INPLASY PROTOCOL

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None declared.

Efficacy and Safety of Chinese Herbal Medicines combined with Cyclophosphamide for Connective Tissue Disease-Associated Interstitial Lung Disease: A Meta-Analysis of Randomized Controlled Trials

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Review question / Objective: **To evaluate the effectiveness and safety of Chinese herbal medicines (CHMs) combined with cyclophosphamide (CTX) for connective tissue disease-associated interstitial lung disease (CTD-ILD) by performing a meta-analysis.**
Condition being studied: **Chinese herbal medicines (CHMs) and cyclophosphamide (CTX) are widely used in the treatment of connective tissue disease-associated interstitial lung disease (CTD-ILD). However, the clinical benefits of CHMs treatment for CTD-ILD are still controversial, and there is no systemic review to summarize and evaluate their efficacy and safety.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 December 2022 and was last updated on 03 December 2022 (registration number INPLASY2022120010).

INTRODUCTION

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Condition being studied: **Chinese herbal medicines (CHMs) and cyclophosphamide (CTX) are widely used in the treatment of connective tissue disease-associated interstitial lung disease (CTD-ILD). However, the clinical benefits of CHMs treatment for CTD-ILD are still controversial, and there is no systemic review to summarize and evaluate their efficacy and safety.**

METHODS

Search strategy: ((((((((((((("Connective Tissue Diseases"[Mesh]) OR (Connective Tissue Disease[Title/Abstract])) OR ("Arthritis, Rheumatoid"[Mesh])) OR (Rheumatoid Arthritis[Title/Abstract])) OR ("Sjogren's Syndrome"[Mesh])) OR (Sjogrens Syndrome[Title/Abstract])) OR ("Lupus Erythematosus, Systemic"[Mesh])) OR (Systemic Lupus Erythematosus[Title/Abstract])) OR ("Scleroderma, Systemic"[Mesh])) OR (Systemic Sclerosis[Title/Abstract])) OR ("Dermatomyositis"[Mesh])) OR (Dermatopolymyositis[Title/Abstract])) AND (("Lung Diseases, Interstitial"[Mesh]) OR ((((((Interstitial Lung Diseases[Title/Abstract]) OR (Interstitial Lung Disease[Title/Abstract])) OR (Lung Disease, Interstitial[Title/Abstract])) OR (Pneumonia, Interstitial[Title/Abstract])) OR (Interstitial Pneumonia[Title/Abstract])) OR (Interstitial Pneumonias[Title/Abstract]))))) AND (("Drugs, Chinese Herbal"[Mesh]) OR ((((((Chinese traditional medicine[Title/Abstract]) OR (Chinese Herbal Drugs[Title/Abstract])) OR (Chinese Plant Extracts[Title/Abstract])) OR (Medicine, Chinese Traditional[Title/Abstract])) OR (Traditional Chinese Medicine[Title/Abstract])) OR (Chinese[Title/Abstract] AND western medicine[Title/Abstract]))))) AND (("Randomized Controlled Trial" [Publication Type]) OR ((randomized[Title/Abstract]) OR (Placebo[Title/Abstract]))).

Participant or population: Patients were individuals who were diagnosed with CTD-ILD. We included only individuals who were definitive CTD as defined by recognized diagnostic criteria at the time of study determination. We included the CTDs commonly associated with ILD: SSc, DM/PM, pSS, RA and SLE.

Intervention: The experimental group were combination treatment of Chinese herbal medicine and cyclophosphamide.

Comparator: The control group were treatment of cyclophosphamide alone.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Inclusion Criteria: Studies were included if they fulfilled the following criteria: (1) population: Patients were individuals who were diagnosed with CTD-ILD. We included only individuals who were definitive CTD as defined by recognized diagnostic criteria at the time of study determination. We included the CTDs commonly associated with ILD: SSc, DM/PM, pSS, RA and SLE; (2) intervention and comparison: Experimental groups were combination treatment of CHMs and CTX, while control groups were treatment of CTX alone. GCs were used as background therapy in both experimental and control groups; (3) outcome: the required outcomes were clinical effective rate, cough and shortness of breath symptoms, lung function [including vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), total lung capacity (TLC), carbon monoxide diffusing capacity (DLCO), maximal voluntary ventilation per minute (MVV)], HRCT score in the lungs, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and number of adverse events (AEs); (4) design: RCT, Including trials published in the form of dissertations. results available in either Chinese or English. Exclusion Criteria: Articles were excluded if they fulfilled the exclusive criteria: (1) study subjects did not meet CTD-ILD diagnostic criteria; (2) both experimental and control groups contained CHMs only therapy, or the control group was treated with other CHMs, or inappropriate interventions; (3) duplicated articles or animal experiments or unavailable data studies or irrelevance to outcome indicators; (4) conference abstracts or case reports or reviews or comments; (5) non-RCT.

Information sources: Two trained investigators independently searched randomized controlled trials (RCTs) of CHMs therapy for CTD-ILD from the following ten different databases: PubMed, EMBASE, Web of science, Cochrane Library, ClinicalTrials.gov, China National

Knowledge Infrastructure, Wanfang Database, China Biological Medicine Database, VIP Journals Database and Chinese Clinical Trial Register, which retrieved from their inception to 28 August 2022.

Main outcome(s): Primary outcomes included clinical effective rate, lung function [including vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), total lung capacity (TLC), carbon monoxide diffusing capacity (DLCO), maximal voluntary ventilation per minute (MVV)], HRCT score in the lungs.

Additional outcome(s): Secondary endpoints included cough and shortness of breath symptoms, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and number of adverse events (AEs).

Data management: RevMan v5.3 and Stata v14.0 were used for this meta-analysis.

Quality assessment / Risk of bias analysis: Two reviewers individually estimated the methodological quality of the included trials based on the bias risk assessment of the Cochrane collaboration tool. The tool had 6 domains, each domain was ranked as "Low," "Unclear" and "High." The 6 domains were (1) method of random allocation; (2) allocation concealment; (3) blinding method; (4) integrity of data; (5) selective reporting; (6) other biases. If disagreements on the assessment were identified, the third author was asked for the final decisions.

Strategy of data synthesis: For continuous data, standardized mean difference (SMD), weighted mean difference (WMD), and a 95% confidence internal (CI) were calculated. For dichotomous data, risk ratio (RR) and a 95% CI were calculated. Statistical heterogeneity was evaluated using the I2 and X2 tests. When heterogeneity was identified (I2 ≥ 50%), a random-effects model was selected, otherwise a fixed-effects model was applied. The source of the heterogeneity was identified by subgroup analysis and sensitivity analysis if heterogeneity exists. When $p < 0.05$, statistically significant differences were considered. Funnel plot, Egger's and Begg's tests would be implemented to evaluate the potential publication bias, when more than 10 studies were included in the meta-analysis.

Subgroup analysis: The source of the heterogeneity was identified by subgroup analysis if heterogeneity exists.

Sensitivity analysis: The source of the heterogeneity was identified by sensitivity analysis if heterogeneity exists.

Country(ies) involved: China.

Keywords: connective tissue disease-associated interstitial lung disease, meta-analysis, randomized controlled trials, cyclophosphamide, Chinese herbal medicine.

Contributions of each author:

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