial to prove the efficacy and safety of combination TCM treatment of HHSYP plus AHP for chronic hepatitis B patients with early liver fibrosis, which will use histological changes as the primary end point. The achievement of this trial will provide reliable data for efficacy and safety of HHSYP plus AHP, which could provide good benefits for early liver fibrosis.Moreover,the success of this study would also confirmedthat the treatment methods of soothing liver, strengthening spleen and activating blood could be suggested for early liver fibrosis and combination treatment of two TCM patents could be considered for liver fibrosis based on TCM syndrome differentiation. This might give physicians new ideas of treatmentsfor early liver fibrosis.

There are still some limitations in our current study. Firstly, control groups, such as groups treated with HHSYP or AHP only, were not designed in this study due to tight expense. However, the anti-fibrosis efficacy and safety of HHSYP or AHP has been confirmed in our previous study, which could provide supplement data for this study. Secondly, our study only enrolls Chinese patients so that the findings of this study may not be applied in patients of other ethnicities. But it will provide reliable data for the TCM combination treatment of early liver fibrosis, which might give a new direction for further international studies on liver fibrosis.

In summary, the findings of this study will verify that TCM combination treatment of HHSYP and AHP could have good benefits and be safe for CHB patients with early liver fibrosis.

Trial Status

Protocol version: V1.1, dated 16 October. 2018. The first participant was enrolled on 26 Sep.2019. Recruitment will be completed on 30 June 2021 due to COVID-19.

Supplementary Materials

The study protocol had been reported according to the standard protocol items: recommendations for international trials. The SPIRIT 2013 Checklist, ethical approval documentation, funding documentation and plans for collection, laboratory evaluation, and storage of biological specimens have been accompanied with this paper (Additional file 1).

Abbreviations

CHB: Chronic hepatitis B; TCM: Traditional Chinese Medicine; HHSYP: He-He-Shu-Yang Particles; AHP : Anluohuaxian pill; ALT: alanine aminotransferase; ULN: upper limit of normal; LSM: liver stiffness measurement; TE: Transient Elastography; ITT: intention-to-treat; PP: per-protocol

Declarations

Ethics approval and consent to participate

This trial has received human ethics approval from Guangdong Provincial Hospital of Chinese Medicine Ethics Review Committee (BF2018-175-01) and was also conformed to the ethical guidelines of the Declaration of Helsinki. Informed consents are being signed for all patients before enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The data used to support the findings of our study will be available from the corresponding author at chixiaolingqh@163.com to other researchers upon request.

Competing interests

The authors declare that they have no competing interests.

Funding

The present study was funded by the Thirteen Five-Year Plan for Major and Special Program of the National Science and Technology of China (2018ZX10725506-003) and the biological resources project collaborated by Guangdong Provincial Hospital of Chinese Medicine and Shanghai chip National Engineering Center (YN2016XP03). The funding bodies do not play roles in study design, data collection, management, analysis, interpretation of data, writing of the report, and the decision to submit the report for publication.

Authors' contributions

XC and ZWconceived and designed the study. XC, HX, JJ, PZ, SW, CZ, YY, CZ, RZ, HL, JW, GZ, JH, JZ, HL, HG, SL, YL, GC, BX, JC, HC and CX are performing the study. ZW and MS will analyze the data. MS wrote the paper. All authors read and approved the final manuscript.

Acknowledgements

We thank all of our friends who gave useful suggestion for the design of this protocol.

References

1. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HLY, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol. Int. 2016.
2. Chon YE, Park JY, Myoung SM, Jung KS, Kim BK, Kim SU, et al. Improvement of Liver Fibrosis after Long-Term Antiviral Therapy Assessed by Fibroscan in Chronic Hepatitis B Patients with Advanced Fibrosis. Am J Gastroenterol. 2017.

3. Park BK, Park YN, Ahn SH, Lee KS, Chon CY, Moon YM, et al. Long-term outcome of chronic hepatitis B based on histological grade and stage. J Gastroenterol Hepatol. 2007.
4. Chi XL, Xiao HM, Xie YB, Jiang JM, Tian GJ, Cai GS, et al. Progression of initially mild hepatic fibrosis in Chronic hepatitis B patients: a prospective repeat liver biopsy study. Hepatology. 2016;64:883a-883a.
5. Latief U, Ahmad R. Herbal remedies for liver fibrosis: A review on the mode of action of fifty herbs. J. Tradit. Complement. Med. 2018.
6. Liver Disease Committee CA of IM. Guideline for the diagnosis and treatment of liver fibrosis with integrative medicine. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006.
7. Xu L, Liu P. Guidelines for diagnosis and treatment of hepatic fibrosis with integrated traditional Chinese and Western medicine (2019 edition). J Integr Med. 2020.
8. Chi XL, Shi MJ, Xiao HM, Xie YB, Cai GS. The score model containing Chinese medicine syndrome element of blood stasis presented a better performance compared to APRI and FIB-4 in diagnosing advanced fibrosis in patients with chronic hepatitis B. Evidence-based Complement Altern Med. 2016.
9. Huang J, Huang H, Jiao Y, Ai G, Huang T, Li L, et al. Effect of anluohuaxian tablet combined with gamma-IFN on schistosomal liver fibrosis. J Huazhong Univ Sci Technol Med Sci [Internet]. 2009;29:53–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19224163.
10. Lu W, Gao YH, Wang ZZ, Cai YS, Yang YQ, Miao YQ, et al. Effects of Anluohuaxianwan on transforming growth factor-beta1 and related signaling pathways in rats with carbon tetrachloride-induced liver fibrosis. Zhonghua Gan Zang Bing Za Zhi [Internet]. 2017;25:257–62. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28494543.
11. Miao L, Yang WN, Dong XQ, Zhang ZQ, Xie SB, Zhang DZ, et al. Combined anluohuaxianwan and entecavir treatment significantly improve the improvement rate of liver fibrosis in patients with chronic hepatitis B virus infection. Zhonghua Gan Zang Bing Za Zhi [Internet]. 2019;27:521–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31357778.
12. Chi X, Xiao H, Jiang J, Tian G, Cai G, Xie Y, et al. Blocking mild liver fibrosis in chronic hepatitis B patients treated with traditional chinese medicine: a multicenter, double-blind, placebo randomized controlled trial. Hepatol Int. 2019.
13. Wang HWuHXiao,Y, Zhihui Lin XC. Regulating effect of Hehe Shuyang Tang on immunologic function of chronic hepatitis B patients with liver-stagnation and spleen-deficiency syndrome. J New Chinese Med. 2016;48:99–102.
14. HuanmingXiao YubaoXie, Xiaoling Chi H. Effect of Hehe Shuyang formula in rats with carbon tetrachloride-induced liver fibrosis. Chinese J Exp Tradit Med Formulae. 2016;22:132–5.
15. General Assembly of the World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent. 2014.
16. Chinese Society of Hepatology CMA. [The guideline of prevention and treatment for chronic hepatitis B: a 2015 update]. Zhonghua Gan Zang Bing Za Zhi [Internet]. 2015;23:888–905. Available from:

https://www.ncbi.nlm.nih.gov/pubmed/26739464.
17. Shiha G, Sarin SK, Ibrahim AE, Omata M, Kumar A, Lesmana LA, et al. Liver fibrosis: Consensus recommendations of the Asian Pacific association for the study of the liver (APASL). Hepatol Int. 2009.
18. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology. 2002.
19. Jung KS, Kim SU. Clinical applications of transient elastography. Clin. Mol. Hepatol. 2012.
20. Orr C, Myers R, Li B, Jiang Z, Flaherty J, Gaggar A, et al. Longitudinal analysis of serum microRNAs as predictors of cirrhosis regression during treatment of hepatitis B virus infection. Liver Int. 2020.
21. Schuppan D, Ashfaq-Khan M, Yang AT, Kim YO. Liver fibrosis: Direct antifibrotic agents and targeted therapies. Matrix Biol. 2018.

Figures

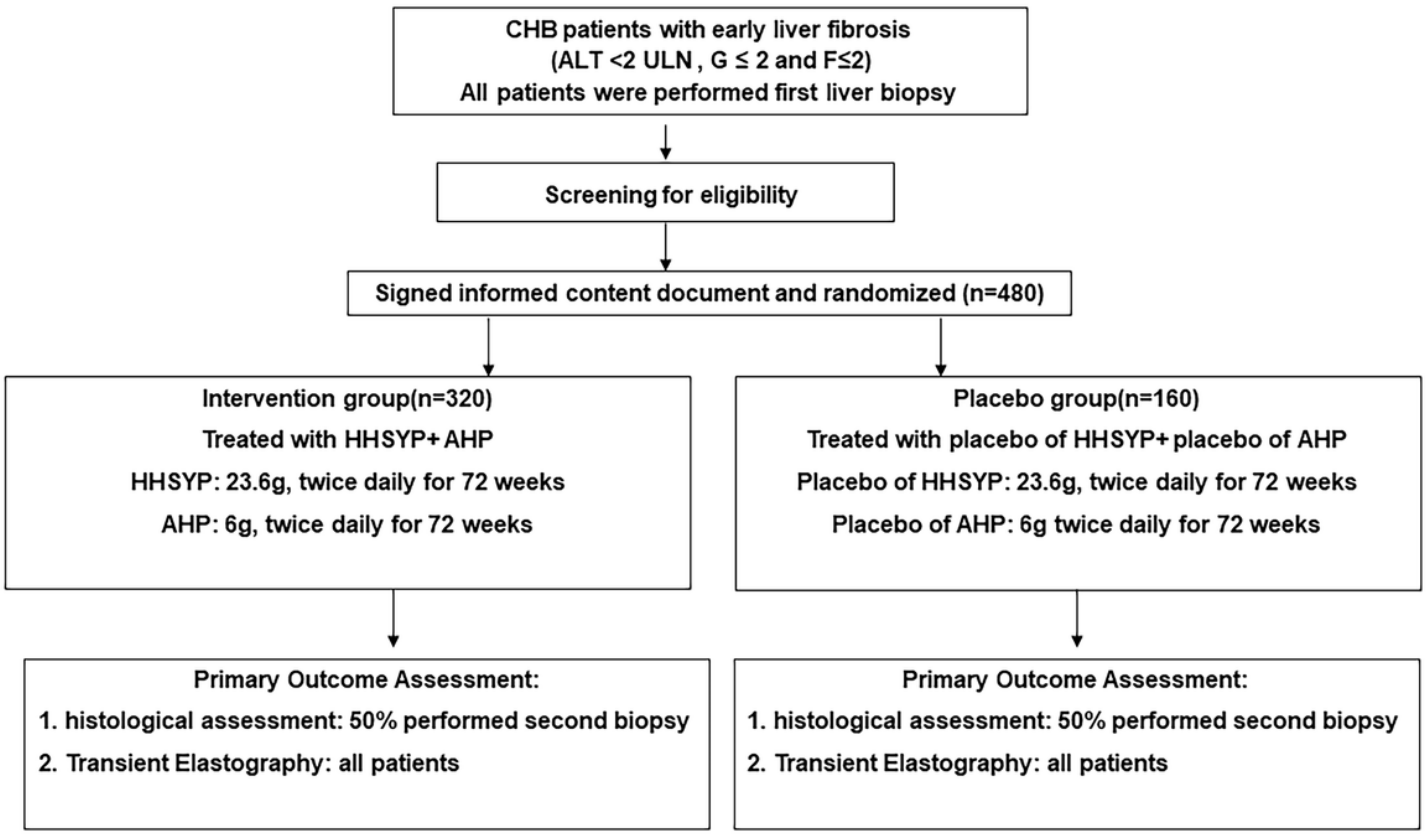

Figure 1

Flow chart of the current trial. TCM: Traditional Chinese Medicine; HHSYP: He-He-Shu-Yang Particles; AHP: Anluohuaxian pill.

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT	-2W-0W	0	W12	W24	W36	W48	W60	W72	72 weeks after TCM anti-fibrosis treatment
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
[Intervention group: HHSYP and AHP]			♦—	—	—	—	—	—♦	
[Placebo group: the placebo of HHSYP and AHP]			♦—	—	—	—	—	—♦	
ASSESSMENTS:									
[baseline variables: age, gender, the level of ALT, HBVDNA, HBeAg status]	X			X		X		X	X
[Primary outcome variables: histological assessment	X						.	X	
[Primary outcome variables: LSM	X		X	X	X	X	X	X	X
[second outcome variables: scores of the TCM symptom, CLDQ and SF-36]	X			X		X		X	X
[safety data variables: routine test of urine, stool and blood, liver and renal function test]	X			X		X		X	X

Figure.2 Time schedule of enrolment, interventions, and assessments

Figure 2

Time schedule of enrollment, interventions, assessment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklist.doc
- Plansforcollectionandstorageofbiologicalspecimens.docx