A review of therapeutic agents for the management of pulmonary arterial hypertension

Stella S Hahn, Mina Makaryus, Arunabh Talwar, Mangala Narasimhan and Gulrukh Zaidi

Abstract: Pulmonary arterial hypertension (PAH) is an uncommon, progressive and life threatening disease characterized by a proliferative vasculopathy of the small muscular pulmonary arterioles resulting in elevated pulmonary vascular resistance and eventually right ventricular failure. An increasing understanding of the pathobiology of PAH and its natural history has led to the development of numerous targeted therapies. Despite these advances there is significant progression of disease and the survival rate remains low. This article reviews the agents currently available for the medical management of PAH.

Keyword: pulmonary arterial hypertension, prostanoid, endothelin receptor antagonist, phosphodiesterase inhibitor, soluble guanylate cyclase stimulator

Introduction
Pulmonary arterial hypertension (PAH) is a proliferative vasculopathy affecting the small muscular arteries and arterioles characterized by endothelial and smooth muscle cell proliferation, medial hypertrophy, and thrombosis in situ of the small pulmonary arteries and arterioles. The World Health Organization (WHO) classified pulmonary hypertension (PH) into five groups based upon etiology and mechanism (Table 1). This review will focus on the therapeutic agents available for the management of group 1 PAH.

Presentation
Patients with PH have a varied spectrum of presentation. A small percentage of patients are asymptomatic on presentation, but may have exertional dyspnea, fatigue, weakness, or dizziness early in the disease process. With disease progression, dyspnea at rest, exertional angina, and palpitations may develop [Udeoji and Schwarz, 2013; McGoon et al. 2004].

Physical exam findings including an accentuated pulmonary component of the second heart sound, early systolic ejection click, a midsystolic ejection murmur, palpable parasternal lift, right ventricular S4 gallop, and a prominent jugular ‘a’ wave are often subtle, but when present can suggest the diagnosis [McGoon et al. 2004]. Signs of more advanced disease can include a diastolic murmur of pulmonary regurgitation and a holosystolic murmur of tricuspid regurgitation. With disease progression, findings indicative of right heart failure can be seen including distended jugular veins, hepatojugular reflex, a pulsatile liver, and peripheral edema. Cyanosis, if present, suggests right-to-left shunting, severely reduced cardiac output, or impairment in intrapulmonary gas transfer [McGoon et al. 2004]. Clubbing is a rare finding, and if present, congenital heart disease or pulmonary veno-occlusive disease should be considered [Holcomb et al. 2000].

Diagnostic testing

EKG
EKG findings can suggest a diagnosis of PH but is not sensitive enough to use as a screening test. Many patients with PH can have a normal EKG [Ahearn et al. 2002]. EKG findings can include right axis deviation, right ventricular (RV) hypertrophy, RV strain, right bundle branch block, or QTc prolongation [Rich et al. 1987; Galie et al. 2015b]. An abnormal EKG is more likely to be seen in severe disease and a normal EKG does not exclude PH [Galie et al. 2016].
Echocardiography
Echocardiography is essential for screening and initial noninvasive assessment of PH. This allows estimation of the pulmonary artery systolic pressure (PASP), assessment of the atrial and ventricular thickness, systolic and diastolic function, valve function, detection of pericardial effusions and intracardiac shunts [Rudski et al. 2010]. If estimated RVSP is greater than 40 mmHg, further evaluation is warranted if there are no other conditions that can cause elevated pressures, such as left heart disease or advanced lung disease, are present [McLaughlin et al. 2009].

Cardiac catheterization
Cardiac catheterization is an essential in the diagnosis of PH and should be performed prior

| Table 1. WHO classification of pulmonary hypertension. |
|------------------------------------------------------|
| **Group 1** Pulmonary arterial hypertension (PAH)    |
| Idiopathic                                           |
| Heritable                                            |
| Drug and toxin induced                               |
| Associated with:                                     |
| - Connective tissue diseases                         |
| - HIV infection                                      |
| - Portal hypertension                                |
| - Congenital heart disease                           |
| - Schistosomiasis                                    |
| Pulmonary veno-occlusive disease                     |
| Persistent pulmonary hypertension of the newborn     |

| **Group 2** Pulmonary hypertension due to left heart diseases |
|---------------------------------------------------------------|
| Systolic dysfunction                                          |
| Diastolic dysfunction                                         |
| Valvular disease                                              |
| Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies |

| **Group 3** Pulmonary hypertension due to lung diseases and/or hypoxemia |
|---------------------------------------------------------------|
| Chronic obstructive pulmonary disease                        |
| Interstitial lung disease                                     |
| Other pulmonary diseases with mixed obstructive/restrictive pattern |
| Sleep disordered breathing                                    |
| Alveolar hypoventilation                                      |
| Chronic exposure to high altitude                            |
| Developmental abnormalities                                   |

| **Group 4** Chronic thromboembolic pulmonary hypertension (CTEPH) |
|-------------------------------------------------------------|
| CTEPH                                                        |
| Other pulmonary artery obstructions:                        |
| - Angiosarcoma                                               |
| - Other intravascular tumors                                |
| - Arteritis                                                  |
| - Congenital pulmonary arteries stenosis                    |
| - Parasites [hydatidosis]                                   |

| **Group 5** Unclear multifactorial mechanisms               |
|-------------------------------------------------------------|
| Hematologic disorders                                       |
| - Myeloproliferative disorders                              |
| - Splenectomy                                                |
| - Chronic hemolytic anemia                                  |
| Systemic disorders                                          |
| - Sarcoidosis                                               |
| - Pulmonary Langerhans cell histiocytosis                   |
| - Lymphangioleiomyomatosis                                  |
| - Neurofibromatosis                                         |
| - Vasculitis                                                 |
| Metabolic disorders                                         |
| - Glycogen storage disease                                  |
| - Gaucher disease                                           |
| - Thyroid disorders                                         |
| Other                                                        |
| - Tumoral obstruction                                       |
| - Fibrosing mediastinitis                                   |
| - Chronic renal failure                                     |
to the initiation of PAH-specific therapy. A right heart catheterization provides direct measurements of right atrial pressures (RAP), pulmonary venous pressure [pulmonary artery wedge pressure (PAWP)], pulmonary blood flow. It also allows for calculation of mixed venous oxygen saturation and pulmonary vascular resistance (PVR) [McGoon et al. 2004].

On right heart catheterization, PAH is defined as a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest with a PAWP of 15 mmHg or less and a PVR greater than 3 Wood units [Hoeper et al. 2013]. Vasodilator testing should be performed in all patients with idiopathic PAH (IPAH) without contraindications to test the presence of pulmonary vasoreactivity for possible long-term calcium channel blocker (CCB) therapy. An acute responder is defined as a reduction in mPAP of at least 10 mmHg to an absolute mPAP of less than 40 mmHg without a decrease in cardiac output [McLaughlin et al. 2009]. At some centers vasoreactivity testing is only performed in patients with IPAH but many centers perform this on all WHO group 1 patients and treat accordingly [Taichman et al. 2014; Hunt et al. 2014].

**Assessment of severity**

Once a diagnosis of PAH is made, evaluation to determine the severity of disease should be performed to assess risk and to guide treatment. WHO functional class is a predictor of survival and can also be used during follow-up as an indicator of disease progression [Humbert et al. 2010; Galie et al. 2016]. The 6-minute walk distance (6MWD) is easy to perform and widely available, and correlates with functional class and survival in patients with PAH [Miyamoto et al. 2000]. Cardiopulmonary exercise testing (CPET) provides information on exercise capacity as well as on gas exchange and cardiac function during exercise [Galie et al. 2016]. Low peak VO2 and peak systolic blood pressure are strong predictors of impaired survival [Wensel et al. 2002]. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels correlate with myocardial dysfunction and is associated with prognosis [Galie et al. 2009b].

**General management**

Goals of therapy include improving quality of life and chances for survival. Patients should be counseled on appropriate diet and low-level aerobic exercise. Heavy physical exertion or isometric exercise should be avoided [McLaughlin et al. 2009]. Immunizations against influenza and pneumococcal pneumonia should be up to date. Nonessential surgery should be avoided and when necessary, should be performed at a PH center. Diuretics are indicated to manage RV volume overload [Taichman et al. 2014; Galie et al. 2016].

Oxygen supplementation should be considered for all patients with hypoxemia to maintain oxygen saturation above 90% at rest and, if possible, with exercise and sleep. High altitudes should be avoided as it may cause hypoxic vasoconstriction and compromise oxygen delivery [Roubinian et al. 2012].

Although controlled data is limited, a survival benefit has been noted in patients on anticoagulation with warfarin in observational studies [Frank et al. 1997]. The recommendation has been to titrate international normalized ratio (INR) to 1.5–2.5 [McLaughlin et al. 2009], however, other studies failed to show a significant survival advantage with warfarin use and the role of anticoagulation in all patients with PAH has been questioned [Preston et al. 2015; Roldan et al. 2016].

High-dose CCBs, most commonly nifedipine and diltiazem, may have sustained hemodynamic benefits in select patients with PAH. Acute vasodilator testing with CCB to identify potential responders may have severe side effects, therefore inhaled nitric oxide (NO) is used for this purpose. An acute responder to NO testing is defined above (see the section on cardiac catheterization). One study showed 10 out of 33 patients acutely had response to NO. Of these, nine patients subsequently had response to CCB and were initiated on long-term treatment with oral CCB. Sustained improvements in hemodynamics were observed in only six of these patients [Sitbon et al. 1998].

Although maternal mortality has significantly improved, pregnancy still remains a considerable risk [Weiss et al. 1998; Jais et al. 2012]. Current expert consensus recommends the use of effective contraception and avoidance of pregnancy. Bosentan may decrease the effectiveness of
hormonal contraception and should be used with caution. If pregnancy occurs, early termination is recommended, but if the patient elects to continue with pregnancy, the patient should be treated at a PH center. Bosentan, ambrisentan, macitentan, and riociguat are category X drugs and are contraindicated in pregnancy. Dual contraceptives should be used by patients of childbearing age who are taking these medications [Taichman et al. 2014].

Specific management

Pathobiologic basis for therapy
An imbalance between vasoconstriction and vasodilation, thrombosis, cell proliferation, and remodeling of the pulmonary arterial walls contribute to PAH. The discovery of three main pathobiologic pathways (NO, endothelin, and prostacyclin) have revolutionized the approach to the treatment of PAH, allowing the development of effective therapies which will be reviewed.

Prostacyclin and thromboxane A2
The endothelium metabolizes arachidonic acids to produce prostacyclin and thromboxane A2. Prostacyclin acts as a potent vasodilator, has anti-proliferative properties and inhibits platelet activation. The IP receptor is the main target of prostacyclin and is expressed in the vascular smooth muscle cell layer found in the pulmonary vasculature. Once activated, conversion of ATP to cyclic AMP (cAMP) results thereby increasing protein kinase A (PKA) activity subsequently leading to vasodilation [Humbert and Ghofrani, 2016]. Thromboxane A2 is a potent vasoconstrictor and platelet agonist [Gerber et al. 1980]. In PAH, the imbalance between prostacyclin and thromboxane A2 is shifted toward the latter and the production of prostacyclin synthase is decreased in the small and medium-sized pulmonary arteries [Christman et al. 1992; Tuder et al. 1999]. Prostanoids are synthetic analogues of prostacyclin that act as a substitution for the decreased endogenous prostacyclin in patients with PAH [Humbert and Ghofrani, 2016]. Table 2 reviews the major trials of prostanoids that are discussed in detail in the following section.

Prostanoids.
Epoprostenol. Epoprostenol is an intravenous prostanoid administered via continuous infusion. It is started at a low dose and titrated up based on symptoms and side effects of the drug as determined by a physician expert in PAH.

A 12-week, prospective, multicenter, randomized, controlled, open-label trial in 81 patients with New York Heart Association (NYHA) functional class III or IV, showed significant improvement in the primary endpoint of 6MWD in patients with epoprostenol (362 m at week 12 versus 315 m at baseline) compared with conventional therapy alone (204 m at week 12 versus 270 m at baseline). Improvements in secondary endpoints, including hemodynamics and quality of life, were also seen. A survival benefit was noted in patients receiving epoprostenol ($p = 0.003$). This was the only randomized control trial in PAH in which a survival advantage was seen; however, the study was small and not blinded [Barst et al. 1996].

In a 12-week, multicenter, open-label, randomized study in 111 patients with scleroderma spectrum of disease, exercise capacity, the primary outcome, improved in the epoprostenol group (316 m versus 270 m at baseline), but decreased in the conventional therapy group (192 m versus 240 m at baseline). Improvements in hemodynamics ($p < 0.001$) and WHO functional class were observed, but no survival benefit was seen [Badesch et al. 2000].

Common side effects include headache, jaw pain, flushing, nausea, diarrhea, skin rash, and musculoskeletal pain. Chronic overdose can result in high cardiac output failure. Catheter-related bloodstream infections are well-documented risks of therapy. Guidelines were published on prevention of central venous catheter-related blood stream infections while on prostanoid therapy [Doran et al. 2008; Rich and McLaughlin, 1999; Barst et al. 1996].

Treprostinil. Treprostinil, an analogue of prostacyclin sharing similar pharmacological actions to epoprostenol, is chemically stable with an elimination half-life of about 4.5 hours compared with 6 minutes for epoprostenol. It was first evaluated using subcutaneous administration in a 12-week, placebo-controlled, multicenter, randomized trial of 470 patients with NYHA functional class II, III, or IV PAH. A dose-related median difference in the primary endpoint of 6MWD of 16 m was seen between the treprostinil and placebo groups. Most common adverse effects included pain or injection site reaction, as well as headache, diarrhea, rash, and nausea [Simonneau et al. 2002].
Table 2. Major trials for prostanoids.

| Authors            | Study                                                                 | Study Size | Duration | Primary Endpoint | Secondary Endpoints                                                                 |
|--------------------|----------------------------------------------------------------------|------------|----------|------------------|-------------------------------------------------------------------------------------|
|                    | **Epoprostenol**                                                      |            |          |                  |                                                                                     |
| Barst et al. [1996]| A Comparison of Continuous Intravenous Epoprostenol (Prostacyclin) with Conventional Therapy for Primary Pulmonary Hypertension | 81         | 12 weeks | 6MWD             | QoL, hemodynamics, survival                                                           |
| Badesch et al. [2000]| Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial | 111        | 12 weeks | 6MWD             | Hemodynamic, signs and symptoms of PH and scleroderma, survival                      |
|                    | **Treprostinil**                                                      |            |          |                  |                                                                                     |
| Simonneau et al. [2002]| Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial | 470        | 12 weeks | 6MWD             | Principal efficacy endpoints: Signs and symptoms of PH, Dyspnea Fatigue Rating, Number of deaths, lung transplantations or discontinuations for clinical deterioration. Borg Dyspnea Scale, Hemodynamics, Minnesota Living with Heart Failure Questionnaire     |
| Tapson et al. [2006]| Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial | 16         | 12 weeks | 6MWD             | Naughton–Balke treadmill time, Borg dyspnea score, hemodynamics                     |
| McLaughlin et al. [2010]| Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial | 235        | 12 weeks | 6MWD             | Time to clinical worsening, Borg Dyspnea Score, NYHA functional class, 12-week trough 6MWD, 6-week peak 6MWD, quality of life, PAH signs and symptoms |
| Tapson et al. [2012]| Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial | 350        | 16 weeks | 6MWD             | Time to clinical worsening, clinical deterioration, combined ranking of 6MWD and Borg dyspnea score, Dyspnea-fatigue index score |
| Tapson et al. [2013]| Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial | 310        | 16 weeks | 6MWD             | Clinical worsening, Borg dyspnea score, combined walk distance and Borg score, NT-proBNP, WHO functional classification, the Cambridge Pulmonary Hypertension Outcome Review, signs and symptoms of PAH, and safety |
| Jing et al. [2013]| Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial | 349        | 12 weeks | 6MWD             | Trough 6MWD, Time to clinical worsening, combined 6MWD and Borg, WHO functional class, Dyspnea-fatigue index, symptoms of PAH, 6MWD at week 4 and 8 |
|                    | **Iloprost**                                                          |            |          |                  |                                                                                     |
| Olschewski et al. [2002]| Inhaled iloprost for severe pulmonary hypertension                   | 203        | 12 weeks | increase in 6MWD by at least 10% and improvement in NYHA functional class | 6MWD, NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, QoL, clinical deterioration, death, need for transplantation |
| Hoeppl et al. [2000]| Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue | 24         | 12 months|                  | 6MWD, hemodynamics                                                                   |
|                    | **Selexipag**                                                         |            |          |                  |                                                                                     |
| Simonneau et al. [2012]| Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension | 43         | 17 weeks | PVR              | Additional hemodynamics, 6MWD, aggravation of PAH, Borg dyspnea score, WHO functional class, NT-proBNP |
| Sitbon et al. [2015]| Selexipag for the Treatment of Pulmonary Arterial Hypertension       | 1156       | 36 months|                  | 6MWD, WHO functional class, death or hospitalization                                  |

6MWD, 6-minute walk distance; IV, intravenous; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; WHO, World Health Organization.
Subcutaneous treprostinil was approved by the FDA in 2002 for use in functional class II, III, and IV PAH [McLaughlin et al. 2009].

A subsequent study evaluating the bioequivalency and pharmacokinetics of intravenously administered treprostinil showed comparative results [Laliberte et al. 2004]. In 2004, intravenous treprostinil was approved by the FDA for use in functional class II, III and IV PAH patients not tolerating subcutaneous infusion [McLaughlin et al. 2009].

Intravenous treprostinil as monotherapy was studied in 16 patients (14 in WHO functional class III, 2 in WHO functional class IV) in a 12-week, open-label, multicenter trial. An improvement of 82 m in the primary efficacy endpoint of 6MWD was seen in 14 patients (13 in WHO functional class III, 1 in WHO functional class IV) who completed the study [Tapson et al. 2006]. The side-effect profile of intravenous treprostinil is similar to epoprostenol. There has been a reported increase in incidence of bloodstream infections, particularly with Gram-negative organisms, in patients receiving intravenous treprostinil. The overall infection rate was higher with intravenous treprostinil as compared to epoprostenol [Doran et al. 2008].

TRIUMPH evaluated the efficacy and safety of inhaled treprostinil in patients with PAH receiving therapy with either bosentan or sildenafil. 235 patients with NYHA functional class III or IV and 6MWD of 200 to 250 m while on treatment with bosentan or sildenafil were randomized to inhaled treprostinil or inhaled placebo four times daily. Treatment was safe and well-tolerated and significant improvements in the primary endpoint of 6MWD as well as quality of life measures were seen [McLaughlin et al. 2010].

The FREEDOM-C Study was a 16-week, multicenter, double-blind, placebo-controlled trial in 350 patients with stable PAH on background ETRA, PDE-5 inhibitor, or both randomized to placebo or oral treprostinil. Initial dosing was 1 mg twice daily with increases of 1 mg increments but due to tolerability issues, doses of 0.5 and 0.25 mg were made available later in the study. There was no statistically significant difference in the primary endpoint of 6MWD, but results suggested there may be a dose-related response. In addition, high discontinuation rates suggested a lower dose may be better tolerated [Tapson et al. 2012].

FREEDOM-C2 was a 16-week, multicenter, randomized, double-blind, placebo-controlled trial in which 310 patients on background ETRA, PDE-5 inhibitor, or both were randomized to oral treprostinil or placebo. Dosing was initiated at 0.25 mg bid with escalation of dosing by 0.25 mg bid every 3 days if clinically indicated. No statistically significant changes were seen in the primary endpoint of 6MWD or secondary endpoints [Tapson et al. 2013].

FREEDOM-M [Jing et al. 2013], a 12-week, randomized, double-blind, placebo-controlled trial, studied the effect of oral treprostinil in 349 treatment-naïve PAH patients. Dosing was originally initiated at 1 mg bid, but due to tolerability issues noted in FREEDOM-C [Tapson et al. 2012], the study protocol was amended to lower the starting dose to 0.5 mg and later 0.25 mg bid. The 6MWD was improved making oral treprostinil the first oral prostacyclin analogue meeting the primary endpoint in a randomized, controlled trial. Most common adverse effects of oral treprostinil included headache, nausea, diarrhea, jaw pain, and vomiting [Jing et al. 2013].

Illoprost. Illoprost is a stable analogue of prostacyclin delivered by an adaptive aerosol device. Inhaled illoprost was studied in a 12-week, multicenter, placebo-controlled, randomized trial of 203 functional class III and IV patients with either IPAH, PAH associated with scleroderma spectrum of diseases or appetite suppressants, or PH related to inoperable chronic thromboembolic disease. The combined primary endpoint of improvement in functional class by at least 1 level and improvement in 6MWD by at least 10% in the absence of clinical deterioration was met by 16.8% of those receiving inhaled illoprost compared with 4.9% receiving placebo. There was a mean increase of 36 m in the overall population in favor of illoprost [Olschewski et al. 2002]. An observational study evaluating 24 IPAH patients treated with illoprost showed there was a sustained benefit in exercise capacity and hemodynamics at 1 year [Hoepner et al. 2000]. Common side effects of inhaled illoprost include cough, headache, flushing, and jaw pain. Iloprost was approved by the FDA in 2004 for functional class III and IV PAH [McLaughlin et al. 2009].

Selexipag. Selexipag, an oral, selective prostacyclin receptor agonist, was evaluated in a proof-of-concept, phase II, randomized, double-blind, placebo-controlled trial of 43 patients which
showed a decrease in mean PVR at 17 weeks [Simonneau et al. 2012]. Subsequently, GRIPHON, a phase III, event-driven, randomized, double-blind, placebo controlled trial, enrolled 1156 patients with WHO functional class II or III. A primary endpoint event (death or complication of PAH) occurred in 347 patients (41.6% in placebo group, 27% in selexipag group). Patients on selexipag had reduction in hospitalizations and disease progression, but mortality benefits were not seen [Sitbon et al. 2015]. It was approved by the FDA for treatment of PAH in December 2015.

**Endothelin-1**

Endothelin-1 (ET-1) exerts its effects by binding to two distinct receptor isoforms in pulmonary vascular smooth muscle cells: endothelin receptor type A (ET\(_A\)) and B (ET\(_B\)) [Davie et al. 2002]. Both ET\(_A\) and ET\(_B\) receptors facilitate vasoconstriction and proliferation of vascular smooth muscle cells. In addition to expression in vascular smooth muscle cells, ET\(_B\) is also found in endothelial cells, fibroblasts, and neuronal cells [Boss et al. 2016]. ET\(_B\) has a dual role and mediates vasodilation via NO, as well as facilitate the clearance of endothelin [Giaid et al. 1993; Benigni and Remuzzi, 1999]. Under normal physiologic conditions, the predominant effect of ET-1 is vasodilation via ET\(_B\) receptors. In PAH, there is a shift in ET-1 activity due to unclear mechanisms and induces potent vasoconstriction and cell proliferation [Aversa et al. 2015]. ET-1 is a smooth muscle mitogen that contributes to the development of PAH [Stelzner et al. 1992]. Endothelin receptor antagonists (ETRA) attempt to reverse the vasoconstriction that occurs in PAH. Both selective and nonselective antagonists are available. Selective antagonism of the ET\(_A\) receptor has greater benefit in PAH than mixed or selective ET\(_B\) antagonism due to the potential vasoconstriction that can result from blockade of the ET\(_B\) receptor [Davenport et al. 2016]. Table 3 reviews the major trials of ETRA that are discussed.

**Endothelin Receptor Antagonists (ETRA)**

**Bosentan.** Bosentan is an orally active dual ETRA that competitively binds the ET\(_A\) receptor with 20 times greater affinity than the ET\(_B\) receptor. It has been shown to improve exercise capacity, hemodynamics, and slow the clinical progression of disease [Davie et al. 2002]. It was initially evaluated in a double-blind, placebo-controlled study of 32 patients with WHO functional class III or IV disease due to IPAH or PAH associated with systemic sclerosis. After 12 weeks of treatment, bosentan improved all endpoints studied including 6MWD, PVR, Borg dyspnea index, and WHO functional class.

A second double-blind, randomized, placebo-controlled trial across 27 centers evaluated 213 patients with severe WHO functional class III or IV PAH, despite general treatment. After 16 weeks of treatment, the primary endpoint of 6MWD was increased by 36 m in the bosentan group *versus* a deterioration of 8 m in the placebo group. Both 125 mg twice daily and 250 mg daily dosing showed a significant treatment effect, though the placebo-corrected improvement was more pronounced for the higher dosing (54 m *versus* 35m). There was no dose response relation for efficacy [Rubin et al. 2002].

The efficacy and safety of adding bosentan in those already receiving stable doses of either inhaled iloprost or oral beraprost was studied in 20 patients. Results showed improvement in 6MWD as well as increases in maximum work rate, VO\(_2\) max, anaerobic threshold, oxygen pulse, and peak systolic blood pressure during maximal exercise on CPET. The therapy was tolerated well, though elevations in liver enzymes were observed in two patients, one was transient and the other was related to alcohol intake. INR decreased in 17 of 20 patients requiring dose adjustments of anticoagulants [Hoepner et al. 2003]. Subsequently, the COMBI study evaluated the efficacy and safety of combination therapy of bosentan and aerosolized iloprost in 40 patients with IPAH. The trial terminated early after interim analysis revealed a low-likelihood of reaching the primary end-point of 6MWD [Hoepner et al. 2006].

BREATHE-2 evaluated the efficacy and safety of the combination of bosentan with epoprostenol. A total of 33 patients with severe primary PAH or PAH related to connective tissue disease with NYHA functional classes III or IV received epoprostenol therapy (2 ng/kg/min) and 2 days later were randomized to receive bosentan or placebo. Another 2 days later the epoprostenol dose was increased to 4 ng/kg/min. Both groups showed improvement in total pulmonary resistance, the primary outcome, as well as all other hemodynamic variables, and the trend was higher in the combination group but did not reach statistical significance [Humbert et al. 2004].
Table 3. Major trials for endothelin receptor antagonists.

| Authors                  | Study                                                                 | Study Size | Duration | Primary Endpoint | Secondary Endpoints                                                                 |
|--------------------------|-----------------------------------------------------------------------|------------|-----------|------------------|-------------------------------------------------------------------------------------|
| **Bosentan**             |                                                                       |            |           |                  |                                                                                     |
| Rubin et al. [2002]      | Bosentan therapy for pulmonary arterial hypertension                   | 213        | 16 weeks  | 6MWD             | Borg dyspnea index, WHO functional class, time to clinical worsening                  |
| Humbert et al. [2004]    | Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2 | 33         | 16 weeks  | Total pulmonary resistance | Hemodynamics, 6MWD, Dyspnea-fatigue rating, NYHA functional class                     |
| Galie et al. [2006]      | Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study | 54         | 16 weeks  | Change in SpO₂   | Hemodynamics, 6MWD, WHO functional class                                             |
| Galie et al. [2008b]     | Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial | 185        | 6 months  | PVR, 6MWD        | Time to clinical worsening, WHO functional class, Borg dyspnea index, hemodynamics   |
| McLaughlin et al. [2015] | Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension | 334        | 16 weeks  | Composite of first morbidity/mortality event | 6MWD, functional class, NT-proBNP, all-cause death                                   |
| **Ambrisentan**          |                                                                       |            |           |                  |                                                                                     |
| Galie et al. [2008a]     | Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy [ARIES] study 1 and 2 | Aries-1 202, Aries-2 192 | 12 weeks | 6MWD             | Time to clinical worsening, WHO functional class, QoL, Borg dyspnea score, NT-proBNP |
| **Macitentan**           |                                                                       |            |           |                  |                                                                                     |
| Pulido et al. [2013]     | Macitentan and morbidity and mortality in pulmonary arterial hypertension | 742        | Event driven [median 115 weeks] | Composite of time to clinical worsening and death from all causes | 6MWD, WHO functional class, death or hospitalization from PAH                      |

6MWD, 6-minute walk distance; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; WHO, World Health Organization.
BREATHE-5, a 16-week, multicenter, randomized, double-blind, placebo-controlled study in 54 patients with WHO functional class III Eisenmenger syndrome randomized in a 2:1 fashion to bosentan or placebo. Primary safety endpoint was systemic pulse oximetry and primary efficacy endpoint was PVR. Bosentan did not worsen oxygen saturation, and compared to placebo, reduced the pulmonary vascular index \((-472 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5})\), decreased the mPAP \((-5.5 \text{ mmHg})\), and increased 6MWD \((53.1 \text{ m})[\text{Galie et al. 2006}].

The EARLY study was a prospective, randomized, double-blind, multicenter trial evaluating 185 patients with WHO functional class II PAH. Primary endpoints were change in PVR and 6MWD at month 6. The mean PVR was 83.2% [95% confidence interval (CI) 73.8–93.7%] of the baseline value in the bosentan group and 107.5% (95% CI 97.6–118.4%) in the placebo group. The mean 6MWD increased in the bosentan group by 11.2 m (95% CI −4.6 to 27 m) and decreased in the placebo group by −7.9 m (95% CI −24.3 to 8.5 m) but did not achieve statistical significance. There was a delay in time to clinical worsening with bosentan compared with placebo, and treatment was associated with lower incidence of worsening functional class [Galie et al. 2008b].

COMPASS-2 was a prospective, double-blind, event-driven trial evaluating 334 symptomatic PAH patients receiving stable sildenafil for greater than 3 months randomized to placebo and bosentan. The study did not demonstrate adding bosentan to stable sildenafil therapy was superior to sildenafil monotherapy in delaying the time to first morbidity/mortality event, the composite primary endpoint [McLaughlin et al. 2015].

Bosentan can potentially be hepatotoxic, and the FDA requires liver function tests be checked monthly in addition to hematocrit checks every 3 months for anemia. Abnormal hepatic function was more frequently reported in the high-dosage bosentan group [Rubin et al. 2002]. Other side effects include the development of edema, syncope, and flushing [McLaughlin et al. 2009].

ETRA as a class may cause testicular atrophy and male infertility, and male patients should be counseled prior to starting these drugs.

Ambrisentan. Ambrisentan is a selective antagonist that competitively binds the ET\(_A\) receptor with 260 times more affinity than the ET\(_B\) receptor, with a bioavailability and half-life that allows for a once-daily oral regimen. ARIES-1 and ARIES-2 were concurrent, double-blind, placebo-controlled studies that evaluated ambrisentan in 202 patients and 192 patients with PAH, respectively. Patients in all WHO functional classes, majority in functional class II (38%) or III (58%), were randomized to receive placebo or ambrisentan orally once daily for 12 weeks. The primary outcome measure, 6MWD, improved from baseline with ambrisentan at each dose group at the end of 12 weeks. ARIES-1 showed an improvement in 6MWD in both 5 and 10 mg groups by 31 and 51 m, respectively, as compared with placebo. ARIES-2 showed improvement in 6MWD in the 2.5 and 5 mg groups by 32 and 59 m, respectively, as compared with placebo.

Both ARIES-1 and ARIES-2 showed improvements in time to clinical worsening but only ARIES-2 showed statistical significance. There was a statistically significant improvement in time to clinical worsening for the combined 5 mg groups compared with combined placebo groups from both studies. Both studies showed improvement in WHO functional class, but did not achieve statistical significance in ARIES-2.

Peripheral edema, headache, and nasal congestion were more common in the ambrisentan groups. No clinically significant elevation in serum aminotransferase was noted, and the mean alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase did not increase from baseline. No clinically significant changes in prothrombin time, INR, or oral anticoagulant dose were observed. A decrease in mean hemoglobin concentration by −0.84 (± 1.2) g/dl was noted in patients on ambrisentan compared with placebo 0.2 (± 1.0) g/dl, so periodic hemoglobin measurements may be required [Galie et al. 2008a].

Macitentan. Macitentan is a dual ETRA developed by modifying the structure of bosentan to increase efficacy and safety [Bolli et al. 2012]. Though it is classified as a mixed antagonist, macitentan tends to be more selective for the \(\text{ET}_A\) receptor [Davenport et al. 2016]. The SERAPHIN study was a multicenter, double-blind, randomized, placebo-controlled, phase III trial designed to evaluate morbidity and mortality with macitentan. A total of 742 patients were randomly assigned to receive placebo,
macitentan 3 or 10 mg. The composite primary endpoint was the time from the initiation of treatment to the first event related to PAH or death from any cause. A total of 287 patients had a primary endpoint event over median treatment period of 115 weeks: placebo (46.4%), macitentan 3 mg (38%), and macitentan 10 mg (31.4%). Worsening of PAH was the most frequent primary endpoint. The hazard ratio (HR) for the primary endpoint with the macitentan 3 mg dose versus placebo was 0.70 (97.5% CI 0.52–0.96; \( p = 0.01 \)), and with the 10 mg dose versus placebo was 0.55 (97.5% CI 0.39–0.76; \( p < 0.001 \)). At 6 months, the placebo group had a decrease in 6MWD by 9.4 m versus an increase in both macitentan 3 and 10 mg groups, 7.4 and 12.5 m, respectively.

The incidence of peripheral edema and of alanine aminotransferase or aspartate aminotransferase levels more than three times the upper limit of normal were similar across all three groups. Higher percentage of patients in both macitentan groups had nasopharyngitis, headache, and anemia [Pulido et al. 2013].

NO

The NO–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) signal-transduction pathway plays an important role in the regulation of pulmonary vascular tone and resistance in PAH [Lang et al. 2012]. Endogenous NO, a potent pulmonary vasodilator, is produced from L-arginine in endothelial cells by endothelial nitric oxide synthase (eNOs). It is also an inhibitor of platelet activation and vascular smooth-muscle cell proliferation and has been shown to play a major role in the pathobiology of IPAH. Reduced levels of eNOs have been seen in the pulmonary vascular tissue of PH patients, particularly those with IPAH [Giaid and Saleh, 1995; McQuillan et al. 1994]. However, in IPAH cases with plexiform lesions eNOs is increased and probably promotes pulmonary endothelial-cell proliferation [Mason et al. 1998]. The enzyme phosphodiesterase type 5 (PDE5) is the predominant phosphodiesterase isoform in the lung that metabolizes cGMP. By selectively inhibiting this enzyme, the PDE5 inhibitors cause an accumulation of intracellular cGMP, resulting in enhanced NO-mediated vasodilation as well as antiproliferative effects on pulmonary vascular smooth muscle cells. Soluble guanylate cyclase stimulators are a newer class of medication that have a dual mode of action. It stimulates sGC directly and increases the enzyme’s activity independently of NO, while also increasing sensitivity to levels of NO [Grimminger et al. 2009]. Tables 4 and 5 review the major trials of PDE5 inhibitors and the soluble guanylate cyclase stimulator that are discussed below.

**Phosphodiesterase type 5 inhibitors**

**Sildenafil.** Sildenafil was approved for PAH by the FDA in 2005. The first randomized, placebo-controlled, double-blind crossover study evaluating the efficacy of sildenafil in PAH was in 2004 [Sastry et al. 2004]. A total of 22 patients with WHO functional class II or III were evaluated after 6 weeks of placebo or sildenafil (dose range 25–100 mg three times daily). Patients were then crossed over to alternate therapy and evaluated after another 6 weeks of treatment. Exercise time was found to have significantly increased by 44% from 475 ± 168 s at the end of placebo phase to 686 ± 224 s at the end of sildenafil phase (\( p < 0.0001 \)). Cardiac index also improved from 2.8 ± 0.9 to 3.45 ± 1.1 l/m² (\( p < 0.0001 \)). PASP as measured by transthoracic echocardiography decreased from 105 ± 17 to 98 ± 24 mmHg, but was not statistically significant (\( p = 0.09 \)).

The SUPER study, a 12-week, double-blind, placebo-controlled trial evaluated 278 patients with symptomatic PAH associated with connective tissue disease were randomized to receive placebo or sildenafil (20, 40, or 80 mg) orally three times daily [Galie et al. 2005]. The primary endpoint of placebo-corrected change from baseline in 6MWD improved by 45, 46, and 50 m in the 20, 40, and 80 mg groups, respectively. The mPAP and PVR also significantly decreased and cardiac index significantly increased in the sildenafil groups. In a post hoc subgroup analysis of the 84 patients with PAH due to connective tissue disease, sildenafil-treated patients had mean increases in 6MWD at week 12 while placebo-treated patients had a mean decrease [Badesch et al. 2007].

The SERAPH study compared the addition of sildenafil to conventional therapy versus bosentan, the standard practice at the time of the study. A total of 26 patients were randomized in a double-blind fashion to receive either drug in incrementally higher doses over a period of 16 weeks. Patients who received sildenafil showed a significant reduction in the primary efficacy measure of RV mass (\( p = 0.015 \)) but the change from
Table 4. Major studies for phosphodiesterase type 5 inhibitors.

| Authors          | Study                                                                 | Study Size | Duration | Primary Endpoint | Secondary Endpoints                                                                 |
|------------------|------------------------------------------------------------------------|------------|----------|------------------|--------------------------------------------------------------------------------------|
| **Sildenafil**    |                                                                        |            |          |                  |                                                                                      |
| Galie et al. [2005] | Sildenafil citrate therapy for pulmonary arterial hypertension         | 278        | 12 weeks | 6MWD             | mPAP, Borg dyspnea scale, WHO functional class, time to clinical worsening           |
| Badesch et al. [2007] | Sildenafil for pulmonary arterial hypertension associated with connective tissue disease | 278        | 12 weeks | 6MWD             | WHO functional class, hemodynamics                                                   |
| Wilkins et al. [2005] | Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study | 26         | 16 weeks | RV mass          | Hemodynamics, 6MWD, plasma BNP levels, QoL                                            |
| Simonneau et al. [2008] | Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial | 265       | 16 weeks | 6MWD             | Hemodynamics, time to clinical worsening, Borg dyspnea score, QoL                   |
| Simonneau et al. [2014] | Long-term sildenafil added to intravenous epoprostenol in patients with pulmonary arterial hypertension | 242       | 3 years  | 6MWD             | WHO functional class, survival status, hemodynamics                                   |
| **Tadalafil**    |                                                                        |            |          |                  |                                                                                      |
| Galie et al. [2009a] | Tadalafil therapy for pulmonary arterial hypertension                  | 406        | 16 weeks | 6MWD             | WHO functional class, time to clinical worsening, Borg dyspnea score, QoL           |
| Oudiz et al. [2012] | Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study | 294       | 52 weeks | 6MWD             | WHO functional class, time to clinical worsening, safety, death and survival         |
| Galie et al. [2015a] | Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension | 605       | mean 609 days | First event of clinical failure | NT-proBNP, 6MWD, WHO functional class, Borg dyspnea index |

6MWD, 6-minute walk distance; BNP, pro-brain natriuretic peptide; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; QoL, quality of life; RV, right ventricular; WHO, World Health Organization.
baseline was not significant in the bosentan group ($p = 0.172$). Similarly, changes in plasma brain natriuretic peptide (BNP) levels were significantly decreased in the sildenafil group ($p = 0.014$). Improvements in 6MWD and cardiac index were seen in both groups [Wilkins et al. 2005].

The safety and effectiveness of oral sildenafil in combination with inhaled iloprost was studied in a randomized, controlled, open-label trial in 30 patients with severe PH. All patients received inhaled NO and aerosolized iloprost and were then randomized to receive sildenafil 12.5 mg, sildenafil 50 mg, sildenafil 12.5 mg plus inhaled iloprost, or sildenafil 50 mg plus inhaled iloprost. Patients who received sildenafil 50 mg plus iloprost had a maximum change in pulmonary vasodilatory potency of $-44.2\%$ (95% CI $-49.5\%$ to $-38.8\%$) compared with $-14.1\%$ (95% CI $-19.1\%$ to $-9.2\%$) in response to NO. The study showed that oral sildenafil acts synergistically with inhaled iloprost to cause strong pulmonary vasodilation without serious adverse events [Ghofrani et al. 2002].

Sildenafil has also been used as an adjunct therapy in patients who experienced deterioration while receiving inhaled iloprost [Ghofrani et al. 2003]. A total of 73 patients had baseline 6MWD of $217 \pm 31$ m that improved to $305 \pm 28$ m within the first 3 months of iloprost therapy. When 6MWD subsequently declined, in 14 of these patients, to $256 \pm 30$ m after $18 \pm 4$ months of therapy, sildenafil was added. 6MWD increased to $346 \pm 26$ m after 3 months of combined therapy, an improvement that was sustained at 12 months.

The addition of sildenafil to bosentan monotherapy was evaluated in 82 patients with IPAH and PAH due to scleroderma experiencing bosentan failure due to worsening symptoms, decline in functional class, or drop in 6MWD by more than 30 m [Mathai et al. 2007]. After addition of sildenafil, functional class improved in 5 of 13 patients with IPAH versus 2 of 12 patients with PAH due to scleroderma. Also, patients with IPAH walked further. It is important to note that bosentan significantly decreases the plasma concentration of sildenafil in patients receiving combination therapy [Paul et al. 2005].

The PACES-1 study was a multinational, 16-week, randomized, placebo-controlled trial of 267 patients which showed that adding oral sildenafil to intravenous epoprostenol improved 6MWD, particularly in the group with baseline distances of 325 m or more, improved hemodynamics, and delayed time to clinical worsening [Simonneau et al. 2008]. Patients completing PACES-1 could receive sildenafil titrated to 80 mg three times daily, as tolerated, in an open-label extension study, PACES-2 [Simonneau et al. 2014]. 6MWD improved or was maintained in 59%, 44%, and 33% of patients at 1, 2, and 3 years, respectively. WHO FC improved or was maintained in 74%, 59%, and 46% of patients at 1, 2, and 3 years, respectively. A total of 66% of patients were known to be alive, 24% were known to have died, and 10% were lost to

### Table 5. Major studies for soluble guanylate cyclase stimulator.

| Authors          | Study                                                                 | Study Size | Duration | Primary Endpoint | Secondary Endpoints                                                                 |
|------------------|-----------------------------------------------------------------------|------------|----------|------------------|---------------------------------------------------------------------------------------|
| Riociguat        | Riociguat for the treatment of chronic thromboembolic pulmonary hypertension | 261        | 16 weeks | 6MWD             | PVR, NT-proBNP, WHO functional class, time to clinical worsening, Borg dyspnea score, QoL |
| Ghofrani et al.  | [2013]                                                                |            |          |                  |                                                                                        |
| Simonneau et al. | [2015]                                                                | 237        | 1 year   | Adverse events   | 6MWD, NT-proBNP, WHO functional class, time to clinical worsening, Borg dyspnea score, QoL |
| Galie et al.     | PATENT PLUS: a blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension | 18         | 12 weeks | Maximum change in supine SBP from baseline within 4 hours of dosing | Maximum standing SBP, supine and standing DBP, and supine and standing heart rate, safety |
|                  | [2015c]                                                               |            |          |                  |                                                                                        |

6MWD, 6-minute walk distance; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; QoL, quality of life; SBP, systolic blood pressure; WHO, World Health Organization.
follow up at 3 years. Patients with 6MWD less than 325 m in PACES-1 who did not improve in 6MWD during the initial 20 weeks of sildenafil treatment had poorer survival.

Common side effects include epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, and rhinitis. At higher doses, incidence of adverse reactions are greater including diarrhea, myalgia, retinal hemorrhage, and visual disturbances with sensitivity to light.

Tadalafil. Tadalafil is a PDE-5 inhibitor with once-daily dosing. The PHIRST study, a 16-week, double-blind, placebo-controlled trial of 405 patients with PAH who were either treatment-naïve or on background bosentan therapy were randomized to receive placebo or tadalafil at 2.5, 10, 20, or 40 mg. Only patients who received tadalafil 40 mg had a statistically significant increase in the primary outcome of 6MWD by 33 m (95% CI 15–50 m) with a greater increase in the bosentan-naïve group. Tadalafil also significantly improved the time to clinical worsening, health-related quality of life, without a statistically significant change in WHO functional class [Galie et al. 2009a].

PHIRST-2 evaluated the long-term safety and efficacy of tadalafil (20 or 40 mg) [Oudiz et al. 2012]. This 52-week, double-blind, uncontrolled, extension study showed improvements in 6MWD achieved in PHIRST were maintained for the duration of the study.

The AMBITION trial studied the effect of initial combination therapy with ambrisentan and tadalafil in 605 patients with WHO functional class II or III. The combination group received ambrisentan 10 mg and tadalafil 40 mg, the ambrisentan group received ambrisentan 10 mg and placebo, and the tadalafil group received 40 mg and placebo once daily. The primary endpoint in a time-to-event analysis was the first event of clinical failure, which was 50% lower among the initial combination therapy group than those who received monotherapy with either drug. Earlier trials compared the addition of a therapy with placebo in patients already receiving treatment and this trial supports that early combination therapy can be beneficial [Galie et al. 2015a].

The most common adverse effects were headaches, myalgia, and flushing. Several case reports have suggested the safety and efficacy of tadalafil use in conjunction with prostacyclins, such as treprostinil or epoprostenol, and other ETRA [Faruqi et al. 2010; Bendayan et al. 2008].

Soluble guanylate cyclase stimulator

Riociguat. Riociguat increases the level of cGMP resulting in vasorelaxation and is thought to prevent progression of vascular remodeling [Lang et al. 2012]. CHEST-1, a phase III, 16-week, double-blind, randomized, placebo-controlled study at 89 centers in 26 countries evaluated patients with inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy, with a 6MWD of 150–450 m, PVR more than 300 dyn·sec·cm⁻⁵, and a mPAP of at least 25 mmHg. A total of 261 patients, most in WHO functional class II or III, underwent randomization to receive riociguat or placebo. At week 16, the primary endpoint of 6MWD increased from baseline by a mean of 39 m in the riociguat group versus 6 m in the placebo group. PVR decreased by 226 dyn·sec·cm⁻⁵ in the riociguat group compared with an increase of 23 dyn·sec·cm⁻⁵ in the placebo group. Riociguat also showed improved mPAP, NT-proBNP levels, WHO functional class, and Borg dyspnea score. No significant difference in the incidence of clinical worsening events was noted between the riociguat and placebo groups [Ghofrani et al. 2013].

Ninety-eight percent of the patients who completed the study entered the long-term extension (LTE) study, CHEST-2, evaluating the long-term safety and efficacy. The study assignments were concealed for the first 8 weeks, and afterwards the treatment was open-label. The first 12 weeks of CHEST-2 showed further increase in 6MWD in the group that received riociguat in CHEST-1, with a mean increase of 63 ± 64 m over baseline with a favorable risk–benefit profile [Simonneau et al. 2015].

The most frequent serious adverse effects were right ventricular failure, syncope, and hemothysis. Drug-related serious adverse events included syncope and gastritis. Others included acute renal failure and hypotension.

Riociguat added to sildenafil. The PATENT PLUS, a randomized, double-blind, placebo-controller, multicenter study evaluated the safety and efficacy of riociguat added to sildenafil. Eighteen patients with symptomatic PAH on sildenafil 20 mg three times daily were randomized to placebo or riociguat...
for 12 weeks. Primary outcome was maximum change in supine systolic blood pressure (SBP) from baseline within 4 hours of dosing and secondary outcomes were maximum standing SBP, supine and standing diastolic blood pressure (DBP), supine and standing heart rate, and safety. There were no differences in primary and secondary outcomes between the riociguat and placebo groups. In the LTE study in which all patients received riociguat, all patients reported adverse effects and there were high rates of discontinuation due to hypotension. There were three (18%) deaths reported in the LTE but not considered drug related by the investigator. In conclusion, the addition of riociguat to sildenafil therapy provided no clear benefit with increased risk of adverse effects. Consequently, concomitant use of riociguat with PDE-5 inhibitors is contraindicated [Galie et al. 2015c].

Conclusion

PAH is a progressive and fatal disease if left untreated. Historically the treatment of PAH had been restricted by a limited number of therapeutic options. However, recent advances in our understanding of the pathophysiological and molecular mechanisms underlying PAH have led to the development of a large number of targeted pharmacologic therapies which improve hemodynamic measures, WHO functional class, and 6MWD. Avoiding a delay in diagnosis, referring early or collaborating care with specialized PAH centers, and instituting appropriately tailored drug therapy remain the top priorities for patient care. Furthermore, combination therapy focused on targeting the multiple pathways leading to PAH is being increasingly used and has led to an overall increase in PAH survival. As a result of this paradigm shift, studies are now evaluating morbidity and mortality as primary endpoints of treatment as opposed to just the 6MWD. Ongoing research with new outcome measures remains essential and continues to provide hope to both the physicians and the patients suffering from this debilitating disease.

Conflict of interest statement

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