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Opinion paper

Safety and therapeutic effects of anti-fibrotic Traditional Chinese Medicine Fuzheng Huayu on persistent advanced stage fibrosis following 2 years entecavir treatment: Study protocol for a single arm clinical objective performance criteria trial

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ABSTRACT

Background: Hepatitis B virus (HBV) infection is an important etiology for chronic hepatitis globally, and especially so in China. HBV infection can lead to the development of cirrhosis through the pathological process of liver fibrosis. The effective suppression of HBV replication with NAs or interferon-alpha can histologically regress the fibrotic pathological process, but there remain patients who have achieved anti-viral responses and normalization of serum liver tests, but not liver fibrosis regression. This subset of patients typically presents with advanced liver fibrosis at baseline. Therefore, it is reasonable to administer the anti-fibrotic agents, coupled with antivirals for patients with advanced liver fibrosis due to HBV, in order to improve the fibrotic regression of the patients. Fuzheng Huayu (FZHY) tablet is a botanical product with evidence demonstrating its efficacy against mild to moderate liver fibrosis. The current clinical trial evaluates the efficacy and safety of the combination therapy of traditional Chinese medicine (TCM) (FZHY and herbal granule) and entecavir for HBV compensated cirrhosis. We will enroll HBV patients who presented with a good viral response after 2 years of entecavir treatment but had advanced liver fibrosis (≥Ishak F5).

Methods: This is a single-arm clinical trial, conducted in 20 centers in mainland China over a period of 60 weeks, including 48 weeks of treatment observation and 12 weeks of follow-up. The main inclusion criteria include HBsAg positive more than 6 months, 2 years administration of entecavir, HBV DNA less than 20 IU/ml, liver fibrotic stage ≥ F5, and Child-Pugh scoring <7 (Stage A). The sample size is estimated to be about 190, considering a 20% drop-out and 60% of patient's compliance for the second liver biopsy so a total of 350 participants will be enrolled. All eligible participants are divided into 3 subgroups according to the TCM clinic pattern. And all patients will take 1 Entecavir tablet (0.5 mg) per day, 4 FZHY tablets (1.6 g) three times a day, and specific TCM granule three times a day, which is decided by TCM clinical patterns (CPs) differentiation. The patients were treated for 48 weeks, and follow-up visits at 12, 24, 36, 48 weeks and 60 weeks. The patients will receive the second liver biopsy at the end of 48 weeks, with a 12 weeks follow-up after that.

The primary endpoint is the proportion of subjects with a 1-point improvement of liver fibrosis stage using the Ishak score from baseline to week 48 in the study, according to consensus readings evaluated by a panel of hepato-pathologists. The secondary endpoints are the brightness-mode ultrasonic, fibrotic biomarkers. The adverse events (AEs) will be recorded for 60 weeks, and the safety of the combination therapy will be evaluated. Meanwhile, the efficacy in the 3 sub-groups will be stratified and analyzed.

Abbreviations: AEs, adverse events, CPs, Clinical Patterns, CRO, Central Clinical Research Organization, CRC, Clinical Research Coodinator, EDC, Electronic Data Collection, FZHY, FuZheng HuaYu, GMP, Good Manufacturing Practice, HBV, Hepatitis B virus, HSCs, Hepatic Stellate Cells, NMPA, National Medical Products Administration, NAs, Nucleos(t)ide analogues, OPC, objective performance criteria, PDGF-BB, Platelet Derived Growth Factor-BB, PHBC-PRO, patient reported outcomes of post-hepatitic B cirrhosis, PI, principal investigator, TCM, Traditional Chinese medicine, TGF-β1, Transforming Growth Factor-beta 1, US FDA, United States Food and Drug Administration, WHO, World Health Organization

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ABSTRACT

Discussion: The study has been designed to test the therapeutic effects and safety of the combination therapy of FZHY and herbal granule with entecavir on persistent advanced stage fibrosis/cirrhosis following 2 years entecavir treatment, and to explore an effective integrative therapy on HBV cirrhosis.
Trial registration: ClinicalTrials.gov. NCT02241616. Registered on September 16, 2014.

1. Background

There has been accumulated evidence showing the effective suppression of HBV DNA, with nucleos(t)ide analogues or interferon-alpha for chronic hepatitis B, can also regress liver fibrosis in chronic hepatitis B, and may even attenuate cirrhosis [1]. The largest study about HBV-related cirrhosis in patients with tenofovir conducted by Marcellin showed the reversal of fibrosis was observed in 74% patients (n = 96 cirrhotic at baseline) [2]. Similar studies have shown regression of cirrhosis in smaller cohorts with a variety of anti-viral drugs including entecavir, lamivudine, and adefovir [3–7]. While it is exciting that cirrhosis can be clinically regressed with successful long-term suppression of HBV replication, there remain some patients who are under effective viral suppression and show normal liver function test, but are not showing liver fibrosis regression.

One explanation for this situation is that there remains a lack of a reliable assessment of the changes in pathology stages for cirrhotic patients. Even Ishak or other scoring system cannot be applicable for all situations. Although some patients may appear to be in stable fibrosis stage, but changes in the qualities of fibrosis, from actively progressive forms to quiescent regressing forms has been observed [8]. Even when these features are evaluated using a new Beijing Classification, some patients may still not show histologic improvement [9]. Therefore, there are unmet needs for the treatment of advanced stage CHB. It is necessary to find a novel and complementary treatment that directly targets the persistently active liver scarring in patients who have shown effective anti-viral responses.

While the United States Food and Drug Administration (US FDA) has not approved any chemical or biological anti-liver fibrotic drugs, we have a long history and rich experience in treating chronic liver diseases with TCM in China. TCM emphasizes clinical profiles based individual treatments, most with composition recipes of botanical herbs reflective of the clinical profile. Recent decades have witnessed a remarkable progress in TCM on liver diseases with herbal products approved by the Chinese National Medical Products Administration (NMPA) for the indication of liver fibrosis after years of experimental research and clinic trials [10]. FZHY, either in capsule or tablet form, is one of the NMPA approved anti-fibrotic botanical products, is invented, and developed by Institute of Liver Disease Shanghai University of Traditional Chinese Medicine. FZHY consists of 6 herbs, with standard quality control and manufacturing (Table 1 and supplementary information). The safety and efficacy were demonstrated through clinical trials inclusive of multiple centers, conducted during 2000–2001, with 93 liver fibrosis patients [11] (experimental: control ratio of 50:43). Participants in these studies underwent liver biopsies before and after treatment, and the results showed that some patients with early and intermediate stage CHB (Metavir F2 to F3, Ishak 3 to 4) showed liver fibrosis regression with 24 weeks of FZHY-treatment.

Table 1
FuzhengHuayu (FZHY) formulation (g/daily dose).

Chinese name	Plant sources	Medicinal parts	Preparation amount (g)
Danshen	*Salvia MiltiorrhizaeBge (Labiatae)*	radix	8
Chongcao	artificial fermentation *cordyceps*	mycelia	4
Taoren	*Prunuspersica* (L.) Batsch (Rosaceae)	fruit	2
Jiaogulan	*Gynostemmapentaphyllum* (Thunb)	whole herb	6
Songhuafen	*Pinusmassoniana*Lamb (Pinaceae)	pollen	2
Wuweizi	*SchisandraeChinensis* (Turcz.) Baill	fruit	2

Despite the success of FZHY as an adjunct to anti-viral suppressive therapy for improving the resolution of CHB-associated fibrosis in early and intermediate stages of CHB, the question of its efficacy and safety in advanced stage patients has not been investigated, particularly in patients with an undetectable HBV DNA level after NAs treatment but still suffer from advanced liver fibrosis. To evaluate its effectiveness and safety in this setting, patients with Ishak stage 5 or 6 CHB following two years of entecavir treatment will be treated with FZHY. We will evaluate whether the addition of FZHY further improves this cohort's fibrosis stages or, at the very least, shift existing scarring from progressive to regressive forms.

2. Objective

The objective of this study is to evaluate the safety and efficacy of integrative medicine (TCM + Western medicine) treatment in HBV compensated cirrhosis who have achieved virologic response and to evaluate the improvement of liver fibrosis stage (Ishak stage).

3. Method and design

3.1. Design/setting

It is a single-arm objective performance criteria (OPC) clinical trial conducted in 20 clinical centers in China spanning 48 weeks, followed by 12-weeks clinical follow-up period (Fig. 1). After training, all the clinical centers will conduct patient recruitment, screening, and follow-up independently. After 48 weeks, the liver biopsies obtained at baseline and after treatment will be compared and evaluated. Clinical trial sites will be supervised by a central Clinical Research Organization (CRO).

A total of 350 patients with hepatitis B cirrhosis who meet diagnostic criteria and inclusion criteria are enrolled across 20 clinical centers nationwide. Each patient will sign an informed consent form before screening.

Patients who have been enrolled in the study will be treated with a 48-weeks drug therapy, and all patients will be followed up on their health status every 12 weeks during this period. At the same time, they will complete a clinical symptom scale according to self-perception (Table 2).

3.2. Diagnostic criteria

The guidelines for the prevention and treatment of chronic hepatitis B (2010 edition) will be used, jointly formulated by Chinese Medical Association [12].

3.3. Inclusion criteria

- Hepatitis B history or more than 6 months history of positive HBsAg
- 2 years of entecavir treatment, serum HBV DNA undetectable (<20 IU/ml), but no immunological response (HBeAg

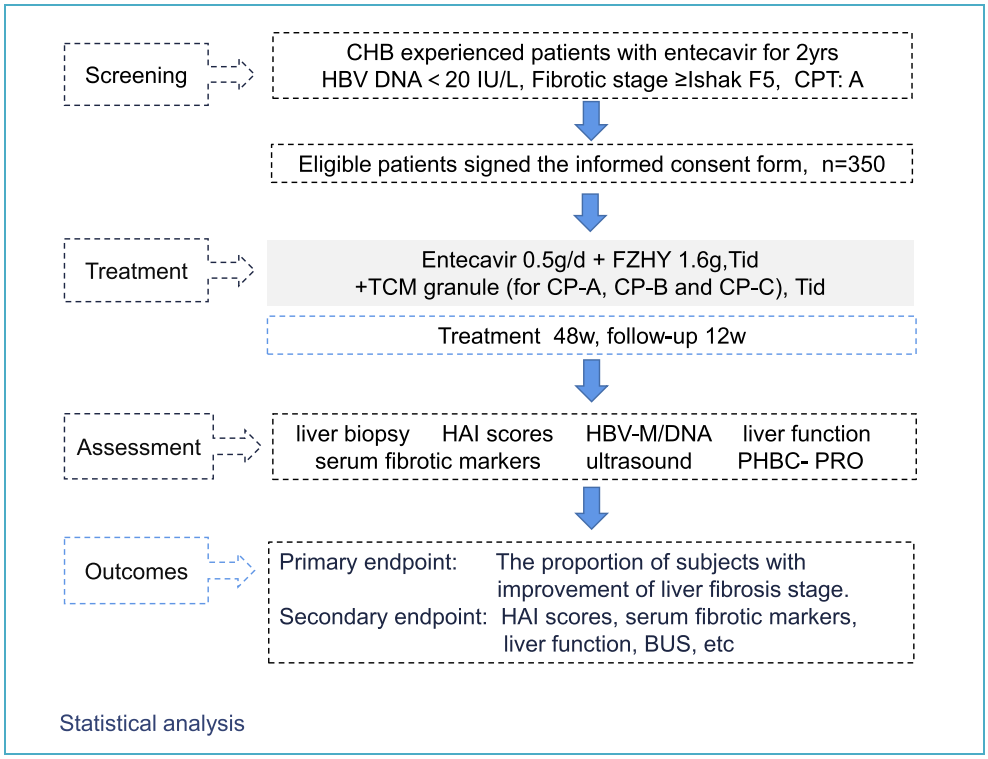

Fig. 1. The flowchart of trial, a summary of the planned study interventions and assessments.

Table 2
Study procedures.

Items	Screening	Treating				Following
	-3d to0d	12 wk±7d	24 wk±7d	36 wk±7d	48 wk±7d	60 wk±7d
Inclusion/Exclusion Criteria	×					
Informed consent	×					
Demographics	×	×	×	×	×	×
Past History	×					
Chief Complaint	×	×	×	×	×	×
Physical exam	×	×	×	×	×	×
Symptom (Rating Scale)	×	×	×	×	×	×
Sign (Rating Scale)	×	×	×	×	×	×
Routine Analysis of Blood, Urine, Stools	×	×	×	×	×	×
urine pregnancy test (Female)	×					
Liver Function	×	×	×	×	×	×
Coagulation studies	×	×	×	×	×	×
Glucose	×	×	×	×	×	×
Alpha-fetoprotein	×	×	×	×	×	×
Kidney Function	×	×	×	×	×	×
Serum lipid	×	×	×	×	×	×
HA/Collagen III/IV/I	×		×		×	×
HBV DNA	×	×	×	×	×	×
HBV-M	×		×		×	×
HIV antibody	×					
FibroTest	×		×		×	×
EKG	×	×	×	×	×	×
Ultrasound	×	×	×	×	×	×
Liver biopsy	×				×	
Study Drug Dispensing and Drug Diary Supply	×	×	×	×		
Study Drug Return and Accountability, Drug Diary Return and Review		×	×	×	×	
Compliance evaluation		×	×	×	×	
Drug Combination		×	×	×	×	×
Safety		×	×	×	×	×

seroconversion and HBsAg loss in HBeAg-positive patients; HBsAg loss or anti-HBs seroconversion in HBeAg-negative patients)
- Ages 18-60
- Ishak fibrosis score of the biopsy ≥5 within 6 months

- Child-Pugh <7 (Stage A)
- Patient is willing and able to provide written informed consent

3.4. Exclusion criteria

- Decompensated liver cirrhosis
- Hepatocellular Carcinoma
- Liver histology conforming to other chronic liver diseases, such as non-alcoholic fatty liver disease, chronic hepatitis C, chronic hepatitis D, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, inherited metabolic liver disease, drug or toxic induced liver injury, parasitic infections, alcoholic liver disease
- Psychiatric history or uncontrolled epilepsy
- Uncontrolled diabetes mellitus
- History of hemoglobin disease (such as alpha- or beta-thalassemia, sickle cell disease, spherocytosis) or patients with toxic or autoimmune hemolytic anemia
- Severe underlying or systemic disease like chronic respiratory failure, cardiovascular disease, kidney failure etc.
- In situ organ transplantation (such as liver, kidney, lung and heart) or bone marrow transplantation and stem cell transplantation.
- Immunocompromised patients such as untreated HIV infection or receiving immunosuppressive therapies (e.g. glucocorticoid compounds, cyclosporin, azathioprine, adrenocortical hormone) within 3 months or chemotherapy drugs (such as cyclophosphamide, ammonia and cancer chemotherapy) and radiation therapy.
- Women who were pregnant or nursing and who planned to become pregnant during the study period.
- Patients who are allergic to the experimental drug.
- History of using other antiviral medication except entecavir or any anti-fibrosis drug(s) within 6 months.
- Patients who are participating in other clinical trials.
- Other situations in which the principal investigator (PI) thinks the patient should be excluded.

3.5. Intervention

All patients will take 1 entecavir tablet (0.5 mg) per day, 4 FZHY tablets (1.6 g) and specific TCM granule three times a day, which is decided by CPs differentiation. All the interventions will be sustained for 48 weeks.

The CPs differentiation and treatment scheme are based on the guidelines which is formulated by the liver disease committee at the Chinese Association of Integrative Medicine [13]. Two specialists with intermediate professional titles will differentiate the CPs according to the patient's symptoms and signs. If the opinions between two physicians are consistent, the type of CPs shall be determined. Otherwise, a specialist with senior professional title shall finally confirm the type of CPs. The patients were clinically assessed into three CPs subgroups as followed, and each will be treated with the appropriate, corresponding TCM Granule.

CP-A.

Main symptoms: 1. Pain in the ribs; 2. Emotional depression; 3. Anorexia or abdominal distension; 4. Lassitude.

Minor symptoms: 1. Tastelessness; 2. Loose stool; 3. Belching; 4. Distending pain in breast or breast lumps; 5. Light red tongue, with thin white or thin yellow fur; 6. Wiry and slow pulse. Subjects who meet one of the main symptoms 1, 2 and one of the main symptoms 3, 4, as well as two minor symptoms, will be assessed with this CPs and be given the TCM Granule XiaoYaoSan.

CP-B.

Main symptoms:1. Bright yellow skin and eyes; 2. Dark urine; 3. Dry mouth, bitter taste or ozostomia; 4. Yellow fur on tongue.

Minor symptoms: 1. Abdominal fullness and distention or anorexia; 2. Nausea or vomiting; 3. Constipation; 4. Fullness in chest and rib-side; 5. Wiry and slippery pulse or wiry and rapid pulse. Subjects who meet two main symptoms and two minor symptoms will be assessed with this CPs and be given the TCM Granule YinChenHaoTang.

CP-C.

Main symptoms: 1. Dizziness and tinnitus; 2. Lumbago or soreness and weakness of waist and knees; 3. Dysphoria in chest, palms, or soles; 4. Insomnia and dreaminess.

Minor symptoms: 1. Dull pain in rib-side that worsens when tired; 2. Dry mouth; 3. Low grade fever; 4. Red tongue with less fur 5. Thread-like pulse. Subjects who meet two main symptoms and two minor symptoms will be assessed with this CPs and be given the TCM Granule YiGuanJian

The drug administrator shall receive, store, distribute and withdraw the drug in accordance with relevant laws and regulations. Other medicines that treat the disease will be prohibited during the trial. If other medications are used, the clinical research coordinator (CRC) will record and fill in the combination of medications used. If the patients have abnormal liver function (ALT > 2 x ULN) during the treatment process, the investigator may use drugs that will protect the liver, including glutathione, polyene phosphatidyl choline, silymarin and liquorice preparations such as compound ammonium glycyrrhizinate and compound glycyrrhizin according to the patient's condition.

4. Patient and public involvement

Patients and the public will not be involved in the development of the research question or in the design of the study. Patients will receive oral and written information about this trial, however, they will not be involved in the recruitment and conduct of the study. After signing an informed consent, the participants will be assessed for eligibility and data collection will begin. Dissemination of the general results (no personal data) will be made on demand.

5. Materials/laboratory analyses

Liver biopsy has been proven to play an important role in the evaluation of liver fibrosis. Participants will undergo a fine-needle liver biopsy at week 0 and week 48. The subjects will provide their blood and bodily fluid for laboratory analysis according to the study procedure. The liver tissue and serum samples will be stored in an equipped BioBank, in which temperature and humidity is strictly regulated.

6. Outcomes

6.1. Primary endpoint

The primary efficacy endpoint of the study is the proportion of subjects with a 1-point improvement of liver fibrosis stage using the Ishak score from baseline to week 48 in the study.

Four pathologists will form an assessment panel, among them one pathologist will function as a coordinator to organize the scoring activity and deal with the disagreements among the pathologists. The final fibrosis score will be obtained by the consensus from 2 or more pathologists.

6.2. Secondary endpoints

(1) Serum fibrotic markers: FibroTest (PT + γ-GT + Apo-A1 + α2 macroglobulin + TBil + haptoglobin), PIIIP, LN, HA, Col- IV
(2) The Ishak HAI score before and after treatment. The efficacy is recognized as: (1) Improvement of inflammation≥2, (2) No improvement, (3) Worsened≥2

(3) Liver stellate cell activation
(4) Liver imaging examination: BUS
(5) Serum liver function (Serum bilirubin, Alanine aminotransferase, Aspartate aminotransferase, γ-glutamate amino transferase, Alkaline phosphatase, Albumin)
(6) Serum HBV biomarkers (HBsAg, HBsAb, HBeAg, HBeAb, HBcAb) and HBV DNA
(7) Change of PHBC-PRO (patient reported outcomes of post-hepatitic B cirrhosis)score.

6.3. Sample size

The histological improvement (more than 1-point decrease in Ishak score) rate by entecavir for 48 weeks was estimated to be 39% based on previous studies [14]. The primary hypothesis is that the improvement rate of the combined treatment will be a goal of 54% which is 15% more than entecavir mono-therapy, and non-inferiority will be established if the 1-sided 97.5% CI of the effective rate is more than 44% (objective performance criterion, pre-specified no inferiority margin 10%). A sample size of 199 achieves 80% power to detect a difference (the difference to be detected by the study) of −0.10 based on a significance level of $\alpha = 0.025$, using a one-tailed exact test. Compensating for probable participant dropout (20%) and second liver biopsy completion rates (70%) of liver biopsies after treatment, the sample size could be expanded to 350.

6.4. Recruitment

The subjects are patients with advanced stage cirrhosis caused by hepatitis B, who visit the clinical centers for follow up after 2 years of entecavir therapy for perceived persistent feelings of being unwell, or clinically suspected, or documented persistent advance stage disease. The researchers will present the details of our trial to patients who meet the diagnostic criteria and obtain their consent to be screened by a series of clinical tests. The eligible participants will be enrolled in the study for further trial.

6.5. Data collection

Both paper and electronic case report forms are designed according to the protocol and the data collection guide is formed. A professional data company is hired to train CRC from the clinical centers according to data collection guideline. All staff must successfully complete applicable project trainings before data collection.

6.6. Data management

The trial adopted an electronic data collection (EDC) management system. The CRC of every clinical center is required to input data accurately and promptly. The data will be reviewed by data administrators and erroneous data will be removed and be sent back to the center.

6.7. Data access

The EDC management system uses a dual control of user role authorization. All users need to fill out the application form, and the system administrator will give them different access permissions according to their different roles in the trial. For example, researchers of each center can only see and revise the content of their own center. Meanwhile, the CRO staff can read the EDC data of each center, but have no right to modify the data.

6.8. Data monitoring

The study will be monitored for quality and regulatory compliance. Monitoring will be performed by Shanghai BioGuider Medical Technology Co. Ltd. The monitoring frequency will be once or twice a quarter, depending on inclusion rates, questions, and pending issues from earlier audits. They will review study records on-site and directly compare them with source documents, discuss the conduct of the study with the investigator, and assess the data quality and study integrity.

6.9. Harms

At the follow-up assessment, participants will be asked to report any new adverse symptoms. Any adverse medical event that occurs during the 60-week study, regardless of its relation to the test drug, should be determined as an adverse event. All adverse event should be recorded in the CRF including time of occurrence, severity, duration, measures and recurrence.

7. Statistical methods

7.1. Analysis sets

The analyses are performed on an intention-to-treat basis. First, we will do descriptive summary statistics for all the data: frequencies, percentages and two-sided 95% confidence interval for categorical variables; and mean, standard deviation, median, minimum, and maximum values for continuous variables. The primary efficacy analysis is performed by testing whether histological improvement rate is greater than 44% at exact one-side 97.5% confidence intervals based on the Clopper-Pearson method, Safety summaries for adverse events regardless of relationship to study drug by System Organ Class and PT will be performed on the Safety Set. Analyses are performed with SAS 9.2 software (SAS Institute Inc, Cary, NC).

7.2. Protocol amendments

Any modification to the protocol, which may affect the conduct of the study, potential benefit of the participants, or participant safety, would require a formal amendment and must be signed off by the principal investigator. Such amendments will be submitted to the ethics committee for review and approval.

7.3. Confidentiality

As stated in the informed consent, information provided as part of the study will be kept confidential and will not be shared with anyone outside the study. We take numerous measures to protect participant confidentiality, including; (1) all data and information is only accessible to study staff and a limited number of data company staff (2) secure storage (e.g., locked file cabinet located in secure building, folder located on password-protected servers located in secure building); of study documents (paper or electronic) containing both participant name and study information.

8. Discussion

Although the incidences of new cases of hepatitis B virus (HBV) infection have since fallen dramatically with the availability of an effective vaccine since 1980, there remains an estimated 350 million people worldwide who chronically infected with the virus [15]. According to the World Health Organization (WHO), about 30% of the global deaths from cirrhosis in 2002 were HBV-related cirrhosis [16]. Most patients, particularly those infected at birth or in early childhood—

which includes most Asian patients—typically develop chronic infection and may experience liver disease progression. Liver fibrosis, characterized as an overproduction and deposition of extracellular matrix in liver, is an important pathological process in chronic hepatitis B. As the liver fibrosis progresses in chronic hepatitis B patients, it could lead to liver cirrhosis and its complications, threatening the patients' health and life. Therefore, it is a crucial strategy to inhibit or reverse liver fibrosis progression for chronic hepatitis and cirrhotic patients due to HBV and other reasons.

The eradication of etiologies for liver fibrogenesis is of course the first option for treatment of fibrotic patients. The accumulated evidence has proved that effective suppression of HBV DNA, with nucleos(t)ide analogues (NAs), can regress liver fibrosis in chronic hepatitis B, and may even regress cirrhosis histologically [1]. However, the efficacy of anti-fibrosis with NAs has some limitations, and almost a third of patients with chronic hepatitis B did not have liver fibrosis regression, especially those with advance fibrotic stages even after prolonging NAs treatment. While confirmation that cirrhosis can clinically regress with successful long-term suppression of HBV replication is exciting, in all of these studies, there remain patients who show effective suppression and normalization of serum liver tests, but with no regression of liver fibrosis. In our current trial, all the patients have received entecavir treatment for 2 years. Although these patients have obtained viral and biochemical responses, as demonstrated by normal test liver functions and undetectable HBV DNA, they still present with advanced liver fibrosis. Therefore, it is reasonable to give the patients the anti-fibrotic agents together with anti-virals. This combination of anti-fibrotic with an effective anti-viral drug would be most useful for liver fibrosis due to HBV and benefit entecavir-treated patients who did not get histological responses.

FZHY is a botanical product, which consists of 6 herbs and manufactured according to Good Manufacturing Practice (GMP) standards. In our previous studies, FZHY was found to reduce extracellular matrix deposition [17,18]. It may have a complex or comprehensive action mechanisms, including the inhibition of hepatic stellate cells (HSCs) activation through regulating cytokines signaling such as transforming growth factor-beta 1 (TGF-β1) and platelet derived growth factor-BB(PDGF-BB) [19], protection of hepatocyte apoptosis [20], decreased injury associated elevated portal pressure [21], and improvement of capillarization of sinusoidal endothelium [22]. In a clinical study, FZHY has shown the beneficial effects on chronic hepatitis B patients with moderate liver fibrosis [11]. However, the effect of FZHY on patients advanced liver fibrosis is not known, and the efficacy and safety of FZHY and ETV combination therapy on cirrhosis due to HBV has yet been evaluated.

In the study, there is a single arm due to the ethnic considerations, the sample size was estimated as the target value as a control according to the literature reports. As far as we know, patients receiving entecavir for one year could get a maximum fibrosis regression of 39% [14], but participants were heterogeneous, including moderated fibrosis and most are naive patients. According to TCM theory, the patients with liver fibrosis had the common or core clinic pattern (Zheng insufficiency and Blood stasis), but different patients could have 3 kinds of accompanying clinic pattern. In clinical practice by Chinese doctors, the patients were prescribed the herbs targeting the core pattern plus herbs targeting the specific accompanying pattern. This intervention seems to be complicated, but accord with the TCM theory and practice reality, would improve the patients' compliance during the trial and widely application later if the trial get the expected results.

Trial status

The recruitment of the trial is still ongoing.

Declarations

Ethics approval and consent to participate

This clinical trial complies with the Helsinki declaration and the relevant Chinese regulations on clinical trial research. Before starting, the study protocol with the written informed consent forms have been peer reviewed and approved by the Institutional Review Board at Shuguang Hospital, Shanghai University of TCM (approval No.2014-331-27-11). Each patient must provide a written informed consent prior to admission to the study. Patients can be selected for clinical trials after the informed consent form was signed voluntarily. Informed consent shall be kept for reference.

Consent for publication

Not applicable.

Funding

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Authors' contributions

Chenghai Liu conceive the study and revise the manuscript. Zhimin Zhao was major contributors to the writing of the protocol. Yangyi Chen and Haina Fan prepare manuscript. All authors read and approved the final manuscript. All of them were involved in the implementation of the trial.

Availability of data and materials

The datasets used and/or analyzed after the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2020.100601.

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