Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial

Yu Yang, Sun Zengtao, Shi Liqing, Zhang Yanping, Zhou Zhaoshan, Zhang Shunan, Chao Enxiang

Yu Yang, Graduate School, Beijing University of Chinese Medicine, Beijing 100029, China
Sun Zengtao, Department of Respiratory Medicine, the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300150, China
Shi Liqing, Respiratory Pyrexia Department, Dongfeng Hospital Affiliated to Beijing University of Chinese Medicine, Beijing 100078, China
Zhang Yanping, Department of Respiratory Medicine, Xiyuan Hospital of China Academy of Traditional Chinese Medicine, Beijing 100091, China
Zhou Zhaoshan, Department of Respiratory Medicine, Qindao Hiser Medical Group, Shandong 266033, China
Zhang Shunan, Department of Respiratory Disease of Traditional Chinese Medicine, China-Japan Friendship Hospital, Beijing 100029, China
Chao Enxiang, Department of Respiratory Disease of Traditional Chinese Medicine, China-Japan Friendship Hospital, Beijing 100029, China

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Correspondence to: Prof. Zhang Shunan, Department of Respiratory Disease of Traditional Chinese Medicine, China-Japan Friendship Hospital, Beijing 100029, China. zhang_shunan@163.com; Prof. Chao Enxiang, Department of Respiratory Disease of Traditional Chinese Medicine, China-Japan Friendship Hospital, Beijing 100029, China. chaoenxiang@163.com

METHODS: One hundred cases with IPF were randomized into the treatment group (80) and control group (20). Both groups were given basic treatment with prednisone. The treatment group was given FGs, and the control group was given Jinshuibao capsules (JCs). Treatment lasted for 6 months. The Medical Research Council Dyspnea Scale (MRCDS), the Saint George's Hospital Respiratory Questionnaire (SGHRQ), pulmonary function, the Traditional Chinese Medicine Syndrome Score (TCMSS), 6-min walking test (6MWT) and blood gas analyses were recorded before the study as well as 3 months and 6 months after treatment.

RESULTS: FGs showed greater efficacy than the control in certain parameters between before the study and 6 months, and between 3 months and 6 months, in the MRCDS, some indicators in the SGHRQ, and the TCMSS. There were no significant differences between the treatment group and control group in the remainder of the indices evaluated. In the treatment group, there were significant differences in before and after treatment in the MRCDS, SGHRQ, TCMSS and 6MWT.

CONCLUSION: FGs were similar to JCs for IPF treatment.

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Key words: Idiopathic pulmonary fibrosis; Dyspnea; Surveys and questionnaires; 6-min walking test; Feiwei granules; Jinshuibao capsules; Randomized controlled trial

INTRODUCTION
Pulmonary fibrosis is an interstitial lung disease. Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing, interstitial pneumonia of unknown cause. It is characterized by diffuse inflammation and structural disorders in alveoli. The most common feature of IPF is progressive dyspnea. The disease carries a dismal prognosis, with an estimated median survival of 2.9 years from the time of diagnosis. Five-year survival for IPF is < 50%.  

Specific therapeutic options for IPF are lacking. Glucocorticoids, immunosuppressive agents, cytotoxic drugs or anti-fibrosis drugs are used commonly, but treatment effects are limited and data from randomized controlled trials scarce.

Symptoms of pulmonary interstitial fibrosis are mainly dry cough, dyspnea, and wheezing (particularly upon exertion). According to the definition described in The Synopsis of the Golden Chamber, "consumptive lung disease" is related to pulmonary interstitial fibrosis.  

Previously we demonstrated within Traditional Chinese Medicine (TCM) theory that lung-kidney deficiency and Qi deficiency with blood stasis are the most common syndromes. Feiwei granules (FGs) are a TCM prescription. FGs are beneficial to the lungs and kidneys, enrich Qi, and activate blood.  

Previously, when treating 32 IPF patients, we showed that FGs improved symptoms in 75% of cases. Liu et al. found that the lung function and quality of life (QoL) of IPF patients were improved significantly after FG treatment. We wished to evaluate the efficacy of FGs against IPF. Data collection included dyspnea scores, QoL scores, total Traditional Chinese Medicine Syndrome Score (TCMSS), 6-min walking test (6MWT), lung function, and blood gas analyses.

METHODS

Design
This was a randomized, controlled, clinical study conducted at three centers in Beijing (China-Japan Friendship Hospital, Dongfang Hospital Affiliated to Beijing University of Chinese Medicine, Xiyuan Hospital Affiliated to China Academy of Chinese Medical Sciences), one in Tianjin (Second Affiliated Hospital of Tianjin University of TCM), and one in Shandong (Qingdao Haici Medical Group).

Ethical approval of the study protocol
The study protocol was approved by the Ethics Committee of Beijing China-Japan Friendship Hospital, and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants (or their representatives) before enrollment.

Participants
One hundred patients were enrolled from January 2009 to December 2012.

Inclusion criteria were: (a) IPF patients diagnosed according to the criteria set by the Chinese Thoracic Society; (b) IPF patients diagnosed as having "lung-kidney deficiency, Qi deficiency with blood stasis" according to TCM principles; (c) disease severity of mild-to-moderate; and (d) patients aged 18-70 years.  

Exclusion criteria were patients: (a) suffering from other primary pulmonary diseases (e.g., bronchial asthma, chronic obstructive pulmonary disease, bronchiectasis, lung cancer); (b) who had used TCM preparations to regulate and supplement their lungs and kidneys, or who had taken other immune system-boosting drugs in the previous month; (c) using oral glucocorticoid drugs long-term; (d) who were pregnant, planning to become pregnant, or lactating; (e) who were allergic; (f) who had severe primary diseases of the heart, brain, digestive system, or hematopoietic system; (g) who did not have the mental capacity to cooperate with the researchers; (h) with a partial pressure of oxygen (PO2) at rest ≤ 50 mmHg; and (i) who had participated in other clinical studies in the previous month.

Medications
The treatment group was given FGs (Pharmaceutical Centre of Beijing China-Japan Friendship Hospital). Each 8-g bag of FG contained Xiyangshen (Radix Panax Quinoquefolii), Sanqi (Radix Notoginseng), Shan-zhuyu (Fructus Macrocarpi), Wuweizi (Fructus Schisandrae Chinensis), Ziwan (Radix Asteris Tatari), Maidong (Radix Ophiopogonis Japonici), Baigou (Semen Ginkgo), and stir-frying with liquid adjuvant Gancao (Radix Glycyrrhizae).

The control group was given Jinshuibao capsules (JCs; Jiminkexin Pharmaceuticals, Jiangxi, China). The basic-treatment group was given prednisone (JCs; Jing Shuguang Pharmaceuticals, Beijing, China).

The basic-treatment group was given prednisone (Beijing Shuguang Pharmaceuticals, Beijing, China). Patients were started on 0.5 mg/kg body weight (q.i.d.) in the first month. In the second month they were given 0.4 mg/kg (q.i.d.), in the third month they were given 0.3 mg/kg (q.i.d.), and then they were maintained on 10 mg/day for the next 9 months.

Randomization
Using the stratified randomization method according to a predetermined proportion of 4:1, the 100 IPF patients were randomized to the treatment group or control group. The data managers were masked throughout this study.

Treatment
Patients in the treatment group underwent basic treatment and treatment with FGs (two bags at a time, b.d.). Those in the control group underwent basic treatment and treatment with JCs (three capsules at a time, t.d.s.). Pharmacologic treatment lasted for 6 months from the date of enrollment. During this time, patients were not permitted to receive other medical interven-
ditions for IPF.

Outcome measures
Data were captured before beginning drug administration and at 3 months and 6 months. Researchers recorded the quantity of drugs accepted, taken and returned, and determined compliance with the medication regimen.

Endpoints
Efficacy outcomes were the Medical Research Council Dyspnea Scale (MRCDS), Saint George’s Hospital Respiratory Questionnaire (SGHRQ), lung function (vital capacity (VC), forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC), FEV₁%, total lung capacity (TLC), diffusing capacity of the lungs for carbon monoxide (DLCO), diffusing capacity of the lungs for carbon monoxide/alveolar volume (DLCO/VA), total TCMSS, MWT and blood gas analyses (pH, PO₂, partial pressure of carbon dioxide (PCO₂), HCO₃⁻).

Safety indices
General medical examination, regular blood and urine tests, electrocardiography [(ECG, liver function (alanine aminotransferase (ALT)), renal function (blood urea nitrogen (BUN), creatinine) and adverse events (signs and symptoms) were recorded before the study as well as at 3 months and 6 months.

Statistical analyses
Analyses were undertaken with SPSS v15.0 (IBM, Armonk, NY, USA). Qualitative data were assessed by the chi-square test, Fisher’s exact test or Wilcoxon rank sum test between two groups. The Student’s t-test was used if quantitative data had a normal distribution, and the Wilcoxon rank sum test if not. Single-factor repeated-measures analysis of variance (Mauchly’s test of sphericity) was used for comparisons before and after treatment within treatment and control groups. All statistical tests and confidence intervals were two-sided. P ≤ 0.05 was considered significant, and P ≤ 0.01 highly significant.

RESULTS

Baseline characteristics
During the study period, 20 (20%) of 100 patients were lost to follow-up, and three (3%) were excluded. There were 62 patients in the treatment group, and 15 in the control group (Figure 1).

There were no significant differences (P > 0.05) in sex (χ² = 4.000, P = 0.261), height (P = 0.364), weight (P = 0.455), systolic blood pressure (P = 0.092), diastolic pressure (P = 0.644), or history of smoking (χ² = 0.542, P = 0.770) between the two groups (Table 1).

MRCDS scores
There was a significant difference between the two groups at baseline (P = 0.000). Then, we compared the change between each follow-up visit. There were no significant differences in MRCDS scores from baseline to 3 months between the two groups (P = 0.111), whereas those from baseline to 6 months (P = 0.001) and from 3 months to 6 months (P = 0.009) were significant. Improvement in MRCDS scores in the treatment group tended to be better after a prolonged period of therapy (Table 2).

Comparison of MRCDS scores from before to after treatment in each group showed that the difference was significant in the FG group (P = 0.000) but not in the JC group (P = 0.254). Taking FGs tended to improve MRCDS scores (Table 3).

SGHRQ scores

Figure 1 Flowchart of the study
Notes: treatment group were treated with Feiwei granules (two bags per time, twice a day); control group were treated with Jinshuibao capsules (three capsules per time, three times a day). SBP: systolic blood pressure; DBP: diastolic blood pressure.

<table>
<thead>
<tr>
<th>Trait</th>
<th>Group</th>
<th>n</th>
<th>Baseline-Months 3</th>
<th>Baseline-Months 6</th>
<th>Months 3-Months 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>62</td>
<td>2.4±0.8</td>
<td>1.8±0.9</td>
<td>1.6±0.9</td>
<td>0.064</td>
</tr>
<tr>
<td>Control</td>
<td>15</td>
<td>1.4±0.8</td>
<td>1.1±0.8</td>
<td>1.5±1.2</td>
<td>0.270</td>
</tr>
</tbody>
</table>

Notes: treatment group were treated with Feiwei granules (two bags per time, twice a day); control group were treated with Jinshuibao capsules (three capsules per time, three times a day).

There was a significant difference between the two groups at baseline (P < 0.05). Differences in respiratory symptoms were significant between each follow-up visit (P < 0.05). There was no significant difference in activity limitation between each follow-up visit (P > 0.05). Disease effects showed no significant difference from 3 months to 6 months (P = 0.614) but a significant difference was observed from baseline to 6 months and from baseline to 3 months (P < 0.05). Total score of the SGHRQ from baseline to 3 months showed a significant difference (P = 0.011 446). Improvements in respiratory symptoms and disease effects were more significant in the treatment group after a prolonged duration of therapy (Table 4). Comparison of SGHRQ scores from before to after treatment in each group showed a significant difference in the FG group (P < 0.05), but not in the JC group (P > 0.05). Taking FGs tended to improve MRCDS scores (Table 5).

**Table 1** Characteristics of the patients at baseline (± s).

<table>
<thead>
<tr>
<th>Trait</th>
<th>Group</th>
<th>n</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>History of smoking (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>62</td>
<td>64.56</td>
<td>166±8</td>
<td>67±10</td>
<td>126±14</td>
<td>76±8</td>
<td>26/36</td>
</tr>
<tr>
<td>Control</td>
<td>15</td>
<td>56.67</td>
<td>167±7</td>
<td>70±13</td>
<td>118±15</td>
<td>75±7</td>
<td>5/10</td>
</tr>
</tbody>
</table>

**Table 2** Comparison of the change in dyspnea scores between different follow-up visits (± s).

**Dyspnea function** lung function (VC, FEV/FVC, FEV%, TLC, DLCO, DLCO/V) between each follow-up visit were not significant (P > 0.05). Differences in FVC between the two groups were significant at baseline (P = 0.0080). There was no significant difference in FVC between each follow-up visit (P > 0.05).

Comparison of lung function from before to after treatment in each group showed that only the difference in DLCO/V, was significant in the FG group (P = 0.003), whereas there was no significant difference in the JC group (P > 0.05). Taking FGs tended to improve DLCO/V.

**TCMSS**

The difference between the two groups was significant at baseline (P < 0.05). Then, we compared the change between each follow-up visit. The difference in the total TCMSS in the treatment group between each follow-up visit was significant (P < 0.05). Improvement in the TCMSS was better in the treatment group (Ta-

**Table 3** Comparison of dyspnea scores from before to after treatment in each group (± s).

**Table 4** Comparison of the change in SGRQ scores between different follow-up visits (± s).

Notes: treatment group were treated with Feiwei granules (two bags per time, twice a day); control group were treated with Jinshuibao capsules (three capsules per time, three times a day). *P > 0.05, †P < 0.05, compared with control group.
There were no significant differences in blood and urine tests, or levels of ALT, BUN, or creatinine between the two groups after treatment in each group showed that differences in PO₂ were significant in the FG group (P = 0.044), whereas there were no significant differences in the JC group (P > 0.05). Taking FGs tended to improve PO₂.

**Safety assessment**

There were no significant differences in blood and urine tests, or levels of ALT, BUN, or creatinine between the two groups (P > 0.05), or from before to after treatment in the FG group (P > 0.05). Abnormal ECGs were not observed in the JC group at baseline. However, three cases of bradycardia, one of occasional premature ventricular contraction, and one of ST-T wave change in the FG group were noted. During treatment, there were no changes in either group.

**DISCUSSION**

Guidelines set by the ATS/ERS/JRS/ALAT in 2011 stated that there were no effective therapeutic options for IPF except lung transplantation. The recommendation for corticosteroids in patients with acute exacerbations of IPF is weak. Long-term use of corticosteroids can result in hypo-immunity and damage to the liver,
kidneys and other organs, can trigger new infections, and can even increase the risk of respiratory failure.\(^\text{11}\) Lung transplantation is restricted by donor sources and expense. Therefore, research has focused on treating IPF with more effective and safe pharmaceutical drugs, some of which are TCMs.

The main component of JCs is powdered Cordyceps fungus, which benefits the lungs and kidneys by securing essence and tonifying Qi. It can be used in the TCM syndromes of lung-kidney deficiency, absence of essence Qi, chronic cough with asthma, fatigue, sleeplessness and forgetfulness, weakness in the waist and knees, irregular menstruation, impotence, and premature ejaculation.

Several studies have shown that the main active ingredients of Cordyceps sinensis are D-mannitol and polysaccharide, as well as other amino acids, nucleotides, sugar alcohols, sterols, peptides, vitamins, inorganic elements and polyamines that are essential for humans. Those compounds can regulate immune function, anti-oxidation actions, and anti-tumor actions, inhibit the inflammatory response, regulate blood lipids, promote tissue repair, adjust immune functions, relax bronchial smooth muscle, regulate metabolism, and resist pulmonary fibrosis.\(^\text{12-14}\) \(^\text{Xu et al.}\)\(^\text{15}\) demonstrated that Cordyceps sinensis liquid can improve the early alveolitis seen in pulmonary fibrosis. Yang et al.\(^\text{16}\) found that Cordyceps mycelia powder can inhibit excess deposition of collagen fibers. Yang et al.\(^\text{17}\) treated rats with pulmonary fibrosis with Cordyceps mycelia powder, and found that it could improve gas exchange, relieve infiltration of inflammatory cells, and suppress and prevent pulmonary fibrosis. JCs are used widely to treat IPF.

In the present study, after consulting experts in respiration disease, we used JCs combined with prednisone as the control group. We found that the efficacy of FGs was similar to that of JCs. FGs improved various indices after administration and were superior to JCs in some indices. Serious treatment-related adverse events were not observed.

The present study had limitations. First, we used prednisone as a basic treatment according to the guidelines on the diagnosis and treatment of IPF set by the Chinese Thoracic Society in 2002. However, in the latest international guideline, prednisone is no longer the recommendation for basic treatment. Second, the observation period was 6 months, whereas the observation period of large international IPF studies is often 48-52 weeks.\(^\text{18}\)

In conclusion, FGs improved dyspnea scores, SGHRQ scores, DLCO/V, total TCSS, and 6-min walking test in IPF patients whose TCM syndrome was lung—kidney deficiency and Qi deficiency with blood stasis. FGs were similar to JCs for IPF treatment. This study indicates that FGs was safe in treating IPF patients. It is beneficial to the treatment based on syndrome differentiation for physicians and convenient for patients. Further study is needed to confirm our pilot findings.

**REFERENCES**


