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Study Protocol

Traditional Chinese medicine in the treatment of idiopathic pulmonary fibrosis based on syndrome differentiation: study protocol of an exploratory trial

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) has a poor prognosis and is often a kind of heavy financial burden to patients. Currently, few treatments are available for IPF. Clinical practice of traditional Chinese medicine (TCM), using a syndrome differentiation approach, offers some treatment success in IPF. However, there is no sufficient evidence-based study of the role of TCM in IPF management to make strong conclusions. This study evaluates the efficacy and safety of TCM in the treatment of IPF.

Methods and design: A multicenter, exploratory, randomized, double-blind and placebo-controlled trial is planned. A total of 80 patients will be enrolled in the study, which will include 26 weeks of treatment. Participants will be randomly assigned into TCM group or control group in a 1:1 ratio. The TCM group will be given TCM granules based on syndrome differentiation. Formulae include Bu-Fei Yi-Qi granule for lung qi deficiency, Bu-Fei Yi-Shen granule for lung-kidney qi deficiency and Yang-Yin Qing-Re granule for yin deficiency and inner heat. The control group will be given a corresponding TCM granule placebo. The efficacy and safety of interventions will be evaluated by the outcome variables, including frequencies of acute exacerbations, pulmonary function, clinical symptoms, dyspnea, health-related quality of life (HRQoL), 6-minute walk distance and safety indicators.

Discussion: It is hypothesized that TCM will decrease the frequency of adverse

events, improve pulmonary function and HRQoL, based on our clinical experience. This trial is the first study of TCM treatment in IPF that is based on syndrome differentiation and will evaluate the efficacy and safety of TCM in IPF.

Trial registration: This study was registered on www.Chictr.org.cn: ChiCTR-IIR-17013532. Register date: November 24, 2017.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and ultimately fatal interstitial lung disease with unknown etiology, as well as specific performance combinations of usual interstitial pneumonia in high resolution computed tomography and pathological manifestations of lung tissues [1]. Although IPF is a rare disease [2], different studies show that its prevalence and disease-related mortality have been rising over time [3–6]. Patients with IPF currently have a poor prognosis, with a median survival of 3 years after diagnosis [6]. Unfortunately, health-related quality of life (HRQoL) for IPF patients is extremely poor. Within two or more years of diagnosis, IPF symptoms are often worse than those of chronic obstructive pulmonary disease (COPD) in patients at stage Ⅳ defined by Global Initiative for Chronic Obstructive Lung Disease [7].

In recent years, a growing number of therapeutic drugs have been investigated for treatment of IPF. However, few evidence-based treatments are currently available. According to the international guidelines [8], nintedanib and pirfenidone are conditionally recommended for the treatment of IPF. They may improve patients' pulmonary function and quality of life, delay disease progression and reduce mortality [9,10]. Despite this, the treatment options for IPF remain unsatisfactory. The high

incidence of drug-related side effects cannot be ignored [9,11,12], and the disease-related economic burden is also heavy [13]. Thus, the development of other effective strategies and treatments for IPF is urgently needed.

Traditional Chinese medicine (TCM) has a long history of successful treatment of respiratory diseases, and a growing body of recent evidence-based research supports the clinical efficacy of TCM. Although IPF is not a named condition in TCM, it is often diagnosed as *feiwei* or *feibi,* depending on its clinical manifestations [14]. Many exploratory researches have been conducted on the TCM treatment of IPF, and a recent meta-analysis of existing data showed that TCM had some positive effects in management of IPF [15]. For example, using Chinese medicine in conjunction with Western medicine showed greater efficacy than using the Western medicine alone in delaying the decline of pulmonary function and quality of life, with good safety. However, research on the use of TCM to treat IPF comprised mostly single-center and small-sample studies. Complicating matters, there is no consensus on the etiology or pathogenesis of IPF in TCM. Thus, a study of the standardized TCM syndrome differentiation treatment scheme and validating research appear necessary.

Our research team has compiled the TCM syndromes most typical for IPF and formed a guideline for TCM syndrome differentiation, through our long-term experience in clinical practice [16]. Chinese medicine granules that correspond to common TCM syndromes have also been explored. Therefore, this study aims to evaluate the efficacy and safety of the proposed TCM treatments for IPF, based on the established TCM syndrome differentiation guidelines.

2. Methods and design

2.1. Study design

This is an exploratory study. At the beginning, an independent expert committee, included clinicians, statisticians and ethics experts, will be set up to perform the study design. A multicenter, exploratory, randomized, double-blind, placebo-controlled trial will be conducted to evaluate the efficacy and safety of TCM treatment, based on syndrome differentiation in IPF. A total of 80 patients will be enrolled and randomly assigned into the TCM and control groups at a ratio of 1:1. All the participants will receive a 26-week treatment. An independent data-monitoring committee has also been set up to review and manage all the data of adverse events (AEs). The study will be conducted according to the principles of the *Declaration of Helsinki* and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

It is hypothesized that the TCM treatment-based syndrome differentiation used in this proposed study will decrease the frequencies of AEs, and improve pulmonary function and quality of life, based on our clinical experience. So, the outcomes,

including frequencies of AEs, pulmonary function, clinical symptoms and signs, dyspnea score, HRQoL, 6-minute walk test (6-MWT) and safety indicators will be evaluated.

The study flow-chart is summarized in Fig. 1.

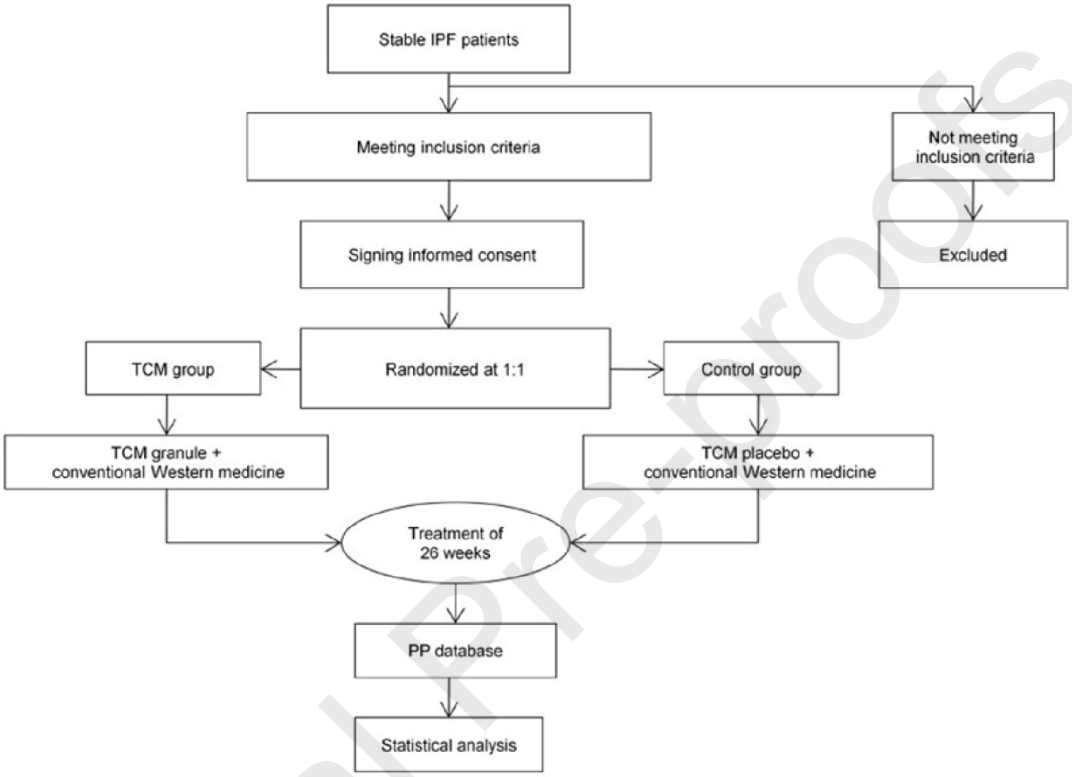

Fig. 1. Technical route of this trial. TCM: traditional Chinese medicine; IPF: idiopathic pulmonary fibrosis; PP: per-protocol.

2.2. Patients' eligibility

2.2.1. Inclusion criteria

Patients must meet the following criteria: (1) meet the diagnostic criteria of stable IPF [1]; (2) be between 40 and 80 years of age; (3) meet the TCM syndrome differentiation criteria: patterns of lung qi deficiency, lung-kidney qi deficiency, and yin deficiency and inner heat [16]; (4) not participate in any other drug trial within one month prior to enrollment; (5) intend to participate in the trial themselves and sign the informed consent form.

2.2.2. Exclusion criteria

Patients who meet the following criteria will be excluded: (1) patients with acute

exacerbation of IPF; (2) women who are pregnant, nursing or may become pregnant; (3) patients with dementia, mental disorders or who are unconscious; (4) patients who also present with severe cardiac dysfunction (Grade Ⅲ or above by New York Heart Association functional classification) [17], severe renal or kidney diseases (twice or more of the normal upper limitation for serum glutamic-pyruvic transaminase, glutamic oxaloacetic transaminase, blood urea nitrogen or creatinine levels, severe neurological diseases or tumor; (5) patients known to be allergic to any used drug.

2.3. Ethics, oversight and recruitment

The study protocol (version 2016.04.11.1.0.1.0) has been approved by the Ethical Research Committee of the First Affiliated Hospital of Henan University of Chinese Medicine with the ID of 2016HL-007-01. Any revision of the study protocol will be submitted to the ethics committee as soon as possible.

IPF patients will be recruited by respiratory physicians from the First Affiliated Hospital of Henan University of Traditional Chinese Medicine, the Second Affiliated Hospital of Henan University of Traditional Chinese Medicine, the Third Affiliated Hospital of Henan University of Traditional Chinese Medicine and Henan Provincial People's Hospital, China. All the patients will sign the informed consent before enrollment. Recruitment lasts for 6 months from May 2016 or until the target sample are completed. The research process will also be supervised by the ethics committee of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine.

2.4. Sample size

This is an exploratory trial. According to our previous research, TCM treatment based on syndrome differentiation could reduce the rate of AEs and alleviate the decline of pulmonary function. Taking the number of AEs and pulmonary function as the primary outcome, 30 patients are needed in each group based on sample size calculations for exploratory clinical trials [18] and our previous research. Considering a 20% of drop-out rate and block factor, approximately 40 patients should initially be recruited into each group. Therefore, the total target sample size is 80.

2.5. Randomization and blinding

A randomized block design will be used to allocate patients who meet inclusion criteria and sign the informed consent. The block size will be 4. All the patients will be randomly assigned to the two groups in a 1:1 ratio, in each center, after a two-week wash-out period. Patient enrollment, randomization and treatment allocation will be performed by 3 different researchers. Syndromes will be determined after treatment allocation, and the patients will be given corresponding TCM granules or placebo during the treatment period. Random numbers for patients from 01 to 80 and drug numbers for every bag were generated using SAS 9.2 (version 9.2, provided by Jiangsu Famous Medical Technology Co., Ltd. in Nanjing, China) and kept by an independent researcher in an opaque envelope with corresponding treatment

allocation. The random number for every patient will be generated at baseline. Then unique drug number will be generated by the computer system at every visit. All the patients and researchers (except for who conducting treatment allocation) will be all blind to the treatment allocation. In case of an emergency, such as AEs needing urgent treatment, the randomization number and treatment allocation will be unsealed for researchers and supervisors as soon as possible.

2.6. Procedures and interventions

Patients in the TCM group will be treated with TCM granules based on the TCM syndromes: Bu-Fei Yi-Qi granule for lung qi deficiency, Bu-Fei Yi-Shen granule for lung-kidney qi deficiency, and Yang-Yin Qing-Re granule for yin deficiency and inner heat. All the granules consist of different combinations of herbal medicines, and the main components of every granule are shown in Table 1. At the same time, the placebo used in this study will contain 5% of the same components as corresponding TCM granule, in addition to the placebo base. Patients in the control group will be treated with corresponding TCM granule placebo.

Table 1. Main components of TCM granules.

Granule name	Applicable TCM syndrome	Main components		Amount (g)
		Chinese name	Latin name	
Bu-Fei Yi-Qi granule	Syndrome of lung qi deficiency	Ren Shen	*Radix Ginseng*	6
		Huang Qi	*Radix Astragali mongolici*	15
		Mai Dong	*Radix Ophiopogonis japonici*	12
		Dang Gui	*Radix Angelicae sinenis*	12
Bu-Fei Yi-Shen granule	Syndrome of lung-kidney qi deficiency	Ren Shen	*Radix Ginseng*	9
		Shu Di Huang	*Radix Scrophulariae buergerianae*	15
		Mai Dong	*Radix Ophiopogonis japonici*	12
		Gua Lou	*Trichosanthes kirilowii Maxim*	15
Yang-Yin Qing-Re granule	Syndrome of yin deficiency and inner heat	Xi Yang Shen	*Panax quinquefolius*	6
		Nan Sha Shen	*Radix Adenophorae strictae*	12

	Gua Lou	*Trichosanthes kirilowii Maxim*	15
	Mai Dong	*Radix Ophiopogonis japonici*	12

TCM: traditional Chinese medicine.

All the TCM granules and placebo were produced by Sichuan New-green Pharmaceutical Technology Development Co. LTD (Sichuan, China; Batch number: 15060095). All the drugs were consistent with the national standards of quality. There is no obvious difference in appearance or odor between TCM granule and placebo. Patients and researchers could not identify the differences by sight or smell. Each type of granule or placebo will be taken orally: patients will take one pre-packaged bag (9.06 g), twice daily for 26 weeks. Drug distribution will be conducted every 3 months. All the unused drugs for each patient will be collected at each visit. To improve patients' adherence to long-term treatment, another drug administration schedule of 5 days on/2 days off will also be adopted.

In addition, other Western medicines will also be applied in both groups. Nintedanib and pirfenidone are recommended in treatment guidelines [8]. However, because of their high cost, most patients do not use them in the treatment of IPF. So, if necessary, patients in the study will be allowed to use symptomatic medicines, including ambroxol hydrochloride tablets, compound methoxyphenamine capsules and budesonide/formoterol inhalers. The manufacturer and production batch of such drugs will not be logged. All medicines will be given according to the manufacturer's instructions. All medicines used by each patient will be recorded.

The schedule of enrollment, interventions and assessments is shown in Fig. 2.

	Sduty period			
	Enrolment	Allocation	Post-allocation	
Timepoint*	-2 weeks	0	13 weeks	26 weeks
Enrollment:				
Eligibility screen	x			
Informed consent	x			
Allocation		x		
Interventions:				
TCM granules for TCM group		♦———	———	———♦
TCM placebo for control group		♦———	———	———♦
Assessments:				
Acute exacerbations		x	x	x
FVC		x		x
DL_{CO}%		x		x
FEV1		x		x
6-MWT		x	x	x
mMRC		x	x	x
Clinical symptoms and signs		x	x	x
CAT		x	x	x
SGRQ		x	x	x
SF-36		x	x	x

Fig. 2. The schedule of enrollment, interventions and assessments. TCM: traditional Chinese medicine; FVC: forced vital capacity; DL_{CO}%: diffusing capacity percentage of the predicted value; FEV1: forced expiratory volume in one second percentage; 6-MWT: 6-minute walk test; mMRC: modified Medical Research Council score; CAT: chronic obstructive pulmonary disease assessment test; SGRQ: St. George's respiratory questionnaire; SF-36: 36-item short-form health survey; x: list specific timepoints in this row.

2.7. Outcome measure

The following outcomes for all the patients will be assessed in person by blinded and independent researchers.

2.7.1. Primary outcomes

Primary outcomes in this study include pulmonary function and AEs.

Pulmonary function, including forced vital capacity (FVC), forced expiratory volume in one second percentage (FEV1) and diffusing capacity percentage of the predicted value (DL_{CO}%), will be the primary outcomes in the study. They will be tested at baseline and post-treatment. A positive value change from baseline for these parameters would indicate the improvement of pulmonary function in IPF.

AEs will be another primary outcome in this study. AE of IPF (AEIPF) is characterized by significant respiratory deterioration of unknown cause over the course of less than one month [19]. It will be assessed by the frequencies of AEIPF-related hospitalizations. A higher number indicates the deterioration of disease and worse prognosis.

2.7.2. Secondary outcomes

The secondary outcomes include clinical symptoms and signs, dyspnea scores, HRQoL and 6-MWT.

Clinical symptoms and signs assessed in this study include cough, expectoration, chest tightness, shortness of breath, fatigue and cyanosis. Each item will be assessed by a value of 0–3, with a higher value indicating a worse disease condition.

Dyspnea will be assessed by modified Medical Research Council score (mMRC), established by the American Thoracic Society [20] on a scale of 0–4, with higher values indicating worse dyspnea.

The COPD assessment test (CAT), St. George's respiratory questionnaire (SGRQ) and 36-item short-form health survey (SF-36) will be adopted to assess patients' HRQoL, with a higher value indicating a better HRQoL for SF-36 and a worse HRQoL for CAT and SGRQ. CAT is a self-evaluation questionnaire including 8 items with a value of 0 to 5 for each item [21]. SGRQ, with 3 domains and 50 items, is a tool to assess health impairment for respiratory diseases [22]. SF-36 is a generic scale with 8 domains and 36 items [23]. The total scores for SGRQ and SF-36 will be calculated by weighting each item independently.

The total distance over flat ground, walked by a patient in 6 minutes (6-minute walk distance in 6-MWT), represents exercise capacity of the patient. A longer distance indicates a better exercise capacity.

All the secondary outcomes will be tested and documented at baseline and every 13 weeks during the treatment period.

2.7.3. Safety outcomes

Safety will also be assessed in this study. Safety outcome assessments, including routine blood, urine and stool tests, liver and kidney function tests, and electrocardiography, will be performed at baseline and post-treatment. AEs will be recorded at any time they occur during the treatment period.

2.8. Quality control

In order to ensure the quality of research, quality control will run throughout the process. First, a reasonable and feasible study protocol has been developed by a formulation team including clinicians, ethicists, methodologists and statisticians. Standard operating procedures were formulated for each important step in the research process, such as enrollment and data collection. All the research participants, including researchers, receptionists and data processors, will be trained in the study protocol. In addition, oversight of the whole study process at each sub-center is another important means of quality control.

2.9. Statistical analysis

The data management and statistical analysis will also be conducted by Jiangsu Famous Medical Technology Co., Ltd. in Nanjing, China. First, EpiData 3.0 will be used to set up a database. Data entry will be performed by two independent researchers. All the raw data will be recorded. Only the per-protocol (patients that completed the entire treatment) dataset will be analyzed. Measurement data will be described by mean ± standard deviation, median and inter-quartile range. Count data will be summarized by frequency or composition ratio. Statistical analyses will be conducted using SAS 9.2.

Data at baseline will be compared between the study groups, including general characteristics and clinical and laboratory outcomes. Outcome measures will also be compared at the end of the treatment period, including pulmonary function, AEs, all-cause mortality and safety indicators. An independent *t*-test will be used to test for differences of continuous variables, and the chi-square test will be used for categorical variables. If necessary, paired *t*-test will be applied to intra-group comparison data with normal distribution and homogeneous variance, and Wilcoxon signed-rank sum test will be used for non-normal distribution or uneven variance. Repeated-measures analysis of variance (ANOVA) will be used to test continuous response variables that are measured at more than two time points for the same patient, such as clinical symptoms and signs, mMRC, HRQoL and 6-MWT. All the *P* values will be for two-sided distributions, with a significant level of 0.05 for α.

3. Discussion

There are some general differences in how TCM and Western medicine understand, manage and treat diseases. The foundation of TCM diagnosis takes into account the disease, syndrome and relevant clinical signs and symptoms, then synthesizes all that information to form a treatment principle. Since treatment based on syndrome differentiation is the core of effective TCM practice, we needed to formulate some standards of TCM syndrome differentiation for this study and their corresponding treatment schemes. In previous studies, we formulated standards of TCM syndrome differentiation for interstitial lung disease [16], and the corresponding treatment protocols showed good applicability in the clinical practice of IPF treatment. However, the results came from clinical experience, which could not be further popularized and applied. Advancing useful clinical application of TCM treatment in IPF will depend on conducting good-quality evidence-based studies, which use syndrome differentiation followed by appropriate TCM treatment.

In this study, TCM syndromes will also be considered in the allocation of patients to study groups. Researchers will evaluate the TCM syndrome of each participant according to their clinical manifestations, prior to their allocation to treatment or control group. One of the three Chinese medicine granules or placebo will be given to

each patient for the duration of the 26-week trial. Other measures will also be taken to prevent the introduction of bias into the study. For example, one group of researchers will diagnose the TCM syndromes, while the generation of randomization codes, treatment allocation and outcome measures will be conducted by other independent researchers to avoid bias as much as possible.

Proper measurement of treatment outcomes is another important factor in evaluating the efficacy of the study interventions. As a clinical trial for TCM, not only disease but also the efficacy characteristics of interventions should be considered in the selection of outcomes. According to our clinical experiments, treatment with TCM may result in improved pulmonary function, quality of life and exercise capacity. AEs are important episodes that can lead to a worse prognosis for an IPF patient [19,24], and most deaths from IPF are precipitated by AEs [25]. Accordingly, AEs are viewed as important indicators of treatment success. Pulmonary function is the most vulnerable physiological function in IPF patients, and is also closely related to AEs, prognosis, quality of life and exercise capacity [19,26,27]. FVC, FEV1 and DLco% of pulmonary function are strong indicators of patient prognosis in IPF and they have been used in other studies [9,10,28–30].

The present work is the first exploratory study of TCM treatment based on syndrome differentiation for the treatment of IPF. This study will provide a preliminary evaluation of the efficacy and safety of TCM treatment based on syndrome differentiation in IPF. However, there are still some limitations to this study. Because there is a lack of preliminary evidence-based research, the target sample size has been calculated based on exploratory research and may be smaller than necessary for the present work. On the other hand, an observation period of 26 weeks may be too short to assess the efficacy and safety of TCM in IPF, a chronic condition. So, data from the present work will be foundational to designing future studies with adequate sample size and an intervention duration better suited to evaluating the short, medium and long-term effects of TCM treatment for IPF.

In conclusion, this study tests the hypothesis that TCM can decrease AEs, improve pulmonary function and improve quality of life based on syndrome differentiation. The results will also provide preliminary evidence-based data to evaluate the role of TCM’s syndrome differentiation approach in the treatment of IPF.

4. Trial status

The trial is ongoing. At the time of manuscript submission, all the targeted patients have been recruited, but the clinical trial has not been completed.

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Author contributions

Xue-qing Yu contributed to the conception and design of the trial. Shu-guang Yang contributed to the data collection, data analysis and manuscript writing. Xue-qing Yu and Shu-guang Yang contributed to the work equally, and should be the co-first author. Yang Xie contributed to the data collection and analysis. Jian-sheng Li contributed to the conception and design, critical revision, and should be the corresponding author. All the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183(6):788–824.

2. Moreo K, Lattimer C, Lett JE, Heggen-Peay CL, Simone L. Integrated transitions of care for patients with rare pulmonary diseases. Prof Case Manag 2017;22(2):54–63.

3. Sgalla G, Biffi A, Richeldi L. Idiopathic pulmonary fibrosis: diagnosis, epidemiology and natural history. Respirology 2016; 21(3):427–37.

4. Raghu G, Chen SY, Hou Q, Yeh WS, Collard HR. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18–64 years old. Eur Respir J 2016;48(1):179–86.

5. Dove EP, Olson AL, Glassberg MK. Trends in IPF-related mortality in the United States: 2000–2017. Am J Respir Crit Care Med 2019;200(7):929–31.

6. Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. Adv Ther 2018;35(5):724–36.

7. Hopkins RB, Burke N, Fell C, Dion G, Kolb M. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. Eur Respir J 2016;48(1):187–95.

8. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med 2015;192(2):e3–19.

9. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22):2083–92.

10. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22):2071–82.

11. Hanta I, Cilli A, Sevinc C. The effectiveness, safety, and tolerability of pirfenidone in idiopathic pulmonary fibrosis: a retrospective study. Adv Ther 2019;36(5):1126–131.

12. Hajari Case A, Johnson P. Clinical use of nintedanib in patients with idiopathic pulmonary fibrosis. BMJ Open Respir Res 2017;4(1):e000192.

13. Diamantopoulos A, Wright E, Vlahopoulou K, Cornic L, Schoof N, Maher TM. The burden of illness of idiopathic pulmonary fibrosis: a comprehensive evidence

review. Pharmacoeconomics 2018;36(7):779–807.

14. Dong CY, Zhang Y, Yu XQ. Discussion on the name of pulmonary interstitial fibrosis in traditional Chinese medicine. Zhong Yi Za Zhi 2016;29(9):3–6 [Chinese].

15. Liu M, Chen MH, Wei CL, Zhao QL. Systematic review and meta-analysis of the efficacy and safety of traditional Chinese medicine in the treatment of idiopathic pulmonary fibrosis. Tianjin Zhong Yi Yao 2018;35(3):200–4 [Chinese].

16. Professional Committee of Pulmonary Diseases of China Association of Chinese Medicine. Diagnostic criteria of traditional Chinese medicine syndromes for diffuse interstitial lung disease (2012 Edition). Zhong Yi Za Zhi 2012;53(13):1163–65 [Chinese].

17. Criteria Committee of New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels. JAMA 1953;153(9):891.

18. Li XY. Calculation of sample size for clinical trial. Zhongguo Jie Ru Xin Zang Bing Xue Za Zhi 2014;22(7):430 [Chinese].

19. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016;194(3):265–75.

20. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988;93(3):580–6.

21. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. Eur Respir J 2009;34(3):648–54.

22. Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. Respir Med 1991;85(Suppl B):25–31.

23. Tarlov AR, Ware JE Jr, Greenfield S, Nelson EC, Perrin E, Zubkoff M. The medical outcomes study. An application of methods for monitoring the results of medical care. JAMA 1989;262(7):925–30.

24.Kakugawa T, Sakamoto N, Sato S, Yura H, Harada T, Nakashima S, et al. Risk factors for an acute exacerbation of idiopathic pulmonary fibrosis. Respir Res 2016;17(1):79.

25. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and

investigation of ethnic differences. Am J Respir Crit Care Med 2014;190(7):773–9.

26.Jeon K, Chung MP, Lee KS, Chung MJ, Han J, Koh WJ, et al. Prognostic factors and causes of death in Korean patients with idiopathic pulmonary fibrosis. Respir Med 2006;100(3):451–7.

27. Kreuter M, Swigris J, Pittrow D, Geier S, Klotsche J, Prasse A, et al. The clinical course of idiopathic pulmonary fibrosis and its association to quality of life over time: longitudinal data from the INSIGHTS-IPF registry. Respir Res 2019;20(1):59.

28. Salisbury ML, Xia M, Zhou Y, Murray S, Tayob N, Brown KK, et al. Idiopathic pulmonary fibrosis: gender-age-physiology index stage for predicting future lung function decline. Chest 2016;149(2):491–8.

29. Behr J, Demedts M, Buhl R, Costabel U, Dekhuijzen RP, Jansen HM, et al. Lung function in idiopathic pulmonary fibrosis—extended analyses of the IFIGENIA trial. Respir Res 2009;10:101.

30. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis—FDA review of pirfenidone and nintedanib. N Engl J Med 2015;372(13):1189–91.