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Research Article

The Efficacy of Treating Pulmonary Fibrosis and Pulmonary Function Injury in COVID-19 with Fuzheng Huayu Tablets: Study Protocol for a Multicenter Randomized Controlled Trial

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ABSTRACT

Introduction: The patients with COVID-19 could be suffered from pulmonary dysfunction and/or fibrosis in recovery period, but there are no certain drugs or treatment to cope with this situation. Our previous studies indicated that Fuzheng Huayu tablets (FZHY) could regress lung fibrosis induced by bleomycin in animals, and improve pulmonary function in patients with chronic obstructive pulmonary disease. Now we design this trial in order to evaluate the effects of FZHY on pulmonary fibrosis and/or pulmonary function injury in the recovery period of COVID-19 and expect to improve the prognosis.

Methods and analysis: This is a randomized, double-blinded, multicenter, placebo-controlled clinical trial from March 1, 2020 to December 31, 2021. 160 patients who had been diagnosed with COVID-19 were enrolled, but currently they are negative in viral test and have developed pulmonary fibrosis or pulmonary dysfunction. They are randomly assigned into control group and experimental group. All patients are given basic treatment such as respiratory function rehabilitation training and vitamin C. The experimental group is given FZHY meanwhile the control group is given placebo. Each patient will be observed for 24 weeks and followed up for 8 weeks. The primary outcome of this trial is the improvement proportion of lung fibrosis judged by HRCT score. Secondary outcomes include six-minute walk distance, clinical symptoms score, oxygen saturation, quality of Life-BREF Score, patient health questionnaire-9 Score and general anxiety disorder-7 score. The safety will also be observed.

Ethics and dissemination: This study has been approved by the IRB of Shuguang Hospital affiliated with Shanghai University of TCM. The results will be presented at national as well as international conferences. The final manuscript will be published in a peer-reviewed journal.

Trial registration number: NCT04279197.

Keywords: Fuzheng huayu tablets (FZHY); Pulmonary fibrosis; Pulmonary function injury; COVID-19; Randomized Controlled Trial (RCT)

INTRODUCTION

On February 11, 2020, World Health Organization (WHO) announced in Geneva that pneumonia infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was named "COVID-19" and characterized COVID-19 outbreak as a "pandemic" on March 11 [1]. Until Feb 1, More than 100 million cases of COVID-19 have been reported globally, including 2,222,647 deaths [2]. The clinical manifestations of COVID-19 are varied, ranging from asymptomatic or mild infections to acute respiratory distress syndrome (ARDS) [3-6]. Unfortunately, although the epidemic is still spreading, apart from social isolation, humans still do not have effective ways to treat COVID-19 [7].

The natural history and prognosis of COVID-19 is not fully understood yet. However, there are increasing evidences indicating that lung fibrosis existed in part of patients with COVID-19. In critical patients who received lung transplantation or took autopsy after death, obvious pulmonary fibrosis was

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observed in their lungs [8,9]. After nucleic acid test (RNA) of SARS-Cov2 became negative or at undetectable level in test twice, these patients were considered as in "recovery phase". However, a lot of patients were not fully recovered actually. About 90% of cases in 90 Patients with COVID-19 pneumonia had residual lesions in computed tomography (CT) scan [10]. Serial thin-section CT imaging showed pulmonary fibrosis in 14 of 32 discharged patients and fibrosis was likely to develop in critical patients, especially in patients with high inflammatory indicators [11]. Patchy ground-glass opacities in the periphery of lower lungs may be present initially, coalescence, consolidation, and organization were undergoing. Ultimate features of fibrosis were [12]. SARS-CoV-2 has certain homology with SARS-COV [13], and its epidemiological characteristics are also similar to that of SARS. According to epidemic history of SARS, survivors developed varying degrees of pulmonary fibrosis [14]. Patients with COVID-19, in particular those with pneumonia, may develop fibrosis following pulmonary interstitial inflammation, which will impair pulmonary function and quality of life [15,16].

Fuzheng Huayu Prescription (FZHY) is a botanic product composed of 6 herbs (Table 1). According to the theory of traditional Chinese Medicine (TCM), It is effective in activating blood circulation and removing blood stasis, enriching essence and nourishing liver. Our clinic study approved that FZHY could regress liver fibrosis due to hepatitis B [17], meanwhile the Phase II clinic trial in US indicated that FZHY could stabilize and regress liver fibrosis due to hepatitis C [18]. The action mechanism of FZHY against liver fibrosis has also been investigated, which was associated with protection of hepatocyte inflammation, inhibition of stellate cell activation, and regulation of hepatic matrix metabolism [19]. It was approved for the marketing by National Medical Products Administration in 2005. Now it has two dosage forms, tablet and capsule, both of which have good quality control with little adverse reactions. Moreover, in our previous studies, FZHY was found to have a good effect on lung interstitial inflammation and fibrosis in bleomycin-induced rats [20-22]. In addition, a clinical observation showed that FZHY could obviously improve pulmonary function in patients with chronic obstructive pulmonary disease (COPD) [23].

Table 1: Fuzheng Huayu (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	*Gynostemma-pentaphyllum* (Thunb)	whole herb	6
Songhuafen	*Pinusmas-soniana Lamb* (Pinaceae)	pollen	2
Wuweizi	*Schisan-draeChinensis* (Turcz.) Baill	fruit	2
Danshen	Salvia MiltiorrhizaeBge (*Labiatae*)	radix	8
Chongcao	artificial fermentation *cordyceps*	mycelia	4
Taoren	Prunuspersica (L.) Batsch (*Rosaceae*)	fruit	2
Jiaogulan	*Gynostemma-pentaphyllum* (Thunb)	whole herb	6
Songhuafen	*Pinusmas-soniana Lamb* (Pinaceae)	pollen	2
Wuweizi	Schisan-draeChinen-sis (Turcz.) Baill	fruit	2

The lung fibrosis in patients with COVID-19 may have similar or common pathological mechanisms with the fibrosis in different organs, and FZHY shows an effect against lung fibrosis in animal study and improve lung functions in patients with COPD. Thus, we design this clinic trial, in which patients with pulmonary fibrosis and dysfunction due to COVID-19 will receive FZHY or placebo in their recovery phase. Because COVID-19 is a new disease and there is no effective treatment yet, we chose the superiority design with placebo-control. The main objective is to evaluate the efficacy and safety of FZHY on lung fibrosis and function in patients with COVID-19, which is expected to improve clinical prognosis.

METHODS

Design

We designed this study as a multi-center, randomized, double-blinded, placebo-controlled clinical trial. The trial has been

registered at ClinicalTrials. gov (ID: NCT04279197). At the time of writing of the trial protocol (version 1.3, Sep 15, 2020), the trial has been enrolling. The study began on March 1, 2020 and will end on December 31, 2021. This protocol has been developed according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 [24]. The checklist is described in detail in Supplemental material 1.

Prior to trial initiation, the investigators and researchers are conducting unified training to ensure that the medical staff involved in the study fully understands all aspects of the trial. The study will be conducted in eight clinical centers across China, namely Shuguang Hospital Affiliated to Shanghai University of TCM, Jingmen No.1 People's Hospital, Union Hospital, and the Tongji Hospital Affiliated to Tongji Medical College, Wenzhou Central Hospital, Hubei Hospital of TCM, Wuhan NO.1 Hospital and Wuhan NO.3 Hospital. Competitive enrollment will be applied in all research centers, to achieve the goal of 160 participants in total. Each participant can only be enrolled once.

The study will consist of five steps: screening/enrollment, allocation, treatment/intervention, end of intervention, and follow-up. During enrollment, participants will be recruited from the outpatient clinics of eight medical centers, where they will undergo physical examination and assessment of eligibility. The maximum time allowed between the assessment and the

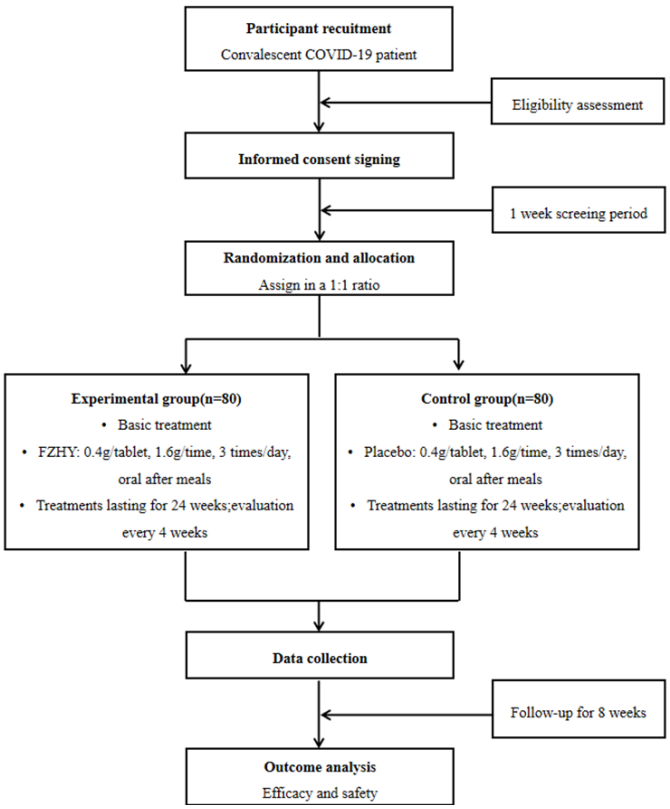

Figure 1: Flow diagram of the progress through the study

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting or dissemination of our research. Study results will be published open access. At request, patients or their representatives will be informed about the results of the trial.

Randomization and allocation

The study uses a minimization dynamic random method. After patients signed the informed consent, completed all screening assessments and received confirmation of eligibility, they will be randomized into the study at ratio of 1:1 using an Interactive Web Randomization System (IWRS) and assigned random-number and drugs. The system should include three stratification factors as follows:

(1) Age: ≥ 50 years vs. <50 years

(2) Pulmonary inflammation: Chest CT shows that there is still acute exudative disease in the lung, but it had been significantly improved vs no acute exudative disease in the lung

(3) 6-minute walk test: ≥ 250 m vs. <250 m

Then, randomization tables were derived from IWRS and sealed using sealed opaque envelopes.

Blinding

The investigators, all patients, data managers, and data supervisors were blinded in this study. Patients will be endowed a random-number through the IWRS automatically, whose number is unique until the end of the entire trial. During the trial, investigators use the random numbers of medicines to distribute the corresponding medicines to all patients. Data managers, data supervisors and investigators record the data of patients only based on the random number.

Sample size

COVID-19 is a novel disease, and there are no specific drugs at present, so there are no references for us to calculate the sample size. Therefore, we applied the adaptive design, and set the sample size as 160 cases (including the maximum dropout rate of 20%), 80 cases in each group. Data Management Committee (DMC) will conduct interim analysis with the same assessments as ones at 24 weeks when 60 participants finished the 8-week visits. And the sample size may be adjusted or increased by DMC according to the results of the interim analysis.

There is no requirement to adjust for multiplicity due to interim analyses, since there are no planned interim analyses with the opportunity to make an early claim of efficacy.

Eligibility criteria

The following inclusion criteria will be applied at the time of randomization: (I) Compliance with the diagnostic criteria for COVID-19 China Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7); (II) COVID-19 RNA in respiratory specimens or blood specimens of patients is negative (>2 times), assayed by real-time fluorescent polymerase chain reaction test (RT-PCR); (III) Pulmonary CT scans within 7 days showed that there were still unabsorbed inflammation or pulmonary fibrosis in the lungs; (IV) Age 18-70; (V) Six-minute walk distance less

than 350 meters; (VI) Participants sign the informed consent.

The following exclusion criteria will be applied: (I) Patients who have undergone lung surgery that affects pulmonary function, such as pulmonary transplantation, pulmonary resection, pulmonary volume reduction, etc; (II) Ones relying on mechanical ventilation to maintain pulmonary function, such as ventilators; (III) patients combined with chronic pulmonary diseases affecting pulmonary function, such as chronic obstructive pulmonary disease etc; (IV) Patients with diseases affecting cardiac function, such as pulmonary circulation hypertension, heart failure, peripheral vascular disease, fibromyalgia, and pacemaker installation; (V) Patients with severe underlying diseases affecting survival, including uncontrolled cardiac, renal, digestive, hematological, neuropsychiatric, immune, metabolic diseases, malignant diseases and severe malnutrition; (VI) Resting heart rate >120 times/min; (VII) Systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg; (VIII) Unstable angina pectoris or myocardial infarction occurring within the last month; (IX) Severe obesity (BMI>30 kg/m2); (X) Allergic constitution, allergic to the drug components involved in the treatment program; (XI) Pregnant or breastfeeding women; (XII) Patients with disabilities who are unable to complete the efficacy evaluation questionnaires; (XIII) Patients with mental illness who cannot control themselves and express clearly; (XIV) Those who are participating in other clinical trials; (XV) Patients with complications or poor compliance will affect the efficacy and safety evaluation judged by the investigators.

Candidates with one or more exclusion criteria will be excluded.

Interventions

Experimental Group: Participants in the experimental group will receive FZHY tablets (0.4 g/tablet, Shanghai Huanghai Pharmaceutical Co., Ltd.) over the course of 24-week treatment period and will be instructed to consumed 1.6 g orally approximately 30 minutes after meals, 3 times/day. The major ingredients of FZHY are listed in Table 1.

Control Group: Participants in the control group will receive placebo over the course of 24-week treatment period and will be instructed to consumed 1.6 g orally approximately 30 minutes after meals, 3 times/day (the same protocol as that used in the experimental group). The placebo suspension consists of a sucrose mixture to produce a similar tablet shape, and the mixture includes 1% FZHY, starch and carboxymethyl starch sodium to produce a similar aroma to that of FZHY tablets.

Basic Treatment: All participants will receive basic treatment with respiratory function rehabilitation training according to the rehabilitation program for discharged patients with COVID-19 issued by the National Health Commission of the People's Republic of China [25] and Vitamin C tablets (0.2 g/time, 3 times/day, oral). The participants will be instructed to continue their daily activities and maintain communication with their treating physician, as well as with the staff involved in the study.

Treatment cycles

The 24-week treatment period was planned in six cycles of 4 weeks, with a return visit between cycles to check for adverse events (AEs) and monitor compliance. All interventions will be stopped after 24 weeks. Follow-up will be conducted on weeks 32.

Drug combination

All drugs except test medicine would be considered combined drugs and will be recorded in the case report form with their trade name, dosage, indications, and duration of medication. The study investigators will judge whether the participant should withdraw from the study on account of the nature of the combined drugs. However, the use of other Chinese patent medicine or western medicine for anti-fibrosis during the study period shall not be allowed.

RESULTS

Primary endpoint

The primary outcome of the trial is the improvement proportion of lung fibrosis after 24 weeks of treatment as judged by HRCT score, which will be evaluated with a computer-aided digital system.

Endpoints

Secondary outcomes include Six-minute walk distance, symptoms score, blood oxygen saturation, quality of life-BREF (QOL-BREF) score, patient health questionnaire -9 (PHQ-9) score, general anxiety disorder-7 (GAD-7) score, which will be assessed at the visit phases as the Table 2. Blood oxygen saturation is recorded daily throughout the study cycle with wearable devices.

Exploratory endpoints

We use SARS-CoV-2-specific IgG and IgM antibody as exploratory indicators. It only needs to be evaluated and documented at week 0 and week 24 of the treatment period.

Safety evaluation

The Chinese herbal medicines in FZHY are all listed in the Pharmacopoeia of the People's Republic of China, and FZHY dose used in this study is within the range in the drug instruction. Nevertheless, the trial will implement adequate measures to monitor for AEs, including observation of vital signs, laboratory tests, recording of concomitant medications. All AEs will be recorded, regardless of severity, in order to assess the safety of FZHY. The specific implementation of such measures is reflected in Table 2.

If an AE occurs, investigators have to determine whether to stop the observation and proceed with the diagnosis and corresponding treatment. If a severe AE occurs, the study investigator must take immediate action to ensure the safety of the participants. In addition, all severe AEs will be reported to

Table 2: Schedule for enrollment, intervention and assessment. Note: wk: week, d: day; *lung CT at the time of enrollment confirms the examination results within the past week; if the end point of treatment is reached in advance, the last time is recorded in the position of week 24 and the date is indi-cated.SARS-CoV-2 nucleic acid test is required once, and the test results are pasted on the test sheet paste of the corresponding visit, and the results are added and recorded in the corresponding visit of the EDC system.

	Screening period	Treatment period									Follow-up period
Item	**-1wk-0d**	**4wk ± 3d**	**8wk ± 3d**	**12wk ± 3d**		**16wk ± 3d**		**20wk ± 3d**		**24wk ± 3d**	**32 wk ± 7d**
Eligibility Criteria	√										
Sign informed consent	√										
Demographic information	√										
Past medical history	√										
Symptoms	Recorded in APP everyday										
Vital signs	√	√	√	√	√		√		√		√
HRCT	√	√	√	√					√		√
Six-min walking test	√	√	√	√	√		√		√		√
Dynamic oxygen saturation	Wrist watch automatic recording and uploading daily										
QOL-BREF	√	√	√	√					√		√
PHQ-9	√	√	√	√					√		√
GAD-7	√	√	√	√					√		√
SARS-CoV-2 specific IgG and IgM antibodies	√								√		
Routine blood test+ CRP	√			√					√		√

Routine urine test	√			√					√		√
Stool-routine	√			√					√		√
ECG	√			√					√		√
Liver and kidney function	√			√					√		√
Randomized grouping	√										
Dissemination of Drugs and Participant Logs	√	√	√	√	√		√		√		
Recovery of residual drugs and participant logs		√	√	√	√		√		√		
Safety evaluation		√	√	√	√		√		√		
Concomitant medication		√	√	√	√		√		√		
AEs and Severe AEs	Record at any time										

the Institutional Review Board of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine within 24 hours.

Data management and monitoring

The principal investigators (PI) at each participating center are responsible for collecting the research medical records, as well as for reviewing and storing these records. The staff at each clinic center records data according to the content of case report forms (CRF) and used the Electronic Clinical Data Management System (DAS for EDC) for electronic data management. The Data Management Plan (DMP), as a guiding document for data management, is written by the DMC and approved by the general PI. The clinical research coordinator (CRC) enters data into the Electronic Data Capture System (EDC) according to CRF content. The clinical research associate (CRA) checks the consistency between CRF and EDC. After data entry is completed and Source Data Verification (SDV) is performed, the electronic signature verification is carried out by the PI at each participating center. CRA locks the database and submits the database to the statistician. After the statistical analysis was completed, the CRA closed the database. If a problem is found during the process, it should be processed and recorded in a timely manner. All documentation on quality control will be maintained in order to objectively assess safety and key outcomes.

Statistical analysis

The modified intent-to-treat (mITT) analysis set will be considered

as the full analysis set. This will include all evaluable patients, ie, all randomized patients who receive at least one dose of Fuzheng Huayu or placebo and who have HRCT test at randomization and at least one post randomization HRCT test.

The primary efficacy endpoint of the study is the improvement proportion of lung fibrosis after 24 weeks of treatment judged by HRCT score, which will be compared between the 2 groups (χ2 test or Fisher's exact test) for the primary analysis. Logistic regression will be performed to adjust for potential confounding factors; variables relevant to the models will be selected based on their clinical interest and/or a threshold p-value ≤ 0.1 during univariate analysis. The final models will express the odd ratios and their 95% confidence intervals as per the Clopper-Pearson method. The unadjusted analysis will be the primary analysis, and the adjusted analysis will be a complementary analysis.

Missing data will be used multiple imputation under the assumption of data missing at random (MAR).

For other secondary endpoints, quantitative data will be compared using the Student's t test or Mann-Whitney U test in accordance with the variable distribution, whereas qualitative data will be compared using χ2 test or Fisher's exact test, as appropriate.

Safety analyses will be performed in all treated subjects. 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.

All statistical analyses will be performed using SAS version 9.4. Tests of statistical significance for all efficacy endpoint analyses will use the 2-sided significance level of 0.05.

Ethics and dissemination

The study has been approved by the IRB of Shuguang Hospital affiliated with Shanghai University of TCM (Approval No. 2020-798-05-01) (Supplemental material 3). Amendments to the study protocol require approval by the ethics committee. All participants will be enrolled only after providing written informed consent. No clinical data or bio-samples will be collected without the participants' consent. The trial is conducted in accordance with national laws, Good Clinical Practice (GCP) guidelines, and the Declaration of Helsinki as revised in 2013.

The results will be disseminated to the public through conference presentations and papers in open access journals.

Ancillary and post-trial care

Although FZHY is much safe for patients with chronic liver diseases, the safety assessment will be fully observed. All participants will receive the compensatory payment for their transportation and nutrition in addition to free examinations and treatments. If, as determined by the Ethics Committee, the participants did suffer injuries related to this study, the investigators would be liable and compensated in accordance with national law.

DISCUSSION

The pandemic COVID-19 is new health crisis threatening the world, although its natural history is not fully understood yet, with a lower mortality rate than SARS. The type and severity of complications in the severe cases with COVID-19 are similar to SARS, and the pneumonia and pulmonary fibrosis could be occurred in some patients [26-28].

The pulmonary fibrosis, caused by kinds of etiologies, could impair respiratory function. There is still short of effective agents against pulmonary fibrosis, although it was reported that Pirfenidone and Nintedanib could be effective for IPF [29-32], which have disadvantages such as expensive price and severe side effects. Therefore, it is very important to develop the agent to inhibit or regress the pulmonary fibrosis, especially for one duo to COVID-19.

The fibrosis in different organs had common features [33], such as activation of fibroblasts and deposition of extracellular matrix. The evidence showed that the sub-epithelial basement membrane often destroyed, which play a pivot role in the pathological development of pulmonary interstitial fibrosis, while matrix metalloproteinase (MMP) regulates the degradation and remodeling of the extracellular matrix of the basement membrane [34]. In our animal experiments, it was found that FZHY could decrease active MMP-2 activity in the fibrotic lungs induced by bleomycin, and indicating that FZHY could improve the lung inflammation and fibrosis through protection of sub-epithelial basement membrane. Therefore, it is rationale for us to apply FZHY for pulmonary fibrosis due to COVID-19.

Hereto, we focus on the COVID-19 patients with pulmonary fibrosis in their recovery phase, which means the patients become negative SASR-2 RNA, but still suffer from pulmonary fibrosis and/or dysfunctions after quarantine and treatments. And these patients will receive FZHY or placebo, in order to evaluate the effectiveness of FZHY on the pulmonary fibrosis and dysfunction due to SRSA-2.

In this trial, we chose the improvement proportion of lung fibrosis judged by HRCT score as the primary endpoints, which can find small, local lesions and ensures accurate analysis of lesion characteristics and distribution based on cross-sectional images and multiplanar reconstruction [35], and semi-quantization also could obtain with image analysis and algorithm. Meantime, we will monitor the oxygen saturation with wearable devices and observe the health-related quality of life as the secondary endpoints, the latter is easy to be accomplished by the participants unlike the St. George's Respiratory Questionnaire [36], which would need at least 10 minutes and not easy to complete without help.

Sample size and duration are very important aspects for clinic trial, however there is very limited information about clinical outcomes in patients with COVID-19. Therefore, we adopt the adaptive design for the trial. Although we preset the sample size of 80 each group, considering general population of 60 patients each arm for moderated size and 20% of dropout rate, the sample could adjust (increase or stop enrollment) when the efficacy is evaluated at the middle course of the trial (8 week) DMC. And the individual duration for observation also is flexible, and the patient could terminate the trial in advance if he or she satisfy the normalized criteria including negative HRCT, Six-minute walk distance >500 m.

CONCLUSION

In short, in view of the characteristics of pulmonary interstitial inflammation and fibrosis in patients with COVID-19 during recovery period, this study plans to establish an effective treatment program for pulmonary fibrosis/dysfunction in COVID-19 to promote the rehabilitation of patients. The study results would not only provide new methods for the treatment of pulmonary fibrosis due to COVID-19 and information for further understanding the natural history of COVID-19, but provide a potential strategy for treating pulmonary fibrosis caused by other etiologies.

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REFERENCES

1. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it.
2. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard.
3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020; 382:1199-1207.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients With 2019 novel coronavirus-infected pneumonia in Wuhan, China. J American Med Asso. 2020; 323:1061-1069.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020; 395:507-513.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497-506.
7. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the post pandemic period. Science. 2020; 368: 860-868.
8. Luo WR, Yu H, Gou JZ, Li XX, Sun Y. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). (2020).
9. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) Pneumonia in two patients with lung cancer. J Thorac Oncol. 2020;15: 700-704.
10. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal changes of ct findings in 90 patients with COVID-19 Pneumonia: A longitudinal study. Radiology. 2020;296: 55-64.
11. Yu M, Liu Y, Xu D, Zhang R, Lan L, Xu H. Prediction of the development of pulmonary fibrosis using serial thin-section CT and clinical features in patients discharged after treatment for COVID-19 pneumonia. Korean J Radiol. 2020;21: 746-755.
12. Goyal N, Chung M, Bernheim A, Keir G, Mei X, Huang M, et al. Computed tomography features of coronavirus disease 2019 (COVID-19): A review for radiologists. J Thorac Imaging. 2020;35: 211-218.
13. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 2020;395: 565-574.
14. Venkataraman T, Coleman CM, Frieman MB. Overactive epidermal growth factor receptor signaling leads to increased fibrosis after severe acute respiratory syndrome coronavirus infection. J Virol. 2017; 91:00182-17.
15. Zumla A, Hui DS, Azhar EI. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. Lancet. 2020;395: e35-6.
16. Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol. 2020;92: 491-494.
17. Wang T, Zhou X, Liu H, Wang J, Zhang P, Zhu Y, et al. Fuzheng Huayu capsule as an adjuvant treatment for HBV-related cirrhosis: A systematic review and meta-analysis. Phytother Res. 2018;32: 757-768.
18. Tarek H. Sa1319 A Phase II, Randomized, placebo-controlled, double-blind, multi-center study to assess the antifibrotic activity of fuzheng huayu in chronic hepatitis c patients with hepatic fibrosis (S-USIIT-01). Gastroenterology. 2014;146(5).
19. Liu C, Hu Y, Xu L, Liu C, Liu P. Effect of fuzheng huayu formula and its actions against liver fibrosis. Chin Med.

2009; 4:12.

20. Lu X, Ye WC, Liu P, Cai ZZ, Liu CH, Zhang W, et al. Therapeutic effect of fuzheng huayu recipe on bleomycin-induced pulmonary interstitial fibrosis in rats. Zhong Yi Za Zhi. 2006; 47:538-40.(in Chinese)

21. Tan SZ, Liu CH, Zhang W, Lu X, Ye WC. Effect of fuzheng huayu recipe on MMP-2 activity and type IV collagen expression in fibrotic lung tissue of rats. Zhong guo zhong yao za zhi. 2007; 32:835-9.

22. Yang K, Tan SZ, Zhang W, Tan YY, Chen Y, Cai ZZ, et al. Herbal compatibility of fuzheng huayu recipe against pulmonary fibrosis. Zhong Yi Za Zhi. 2009; 50:732-6.

23. Zhang W, Bi XL, Bao BQ, Yu HM, Tao HM. Research on Fuzheng Huayu Capsule treating chronic obstruct pulmonary in clinic. Liao Ning Zhong Yi Za Zhi. 2008; 36:1174-5.

24. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krle A-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013; 158:200-7.

25. National Health Commission of the People's Republic of China.

26. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology. 2010;15: 543-50.

27. Hui DS, Wong KT, Ko FW, Tam LS, Chan DP, Woo J, et al. The 1-Year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest. 2005; 128:2247-61.

28. Marchioni A, Tonelli R, Ball L, Fantini R, Castaniere I, Cerri S, et al. Acute exacerbation of idiopathic pulmonary fibrosis: lessons learned from acute respiratory distress syndrome? Crit Care. 2018; 22: 80.

29. Cottin V, Maher T. Long-term clinical and real-world experience with pirfenidone in the treatment of idiopathic pulmonary fibrosis. Eur Respir Rev. 2015; 24:58-64.

30. Hanta I, Cilli A, Sevinc C. The effectiveness, safety, and tolerability of pirfenidone in idiopathic pulmonary fibrosis: A retrospective study. Adv Ther. 2019; 36:1126-31.

31. Tepede A, Yogaratnam D. Nintedanib for idiopathic pulmonary fibrosis. J Pharm Pract. 2019; 32:199-206.

32. Crestani B, Huggins JT, Kaye M, Costabel U, Glaspole I, Ogura T, et al. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: Results from the open-label extension study, INPULSIS-ON. Lancet Respir Med. 2019; 7: 60-68.

33. Majo J, Klinkhammer BM, Boor P, Tiniakos D. Pathology and natural history of organ fibrosis. Curr Opin Pharmacol. 2019; 49:82-9.

34. Gueders MM, Foidart JM, Noel A, Cataldo DD. Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs in the respiratory tract: Potential implications in asthma and other lung diseases. Eur J Pharmacol. 2006; 533:133-44.

35. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT clinical practice guideline. Am. J. Respir. Crit. Care Med. 2018;198: e44-68.

36. Furukawa T, Taniguchi H, Ando M, Kondoh Y, Kataoka K, Nishiyama O, et al. The St. George's respiratory questionnaire as a prognostic factor in IPF. Respir Res. 2017; 18: 18.