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THERAPEUTIC APPROACHES FOR THE TREATMENT OF PULMONARY HYPERTENSION

Diana Malaeb[1]*, Fouad Sakr[2], Mariam Dabbous[3]

[1]PharmD Department, School of Pharmacy, Lebanese International University, Beirut, Lebanon
[2]Biomedical Sciences Department, School of Pharmacy, Lebanese International University, Beirut, Lebanon
[3]Pharmaceutical Sciences Department, School of Pharmacy, Lebanese International University, Beirut, Lebanon

***Corresponding author e-mail:** diana.malaeb@liu.edu.lb

ABSTRACT

Pulmonary hypertension is a progressive symptomatic fatal disease. It is a diagnosis of exclusion. The main goal of therapy is to lower pulmonary arterial pressure and pulmonary vascular resistance while preserving systemic pressure. Current treatments including calcium channel blockers, endothelin-1 antagonists, prostanoids, phosphodiesterase inhibitors, and prostacyclins. These treatments are palliative, may slow the progression of the disease, relief symptoms, and improve quality of life, but do not cure it. The article reviews the current updated therapeutic treatment, pharmacological action, doses, and adverse drug reaction.

Keywords: Pulmonary hypertension, Pulmonary artery hypertension, Endothelin antagonists, Phosphodiesterase-5 inhibitors

INTRODUCTION

Pulmonary hypertension (PH) is generally defined as abnormally high pulmonary vascular pressure. Pulmonary artery hypertension (PAH) is a category of PH resulting from restricted flow through the pulmonary arterial circulation, which leads to pathological increases in pulmonary vascular resistance (PVR) and ultimately to right heart failure. PAH is clinically defined as a mean pulmonary artery pressure (mPAP) of greater than 25 mm Hg at rest in the setting of a normal pulmonary arterial wedge pressure of 15 mm Hg or less with a PVR greater than 3 Wood units.[1-2]

Causes and Pathogenesis: The pathobiological mechanisms of PAH have recently been reviewed. The PAH "phenotype" is characterized by endothelial dysfunction, a decreased ratio of apoptosis/proliferation in pulmonary artery smooth muscle cells (PASMCs), and a thickened disordered adventitia in which there is excessive activation of adventitial metalloproteases.[1] Like cancer and atherosclerosis, PAH does not have a single cause: a "multi-hit model" is more likely.[3] Conditions that predispose to pulmonary hypertension include congenital or acquired valvular disease, left ventricular systolic dysfunction, impaired left ventricular diastolic function, and congenital disease with shunt, as well as, pulmonary embolus and pulmonary vein thrombosis/stenosis.[1] PAH is inherited in less than 10% of cases.[4-5] In the vascular lumen, PAH is characterized by platelets that are depleted of serotonin and elevation of plasma serotonin.[6] Endothelial dysfunction is common in PAH. The PAH endothelium is characterized by increased production of vasoconstrictor/mitogenic compounds, such as endothelin and thromboxane, and deficient production of vasodilators, such as prostacyclin.[7–9] Elevated levels of fibrinopeptide A and plasminogen activator inhibitor-1 and reduced levels of tissue plasminogen activator contribute to

the procoagulant state. Endothelial injury may also expose the underlying smooth muscle cells to circulating mitogens and growth factors that stimulate cell proliferation.[1]

CLASSIFICATION AND DIAGNOSIS

The World Health Organization (WHO) classifies PH into 5 categories.[10]

Category I PH (PAH): is diverse and is unified by histological similarities amongst the represented diseases and the shared elevation of PVR. Category 1 includes idiopathic and familial PH, as well as PH associated with conditions such as collagen vascular disease, congenital shunts, cirrhosis and portal hypertension, HIV, hemoglobinopathies, and schistosomiasis. It also includes PH associated with drugs, such as anorexigens or amphetamines.[11]

Category 2 PH: is the collection of PH syndromes resulting from left ventricular (LV) or left-sided valvular disease. Whether due to mitral stenosis, cardiomyopathy, or LV diastolic dysfunction; Category 2 patients have PH due in large part to increased left atrial pressure. Category 2 is the most common form of PH and while there is no approved PH-specific therapy for this category, PH confers adverse prognosis to these patients. Classically, Category 2 patients are defined at catheterization by an elevated pulmonary-wedge pressure and a modest transpulmonary gradient (usually <10 mm Hg difference between mean PA and wedge pressure). However, increasingly cases are identified where the transpulmonary gradient is increased disproportionately.[12] In such cases, there is likely pulmonary vascular remodeling.[10]

Category 3 PH: is secondary to chronic lung diseases, hypoxia, or both (e.g., sleep apnea). This category of PH is characterized by mild elevations in mPAP.[13] As with Category 2, however, there are Category 3 patients in whom the PH is disproportionately severe, as compared to their lung disease.[10]

Category 4 PH (CTEPH): is unique because it represents the form of PH that is curable without transplantation.[14] Perfusion lung scanning can be helpful for the diagnosis, but will not reveal the proximal extent of the thromboemboli. In addition, patients with nonocclusive thrombi may have normal distal lung perfusion in those segments giving a false negative impression. While noninvasive imaging is key to the diagnosis of CTEPH, there are cases in which the CT angiography fails to detect the intimately incorporated thrombus, which forms a neointima.[15]

Category 5 PH: represents a heterogeneous collection of PH syndromes secondary to systemic diseases (i.e., sarcoidosis, histiocytosis X), hematological disorders (such as polycythemia vera or chronic myeloid leukemia) and extrinsic compression of the pulmonary artery.[10]

In general, the most common presenting symptoms of PH include dyspnea on exertion, fatigue, chest pain, syncope, palpitations, and lower extremity edema.[1] Diagnosis of PAH requires a comprehensive evaluation that includes pulmonary function testing, connective tissue disease serology, echocardiography, cardiac catheterization, and tests to exclude chronic thromboembolic disease.[16] Similarly, screening is recommended in high risk patients such as those with genetic mutations predisposing to pulmonary hypertension, first degree relatives in a familial PAH family, patients with scleroderma, patients with portal hypertension prior to liver transplantation, and patients with congenital systemic to pulmonary shunts using doppler echocardiography.[16]

PHARMACOTHERAPY

Calcium Channel Blockers: Calcium channel blockers (CCBs) exert a pulmonary vasodilator effect with reduction in the mPAP and increase in quality of life and survival.[17] They are used in patients with idiopathic pulmonary arterial hypertension (IPAH) who demonstrate a favorable response to acute vasodilator testing.[18] The response to CCBs is defined as a fall in mPAP of greater than or equal to 10 mm Hg, to a mPAP less than or equal to 40 mm Hg, with an unchanged or increased cardiac output.[1] In a large retrospective study in which IPAH patients were treated with CCBs, after demonstrating acute pulmonary vasoreactivity, long-term CCB responders had a survival of 97% at an average follow-up of 7 years.[19] On the contrary, CCB non-responders had a survival of only 48% at 5 years and several patients in this group were transplanted or started on prostaglandin analogs or endothelin receptor antagonist therapy.[19] The most commonly used calcium channel blockers are long acting nifedipine, diltiazem, or amlodipine.[1] Verapamil is contraindicated because of its negatively inotropic effect.[20] CCBs should be started at a low dose and up-titrated cautiously to the maximum tolerated dose. The daily doses of these drugs that have shown efficacy in IPAH are 120–240 mg for nifedipine, 240–720 mg for diltiazem, and up to 20 mg for amlodipine.[18] Upon dose up-titration it is recommended to draw special attention to hypotension, obstipation, and any signs of right heart failure; [18] and never initiate in subjects with

hemodynamic instability, heart failure (cardiac index below 2 l/min/m^2 and right atrial pressure above 20 mm Hg) or previous adverse reactions to the medication.[21-22] Close follow-up is required to assure sustained benefits of CCB therapy.[17]

Endothelin Antagonists: Activation of the endothelin (ET)-1 system has been demonstrated in both plasma and lung tissues of PAH patients. Although it is not clear if the increases in ET-1 plasma levels are a cause or a consequence of PH, studies on tissue ET system expression support a prominent role for ET-1 in the pathogenesis of PAH.[8] Two distinct ET receptor isoforms have been identified, ETA and ETB.[23] Endothelin A receptors are expressed on smooth muscle cells and cardiac myocytes; ETB receptors are localized on vascular endothelial cells and smooth muscle cells.[24] Activation of ETA and ETB receptors on smooth muscle cells results in vasoconstriction, and cell proliferation and hypertrophy. Activation of ETB receptors on endothelial cells leads to release of vasodilators, i.e., nitric oxide and prostacyclin, which also appear to have anti-proliferative properties. [25-26] In addition, endothelial ETB receptors are involved in the clearance of ET-1, primarily in the vascular beds of the lungs, kidneys, and liver.[27] All approved compound belonging to this drug class (bosentan, ambrisentan) are presumed potentially hepatotoxic and can only be prescribed by registered prescribers. Regular controls of aminotransferases in 4-week intervals are required.[18]

Bosentan: Bosentan is an oral active dual endothelin-A and -B receptor antagonist and is approved for the treatment of PAH in WHO functional class II and III.[28] Adverse effects of bosentan include flushing, edema, nasal congestion, teratogenicity, and mild anemia. Bosentan displays drug-to-drug interactions with glyburide, cyclosporine, estrogen-based oral contraceptives, and sildenafil.[20] Increases in hepatic aminotransferases occurred in 10% of the subjects but were found to be dose dependent and reversible after dose reduction or discontinuation. For these reasons, liver function tests should be performed at least monthly in patients receiving bosentan.[29]

Sitaxsentan sodium: Sitaxsentan sodium is a selective oral ETA receptor antagonist, with a high oral bioavailability (>90%) and a long duration of action (half-life of 10 hr in PAH patients).[30] It has been assessed in patients with WHO/NYHA class II/III PAH.[31-32] Sitaxentan had initially shown comparable effects to bosentan in iPAH and PAH, but withdrawn from market due to two fatal cases of liver failure.[33] Sitaxsentan can reduce the required dose of warfarin and increase bleeding risk if the INR is not monitored appropriately.[34]

Ambrisentan: Ambrisentan is a non-sulfonamide, propanoic acid-class, selective ETA receptor antagonist.[35] It is approved for the treatment of PAH in WHO functional class II and III with a target dose of 5–10 mg once daily. Liver function tests should be monitored at least monthly.[36-37] Caution is suggested for the co-administration of ambrisentan with ketoconazole and cyclosporine.[29]

Phosphodiesterase-5 Inhibitors: Phosphodiesterase (PDE) inhibitors increase cyclic mononucleotides (cyclic AMP and cyclic GMP) by inhibiting their degradation, which leads to vaso-relaxation.[38-39]

Sildenafil: Sildenafil is an orally active, potent and selective inhibitor of phosphodiesterase type-5 (PDE-5) that increases the intracellular concentration of cGMP.[40] It is approved for the treatment of PAH in functional class II and III at a dose of 20 mg three times daily with an upper dose escalation up to 80 mg three times daily, resulting in further improvement of the clinical condition and pulmonary hemodynamics.[41-42] Most side effects of sildenafil were mild to moderate and mainly related to vasodilation and include headache, flushing, dyspepsia, nasal congestion, and epistaxis.[20-29] Nitrates must be avoided in patients taking PDE-5 inhibitors because the additive effects of the drugs may cause severe systemic hypotension.

Tadalafil: Tadalafil is selective PDE-5 inhibitor, currently approved for the treatment of erectile dysfunction.[29] It is approved for the treatment of PAH in functional class II and III and the target dose is 40 mg once daily given orally.[43] Tadalafil has similar side effects profile to sildenafil. Unlike sildenafil, due to tadalafil hepatic metabolism and renal clearance, dose adjustments are recommended for patients with renal and/or hepatic function impairment.[44]

Prostacyclins

Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilatation of all vascular beds studied. It is the most potent endogenous inhibitor of platelet aggregation and has both cytoprotective and anti-proliferative activities. Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites.[45]

Epoprostenol: Intravenous epoprostenol is the first available drug specific for PAH and remains the most appropriate first-line agent in the critically ill. Epoprostenol improves symptoms, hemodynamics,

and long-term survival in PAH. [46-47] It is FDA approved for WHO classes III.[46] Presently, because of the complex administration and cumbersome follow-up, epoprostenol use is mainly confined to highly experienced centers because it must be administered continuously by means of infusion pumps. Patients must keep a central venous catheter (CVC) and handle drug preparation and infusion.[47] Unfortunately, substantial side-effects have been reported, namely flushing, headache, and sudden death after abrupt discontinuation, as well as risk of infection related to CVC. [1] Complications of therapy include pump malfunction; dislodgement, occlusion, or fracture of the indwelling catheter; and catheter infections ranging from local abscess and cellulitis to bacteremia and sepsis, which can be mono- and poly-microbial.[29] Optimal dose varies between individual patients, ranging from 20 to 40 ng/kg/min.[48-49]

Iloprost: Iloprost is a chemically stable prostacyclin analogue available for intravenous, oral, and aerosol administration.[50] Inhaled therapy via special nebulizers, at a dose of 2.5–5 μg six to eight times per day for PAH, is an attractive concept that has the theoretical advantage of being selective for the pulmonary circulation.[34] It has been shown to improve hemodynamics, exercise capacity, quality of life, and survival.[51-52] As with other systemic prostanoids, there is a risk of life-threatening catheter infections and other side effects that typically occur during treatment with prostanoids (including hypotension, flushing, jaw pain, headache, nausea, diarrhea, etc.).[18] It can be used as an alternative to parental prostacyclins in patients who refuse or do not have the ability to tolerate the complexity of those agents.[34]

Treprostinil: Treprostinil is a tricyclic benzidine analogue of epoprostenol with a half-life 3 to 4 hours,[34] with sufficient chemical stability to be administered at ambient temperature.[29] These characteristics allow administration of the compound by the intravenous as well as the subcutaneous route. Intravenous and subcutaneous treprostinil have similar hemodynamic effects to intravenous epoprostenol**.**[53] Treprostinil has been recently FDA approved for intravenous use in patients with PAH; the effects appear to be comparable with those of epoprostenol but at a dose 2 to 3 times higher. It is more convenient for the patient because the reservoir can be changed every 48 hours as compared to 12 hours with epoprostenol.[29] Infusion site pain was the most common adverse effect of treprostinil, leading to discontinuation of the treatment in some cases; in addition to flushing, jaw pain, and body aches, and these may also limit the achievable dose.[54]

Inhaled Nitric Oxide: Inhaled nitric oxide (iNO) is an odorless gas that rapidly diffuses across the alveolar-capillary membrane into the pulmonary artery smooth muscle. It activates soluble guanylate cyclase that in turn increases the levels of cGMP, leading to vasodilation.[55] It increases pulmonary perfusion only in ventilated areas, which can improve gas exchange and decrease PVR without increasing intrapulmonary shunting.[56] It is used in neonates with hypoxic respiratory failure and clinical or ECG evidence of pulmonary hypertension.[57] iNO is most effective in patients with severe persistent pulmonary hypertension who have minimal underlying parenchymal lung disease (idiopathic persistent pulmonary hypertension).[58] Although it is not FDA approved, it may be a treatment option for children and adult hemodynamically unstable, ICU patients, and postoperatively.[56] iNO half-life is very short since it is rapidly inactivated in the alveolar capillaries preventing effects on the systemic vasculature.[59] It is administered by conventional or high frequency ventilation in doses of 5–20 ppm. The patient should be weaned from iNO over a period of 12–48 hours as tolerated. Adverse effects include methemoglobinemia, accumulation of nitrogen dioxide (NO_2), and rebound PAH.[60] Therefore, precise monitoring of nitrogen dioxide, nitric oxide, and oxygen (partial pressure of arterial oxygen [PaO2]) concentrations should be performed, as well as, periodic measurement of methemoglobin is also recommended.[61]

ADJUNCTIVE THERAPY

Oral Anticoagulants: Use of warfarin is advised to manage PAH and chronic pulmonary thromboembolism; on the basis of documented coagulation diathesis and reported survival benefits in patients with these conditions.[62- 64] Abnormalities in coagulation and fibrinolytic pathways have also been reported, and mural thrombi have been shown in central elastic pulmonary arteries of patients with IPAH.[65] Oral anticoagulants is recommended in PAH patients unless there are contraindications with a recommended target INR from 1.5 to 2.5,[66] or at some centers from 2.0 to 3.0. [29]

Inotropes: The effects of adrenergic inotropic drugs on the failing right ventricle have received little attention by investigators. Data on humans are available mostly for the prevalent beta-2 adrenergic receptor agonist isoproterenol that was administered to IPAH patients for its supposed effects of vasodilatation on pulmonary circulation.[67-69]

Dobutamine is a prevalent beta-1 adrenergic receptor agonist that exerts inotropic and vasodilator effects comparable to isoproterenol but has a less

pronounced chronotropic activity.[67] Dopamine is a beta, alpha, and dopaminergic receptors agonist, and its profile of action may present some advantages over the prevalent beta-receptor agonist drugs. In fact, the alpha-adrenergic activity helps to preserve the blood pressure levels and even to increase them.[67] The absence of systemic hypotensive effects, together with the renal blood flow increase, suggests the use of dopamine alone or in combination with dobutamine as the inotropic strategy of choice in PAH patients. Although digoxin has been shown to improve cardiac output acutely in IPAH, its efficacy is unknown when administered chronically. It may be given to slow ventricular rate in patients with PAH who develop atrial tachyarrhythmias.[70]

Diuretics: Diuretics are used to prevent volume overload; and the discomfort and complications of edema, ascites, and malabsorption associated with bowel edema. Electrolytes and renal function should be observed closely.[34] Although there are no randomized controlled trials of diuretics in PAH, clinical experience shows clear symptomatic benefit in fluid-overloaded patients treated with this therapy. Therefore, diuretics are used according to the clinical situation. For instance, spironolactone can be used as an adjunctive therapy;[71] whereas, thiazides can be used sparingly to augment loop diuretics.[34]

Oxygen Therapy: Oxygen content of arterial blood and oxygen delivery to tissues are generally not reduced unless the PaO_2 falls < 60 mm Hg.[72] Most patients with lung diseases are hypoxemic because of altered ventilation-perfusion matching.[73] For patients who are hypoxemic at rest (PaO_2 < 55 to 59 mm Hg), treatment with continuous oxygen therapy improves survival. Ambulatory oxygen may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise.[71] Since there are no randomized data to suggest that long-term of oxygen therapy is beneficial in patients with PAH, the decision for oxygen therapy has to be made on an individual basis.[18]

CONCLUSION

PAH is frequently life-threatening and requires aggressive management. Previously the prognosis for all patients was very poor; however, the current medical therapy approved for the treatment of PAH as endothelin antagonists, phosphodiesterase inhibitors, and prostacyclins, have sustained benefits on hemodynamic function and exercise capacity, therefore improved patient quality of life and overall survival. Treatment strategies that combine medications and target multiple pathogenic pathways have now been demonstrated to be both safe and more effective than monotherapy, and are emerging as the preferred approach for management of many patients; while continued research on agents that that directly target vascular remodeling is warranted.

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