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Comparative Effectiveness of Pharmacologic Interventions for Pulmonary Arterial Hypertension

A Systematic Review and Network Meta-Analysis

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BACKGROUND: We conducted a systematic review and network meta-analysis to examine comparative efficacy and tolerability of pharmacologic interventions for pulmonary arterial hypertension (PAH).

METHODS: MEDLINE, the Cochrane Register, EMBASE, CINAHL, and clinicaltrials.gov were searched (January 1, 1990 to March 3, 2016). Randomized controlled trials (RCTs) studying the approved pharmacologic agents endothelin receptor antagonists (ERA), phosphodiesterase inhibitors (PDE5i), the oral/inhaled (PO/INH) and IV/subcutaneous (SC) prostanoids, and riociguat and selexipag, alone or in combination, for pulmonary arterial hypertension (PAH) and reporting at least one efficacy outcome were selected.

RESULTS: Thirty-one RCTs with 6,565 patients were selected. In network meta-analysis, when compared with a median placebo rate of 14.5%, clinical worsening was estimated at 2.8% with riociguat (risk ratio [RR], 0.19; 95% CI, 0.05-0.76); at 3.9% with ERA + PDE5i (RR, 0.27; 95% CI, 0.14-0.52), and at 5.7% with PDE5i (RR, 0.39; 95% CI, 0.24-0.62). For improvement in functional status, when compared with 16.2% in the placebo group, improvement in at least one New York Heart Association/World Health Organization (NYHA/WHO) functional class was estimated at 81.8% with IV/SC prostanoids (RR, 5.06; 95% CI, 2.3211.04), at 28.3% with ERA + PDE5i (RR, 1.75; 95% CI, 1.05-2.92), and at 25.2% with ERA (RR, 1.56; 95% CI, 1.22-2.00). Differences in mortality were not significant. Adverse events leading to discontinuation of therapy were highest with the PO/INH prostanoids (RR, 2.92; 95% CI, 1.68-5.06) and selexipag (RR, 2.06; 95% CI, 1.04-3.88) compared with placebo.

CONCLUSIONS: Currently approved pharmacologic agents have varying effects on morbidity and functional status in patients with PAH. Future comparative effectiveness trials are warranted with a focus on a patient-centered approach to therapy.

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KEY WORDS: comparative efficacy; network meta-analysis; pulmonary arterial hypertension

ABBREVIATIONS: 6MWD = 6-min walk distance; ERA = endothelin receptor antagonist; FDA = Food and Drug Administration; GRADE = Grading of Recommendations Assessment, Development, and Education; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase-5 inhibitor; RCT = randomized controlled trial; RR = risk ratio; SUCRA = surface under the cumulative ranking area; WHO = World Health Organization; WMD = weighted mean difference

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Pulmonary arterial hypertension (PAH) or World Health Organization (WHO) group 1 pulmonary hypertension is a progressive disease associated with significant morbidity and a 5% to 15% annual mortality rate.[1-3] In recent years, a number of drug classes to treat PAH have been approved for clinical use. These include endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE5i), parenteral and nonparenteral prostacyclins, a soluble guanylate cyclase stimulator, and a prostacyclin-receptor agonist. Although randomized controlled trials (RCTs) have compared individual drugs to conventional therapy or placebo, head-to-head comparisons of different pharmacologic agents are limited. Conventional meta-analyses are limited by estimates between two interventions compared directly with each other, precluding assessment of comparative efficacy and safety of all available interventions.[4-7] Hence, evidence regarding the best treatment, either alone or in combination, is limited, leaving such decisions to individual clinical judgment.[8,9] A network meta-analysis approach can bridge this gap and guide both clinical decision-making and future research.[10,11]

Therefore, we performed a network meta-analysis combining direct and indirect evidence to evaluate comparative efficacy and safety of all US Food and Drug Administration (FDA)-approved pharmacologic interventions, alone or in combination, in patients with PAH.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for network meta-analysis and was conducted following a priori established protocol (PROSPERO-CRD42016036803).[12,13] We followed the International Society for Pharmacoeconomics and Outcomes Research approach on interpreting network meta-analyses for health-care decision-making.[14,15] We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) to appraise quality of evidence.[16]

Selection Criteria

We included phase II or phase III RCTs with a minimum of 8 weeks of follow-up, meeting the following criteria: (1) Patients were primarily adults with symptomatic PAH (group 1 pulmonary hypertension). Some trials studied subjects 12 years of age and older and were included; however, trials restricted to pediatric or neonatal patients were excluded. (2) Interventions included all FDA-approved drugs specifically for PAH, including ERA (bosentan, ambrisentan, macitentan), PDE5i (sildenafil, tadalafil), oral/inhaled (PO/INH) prostanoids (treprostinil, iloprost), IV/subcutaneous (SC) prostanoids (epoprostenol, treprostinil), the soluble guanylate cyclase simulator riociguat, and the selective prostacyclin-receptor agonist selexipag, alone or in combination, administered for 8 weeks or longer. (3) The comparator consisted of another active agent, placebo, or conventional therapy. (4) Outcomes included trials reporting any of the efficacy outcomes (clinical worsening, hospitalization, mortality, and improvement in functional class or 6-min walk distance [6MWD]). As in prior studies,[4,7] RCTs in which a PAH therapy was initiated on the background of another PAH-specific cointervention were included as trials of active agents against placebo, and nature and rates of background therapy in each arm were examined narratively. Detailed exclusion criteria are presented in e-Appendix 1, Methods.

Search Strategy

The search strategy was designed and conducted by an experienced medical librarian with input from study investigators. Multiple databases were searched for RCTs of pharmacologic therapy for PAH until March 3, 2016 (details in e-Appendix 1, Methods). Figure 1 shows study selection and e-Table 1 details the reasons for exclusion of randomized trials.

Data Abstraction and Quality Assessment

Data were abstracted independently by two reviewers using a standardized data abstraction form, and discrepancies were resolved after mutual agreement and discussion with a third reviewer. The risk of bias for individual studies was assessed using the Cochrane Risk of Bias assessment tool.[17]

Outcomes Assessed

We defined five major efficacy outcomes and one safety outcome. The efficacy outcomes were selected to reflect two aspects of PAH therapy. First, improvements in patient morbidity and mortality were assessed by reduction in (1) study-defined clinical worsening, representing a composite of death, PAH-related hospitalization, lung transplantation, atrial septostomy, initiation of rescue therapy and deterioration of functional class or worsening of 6MWD, varying across studies (e-Table 2) (primary efficacy outcome); (2) PAH-related hospitalization; and (3) all-cause mortality. Second, improvement in functional status was assessed by two outcomes: (1)

Campus, Aurora, CO; the Knowledge and Evaluation Research Unit (Drs Wang and Murad) and the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN; and the Division of Biomedical Informatics (Dr Singh), Department of Internal Medicine, University of California San Diego, La Jolla, CA.

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