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Comparative study on the effectiveness of drugs for pulmonary arterial hypertension

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Abstract
Pulmonary arterial hypertension (PAH) is a chronic and progressive disease characterized by the elevation of the mean pulmonary arterial pressure (mPAP) that leads to morbidity and premature mortality. Although PAH affects males and females of all ethnicities and ages, the disease most commonly affects women and people between 20 and 40 years of age. In adults, the prevalence of PAH is approximately 12 to 50 cases per million people.
PAH is classified as Group 1 of the pulmonary hypertension (PH) classification. Four subgroups of Group 1 include idiopathic PAH, heritable or familial PAH, drug- and toxin-induced PAH, and PAH associated with concurrent medical conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis.

Keywords: drugs, arterial, hypertension

Introduction

The mechanisms contributing to disease progression involve vasoconstriction, endothelial dysfunction, dysregulated smooth muscle cell growth, inflammation, and thrombosis that typically lead to overload of right ventricle and progressive right-sided heart failure. The therapeutic objectives of drugs for PAH are to normalize these mechanisms. Treatment of PAH is generally categorized as supportive therapy or advanced therapy. Supportive therapy includes use of diuretics, oxygen, anticoagulants, and digoxin. Many patients with PAH initially receive supportive therapy despite limited or no evidence of effectiveness. Consequently, the majority of patients with PAH will ultimately require advanced therapy, which is directed at the disease itself.

PAH is an uncommon and serious condition. The numbers of medications and treatment strategies for PAH have rapidly evolved in recent years, and this trend is expected to continue in the future. Given the rapid expansion in therapeutic options for PAH, the public drug plans require recommendations and advice regarding the currently approved and available treatments. While these advances provide clinicians and patients with additional treatment options, they necessitate an assessment of their comparative effectiveness and safety to ensure pharmacological interventions are used optimally, accounting for both their respective clinical and economic value.

Research work noted that sildenafil and tadalafil should be avoided in patients with specific contraindications identified in the respective product monographs (e.g., concurrent nitrate use). Research work was unable to identify potential additional criteria because of evidence gaps. Research work noted there was no evidence to guide the duration of treatment with sildenafil or tadalafil before changing to or adding another drug. The decision to change from or add to initial therapy with either sildenafil or tadalafil should be based on patient-specific factors and response (effectiveness and harms), and should be determined by PAH specialists working in one of India's designated PH centres.

For patients who are unable to receive sildenafil or tadalafil, no recommendation with respect to specific alternative initial therapies could be made within the context of the therapeutic review because of insufficient evidence. Substantial heterogeneity was noted across the studies included in the NMA; this is an important limitation of the therapeutic review.

The specific inclusion criteria of the RCTs that formed the evidence base of the therapeutic review did not include all types of PAH patients seen in clinical practice, in terms of disease stability and presence of comorbidities.

Only a very small proportion of patients enrolled in the included RCTs were classified as FC I PAH (< 1%). This low number of patients did not allow for a conclusion to be reached or a recommendation developed for this patient group. Intravenous epoprostenol is the only drug that has shown reduced mortality compared with placebo. This effect was predominantly observed in patients with more severe disease, i.e., FC III and IV, who made up a large portion of the patients in all epoprostenol studies (74% FC III and 26% FC IV).

In most RCTs assessing drugs for PAH, the key outcome studied was the change from baseline in six-minute walk distance (6MWD), a measure that does not reliably reflect the benefit in such clinical outcomes as death, hospitalization, and initiation of PAH rescue therapy. The effect of treatment on FC was incorporated as the measure of treatment efficacy within the economic model because it is the only measure of clinical efficacy that has been demonstrated to be associated with quality of life in PAH. However, this may not capture the full quality of life benefits of treatment, which would be better reflected through direct measurement of quality of life in patients receiving PAH therapies.

Research Study

Research work acknowledges that doses of sildenafil exceeding those recommended in the product monograph are used in Canadian clinical practice in order to adequately treat patients with PAH. In the feedback received from patients, the preference, mentioned several times, for using an oral medication rather than an injectable medication was noted. Based on how harms data were reported in RCTs, it was not possible to identify patients at greater risk for AEs.

The following points summarize the key concerns of patients and caregivers, as documented in the patient group submissions:

PAH has a significant impact on the lives of patients. Learning that one has this progressive and typically terminal illness is a shock. It forces immediate and drastic lifestyle changes on the part of the person with the disease. Patients with PAH have a day-to-day life that is difficult, exhausting, and challenging.

Patients commonly experience depressed mood, anxiety, and feelings of helplessness and hopelessness as they are faced with a serious illness with a high risk of death within a few years. Patients progressively lose the ability to care for themselves and increasingly need the help of caregivers. Patients with children have limited ability to care for them, and once diagnosed with PAH, pregnancy is contraindicated. Many patients have to give up careers and dreams of starting a family in the prime of their lives.

Therapy generally results in the reduction in the severity of PAH, but response is highly variable from day to day and person to person. While drug therapy delays the progression of the disease, alleviates some of the symptoms, and makes certain tasks easier, patients are frustrated by the fact that there is still no cure for PAH. Patients are also frustrated by the difficulties in gaining access to drug therapy, particularly combination therapy, depending on their residential location in India. This has resulted in some patients staying on monotherapy with suboptimal control of their disease.

The impact on caregivers can be severe. They take the brunt of the work around the home, face increased financial responsibilities, and become psychological support systems for the patients. They give up considerable amounts of their own personal time and resources to care for the patient.

Evidence on monotherapy was available for the following drug therapies: macitentan (one RCT), riociguat (one RCT), ambrisentan (three RCTs), bosentan (four RCTs), sildenafil (one RCT), tadalafil (one RCT), epoprostenol (three RCTs), and treprostinil (four RCTs). Evidence of dual (add-on therapy) was available from the following combinations: macitentan added to PDE-5 inhibitors or prostanoids (one RCT), riociguat added to ERA (one RCT), and tadalafil added to ERA (two RCTs).

The severity of PAH was based on a number of clinical parameters, including the New York Heart Association (NYHA) or WHO FC, which ranges from class I to IV, with class IV representing patients with the most severe symptoms. The outcomes of interest were mortality, hospitalization, clinical worsening, WHO FC (improved, unchanged, worsened), 6MWD, Borg dyspnea index (BDI), pulmonary hemodynamics (pulmonary vascular resistance [PVR], mPAP cardiac index [CI]), health-related quality of life (HRQoL), and safety data (serious adverse events [SAEs], discontinuation due to AEs, total AEs).

Discussion

For clinical worsening, data from eight treatment options (macitentan 10 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, and placebo) were subjected to meta-analyses. Despite the slight difference in definition among studies, clinical worsening (a mortality and morbidity composite outcome) was generally defined as time to first occurrence of all-cause death, worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, heart or lung transplantation, or atrial septostomy.

Direct pairwise meta-analysis showed that all treatments were numerically favoured in reducing the risk of clinical worsening compared with placebo. Treatment effects (relative risk [RR]) ranged from 0.25 (tadalafil) to 0.59 (macitentan). A statistically significant difference versus placebo was reached for macitentan, ambrisentan 5 mg, and bosentan, but not for riociguat, ambrisentan 10 mg, sildenafil, and tadalafil in a treatment-naive population. The treatment effects versus placebo estimated from NMA were similar, in both magnitude and direction, to the results of direct pairwise estimates, with RRs ranging from 0.21 for tadalafil to 0.46 for macitentan. There were no statistically significant differences between drugs with respect to clinical worsening outcomes.

Excluding the study examining the efficacy of macitentan (a long-term study with median follow-up of 115 weeks) from the analysis did not affect the effect sizes of other treatments. Likewise, sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect, suggesting the robustness of the results. Clinical worsening has been recommended for use as a clinically relevant primary outcome in studies evaluating drugs for the treatment of PAH because it measures treatment effects on mortality and morbidity. It is reasonable for clinical worsening to be a composite outcome, largely because of the low event rates for the individual mortality and morbidity components.37 However, the definition of a clinically important difference between treatment groups with respect to clinical worsening in these studies has yet to be determined.

For FC improvement, data from nine treatment options (riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were subjected to meta-analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients with FC improvement were available from published sources for macitentan.

Direct pairwise metaanalysis showed that, for naive populations, epoprostenol, sildenafil, and tadalafil showed statistically significant improvement in FC compared with placebo, while riociguat, ambrisentan, bosentan, and treprostinil did not. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Epoprostenol, which had the largest treatment effect versus placebo, was statistically significantly superior compared with all other treatments in the naive populations.

For FC worsening, data from eight treatment options

(riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and placebo) were subjected to meta-analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients experiencing FC worsening were available from published sources.

Direct pairwise meta-analysis showed that all treatments were numerically favoured in the reduction of FC worsening compared with placebo. Statistically significant differences were reached only for ambrisentan (5 mg and 10 mg) and riociguat (max 2.5 mg) in naive populations. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. There were no statistically significant differences between riociguat and other drugs or between other drugs themselves. Sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect, suggesting the robustness of the results. The MCID of WHO FC worsening is unknown.

For 6MWD, data for all 11 treatment options (macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were subjected to meta-analyses. The 6MWD measures the distance a patient can walk in six minutes. Change from baseline in 6MWD is the most widely used outcome in trials of drugs for PAH. However, while some evidence suggests baseline 6MWD and absolute distance walked in six minutes are correlated with mortality and morbidity outcomes in PAH, change from baseline in 6MWD has been inconsistently correlated with these outcomes.

Conclusion

Change in 6MWD from baseline was used as the primary outcome in many of the included studies, except for the macitentan study, in which it was a secondary outcome. Direct pairwise meta-analysis showed that all drugs, except macitentan, statistically significantly increased 6MWD compared with placebo in the naive populations. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Increase in 6MWD with riociguat (both doses) was not statistically significantly different compared with all other drugs. Numerically, epoprostenol showed the highest increase in 6MWD compared with all remaining drugs. The mean differences in 6MWD relative to other drugs ranged from 18.3 m (compared with ambrisentan 5 mg) to 56.9 m (compared with macitentan 10 mg). The MCID for the change in 6MWD from baseline has been estimated to be 33.0 m (range: 25.1 m to 38.6 m). Sensitivity analysis was not performed for this outcome.

Extensive deterministic sensitivity analyses were conducted to assess the impact of changes in parameter inputs (parameter uncertainty) and model assumptions (structural uncertainty). A probabilistic sensitivity analysis was also conducted to estimate the extent of uncertainty surrounding the estimates.

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