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Evidence-Based Integrative Medicine

Effectiveness and Safety of Chinese Medicine for Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis*

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ABSTRACT **Objective**: To evaluate the effectiveness and safety of Chinese medicine (CM) for Idiopathic pulmonary fibrosis (IPF) patients. **Methods**: To screened relevant articles, PubMed, Cochrane Library, Excerpta Medica Datase (EMBASE), China National Knowledge Infrastructure (CNKI), Chinese VIP Information (VIP), Wanfang Database and Chinese Biomedical Database (CBM) were searched in English or Chinese until December 2015 for randomized controlled trials, which compared CM treatment (CM group) with Western medicine or placebo (control group) on IPF. The outcome measures included acute exacerbation, pulmonary function, the St George's respiratory questionnaire (SGRQ) scores, 6-minute walk test (6MWT) distance, adverse events and mortality. **Results**: This meta-analysis included 25 randomized controlled trials involving 1,471 patients. Compared with the control group, CM group was superiori in reducing the risk of exacerbation [relative risk (RR)=0.40, 95% CI 0.22 to 0.72, P<0.05], improving in forced expiratory volume in one second (FEV1) [standard mean difference (SMD)=0.62, 95% CI 0.40 to 0.84, P<0.01] and diffusion capacity for carbon monoxide (DLCO, SMD=0.40, 95% CI 0.22 to 0.58, P<0.01), but there was no significant difference in vital capacity (VC, SMD=0.10, 95% CI –0.12 to 0.31, P>0.05). This meta-analysis also revealed that CM therapy significantly decreased the SGRQ score (SMD=–0.60, 95% CI –1.14 to –0.05, P<0.05) and improved 6MWT distance (SMD=0.59, 95% CI 0.34 to 0.84, P<0.01), compared with the control group. Meanwhile, CM therapy was associated with a low incidence of adverse effects (RR=0.19, 95% CI 0.08 to 0.43, P<0.01). However, there was no significant difference in mortality (RR=0.24, 95% CI 0.05 to 1.10, P>0.05) between CM and control groups. **Conclusions**: The pooled outcomes suggest that CM treatment appears benefit in reducing the risk of exacerbation, improving lung function and decreasing the incidence of adverse effects and enhancing the quality of life. However, the outcomes were limited because of the low quality of the included studies. More rigorous clinic trials need to be carried out to provide sufficient and accurate evidence in the future.

KEYWORDS idiopathic pulmonary fibrosis, Chinese medicine, meta-analysis

Idiopathic pulmonary fibrosis (IPF) is an irremediable disease which is clinically characterized by shortness of breath on exercise and dyspnea, and leads to deterioration of lung function and ultimately respiratory failure and even death. Though the specific aetiology of IPF is incompletely understood, emphysema, lung cancer, pulmonary hypertension, gastroesophageal reflux disease is related to the cause of IPF has been confirmed.[1-4] Epidemiological documents suggest that the incidence of IPF is 4.6–16.3 per 100,000 and the survival time is only 3–5 years.[5]

The major objective of the current pharmacotherapy is to delay the progression of IPF,[6] while most of Western medicine (WM) drugs have unsatisfactory effect with complaints including nausea, osteoporosis, dizziness and photosensitivity.[4] Therefore, it is critical to select other safe and potentially useful medications for the treatment of IPF.

Chinese medicine (CM) has taken responsibility for guarding the health of Chinese people for thousands of years. Obstruction of phlegm and blood

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stasis, the yin deficiency of Fei (Lung) and Shen (Kidney) have become two important concepts in CM to explain IPF. Therapeutic strategies of CM on IPF are mainly focused on activating circulation to remove blood stasis and tonifying deficiency. Moreover, many kinds of Chinese herbs like ligustrazine and its extracts are widely used for IPF patients in China.[7] Meanwhile, animal experiments have shown that the curative effect for bleomycin induced pulmonary fibrosis in rats included reducing the content of hydroxyproline and increasing weight.[8,9] However, the evidences have not been evaluated. This meta-analysis was designed to evaluate the current evidence of effectiveness and safety of CM treatment for IPF patients.

METHODS

Search Strategy

The protocol has been registered in PROSPERO (reference: CRD42015027933). Two researchers independently identified relevant randomized controlled trials until December 2015 from 3 English databases and 4 Chinese databases: PubMed, Cochrane Library, Excerpta Medica Datase (EMBASE), China National Knowledge Infrastructure (CNKI), Chinese VIP Information (VIP), Wanfang Database and Chinese Biomedical Database (CBM). Terms were searched included (pulmonary fibrosis OR IPF OR lung fibrosis) AND (Chinese medicine OR herbal medicine OR Chinese herbal medicine OR Chinese medicine OR Chinese herbal drug OR herbal medicine OR herbal formula OR Chinese patent drug OR Chinese patent medicine). In order to ensure a more thorough search, all relevant publications were researched, including dissertation and conference proceedings.

Inclusion Criteria

The included randomized controlled trials reported the role of various forms of CM for IPF treatment, regardless of language, population characteristics and publishing status. The selected studies should contain at least one of the following comparisons: (1) CM versus placebo, (2) CM versus WM, (3) CM plus WM versus placebo plus WM, (4) CM plus WM versus WM. In addition, at least one of the following outcome measures was used: (1) acute exacerbation, (2) pulmonary function, (3) St. George's Respiratory questionnaire (SGRQ) scores, (4) 6-minute walk test (6MWT) distance, (5) adverse events, and (6) mortality.

Exclusion Criteria

The studies were excluded if they contained any of the following criteria: (1) IPF was not diagnosed by high resolution computed tomography (HRCT) or histopathological methods, (2) duplicated publications, (3) case reports, reviews and abstracts, (4) animal experiments, (5) review articles without original data, and (6) control was another CM treatment.

Data Collection and Management

The information of data was independently extracted by two reviewers. Disagreement about the detail of study was consulted by a third author until it was resolved by consensus. Extracted data information included: the first author, date, number of patients in each group, major active constituent of herbal, specific methods of intervention on experimental group and control group, course of treatment and outcome. The outcome measures were the clinical effect including the acute exacerbation, pulmonary function, SGRQ scores, 6MWT distance, adverse events and mortality.

Assessment of the Quality of Studies

Two reviewers independently assessed the quality of all relevant studies according to the Cochrane recommends the assessment tool consisting of these domains: random sequence generation, allocation concealment, blinding of participants, binding of outcome date, incomplete outcome date, selective reporting and other bias.[10] For each item, there were three gardes of risk: low risk of bias, unclear and high risk of bias. When inadequate information was presented in the article, it could not be judged by "high" or "low" explicitly, so it was accounted as "unclear".

Statistical Analysis

All included studies were analyzed using the STATA 12.0 and Revman 5.3 statistical software. Continuous data was calculated as standardized mean difference (SMD). For binary outcome data, risk ratio (RR) were used to calculate a summary. Statistical heterogeneity of studies was indentified by using a standard Chi-squared test and the I^2 statistic. A random-effect model was used when a Chi-squared test (P<0.10) or I^2>50% revealed that significant evidence of homogeneity between studies, or a fixed-effect model was used. Publication bias of studies was calculated using a Begg's rank correlation test. P values less than 0.05 indicated significant difference.

If the number of included trials was sufficient, sensitive analysis was used to assess the stability of the results.

RESULTS

Description of Included Trials

In total, 914 potentially correlative articles were included according to our designed research strategy. After screening of title and abstract, 822 articles were excluded. The full-texts of the remaining 92 articles were then checked according to the inclusion criteria, 25 articles were eventually included in the meta-analysis (Figure 1).

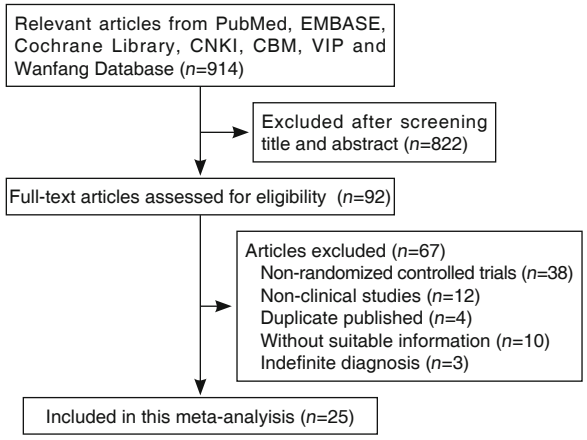

Figure 1. Flowchart Showing the Progress of Studies Selection Risk of Bias of the Included Studies

In summary, 25 studies involved 1,471 participants were included in the meta-analysis, of whom 794 participants were assigned to the CM treatment group and 677 participants to the control group. The sample size of the included studies varied from 25 to 195, aged 33–80 years old. The treatment duration lasted from 3 weeks to 24 months. Publication year of included articles ranged from 1998 to 2015. The characteristics of the 25 included studies are given in Appendix 1.

All 25 included studies[11-35] mentioned randomized control and used parallel design, but only 1 study[14] elaborated on the method used; whereas only 3[16,31,33] included studies provided information to assess the performance of blinding, 2[31,33] of the them used the double blind method, the other study[16] used the single blind method. None included studies mentioned allocation concealment. while, due to incomplete information provided, whether there was other bias in all included studies was uncertain. The risk of bias of 25 included studies are shown in Appendixes 2 and 3.

Acute Exacerbation

Four studies[11-14] reported acute exacerbation of IPF including 107 patients in the CM group and 99 in the control group. Acute exacerbation has been defined as an acute worsening and critical event in the clinical course of IPF. As shown in Figure 2, the heterogeneity was not significant (I^2=0%, P=0.88), so the fixed-effect model was used. The pooled analysis showed that CM therapy significantly reduced the risk of exacerbation compared with the control group (RR 0.40, 95% CI 0.22 to 0.72, P<0.05). Begg's rank correlation test result indicated no potential publication bias (P=0.31).

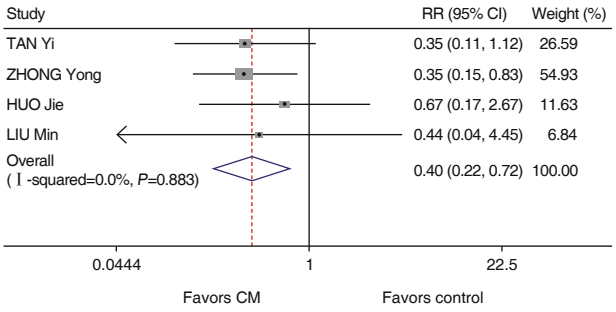

Figure 2. Risk of Exacerbations of CM and Control Groups by Forest Plots

Lung Function

Seven studies[11,15-20] focused on the change of forced expiratory volume in 1 s (FEV1) of IPF patients before and after treatment included 175 patients in the CM group and 169 in the control group. As shown in Figure 3, heterogeneity was not significant (I^2=0%, P=0.49), so the fixed-effect model was used. The pooled result revealed that CM treatment significantly improved FEV1 compared with the control group (SMD 0.62, 95% CI 0.40 to 0.84, P<0.01). Begg's rank correlation test result indicated no potential publication bias (P=0.23). After removing all the 7 studies, there was no significant difference, sensitive analysis demonstrated that the pooled result was stable.

Seven studies[15,21,22-26] identified the vital capacity (VC) of the predicted values of IPF. The meta-analysis included 198 patients in the CM group and 153 in the control group. As shown in Figure 3, heterogeneity was not significant (I^2=0%, P>0.05), so the fixed-effect model was used. There were no significant differences between CM group and control group (SMD=0.10, 95% CI –0.12 to 0.31, P=0.37). As shown in Figure 3, the potential publication bias was not found using the Begg's rank correlation test (P=0.23). Sensitive analysis did not show

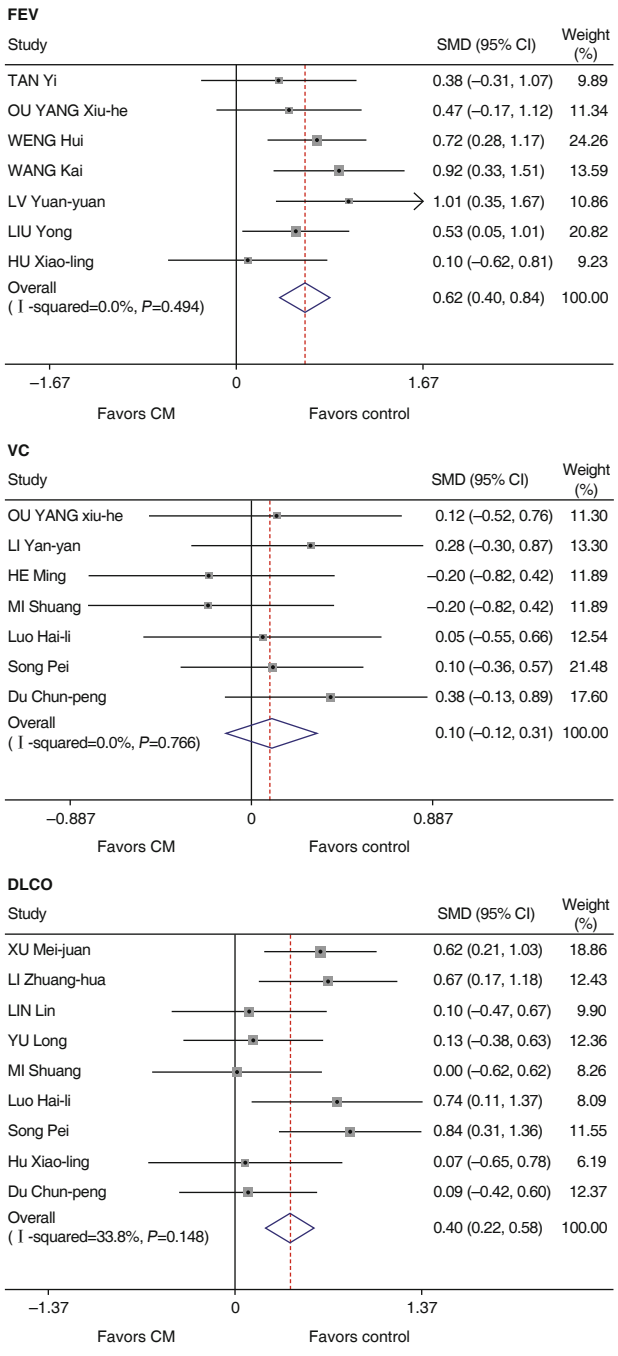

Figure 3. Lung Function of CM and Control Groups by Forest Plots

any major influence on the pooled result after removing all the included studies.

Nine studies[20,23-26,27-30] evaluated the changes in diffusion capacity for carbon monoxide (DLCO) of the predicted values included 259 patients in the CM group and 243 in the control group. As shown in Figure 3, heterogeneity was not significant (I^2=33.8%, P=0.15), so the fixed-effect model was used. There was significant difference between the CM and control groups (SMD=0.40, 95% CI 0.22 to 0.58, P<0.01). Begg's rank correlation test outcome demonstrated that the potential publication bias was not existed (P=0.60). Sensitive analysis indicated that the pooled estimations were stable after all the 9 studies were sequentially excluded.

Quality of Life

SGRQ Score

Two studies[31,32] involving 33 patients in the CM group and 27 in the control group evaluated the quality of life using the SGRQ score. As shown in Figure 4, heterogeneity was significant (I^2=85.1%, P=0.01), so the random-effects model was used. The pooled analysis denoted that CM therapy significantly decreased the SGRQ score compared with the control group (SMD=–0.59, 95% CI –1.14 to –0.05, P<0.05). Begg's rank correlation test result revealed that the potential publication bias was not observed (P=1.00).

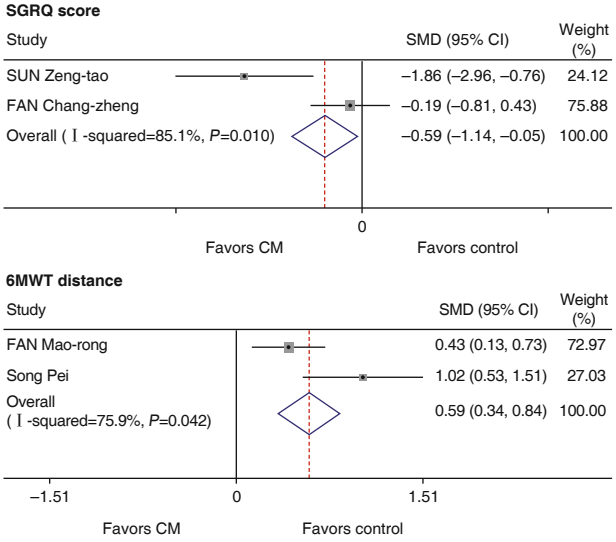

Figure 4. Quality of Life of CM and Control Groups by Forest Plots

Change in 6MWT Distance

Two studies[25,33] evaluated the change in the 6MWT distance before and after treatment included 193 patients in the CM group and 92 in the control group. As shown in Figure 4, heterogeneity was significant (I^2=75.9%, P=0.04), so the random-effects model was used. The pooled data indicated that CM treatment significantly improved the 6MWT distance compared with control group (SMD=0.59, 95% CI 0.34 to 0.84, P<0.01). Funnel plot indicated that the potential publication bias was not existed (P=1.00).

Adverse Events

Four studies[14,29,33,34] including 238 patients in

CM group and 144 in the control group described adverse events. The most common adverse events included gastrointestinal reaction, dizziness and edema. Most of them were not severe, and disappeared soon after symptomatic treatment. Heterogeneity was not significant (I^2=35.2%, P=0.20), so the fixed-effect model was used. The pooled data suggested that CM treatment was associated with a low incidence of adverse effect compared with the control group (SMD=0.19, 95% CI 0.08 to 0.43, P<0.01). Begg's rank correlation test result indicated that no potential publication bias existed (P=1.0). The results are shown in Appendix 4.

Mortality

Four articles[11,13,14,35] involving 69 patients in CM group and 57 in the control group reported the mortality. Heterogeneity was not significant, (I^2=0%, P=1.00), so the random-effects model was used. There was no significant difference between the CM and control groups (SMD=0.26, 95% CI 0.05 to 1.10, P>0.05). Begg's rank correlation test result indicated that the potential publication bias was not found (P=0.09). The results are shown in Appendix 5.

DISCUSSION

To date, the explicit mechanism of IPF is not completely elucidated. The accumulation of extracellular matrix proteins is the basic pathological changes of IPF according to recent researches.[36,37] However, no medicines have proot to control the development of IPF effectively and safely.[38,39] Recently studies revealed that CM treatment of IPF became accessible and provided new thoughts for resolving this question.[40,41]

This meta-analysis reviewed of 25 randomized trials provided reliable evidence on the therapeutic effect and safety of CM in treating IPF. We also estimated the impact of various treatment outcomes, which made our results specific and meaningful for treatment of IPF. CM therapy was associated with a reduced risk of exacerbation. Moreover, CM treatment improved FEV1 and DLCO, but it wasn't significant to change in VC. We also observed other relevant results, including improved 6MWT distance, decreased SGRQ score and reduced incidence of adverse events, but CM didn't decrease the mortality. These outcomes have a moderate quality grade and we should consider that future studies may change the estimate of effect. These outcomes are exciting, indicating CM treatment may be beneficial to control IPF progression and improve the quality of life in IPF patients.

Acute exacerbation of IPF characteristics by suddenly aggravated dyspnea with exacerbating respiratory function has been gradually recognized as a frequent and emergency event, which may occur at any moment during the progress of IPF.[42] Acute exacerbation of IPF causes a high mortality rate and lack of effective treatments. Therefore, control over acute exacerbation in IPF patients is the primary treatment objective.[43] Our meta-analysis demonstrated that CM treatment could reduce risk of IPF exacerbation, which was consistent with other studies.[44]

IPF patients are often subjected to poor quality of life because of restricted movement and breathing difficulty. Therefore, it is quite essential to appraise quality of life in IPF patients.[45] The meta-analysis assessed the quality of life by using the 6MWT distance and SGRQ. Two studies reported a significant improvement in the 6MWT distance of IPF patients with CM treatment. Pooled analysis of two studies denoted that CM treatment significantly decreased the SGRQ score. The pooled outcomes were positive, but the number of included studies was too small, so we are uncertain whether the results were reliable. More investigations were needed to confirm the outcomes.

The pooled results showed that the incidence of adverse events in CM treatment was less than that in the control group. Pooled analysis of four studies indicated that CM treatment could not reduce all-cause mortality. However, the conclusion about the safety and effect of CM treatment was not reliable due to the small number of the included articles. More clinical trials with follow-up are required to assess accurately the safety and effect of CM treatment.

In conclusion, CM appears benefit in the treatment of IPF and seems to be relatively safe during the course of treatment. However, due to the limited quantity of the included trials, we can't draw precise final results. More rigorous clinic trials included double-blind, randomized, placebo controlled designs are required to provide more accurate evidence for the future.

Conflict of Interest

All authors declare no conflict of interests.

Author Contributions

Wu Q, Zhou XM conceived and designed this study. Wu Q, Zhou Y, Feng FC performed the data extraction, analysis, interpretation and wrote the initial draft. Zhou XM assisted with data interpretation. All authors contributed to the final manuscript.

Electronic Supplementary Material: Supplementary materials (Appendixes 1–5) are available in the online version of this article at https://doi.org/10.1007/s11655-017-2429-5.

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