CHEST

Original Research

PULMONARY VASCULAR DISEASE

Comparative Effectiveness and Safety of Drug Therapy for Pulmonary Arterial Hypertension

A Systematic Review and Meta-analysis

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Background: **Current treatments for pulmonary arterial hypertension (PAH) have been shown to improve dyspnea, 6-min walk distance (6MWD), and pulmonary hemodynamics, but few studies were designed to compare treatment regimens or assess the impact of treatment on mortality.**
Methods: **We conducted a systematic review to evaluate the comparative effectiveness and safety of monotherapy or combination therapy for PAH using endothelin receptor antagonists, phosphodiesterase inhibitors, or prostanoids. We searched English-language publications of comparative studies that reported intermediate or long-term outcomes associated with drug therapy for PAH. Two investigators abstracted data and rated study quality and applicability.**
Results: **We identified 28 randomized controlled trials involving 3,613 patients. We found no studies that randomized treatment-naive patients to monotherapy vs combination therapy. There was insufficient statistical power to detect a mortality difference associated with treatment. All drug classes demonstrated increases in 6MWD when compared with placebo, and combination therapy showed improved 6MWD compared with monotherapy. For hospitalization, the OR was lower in patients taking endothelin receptor antagonists or phosphodiesterase-5 inhibitors compared with placebo (OR, 0.34 and 0.48, respectively).**
Conclusions: **Although no studies were powered to detect a mortality reduction, monotherapy was associated with improved 6MWD and reduced hospitalization rates. Our findings also suggest an improvement in 6MWD when a second drug is added to monotherapy.**

CHEST 2014; 145(5):1055–1063

Abbreviations: 6MWD = 6-min walk distance; *df* = degrees of freedom; PAH = pulmonary arterial hypertension; RCT = randomized controlled trial

Pulmonary arterial hypertension (PAH) is a rare disease characterized by increased pulmonary vascular resistance leading to right ventricular pressure-volume overload and ultimately right-sided heart failure and premature death.[1] The goals of medical treatment of PAH are to improve patients' symptoms and slow the rate of disease progression. Currently, there are three main classes of medications[2] used to treat PAH: endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin analogs, each of which has been shown to improve dyspnea, 6-min walk distance (6MWD), pulmonary hemodynamics, and functional class. It is unknown whether combination drug therapy (using two or more drugs with different mechanisms of action) will improve these clinical indexes or be cost effective, because few studies have been powered to detect an effect on mortality or have compared the effectiveness or safety of two or more medications. The aim of this systematic review is to evaluate the intermediate and long-term comparative effectiveness and safety of monotherapy vs combination therapy for PAH using endothelin receptor antagonists, phosphodiesterase inhibitors, or prostanoids.

Materials and Methods

This article summarizes key methods and findings from a comparative effectiveness review commissioned by the US Agency for Healthcare Research and Quality.[3] Further details of the topic refinement, literature search, methods, and conclusions can be found in the full report.

Literature Search

We searched MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from 1995 through August 2012. We identified English-language clinical studies relating to the comparative effectiveness and safety of monotherapy and combination therapy in the treatment of PAH.

Study Selection and Data Abstraction

Using prespecified inclusion and exclusion criteria, titles and abstracts were examined for potential relevance by two independent reviewers. Inclusion criteria were patients with PAH; pharmacotherapy with calcium channel blockers, prostanoids (epoprostenol, treprostinil, iloprost), endothelin antagonists (bosentan, ambrisentan), or phosphodiesterase inhibitors (sildenafil, tadalafil); comparison of one pharmacotherapy vs another (or vs placebo or standard therapy) or monotherapy vs combination therapy; reporting of intermediate or long-term outcomes or adverse effects of pharmacotherapies; randomized controlled trial (RCT) or observational study with an appropriate comparator; and English-language, peer-reviewed publication. Included articles then underwent full-text screening by two additional independent reviewers to determine eligibility. Any disagreements were resolved by discussion or by a third-party arbitrator.

We collected data on demographics, interventions, outcomes, and adverse events. We evaluated the quality of individual studies using the general approach described in the US Agency for Healthcare Research and Quality's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[4] Studies were rated as good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting.

Data Synthesis

We conducted meta-analyses for comparisons when two or more studies reported the same outcome. We used random effects models to quantitatively synthesize the available evidence and to calculate summary estimates. When meta-analysis was not appropriate, studies were summarized and presented in tabular form. For analyses that included four or more studies, we used graphical displays and test statistics (Q and I^2 statistics) to assess heterogeneity, recognizing these may be limited because of the small number of studies. We present summary estimates and CIs in our data synthesis.

We use the term "background treatment" when patients were taking a preexisting medication prior to randomization to a second drug. Thus, the trial of iloprost plus bosentan vs bosentan alone (ie, the Combination Therapy of Bosentan and Aerosolised Iloprost in Idiopathic Pulmonary Arterial Hypertension [COMBI] trial[5]) would be described as a trial of iloprost with bosentan background therapy and would be construed to examine the efficacy of combination vs monotherapy; it is also relevant to the efficacy of iloprost. We assumed independent and additive effects of the experimental drug relative to any or all of the other background therapies received by the patients enrolled in the trial (including other PAH-specific drugs, supplemental oxygen, vasodilators, and so forth).

Results

Literature Review

Searches of PubMed, the Cochrane Database of Systematic Reviews, and EMBASE yielded 28 RCTs (represented by 36 articles), involving a total of 3,613 patients, that evaluated the comparative effectiveness and safety of monotherapy or combination therapy for PAH (Figure 1).[5-30] Of the 28 included RCTs, 18 (64%) were rated good quality, nine (32%) fair quality, and one (4%) was poor quality. Studies were conducted in a variety of centers and countries; most studies were multicenter trials, three were single-center trials, and four did not report the number of centers. Mean ages of patients ranged from 28 to 50 years. Twenty studies enrolled patients with PAH, four studies enrolled patients with PAH associated with systemic sclerosis (formerly scleroderma),[7,12,21] and two studies enrolled patients with Eisenmenger syndrome.[10,23] Two studies enrolled patients with PAH in addition to patients with category III or IV pulmonary hypertension.[17,18]

Twenty-two studies compared a single drug (monotherapy) with either placebo or standard therapy, and one was a head-to-head comparison of bosentan and sildenafil. The remaining five studies compared combination therapy with monotherapy.

Detailed Analysis of Drug Therapies

We report on the outcomes of mortality, 6MWD, hospitalization, hemodynamic measures (ie, pulmonary vascular resistance, mean pulmonary arterial pressure, cardiac index), and commonly reported adverse reactions. The comparative analyses of pharmacotherapies are head-to-head comparisons by individual drug; monotherapy vs placebo or standard therapy by individual drug; monotherapy vs placebo or standard therapy by

Manuscript received August 9, 2013; revision accepted November 15, 2013; originally published Online First December 26, 2013.
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Funding/Support: This project was funded under the Agency for Healthcare Research and Quality, US Department of Health and Human Services [Contract No. 290-2007-10066-I].
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DOI: 10.1378/chest.13-1864