INPLASY PROTOCOL

To cite: Li et al. A Bayesian Network Meta-analysis on the Efficacy and Safety of Novel Targeted Drugs for Type I Pulmonary Hypertension. Inplasy protocol 2020120023. doi: 10.37766/inplasy2020.12.0023

Received: 03 December 2020

Published: 04 December 2020

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Support: **Guangzhou Science and technol.**

Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None.

A Bayesian Network Meta-analysis on the Efficacy and Safety of Novel Targeted Drugs for Type I Pulmonary Hypertension

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Review question / Objective: **With the launch of targeted drugs, more and more patients receive a single targeted drug or a combination of targeted drugs treatment. Unfortunately, there was no head-to-head comparison among the targeted drugs to indicate their differences in efficacy and safety, which is still a problem whether is the best choice for patients with pulmonary arterial hypertension. Currently, a amount of clinical trials and meta analysis have provided valuable experience and suggestions for the selection of targeted drugs. However, it's the variety of targeted drugs and the inconsistent quality of randomized controlled trials (RCTs) that makes the treatment choice of targeted drugs more complex. Therefore, our aim is to conduct a more comprehensive meta analysis, select high-quality randomized controlled trials(RCTs), take multiple intervention measures and extract more outcome indicators to evaluate the therapeutic efficacy and safety of targeted drugs, so as to solve the existing contradictions and provide more convincing evidence for clinical practice of pulmonary hypertension.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 December 2020 and was last updated on 04 December 2020 (registration number INPLASY2020120023).

INTRODUCTION

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Condition being studied: Pulmonary arterial hypertension (PAH) is classified as a group 1 pulmonary hypertension (PH) and is defined by mean pulmonary artery pressure ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg and pulmonary vascular resistance >3 Wood units, in the absence of other causes of precapillary PH (such as lung disease, chronic thromboembolic disease and other rare diseases). For a definitive diagnosis of PAH, a hemodynamic assessment by right heart catheterization is required.Epidemiological survey in the West showed that about 15 people per million suffered from PAH. Most of them had fatigue, dyspnea, angina pectoris, hemoptysis, or even right heart failure.

METHODS

Participant or population: The inclusion criteria 1 The subjects researched by the trial must bediagnosed with PAH (WHO Group I PH) 2 The patients assessed were mainly adults (if most patients were adults, patients under 14 years old were allowed) 3 The minimal follow-up period was 12 weeks The exclusion criteria 1 The patients were diagnosed as type II, III, IV and V pulmonary hypertension 2 Most of the patients were younger than 14 years old.

Intervention: The inclusion criteria Interventions must be new targeted drugs, including Endothelin receptor antagonist (ERA)(Bosentan , Ambrisentan, Aacitentan) Phosphodiesterase 5 inhibitor (PDE-5i) (Sildenafil, Tadalafil, Vardenafil) Soluble guanylate cyclase stimulator(sGCS) (Riociguat) Prostaglandin I²(PGI2) (Epoprostenol, Iloprost, Treprostinil, Selexipag, Beraprost) The exclusion criteria The trial investigating on the unreleased drug or drug which cannot be covered by the loop would be excluded.

Comparator: The compared interventions must be drug combination for PAH or placebo, without requirement on specific target or mechanism.

Study designs to be included: It must be an RCT, and the word "random grouping" appears in the article and the random method is indicated, without limitation on blinding.

Eligibility criteria: Studies will be included if they conforming to the following criteria: (1) randomized controlled trail (RCT) as study design; (2) patients were definitely diagnosed as group 1 pulmonary arterial hypertension (PAH) according to the clinical classification of PAH; (3) patients with PAH (group 1 pulmonary hypertension) were primarily adults (allowing patients under 14 years old if most of the participants were adults); (4) patients receiving at least one of the targeted drugs: ERAs (bosentan, ambrisentan and macitentan), PDE-5Is (sildenafil, tadalafil and vardenafil), sGCS (Riociguat), PGI2 (epoprostenol, iloprost, treprostinil, selexipag and beraprost), and a combination of targeted drugs, regardless of drug dosage ; (5) the minimum follow-up period was 12 weeks. The exclusion criteria were: (1) non-RCTs, studies with insufficient data, duplicated publications, conference reports, systematic reviews, or different studies from same sample origin; (2) participants restricted neonatal patients or pediatric; (3) crossover, 2×2 factorial, retrospective studies; (4) studies on patients from other WHO PH groups or no date for PAH was available.

Information sources: Relevant articles were searched and selected from published data in electronic databases PubMed, Cochrane Library, CNKI, Ovid, Wanfang and VIP database (from inception until October 1,

2020)with the restriction on language: English and Chinese.

Main outcome(s): 6 - minute walking test(6MWT) is an objective method to evaluate the exercise tolerance of patients. It is to let the subjects walk on foot and test their walking distance at the fastest speed they can bear within 6 minutes.

Additional outcome(s): 1 mean pulmonary arterial pressure （mPAP）: Mean pressure of pulmonary artery during the whole cardiac cycle in normal adults at rest 2 pulmonary vascular resistance （PVR）: the resistance of blood flow by vascular wall and the resistance caused by elastic relaxation and contraction of blood vessels 3 mean right atrial pressure （mRAP） 4 Death：number of deaths during the trial 5 clinical worsening: Clinical worsening is the amount of any aggravations ever happened during the trial 6 adverse event (AE): the general adverse event occurred during the trial 7 Severe adverse event (SAE):the severe adverse event occurred during the trial 8 WHO functional class, FC improve: the improvement of WHO functional class during the trial.

Quality assessment / Risk of bias analysis: The included RCTs were evaluated according to the quality evaluation criteria recommended in the Cochrane intervention system manual 1.bias arising from the randomization process; 2.bias due to deviations from intended interventions; 3.bias due to missing outcome data; 4.bias in measurement of the outcome; and 5.bias in selection of the reported result.

Strategy of data synthesis: The network meta-analysis was performed using Stata (version 16.0, Stata SE), WinBUGS (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK), and R software (version 4.0.3, R foundation for statistical computing). The odds ratio (OR) with corresponding 95% confidence interval (CI) and mean difference（MD）with corresponding 95% confidence interval (CI) were utilized to compare different agents with respect to various clinical outcomes. We conducted conventional meta-analyses for treatments that were directly compared in RCTs by Bayesian random-effects model. Convergence was checked using the Brooks-Gelman-Rubin diagnostic and trace plots .Moreover, an I^2 value less than 50% indicates that there is no significant heterogeneity. an I^2 value greater than 50% indicates significant heterogeneity. The stability of the results was obtained by sensitivity analyses with discarding each study sequentially. we used surface under the cumulative ranking (SUCRA) probability, which present as a percentage the efficacy or safety of every intervention that is always best without uncertainty . Node-splitting approach was used to assess the inconsistency.

Subgroup analysis: About half of the causes of PAH in the Western population are IPAH, HPAH and drug-associated PAH, and connective tissue diseases which systemic sclerosis accounts for about 2/3 of are the most common cause in APAH. And the causes of PAH in the Asian population are significantly different with the Western population.In the Asian population, Congenital heart disease is the most common cause of PAH, followed by IPAH and PAH associated with connective tissue disease in which systemic lupus erythematosus and Sjogren's syndrome are the most common cause.Therefore, in order to avoid the difference of treatment outcomes because of populations from different districts, patients were divided into groups depending on Asian or non-Asian populations to verify internal consistency of the results of the clinical trial or explore the optimal benefit population.

Sensibility analysis: Stratified meta-analysis was performed on the included literature according to the size of the sample size to investigate whether the conclusions had changed.

Country(ies) involved: China.

Keywords: Pulmonary arterial hypertension; Endothelin Receptor Antagonists; Phosphodiesterase 5 inhibitor; Soluble guanylate cyclase; Prostacyclin analogues.

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