INTRODUCTION

Review question / Objective: Our participants: Patients with interstitial lung disease associated with connective tissue disease ≥ 18 years old. Intervention and comparisons: The experimental group is one of the current biological agents, and the medication scheme is subject to the drug instructions. The comparisons control group was treated with placebo or routine treatment. Outcome measures: The primary study outcome should include changes in forced vital capacity (FVC) and/or diffusing capacity of the lungs for carbon monoxide (DLCO) for lung function, and Modified Rodnan Skin Score after 12, 24, or 48 weeks of treatment.

Condition being studied: Connective tissue disease (CTD) is a kind of autoimmune disease with multi-system damage based on chronic inflammation of blood vessels and connective tissue. Lung is the most frequently involved target organ in CTD because of its rich connective tissue such as vascular collagen. Interstitial lung disease is a group of progressive fibrous lesions involving lung parenchyma. In the case of rheumatoid arthritis RA, it is found that the related lesions may appear earlier in the lungs than in joints. 14% of RA-ILD patients are diagnosed with ILD one to five years before the diagnosis of RA. The risk of ILD increases with the duration of RA. At present, the application of various biological agents for CTD-ILD emerges one after another and has good curative effect.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 October 2022 and was last updated on 14 November 2022 (registration number INPLASY2022100027).
study outcome should include changes in forced vital capacity (FVC) and/or diffusing capacity of the lungs for carbon monoxide (DLCO) for lung function, and Modified Rodnan Skin Score after 12, 24, or 48 weeks of treatment.

**Condition being studied:** Connective tissue disease (CTD) is a kind of autoimmune disease with multi-system damage based on chronic inflammation of blood vessels and connective tissue. Lung is the most frequently involved target organ in CTD because of its rich connective tissue such as vascular collagen. Interstitial lung disease is a group of progressive fibrous lesions involving lung parenchyma. In the case of rheumatoid arthritis RA, it is found that the related lesions may appear earlier in the lungs than in joints. 14% of RA-ILD patients are diagnosed with ILD one to five years before the diagnosis of RA. The risk of ILD increases with the duration of RA. At present, the application of various biological agents for CTD-ILD emerges one after another and has good curative effect.

**METHODS**

**Participant or population:** Our participants include patients with interstitial lung disease associated with connective tissue disease ≥ 18 years old, And connective tissue diseases include systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome and et al.

**Intervention:** The experimental group is one of the current biological agents, and the medication scheme is subject to the drug instructions.

**Comparator:** The comparisons control group was treated with placebo or routine treatment.

**Study designs to be included:** Our study is mainly based on RCT, and some retrospective studies are included. Retrospective study of the control group should be routine treatment rather than self-control before and after.

**Eligibility criteria:** Exclusion criteria: ① non-English literature; ② There is no corresponding outcome index; ③ The treatment plan is inconsistent with the drug instructions; ④ The baseline characteristics and outcome data of patients in corresponding groups were not provided. In the final, if several publications of the same trial were identified, the newest version and most comprehensive data were included.

**Information sources:** A systematic literature retrieval was executed in PubMed, Cochrane, and the Embase. The time endpoint of the online search was October 06, 2022.

**Main outcome(s):** The primary study outcome should include changes in forced vital capacity (FVC) and/or diffusing capacity of the lungs for carbon monoxide (DLCO) for lung function.

**Quality assessment / Risk of bias analysis:** We assessed the risk of bias in the included randomized controlled trials (RCTs) using the Cochrane “risk of bias” assessment tool, including the domains of allocation, blinding, incomplete outcome data, selective reporting, and other bias. The Newcastle–Ottawa scale was used to assess the quality of the included retrospective studies. Each study was scored according to the selection, comparability, and outcome.

**Strategy of data synthesis:** Review Manager version 5 (RevMan; the Cochrane Collaboration; Oxford, England) was used to perform the meta-analysis. The heterogeneity among studies was evaluated using the chi-squared test and I². A fixed effects model was used when there was no significant heterogeneity (I² 0.05). Otherwise, a random effects model was used.

**Subgroup analysis:** We plan to do subgroup analysis according to different medications, such as grouping patients who use the same type of monoclonal antibody into one group.
Sensitivity analysis: We will consider running sensitivity analysis to identify the robustness and stability of merged results by excluding studies with high risk of bias.

Country(ies) involved: China.

Keywords: biological agents; Connective tissue disease-associated interstitial lung disease; Efficacy; Safety; Long-term.

Contributions of each author:
Author 1 - Guancheng Ye.
Author 2 - Jiajing Liu.
Author 3 - Jiqqi Chen.
Author 4 - Fenglan Pu.
Author 5 - Chunyan Zhang.
Author 6 - Guiying Peng.
Author 7 - Jie Li.