Pulmonary Arterial Hypertension

Pathobiology, Diagnosis, Treatment, and Emerging Therapies

Warren D. Rosenblum, MD

Abstract: Pulmonary hypertension is a rare disorder caused by vasoconstriction of the pulmonary arteries that leads to elevation of pulmonary vascular resistance, right ventricular failure, and ultimately death. Hypertrophy and proliferation of the pulmonary vascular endothelium leads to remodeling of this vascular system, resulting in a progressive disorder. In the past decade the molecular mechanisms and pathobiology of this disorder has become clearer. In addition, a host of new medical treatments and therapies are now available for what has been previously known to be a devastating disorder. Although much needs to be learned, this review will discuss our current knowledge, results of clinical trials, along with treatment options and emerging therapies available for the treatment of this disorder.

Key Words: pulmonary hypertension, endothelin receptor antagonists, phosphodiesterase 5 inhibitors, prostacyclin, right heart failure

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Pulmonary arterial hypertension (PAH) is a progressive disease that can be caused by a variety of disorders, resulting in pulmonary vascular endothelial remodeling and elevated pulmonary artery pressure (PAP). The long-term consequences of these changes may lead to right ventricular (RV) failure and ultimately death. Pulmonary hypertension (PH) is defined hemodynamically as a mean PAP (mPAP) >25 mm Hg at rest or >30 mm Hg with exercise, provided the pulmonary capillary wedge pressure is <15 mm Hg; this is typically determined by cardiac catheterization.[1] Conventionally, the diagnosis and initial measurement of PAP is obtained by Doppler echocardiography. The echocardiographic definition of PH is a Doppler tricuspid regurgitant velocity >2.8 m/s which corresponds to a systolic PAP of ≥40 mm Hg, assuming a right atrial pressure of 10 mm Hg.[2]

The initial classification of PH was undertaken at the World Health Organization (WHO) symposium in Evian, France whereupon 4 groups were identified: PAH, pulmonary venous hypertension, PH associated with disorders of the respiratory system, and PH due to chronic thromboembolic disease. As it was realized that other conditions were implicated in the development of PAH and that the prevalence was increasing, the WHO Third Symposium in Venice in 2003 revised the classification of group I PAH (Table 1).[4] The prevalence of PAH is estimated to be approximately 30 to 50 per million population.[4]

Before disease-specific treatments were available, the NIH recognized PAH as a disorder that needed further characterization. In 1991 an NIH registry of patients with PH revealed the median survival of patients with untreated disease to be 2.8 years from initial diagnosis.[5]

From the Division of Cardiology, Department of Medicine, New York Medical College/Westchester Medical Center, Valhalla, NY.
Correspondence: Warren D. Rosenblum, MD, Division of Cardiology, Westchester Medical Center, Macy Pavilion, Valhalla, NY 10595. E-mail: rosenblumw@wcmc.com.
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BIOLOGIC CHARACTERISTICS OF PULMONARY HYPERTENSION AND ETIOLOGIES

The pulmonary artery is a highly compliant vessel that is able to accommodate high flow without significant vascular resistance. In the setting of PAH, the pathologic changes that are seen are common to most forms of PAH. Microscopically, one sees proliferation of the endothelium, medial hypertrophy and plexiform lesions (30%–60%). In addition, other pathologic patterns include in situ thrombosis (40%–50%) with eccentric intimal fibrosis and intimal proliferation with fibrosis of the veins and venules due to a veno-occlusive disorder (<10%).[1] Extensive pathologic examinations of the pulmonary vasculature in patients with PAH are difficult to obtain as lung tissue biopsies of patients with PAH are rarely performed and most pathologic information is obtained at autopsy. It is felt, however, that medial hypertrophy is an early manifestation of PH and is easier to reverse when treatment is initiated at its early stage compared with the more complex intimal hyperplasia and plexiform lesions.

In the past, the prevalence of PH was typically difficult to assess, as it was not commonly thought of as a diagnosis. However, as more clinicians are becoming cognizant of its presence and the effects of elevated pulmonary pressures on the human body, its prevalence is increasing. In the UNCOVER study of patients with systemic sclerosis screened for PAH, 13% of new patients who were previously unknown to have PAH were discovered, with an overall prevalence of 26.7%.[6] In patients with scleroderma that also have PAH, mortality was increased with or without evidence of lung involvement. In fact, median survival for patients with untreated PAH was 12 months.[7]

A growing number of patients born with congenital heart disease develop PAH, as these patients are living into adulthood. The majority of these patients have significant left to right shunts such as atrial or ventricular septal defects, patent ductus arteriosus or surgical shunts. More complex lesions such as double outlet right ventricle, transposition of the great vessels with associated ventricular septal defects, and truncus arteriosus also may result in PAH and subsequently Eisenmengers physiology. The degree of PH in patients with congenital heart disease is multifactorial and is influenced by the degree of left to right shunting seen and the duration of its existence. In patients with Eisenmenger's syndrome, mean age of death is 45 years if left untreated.[8]

Over 5 million patients in the United States have congestive heart failure and every year approximately 500,000 new cases are diagnosed. More than half of advanced heart failure patients have PH. Approximately 10% to 20% of patients with heart failure with preserved left ventricular function develop PH. It has been shown that PH is an independent risk factor and conveys an increased mortality in those patients whose pulmonary vascular resistance is >3.0 Woods units.[9]

PAH due to liver disease and cirrhosis of the liver has become an increasing concern, especially in the population of patients considered potential candidates for liver transplantation. PAH due to liver disease is known as porto-pulmonary hypertension. The mortality of patients undergoing orthotopic liver transplantation with associated PAH is increased if the mPAP is >35 mm Hg. The

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TABLE 1. Revised WHO Classification of Group I Pulmonary Arterial Hypertension

Pulmonary arterial hypertension
Idiopathic pulmonary arterial hypertension
Familial pulmonary arterial hypertension
Associated with pulmonary arterial hypertension
Collagen vascular disease
Congenital systemic-to-pulmonary shunts
Portal hypertension
HIV infection
Drugs and toxins
Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Pulmonary hypertension with left heart disease
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Pulmonary hypertension associated with lung diseases and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Adapted from *Primary Pulmonary Hypertension: Executive Summary From the World Symposium on Primary Pulmonary Hypertension*. Evian, France: World Health Organization; 1998.[3]

majority of these patients are discovered during screening tests such as right heart catheterization or echocardiography, as part of their preliver transplant evaluation. Up to 10% to 20% of patients evaluated will be identified as having asymptomatic elevated PAPs. Approximately 15% of these patients will have elevated PAPs due to the high output state that exists with normal pulmonary vascular resistance, and 85% of these patients will have high pulmonary vascular resistance.[10]

Other associated diseases that are associated with the development of PAH include pulmonary emboli, high altitude residence, the use of diet drugs such as fenfluramine and dexfenfluramine, schistosomiasis, chronic hemolytic anemia, and patients infected with the human immunodeficiency virus.

PATHOPHYSIOLOGY OF PULMONARY ARTERIAL HYPERTENSION

Several pathways have been implicated in the development and progression of PAH and it is not believed any one particular mechanism is responsible for the pathophysiologic changes seen. Down-regulation of potassium channels has been implicated when pulmonary vascular vasoconstriction is seen. Both human cellular and rat models of hypoxia-induced vasoconstriction reveals significant down-regulation of the Kv1.5 and Kv2.1 channels and research directed towards up-regulation of the potassium channels is ongoing.[11] Matrix metalloproteinases (MMP's) have also been implicated in the pathobiology of PH. MMP's are a variety of matrix degrading proteases that are linked to extracellular matrix turnover, smooth muscle and endothelial cell proliferation and migration. It has been found that MMP levels are increased in patients with elevated PAPs and MMP inhibitors are in the development stage for the treatment of PAH.[12] In patients with familial PAH, 2 important genetic mutations have been discovered and implicated in the pathogenesis of PAH. Bone morphogenetic proteins (BMPs) are part of the transforming growth factor-β cytokine family and have been shown to regulate apoptosis, cell growth, and differentiation. Mutations in BMP receptor-2 are found in patients with familial PAH. Loss of native BMP function results in vascular smooth muscle proliferation and thereafter PH. Activin-receptor-like-kinase-1 (ALK-1) is a transducer of activin which belongs to the transforming growth factor-β super family of cytokines, directly integrated into the development of cellular signaling and differentiation. Mutations of ALK-1 are seen in patients with hereditary hemorrhagic telangiectasia. These mutations are responsible for smooth muscle proliferation and inhibition of apoptosis leading to PAH.

Endothelin-1 (ET-1) has been implicated in many vascular disorders such as atherosclerosis and hypertension and is a known powerful vasoconstrictor and smooth muscle mitogen that is synthesized and secreted by vascular endothelial cells. Endothelin-1 can stimulate cell growth and inhibit apoptosis in a variety of tissues. Endothelin-1 synthesis occurs when big ET-1 is cleaved by ET converting enzyme. There are 2 ET receptors that ET-1 binds to, ET-A and ET-B receptor. The ET-A receptor is found on smooth muscle cells of blood vessels and its binding results in vasoconstriction and proliferation of vascular smooth muscle. ET-B receptors are found in endothelial cells and vascular smooth muscle cells. ET-B receptors are directly involved in the clearance of ET-1 in the pulmonary and renal vasculature. Binding of the ET-B receptor results in smooth muscle dilation and the release of nitric oxide (NO).[13] Very little ET-1 is found in normal lung tissue, however, in patients with PAH, ET-1 levels are significantly elevated and are most prominently seen in the pulmonary vascular endothelium.[14] Similarly, plasma levels of ET-1 are also elevated in patients with PAH compared with normal controls by an order of magnitude (20 pg/mL vs. 2 pg/mL).[15]

Prostacyclin, a potent lipid mediator of endothelial function, is produced by the enzymatic breakdown in endothelial cells of arachadonic acid and prostaglandin H_2 to the active molecule by prostaglandin-H_2 synthase and prostacyclin synthase, respectively. Prostacyclin is a potent vasodilator that can inhibit platelet aggregation and smooth muscle cell proliferation. The ability of prostacyclin to relax smooth muscle cells is due to the generation of elevated cAMP levels through coupled G_s protein-coupled receptors found on platelets and endothelial cells. In patients with severe PAH, prostacyclin synthase levels are significantly reduced in the small, medium and large vessels of the pulmonary arteries.[16] Conversely, thromboxane A_2 is an additional metabolite of arachadonic acid that is a potent vasoconstrictor and platelet activator. Thromboxane A_2 levels are elevated in patients with PAH both due to primary and secondary causes, suggesting an important lipid mediator imbalance in this disease process.[17]

NO is an endogenous vasodilator that inhibits platelet aggregation, smooth muscle cell growth and contraction. It is produced from oxygen and the precursor L-arginine by NO synthase (NOS)

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utilizing tetrahydrobiopterin as an essential cofactor for NOS function. NO activates soluble guanylyl cyclase to synthesize cGMP from GTP. cGMP activates cGMP-dependent protein kinase that results in decreased intracellular calcium leading to smooth muscle relaxation. cGMP is degraded by phosphodiesterase-5 enzyme (PDE-5) into GMP. Similar to prostacyclin synthase levels, it has been shown that endothelial NOS levels and NO metabolites are diminished in the pulmonary arteries of patients with PAH.[18,19] In addition, in patients with chronic PAH, PDE-5 levels are increased in lung tissue, promoting the degradation of cGMP.[20]

Serotonin (5-hydroxytryptamine) is a potent vasoconstrictor that has been found to promote pulmonary artery smooth muscle hyperplasia through its actions as a smooth muscle mitogenic agent. Serotonin, when exposed to cultured smooth muscle cells from patients with PAH, enhances proliferation of these cells in a disproportionate manner when compared with other growth factors.[21] Genetic variation in the serotonin transporter (5-HTT) and the 5-hydroxytryptamine 2B receptor have been found in lung tissue of patients with PAH. Transgenic mice that over express 5-HTT develop PAH and have been shown to have decreased transcription of Kv1.5 involved in vasoconstricion.[22]

Vasoactive intestinal peptide (VIP) is an endogenous polypeptide that is part of the glucagon-secretin neurohormonal axis. VIP is a potent systemic and pulmonary vascular vasodilator in addition to its ability to control salt and water balance. Immunohistochemistry and radioimmunoassay of lung tissue in patients with PAH reveal low levels of VIP. Administration of inhaled VIP in pilot studies has demonstrated favorable results in improving mixed venous saturation and 6-minute walk test distances.[23] Various inflammatory agents such as antinuclear antibodies, inflammatory cytokines such as interleukins 1β and 6, various chemokines, platelet-derived growth factors, and soluble CD-40 ligand have been found to be present in endothelial cells of PH arteries.[24]

CLINICAL FINDINGS

Upon examination of a patient with PAH, auscultation of the heart may reveal the presence of a loud P2 component of the second heart sound, a RV lift if RV hypertrophy is present, a systolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonic regurgitation, in addition to an RV S4 gallop. Patients who develop RV failure will have venous jugular distension with a prominent V wave, evidence of an RV S3 gallop and peripheral edema. In more advanced RV failure, hepatomegaly and abdominal ascites may also be found. Approximately half of the patients with PAH will have prominent hilar pulmonary arteries and 70% of the patients will have RV encroachment of the retrosternal clear space on posteroanterior and lateral chest x-rays, respectively. An analysis of electrocardiograms from patients with PAH may reveal right axis deviation and RV hypertrophy, however, the sensitivity and specificity of these findings limit the EKG's ability to definitively diagnose this disorder. The presence of a pericardial effusion, the elevation of mean right atrial pressures or a reduction of the cardiac index are consistent with right-sided heart failure, and along with poor performance on 6-minute walk testing and WHO class III or IV symptoms, predict poor survival.

DIAGNOSTIC TESTING

Once PH is clinically suspected, there needs to be a systematic diagnostic approach in determining the etiology and clinical characteristics. It is also vital to establish the patient's functional adaptation to the disorder. Initial screening of patients based on clinical suspicion, a complete medical history, physical examination findings or the coincidental finding of elevated pulmonary pressures based on routine screening tests should subsequently lead to definitive detection. This is usually undertaken by the primary care specialist with the combination of chest x-ray, ECG and echocardiographic evaluation. Further classification of the clinical situation needs to be performed most commonly by a combination of pulmonary function testing, high resolution and CT angiography, ventilation perfusion scanning, pulmonary angiography, sleep study and a hematologic workup for connective tissue disorders, coagulopathies, liver abnormalities, and human immunodeficiency virus testing. Subsequently, exercise function is evaluated either by a 6-minute walk test distance and/or maximal oxygen consumption stress testing. In most PAH centers, 6-minute walk testing is the preferred method of evaluation for functional capacity since most of the major clinical trials use this method to evaluate this parameter. Functional classification of PAH is best described by the WHO functional classes that parallel the New York Heart Association classification of congestive heart failure. Class I patients have no limitation of physical activity, class II patients have slight limitation of physical activity, class III patients develop marked limitation of physical activity, and class IV patients are unable to perform any physical activity without symptoms or may have rest symptoms (Table 2).[3] Definitive diagnostic characterization of the clinical diagnosis should then result in a right heart catheterization along with vasoreactivity testing. Right heart catheterization allows the clinician to accurately measure the degree of PH, obtain the cardiac output, confirm low left-sided filling pressures, evaluate for left to right shunting, obtain measurements of pulmonary artery oxygen saturation, and calculate the pulmonary vascular resistance. Vasoreactivity testing is performed with pulmonary arterial vasodilators such as oxygen, adenosine, inhaled NO or intravenous prostacyclin. The presence of vasoreactivity portends a better prognosis, however, the incidence of a positive vasoreactivity test is between 8.6% and 26.5%. The American College of Chest Physician definition of a positive vasoreactive response is a fall to a mPAP of 40 mm Hg or a fall by 10 mm Hg without a significant change in the cardiac output.[25]

TABLE 2. World Health Organization Classification of Functional Class in Patients With Pulmonary Hypertension

Class	Description
I	Patients with pulmonary hypertension who have no limitations at rest or with any physical activity. Ordinary physical activity does not result in fatigue, dyspnea chest discomforts or near syncope.
II	Patients with pulmonary hypertension who have slight limitations performing moderate activity resulting in either fatigue, dyspnea, chest discomforts or near syncope but do not have rest symptoms.
III	Patients with pulmonary hypertension who have significant symptoms with activities but no symptoms at rest. Minimal activities result in either fatigue, dyspnea chest discomforts or near syncope.
IV	Patients with pulmonary hypertension who have symptoms with activities of daily living or at rest resulting in fatigue, dyspnea, chest discomforts or near syncope. Signs of right ventricular failure may be present.

Adapted from *Primary Pulmonary Hypertension: Executive Summary From the World Symposium on Primary Pulmonary Hypertension*. Evian, France: World Health Organization; 1998.[3]

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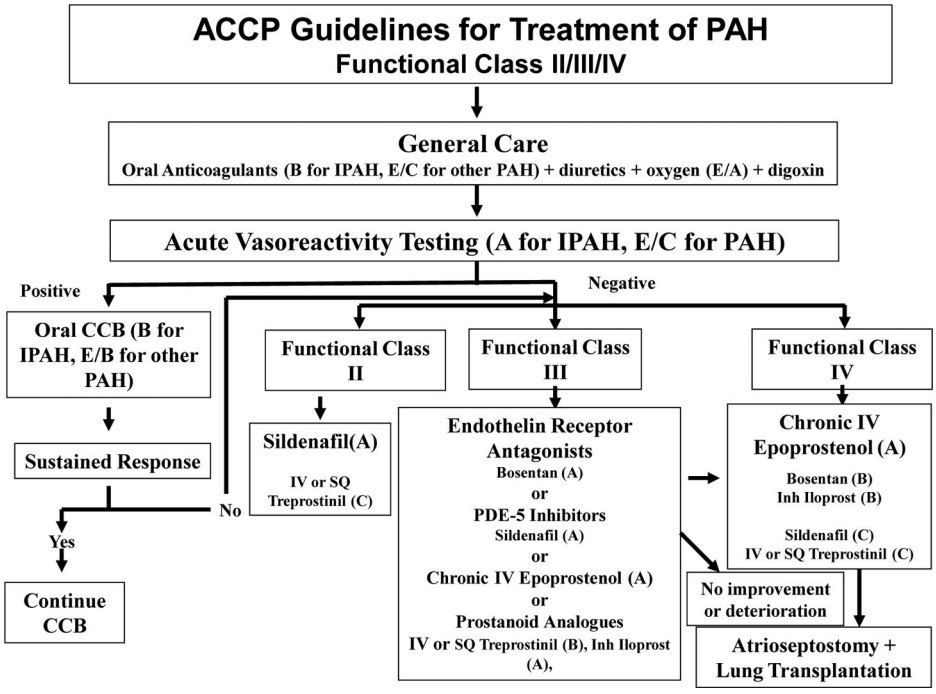

FIGURE 1. Current ACCP treatment guidelines for the approach to a patient with pulmonary hypertension. A indicates strong recommendation; B, moderate recommendation; C, weak recommendation; E/A, strong recommendation based on expert opinion only; E/B, moderate recommendation based on expert opinion only; E/C, weak recommendation based on expert opinion only. Adapted from *Chest.* 2007;131: 1917–1928.[25]

In 1988, Rich described the clinical progression of hemodynamic changes seen in patients with idiopathic and associated PH. In the preclinical or asymptomatic stage and in the stable symptomatic stage, the mPAP rises steadily without a significant change in the cardiac output. The third stage is a clinical state of progressive decline whereupon the pulmonary vascular resistance continues to climb and the absolute PAPs begin to plateau, while the cardiac output begins to decline. In the final stage, signs and symptoms of RV failure are now evident, the right atrial pressure and pulmonary vascular resistance rise, the cardiac output declines, and due to limited cardiac output, the PAP similarly may decline. In patients with idiopathic PAH, this progression occurs rapidly and the timing of these events are between 2 and 5 years, whereas in patients with associated forms of PAH, the time course can be much longer, on the order of 20 to 30 years.[26]

TREATMENT OPTIONS

There are many conventional therapeutic options available for the treatment of PH, including supplemental oxygen therapy to treat hypoxemia, diuretics to relieve right-sided volume overload, and inotropic agents such as digoxin to increase RV inotropy. Unfortunately, many of these treatment options are not supported by controlled clinical trials, but never the less are considered standard background therapy. Anticoagulation with warfarin is known to prevent in situ small vessel thrombosis and improve survival in patients with primary PH.[27] Nifedipine, diltiazem or amlodipine are considered the calcium channel blockers of choice in the treatment of PAH for those patients who have been shown to be reactive in a vasodilator challenge as previously described. It has been demonstrated that patients with idiopathic PAH that are vasoresponsive can have a dramatic improvement in survival up to 95% at 5 years.[26] The American College of Chest Physicians has updated their treatment guidelines to assist the clinician in determining the best options and approach to a patient with PAH (Fig. 1).[25]

Endothelin Receptor Antagonists

As stated previously, ET-1 is a very potent vasoconstrictor resulting in increased pulmonary vascular resistance and it has proliferative effects on the vascular smooth muscle cells. Blockade of the ET receptor has been used in the treatment of PH. Several ET receptor antagonists have been identified and differ in their selectivity towards the ET-A and ET-B receptor. Binding of ET-1 to the ET-A receptor results in vasoconstriction and smooth muscle proliferation, and pharmacologic agents specifically targeting the ET-A receptor have been studied clinically.

Bosentan shows 20:1 ET-A/ET-B selectivity, ambrisentan has a 100:1 selectivity, and the investigational drug sitaxsentan has a 6500:1 selectivity. The Bosentan Trial of Endothelin Antagonist Therapy (BREATHE-1) study revealed the ability of oral bosentan in patients with PAH to improve 6-minute walk test distance, improve Borg dyspnea scores and time to clinical worsening as early as 16 weeks after initiating therapy. A 44 m placebo adjusted difference in 6-minute walk test distance in the BREATHE-1 patient population treated with bosentan was noted.[28] The recommended treatment dose is 125 mg BID after careful up titration. Bosentan can increase transaminase levels (4%) in a reversible pattern. As a result of the potential for elevated transaminases, patients receiving bosentan require monthly monitoring of liver function during continuous therapy. It is recommended that if the transaminase levels are increased 3 times the upper limit of normal, the dose either needs to be held or decreased until the transaminase levels return to a normal range before resuming therapy.

Ambrisentan is a more selective ET-A receptor antagonist that is currently clinically available. The Ambrisentan in Pulmonary Artery Hypertension, Randomized, Double-Blinded, Placebo-Controlled, Multicenter, Efficacy Study (ARIES I and II) showed the efficacy of ambrisentan to improve 6-minute walk test distance and time to clinical worsening, and received Food and Drug Administration (FDA) approval for functional class II and III patients. Although ambrisentan is in the same pharmacologic class as bosentan and requires transaminase monitoring, elevation of transaminases were not seen in any patients treated with ambrisentan. Side effects more commonly seen were nasal congestion, peripheral edema, and headaches.[29]

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Sitaxsentan is the most selective ET-A receptor antagonist clinically available. The Sitaxsentan to Relieve Impaired Exercise trials (STRIDE 1 and 2) did show 6-minute walk test distance improvement and functional class improvement. There had been reported prior cases of fatal hepatitis at higher doses in the STRIDE 2 patient population comparable with placebo.[30,31] Currently, sitaxsentan is only approved in Europe, Canada, and Australia, but not in the United States.

Phosphodiesterase-5 Inhibitors

Sildenafil is currently approved for the treatment of WHO class II and III patients. The Sildenafil Use in Pulmonary Arterial Hypertension trial (SUPER-1) showed improvement in 6-minute walk test distances in the 20, 40, and 80 mg TID dosing of sildenafil compared with placebo as early as 4 weeks and extending to 12 weeks. No significant improvements were noted beyond the 20 mg TID dosing in the short-term trial.[32] Therefore, it is only recommended that the lower dose be used in clinical practice. An uncontrolled extension trial showed Kaplan Meier survival to be 94% at 1 year.[33] Tadalafil is the second PDE inhibitor that has recently been approved by the FDA. The results of the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST-1) study showed a 33 m improvement in 6-minute walk test distance adjusted for placebo at 16 weeks in naive treatment plus combined therapy with bosentan, and a 44 m improvement in patients on monotherapy.[34]

Prostanoids

Prostacyclin synthase levels are low in patients with PAH; the production of prostacyclin is diminished, preventing adequate vasodilation and loss of the antiproliferative effects on the smooth muscle cells in the vascular wall. Through their actions as potent pulmonary artery vasodilators, prostanoid medications have been used in the treatment of PAH for over 15 years. Epoprostenol, iloprost, and treprostinil are the only 3 FDA-approved prostanoids currently available.

Epoprostenol is the most comprehensively studied of all the prostanoids. It has been shown to have favorable hemodynamic effects including lowering mPAP and pulmonary vascular resistance and increasing cardiac output. Originally, epoprostenol was used as a bridge for patients waiting for lung transplantation. Its effects were ultimately found to be so favorable that many clinicians and patients preferred to remain on chronic epoprostenol therapy rather than be listed for lung transplantation. Clinical trials have shown beneficial improvements in 6-minute walk test distances up to 60 m at 12 weeks when adjusted for patients receiving only conventional therapy. In addition, survival has been shown to be improved in epoprostenol-treated patients even when adjusting for changes in stroke volume and systemic vascular resistance.[35] Difficulties in administration include the need for permanent IV access resulting in infected catheters, flushing, thrombocytopenia, gastrointestinal disturbances, headaches, and pain on mastication.

Iloprost is available as an inhaled prostanoid agent through a nebulizer device. In a randomized, placebo-controlled study, inhaled iloprost improved placebo adjusted 6-minute walk test distance by 40 m and improved NYHA functional class. Long-term effects of iloprost on survival are not known at this time. Frequent inhalations (6–9 times a day) and duration of each inhalation session are impediments in regards to compliance. Common side effects include flushing, cough, headache, and jaw pain on mastication. Iloprost is currently FDA approved for functional class II and III patients.

Treprostinil is a room temperature stable prostanoid that has the pharmacologic profile of epoprostenol with a much longer half life, permitting subcutaneous administration rather than intravenous administration. In 470 patients randomized in a placebo controlled study, subcutaneous treprostinil improved placebo adjusted 6-minute walk test distance by 16 m in a dose dependent manner.[36] Side effects are similar to the other prostanoid agents.

Combination Therapy Treatment

It is conventional wisdom, when monotherapy is insufficient for the management of patients with more advanced PAH, to add a second or third agent. Unfortunately, randomized clinical studies supporting this approach are scant. Clinical trials are needed to compare mono versus combined therapy, with walk test distance and survival endpoints considered. The STEP trial was a small study showing the efficacy and safety of adding inhaled iloprost to oral bosentan treatment. This study revealed a placebo-adjusted improvement in 6-minute walk test distance of 26 m along with hemodynamic parameters and time to clinical worsening at 12 weeks which was borderline significant.[37] In a study adding sildenafil to patients on a stable dose of intravenous epoprostenol, 6-minute walk test distance was improved by 28.8 m with an improvement in time to clinical worsening, cardiac output and mPAPs.[38] Several ongoing combination therapy trials are in progress and will elucidate further the role of combination therapy such as the Compass 2 trial (bosentan and sildenafil) and the Vision trial (iloprost and sildenafil). Results are expected to be reported in late 2009.

Future Treatments for PAH

With the impressive development of new and multitargeted therapies for treating PAH, it has been seen early on that symptoms and functional capacity dramatically improve. Unfortunately, it is not clear that longer term survival has been significantly impacted upon despite these new therapies. There is no evidence that these therapies will allow patients to improve their survival past the first decade of their disease process. It is imperative that the development of new modalities of treatment and ongoing research into the mechanisms of the disease process be pursued to have a long-term impact in preventing disease progression. The future direction of developing therapies in PAH include more selective ET-A receptor antagonists, newer prostanoids or agents that will increase NO levels with further targeting of the vascular endothelium resulting in enhanced vasodilation. Interest in gene therapeutic methodology may target potassium channels, NOS, prostacyclin synthase and vascular endothelial growth factors. Reseeding the diseased endothelium with endothelial progenitor cells has been proposed to aid in the maintenance of vascular health. Novel agents such as rho and tyrosine kinase inhibitors may be useful in the treatment of PAH and impact on the apoptosis resistant pulmonary vasculature in this disease state. As new therapies are developed, further clinical studies need to be performed to discover the most efficacious and safest treatment to improve symptoms, functional capacity and prolong survival.

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