Review Article

Overview of current therapeutic approaches for pulmonary hypertension

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ABSTRACT

There have been tremendous strides in the management of pulmonary hypertension over the past 20 years with the introduction of targeted medical therapies and overall improvements in surgical treatment options and general supportive care. Furthermore, recent data shows that the survival of those with pulmonary arterial hypertension is improving. While there has been tremendous progress, much work remains to be done in improving the care of those with secondary forms of pulmonary hypertension, who constitute the majority of patients with this disorder, and in the optimal treatment approach in those with pulmonary arterial hypertension. This article will review general and targeted medical treatment, along with surgical interventions, of those with pulmonary hypertension.

Key Words: pulmonary hypertension, pulmonary arterial hypertension, therapy, treatment

BACKGROUND

Pulmonary hypertension (PH) is a disorder of the pulmonary vasculature that results in increased pulmonary arterial pressure and is defined as a mean pulmonary arterial pressure (mPAP)≥25 mm Hg at rest.[1] Pulmonary arterial hypertension (PAH) is a subset of PH that results from increased vascular resistance in the pulmonary arteries and may ultimately result in right heart failure. PH can be idiopathic or associated with a variety of disorders but is broadly classified into five groups based upon shared pathophysiologic and clinical features: I. pre-capillary or pulmonary arterial hypertension (PAH); II. PH with left heart disease (e.g., left ventricular dysfunction and valvular heart disease); III. PH associated with disorders of the respiratory system; IV. PH caused by chronic thromboembolic disease (CTEPH); and V. PH associated with miscellaneous disorders, such as sarcoidosis (Table 1).[1] A key point in caring for patients with PH is that the correct etiology must be established, and the severity of disease quantified, before treatment can be considered. PAH, which results from intrinsic disease of the pulmonary vessels, is amenable to specific medical therapy, while treatment of other forms of PH is generally supportive and aimed at the underlying disorder. While other forms of PH are more prevalent, PAH has garnered much attention over the past several decades due to its frequent occurrence in healthy young to middle-aged adults, and more recently, the explosion of knowledge illuminating disease pathogenesis and of newly available therapies.

The reported prevalence of PAH is 15 per million, with a mean age at diagnosis of 50±15 years; women constitute three-quarters of those affected.[2,3] Notably, the average duration between symptom onset and diagnosis is over 2 years.[3] Idiopathic PAH, that which occurs with neither a family history of PAH nor an identified risk factor or associated clinical condition, accounts for 40% of PAH diagnoses, based on data from a recent U.S. registry.[3] Heritable PAH, caused by somatic mutations in genes of the transforming growth factor β (TGF-β) receptor

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Access this article online	
Quick Response Code:	**Website:** www.pulmonarycirculation.org
	DOI: 10.4103/2045-8932.83444
	How to cite this article: Stamm JA, Risbano MG, Mathier MA. Overview of current therapeutic approaches for pulmonary hypertension. Pulm Circ 2011;1:138-59.

family, accounts for approximately 5% of patients with PAH, although similar mutations have been found in up to 20% of those with apparent idiopathic PAH.[2,4,5] A number of drugs and medications have been associated with the development of PAH; the most notorious of these include the appetite suppressants fenfluramine and dexfenfluramine, although methamphetamine use has been more recently indicted as a cause of drug-related PAH.[6,7]

Associated PAH is that which occurs in the presence of some other systemic disease; approximately 50% of PAH patients fall into this category.[3] While many of the connective tissues diseases have been associated with PAH, the most common etiology is that of the systemic sclerosis spectrum of disease, particularly limited systemic sclerosis.[8,9] A significant proportion of patients with uncorrected congenital heart disease, particularly those with systemic to pulmonary shunts, will develop PAH and Eisenmenger syndrome.[1] PAH is also an uncommon but documented complication of HIV infection, chronic hemolytic anemia, and cirrhosis with portal hypertension.[1] Finally, in developing countries, schistosomiasis is a frequent cause of PAH, with an estimated 200 million people infected worldwide. Indeed, chronic schistosomiasis infection may be one of the most common causes of PAH worldwide.[10]

PATHOPHYSIOLOGY

The pathophysiology of PAH has recently been reviewed and is beyond the scope of this article.[11,12] However, a basic understanding of the normal pulmonary circulation, and of the abnormalities seen in those with PAH, is essential to the discussion and application of therapy. The remarkable progress made in clarifying the molecular pathways that contribute to the pathogenesis of PAH has resulted in the identification of multiple therapeutic targets and forms the basis of both currently available and investigational agents. All of the approved PAH-specific medications target one of three pathways: the prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway.

The normal pulmonary circulation is capable of accommodating the entire cardiac output at perfusion pressures that are approximately 20% those of the systemic circulation, even with conditions of increased cardiac output such as exercise. The pulmonary circulation accomplishes this by dilation of the vasculature already receiving the cardiac output and recruitment of unused vasculature; through these mechanisms the pulmonary circulation minimizes increases in perfusion pressure and maximizes gas exchange surface area. The local production of several humoral mediators, including nitric oxide (NO) and prostacyclin, contribute to the maintenance of a low vasomotor tone.

In contrast to normal pulmonary vascular physiology, PH can be caused by either narrowing of the precapillary vessels (arteries and arterioles), loss of vascular surface area, and/or passive pressure from the postcapillary

Table 1: Classification of pulmonary hypertension, Dana Point (2008)

PH Group	Subtypes	Specific examples
Group I: Pulmonary Arterial Hypertension	Sporadic or Idiopathic PAH	
	Heritable PAH	BMPR2, ALK1, others
	Drug- and toxin-induced PAH	Anorexigens, methamphetamines, others
	Conditions associated with PAH	Collagen vascular diseases
		Congenital systemic to pulmonary shunts
		Portal hypertension
		HIV infection
		Chronic hemolytic anemias
		Schistosomiasis
	Associated with significant venous or capillary involvement	Pulmonary veno-occlusive disorder
		Pulmonary capillary hemangiomatosis
Group II: PH owing to left heart disease	Systolic or non-systolic dysfunction, valve disease	
Group III: PH owing to lung diseases and/or hypoxemia	Chronic obstructive pulmonary disease	
	Interstitial lung disease	
	Sleep-disordered breathing and alveolar hypoventilation disorders	OSA, OHS, neuromuscular disorders
	Chronic exposure to high-altitudes	
Group IV: Chronic thromboembolic PH	Chronic thromboembolic pulmonary hypertension	
Group V: PH with unclear or multifactorial mechanisms	Hematologic disorders	Myeloproliferative disorders, splenectomy
	Systemic disorders	Sarcoidosis
	Metabolic disorders	Glycogen storage diseases

ALK1: activin-like kinase, type I; **BMPR2:** bone morphogenetic protein, type II; **HIV:** human immunodeficiency virus; **OSA:** obstructive sleep apnea; **OHS:** obesity hypoventilation syndrome; **PAH:** pulmonary arterial hypertension; **PH:** pulmonary hypertension

vessels (Table 2). In PAH, the classic histological finding is the plexiform lesion. While neither sensitive nor specific for PAH, the plexiform lesion, a localized proliferation of endothelial cells, smooth muscle cells, fibroblasts and extracellular matrix, is found in pre-capillary and intra-acinar pulmonary vessels. Along with medial hypertrophy and intimal thickening by smooth muscle cells and fibroblasts, resistance to blood flow within plexiform lesions is secondary to endothelial-lined channels that narrow the vascular lumen.[13] Activation and expression of adhesion molecules by endothelial cells results in a procoagulant state, with thrombin deposition and platelet adhesion. The sum of these abnormalities in the pulmonary vasculature of those with PAH is unregulated vasoconstriction, smooth muscle cell proliferation out of proportion to apoptosis, and microvascular thrombosis.[12]

Studies of the pulmonary vasculature in idiopathic PAH suggest endothelial injury and dysfunction occur early in the process. In idiopathic PAH, expression of pulmonary endothelial nitric oxide synthetase and prostacyclin synthetase are reduced while levels of endothelin-1 and thromboxane are increased.[11,14] Prostacyclin and nitric oxide (NO) are potent vasodilators and inhibitors of platelet activation and vascular smooth muscle proliferation. The effects of prostacyclin are mediated through adenylate cyclase and the 2nd messenger cyclic adenosine monophosphate (cAMP).[15] Nitric oxide is synthesized from L-arginine by NO synthetases; this readily diffusible gas enters smooth muscle cells and mediates vascular relaxation through stimulation of soluble guanylate cyclase, generating the 2nd messenger cyclic guanosine monophosphate (cGMP). cGMP is subsequently regulated by a phosphodiesterase (PDE-5) which metabolizes cGMP and thus inhibits NO-mediated vasodilation.[11] Endothelin-1 and thromboxane are potent pulmonary vasoconstrictors and mitogens. Serotonin, another pulmonary vasoconstrictor, may also play a role.[16] Other mechanisms that have been postulated to explain the development of PAH include disordered mitochondrial metabolism in which glucose metabolism is shifted from oxidative phosphorylation to that of glycolysis despite adequate oxygen tension, a property shared with some malignant cells; this pseudohypoxic state fosters cellular proliferation and resistance to apoptosis.[17] Another potential mechanism underlying PAH is decreased expression or function of smooth muscle potassium receptors, which results in membrane depolarization and increased concentrations of intracellular calcium. Calcium is an important regulator of vasomotor tone and proliferation; the sustained increase in intracellular calcium levels promotes smooth muscle proliferation and contributes to vascular remodeling.[18,19] Finally, growth factors and inflammatory mediators are implicated in the abnormal proliferation and migration of pulmonary vascular cells. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are potent mitogens and chemoattractants for endothelial cells, smooth muscle cells, and fibroblasts; the activity of both VEGF and PDGF are increased in PAH.[20-22] These cellular pathways are not mutually exclusive and likely interact in the development of PAH.

Table 2: Relationship between vascular lesion location, pathologic process, and corresponding forms of PH

Vascular lesion location	Pathologic process	Corresponding form of PH
Pre-capillary	Intravascular obstruction or vascular remodeling	Vasculopathy caused by drugs/toxins, connective tissue disease, inherited disorders, or idiopathic PAH; chronic pulmonary emboli
Capillary	Destruction of intra-pulmonary capillary bed	Emphysema; interstitial lung disease
Post-capillary	Passive pressure from elevated left atrial pressure or LVEDP	Left ventricular failure with depressed systolic or preserved ejection fraction; valve disease

LVEDP: left ventricular end-diastolic pressure; **PAH:** pulmonary artery hypertension; **PH:** pulmonary hypertension

MANAGEMENT: GENERAL PRINCIPLES

Regardless of the etiology of PH, general supportive care is similar for all PH patients and focuses on improving symptoms and quality of life, mitigating disease progression as much as possible, and improving mortality. Most of the following interventions have either not been studied in large randomized trials, or have been restricted to those with idiopathic PAH; the extrapolation to other populations with PH is based on expert recommendation rather than sound evidenced-based medicine.[23-25]

Diuretics and volume status

All patients with pulmonary hypertension should be educated about and adhere to a sodium-restricted diet. Daily monitoring of body weight can help reinforce dietary adherence and alert the patient and physician of early fluid retention. Despite adequate lifestyle measures, diuretics are widely used in those with pulmonary hypertension to control volume status, improve symptoms and decrease RV loading. Although particular agents and doses have not been well-studied, in recent trials of PAH targeted therapies 49-70% of patients received some form of diuretic therapy.[25] Caution must be exercised not to aggressively diurese patients with significant PH

as intravascular volume depletion may be accompanied by exertional or orthostatic pre-syncope or frank loss of consciousness due to the preload dependent state of the RV in those with advanced PH.

Oxygen supplementation

Hypoxia is a potent pulmonary vasoconstrictor and can be seen in PAH patients for a number of reasons, including reduced diffusion capacity, right to left shunting, and low cardiac output with resultant low mixed venous oxygen saturation. As a consequence, all patients with PAH should be assessed for resting, nocturnal and exertional hypoxia and supplemental oxygen provided as necessary to maintain normoxia. While oxygen therapy has not been specifically studied in the PAH population, long-term supplemental oxygen is likely beneficial in patients with PAH who have hypoxemia. In older but paradigm-setting studies in those with chronic obstructive lung disease and hypoxia, long-term oxygen therapy improved mortality.[26-28] A subset of these patients had invasive hemodynamics measured at the beginning and end of these trials; supplemental oxygen stabilized or marginally reduced pulmonary artery pressures in those receiving oxygen while those in the untreated control groups had continued progression of their pulmonary vascular disease. A subsequent study found similar results, with a reduction in mean pulmonary artery pressure with the initiation of supplemental oxygen, although no subject had normalization of pulmonary hemodynamics.[29] Notably, the studies that showed the largest improvement in pulmonary vascular pressures involved the longest use of daily oxygen therapy (≥18 hours); therefore, if hypoxia is present, patients should be encouraged to wear their oxygen continuously.[30] Likewise, PAH patients should be cautioned regarding exposure to high altitudes or commercial air travel without supplemental oxygen, either of which could worsen hypoxia and result in increased pulmonary vasoconstriction.

Exercise

While many patients with chronic cardiopulmonary conditions have been found to benefit physically and emotionally from physical rehabilitation programs,[31-33] strenuous exercise has traditionally been avoided in those with PAH due to concerns of worsening pulmonary pressures and precipitating syncope or sudden cardiac death.[34] More recently, a randomized trial of monitored exercise in a small group of patients with clinically stable PAH or CTEPH showed improved six-minute walk distances and quality of life after 15 weeks. Specifically, the patients in the treatment group performed daily interval stationary bicycle training (10-25 min./day), walking on flat surfaces (60 min./day), and low-resistance weight training (30 min./day), along with instruction in breathing techniques and stretching, with a resultant mean increase in the six-minute walk distance of 111 m. Exercise training was well tolerated in this group of PAH patients with no significant adverse effects, although the first 3 weeks of exercise training occurred in an inpatient arena and all exercise sessions occurred in a monitored health-care setting.[35] Therefore, while low-level aerobic and strength training is likely to benefit those with clinically stable PAH, as it does with other cardiopulmonary disorders, prescribed exercise should occur in the context of a formal rehabilitation program with appropriate monitoring and support personnel.

Anticoagulation

Thrombophilia is thought to contribute to the pathogenesis of PAH. Apart from those with CTEPH, in which anticoagulation is mandatory, most guidelines recommend therapeutic anticoagulation only in patients with idiopathic PAH.[23,24] However, this recommendation is based upon on a few studies that are either retrospective or non-randomized in nature. In an early investigation, Rich and colleagues found that in a non-randomized, prospective study of patients with idiopathic PAH that those receiving warfarin had improved mortality compared to those who did not receive anticoagulation, even while controlling for baseline hemodynamic parameters and vasoreactivity status.[36] Fuster and coworkers subsequently reported in a single-center retrospective review of patients with idiopathic PAH that prescription of warfarin was one of the strongest identified favorable prognostic indicators.[37] Finally, in the most recent and largest report on the topic, Frank et al. found that in a retrospective multi-center review of patients with either idiopathic or anorectic induced PAH that anticoagulation improved symptoms and mortality (mean survival time of 7.2±0.6 years versus 4.9±0.6 years, $P \leq 0.05$, in those that did and did not receive anticoagulation).[38] Thus, while there is consistent evidence that anticoagulation improves outcomes in those with PAH, there is as of yet no randomized trial showing a benefit. Moreover, unanswered are the clinically relevant questions of whom to treat, since the available studies included only those with idiopathic or anorectic-related PAH, and when to treat, as no study specifically addressed severity of disease.

Pregnancy

Pregnancy is considered to pose an extreme risk to the health of women with PAH, due to the limited ability of the right heart to compensate for the increased cardiovascular demands of pregnancy and labor, in which cardiac output and blood volume can increase by up to 40%. In the era before specific PAH therapy was available, mortality rates for pregnant women were reported to be as high as 35-50% in those with idiopathic PAH or PAH due to congenital heart disease, with most deaths

occurring in the immediate post-partum period due to refractory right heart failure, sudden cardiac death, or thromboembolism.[39,40] More recently, in retrospective observational studies, women with PAH who elected to continue their pregnancies have had improved outcomes through the use of PAH-targeted therapies and elective induction of labor in specialized centers, although these studies are small in size and uncontrolled in design.[41,42] While neonatal survival in those women who carry their pregnancies to term is greater than 80%, the marked risk of death to the mother is the basis of the recommendation that all women with PAH avoid pregnancy through either effective contraception or elective termination.[24] While pregnancy prevention should be reviewed with all women with PAH of childbearing potential, there is a dearth of evidence upon which to a base contraception decisions. Hormonal contraceptives are convenient and available in many formulations but pose an increased risk of venous thrombosis; consideration should be given to surgical or non-hormonal methods.

Mental health in chronic illness

Finally, as with many chronic medical conditions, patients with PAH suffer from an increased burden of anxiety and depression but only a minority are receiving therapy for these conditions.[43] While most of the relevant literature comes from studies of those with chronic heart and lung disease rather than PAH per se, the prevalence of these disorders, which ranges from 10-45%, is significant.[44,45] Moreover, the presence of mood disorders is associated with lower treatment adherence, higher medical costs, and is an independent predictor of mortality.[44,45] While specific screening and management interventions have not been established for PAH, a recent randomized trial of coping skill education and support group participation in a cohort of patients with chronic left-ventricular heart failure realized significant improvements in depression and anxiety, although there was no effect on the rate of hospitalization or mortality over one year.[46] As PAH remains an incurable disease that, while amenable to medical therapy, often progresses over time, patients with PAH should regularly be assessed for depression and/or anxiety disorders. Through screening and with assistance from mental health professionals, PAH patients can receive both treatment for existing mood disorders and preparation for dealing with a chronic disease and, if the need arises, end of life care.

MANAGEMENT: PULMONARY ARTERIAL HYPERTENSION SPECIFIC

There three major classes of PAH specific therapies include prostanoids, endothelial receptor antagonists (ETRA) and phosphodiesterase-5 (PDE5) inhibitors. Treatment decisions in PH care are centered upon both the underlying etiology and the severity of disease. It is a paradox of PH that while the overwhelming majority of patients with PH have disease secondary to either chronic left heart or lung disease, most of the major clinical trials and therapeutic advances have focused on patients with Group I disease (PAH). Consequently, all of the pulmonary vascular-targeted PH therapies are approved only for use in those with PAH, and it is imperative that an underlying cause, if any, be discovered in the initial evaluation of PH patients. Expert opinion regarding treatment is predicated upon assessment of World Health Organization (WHO) functional class (Table 3) and risk assessment (Table 4 and Fig. 1).[23-25,47]

Vasoreactivity and calcium channel blockers

Determining acute vasodilator response in patients with PAH may help identify long-term responders who have an improved prognosis compared to non-responders and may reduce the need of costlier PAH specific therapies by utilizing the less expensive calcium channel blockers (CCB). Until recently only acute vasodilator responders treated with CCB with idiopathic PAH[36,48] have a survival benefit. Patients with other etiologies of PH have been investigated[49,50,51] but generally, among these patients who are acutely vasoresponsive, there is no survival advantage. However, a recent study[52] did demonstrate a survival advantage not only in idiopathic PAH patients but PH in Groups III-V. Vasodilator testing at the time of diagnostic

Table 3: World Health Organization classification of functional capacity in patients with PH

WHO functional class	Clinical description
I	Patients with PH with no limitation of usual physical activity; ordinary physical activity does not cause dyspnea, chest pain, or presyncope
II	Patients with PH with mild limitation of physical activity; no discomfort at rest but normal physical activity causes dyspnea, fatigue, chest pain or presyncope
III	Patients with PH with marked limitation of physical activity; no discomfort at rest but less than ordinary activity causes dyspnea, fatigue, chest pain or presyncope
IV	Patients with PH who are unable to perform any physical activity; dyspnea and/or fatigue are present at rest and symptoms are worsened with any physical activity. Syncope may occur with exertion

PH: pulmonary Hypertension; **WHO:** World Health Organization

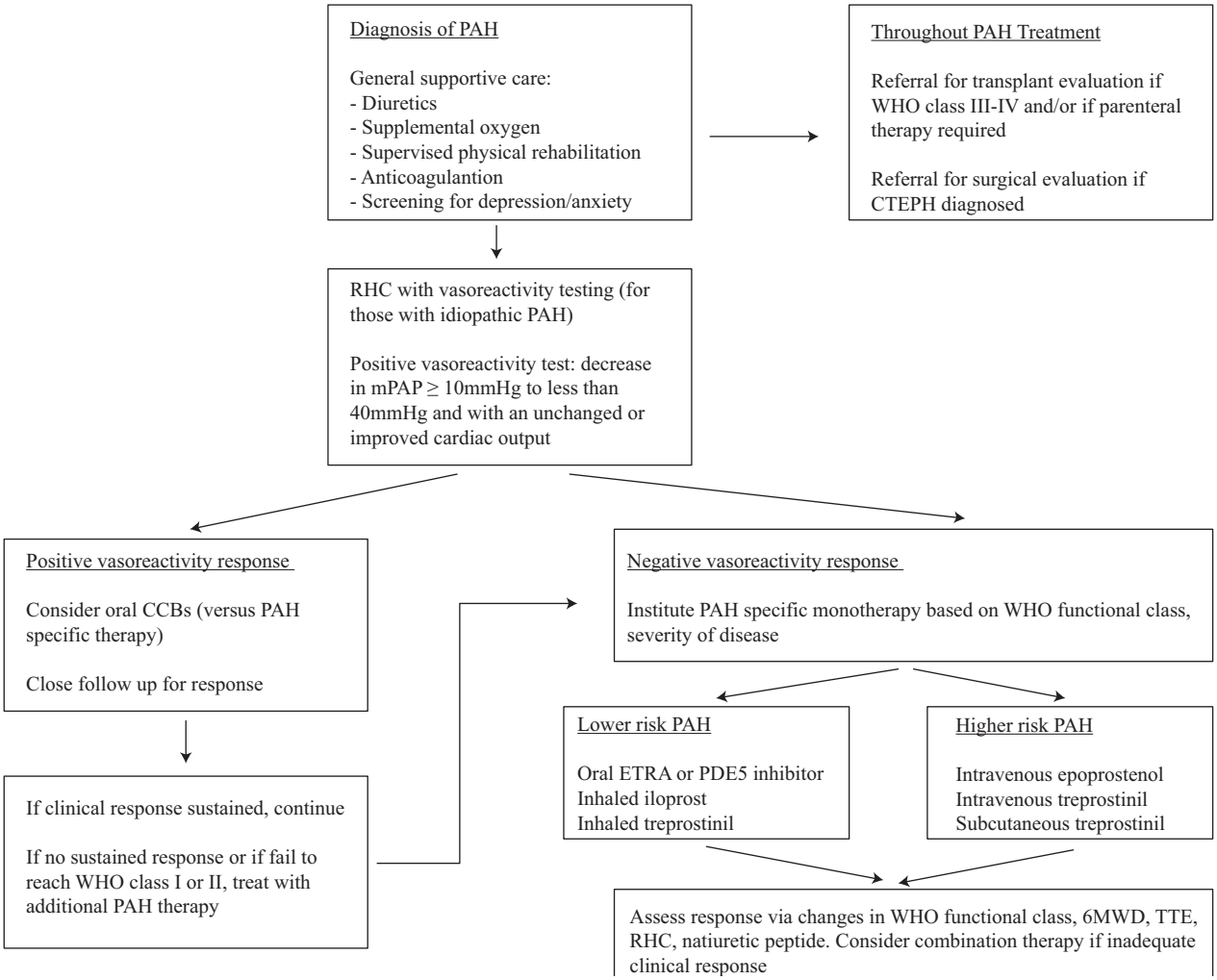

Figure 1: Treatment Algorithm for PAH. Lower risk PAH constitutes those patients with no evidence of right heart failure, WHO II or III functional status, preserved 6MWD and minimally elevated natriuretic peptide levels. Higher risk PAH patients have clinical or hemodynamic evidence of right heart failure, WHO class IV functional status, short 6MWD or significantly elevated natriuretic peptide levels. (6MWD: six-minute walk distance; FC: functional class; CCB: calcium channel blocker; ETRA: endothelial receptor antagonist; PAH: pulmonary arterial hypertension; PDE5: phosphodiesterase 5 inhibitor; RHC: Right heart catheterization; TTE: transthoracic echocardiogram; WHO: World Health Organization).

right heart catheterization has been performed with several different agents including intravenous epoprostenol[53] or adenosine[54] and inhaled nitric oxide (NO).[55]

A positive response to acute vasodilator testing is currently defined as a decrease in mPAP of ≥10 mmHg to value <40 mmHg without a decrease in cardiac output.[48,56] While Sitbon et al. found that 12.6% of those with idiopathic PAH demonstrated a positive vasoreactive response at initial evaluation, only 6.8% of this group maintained long-term response to calcium channel blockers. Patients with idiopathic PAH may therefore benefit from acute vasodilator testing for prognostic and treatment purposed. If a vasodilator response is seen and treatment with CCB attempted, close follow up is essential to ensure an appropriate and sustained hemodynamic response.

Prostanoids

The Food and Drug Administration (FDA) has approved prostacyclin analogues for the treatment of Group I PH (PAH). Epoprostenol was approved in 1995 as continuously infused intravenous (IV) therapy for World Health Organization (WHO) functional class (FC) III-IV idiopathic PAH, heritable PAH, and connective tissue disease related PAH (CTD-PAH). Treprostinil has three modes of delivery: continuously infused subcutaneous (SC), IV, and intermittently inhaled. The SC and IV formulations of treprostinil were approved in 2002 for WHO functional classes II-IV idiopathic PAH, heritable PAH, congenital systemic to pulmonary shunts and CTD-PAH. Inhaled treprostinil was FDA approved in 2009 for WHO FC III idiopathic PAH, heritable PAH and CTD-PAH. Inhaled iloprost is FDA approved as inhaled therapy for WHO FC III-IV idiopathic PAH, heritable PAH and CTD-PAH in 2004.

Table 4: WHO group I assessment of PAH severity (REVEAL PAH Registry)

Test	Finding	HR 1-y M *
Vital signs	Heart rate>92 beats per minute	1.39
	Systolic blood pressure<110 mmHg	1.67
WHO functional class	Class I†	0.42
	Class III†	1.41
	Class IV†	3.13
Six-minute walk distance	≥440 m	0.58
	<165 m	1.68
Echocardiography	Pericardial effusion	1.35
Right heart catheterization	mRAP>20 mmHg	1.79
	PVR>32 Wood Units	4.08
Brain natriuretic peptide	<50 pg/mL	0.50
	>180 pg/mL	1.97
DLCO	≥80% predicted	0.59
	≤32% predicted	1.46

*Hazard ratio for 1-year mortality, adjusted for age, gender, and significant comorbidities, †compared to WHO class II, **DLCO:** diffusion capacity, carbon monoxide; **mRAP:** mean right atrial pressure; **PAH:** pulmonary artery hypertension; **PVR:** pulmonary vascular resistance; **REVEAL:** registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; **WHO:** World Health Organization

Prostanoid: *Epoprostenol*

Clinical trials

The first and only randomized, controlled trial to demonstrate a mortality benefit with PAH specific therapy was reported in 1996 by Barst et al.[57] This was a prospective, randomized, open label multicenter trial of 81 FC III/IV patients with idiopathic PAH treated with conventional therapy (diuretics, digoxin and warfarin) versus conventional therapy with IV epoprostenol. The primary endpoint was 6-minute walk distance (6MWD) which improved in the therapy group by a mean of 32 meters over a twelve week period, with a mean placebo corrected distance improvement of 47 meters. Secondary endpoints that were met were hemodynamics (decreased mPAP and pulmonary vascular resistance (PVR) and increased cardiac index), quality of life and mortality. Eight patients on conventional therapy died while no treatment subjects died (P=0.003). Additional studies performed validated the survival effect, improved functional class, exercise endurance and improved hemodynamics in IV epoprostenol treated patients with advanced idiopathic PAH when compared to historical controls[58] and to predicted survival based on the National Institutes of Health (NIH) survival equation (*see* Prognosis section, below).[59]

Badesch et al.[60] reported the first large scale open-label, randomized, multicenter trial to evaluate the utility of continuous infusion of epoprostenol in the treatment of 111 moderate to severe scleroderma associated PAH (SSc-PAH) patients. After 12 weeks of therapy, those randomized to the epoprostenol group had improved hemodynamic parameters, functional class, and achieved a 6MWD of 108 meters greater than those in the conventional group. Unlike previous epoprostenol-treated idiopathic PAH patients,[57-59] no survival benefit was found in the SSc-PAH patients treated with epoprostenol, likely related to an underpowered study and a greater complexity of illness and multiorgan involvement in the SSc-PAH subjects.

Various other groups of patients have demonstrated symptomatic and hemodynamic benefit from IV epoprostenol therapy but not demonstrated a survival benefit. Congenital heart disease patients[61] have seen improvements in hemodynamics and functional class. Patients with portopulmmonary PAH[62] have improved hemodynamics while those with HIV associated PAH[63] had improved hemodynamics and 6MWD. Finally, those with CTEPH[64] have improved hemodynamics, functional class and 6MWD that sustained at mean follow-up of 19.6 months.

Clinical application and considerations

IV epoprostenol is typically reserved for individuals with severe PAH. To date it is the only medication that has a mortality benefit.[57] Objective hemodynamic values are usually the trigger to consider parenteral therapy. A right heart catheterization result that shows a moderate to severe elevation in pulmonary arterial pressures with a reduced cardiac index (<2.0 L/min./m^2) and an elevated RAP (>12 mmHg) should be considered for parenteral therapy. The decision to initiate IV therapy must be individualized, as comorbidities, capabilities, and goals of care for each patient are different.

Epoprostenol use can be challenging. It is continuously infused medication that requires a tunneled central venous catheter, an infusion pump, and ice packs to keep the medication cold; moreover, the drug has an incredibly short half-life. Patients may face complications of thrombosis, line infection and infusion interruptions, the latter of which can result in hemodynamic collapse. Additionally, dose dependent side effects may be intolerable and include headache, jaw pain (trismus), flushing, nausea, diarrhea, skin rash and musculoskeletal pain of a severity requiring narcotic pain management. Individuals must be screened carefully to determine if they are able to commit to long-term use of this medication.

Prostanoid: *Treprostinil*

Clinical trials

Treprostinil, can be administered as a subcutaneous (SC), IV or inhaled therapy; the efficacy of all 3 modes of delivery has been demonstrated in clinical studies.

Subcutaneous: SC treprostinil was evaluated in a 12-week multicenter, randomized, double-blind, placebo controlled trial of 470 functional class II-IV PAH subjects with idiopathic PAH, connective tissue disease, and patients with systemic to pulmonary shunts.[65] Enrolled subjects were randomized to conventional therapy (which included oral vasodilators, anticoagulants, diuretics and digoxin) plus SC treprostinil versus conventional therapy plus placebo. The primary endpoint of 6MWD was met with a modest improvement of 16 meters (P=0.006); improvement in 6MWD was found to be dramatically dose-related. Additional statistically significant endpoints were improved hemodynamics, quality of life and dyspnea scores.

An open-label extension study[66] of 860 WHO FC II-IV idiopathic PAH and associated PAH subjects, which included previously enrolled SC treprostinil subjects[65] and de novo treatment subjects, evaluated the long-term outcome and efficacy of SC treprostinil as monotherapy. Follow-up of all subjects for a period of 1-4 years after enrollment, which included 130 subjects treated with additional PAH therapy, compared to those with SC treprostinil as monotherapy (n=730), showed no difference in survival. Idiopathic PAH subjects (n=332) treated with SC treprostinil demonstrated improved survival over the NIH predicted survival equation.

A post-hoc analysis of a randomized, double blind placebo-controlled study, by Oudiz et al.,[67] evaluated 90 patients with PAH due to connective tissue disease, with almost half of those with SSc (n=45). Patients treated for 12 weeks with SC treprostinil were able to walk a median value of 25 m more than those treated with placebo. Patients also had improved hemodynamic parameters and a trend toward improved quality of life measures. This post-hoc analysis was not powered to detect a difference in mortality between the two groups.

Intravenous: Based upon the bioequivalence with subcutaneous treprostinil[68] the FDA approved IV treprostinil in 2004 for the treatment of WHO FC II, III and IV PAH and in patients requiring transition from epoprostenol therapy. A 12 week, multi-center, prospective, open-label, uncontrolled study of 16 WHO FC III, IV PAH subjects evaluated the safety and efficacy of monotherapy with IV treprostinil.[69] The primary endpoint of improved 6MWD was met with an increase of 82 m (319+22 to 400+26 m; P=0.001) as well as secondary endpoints of improved dyspnea score and hemodynamics. Thirty-one WHO FC II and III patients on stable epoprostenol therapy for at least 3 months were transitioned to IV treprostinil[70] over 24-48 hours while hospitalized. The 27 subjects that completed the 12-week study maintained their 6MWD of 439+16 m with a modest increase in mPAP and decrease in cardiac index (CI). Interestingly, upon hospital discharge after the transition was made, the doses of treprostinil and epoprostenol were equivalent at 47+24 ng/kg/min. and 40+4 ng/kg/min., respectively. All subjects on treprostinil subsequently required dose increases. At week 6 the mean dose was 60+23 ng/kg/min. (range: 15-96 ng/kg/min.) and at week 12 the mean dose increased to 83+38 ng/kg/min. (range: 24-180 ng/kg/min.). This finding of IV treprostinil dose being approximately twice that of epoprostenol has been also noted in subsequent publications.[71]

Inhaled: In 2006 Voswinckel et al.[72] published the results of 3 pilot studies evaluating the hemodynamic effects of inhaled treprostinil in a total of 123 patients with idiopathic PAH. The primary study endpoint was a change in PVR. The first study evaluated 44 subjects with moderate-severe PAH in a randomized, open label, single blind, crossover study where the primary objective compared acute hemodynamic effects and systemic side effects of inhaled treprostinil (n=22) with inhaled iloprost (n=22) at comparable doses. The second study evaluated the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a dose of 30µg and explored the highest tolerated single dose. The third was a randomized, open-label, single blind study to explore the shortest possible inhalation time for a 15µg dose of treprostinil.

The study showed that the maximum effects of treprostinil and iloprost on PVR were comparable, however the treprostinil effect lasted longer (P<0.0001). The treprostinil group exhibited a sustained increase in cardiac output with no decrease in systemic arterial pressure. Neither drug had affected gas exchange. The treprostinil dose of 30 µg maximally reduced PVR when compared to the other formulations, without a dose response. The study demonstrated that the optimal dose to be 9 breaths via ultrasonic nebulizer four times daily, which delivers approximately 54 µg of treprostinil.[73]

The TRIUMPH-1 trial evaluated the safety and efficacy of 235 WHO FC III/IV PAH patients with a baseline 6MWD of 200-450m who were randomized to inhaled treprostinil or placebo while on baseline bosentan (70%) or sildenafil (30%).[74] The primary endpoint was met with a placebo adjusted increase in 6 MWD of 20 m (P=0.0004) and secondary endpoints of quality of life and biomarkers. There were no reported improvements in time to clinical worsening, functional class, or dyspnea score.

Clinical application and considerations

SC treprostinil therapy avoids the complications of a permanent central venous catheter and does not require daily mixing and preparation as the drug is dispensed in pre-mixed syringes. In addition, cassettes can be changed every 48 hours and do not require ice packs. The package insert recommends changing the subcutaneous site every 3-4 days; however, if an optimal site is found it can be used for 2-4 weeks.[75] The most common side effects are pain at the SC infusion site. The etiology of pain is unclear and does not appear to be dose related.[65] Management protocols that include pharmacologic (local and systemic) and non-pharmacologic options, as well as physician and patient communication as to optimal site placement, are important aspects of infusion site maintenance.[76]

Pivotal clinical studies may have treated subjects with lower doses than are currently being clinically used.[65,71,79] Post trial experience in poster and abstract form[76] regarding SC treprostinil have indicated that dosing is considerably higher than in clinical studies, with mean doses of 40.6–44 ng/kg/min. (range 26-72 ng/kg/min.) by 12 months. Current expert opinion[76] recommends a goal dose range is 40-80 ng/kg/min. by month 6 of therapy. Site pain and discomfort should not limit dose escalation. In fact, rapid dose escalation has been associated with improved infusion site pain and exercise capacity when compared to slow escalation.[77]

PAH patients who are unable to manage SC treprostinil infusion, or require higher doses of therapy, have the option of IV treprostinil. Although the two formulations are bioequivalent and share similar elimination half lives, initial rapid up-titration of IV treprostinil has been associated with improved dyspnea.[69] There are no proposed guidelines for titration management of IV treprostinil. The dose can be increased several times per week at 1-2 ng/kg/min. increments to a goal of 40 ng/kg/ min.; the upper limits of IV therapy in previously reported trials have ranged from 62-83 ng/kg/min,[69,70] this is approximately twice the dose seen in epoprostenol use.

Regardless of the method of administration, treprostinil produces typical prostanoid side effects of jaw pain, headache, chest pain, flushing, nausea and diarrhea. Patients tend to experience symptoms with medication up-titration with eventual resolution after adjusting to the new dose. Intravenous treprostinil had reports of a significantly higher rate of catheter infections, in particular Gram-negative organisms when compared to epoprostenol.[78] This however has been resolved once a closed-hub system and waterproofing of the catheter hub connections for showering were implemented.[79]

Prostanoid: *Iloprost*

Clinical trials

Iloprost is a prostacyclin analogue available in inhaled form, with a terminal half-life of 25 minutes. Due to the short half-life, lasting approximately 30-60 minutes, iloprost requires multiple daily inhalations (6-9 inhalation sessions per day).

In the AIR study Olschewski et al.[80] evaluated 203 patients in a 12-week, double blind, randomized, placebo-controlled multicenter trial. Subjects included in the study had idiopathic PAH, CTD-PAH, appetite suppressant associated PAH and inoperable CTEPH and were WHO FC III-IV. Patients were permitted to continue standard conventional therapy. The trial utilized a novel composite endpoint to determine response to therapy. In order to meet the primary endpoint subjects had to increase 6MWD by 10% and improve WHO FC by one class in the absence of clinical deterioration or death. Seventeen percent of subjects on iloprost met the combined endpoint, compared to 4% of those receiving placebo ($P<0.05$). The mean increase in 6MWD in all subjects was 36m; the subset of those with idiopathic PAH demonstrated a mean increase of 59m. Hemodynamic values were unchanged when comparing pre-inhalation of iloprost to baseline values. Post-inhalation decreases in PVR and pulmonary artery pressure were noted with associated increases in cardiac output and mixed venous O_2 saturation.

Iloprost monotherapy was evaluated in an open label prospective study of 76 idiopathic PAH patients with WHO FC II-IV symptoms.[81] Subjects were evaluated according to prospectively defined endpoints of death, transplant or a switch to parenteral therapy or addition of oral therapy during a median follow-up period of 383 days. Event free survival at 12, 24, 36, 48 and 60 months was 53, 29, 20, 17 and 13%.

Clinical application and considerations

Side effects of treatment are related to the vasodilatory properties of the drug with skin flushing, syncope and jaw pain and related to the drug delivery system with increased cough.[80] A potential drawback is the need to perform 6-9 inhalations per day.

Prostanoid pharmacology

Epoprostenol is the first synthetic prostanoid to be approved by the FDA. The only formulation available is offered intravenously. Due to vein irritation seen in all prostanoids, epoprostenol needs to be continuously infused through a central venous catheter. The plasma half-life is similar to that of endogenous prostacyclin (3-5 min.). Patients need to mix the powered drug with a highly basic solvent that must be used within 12-24 hours. The initial in-hospital dose of epoprostenol is 2 ng/kg/min.

with an optimal dose range of 22-40 ng/kg/min. when utilized as monotherapy. Unlike standard epoprostenol, recently marketed room temperature (thermostable) epoprostenol is a chemically stable compound that does not require cooling with ice packs and can be reconstituted with sterile water or sodium chloride rather than highly basic solutions. Thermostable epoprostenol can be mixed days ahead of time and stored until needed. When prescribing epoprostenol, care must be taken to not overdose patients as chronic overdose can result in high output cardiac failure.[82]

Treprostinil, as compared to standard epoprostenol, is neutral pH and chemically stable at room temperature with an elimination half-life of 4.6 hours for subcutaneous therapy and 4.4 hours for intravenous therapy.[83] Specific biological effects have been noted in treprostinil. In adult rat cardiomyocytes, treprostinil potentiated the positive inotropic effects of catecholamines.[84] This may be clinically relevant in humans as subjects with right heart failure have increased cathecholamine drive; this effect may theoretically augment cardiovascular performance.

Due to the method of administration, inhaled iloprost exhibits selective intrapulmonary activity. Drug deposition relies upon the proximity of the terminal airways to the small pulmonary arteries and acts directly on the pulmonary artery wall.[85] Nebulization of iloprost into small particles[86] results in alveolar deposition and the need for a reduced dose compared to intravenous infusion of iloprost.[80]

Postscript, prostanoids

Overall prostanoids are the "go to" therapy for advanced PAH patients. Decision on specific prostanoid therapy depends upon whether the patient capability and preference in regards to SC, IV or inhalation therapy. Our recommendation is to initiate parenteral therapy in subjects who have a hemodynamic profile of moderate to severe elevation in pulmonary arterial pressures with a depressed cardiac index (< 2.0 L/min./m^2) and an elevated RAP (>12 mmHg). If patients on oral PAH specific therapy have worsening symptoms and hemodynamics, a step up to inhaled prostaoinds may be initiated, particularly if a patient is not amenable to parenteral therapy.

Endothelin receptor antagonists (ETRA)

Bosentan and ambrisentan are FDA approved endothelial receptor antagonists (ETRA) for the treatment of Group I PAH. Bosentan, approved in 2001, is available as twice daily oral therapy for WHO FC II-IV related to idiopathic PAH, heritable PAH, congenital systemic to pulmonary shunts and CTD-PAH. Ambrisentan was FDA approved in 2007 and is available as once a day oral therapy only for idiopathic PAH, heritable PAH and CTD-PAH. Sitaxentan, a selective endothelial receptor antagonist, was recently withdrawn from the market and ongoing clinical trials were suspended due to fatal liver failure. Sitaxentan will not be reviewed in this article.

ETRA: Bosentan

Clinical trials

Bosentan is a synthetic nonpeptide pyrimidine derivitave that irreversibly binds to the endothelial receptors A and B.[87] It is the first FDA approved oral agent available for the specific treatment of PAH.

In 2001 Channick et al. reported the results of the first oral PAH specific therapy in a double-blind, placebo controlled trial with bosentan in 32 idiopathic PAH and SSc-PAH WHO FC III subjects.[88] The study met its primary endpoints of improved 6MWD and secondary endpoints of improved functional class and hemodynamic values after 12 weeks of treatment. The subsequent larger, multicenter controlled trial, BREATHE-1, studied 213 WHO FC III/IV subjects with idiopathic PAH and CTD-PAH.[89] Patients were randomized to 125mg or 250mg twice daily bosentan or placebo for 16 weeks. There was no difference between the primary endpoint of 6MWD between the 125mg or 250mg groups. The combined placebo adjusted improvement in the 6MWD was 44m (P<0.001). There was an increase in the time to clinical worsening and improvement in WHO FC in the bosentan groups. This study was not adequately powered to detect a difference in mortality. Survival has been shown to be similar in FC III idiopathic PAH subjects treated with bosentan compared to historical subjects treated with epoprostenol.[90] Sitbon et al. noted sustained improvements in exercise capacity, functional class and hemodynamics in subjects with Group I PAH followed for 12 months.[91] Subsequent studies have evaluated bosentan in HIV associated PAH,[92,93] portopulmonary hypertension[94] and inoperable CTEPH[95,96] with favorable results.

Most trials treating Group I PAH evaluated subjects with WHO FC III. The issue of whether early medical intervention would be beneficial in those with milder disease (WHO FC II) was the goal addressed by Galiè and colleagues in the Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients (EARLY) trial.[97] This trial was a randomized, double-blind placebo controlled, multi-center study which evaluated treatment with 125 mg twice daily of bosentan versus placebo for 6 months. Individuals treated with PAH specific medications were prohibited with the exception of the PDE5 inhibitor sildenafil. One hundred eighty five WHO FC II subjects with idiopathic PAH, heritable PAH, CTD-PAH, anorexigen-related PAH, HIV-related PAH and congenital heart disease associated PAH were enrolled. Those treated with bosentan met the primary endpoint of a significant decrease in PVR (17%

decrease in bosentan versus an increase of 8% in controls). The decrease in PVR was associated with a decrease in mPAP and an increase in CI. 6MWD was not significantly different between bosentan and placebo groups. This was regarded as a *ceiling effect,* related to the treatment of PAH patients with mild pulmonary vascular disease. Time to clinical worsening was improved in the bosentan group and more subjects in the bosentan group had lower incidence of worsening functional class. Despite the lack of significant improvement in 6MWD in the bosentan treatment group, the hemodynamic and clinical outcomes of the EARLY trial provided evidence that led to the approval for WHO FC II patients.

A post hoc analysis by Denton et al.[98] of two randomized, double-blind placebo controlled studies evaluated 52 patients with WHO FC III or IV SSc-PAH. After 12-16 weeks of therapy those treated with bosentan had stable 6 MWD and a delay in time to clinical worsening; the authors concluded that treatment with bosentan slowed disease progression. Girgis et al.[99] performed a retrospective evaluation of 17 patients with SSc-PAH versus 19 patients with idiopathic PAH in whom bosentan was the first-line single agent for at least 6 months. Mortality evaluated 1 and 2 years after treatment showed that the idiopathic PAH group had a non-statistically significant increase in survival (100% at years 1 and 2) in comparison to the SSc-PAH group, which had survival was 87% at year 1 and 79% at year 2. Functional status improved by almost one class in the idiopathic PAH group, but remained stable or deteriorated in the SSc-PAH patients.

Clinical application and considerations

The adverse events associated with bosentan are related to systemic vasodilatation with headache, nasopharyngitis, dizziness and lower extremity edema being most common. None of these events were statistically different between the bosentan and placebo group in the BREATHE-1 trial. The hepatic clearance of bosentan raised concern for serious hepatotoxicity in treated individuals. An increase in liver function tests (LFT) greater than 3 times the upper limit of normal (ULN) was noted in 12 and 14% of subjects who had received 125mg and 250mg of bosentan twice daily, respectively.[89] Although most LFT abnormalities were transient patients treated with bosentan require monthly lab draws. Hepatic function generally normalizes with treatment interruption.

Bosentan induces the cytochrome P450 enzymes CYP3A4 and 2C9. Concomitant administration of bosentan with warfarin may reduce plasma warfarin concentrations. [100] Bosentan may increase the metabolism, and therefore reduce drug levels, when co-administered with cyclosporine, erythromycin, amiodarone, diltiazem, HIV protease inhibitors, and the azole antifungals. These drug interactions may require appropriate medication dose adjustments.

ETRA: Ambrisentan

Clinical trials

A double-blind, randomized dosing strategy study evaluated 64 patients with idiopathic PAH, HIV and anorexigen-associated PAH and CTD-associated PAH. Four doses of ambrisentan (1, 2.5. 5 and 10mg) were evaluated during the 12-week study which had a subsequent 12 week open label extension study, permitting dose adjustment. The initial 12 weeks demonstrated an increase in 6MWD of 34-38m in all 4 dosing groups. By the 24th week further increases in exercise capacity were noted with all subjects experiencing an overall 6MWD increase of 54m.

Two nearly identical concurrent studies, ARIES 1 and 2, evaluated three doses of once-daily oral ambrisentan (2.5, 5 and 10mg) in 394 treatment-naïve subjects diagnosed with idiopathic PAH or associated PAH (HIV, anorexigen and CTD).[101] These multicenter, randomized, double-blind placebo controlled studies both met their primary endpoint, with a combined drug improvement in 6MWD of 31-59m when comparing baseline to week 12. Secondary endpoints of dyspnea scores and biomarkers were also improved in both studies. Time to clinical worsening was improved only in ARIES-2 study while WHO FC improved only in the ARIES-1 trial.

Subjects who had completed ARIES 1 and 2 were eligible to enroll into the open label safety and efficacy extension study, ARIES-E. At two years of follow-up, subjects in the 5 and 10 mg ambrisentan group maintained 6MWD at 23 and 28m respectively. Twelve subjects experienced increases in hepatic enzymes with two subjects requiring drug discontinuation.[102] More recently Klinger et al. performed a restrospective evaluation of the long-term hemodynamic effects of ambrisentan in the ARIES-E cohort. Sixty-eight subjects had a follow-up right heart catheterization (RHC) a median time of 60 months after initiating ambrisentan monotherapy. Significant improvements were noted in mPAP, PVR and CI in both the 5 and 10mg treatment groups when compared to baseline values at 2 years of follow-up. This study showed a statistically significant correlation between improvement in 6MWD and decreases in mPAP and PVR.

Clinical application and considerations

Ambrisentan is well-tolerated. Lower extremity edema, headache and nasal congestion appears to be the drugs main side-effects. The incidence of hepatic injury is much less than bosentan. The ARIES-1 and 2 study had no patients with LFTs >3 times the ULN.[101] Recently the FDA has removed the black box warning related to liver injury

based upon post-marketing analysis that showed the risk of hepatotoxicity was low in ambrisentan.

Ambrisentan is eliminated through phase II hepatic glucuronidation and metabolism is through the cytochrome P450 enzyme 3A4, similar to bosentan. However warfarin dose adjustment is not necessary with ambrisentan use. All ETRAs are teratogenic and should not be used during pregnancy. Bosentan, unlike ambrisentan, may decrease the efficacy of oral contraceptives.[103] Therefore it is recommended that two forms of contraception be employed by patients treated with ETRAs.

Pharmacology

Endothelin-1 is a vasoconstrictor and smooth muscle mitogen that is overexpressed in the lungs of patients with PAH.[104] Endothelin binds to receptors $Endothelin_A$ and $Endothelin_B$ (ET_A and ET_B) which results in deleterious remodeling of the pulmonary vasculature. Endothelin receptor antagonists are either nonselective receptor antagonists (block ET_A and ET_B) or single receptor antagonists (blocks ET_A only). ET_A receptors have been isolated predominately in the smooth muscle cells of the pulmonary artery, airways, lung fibroblasts and cardiomyocytes. ET_B receptors predominate in pulmonary vascular endothelial cells with a lesser expression in pulmonary artery smooth muscle cells and fibroblasts.[87] There is a theoretical benefit of employing specific receptor antagonist over a dual receptor antagonist as blockage of the ET_A receptors may promote the production of vasodilatory and antimitogenic substances activated through the ET_B pathway. The clinical implication of this difference is currently a debated topic. The mean terminal half-life of bosentan is around 5 hours[105] and takes up to 5 days to reach steady state.[106] Ambrisentan is a nonsulfonamide that selectively antagonizes ET_A. Ambrisentan is rapidly absorbed into the systemic circulation with a half-life of approximately 15 hours.[107] The longer half-life allows for once daily dosing of ambrisentan.

Postscript, ETRAs

There is currently no data to establish the benefit of one ETRA over the other. The decision to utilize ambrisentan or bosentan may be, in part, guided by patient preference. Ambrisentan may appeal to patients due to the once daily dosing and additional benefit of a lower incidence of hepatic injury. The decision to follow monthly LFTs may vary with provider preference.

Phosphodiesterase-5 (PDE5) inhibitors

Currently sildenafil and tadalafil are the only FDA approved oral PDE5 inhibitors for the treatment of WHO FC II-III PAH. Sildenafil, approved in 1998, is available as three times daily oral and IV formulations for idiopathic PAH and connective tissue disease associated PAH. Tadalafil, approved in 2003, is available as once a day oral therapy for idiopathic PAH, heritable PAH and CTD-PAH. Vardenafil is not currently FDA approved for PAH but a recent clinical trial has shown its beneficial use in idiopathic PAH, CTD-PAH and congenital systemic to pulmonary shunts.[108]

PDE5 Inhibitor: Sildenafil

Clinical trials

Oral sildenafil: The Sildenafil Use in Pulmonary Arterial Hypertension (SUPER-1) study evaluated 278 WHO FC II-III subjects with idiopathic PAH, connective tissue disease and systemic to pulmonary shunts in a 12 week, double blind, placebo controlled trial.[109] The trial compared subjects assigned to placebo and 20, 40 or 80mg of sildenafil in a 1:1:1:1 ratio. Subjects on IV prostanoids, bosentan, treprostinil, iloprost or L-arginine were excluded. The primary endpoint, 6MWD, was met in the 20, 40 or 80mg sildenafil groups (the baseline 6MWD was 339-347m), although a dose-response effect on 6MWD was not demonstrated. The mPAP and PVR decreased significantly in the three groups studied compared to placebo and the reduction in PVR was dose dependent. All doses resulted in an improvement in WHO FC but did not decrease time to clinical worsening.

The open-label, uncontrolled SUPER-1 extension study, SUPER-2[110] followed subjects taking 80mg sildenafil three times daily, for at least 3 years; the majority of which were WHO FC II-III. One hundred seventy subjects completed both studies and were followed for a median of 1,242 days. Sixty percent of these patients maintained or improved their functional status, and a conservative 3-year survival estimate was 68%. A surprisingly low number of subjects, 3%, 10% and 18%, required additional PAH specific therapy at years 1, 2 and 3, respectively. It was notable that patients with baseline 6MWD <325m in SUPER-1 who lacked improvement in 6MWD during the first 12 weeks of sildenafil therapy exhibited worse survival.

A follow up post-hoc analysis of 84 subjects from the SUPER-1 study of patients with connective tissue disease associated PAH[111] suggested improved 6MWD and hemodynamics in this subgroup as well.

Sildenafil has been investigated in patients with CTEPH,[112-113] COPD associated PH,[114] and PH related to ILD.[115,116] These studies have suggested potential benefit, but larger studies are needed to draw firm conclusions.

The Sildenafil versus Endothelial Receptor Antagonist for Pulmonary Hypertension (SERAPH) study[117] directly compared sildenafil and bosentan as first line therapy in 26 WHO FC III idiopathic PAH and connective tissue disease associated PAH followed for 16 weeks.

The sildenafil group met its primary outcome in with a decrease in right ventricular mass and both sildenafil and bosentan groups had improvements in 6MWD and CI. The authors conclude that sildenafil and bosentan should be considered equivalent therapies for this patient population.

Intravenous (IV): Hospitalized patients on chronic PDE5 inhibitor therapy who cannot tolerate a discontinuation of oral therapy can be transitioned to IV sildenafil. Recently the pharmacokinetic and pharmacodynamic effects of 10mg of IV sildenafil were compared to 20mg of oral sildenafil and were found to be similar in a single center open label study.[118]

Clinical application and considerations

The side effect profile for PDE5 inhibitors are generally similar with common side effects of headache, flushing, nasal congestion, dyspepsia and myalgias, primarily attributed to the drugs vasodilatory effects.[109,111,119] These adverse events are often transient, mild to moderate in nature and dose-related. A major concern for patients treated with PDE5 inhibitors is hypotension, especially with the concomitant administration of nitrates. Both nitrates and PDE5 inhibitors increase cGMP via the NO pathway and subsequently lower systemic blood pressure. Nitrates are contraindicated in patients treated with PDE5 inhibitors.

Visual disturbances are noted with sildenafil, including blurry vision, blue-green color changes and light sensitivity, and have been attributed to differences in PDE selectivity. These effects are related to inhibition of a retinal form of PDE, namely PDE6,[120] which does not occur with the more selective PDE5 inhibitor tadalafil. More serious sensory effects have been documented. Nonarteritic anterior ischemic optic neuropathy (NAION)[121] and sudden sensorineural hearing loss[122] have been described in case reports of PDE5 inhibitors used in erectile dysfunction. These disturbances were not found in the >3 years of follow-up of chronic sildenafil administration in the SUPER-2 trial.[110]

PDE5 Inhibitor: *Tadalafil*

Clinical trials

The Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Trial is a 16-week, randomized, double blind, double dummy, placebo controlled multicenter trial which studied the efficacy and tolerability of 4 doses of tadalafil on 405 PAH subjects with and without background bosentan therapy.[119] Unlike the SUPER-1 study, subjects on 40mg of tadalafil had significantly improved time to clinical worsening when compared to placebo, as well as a reduction in the incidence of clinical worsening (relative risk reduction 68% less than placebo). Exercise capacity was improved with all doses of tadalafil studied in a dose dependent manner. Only the 40mg dose met the pre-specified value for statistical significance of <0.01, with a placebo corrected 6MWD of 33m. The placebo corrected 6MWD was improved in the treatment naïve (no background bosentan) tadalafil subjects moreso than in those on background bosentan. Hemodynamic data available for 93 subjects available showed improved hemodynamics in the 40mg group, with better results noted in tadalafil naïve subjects. Use of tadalafil did not demonstrate significant improvement in other secondary outcomes.

Clinical application and considerations

The adverse events related to tadalafil are similar in the SUPER-1 and PHIRST trials, with the most common reactions related to the vasodilatory properties of the drug. Visual disturbances however should not be as prominent with tadalafil, given its more selective PDE5 inhibition.[120]

Pharmacology

Although the magnitude of hemodynamic effect of sildenafil was dose dependent in the SUPER-1 trial, the FDA recommended 20mg three times daily based upon the absence of dose dependence in 6MWD. The peak vasodilatory effect of sildenafil is 60 minutes[123] with a terminal half-life of 4 hours for sildenafil.[124] Sildenafil is metabolized hepatically through the cytochrome P450 3A4 isoform. Dose adjustment is not necessary mild to moderate hepatic impairment but sildenafil use in severe hepatic impairment has not been studied. Concomitant use of medications metabolized through this pathway, such as HIV protease inhibitors and macrolides, may increase sildenafil levels. No dose adjustment is necessary in renal impairment.[125]

The peak vasodilatory effect for tadalafil is 75-90 minutes[123] and the terminal half-life is 17.5 hours.[124] Like sildenafil, tadalafil is metabolized hepatically through the cytochrome P450 3A4 isoform. Unlike sildenafil, tadalafil needs dose adjustment (from 40mg to 20mg) in the setting of hepatic impairment.[126]

Postscript, PDE5 inhibitors

Patient preference may dictate the drug selection between tadalafil and sildenafil, with once daily tadalafil therapy as an appealing option. Unlike the SUPER trials, the PHIRST trial showed an increase in time to clinical worsening with tadalafil. A patient that fails tadalafil monotherapy can advance to add-on therapy or switch drug classes. In contrast, sildenafil can be uptitrated from 20mg. The SUPER-2 study demonstrated that nearly all subjects were on maximal dose of 80mg three times daily and only 18% of WHO FC II-III subjects advanced to additional

PH specific therapy within 3 years. Hemodynamic improvements are similar in sildenafil and tadalafil; however sildenafil improves areterial oxygenation[123] likely through a favorable impact on ventilation perfusion matching.

Combination therapy

Combination therapy for PAH is a logical step from single drug regimens due to the progressive and incurable nature of the disease in most patients and due to the availability of agents that target different molecular pathways. While the most efficacious combination of medications, along with the issue of sequential versus concurrent initiation, is uncertain and an active area of investigation, several studies are available to guide current therapy. The addition of inhaled iloprost to patients who remained symptomatic despite oral bosentan therapy resulted in improved functional class, 6MWD, and hemodynamics.[127] The addition of high dose sildenafil to symptomatic PAH patients treated with parenteral epoprostenol likewise resulted in improved functional class, 6MWD, and hemodynamics.[128] In a study combining 2 oral agents, the addition of tadalafil to background bosentan therapy, resulted in improved 6MWD and health-related quality of life.[119] Finally, the addition of inhaled treprostinil to either oral bosentan or sildenafil therapy resulted in improved 6MWD, health-related quality of life and natriuretic peptide levels.[74]

Overall these studies, although limited in size and few in number, suggest that combination therapy results in clinical improvement and is well-tolerated. Notably these studies, similar to many other PAH investigations, were brief and were not powered to assess mortality, making assumptions about long-term outcomes difficult. Ongoing combination studies include the addition of bosentan to patients already on therapy with sildenafil (COMPASS 2, NCT00303459), the use of ambrisentan and tadalafil in patients with systemic sclerosis (ATPAHSS, NCT01042158), the addition of sildenafil to background bosentan therapy (NCT00323297), and concurrent initiation of PAH therapy with both ambrisentan and tadafil (AMBITION, NCT01178073). Consideration should be given to enrolling patients into one of these or other studies when using PAH therapy in combination.

INVESTIGATIONAL THERAPIES

Imatinib

The platelet derived growth factor (PDGF) signaling pathway is thought to play a causative role in the pathogenesis of PAH.[22,129] Imatinib mesylate, a tyrosine kinase inhibitor antagonizes the PDGF pathway and may prove to be efficacious in the treatment of PAH In a phase II investigation in those with PAH, imatinib was well tolerated and improved pulmonary vascular resistance and cardiac output, although there was no improvement in 6MWD. An additional study evaluating the long term safety and efficacy of imatinib in PAH is ongoing (NCT01117987).

Riociguat

The favorable effects of nitric oxide are mediated through soluble guanylate cyclase (sGC) and the 2nd messenger cGMP.[11] Currently targeted by the PDE5 inhibitors, another potential approach to augmenting the nitric oxide pathway is through direct stimulation of sGC. Riociguat, the first of a new class of medication, activates sGC independently of nitric oxide.[130] In a phase II study in those with PAH or CTEPH, riociguat was well tolerated and demonstrated improvements in 6MWD and hemodynamics.[131] Phase III trials are currently ongoing (NCT00863681, NCT00810693).

DISEASE PROGRESSION AND MONITORING RESPONSE TO TREATMENT

Once the patient has been diagnosed with pulmonary hypertension and initiated on PAH specific therapy the goal of subsequent visits, set at 3-6 month intervals depending on the severity of disease, is to monitor response to therapy. A general assessment of the patient will elicit whether the patient has improved symptomatically or in activities of daily living. Metrics of interest include functional class, 6MWD, physical exam, and right heart function. Evaluating objective endpoints including exercise capacity, serum biomarkers and right heart function after initiating therapy may also be helpful.[132]

The six-minute walk test is a simple, easy to perform evaluation that is a measure of exercise capacity and correlates with peak aerobic capacity.[133] It is a common primary endpoint in clinical trials and is an accepted marker for therapeutic response by regulatory agencies. The six-minute walk test offers prognostic information as it is an independent predictor of death in idiopathic PAH.[134] However reproducibility of the 6MWD can vary depending on the underlying disease state of the patient population being studied.[135-137] Evaluation of non-invasive biomarkers can help determine response to therapy. Natriuretic peptides (BNP and NT-proBNP) are associated with right ventricular dysfunction in PAH.[138,139]

Rather than interpreting individual endpoints to assess response to therapy, evaluating a composite endpoint may be beneficial. The AIR study[80] evaluated inhaled iloprost and utilized a novel composite endpoint to determine response to therapy. In order to meet the primary

endpoint study subjects had to increase 6MWD by 10% and improve WHO FC by one class in the absence of clinical deterioration or death at any point. In another study, the concept of goal-oriented treatment was evaluated by Hoeper et al.[140] in 123 patients with WHO class III or IV PAH that were followed for 3 years. Subjects that did not reach treatment goals while on monotherapy received combination therapy according to a pre-defined strategy. Statistically significant improvement in survival was noted in patients who met the pre-established treatment goals of 6MWD > 380m, peak VO_2 >10.4ml/min./kg while maintaining a systolic blood pressure >120 mmHg when compared to historical controls. Although at this time exercise testing is not commonly performed, this study has established the benefit of using goal-directed treatment goals.

There is a paradox in defining severity of PAH hemodynamically by mPAP. Responses to pharmacologic therapy may elicit improvements in exercise capacity but do not always translate into a meaningful reduction in pulmonary artery pressures. Seldom do patients entirely return to normal pulmonary arterial pressures despite improvement in symptoms, biomarkers, right heart function, 6MWD or WHO functional class. This may indicate that improvements and preservation of right heart function and cardiac output are likely the true goals of therapy, with improvements of exercise capacity as mere reflections of these hemodynamic changes. Patients treated with PAH specific therapy have improvements in specific echocardiographic and Doppler parameters.[141] We believe that following changes in right ventricular size and function in patients on therapy is a very useful parameter to trend progression of disease. A repeat right heart catheterization after diagnosis can be helpful in patients with a change in symptoms or an unexpected response to therapy. The authors do not make it a common practice to routinely re-evaluate hemodynamics with heart catheterization, though this can be physician and facility dependent.

MANAGEMENT: SURGICAL THERAPIES FOR PAH

While medical therapy, either general supportive care for non-group I PH and targeted vascular therapy for those with PAH, is the cornerstone of treatment, there are surgical therapies available for those with some forms of PH. Indeed, the only potential cure for PH is via a surgical procedure, as the currently available medical therapies only improve symptoms and do not reverse the underlying pathophysiologic process. The treatment of choice for patients with CTEPH is pulmonary endarterectomy, a procedure that can significantly ameliorate, if not cure, pulmonary vascular disease in selected patients. More generally applicable, patients with refractory or progressive PAH may be candidates for the salvage procedure of atrial septostomy or the curative process of lung transplantation.[142]

Pulmonary endarterectomy

CTEPH is the only cause of PH that is potentially curable; therefore the importance of recognizing and diagnosing this entity is paramount. Several recent reviews provide more in depth discussion of this topic.[143,144] Briefly, CTEPH is a long-term complication of pulmonary embolism; approximately 4% of patients experiencing a pulmonary embolism will subsequently develop CTEPH.[145] However, the majority of patients with CTEPH lack a history of venous thromboembolism. There are about 2500 new cases per year of CTEPH in the US, although the estimated number of unreported or unrecognized cases is likely much higher.[143] The pathophysiology of CTEPH is complex and poorly understood. Obstruction of the proximal pulmonary arteries by organized thromboembolic material and increased resistance to flow is likely the initial insult. Subsequently vascular remodeling occurs in both large and small pulmonary vessels, with intimal thickening, collagen deposition, and calcification. The small vessel arteriopathy seen in CTEPH is similar to that seen in idiopathic PAH and may reflect vascular remodeling in response to increased flow in those parts of the distal pulmonary arterial bed unobstructed by more proximal thrombotic material.[144]

Pulmonary endarterectomy (PEA) is a true endarterectomy that involves stripping the diseased intimal layer from the proximal pulmonary arteries; this procedure differs from embolectomy performed in some cases of acute pulmonary embolism. PEA is performed via median sternotomy on cardiopulmonary bypass with deep hypothermic arrest to minimize blood loss.[146] In most patients, RV afterload reduction by removal of obstructive material from the pulmonary vasculature will result in an immediate and significant decrease in pulmonary artery pressures.[146,147] While PEA is the treatment of choice for CTEPH, not all patients diagnosed with CTEPH are surgical candidates. The decision of whether PEA is feasible for specific patients must be made at a center with expertise in this procedure. General considerations include evidence of surgically accessible thrombi, degree of pulmonary vascular resistance as measured during right heart catheterization, and patient comorbidities.[148] In particular, an elevated pulmonary vascular resistance in the absence of substantial thromboembolic disease on pulmonary angiogram suggests a predominance of small vessel disease that will not benefit from surgical intervention. Unfortunately, there is as of yet no accepted preoperative classification system that reliably

defines operable versus non-operable CTEPH disease, reinforcing the recommendation that patients with CTEPH be evaluated at centers that have experience in this procedure.

In a recent publication from the University of California at San Diego Medical Center, the institution with the most experience with PEA, the overall mortality associated with the procedure was 4.7%, with most deaths attributable to residual pulmonary vascular disease and right heart failure.[146] This operative mortality rate has dropped significantly since PEA was first begun in the 1970s, likely due to improved operative technique; during this early period approximately 20% of patients did not survive the procedure.[147]

Patients who successfully undergo PEA have excellent long-term outcomes.[149-151] Most of the hemodynamic improvement associated with PEA occurs within the first 3 months, with reductions in PVR and improved cardiac output.[150,151] Reflective of the improved hemodynamics, functional class likewise improves. One group reports that contrary to the preoperative state, in which 97% of patients were functionally limited (WHO class III-IV), at 3 months this prevalence decreased to 12%.[150] At 4 years post-PEA, the same study group had excellent functional status, with 74% in WHO class I and none in class IV.[150] While there is marked improved in hemodynamics and physical stamina in the majority of patients, approximately 25% will have some degree of persistent PAH after PEA. These patients often require targeted PAH medical therapy, although recent publications do not indicate increased mortality in those with persistent PAH who survive the perioperative period. Freed and colleagues report that at 5 years after PEA, survival was 90% in both those with and without residual PAH.[151] Regardless of whether residual PAH is present, all patients who have CTEPH and undergo PEA must remain on lifelong anticoagulation.[146]

Transplant

Transplantation, either lung or heart/lung, is the final treatment option for those with PAH who are failing medical therapy. Most transplant centers now perform double-lung or combined heart-lung transplantation for PAH, due to the high incidence of reperfusion injury and worse outcomes with single lung transplantation.[142] The decision of whether to perform double lung or combined heart-lung transplantation for PAH is center specific, but, in general, heart-lung transplantation is performed when there is either significant impairment of cardiac function (inotrope dependence) or in the setting of complex congenital heart disease.[142,152] The International Society for Heart and Lung Transplantation (ISHLT) recommends that patients with PAH be referred for transplant evaluation if they have either WHO functional class III or IV disease, irrespective of ongoing therapy, or if they have rapidly progressive disease.[153] Overall PAH accounts for 3.5% of all lung transplants performed since 1990. Interestingly, the percentage of lung transplants performed for PAH is decreasing over time, with a prevalence of 12% in 1990 compared to 2% in 2008, likely a reflection of improved medical therapy.[154]

Lung organ allocation in the U.S. is currently dictated by the potential recipient's Lung Allocation Score (LAS), a metric devised and implemented by the Organ Procurement and Transplantation Network in 2005. The LAS attempts to equitably assign donor organs based transplant benefit; in particular, a complex calculation is performed that quantifies the urgency of transplant with expected transplant outcome (1 year post-transplant survival).[155] The goals of the LAS are to minimize wait list mortality while maximizing transplant benefit, ensuring efficient allocation of scarce donor organs. Some of the factors included in the LAS calculation include forced vital capacity, functional status, age, six-minute walk distance, serum creatinine, pulmonary artery systolic pressure, and pulmonary capillary wedge pressure.[155] While the goals of the LAS have in general been accomplished, with more transplants occurring in those with more severe disease and a concordant decrease in wait-list mortality, the beneficial effect of those with PAH awaiting transplant has been less clear.[156] Like other groups with lung disease, those with PAH have seen an increased rate of transplants occurring in those on the waitlist. However, unlike other subgroups, those with PAH have not experienced a decline in wait list mortality after implementation of the LAS system. (20% mortality at 12 months on wait list in LAS era, compared to 14% mortality at 12 months on the wait list in the pre-LAS era, p=0.19).[156] While the reasons for the failure of the LAS score to improve wait list mortality in PAH patients is uncertain, one potential explanation is the fact that patients with PAH are listed for double lung transplant; a simple scarcity of donor organs, which may favor those listed for single lung transplant, may account the observed findings. Another possibility is that the LAS does not accurately capture the mortality risk of those with PAH. Of all lung diseases, those patients with PAH have the lowest average LAS (denoting less priority for receiving donor organs).[155,156] The LAS score does not incorporate many of the hemodynamic parameters known to be associated with mortality in PAH, such as right atrial pressure or cardiac index.[157,158] Although successful in regards to lung transplantation as a whole, the LAS system appears to need further refinement to accurately assess mortality risk in those with PAH.

The outcomes of those with PAH who undergo lung transplantation are worse in the short term, but better in the long term, compared to all patients who undergo lung

transplantation. According to ISHLT data, which reflects both U.S. and international experience, overall survival for lung transplant recipients is 88% at 3 months and 78% at 1 year, with a median survival of 5.2 years. In comparison, patients with PAH have a 3-month survival rate of only 74% but a median survival of 8.6 years.

Atrial septostomy

Finally, as a palliating or bridging procedure, percutaneous balloon atrial septostomy (AS) decompresses the right ventricle via the creation of a right to left inter-atrial shunt, decreasing right heart filling pressures and improving cardiac output and systemic oxygen delivery at the expense of arterial oxygen saturation. Indications for AS include refractory right heart failure and/or recurrent syncope despite maximum medical therapy, including targeted PAH therapy, or as a bridging procedure while the patient is awaiting transplantation.[142] Despite its conceptual appeal, AS is rarely undertaken, with only approximately 300 procedures performed worldwide; furthermore, there is scant evidence upon which to inform patient care decisions, as most of the available medical literature consists of small case series.[159-161] Expert-based consensus guidelines define as contraindications to AS the following: a mean right atrial pressure > 20 mmHg, a resting arterial oxygen saturation of <90% on room air, or a left ventricular end diastolic pressure (LVEDP) of > 18 mmHg.[142] The expected response to AS is a decrease in mean right atrial pressure with an increase in cardiac output and systemic oxygen delivery. The procedural related mortality of AS ranges from 9-22%.[142,160,161] The most significant procedure-related complication is refractory hypoxemia; while all patients will have an expected reduction in arterial oxygen saturation with AS and require supplemental oxygen, 30-40% of patients can experience refractory hypoxemia.[160] Patients who undergo and survive AS have improved functional status, with most patients improving one WHO functional class.[160,161] Overall, AS may benefit those with progressive right heart failure despite available medical therapies, either as a palliative procedure or as a bridge to transplantation, but it should only be undertaken in centers experienced in the care of PH patients and with a clear understanding of the potential risks of the procedure.

PROGNOSIS

The prognosis of those with PH is dictated by both the etiology of the underlying disorder and the ability of the right ventricle to adapt to the elevated pulmonary vascular pressures. In an early description from the National Institutes of Health (NIH), the 3-year survival rate of those with idiopathic PAH was 48%.[162] In more recent American and French cohorts, 3-year survival rates have increased to 58-72%, likely due to treatment advances.[158,163] Across the spectrum of disorders causing PAH, those due to connective tissue diseases, particularly systemic sclerosis, have a worse prognosis than those with idiopathic PAH; in comparison, those with congenital heart disease related PAH have a better prognosis.[164] Within disease states that are complicated by PH, including left heart disease and chronic lung disease, the presence of PH is usually associated with a worse prognosis compared to disease of similar severity not complicated by PH.[165-167]

Despite the observed improvements in population survival, there is great heterogeneity in the outcomes of patients with PH, and clinicians should recognize the functional and hemodynamic characteristics that denote individual prognosis. The factors that impact survival and give insight into a patient's disease course are outlined below and in Table 5. Most of the available data come from studies in those with PAH; their applicability to those with other forms of PH is unknown. Limited functional status, as assessed via the New York Heart Association (NYHA) classification system, has long been correlated with worse outcomes.[158,162,163] Likewise, objective measures

Table 5: Factors associated with worse survival in PAH*

Indicator	NIH cohort (1991)[162]	French cohort (2010)[158]	American cohort (2010)[163]
Age	No	Yes (≥63 years)	Yes (>60 years, men only)
Functional Class (NYHA)	Yes (Class III-IV)	Yes (Class III-IV)	Yes (class III-IV)
Exercise Capacity (6MWD)	N/A	Yes (<250 m)	Yes (< 165 m)
Hemodynamics-mRAP	Yes (≥20 mmHg)	Yes	Yes (> 20 mmHg)
Hemodynamics- CI	Yes (< 2 L/min·m^2)	Yes	No
Hemodynamics-PVR	Yes	No	Yes (>32 Wood Units)
Pericardial effusion	N/A	N/A	Yes
Natriuretic Peptide	N/A	N/A	Yes (BNP>180 pg/mL)

*Clinical factors listed with cutpoints, if available. **6MWD:** six-minute walk distance; **BNP:** brain natiuretic peptide; **CI:** cardiac index; **mRAP:** mean right atrial pressure; **N/A:** not assessed in this particular study; **NIH:** National Institutes of Health; **NYHA:** New York Heart Association; **PAH:** pulmonary artery hypertension; **PVR:** pulmonary vascular resistance; **REVEAL:** Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management

of decreasing exercise tolerance, most commonly six-minute walk distance, have correlated with increased mortality.[57,158,163] Invasively measured hemodynamics allow quantification of right ventricle function and are powerful indicators of survival. In particular, measurements associated with a decompensated right ventricle, including elevated right atrial pressure and decreased cardiac index, are consistent markers of worsened outcomes.[58,59,158,162] Notably, the absolute level of pulmonary artery pressure is not a consistent indicator of prognosis, likely due to the eventual decrease in pulmonary pressure that occurs in association with a failing right ventricle.[24] Assessment of pulmonary vasodilator response is commonly performed via right heart catheterization in the evaluation of those with PH. Although the purpose of vasodilator testing was initially to determine suitability for treatment with calcium channel blockers, the results of vasodilator testing may also have prognostic value. Specifically, those with a positive vasodilator response, variably defined across studies, appear to have better survival compared to those who are not vasodilator responsive.[36,59,168,169] However, these studies are confounded by the fact that patients who displayed vasodilator response were often treated differently than those who did not display vasodilator response,[168,169] and not all studies have found an association between vasodilator response and outcome.[170] Therefore, the prognostic value of vasodilator response in the modern treatment era is uncertain. Echocardiography is a commonly used screening test in the evaluation of PH. While prognostic data from echocardiography are not as well validated compared to the information available from right heart catheterization, the presence of a pericardial effusion on echocardiography has consistently been associated with a shortened survival.[163,171,172] Finally, elevations in several biomarkers, including natiuretic peptides and cardiac troponins, have also been associated with worse prognosis in PAH.[163,173,174]

The above clinical factors yield a general impression of an individual's prognosis and may be sufficient for everyday practice. There are, however, several predictive equations that give a more precise estimate of a patient's probability of one year survival: the older NIH equation and the newer REVEAL formula.[162,163] The NIH equation, which incorporates only the hemodynamic parameters of mean pulmonary artery pressure, cardiac index, and mean right atrial pressure, was derived from a cohort of PAH patients in the era before widespread targeted PAH treatment and may not be applicable in the modern era. The REVEAL equation was derived in a modern cohort of American patients and incorporates multiple variables, including demographics, hemodynamics, and functional status. Both of these equations are computationally complex and are not easily performed at the bedside.

The improved survival in those with PAH over the past 2 decades is often attributed to improvements in medical therapy. However, improvements in mortality have not been well documented in the plethora of PAH therapeutic trials as the majority of clinical studies use surrogate endpoints, such as functional status or hospitalizations, rather than survival. Remarkably, only one trial, studying the use of IV epoprostenol, has shown a mortality benefit of targeted PAH therapy.[57] Longer term follow up of PAH patients treated with IV epoprostenol has also demonstrated survival benefit compared to historical controls, with 1- and 3-year survival rates of 88% and 63%, respectively, compared to expected survival rates of 59% and 35% (based on the NIH equation).[59] Likewise, non-controlled observational studies also suggest that other PAH therapies, including bosentan and treprostinil, improve survival.[66,175] More recently, a meta-analysis of major PAH trials (restricted to those trials with placebo controls) reported an aggregate 43% reduction in all-cause mortality with the currently available medical therapies (1.54% vs. 3.80% in the treatment and control arms, respectively, RR=0.57, p=0.023).[176] Like the aforementioned epoprostenol trial, all but one of the 21 trials included in this analysis enrolled patients with FC III-IV disease, and although the overall mortality rate appears low, the mean study duration was only 14 weeks.

CONCLUSIONS

While the survival of those with PAH has clearly improved over the past 20 years and is likely due to improvements in targeted medical therapy and overall supportive care, there is much research that yet needs to be done. The available literature is mostly limited to those with PAH and the impact of these targeted therapies on the more widely prevalent secondary forms of PH is uncertain. In addition, most study designs utilize surrogate outcomes rather than survival and are short in duration, neither of which are reflective of the outcome of most interest to patients and physicians or that reflect the long-term use of these medications in this chronic, incurable disease. Finally, most studies have assessed the impact of a single agent in comparison to placebo; head to head comparisons of available agents are still few in number and combination therapy, as commonly practiced, is not well defined by the current literature. Studies currently underway should help address these important questions.

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Source of Support: Nil, **Conflict of Interest:** None declared.