Effects of Qizhukangxian granules on idiopathic pulmonary fibrosis: a randomized, double blind, placebo-controlled and multicenter clinical pilot trial

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Abstract

OBJECTIVE: To evaluate the effects of Qizhukangxian granules (QG) on idiopathic pulmonary fibrosis (IPF).

METHODS: This is a randomized, double blind, placebo-controlled and multicenter clinical pilot trial. Six medical centers in Tianjin, China, participated in the study. A total of 120 IPF patients were enrolled and randomized into two groups, with 60 patients in each group. The treatment group was treated with QG, while the control group received a Qizhukangxian placebo. The pharmacological treatment lasted for 48 weeks from the enrollment date. The indexes of patients were recorded on the admission day and at the end of the 24th and 48th weeks. Data were analyzed to study the effects of QG; forced vital capacity, change in forced vital capacity and maximal 6-min walk test (6MWT) distance were the primary endpoints. Secondary endpoints were percentage of patients with episodes of acute exacerbation of IPF, pulmonary function, changes in pulse oxygen saturation during the 6MWT, dyspnea score, St. George’s respiratory questionnaire score, arterial blood gas analyses and the total Traditional Chinese Medicine symptom pattern score.
RESULTS: After 24 weeks of treatment, QG showed greater efficacy than the placebo in certain parameters, including the dyspnea score. Traditional Chinese Medicine symptom pattern score and some indicators in the St. George’s respiratory questionnaire score. Analysis of the indexes obtained from all patients at the end of the 48th week showed that the therapeutic effects in the treatment group were significantly better than those in the control group because remarkable differences were observed in most of the primary and secondary endpoints between the two groups, except for the maximal distance of the 6MWT and arterial blood gas analyses. No adverse reaction was observed in either group during the 48-week trial treatment period.

CONCLUSION: QG could effectively treat IPF patients by ameliorating pulmonary function, improving the quality of life and lowering the percentage of acute exacerbations.

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Keywords: Idiopathic pulmonary fibrosis; Vital capacity; Walk test; Randomized controlled trial; Qizhukangxian granules

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease defined by a histopathological pattern of usual interstitial pneumonia (UIP) on either a high-resolution computed tomography (HRCT) scan or surgical lung biopsy and characterized by progressive dyspnea. The incidence of IPF is estimated to be 6.8 to 16.3 per 100,000 and appears to have increased in recent years. The disease has a very poor prognosis, with a life expectancy of 2 to 6 years and an estimated median survival of 2 to 3 years after diagnosis. The 5-year survival rate of IPF is less than 30%.

Despite decades of extensive research, effective treatments for IPF are disappointingly limited. Glucocorticoids, antioxidants, immunosuppressive agents and cytotoxic drugs are commonly used but show no appreciable effects on clinical outcomes. Although clinical trials of pirfenidone and nintedanib have shown that each drug reduces the rate of decline of lung function and increases progression-free survival in IPF, these drugs have significant side effects and are too expensive for therapy for most patients.

Many studies of Traditional Chinese Medicine (TCM) have found that some Chinese medicines have positive effects when treating IPF patients. However, most studies lack reasonably designed research schemes and data from randomized controlled trials are scarce. In this paper, we investigated the therapeutic effects of Qizhukangxian granules (QG) for treatment of IPF patients.

METHODS

Design

This is a randomized, double blind, placebo-controlled and multicenter clinical pilot study conducted in six medical centers (The Second Affiliated Hospital of Tianjin University of TCM, The First Affiliated Hospital of Tianjin University of TCM, Tianjin Chest Hospital, The Affiliated Hospital of Tianjin Armed Police Medical College, Tianjin Beichen TCM Hospital and Tianjin Dongli TCM Hospital), which are six tertiary referral hospitals in Tianjin, China.

The sample size was calculated using an inspection level where $\alpha = 0.05$, the test power was 0.90, the non-compliance rate was 10% and the dropout rate for follow-up was 15%.

Ethics

The trial was approved by the Ethics Committee of The Second Affiliated Hospital of Tianjin University of TCM and adhered to the principles of the Declaration of Helsinki. The protocol and its informed consent form were judged by the Ethics Committee to be ethically and scientifically satisfactory for the study aims. Written informed consent was obtained from all participants or their representatives before enrolling.

Participants

According to the inclusion and exclusion criteria, 120 IPF patients were enrolled from August 1, 2013 to July 31, 2016.

Inclusion criteria: (a) IPF patients diagnosed according to the evidence-based guidelines for the diagnosis and management of IPF published in 2011; (b) IPF patients who were diagnosed as having a pattern of “Qi deficiency and blood stasis” according to TCM principles; (c) lung function test: a predicted forced vital capacity (FVC) ranging from 50% to 90%, a predicted carbon monoxide diffusing capacity (DLCO) ranging from 30% to 90%, a ratio of the forced expiratory volume in 1 s (FEV1) to the FVC of at least 80%; (d) a partial pressure of oxygen (PO2) of at least 50 mm Hg with the patient at rest and breathing room air; (e) patients from 18 to 75 years of age; (f) the informed consent form was completed and submitted.

Exclusion criteria: (a) patients suffering from other primary pulmonary diseases such as bronchiectasis, tuberculosis, asthma, chronic obstructive pulmonary disease, or lung cancer; (b) aggravated dyspnea in the past 6 months; (c) currently experiencing an acute exacerbation of IPF (AE-IPF); (d) fasting blood glucose level exceeding 11.1 mmol/L; (e) severe primary disease of the heart, brain, or digestive system or mental diseases; (f) comorbid conditions including malignancy, bleeding.
ing tendency, severe hepatic dysfunction (serum level of alanine transaminase or aspartate transaminase two-fold above the upper limit of normal), or renal dys-
function (serum creatinine level above the upper limit of normal); (g) use of immune suppressants or anti-fi-
brotic drugs including interferon and colchicine; (h) use of oral glucocorticoid (prednisone at a dose ≥ 15 mg/d or the equivalent in the past 3 months; (i) pa-
tients who had used TCM to supplement the Qi of the lung and kidney or who had activated blood stasis to treat IPF or other diseases in the past 3 months; (j) cur-
cently pregnant, planning to be pregnant, or lactating; (k) participation in another clinical trial in the past 3 months; (l) allergic constitution or Chinese herb allergies.

Medicines
(a) QG [produced by the Pharmaceutical Centre of the Second Affiliated Hospital of Tianjin University of TCM, Tianjin, China; composed of Huangqi (Radix Astragali Mongolici), Ezhu (Rhizoma Cucurbitae Photo-
caulis), Danggui (Radix Angelicae Sinensis), Shanzhuyu (Fructus Macrocarpi), Ziwan (Radix Asteris Tatari), Huangqin (Radix Scutellariae Batalensis), Zhebeimu (Bulbus Frutillariae Thunbergii) and Gancao (Radix Glycyrrhiza), 8 g/bag];
(b) Qizhukangxian placebo (QP) [produced by the Pharmaceutical Centre of the Second Affiliated Hospital of Tianjin University of TCM, Tianjin, China; com-
posed of 5% crude QG drug and 95% starch, 8 g/bag].

Randomization and blindness
Using the stratified block randomization method, ac-
cording to a predetermined proportion of 1:1:1, the 120 IPF patients were randomized to the treatment (QG) group or the control (QP) group, with 60 patients in
each group. Staff members who were not involved in this clinical trial were involved in the randomization process. After enrollment in the study, the participants were given a fixed prescription and received study med-
ications from the pharmacy staff according to the en-
rollment sequence. Both QG and QP had the same ap-
pearance, shape, color and packaging; therefore, the re-
searchers and participants were not aware of the differ-
ence.

Treatments
During the trial, patients in the treatment group were treated with QG {two bags per treatment, twice a day}, while those in the control group treated with QP {two bags per treatment, twice a day}. All patients were guid-
ed on medicinal use by health education. The pharma-
cological treatment lasted for 48 weeks from the date of enrollment. During this period, patients were not permitted to receive other medicinal interventions for IPF.

Measurement
The participants were asked to follow-up in the hospi-
tal at the end of the 12th, 24th, 36th and 48th weeks after they were enrolled. The safety indexes were mea-
sured at all follow-up visits, whereas the efficacy index-
es were assessed only at the end of the 24th and 48th weeks.

The primary endpoints were defined as the FVC, change in FVC (24th week–baseline, 48th week–baseline and 48th week–24th week) and the maximal dis-
ance of the 6MWT.

The secondary endpoints were defined as the percentage of the patients with AE-IPF episodes; the total score of a TCM symptom pattern form (TC-
MSP): (a) the TCM symptom pattern mainly included cough, expectoration and shortness of breath. The se-
verity of each symptom was divided into four grades:
none (score: 0), mild (score: 2), moderate (score: 4) and severe (score: 6). The TCMS was completed and the scores of each symptom were summed. A higher to-
tal score indicated more serious symptoms. The percentage of predicted FEV1 (FEV1%) and the percentage of predicted FVC (FVC%) were used to eval-
uate the functional status of the patients. The percentage of predicted DLCO (DLCO%) were used to eval-
uate the gas exchange function of the lungs. The ratio of DLCO to FVC (DLCO/FVC) was used to eval-
uate the impairment of lung diffusion function.

Analyses of arterial blood gas (ABG) included the partial pressure of oxygen (PaO2), partial pressure of car-on dioxide (PaCO2) and oxygen saturation of blood (SaO2).

The percentage of the patients with AE-IPF episodes; The total score of a TCM symptom pattern form (TC-
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uate the functional status of the patients. The percentage of predicted DLCO (DLCO%) were used to eval-
uate the gas exchange function of the lungs. The ratio of DLCO to FVC (DLCO/FVC) was used to eval-
uate the impairment of lung diffusion function.
Efficacy criteria according to the reference
After the 48-week treatment, we ranked the clinical efficacy into four grades including clinical control, significantly effective, effective and ineffective according to the guide for clinical research for new TCM (trial version). 12

Statistical analysis
Data were statistically analyzed by a third party. Ranked data were assessed by ridit analysis. Quantitative data are summarized as the mean ± standard deviation (\(\bar{x} \pm s\)). Paired t-tests were used for before and after treatment comparisons within the treatment and control groups, while independent samples t-tests were used for comparisons between the two groups. \(\chi^2\) tests were applied to compare qualitative data. Non-parametric tests were used when data were not normally distributed. Statistical analysis was performed using SPSS 11.5 software (SPSS Inc., SPSS Statistics for Windows, Chicago, IL, USA) and a value of \(P < 0.05\) was considered statistically significant.

RESULTS

Baseline characteristics of the enrolled patients
From August 2013 through July 2016, a total of 120 patients were enrolled; 60 were assigned to receive QG and 60 were assigned to receive QP. Six patients (two patients in the QG group and four patients in the QP group) withdrew from the study. Six patients died during the study, including two patients in the QG group and four patients in the QP group. A total of 108 patients completed the entire study (Figure 1).

All data from the 120 participants were included in the statistical analysis. For the ranked analyses, values missing because of death were assigned to the worst ranks. In the mean change analyses, values missing because of death were assigned to the worst possible outcome, that is, FVC = 0. Values missing for reasons other than death were recorded as the average value for the three patients with the smallest sum of squared differences at each visit (Figure 1).

Among the 120 IPF patients, 99 were diagnosed with a definite UIP pattern according to HRCT and the others were diagnosed with a probable UIP pattern. There were no significant differences \((P > 0.05)\) in the baseline characteristics between the QG group and the QP group (Table 1).

FVC
No significant difference \((P > 0.05)\) in the FVC was observed between the two groups before treatment. At the end of the 24th week, no significant difference \((P > 0.05)\) was found between the groups, whereas a significant difference \((P < 0.05)\) was observed at the end of the 48th week (Table 2). When comparing the FVC at the end of the 24th and 48th weeks with the baseline value, significant differences \((P < 0.05)\) were found in the two groups. When comparing the FVC at the end of the 48th week with that at the 24th week, a significant difference \((P < 0.05)\) was observed in the two groups (Table 2).

Change in the FVC
No significant difference \((P > 0.05)\) was noted between

![Flowchart of the study](image-url)

Figure 1 Flow chart of the study
QG: Qizhukangxian granules; QP: Qizhukangxian placebo.
the two groups in the change in FVC between the 24th week and the baseline; however, a significant difference ($P < 0.05$) was observed in the change in FVC between the 48th week and the baseline. Meanwhile, a significant difference ($P < 0.05$) was found in the change in FVC between the 48th week and 24th week (Table 3).

**Maximal distance of the 6MWT**

There was no significant difference ($P > 0.05$) in the 6MWT between the two groups before treatment. Additionally, no significant difference ($P > 0.05$) was found between the two groups at the end of the 24th or 48th weeks (Table 4).

When comparing the maximal distance of the 6MWT at the end of the 24th and 48th weeks with the baseline value, no significant difference ($P > 0.05$) was noted at the end of the 24th week in the two groups, whereas a significant difference ($P < 0.05$) was observed at the end of the 48th week in the two groups. When the maximal distance of the 6MWT at the end of the 48th week was compared with that at the 24th week, a significant difference ($P < 0.05$) was observed in the two groups (Table 4).

**Percentage of patients with AE-IPF episodes**

No significant difference ($P > 0.05$) was found between the two groups in the percentage of patients with AE-IPF episodes at the end of the 24th week; however, a significant difference ($P < 0.05$) was observed at the end of the 48th week (Table 5).

**Pulmonary function test**

No significant differences ($P > 0.05$) in FVC%, FEV1, FEV1%, DLCO and DLCO% were observed between the two groups before treatment. At the end of the 24th week, no significant differences ($P > 0.05$) in FVC%, FEV1, FEV1%, DLCO and DLCO% were noted between the two groups. At the end of the 48th week, significant differences ($P < 0.05$) in FVC%, DLCO and DLCO% were found between the two groups; however, no significant differences ($P > 0.05$) in FEV1 and FEV1% were observed between the two groups (Table 6).

### Table 1 Baseline characteristics of the enrolled patients ($\bar{x} \pm s$)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group ($n = 60$)</th>
<th>Control group ($n = 60$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.1±5.0</td>
<td>59.6±5.3</td>
</tr>
<tr>
<td>Male sex (n/%)</td>
<td>53/88.33</td>
<td>54/90.00</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6±2.8</td>
<td>25.6±2.7</td>
</tr>
<tr>
<td>Han nationality (n/%)</td>
<td>60/100</td>
<td>60/100</td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>1.4±0.6</td>
<td>1.3±0.6</td>
</tr>
<tr>
<td>History of smoking (n/%)</td>
<td>43/71.67</td>
<td>45/75.00</td>
</tr>
</tbody>
</table>

Notes: the treatment group was treated with Qizhukangxian granules (two bags per treatment, twice a day); the control group was treated with a Qizhukangxian placebo (two bags per treatment, twice a day). BMI: body mass index. Compared with the treatment group, ‘$P > 0.05$’.

### Table 2 Comparison of FVC (L, $\bar{x} \pm s$)

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>Baseline</th>
<th>24th week</th>
<th>48th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>60</td>
<td>3.0±0.6</td>
<td>2.6±0.5*</td>
<td>2.3±0.5*</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>3.0±0.6</td>
<td>2.6±0.7*</td>
<td>1.9±0.5*</td>
</tr>
</tbody>
</table>

Notes: the treatment group was treated with Qizhukangxian granules (two bags per treatment, twice a day); the control group was treated with a Qizhukangxian placebo (two bags per treatment, twice a day). FVC: forced vital capacity. Compared with the treatment group, ‘$P < 0.05$’; compared with the baseline, ‘$P < 0.05$’; compared with the 24th week, ‘$P < 0.05$’.

### Table 3 Comparison of the changes in FVC (L, $\bar{x} \pm s$)

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>24th week-baseline</th>
<th>48th week-baseline</th>
<th>48th week-24th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>60</td>
<td>-0.32±0.11</td>
<td>-0.71±0.21*</td>
<td>-0.34±0.12*</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>-0.38±0.09</td>
<td>-1.23±0.36</td>
<td>-0.65±0.18</td>
</tr>
</tbody>
</table>

Notes: the treatment group was treated with Qizhukangxian granules (two bags per treatment, twice a day); the control group was treated with a Qizhukangxian placebo (two bags per treatment, twice a day). FVC: forced vital capacity. Compared with the control group, ‘$P < 0.05$’.

### Table 4 Comparison of the maximal distances of the 6MWT (m, $\bar{x} \pm s$)

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>Baseline</th>
<th>24th week</th>
<th>48th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>60</td>
<td>463±78</td>
<td>464±87*</td>
<td>427±82**</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>469±83</td>
<td>460±91</td>
<td>410±73**</td>
</tr>
</tbody>
</table>

Notes: the treatment group was treated with Qizhukangxian granules (two bags per treatment, twice a day); the control group was treated with a Qizhukangxian placebo (two bags per treatment, twice a day). 6MWT: 6-min walk test. Compared with the control group, ‘$P > 0.05$’; compared with the baseline, ‘$P > 0.05$’; compared with the 24th week, ‘$P < 0.05$’.
Compared with the baseline values, the FVC%, DLCO and DLCO% of the end of the 24th and 48th weeks had decreased significantly ($P < 0.05$) in the two groups, whereas no significant differences ($P > 0.05$) were observed in the FEV, and FEV,% in the two groups. When comparing the values at the end of the 48th week and 24th week, there were significant differences ($P < 0.05$) in the FVC%, whereas no significant differences ($P > 0.05$) were found in the FEV, and FEV,% in the two groups. Compared with the values at the end of the 24th week, the DLCO and DLCO% at the end of the 48th week had decreased significantly ($P < 0.05$) in the control group; however, the differences were not statistically significant ($P > 0.05$) in the treatment group (Table 6).

**Dyspnea scores**

There was no significant difference ($P > 0.05$) in dyspnea score between the two groups before treatment. At the end of the 24th and 48th weeks, significant differences ($P < 0.05$) were observed in the dyspnea score between the two groups (Table 7).

When comparing the dyspnea scores at the end of the 24th and 48th weeks with the baseline value, significant differences ($P < 0.05$) were found at both follow-up visits in the two groups. When the values at the end of the 48th and 24th weeks were compared, there was no significant difference ($P > 0.05$) in the treatment group, whereas a significant difference ($P < 0.05$) was observed in the control group (Table 7).

**Change in SPO, during the 6MWT**

No significant difference ($P > 0.05$) was observed between the two groups before treatment. No significant difference ($P > 0.05$) was found between the two groups in the change in SPO, during the 6MWT at...
the end of the 24th week; however, a significant difference \((P < 0.05)\) was observed at the end of the 48th week (Table 8).

When comparing the changes in \(\text{SPO}_2\) during the 6MWT of the end of the 24th and 48th weeks with the baseline values, no significant differences \((P > 0.05)\) were observed for either follow-up visit in the two groups. Additionally, no significant differences \((P > 0.05)\) were found in the two groups for the values at the end of the 48th and 24th weeks (Table 8).

**SGRQ scores**

Before treatment, the differences in respiratory symptoms, activity limitation, disease affect and total score were not significant between the two groups \((P > 0.05)\). At the end of the 24th and 48th weeks, significant differences \((P < 0.05)\) were observed in respiratory symptoms, disease affect and total score between the two groups (Table 9).

When comparing the scores of the end of the 24th and 48th weeks with the baseline values, significant differences \((P < 0.05)\) were found in respiratory symptoms, disease affect and total score at both follow-up visits in the two groups. When the scores of the end of the 48th week were compared with those at the 24th week, a significant difference \((P < 0.05)\) was found in respiratory symptoms in the control group; meanwhile, remarkable differences \((P < 0.05)\) were observed in disease affect and total score in the two groups (Table 9).

**ABG analyses**

When comparing the two groups before treatment and at the end of the 24th and 48th weeks, the differences in \(\text{ABG}\) including the \(\text{PaO}_2\), \(\text{PaCO}_2\) and \(\text{SaO}_2\) were not significant \((P > 0.05)\). When the \(\text{ABG}\) analysis at the end of the 24th and 48th weeks was compared with the baseline values, no significant differences \((P > 0.05)\) were found in the \(\text{PaO}_2\), \(\text{PaCO}_2\) and \(\text{SaO}_2\) at both follow-up visits in the two groups. When comparing the \(\text{ABG}\) of the end of the 48th week with that at the 24th week, there were also no significant differences \((P > 0.05)\) in the \(\text{PaO}_2\), \(\text{PaCO}_2\) and \(\text{SaO}_2\) in the two groups.

**TCMSP**

Before treatment, the difference in the TCMSP score was not significant \((P > 0.05)\) between the two groups. At the end of the 24th and 48th weeks, significant differences \((P < 0.05)\) in TCMSP scores were observed between the two groups (Table 10).

When comparing the TCMSP scores at the end of the 24th and 48th weeks with the baseline value, significant differences \((P < 0.05)\) were observed at both follow-up visits in the two groups. When the values at the end of the 48th and 24th week were compared, no significant difference \((P > 0.05)\) was found in the treatment group, whereas a remarkable difference \((P < 0.05)\) was observed in the control group (Table 10).

**Clinical efficacy**

The total clinical efficacy in the treatment group was 51.67\%, which was significantly higher than the value of 11.67\% in the control group \((P < 0.05)\) after the 48 weeks of treatment (Table 11).

**Safety assessment**

No adverse reactions were observed in either group during the trial treatment period.

### Table 9: Comparison of SGRQ scores (scores, \(\bar{x} \pm s\))

<table>
<thead>
<tr>
<th>Item</th>
<th>Group</th>
<th>(n)</th>
<th>Baseline</th>
<th>24th week</th>
<th>48th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory symptoms</td>
<td>Treatment</td>
<td>60</td>
<td>55±17</td>
<td>46±13(a)</td>
<td>44±13(a)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>60</td>
<td>53±16</td>
<td>62±16(a)</td>
<td>70±19(a)</td>
</tr>
<tr>
<td>Activity limitation</td>
<td>Treatment</td>
<td>60</td>
<td>55±9</td>
<td>53±15</td>
<td>54±18</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>60</td>
<td>54±12</td>
<td>55±18</td>
<td>53±20</td>
</tr>
<tr>
<td>Disease affect</td>
<td>Treatment</td>
<td>60</td>
<td>52±16</td>
<td>40±11(a)</td>
<td>32±7(a)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>60</td>
<td>53±15</td>
<td>61±14(a)</td>
<td>69±10(a)</td>
</tr>
<tr>
<td>Total score</td>
<td>Treatment</td>
<td>60</td>
<td>55±16</td>
<td>45±14(a)</td>
<td>36±12(a)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>60</td>
<td>54±15</td>
<td>62±19(a)</td>
<td>70±17(a)</td>
</tr>
</tbody>
</table>

Notes: the treatment group was treated with Qizhukangxian granules (two bags per treatment, twice a day); the control group was treated with a Qishihuangxian placebo (two bags per treatment, twice a day). SGRQ: St. George’s respiratory questionnaire. Compared with the control group, \(^aP < 0.05\); compared with the baseline, \(^bP < 0.05\); compared with the 24th week, \(^cP < 0.05\).

### Table 10: Comparison of TCMSP (scores, \(\bar{x} \pm s\))

<table>
<thead>
<tr>
<th>Group</th>
<th>(n)</th>
<th>Baseline</th>
<th>24th week</th>
<th>48th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>60</td>
<td>15±4</td>
<td>10±2(a)</td>
<td>9±3(a)</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>15±3</td>
<td>19±5(c)</td>
<td>24±4(c)</td>
</tr>
</tbody>
</table>

Notes: the treatment group was treated with Qizhukangxian granules (two bags per treatment, twice a day); the control group was treated with a Qishihuangxian placebo (two bags per treatment, twice a day). TCMSP: the total score of a Traditional Chinese Medicine symptom pattern form. Compared with the control group, \(^aP < 0.05\); compared with the baseline, \(^bP < 0.05\).
DISCUSSION

Our research focused on finding sufficient evidence to support the use of specific pharmacologic therapies, including TCMs,\textsuperscript{19,20} for IPF patients. Our findings showed that the FVC and FVC\% in the treatment group were significantly higher than those of the control group at the end of the 48th week, while there was no significant difference between the two groups at the end of the 24th week. Table 3 shows that compared with the control group, no significant difference in the change in FVC was found between the 24th week and the baseline in the treatment group, whereas the changes in FVC between the 48th week and the baseline and between the 48th week and the 24th week were significantly lower in the treatment group. This indicated that patients might obtain more long-term benefit from QG intervention. However, the FVC and FVC\% of the two groups continuously decreased; therefore, we concluded that QG could only postpone, but not completely prevent or restore, the tendency of FVC and FVC\% decline. Additionally, QG had no effect on the reduction of the maximal distance of the 6MWT and ABG analyses during the whole treatment period, yet it could decrease the change in SPO\(_2\) during the 6MWT at the end of the 48th week, as shown in Tables 4 and 8. Moreover, Table 5 shows that the percentage of patients with AE-IPF episodes at the end of the 48th week in the treatment group was approximately one third of that in the control group, whereas no remarkable difference was found between the two groups at the end of the 24th week.

Additionally, the other three indicators shown in Tables 7, 9 and 10, namely the dyspnea score, TCMSP score and respiratory symptoms score on the SGRQ, were significantly lower in the treatment group than those in the control group at the end of the 24th and 48th weeks. Therefore, QG can effectively relieve the symptoms of IPF patients such as cough, expectoration and dyspnea. Additionally, Table 9 shows that the quality of life can be improved because the disease affects scores and total SGRQ scores were lower in the treatment group than in the control group at the end of the 24th and 48th weeks.

Moreover, QG might protect pulmonary diffuse function from deteriorating as the DLCO and DLCO\% were higher in the treatment group at the end of the 48th week. In particular, QC might impede the decline of DLCO and DLCO\%, as shown in Table 6. Additionally, Table 11 demonstrates that the total clinical efficacy in the treatment group was significantly higher than that in the control group after 48 weeks of treatment.

According to these findings, we can conclude that QG is effective in treating IPF patients because analyses of the indexes obtained from all patients at the end of the 48th week showed that the therapeutic effects in the treatment group were significantly better than those in the control group This conclusion is supported by remarkable differences in most of the primary and secondary endpoints between the two groups, except for the maximal distance of the 6MWT and ABG analyses. In TCM, IPF is similar to a "consumptive lung disease" according to the definition described in the Synopsis of Golden Chamber. From the perspective of TCM theory, IPF mainly affects the lung in the early stage and, along with the progression of the disease, eventually leads to Ben deficiency and a Biao excess pattern characterized by Qi deficiency of the lung, spleen and kidney accompanied by blood stasis and phlegm retention. The pathogenesis of IPF is an anti-pathogenic Qi deficiency and pathogenic Qi excess. Therefore, the treatment principle of supplementing vital Qi combined with activating blood circulation, dispelling blood stasis and resolving phlegm is used. QG is formulated based on this treatment principle; therefore, it can improve the Zang-Fu organ function to delay progression of the disease in IPF patients.

There were some limitations to our study. First, some selection bias occurred in our trial. Our participants were treated in diverse types of medical centers; some centers were TCM or integrative medicine hospitals, while others were modern Western Medicine hospitals. Additionally, all medical centers were located in different districts of Tianjin. However, all patients resided in the same city in China and were Han Chinese. Second, because of financial constraints, in our study, only 120 patients were enrolled, which is a smaller sample size than that of other large international IPF clinical trials. Third, none of our enrolled patients were prescribed any other medicine that might be beneficial to IPF patients, such as pirfenidone, as a baseline or positive control treatment.\textsuperscript{21,22} Thus, we were not able to examine the advantages and disadvantages of the effects of QG.
on IPF compared with other potentially effective and safe drugs.

In conclusion, our study suggests that QG could effectively treat IPF patients by delaying the decline of pulmonary function, relieving the clinical symptoms, improving the quality of life and lowering the percentage of acute exacerbation without obvious side effects during a 48-week treatment period. QG might be an alternative to IFP treatment. Using in vivo and in vitro studies, we plan to further confirm our pilot findings with larger sample size clinical trials and to explain the mechanism underlying the effects of QC.

REFERENCES