INPLASY PROTOCOL

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None.

Comparative efficacy and safety of tyrosine kinase inhibitor for systemic sclerosis - associated interstitial lung diseases A Bayesian network meta-analysis protocol

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Review question / Objective: **A series of studies revealed its potential application as an anti-fibrosis drug in SSc fibrosis, with good efficacy and fewer toxic and side effects. No similar studies have been found so far. Currently, the advantages and disadvantages of TKI therapy for SSC have not been compared. We will try to include as many high-quality, multicenter clinical studies and evidence as possible in NML.**
Condition being studied: **Systemic sclerosis - associated interstitial lung diseases has gradually become one of the main causes of death of systemic sclerosis, and its pulmonary fibrosis status also seriously affects the prognosis of patients with systemic sclerosis. Its treatment is still in the exploratory stage. Conventional treatment was immunotherapy (e.g. cyclophosphamide, azathioprine, mycophenolate mofetil, etc.), but the results were not satisfactory. Tyrosine kinase inhibitors (TKI), a compound that inhibits tyrosinase activity, have been found to inhibit the pathogenesis of fibrosis. Therefore, we used the method of network meta-analysis to systematically compare the efficacy of various tyrosine kinase inhibitors in the treatment of this disease.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 December 2020 and was last updated on 31 December 2020 (registration number INPLASY2020120150).

INTRODUCTION

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METHODS

Participant or population: The diagnosis of SSc will follow the American College of Rheumatology standards in 198029 or the European Union standards and the American College of Rheumatology(ACR) in 201330. Proof of functional lung involvement (including forced vital capacity (FVC) 45% to 80% normal and/or diffusion capacity (DLCO) 30% to 70% normal) and/or HRCT ILD (frosted glass, reticular abnormalities, and/or cellular changes, et al.) is required in patients with SSC-ILD. Factors such as age, race, severity of illness, and course of illness are not restricted.

Intervention: Tyrosine kinase inhibitors were used in the trial group. Tyrosine kinase inhibitors include Nintedanib, Dasatinib, and Imatinib. Placebo treatment was administered to the control group. Both groups can be treated either orally or by injection. We will eliminate RCTs using two or more tyrosine kinase inhibitors.

Comparator: The control group received placebo treatment, including oral medication or injection behavior therapy.

Study designs to be included: All RCTs using TKI in treating systemic sclerosis - associated interstitial lung diseases, also related clinical trials, including I/II early stage, phase III trials, prospective and retrospective observational studies. But meta-analyses, case reports, and studies with insufficient data will be excluded. Language is not restricted.

Eligibility criteria: We included a study to determine whether a patient was diagnosed with systemic sclerosis associated pulmonary interstitial fibrosis based on evidence of functional lung involvement and/or evidence of HRCT ILD.2) Experimental group and control group;3) The control group received placebo treatment, including oral medication or injection treatment;4) The type of study was a randomized controlled trial.

Information sources: We will search the Cochrane Library, PubMed, Embase, Clinical Trials, CNKI Database, VIP, Wanfang Database, and China Biomedical Database. The search strategy will be constructed in the form of Medical Subject Headings (MeSH) combine with keywords. We will also search ongoing trial registers in the trial registry websites.

Main outcome(s): The primary efficacy end point was in 52 weeks to evaluate years of decline rate of the forced vital capacity (FVC), the secondary end point was to achieve improved Ronan Skin Score (modified Rodnan Skin Score, MRSS), 52 weeks, st George's respiratory questionnaire (SGRQ) scores, pulmonary function test (PFT) results, Mahler transitional dyspnea index (TDI) and pulmonary HRCT absolute change compared to the baseline. The safety outcome was the number of patients who withdrew due to adverse events (AEs). One or more primary efficacy end points must be covered in the included literature.

Quality assessment / Risk of bias analysis: Two researchers will independently evaluate the quality of each trial based on the Cochrane Handbook Version5.1.0 recommended Cochrane Bias risk assessment tool. To evaluate the risk of bias in quality evaluation, the three judgment words of "high risk," "low risk," and "unclear risk" are used, which can be divided into 7 aspects: Whether the generation of random sequences is

standard; Whether the allocation of interventions is foreseen; Whether the investigator and subject were blinded; Whether the outcome data is complete; Describe the method of applying the blind method to evaluators; The existence of selective reporting; The other.

Strategy of data synthesis: Revman5.1 software and Markov chain-Monte carlo (MCMC) method were used to analyze bayesian mesh meta-analysis. Three Markov chains were used for simulation, and the number of iterations was set at 50,000 (the first 20,000 are used for annealing to eliminate the effect of the initial value, and the last 30,000 are used for sampling). Convert different types of data into dichotomous variables or continuous variables and import Revman5.1 software; MH method was used for dichotomous variables, and IV method was used for continuous variables, both of which were analyzed by random effect model, and dichotomous variables were expressed by the ratio (OR). If OR is equal to 1, there is zero difference in treatment effect between the trial group and the control group; if OR>1, the treatment effect of the experimental group is good; if OR is less than 1, it is opposite. A continuous variable is expressed by mean difference (MD); if MD is equal to 0, there is zero difference in treatment effect between the trial group and the control group; if MD >0, the treatment effect of the experimental group is good; if MD is less than 0, it is opposite.

Subgroup analysis: We will consider subgroup analysis if the data is abundant and heterogeneous.

Sensibility analysis: In order to confirm the dependability of the results of this study, a sensitivity analysis was performed using symptom improvement rate as an indicator to evaluate clinical similarity and included study methodology.

Country(ies) involved: China.

Keywords: systemic sclerosis - associated interstitial lung diseases(SSC-ILD), network meta-analysis, protocol, tyrosine kinase inhibitors(TKI).

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