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Treatment of pulmonary hypertension

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Summary

Pulmonary arterial hypertension (PAH) is a chronic progressive disease of the pulmonary vasculature characterized by elevated pulmonary arterial pressure and secondary right ventricular failure. PAH is considered a life-threatening condition unless treated. This article provides a comprehensive review of controlled and uncontrolled trials to define the risk-benefit for different therapeutic options of this clinical disorder. Relevant published articles were identified through searches of the National Center for Biotechnology PubMed database. All therapeutic measures for PAH were discussed. Six drugs have been approved in the United States for the treatment of PAH. Extensive medical advancement has been achieved in treatment of PAH. However, none of the approved therapies have shown ability to cure the disease. New research should be performed to develop promising new therapies.

key words: **pulmonary arterial hypertension • calcium channel blockers • phosphodiesterase-5 inhibitors • prostanoids • endothelin receptor antagonists • lung transplantation**

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Background

Pulmonary arterial hypertension (PAH) is a chronic progressive disease of the pulmonary vasculature, characterized by elevated pulmonary arterial pressure and secondary right ventricular failure. PAH is caused by numerous disorders listed in Table 1. A resting mean pulmonary arterial pressure (mPAP) between 8 and 25 mm Hg is considered normal. PAH is defined as a mean pulmonary artery pressure at rest greater than 25 mm Hg in the presence of a pulmonary capillary wedge pressure of 15 mm Hg or less [1].

The estimated incidence of primary pulmonary hypertension is 1–2 cases per 1 million persons in the general population. Pulmonary hypertension is more common in women than in men (ratio: 1.7 to 1) [2]. Pulmonary hypertension is most prevalent in persons 20 to 40 years of age [3]. In persons older than 50 years of age, cor-pulmonale, the consequence of untreated PAH, is the third most common cardiac disorder (after coronary and hypertensive heart disease) [2,4]. The mean life expectancy from the time of diagnosis in patients with idiopathic PAH before the availability of disease-specific targeted therapy is 2.8 years [5].

All relevant published articles on the treatment of PAH were identified through searches of the National Center for Biotechnology PubMed database.

At present there are 6 approved drugs for the treatment of PAH in the United States with randomized clinical trials demonstrating their effectiveness. However, there has never been a single randomized clinical trial for PAH that lasted beyond 16 weeks that has demonstrated sustained clinical benefit or any reduction in mortality. Nevertheless, significant advances in management of PAH have occurred, and targeting the prostacyclin pathway, the nitric oxide pathway, or the endothelin pathway have either received regulatory approval or are under regulatory review [6]. Supportive therapy of PAH includes: oxygen, diuretics, digoxin, oral vasodilators, and anticoagulation (mainly with warfarin) [7,8].

Treatment starts with a baseline assessment of disease severity followed by primary therapy directed at the underlying pathophysiology of the PAH. While traditional therapies continue to play important roles in managing PAH, agents such as epoprostenol, treprostinil, bosentan, ambrisentan, iloprost, and sildenafil have been approved by the United States Food and Drug Administration (FDA). Since advanced pulmonary hypertension is less responsive to therapy, early identification and management of pulmonary hypertension is recommended.

Enhancing functional capacity, which can be measured objectively by performing a 6-minute walk test, and improving symptoms such as dyspnea are treatment objectives. Another important goal is to prevent disease progression and need for hospitalization, lung transplantation, or atrial septostomy.

Clinical Classification

The 2003 World Symposium on Pulmonary Hypertension set forth a new classification system that categorizes pulmonary hypertension on the basis of shared clinical attributes (Table 1). Pulmonary hypertension is classified into 5 groups, based largely on diagnostic and treatment implications. This new clinical classification helps clinicians evaluate

Table 1. Pulmonary hypertension classification system from the 2003 world symposium on pulmonary hypertension.

1.	**Pulmonary arterial hypertension**
1.1.	Idiopathic pulmonary arterial hypertension
1.2.	Familial pulmonary arterial hypertension
1.3.	Associated with pulmonary arterial hypertension
1.3.1.	Collagen vascular disease
1.3.2.	Congenital systemic to pulmonary shunts
1.3.3.	Portal hypertension
1.3.4.	Human immunodeficiency virus
1.3.5.	Drugs and toxins
1.3.6.	Other diseases (thyroid disorders, glycogen storage disease, Gaucher's disease, hemoglobinopathies, hereditary hemorrhagic telangiectasia, myeloproliferative disease, splenectomy)
1.4.	Associated with venous or capillary involvement
1.4.1.	Pulmonary venoocclusive disease
1.4.2.	Pulmonary capillary hemangiomatosis
1.5.	Persistent pulmonary hypertension of the newborn
2.	**Pulmonary hypertension with left heart disease**
2.1.	Left-sided atrial or ventricular heart disease
2.2.	Left-sided valvular heart disease
3.	**Pulmonary hypertension associated with lung disease and/or hypoxemia**
3.1.	Chronic obstructive pulmonary disease
3.2.	Interstitial lung disease
3.3.	Sleep-disordered breathing
3.4.	Alveolar hypoventilation disorders
3.5.	Long-term exposure to high altitude
3.6.	Developmental abnormalities
4.	**Pulmonary hypertension due to chronic thrombotic/ embolic disease**
4.1.	Thromboembolic obstruction of proximal pulmonary arteries
4.2.	Thromboembolic obstruction of distal pulmonary arteries
4.3.	Non-thrombotic pulmonary embolism
5.	**Miscellaneous**
	Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Adapted from reference 9

Table 2. World Health Organization functional class classification.

Class I	Patients with pulmonary hypertension without limitation of physical activity. Ordinary physical activity does not cause dyspnea, fatigue, chest pain, or near syncope
Class II	Patients with pulmonary hypertension with slight limitation of physical activity.
Class III	Patients with pulmonary hypertension with marked limitation of physical activity.
Class IV	Patients with pulmonary hypertension with inability to perform any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue are present at rest

Adapted from reference 9.

Table 3. Dana Point-2008 updated clinical classification of pulmonary hypertension.

1.	**Pulmonary arterial hypertension**
1.1.	Idiopathic pulmonary arterial hypertension
1.2.	Heritable
1.2.1.	Bone morphogenetic protein receptor type 2
1.2.2.	Activin receptor-like kinase type 1.endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3.	Unknown
1.4.	Associated with
1.4.1.	Connective tissue diseases
1.4.2.	Human immunodeficiency virus infection
1.4.3.	Portal hypertension
1.4.4.	Congenital heart diseases
1.4.5.	Schistosomiasis
1.4.6.	Chronic hemolytic anaemia
1.5.	Persistent pulmonary hypertension of the newborn
1′.	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2	**Pulmonary hypertension owing to left heart disease**
2.1.	Systolic dysfunction
2.2.	Diastolic dysfunction
2.3.	Valvular diseases
3.	**Pulmonary hypertension owing to lung diseases and/or hypoxia**
3.1.	Chronic obstructive pulmonary disease
3.2.	Interstitial lung disease
3.3.	Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4.	Sleep-disordered breathing
3.5.	Alveolar hypoventilation disorders
3.6.	Chronic exposure to high altitude
3.7.	Developmental abnormalities
4.	**Chronic thromboembolic pulmonary hypertension**
5.	**Pulmonary hypertension with unclear multifactor mechanisms**
5.1.	Hematologic disorders: myeloproliferative disorders, splenectomy
5.2.	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitits
5.3.	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4.	Others; tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Adapted from reference 10.

individual patients, standardize diagnoses, design clinical studies, and modify treatment [9]. In addition, the World Health Organization classifies patients into 4 functional classes (Table 2) [9]. Table 3 shows the updated clinical classification of pulmonary hypertension (Dana Point, 2008) [10].

Clinical Diagnostics

All patients should have a Doppler echocardiogram to diagnose the presence and severity of pulmonary hypertension, right ventricular size and function, left ventricular systolic and diastolic function, presence and severity of valvular heart disease, and other possible causes of pulmonary hypertension [11]. Right heart catheterization should be performed in patients who after noninvasive screening are considered to have probable PAH with measurement of pulmonary artery pressure, calculation of pulmonary vascular resistance, and performance of vasodilator testing [12]. Right heart catheterization should be performed prior to initiation of pulmonary vasodilator therapy.

Primary Therapy

Primary therapy targets the underlying cause of PAH. Primary therapy includes oxygen, diuretics, exercise, digoxin, and anticoagulant therapy. Periodic assessments should be done after starting primary therapy to determine whether advanced therapy is needed.

General Measures and Supportive Therapy

Diuretics

Diuretics are used to reduce fluid retention in PAH, diminishing hepatic congestion and peripheral edema. However, diuretics should be administered with caution since they can cause reduced preload to both the right and left ventricles, inducing arrhythmias due to hypokalemia and metabolic alkalosis [5].

Exercise

Exercise used to be considered a high risk for sudden cardiac death, worsening of right heart failure, and increased pulmonary remodeling in patients with pulmonary hypertension. Therefore, many doctors recommended that severely affected patients should avoid exercise [13]. A prospective, randomized controlled trial showed that low-level exercise training significantly improved exercise capacity, 6-minute walk test, quality of life, World Health Organization functional class, and peak oxygen consumption [14]. The American College of Cardiology Foundation/American Heart Association Expert Consensus document encourages low-level graded aerobic exercise, such as walking, as tolerated [12]. Patients are also advised to avoid physical exertion or isometric exercises, as they can induce syncope [15].

Oxygen

Continuous oxygen administration remains the mainstay of therapy in group III PAH patients. Two large trials studying patients with chronic obstructive pulmonary disease (COPD), the most common cause of group III PAH, showed that continuous oxygen therapy reduced mortality, but the survival advantage did not appear until after 500 days of therapy [16,17].

In patients with PAH, exposure to high altitude can provoke pulmonary vasoconstriction and may not be tolerated. These patients may need oxygen therapy in commercial aircraft. Supplemental oxygen is recommended to patients with a preflight oxygen saturation of <92% [18]. Oxygen is administered at 1 to 4 L/minute to maintain oxygen saturation above 90% at rest as well as during exercise and sleep.

Digoxin

Digoxin has beneficial as well as harmful effects in patients with pulmonary hypertension. Digoxin improves left ventricular ejection fraction in group III pulmonary hypertension patients with COPD and biventricular failure [19]. Digoxin also helps in slowing the ventricular rate in patients with supraventricular tachyarrhythmias associated with right ventricular dysfunction; however, these patients are vulnerable to digitalis toxicity and require close monitoring.

Anticoagulation Therapy

Patients with PAH are vulnerable for thromboembolic disease due to sluggish blood flow, dilated right heart chambers, venous stasis, and a sedentary lifestyle in an already compromised pulmonary circulation. Many studies have shown that anticoagulation is indicated in patients with idiopathic PAH, hereditary PAH, and drug-induced PAH [6,13]. Patients with advanced PAH should receive anticoagulation in the absence of any contraindications [15]. A reduction in mortality with warfarin therapy was observed in 5 out of 7 studies evaluating the effect of warfarin in patients with group I PAH [6].

Diet

A sodium-restricted diet (less than 2,400 mg/day) is recommended in patients with PAH. This is especially important in patients with right heart failure [15].

Pregnancy and PAH

Hemodynamic fluctuations during pregnancy, delivery, and the post-partum period can be distressing in patients with PAH. A study by Weiss et al demonstrated a 30% to 50% mortality rate. According to current guidelines, pregnancy should be avoided or terminated early to reduce stress in women with PAH [20,21]. The question of which choices are available for contraception to avoid pregnancy remains to be resolved. Since estrogen-containing oral contraceptive pills can increase the risk of thromboembolism, lower-dose preparations with concurrent anticoagulation is a rational choice [15]. Surgical sterilization and barrier methods are also reasonable alternatives [15].

Advanced Therapy

Advanced therapy is considered for the patients with persistent PH and a WHO functional class II, III, or IV despite adequate primary therapy.

General Approach

Patients selected for advanced therapy should undergo hemodynamic assessment prior to the initiation of advanced therapy. As recommended, patients with group 1 PAH should undergo an acute vasoreactivity test with inhaled nitric oxide, intravenous adenosine or intravenous epoprostenol. The test is considered positive if the mean pulmonary artery pressure decreases at least 10 mm Hg and to a value less than 40 mmHg, with an increased or unchanged cardiac output, and a minimally reduced or unchanged systemic blood pressure [6]. Patients with a positive vasoreactivity test should be given a trial of calcium channel blocker (CCB) therapy. In those with a negative vasoreactivity test, advanced therapy should be considered. Combination advanced therapy should be considered for refractory cases. Atrial septostomy or lung transplantation is considered for cases that are refractory to all medical interventions.

Calcium Channel Blockers

Some patients with group I PAH, who are vasoreactive (reduction of mean pulmonary arterial pressure [mPAP] ≥10 mm of Hg to reach a mPAP ≤40 mm Hg with a normalized or increased cardiac output with acute pulmonary vasodilator challenge with either inhaled nitric oxide or intravenous epoprostenol) at the time of cardiac catheterization, do well with CCB therapy [7]. However, only a small number of patients with group I PAH (<10%) have a positive vasoactive response [6]. Long-acting nifedipine or diltiazem,

or amlodipine can be initiated with a low dose and then increased to the maximal tolerated dose. A sustained-release preparation can minimize adverse events, especially systemic hypotension. Verapamil should be avoided because of its negative inotropic effects [7]. Patients with PAH on CCBs should be reassessed after 3 to 6 months of initiating therapy [22]. Although WHO functional class IV patients are less likely to respond than class II or III patients, some class IV patients may respond favorably to a vasoreactive test and can benefit from use of CCBs [6]. These patients need to be evaluated in a specialized PAH center [6]. If the patient does not improve to WHO class I or II, alternative therapy should be added [7].

Phosphodiesterase-5 (PDE5) Inhibitors

Sildenafil, tadalafil and vardenafil are approved for erectile dysfunction because they prolong the vasodilatory effect of nitric oxide (NO). NO activates guanylate cyclase, which increases cGMP production, which causes vasorelaxation. Its effect is short- lived since PDE5 degrades cGMP rapidly. PDE5 inhibitors can prolong the effect of cGMP vasodilation by inhibiting PDE5 [12].

Sildenafil

In a large randomized, double- blind, placebo-controlled trial, 278 patients with PAH associated with connective tissue disease or with repaired congenital systemic-to-pulmonary shunts were assigned to placebo or sildenafil (20, 40, or 80 mg orally 3 times a day) for 12 weeks [23]. An improvement in 6-minute walk test results, a reduction in mPAP, and an improvement in functional class was observed with all doses of sildenafil. Adverse effects such as headache, flushing, epistaxis, dyspepsia, and diarrhea were observed in the sildenafil group [23]. The FDA has approved a dose of sildenafil 20 mg 3 times daily for treatment of PAH.

Tadalafil

Tadalafil is an FDA approved drug for use in erectile dysfunction. This drug is undergoing clinical studies for its use in patients with PAH.

Vardenafil

Vardenafil has been considered to be a more specific PDE5 inhibitor than sildenafil and tadalafil, possibly due to its slower dissociation rate from the PDE5. Certain factors such as cost of vardenafil, favorable effects of vardenafil therapy on symptoms, exercise capacity, hemodynamics, and clinical outcomes in treatment-naïve patients with PAH suggest that vardenafil is useful as a first-line treatment of PAH in developing countries [24].

Ghofrani et al showed that sildenafil, tadalafil, and vardenafil varied in their rate of onset, pulmonary vascular selectivity, and effect on oxygenation [25]. Only sildenafil improved arterial oxygenation.

Prostanoids

Prostacyclin is a potent vasodilator of all vascular beds and an inhibitor of platelet aggregation. Prostacyclin also appears to have cytoprotective and antiproliferative activities. In PAH, dysregulation of the prostacyclin metabolic pathways has been demonstrated as reduced prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites [26]. Prostanoids have been the mainstay of PAH treatment for more than a decade. Epoprostenol, treprostinil, and iloprost are 3 commercially available prostanoids.

Epoprostenol

A 12-week open, randomized, multicenter clinical trial compared the effects of intravenous infusion of epoprostenol plus conventional therapy with conventional therapy alone in 81 patients with severe PAH (WHO functional class III or IV) [27]. Epoprostenol improved mean pulmonary arterial pressure (–8% *vs.* +3%), pulmonary vascular resistance (–21% *vs.* +9%), and exercise capacity (6-minute walk test: +47 meters *vs.* –66 meters) [27]. Continuous intravenous infusion of epoprostenol was associated with hemodynamic and symptomatic improvement as well as survival in patients with severe PAH [27]. Eight patients randomized to conventional therapy died during the 12-week study period, suggesting a survival benefit from epoprostenol (P=0.003) [27]. A study by Sitbon et al of 178 functional class III and IV PAH patients treated with intravenous epoprostenol showed 1-, 2-, 3-, and 5- year survival rates of 85%, 70%, 63% and 55%, respectively [28]. Another study of 162 functional class III and IV patients with PAH showed that intravenous epoprostenol resulted in improved survival with 1-, 2-, and 3- year survival rates of 88%, 76%, and 63%, respectively, compared to 59%, 46%, and 35%, respectively, based on historical data [29].

In other groups of PAH such as group I, intravenous epoprostenol can improve hemodynamic and functional capacity. However, survival benefits have not been adequately evaluated [17,30,31]. Intravenous epoprostenol is started at 2 ng/kg/min. The dose is further adjusted according to symptoms of PAH and adverse effects. The optimal dose range for chronic therapy is 25 and 40 ng/ml/min for most adult patients when used as monotherapy [15]. Adverse drug effects include jaw pain, diarrhea, arthralgia, thrombosis, pump malfunction, and interruption of the infusion. Epoprostenol has been approved by the FDA for treatment of PAH. Epoprostenol use should be limited to centers experienced with its administration and performing systematic follow-up of patients.

Treprostinil

Treprostinil has an elimination half-life of 4.5 hours. In a multicenter, randomized, placebo-controlled trial of 470 patients with functional class II, III, or IV PAH, subcutaneous infusion of treprostinil for 12 weeks resulted in a dose-related modest but statistically significant improvement in 6-minute walk test results in patients treated with treprostinil but not with placebo [32]. A retrospective, single-center study also showed that long-tern treatment with subcutaneous treprostinil caused sustained improvement in functional and hemodynamics parameters in patients with moderate to severe PAH [33]. This study also demonstrated that addition of bosentan to continuous subcutaneous infusion of treprostinil was associated with further improvement of

hemodynamic and functional parameters and functional class [33]. The long-term survival rate for subcutaneous treprostinil monotherapy was 88% at 1 year and 70% at 4 years [34] and for epoprostenol was 69% at 1 year and 38% at 4 years [29]. The FDA approved subcutaneous treprostinil for use in functional class II, III and IV PAH.

A prospective, multicenter, open label, 12-week trial that intravenous treprostinil improved the 6-minute walk test results by 82 meters in 16 functional class III and IV PAH patients [35]. In a similar study of 31 functional class II and III PAH patients on epoprostenol, 27 patients were transitioned from epoprostenol to treprostinil [36]. At week 12, exercise endurance measured by the 6-minute walk test was maintained in these 27 patients. Adverse effects of intravenous treprostinil are the same as those of intravenous epoprostenol.

In 2004 the FDA approved the use of intravenous treprostinil in WHO class II, III and IV PAH patients in whom subcutaneous infusion is not tolerated. The Centers for Disease Control and Prevention report emphasized the increased risk of blood stream infections, especially gram-negative infection, in patients receiving intravenous treprostinil [37]. Catheter infections can be life-threatening, and this concern has caused the catheter care recommendations to be revised [38].

Iloprost

Iloprost is a stable analogue and long-acting vasodilator. Several open label, uncontrolled studies of patients with severe PAH demonstrated significant clinical improvement with long-term use of aerosolized iloprost [39–41]. A multicenter, placebo-controlled, randomized trial of inhaled iloprost in 207 patients with functional class III and IV PAH demonstrated that therapy with iloprost is associated with improvement in functional class by at least 1 level and improvement in the 6-minute walk test results by at least 10% without any clinical deterioration [42]. A multicenter, placebo- controlled, randomized trial of 67 patients with WHO functional class III or IV PAH demonstrated that this combination therapy of inhaled iloprost with bosentan is safe and well tolerated and is associated with improvement in 6-minute walk distance, hemodynamic parameters, and WHO functional class [43]. Event-free survival rates for patients treated with iloprost monotherapy are 53%, 29%, and 20% at 1, 2, and 3 years, respectively [44]. Adverse effects of inhaled iloprost include headache, jaw pain, flushing, and cough. Inhaled iloprost was approved by the FDA in 2004 for functional class III and IV PAH.

Endothelin Receptor Antagonists

Endothelin-1 is a potent vasoconstrictor and is overexpressed in the plasma and lung tissue of patients with primary PAH [45]. Since endothelin-1 has a pathogenic role in PAH, blockade of endothelin-1 receptors could be valuable [46].

Bosentan

In a double-blind, placebo-controlled trial, 216 patients with WHO functional class III to IV PAH were randomized to placebo or bosentan 125 or 250 mg twice daily for 16 weeks [47]. The primary end-point was change in exercise capacity in the 6-minute walk test. This study showed that bosentan improved the 6-minute walk test performance by 36 meters, whereas deterioration of exercise capacity was seen in the placebo group. Bosentan also reduced the rate of time to clinical worsening (defined as time to death, lung transplantation, hospitalization for PAH, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy) compared to placebo. Asymptomatic increase in hepatic function test results, syncope, and flushing occurred more frequently in the bosentan group. Abnormal hepatic function was related to the dose of bosentan [47].

Another double-blind, multicenter, randomized, placebo-controlled study of 54 patients with functional class III PAH due to Eisenmenger syndrome randomized bosentan *vs.* placebo for 16 weeks [48]. Compared to placebo, bosentan decreased the peripheral vascular resistant index and mPAP and improved exercise capacity. In another study of 168 PAH patients, bosentan decreased the peripheral vascular resistance index and improved the secondary end-point of time to clinical worsening [49].

First-line therapy with bosentan in 169 patients with PAH in 2 placebo-controlled trials showed Kaplan-Meier survival estimates of 96% at 1 year and of 89% at 2 years [50]. In contrast, predicted survival of these patients was 69% and 57%, respectively [50]. Another study comparing 139 patients with functional class III PAH treated with bosentan with historical data from 346 similar patients treated with epoprostenol showed that survival estimates after 1 and 2 years were 97% and 91%, respectively, for the patients treated with bosentan *vs.* 91% and 84%, respectively, for the patients treated with epoprostenol [51]. When matched cohorts of 83 patients each were selected, survival estimates were similar [51].

Bosentan is widely used in the treatment of PAH. According to FDA guidelines, liver function tests should be checked every month and hematocrit should be checked every 3 months in patients treated with bosentan. Since bosentan is potentially teratogenic, barrier contraceptive methods are recommended instead of hormonal methods of birth control [15]. There is also a risk of male infertility and testicular atrophy, so young males receiving bosentan should be counseled about these possible adverse effects before starting therapy [15].

Sitaxsentan

In a randomized, double-blind, placebo-controlled trial, 178 patients with functional class II, III, and IV PAH were randomized to receive placebo, sitaxsentan 100 mg, or sitaxsentan 300 mg orally once daily [52]. Sitaxsentan was associated with improvement in exercise capacity measured by the 6-minute walk test and functional class after 12 weeks of treatment. Elevated aminotransferase values were reversible.

In a randomized, placebo-controlled 18-week study of 245 patients with PAH, 62 patients were treated with sitaxsentan 50 mg orally daily, 61 patients with sitaxsentan 100 mg orally daily, 60 patients with bosentan, and 62 patients with placebo [53]. Compared with placebo, sitaxsentan 100 mg daily increased the 6-minute walk test performance by 31.4 meters ($p=0.03$) and improved the functional class ($p=0.04$).

Compared with placebo, sitaxsentan 50 mg daily increased the 6-minute walk test performance by 24.2 meters (p=0.07), and bosentan improved the 6-minute walk test results by 29.5 meters (p=0.05) [53].

Sitaxsentan is pending approval by the FDA. This drug is currently approved in the European Union, Canada, and Australia [15].

Ambrisentan

In a double-blind study of 64 patients with PAH randomized to receive ambrisentan 1 mg daily, 2.5 mg daily, 5 mg daily, or 10 mg once daily for 12 weeks, a significant increase in the 6-minute walk test performance was observed with all doses of ambrisentan [54]. Two placebo-controlled trials randomized 202 and 192 patients with PAH respectively to placebo or ambrisentan for 12 weeks [55]. Doses of ambrisentan 5 and 10 mg daily were compared with placebo in 1 study and 2.5 and 5 mg daily doses of ambrisentan were compared with placebo in the other study. At 12 weeks, ambrisentan improved exercise capacity in both studies. Ambrisentan was associated with a low risk of aminotransferase abnormalities.

A post-hoc analysis of 68 patients treated with ambrisentan who had a right heart catheterization at 60 weeks from initiation of ambrisentan (range 14–158 weeks) showed sustained improvements in pulmonary hemodynamics in patients with PAH [56]. These changes correlated with improvements in exercise capacity.

The FDA approved ambrisentan in 2007, with mandatory checking of liver function tests monthly. Monthly pregnancy tests in women of child bearing potential and periodic hemoglobin checks are required. In addition, testicular atrophy and contraception precautions are the same as for bosentan [15]. Recently, the FDA removed the boxed warning of liver injury related to ambrisentan since they concluded that the risk of liver injury with the drug is low [57].

Combination Therapy

The goal of combination therapy is to increase efficacy and reduce toxicity and to improve functional status and quality of life in patients who have failed to achieve the desired level of functioning with monotherapy. Only a few clinical trials have evaluated the efficacy of combination therapy in PAH. Inhaled iloprost has been studied in patients who were symptomatic while on bosentan therapy for at least 3 months. After 12 weeks, improvement in the 6-minute walk test performance (30 meters in the iloprost group *vs.*4 meters in the placebo group), time to clinical worsening, and post-inhalation mPAP and pulmonary vascular resistance were found [58]. However, a study with a similar design failed to confirm these results [59].

A 16-week study was performed with addition of either sildenafil or placebo to 267 PAH patients who remained symptomatic while on intravenous epoprostenol for at least 3 months. Patients treated with sildenafil showed an improvement in the 6-minute walk test results, adjusted for placebo, of 28.8 meters at 16 weeks, an increase in cardiac output, a decrease in mPAP, and a longer time to clinical worsening [60]. A 16-week, placebo-controlled study of 405 patients with PAH treated with bosentan showed that addition of tadalafil 40 mg daily to bosentan improved exercise capacity and quality of life measures and reduced clinical worsening [61].

Invasive Therapies

Many patients with PAH experience progressive functional decline because of right heart failure despite advanced medical therapies. Interventional and surgical therapeutic options, atrial septostomy and lung or combined heart and lung transplantation should be considered for these patients [62–64]. Surgical thromboendarterectomy may be beneficial for patients with PH due to chronic pulmonary thromboembolic disease.

Atrial Septostomy

Atrial septostomy is recommended for patients with severe PAH and right heart failure despite maximal medical therapy. The goals of atrial septostomy are palliative care and clinical stability until lung transplantation is performed. Atrial septostomy creates a shunt between the right and left atria, decreasing right ventricular filling, improving right ventricular function, and increasing left ventricular filling. While decreasing systemic oxygen saturation is a concern, increasing cardiac output can augment overall systemic oxygen delivery [15]. Hemodynamic benefits and clinical improvement were reported in several studies [65–67].

Lung and Combined Heart and Lung Transplantation

Lung transplantation is the last considered therapy option for selected patients with PAH. Single lung transplantation (SLT_x), double lung transplantation (DLT_x), and combined heart and lung transplantation (HLT_x) have been performed worldwide in adults for the primary indication of PAH [68]. In PAH patients undergoing lung transplantation, the International Society for Heart and Lung Transplantation registry reports 1-, 3-, 5-, and 10- year survivals of 66%, 57%, 47%, and 27%, respectively [68].

There are no guidelines for the optimal type of lung transplantation. Some centers prefer to do DLT_x to avoid the lung reperfusion injury in the donor lung that has been reported with SLT_x [69]. DLT_x generally is reserved for patients with intractable right heart failure. PAH in the setting of congenital heart disease is an indication for HLT_x, although, in some cases SLT_x or DLT_x in combination with congenital cardiac abnormality repair can be done [70].

Pulmonary Thromboendarterectomy (PTE)

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) should have a pulmonary angiogram. If the patient is an acceptable surgical risk and has surgically accessible disease, PTE should be performed [71].

Non-Pulmonary Arterial Hypertension Pulmonary Hypertension

Space limitation prevents a discussion of treatment guidelines for non-pulmonary arterial hypertension, pulmonary

hypertension related to chronic lung disease, left heart disease, and venous thromboembolism. However, their treatment guidelines are well reported by Hoeper et al [72].

Disclosure

The authors disclose that they do not have a significant financial interest or other relationship with any product manufacturer or provider of services discussed in this article. The authors do not discuss the use of off-label products, which includes unlabeled, unapproved, or investigational products or devices.

Addendum

Tadalafil was also approved for adults with pulmonary arterial hypertension (PAH) and inhaled nitric oxide for the neonatal subtype of PAH. Sixasentan is not currently being used for treatment of PAH due to concerns about irreversible liver damage.

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