International Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Comparative efficacy and acceptability of endothelin receptor antagonists for pulmonary arterial hypertension: A network meta-analysis

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ARTICLE INFO

Article history:
Received 22 July 2016
Received in revised form 25 October 2016
Accepted 16 December 2016
Available online xxxx

Keywords:
Pulmonary arterial hypertension
Endothelin receptor antagonists
Network meta-analysis

ABSTRACT

Background: Endothelin receptor antagonists (ERAs) such as ambrisentan, sitaxsentan, bosentan and macitentan are primary drug therapies for pulmonary arterial hypertension (PAH) patients. However, the optimal drugs for PAH remained controversial due to heterogeneous nature of randomized control trials (RCTs).
Methods: Apart from traditional meta-analysis, network meta-analysis (NMA) was performed in this study for multiple comparisons among PAH therapies. The 6 minute walking distance (6MWD) and clinical worsening were efficacy outcomes whereas serious adverse effects (SAE) and all-cause discontinuation were acceptability outcomes. The weighted mean difference (WMD) and odds ratio (OR) along with their 95% confidence interval (95% CI) or 95% credible interval (95% CrI) were used to evaluate the positive and negative effects of these therapies on PAH patients.
Results: By synthesizing direct evidence from 10 studies with a total number of 2172 patients, we discovered that all of the four PAH therapies significantly increased the average 6MWD in comparison to the placebo (P-value < 0.05). Moreover, bosentan and ambrisentan both showed significant association with a decrease in the risk of clinical worsening compared to placebo. Regarding of all-cause discontinuation, ambrisentan is the only therapy which was significantly associated with a risk decrease compared to placebo. However, there was no sufficient evidence suggesting significant difference in any efficacy or acceptability outcomes between any two of the PAH therapies (P-value > 0.05).
Conclusion: Ambrisentan could be considered as the most appropriate therapy among the four ERAs for PAH patients. Bosentan also behaved well, but it is not as safe as ambrisentan.

1. Introduction

Pulmonary arterial hypertension (PAH) is a fatal disease associated with pulmonary artery hyperplasia and remodeling, leading to increased pulmonary circulation resistance and right ventricular posterior load, eventually producing right heart failure [1]. About 15 people per million suffered from PAH [2] and PAH patients customarily possessed poor prognosis with 1-, 3-, 5-, and 7-year mortality rates (from the initial diagnosis) of 15%, 32%, 43%, and 51%, respectively [3]. Currently, there are three types of therapeutic drugs recommended, including endothelin receptor antagonists (ERAs), prostacyclin (PGI2 analogues) and phosphodiesterase 5 inhibitor (PDE-5 inhibitors).

As a conventional therapeutic drug for PAH, ERA has been demonstrated to relax blood vessel as well as inhibit vascular proliferation and remodeling [4]. The efficacy of ERA, including ambrisentan, bosentan, macitentan and sitaxsentan, has been evaluated and compared with placebo in previous studies [5–17]. Theoretically, ERA acts on the endothelin pathway by blocking binding of endothelin-1 (ET-1) to its receptors, endothelin type-A [ET_A] and type-B [ET_B] [18,19], which differed in their PAH-associated etiologies. For instance, ET_A receptor is able to shrink vessels by increasing intracellular calcium concentration, while ET_B could make vascular relaxation by stimulating the release of nitric oxide and prostaglandin [20]. Bosentan is considered as an orally active antagonist of ET and previous studies suggested that bosentan contributed to the improvement of hemodynamics and exercise capacity along with the reduction in PAH patients' clinical deterioration [15]. A meta-analysis suggested that bosentan was more effective than placebo for PAH, but it may result in abnormal liver function which is risky for PAH patients [21]. Moreover, macitentan is also

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http://dx.doi.org/10.1016/j.ijcard.2016.12.092
0167-5273/

effective for PAH as it enhances tissue penetration and elongates receptor binding [22,23].

Noticeably, sitaxsentan and ambrisentan served as two selective ET_A receptor antagonists, which have been demonstrated to improve exercise capacity and hemodynamics with a low incidence of hepatic toxicity [5,24,25]. Ambrisentan, a propanoic acid–based non-sulfonamide, is superior to other approved treatment options for its long-term efficacy-to-safety profile [9,26].

Unfortunately, there was no head-to-head comparison among the four ERA therapeutic drugs to indicate their differences in efficacy, tolerability and other clinical outcomes. Compared with traditional meta-analysis, network meta-analysis (NMA) provided us with a more comprehensive viewpoint which synthesizes both direct and indirect evidence [27–29]. Therefore, a NMA was carried out in our study to compare the four drugs mentioned above so that the most appropriate and efficacious therapy for PAH patients can be identified.

2. Material and methods

2.1. Identification of articles

Relevant studies were searched and selected from online databases including PubMed, Embase, and Cochrane Library without any restriction on language. The following terms together with their corresponding synonyms were used to perform systematic searching and review: “pulmonary arterial hypertension”, “endothelin receptor antagonists”, “ambrisentan”, “sitaxsentan”, “bosentan”, “macitentan” and “randomized controlled trial”. Then, we manually examined the reference list for each relevant study to avoid any omission of valuable document. Two reviewers independently retrieved the relevant studies and different opinions were settled by discussion. Apart from the initial literature search and identification, we also update our literature at the end of the research project.

2.2. Study inclusion criteria

The following inclusion criteria were created to determine the eligibility of studies: 1) randomized clinical trials (RCTs) which compared any of bosentan, sitaxsentan, macitentan, ambrisentan and placebo; 2) patients had documented (WHO FC II, III, IV) symptomatic PAH, idiopathic PAH or PAH associated with other diseases; 3) the age of patients is between 12 and 80; 4) patients may have received concomitant treatments such as anticoagulants, vasodilators, diuretics, cardiac glycosides and supplemental oxygen; 5) the endpoint of 6-minute walking distance (6MWD), clinical worsening, serious adverse effects (SAE), death and all-cause discontinuation were assessed; 6) full-content of the study can be accessed and sufficient data can be derived; and 7) the corresponding treatment duration as well as the dose for each group must have been specified. Besides that, patients were excluded if they had any of the following disease within the last two years: significant parenchymal lung disease, portal hypertension, chronic liver disease, human immunodeficiency virus infection, hepatic dysfunction, renal insufficiency, thromboembolic disease, obstructive sleep apnea and left-sided heart disease.

2.3. Data extraction and outcome measures

The following information was extracted from selected studies to implement the process of evidence synthesis: study characteristics (author, publication year, sample size, study duration and dosage) together with drug efficacy and acceptability indicators i.e. 6MWD, clinical worsening, SAE, death and all-cause discontinuation.

6MWD is considered as an appropriate measure for patients with chronic heart disease by measuring functional exercise capacity in clinical trials [30]. Although it is affected by several confounding factors, 6MWD is still used as the primary efficacy indicator for PAH since it is simple, inexpensive, safe and reproducible [30]. SAE includes acute cholecystitis, upper abdominal pain, respiratory failure, biliary colicas, cholelithiasis, vasovagal syncope, angina pectoris, liver function abnormalities and sinus tachycardia [16]. Unfortunately, most of the studies did not mention their criteria for SAE. This could bring some limitation to our conclusion on safety. SAE, death and all-cause discontinuation were acceptability outcomes of PAH therapies.

2.4. Statistical analysis

We began to analysis with traditional meta-analysis which carried out a direct comparison between one treatment and placebo. Weighted mean difference (WMD) together with 95% confidence interval (95% CI) was used to evaluate whether there was significant difference in 6MWD between two PAH therapies. Moreover, odds ratios (ORs) and the corresponding 95% CIs were used to determine the effect of treatments on clinical worsening, SAE, death and all-cause discontinuation. Heterogeneity was assessed by the statistic of I^2 and significant heterogeneity was presented if $P_h < 0.05$ or $I^2 > 50\%$. When significant heterogeneity existed among eligible studies, random-effect model (*DerSimonian-Laird*

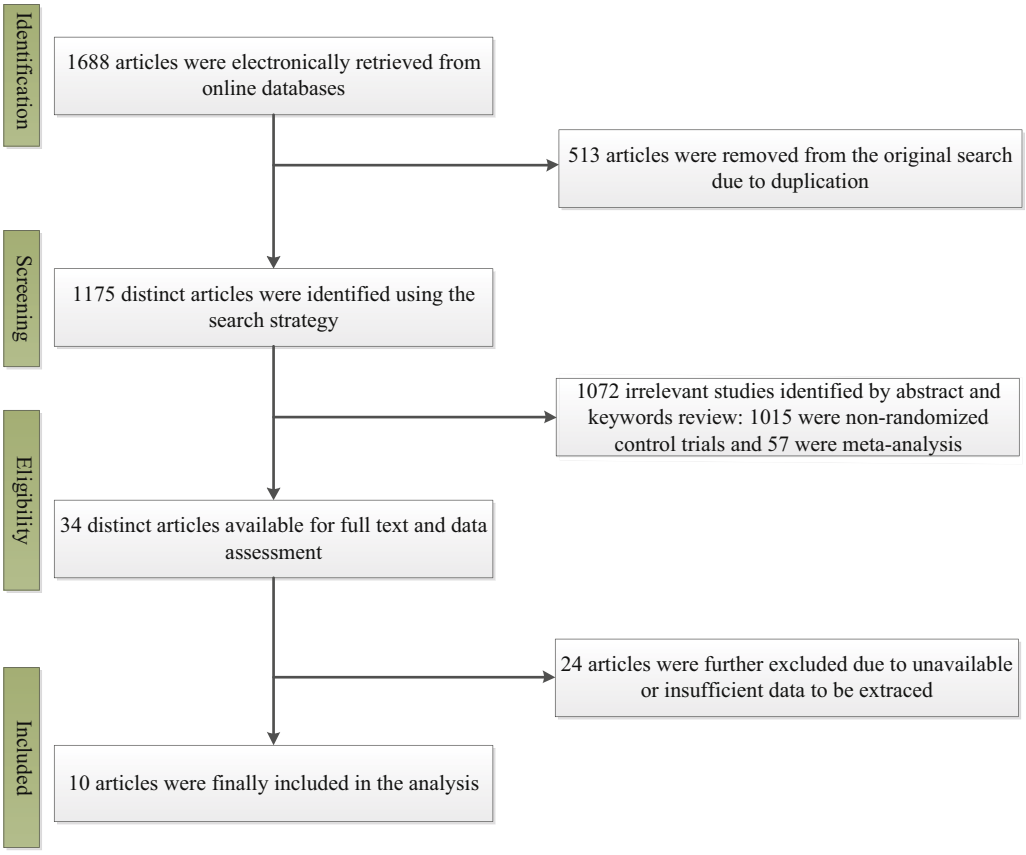

Fig. 1. Literature selection flow chart: the thorough process of systematic review and literature selection.

Please cite this article as: M.-M. Duo-Ji, Z.-W. Long, Comparative efficacy and acceptability of endothelin receptor antagonists for pulmonary arterial hypertension: A network meta-anal..., Int J Cardiol (2016), http://dx.doi.org/10.1016/j.ijcard.2016.12.092