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ORIGINAL ARTICLE

Targeted Treatments for Pulmonary Arterial Hypertension: Interpreting Outcomes by Network Meta-analysis

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Background No meta-analysis for indirect comparisons has been conducted to study the effectiveness of treatments for pulmonary arterial hypertension (PAH).

Methods Our search covered the literature up to December 2014. The following five classes of agents indicated for PAH were evaluated: 1) oral endothelin receptor antagonists (ERAs); 2) oral phosphodiesterase type 5 inhibitors (PDE-5Is); 3) prostanoids administered by oral, intravenous, subcutaneous or inhalatory route; 4) selective non-prostanoid prostacyclin receptor (IP receptor) agonists (sPRAs); 5) soluble guanylate cyclase stimulators (sGCSs). Our methodology was based on standard models of Bayesian network meta-analysis. The end-point of our analysis was clinical worsening. Odds ratio was the outcome measure along with 95% credible intervals.

Results Our search identified 17 randomised controlled trials (4,465 patients). There were 15 head-to-head comparisons (five direct, 10 indirect). As expected, nearly all values of odds ratio estimated for the direct comparisons versus placebo favoured the treatment arm at levels of statistical significance. More interestingly, none of the 10 head-to-head indirect comparisons between active agents showed any statistically significant difference.

Conclusion Our results indicate that these five classes of agents for PAH are more effective than placebo and show no significant difference in effectiveness from one another. In this context, choosing the treatment for an individual patient is a quite difficult task.

Keywords Meta-analysis • Pulmonary arterial hypertension • Endothelin receptor antagonists • Phosphodiesterase type 5 inhibitors • Prostanoids • Soluble guanylate cyclase stimulators • Prostacyclin

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease with high morbidity and mortality. The progression of the disease can lead to limited exercise capacity, right heart failure and eventually death [1]. The rate of survival of PAH patients at five years from diagnosis is only 57% [2]. The main treatments currently available for PAH have vasodilatory and/or antiproliferative effects.

The most commonly used targeted therapies for PAH include prostacyclin analogues (administered by oral, intravenous, inhaled and subcutaneous routes), oral endothelin receptor antagonists (ERAs), and oral phosphodiesterase type 5 inhibitors (PDE-5Is) [3,4]. Because the oral route is

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the most convenient and usually the safest and least expensive, it is the one most often used. Intravenous, inhaled and subcutaneous routes can only be recommended in patients with WHO functional class III/IV [1,2].

Meta-analyses have suggested that oral pulmonary vasodilators are beneficial in decreasing clinical worsening and increasing 6-min walk distance [5]. However, many new oral agents have been made available for PAH in recent years [including new oral prostanoids, e.g. treprostinil; selective non-prostanoid prostacyclin receptor (IP receptor) agonists, e.g. selexipag; soluble guanylate cyclase stimulators, e.g. riociguat] that deserve to be assessed in meta-analyses or systematic reviews.

In the present study, we performed an updated meta-analysis on PAH treatments including the information from recently published randomised controlled trials (RCTs).

Methods

Our literature search was conducted in PubMed (last query on 31 December 2014) and covered the period from January 2000. A single search term (''pulmonary hypertension'' OR ''pulmonary arterial hypertension'') was employed in combination with the filter ''randomized controlled trials''. Since the number of citations was small (less than 600), we analysed all of these articles by examining the abstract or, when necessary, the full text, and we identified the RCTs that met our inclusion criteria. These criteria comprised: a) adult patients diagnosed as PAH (including associated pulmonary arterial hypertension, APAH, and idiopathic pulmonary arterial hypertension, IPAH); b) clinical material represented by a RCT; c) targeted therapies administered to at least one study arm; d) follow-up of eight weeks or more. Our PubMed search was supplemented by searching two other sources of information (EMBASE and Cochrane reviews).

The end-point of our analysis was clinical worsening. This composite endpoint was defined as one of six different events/conditions: death, lung transplantation, inter-atrial fistulisation, hospitalisation due to decompensated PAH, initiation of a new therapy, or worsening WHO functional classes

For each trial, we extracted the basic information needed for our analysis as well as the information on the primary

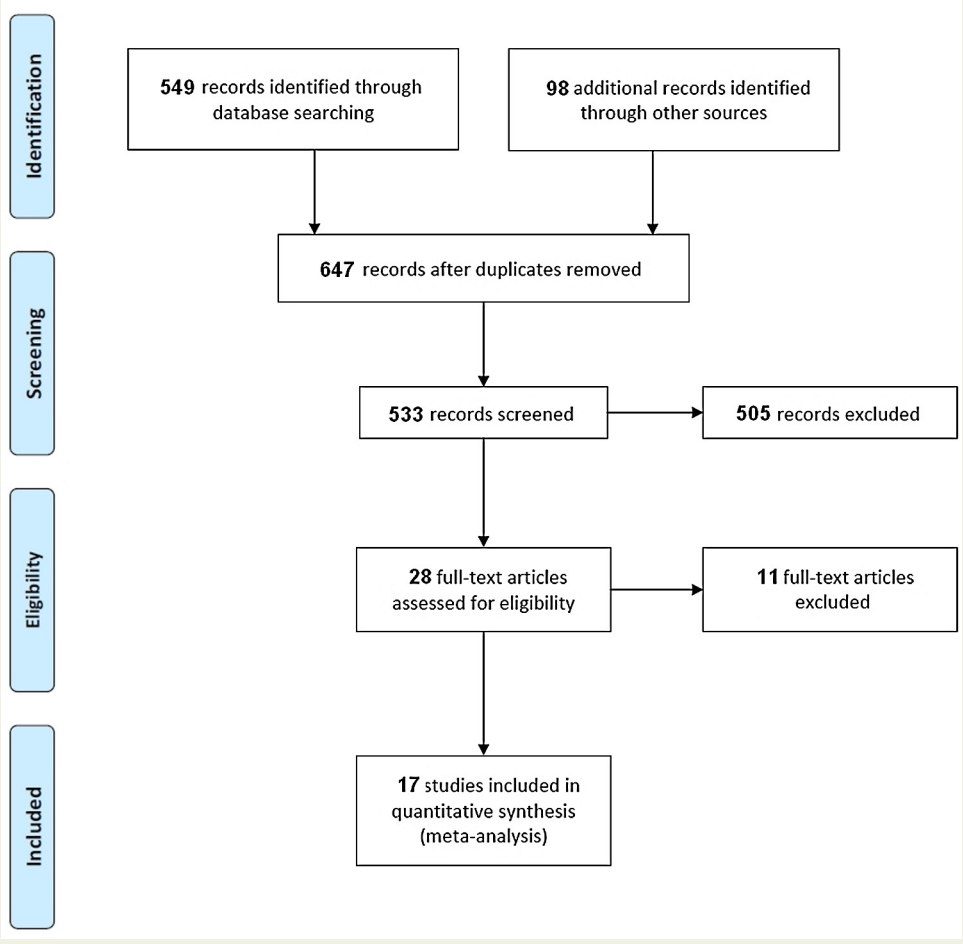

Figure 1 PRISMA schematic. This flow chart summarises the literature search and the selection process that identified the 17 RCTs included in our analysis.