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STUDY PROTOCOL

The Adjunctive Efficacy of Fuzheng Huayu Tablet on Portal Hypertension with HBV Related Cirrhosis: A Protocol for a Multicenter Randomized Controlled Trial

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Background: Portal hypertension (PH) is a consequence of liver fibrosis and can lead to decompensated cirrhosis with complications such as ascites and gastroesophageal hemorrhage, etc. Liver fibrosis and hepatic architecture disorder contribute to the formation and development of PH. There is an unmet need for curing drugs to improve PH and preventing the occurrence of complications. It is not well known whether anti-liver fibrotic medicines can reduce the risk of PH and decompensated cirrhosis due to HBV, which could be validated by clinical trials.

Methods/Design: This is a non-blind, non-placebo-controlled, randomized, multicenter clinical trial. One hundred and ninety-two patients with HBV-related cirrhosis with or without mild gastroesophageal varices in the compensatory stage were enrolled in protocol A. The control group received entecavir (ETV), while the experimental group received Fuzheng Huayu Tablets (FZHY) and ETV. One hundred and eighty-four CHB patients with moderate or severe gastroesophageal varices in the compensatory stage of HBV cirrhosis were enrolled in protocol B. The control group received ETV plus carvedilol (CDL), while the experimental group received FZHY, ETV, and CDL. Both protocols were carried out with 96 weeks of treatment and 12 weeks of follow-up. The primary outcome was the incidence of liver decompensation events in cirrhotic patients. The secondary outcomes included grades of gastroesophageal varices (GEV), liver stiffness measurement, and liver functions. The safety of the testing medicines was also observed.

Discussion: Through a multi-center, controlled clinical trial, with the main endpoints of liver decompensated events, we aim to evaluate the clinical efficacy and safety of anti-fibrotic product FZHY on PH in patients with HBV-caused cirrhosis.

Trial Registration: Clinical Trials.gov, ID: NCT 02945956/02945982. Registered on Oct 26, 2016.

Keywords: portal hypertension, chronic hepatitis B, cirrhosis, decompensation, esophageal varices, Fuzheng Huayu Tablet

Background

Portal hypertension (PH), characterized by an elevated pressure gradient between the portal venous system and the inferior vena cava, is a primary consequence of liver cirrhosis. It serves as a critical driver for the development of severe complications, including ascites, gastroesophageal varices (GEV) and hemorrhage, hepatic encephalopathy (HE).[1] Therefore, reducing the PH in cirrhosis, as well as eliminating or controlling of etiologies of liver diseases, could result in better outcomes for the patients.[2,3]

The main purpose of treating PH with cirrhosis patients is to prevent decompensation events in patients including variceal hemorrhage etc. Nowadays there were kinds of available options for the management of PH as follows: (1) pharmacological agents such as nonselective β-blockers (NSBB) including propanol and carvedilol (CDL), vasopressin

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and analogues, etc. (2) endoscopic treatment including endoscopic sclerotherapy and band ligation. (3) Shunt surgery or transjugular intrahepatic portosystemic stent shunt (TIPSS), etc. The pharmacological medicines were widely used for the primary prevention of PH. However, the available drugs such as NSBB had some limitations. These drugs were mainly targeted to the splanchnic vasodilatation and decreased portal blood inflow. Besides, they had less or no obvious effect on intrahepatic vascular resistance (IHVR), which is a major contributor to PH. Additionally, these drugs could disbenefit the survival rate in patients with the end-stage liver disease or renal impairment.[4] IHVR is attributed to both structural remodeling of the liver architecture and increased intrahepatic vascular tone, which are mainly caused by the activation of hepatic stellate cells (HSCs) and dysfunction of liver sinusoidal endothelial cells (LSECs).[5,6] Given the limitations of current pharmacological therapies and the pathogenesis of IHVR, there is an emerging need to develop new treatments that can effectively control IHVR and reduce PH.

Fuzheng Huayu (FZHY) is a herbal product against liver fibrosis. It can reduce portal pressure in cirrhosis animal models[7] and lower the risk of variceal hemorrhage in cirrhotic patients.[8] The action mechanisms underlying FZHY against liver fibrosis included the inhibition of HSCs activation and improvement of liver sinusoidal capitalization.[9] These actions could help improve IHVR and reduce PH in cirrhosis patients. Therefore, based on efficacy and action mechanisms of FZHY on liver fibrosis, we designed a multi-center, randomized controlled clinical trial to evaluate the clinical efficacy and safety of FZHY in treating PH in patients with hepatitis B virus (HBV)-induced cirrhosis.

Methods and Design

Study Design

The trial is a non-blind, parallel-group, 1 to 1 randomized, non-placebo-controlled, multicenter clinical trial. The trial recruits patients with HBV induced compensated cirrhosis, who were divided into sub-two groups or 2 treatment protocols according to PH degree. Protocol A included patients with non or grade I GEV, who were randomized into control and experimental groups, and received entecavir (ETV) or FZHY+ETV, respectively. Protocol B included patients with grade II or grade III GEV, who were randomized into control and experimental groups, and received ETV+ CDL or FZHY+ETV+CDL, respectively. All patients were treated for 96 weeks and follow-up visits for 12 weeks post-treatment. The participants would finish follow-up visits for all clinic information even if they were terminated for the medication due to adverse events or any other reasons. The trial flowchart was shown as Figure 1.

The study procedure is outlined in Table 1, which provides a detailed schedule of the trial's timeline and key events. This trial protocol (v3.0, dated September 24, 2018) was complied with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). (Supplementary Table 1)

Data Collection and Management

This multicenter trial was conducted across 8 hospitals in the Chinese mainland, with the first patient being randomly assigned on May 17, 2018. A total of 192 patients will be enrolled in Protocol A and 184 patients in Protocol B. The trial complies with the Declaration of Helsinki. The trial has obtained ethical approval from the Institutional Review Board (IRB) of Shuguang Hospital affiliated with Shanghai University of Traditional Chinese Medicine (Approval No. 2017–560-43). Additionally, the trial has been registered on ClinicalTrials.gov with identifiers NCT02945956 (Protocol A) and NCT02945982 (Protocol B). Shanghai committee of science and technology is the trial sponsor. Professor Chenghai Liu is Principal Investigator (PI) for the clinic trial. To ensure the successful conduct of this trial, a Trial Management Group (TMG) has been established to assist with design development, coordination, and strategic management. Furthermore, an independent Data Monitoring Committee (DMC) has been formed to provide oversight into safety and efficacy considerations, sample size estimation, and study conduct (see Table 2). This committee will play a critical role in ensuring the integrity and validity of the trial results.

Clinical data management will be performed by the sponsor design according to procedures described in a comprehensive data management plan. The data management plan will include procedures for processing the data from this study. In the case where clinical data management is provided by an external vendor, the data management plan

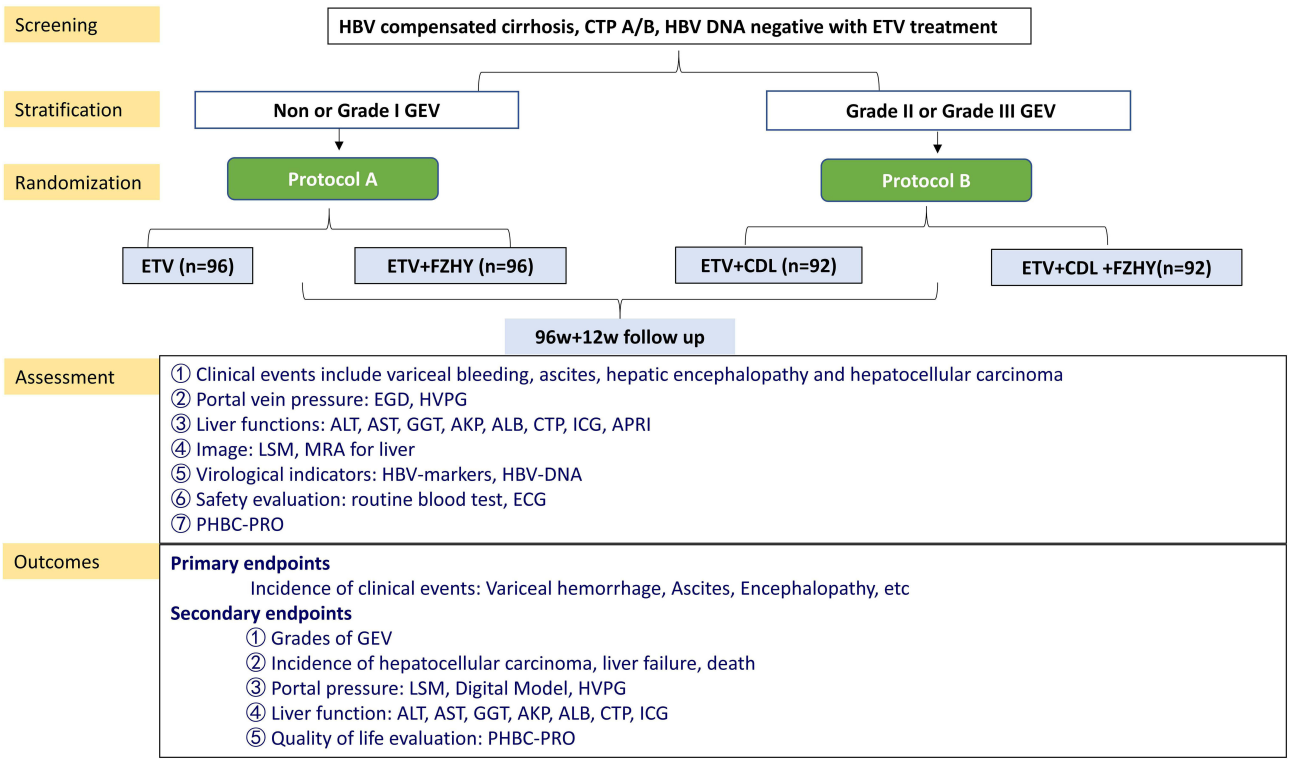

Figure 1 The flowchart of trial study and the main study design.

will describe the responsibilities of the sponsor and describe the responsibilities of the design. In particular, the data management plan will include a list of the standard operating procedures that apply to this study.

After reviewing safety and efficacy data, the DMC will recommend continuation, modification, or discontinuation of the study. Details of DMC responsibilities and procedures are specified in the DMC charter. Representatives of the sponsor will serve only as coordinators of the committees.

Table 1 Study Procedure

Items	Screening	Treatment								Follow Up
	−1wk - 0d	12wk±7d	24wk±7d	36wk±7d	48wk±7d	60wk±7d	72wk±7d	84wk±7d	96wk±7d	108wk±7d
Inclusion/Exclusion Criteria	√									
Informed consent	√									
Demographics	√	√	√	√	√	√	√	√	√	√
Past medical history	√									
Chief Complaint	√	√	√	√	√	√	√	√	√	√
Physical exam	√	√	√	√	√	√	√	√	√	√
Perceived symptoms (rating scale)	√	√	√	√	√	√	√	√	√	√
Physical signs (rating scale)	√	√	√	√	√	√	√	√	√	√
Routine analysis of Blood, Urine, Stools test	√	√	√	√	√	√	√	√	√	√
Urine pregnancy test (Female)	√									
Liver Function	√	√	√	√	√	√	√	√	√	√

(*Continued*)

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Table 1 (Continued).

Items	Screening	Treatment								Follow Up
	−1wk - 0d	12wk±7d	24wk±7d	36wk±7d	48wk±7d	60wk±7d	72wk±7d	84wk±7d	96wk±7d	108wk±7d
Coagulation	√	√	√	√	√	√	√	√	√	√
Serum glucose	√	√	√	√	√	√	√	√	√	√
Kidney Function	√	√	√	√	√	√	√	√	√	√
Serum lipids	√	√	√	√	√	√	√	√	√	√
Child-Turcotte-Pugh Scoring system (CTP)	√	√	√	√	√	√	√	√	√	√
Alpha-fetoprotein	√	√	√	√	√	√	√	√	√	√
HBV DNA	√	√	√	√	√	√	√	√	√	√
HBV-M	√		√		√		√		√	
EKG	√	√	√	√	√	√	√	√	√	√
Ultrasound	√		√		√		√		√	
FibroScan	√		√		√		√		√	
MRA, Spleen volume	√								√	
Esophago Gastro Duodenoscopy (EGD)	√				√				√	
Indocyanine green retention test (ICG)	√		√		√		√		√	
Random grouping	√									
Study Drug Dispensing and Drug Diary Supply	√	√	√	√	√	√	√	√		
Drug Diary Return and Review		√	√	√	√	√	√	√	√	
Compliance evaluation		√	√	√	√	√	√	√	√	
Drug Combination		√	√	√	√	√	√	√	√	√
Safety evaluation		√	√	√	√	√	√	√	√	√

Table 2 Trial Oversight Committees

Name	Hospital	Role
Chenghai Liu	Shuguang Hospital	Principal investigator
Yongping Mu Hongtu Gu		Co-investigator
Jing Lv		Project Secretary
Yingzi Tan Li Shen Zhaojun Tang		Head of data management
Lianjun Xing	Longhua Hospital	Co-investigator
Xiao Yu Jielu Pan		Co-investigator

(*Continued*)

 https://doi.org/10.2147/OAJCT.S525478

Table 2 (Continued).

Name	Hospital	Role
Wei Jiang	Zhongshan Hospital	Co-investigator
Lili Liu		Co-investigator
Qing Xie	Ruijin Hospital	Co-investigator
Hui Wang Baoyan An		Co-investigator
Qing Guo		Co-investigator
Xiaorong Chen	Shanghai Public Health Center	Co-investigator
Yunfei Lu		Co-investigator
Ying Zhu	First Affiliated Hospital of Dalian Medical University	Co-investigator
Liying Yao		Co-investigator
Bitao Chen	Jingzhou first people's Hospital	Co-investigator
Jing Wang	Affiliated Hospital of Traditional Chinese Medicine of Southwest Medical University	Co-investigator
Ding Zheng		Co-investigator

Eligibility Criteria

To participate in this clinical trial, patients must meet specific eligibility criteria, as outlined in Box 1. Key requirements include HBV-related cirrhosis, undetectable HBV-DNA load level experienced with ETV treatment, undergoing an endoscopic examination within 2 weeks of being recruited to assess PH.

According to IRB regulation, patients have the right to withdraw for any reason at any time during the study and guarantee that future treatment will not be affected. In addition, treatment may be terminated if the following events occur in the study. The withdrawal criteria for the trial are outlined in Box 1.

Box 1 Eligibility Criteria

General inclusion criteria

Age range from 18 to 65 years old

Cirrhosis defined by any of the following:

- Characteristic radiological findings; one or more of
  - Heterogeneous liver with irregular contour
  - Splenomegaly
  - Ascites
  - Varices
  - Recanalized umbilical vein
  - Gastroesophageal varices
- Fibrosis score > ISHAK stage 4 on liver biopsy

HBV-related defined by any of the following:

-Previous history of chronic hepatitis B

-HBsAg positive for more than 6 months

Negative HBV-DNA defined as HBV DNA < 50 IU/mL

Antiviral therapy with ETV

Child-Pugh score < 9

Capacity to provide informed consent

(*Continued*)

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Box 1 (Continued).

Subgroup inclusion criteria

Protocol A

- Non GEV without red sign
- Grade I GEV: varicose veins go straight diameter<0.3cm without red sign

Protocol B

-Grade II GEV defined by any of the following:

-Straight or slightly circuitous diameter≥ 0.3cm with red sign

-Snake-shaped, tortuous uplift diameter≥ 0.5cm without red sign

-Grade III GEV defined by any of the following:

-Beaded, nodular diameter≥ 1.0cm

-Tuberculate diameter≥1.5cm

Exclusion criteria

Taken anti-hepatic fibrosis drugs in the past 6 months

Accompanied with liver cancer

Mental history or uncontrollable epilepsy

Uncontrolled diabetic patients

Hemoglobin history and other reasons such as hemolytic anemia caused by autoimmune diseases

Severe underlying diseases, including chronic respiratory failure, circulatory failure, renal failure, etc

In situ organ transplantation (such as liver, kidney, lung, heart) or bone marrow and stem cell transplantation

Immunodeficiency patients, such as HIV infection, etc

Women in pregnancy or lactation and women planning to be pregnant during the study period

Allergic to experimental drugs

Patients who have been participated in other clinical trials

Other situations that researchers believe are not suitable for grouping

Withdrawal criteria

Any anticipated adverse events

Decompensation of liver function within 3 months after admission

Disobedience to treatment

Pregnancy in the study

Intolerant adverse events (patients or researchers can decide to withdraw from the study)

The emergence of diseases or factors that unrelated to treatment

Lost to follow-up

Recruitment

Potential recruits are approached by local clinic teams and provided with informed consent form (ICF). They are given at least 24 hours to review the document before providing their consent. Consent is obtained by appropriately trained clinicians or delegated staff members.

Sample Size Estimation

Protocol A (population with non or grade I GEV): the literature reports that the effectiveness of antiviral monotherapy for one year on stabilizing or reducing the liver stiffness measurement (LSM) was about 60% for HBV cirrhosis patients with non or grade I GEV, while the one of the combination of anti-viral and FZHY for 1 year was about 78%–90%.[10] Therefore, it is estimated that the efficacy of FZHY plus ETV on cirrhotic PH with grade I GEV for 96w treatment could receive 80%, while the antiviral was about 60%. This sample was calculated as $N = (U\alpha + U\beta)^2 \times 2 \times P \times (1 - P)/(P_1 - P_2)$,[2] $P = (P_1 + P_2)/2$, in which $\alpha = 0.05$ (bilateral), power = 0.80, p1 = 0.60, p2 = 0.80, n1: n2 = 1:1. Therefore, the sample in each group was at least 79 patients, given the withdrawal rate of about 20%, the total cases will require 192 cases with 96 cases in each group.

Protocol B (population with grade II or III GEV): According to literature reports, the effectiveness of the combination therapy with FZHY+ETV for 2 years on grade II or III GEV in PH by HBV was about 43.5%, while one of ETV

monotherapy was 15% in patients.[8] In the study, it is anticipated that the combination of FZHY plus ETV for 96 weeks could improve 20% of effectiveness compared to the control group (ETV). These samples were estimated as $N = (U\alpha + U\beta)^2 \times 2 \times P \times (1- P)/(P_1-P_2)$,[2] $P = (P_1+P_2)/2$, in which $\alpha = 0.05$ (bilateral), power = 0.80, p1 = 0.15, p2 = 0.35, n1: n2 = 1:1. Therefore, the sample of each group was at least 73 cases, with the withdrawal rate of 20%, the total sample size was 184 cases with 92 cases in each group.

Randomization

Randomizing protocols should be made before the start of study. Participants who meet all inclusion criteria and do not meet any exclusion criteria will undergo the randomization process after signing the ICF. The randomization will be carried out using a central random system. The patients will be divided into groups in a 1:1 proportion. The trial drugs will be dispatched by staff at the central clinic hospital.

Blinding

This study is designed as an open-label trial. However, to minimize bias, the experts responsible for assessing patients' outcomes will be blinded to the study arm assignments during analysis. This will help ensure that the assessments are objective and unbiased.

Interventions

All participants in this study will receive ETV as the basic treatment. In addition to ETV, participants in Protocol B will receive CDL as an adjunctive treatment. The use of anti-fibrotic herbs or products is strictly prohibited throughout the study. The detailed interventions are outlined in Table 3. Patients should take FZHY after meals. ETV and CDL must be taken on an empty stomach at the same time every day. All drugs should be stored at room temperature.

If the patient does not take FZHY or ETV, he should be told to make up the untaken dose as soon as possible within a day. If it is more than one day, he should skip the untaken dose and continue to take it the next day as required. The untaken dose should be recorded.

Primary Outcome

The primary outcome is the incidence of variceal bleeding, ascites, and hepatic encephalopathy.

Secondary Outcomes

Estimation of the 48- and 96-weeks GEV

Incidence of hepatocellular carcinoma, liver failure, and death.

- Estimation of portal pressure: Liver stiffness measurement was performed on patients at baseline and every 24 weeks using FibroScan (Echosens, Paris, France) or FibroTouch (FibroTouch-FT5000, iLivTouch series, Wuxi Hisky Medical Technologies, China). Digital Model was based on Magnetic Resonance and aspartate

Table 3 Drug Interventions

	Control Group	**Experimental Group**
Protocol A		
Treatment	ETV, 0.5mg, qd	ETV, 0.5mg, qd +FZHY, 1.6 g, tid
Protocol B		
Treatment	ETV, 0.5mg, qd + CDL, 5mg qd (first week) 10mg qd (since the second week)	ETV, 0.5mg, qd +CDL, 5mg qd (first week) 10mg qd (since the second week) +FZHY, 1.6 g, tid

aminotransferase-to-platelet ratio index (APRI) were used for estimating the portal vein pressure (mmHg) = 2.529 + 1.572 √ splenic vein diameter (mm) + 0.231 √ spleen volume/body mass index (cm3/kg) + 3.44 √ APRI, APRI = AST (ULN)/PLT ($\times 10^9$ / L) √ 100. It would be tested at baseline and 96 weeks during the study.

- Retention rate of indole cyanide green (ICG): ICG was performed on patients at and every 24 weeks using Pulse Dye Densito-Graph Analyzer (DDG-3300K, Nihon Kohden Corporation, Tokyo, Japan)
- Liver function: Laboratory examination (alanine aminotransferase, aspartate aminotransferase, glutamate aminotransferase, alkaline phosphatase, albumin, total bilirubin and routine blood): would be tested at baseline, as well as 12, 24, 36, 48, 60, 72, 84, and 96 weeks during the study and 12 weeks of follow-up after post-treatment.
- Quality of life evaluation: Traditional Chinese Medicine Liver Disease Outcome Rating Scale (PHBC-PRO): mainly based on patients' personal feelings (ie, patient reports) is used, which mainly involves consultation and is filled by patients themselves. PHBC-PRO would be tested at baseline, as well as 12, 24, 36, 48, 60, 72, 84, and 96 weeks during the study and 12 weeks of follow-up after post-treatment.

Safety Evaluation

Vital signs, physical examination, adverse events, and concomitant drugs were evaluated. In addition, electrocardiogram examination should be performed as part of safety screening.

Adverse Events

According to the classification of adverse drug reactions to develop severity, moderate and severe need to stop medication:

1. Mild adverse reactions: no treatment required, and it will not complicate the original disease. The drug that causes the reaction does not have to be discontinued, or the adverse reactions resolve after the drug is withdrawn.
2. Moderate adverse reactions: The symptoms are obvious, but the drug only causes moderate damage to important organs and systems, requiring treatment or hospitalization or delayed discharge for more than one day.
3. Serious adverse reactions: fatal or life-threatening, even reduce life expectancy, the drug causes severe organ or system damage (even transient), and last for more than 1 month.

Statistical Analysis

All patients who were randomized and took at least one dose of study medication, according to the modified Intention-to-treat principle, were included in the full-analysis set (FAS). Patients who fully complied with the protocol and with good treatment compliance were included in the per-protocol set (PPS). Safety analyses (SS) were conducted among patients who received at least one dose of study drug. The primary efficacy analysis was completed for the FAS and the PPS. A secondary efficacy analysis was performed on the FAS population.

Logistic regression analysis was used to compare the differences between groups in the primary efficacy, with age, sex, and course of disease as covariates. Between-treatment comparisons of the continuous data of secondary efficacy were performed using the *t*-test or the Wilcoxon rank sum test dependent on variable normality. The categorical data of secondary efficacy were compared by Chi-square test or Fisher's exact test.

Safety analyses will be performed in all subjects treated. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All TEAEs, Grade 3–4 AEs, treatment-related AEs, Grade 3–4 treatment-related AEs, SAEs, treatment-related SAEs, and AEs leading to discontinuation will be tabulated using worst grade per NCI CTCAE v 5.0 criteria by system organ class and preferred term.

A two-sided P value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed with SAS 9.4 software (SAS Inst., Inc., Cary, NC, USA)

Ethics

This study must be approved by the Hospital Medical Ethics Committee, and the enrolled patients sign an informed consent. After treatment, eligible participants shall receive 12-weeks follow up visit for their quality of life and serum liver function tests, etc.

Discussion

A normal portocaval pressure gradient of less than 5 mmHg between the portal vein and the inferior vena cava is crucial for maintaining normal portal blood circulation in healthy individuals. When this pressure gradient exceeds 5 mmHg, PH occurs, which plays a key role in the pathological progression of chronic liver diseases (CLDs). PH is a significant contributor to various complications, including ascites, encephalopathy and variceal bleeding. PH is also a leading cause of death and liver transplantation in patients with CLDs. Although the non-cirrhosis causes of PH received increasing attention recently, such as the prehepatic vein occlusion by splenic vein thrombosis and post-hepatic obstacle by Budd-Chiari syndrome, etc.[11] Liver cirrhosis was still the most common etiology for PH. As the PH developed, cirrhosis could transit from compensated into decompensated state, characterized by ascites and variceal hemorrhage, etc. Therefore, managing cirrhosis PH is essential to prevent complications and improve patient outcomes.

The main underlying mechanisms of PH involve an increase in both resistance to portal flow and portal venous inflow.[12] In cirrhosis, fibrous tissue accumulates, nodules form, and blood vessels are distorted. These changes increase IHVR, leading to elevated portal pressure. Subsequently, splanchnic vasodilation occurs, increasing portal blood flow and further raising the pressure. Therefore, the PH could be reduced mechanically by placement of TIPSS or by pharmacological therapy according to the mechanical bases. Studies from the 1960s and 1970s showed that the use of surgical shunts to prevent first variceal bleeding reduced the risk, but it increased the incidence of HE and mortality.[13] It has been extrapolated from these data that prophylactic TIPSS to prevent first variceal hemorrhage in the setting of compensated cirrhosis with high-risk varices should not be recommended. As for medicine, elimination or control of the underlying etiologies such as antiviral, immunosuppression, and alcohol cessation may reduce PH. The options targeting splanchnic vasodilation were effective, such as NSBB, terlipressin, somatostatins and analogues. However, the initial and pivot factor—IHVR was still lacked. As mentioned above, liver fibrosis was the major cause of IHVR. Therefore, efforts should be made to improve liver fibrosis. However, focusing on improving liver fibrosis to restore the hepatic architecture is still an unmet need.

FZHY is a patent botanic product composed of 6 herbs, with an indication for liver fibrosis approved by the Chinese Food and Drug Administration in 2002. The previous evidence had approved that FZHY could improve liver fibrosis due to HBV,[5] and the Phase II clinical trial in the US indicated that FZHY also could stabilize and improve liver fibrosis due to hepatitis C virus.[6] Animal experiments had shown that FZHY could alleviate portal pressure with dimethylnitrosamine-induced cirrhosis in rats.[7] The accumulated data had showed that the mechanism underlying FZHY against liver fibrosis were multiple and complicated,[14] among them, the inhibition of HSCs activation, and improvement of LSECs de-differentiation and hepatic sinusoidal capillarization were predominant.[15,16] Therefore, it could be postulated that FZHY may be capable of improving the intrahepatic resistance through its effect on liver fibrosis and hepatic microcirculation and contributing to reducing the PH in cirrhosis patients.

In this trial, cirrhosis patients were stratified into two subgroups based on the degree of GEV observed by endoscopy. Each subgroup was then randomly divided into a control group and an experimental group according to a specific protocol. The control group received ETV for antiviral treatment, and the experimental group received ETV plus FZHY for anti-fibrosis. Additionally, patients with grade II and III GEV received CDL on top of their other medications. After 96 weeks treatment, the decompensation events in the patients including ascites, bleeding and HE etc. would be observed as the primary endpoint, as well as GEV and portal pressure would be observed too. Meanwhile, we may analyze clinical serum samples to investigate gene expression profiles using RNA sequencing, proteomics and other techniques for a more comprehensive study.[17] These methods will allow us to identify genes and proteins that show significant differences in expression before and after treatment with FZHY. Furthermore, signaling pathways associated with PH to clarify the regulatory mechanisms of FZHY.

The protocol had several limitations, for example, a single-blind design could inherently carry the risk of assessment bias. This potential bias could result in an exaggerated perception of symptom improvement, ultimately compromising the accurate assessment of the treatment protocol's true effectiveness. These problems could be minimized by training for standard assessment and multiple parameters design etc.

In conclusion, with this trial, the efficacy and safety of the combination therapy with ETV and FZHY on cirrhosis PH were evaluated, and the result could provide a new regime for PH with combination of anti-viral and anti-liver fibrosis products.

Trial Status

Protocol version: 3.0, dated Sept 24, 2018. Recruitment is completed, data collection still in progress, started May 17, 2018, and anticipated end date is March 29, 2023.

Abbreviations

ALB, albumin; ALT, alanine aminotransferase; AKP, alkaline phosphatase; AST, aspartate aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; CTP, Child-Turcotte-Pugh; CDL, carvedilol; CLDs, chronic liver diseases; DMC, data Management Controller; GEV, gastroesophageal varices; GGT, glutamate aminotransferase; ECG, electrocardiogram; ETV, entecavir; EDC, electronic Data Collection; eCRF, electronic Case Report Form; FZHY, FuZheng HuaYu; HBV, hepatitis B virus; HVPG, hepatic venous pressure gradient; HIV, human immunodeficiency virus; ICG, Indocyanine green; IHVR, intrahepatic vascular resistance; LSM, liver stiffness measurement; MVD, microvessel density; NSBB, non-cardioselective β-blocker; PI, principle Investigator; PH, Portal hypertension; PHBC-PRO, patient reported outcomes of post-hepatic B cirrhosis; PPS, per protocol set; TIPSS, transjugular intrahepatic portosystemic stent shunt; TCM, Traditional Chinese medicine.

Data Sharing Statement

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG.

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Author Contributions

Zhengxin Li and Yanan Guo contributed equally to this article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Prof. Dr. Chenghai Liu reports a patent "Fuzheng Huayu tablet" issued as the fifth inventor (patent no: ZL9911 3887.2). The authors of this paper have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

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