Published in final edited form as:

Future Cardiol. 2013 May ; 9(3): . doi:10.2217/fca.13.6.

Pharmacologic treatments for pulmonary hypertension: exploring pharmacogenomics

Julio D Duarte^{*1,2}, Rebekah L Hanson¹, and Roberto F Machado^{2,3}

¹Department of Pharmacy Practice, University of Illinois at Chicago College of Pharmacy, Chicago, IL 60612, USA

²Institute for Personalized Respiratory Medicine, University of Illinois at Chicago, Chicago, IL 60612, USA

³Section of Pulmonary, Critical Care, Sleep & Allergy, University of Illinois at Chicago College of Medicine, Chicago, IL 60612, USA

Abstract

Pulmonary hypertension (PH) is a disease with multiple etiologies and is categorized into five broad groups. Of these groups, pulmonary arterial hypertension (PAH) is the most studied and, therefore, all of the currently available drug classes (prostacyclin analogs, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors) were developed to treat PAH. Thus, limited treatment data exist for the less-studied non-PAH forms of PH. Pharmacogenomics can be a tool to better understand the pathways involved in PH, as well as to improve personalization of therapy. However, little pharmacogenomic research has been carried out on this disease. New treatments for PH are on the horizon, deriving from both repurposed currently available drugs and novel therapeutics.

Keywords

endothelin receptor antagonist; pharmacogenetics; pharmacogenomics; phosphodiesterase type 5 inhibitor; prostacyclin analog; pulmonary hypertension

Pulmonary hypertension (PH) is a progressive disease that confers a 1-year mortality of approximately 10–15% [1,2]. It is broadly defined as an increase in mean pulmonary arterial pressure (PAP) of at least 25 mmHg at rest, as assessed by right heart catheterization (RHC). This increase in pressure stems from increased pulmonary vascular resistance and ultimately leads to right heart failure. PH is classified by WHO into five broad categories, each with a different etiology and pathogenesis (**Box 1**) [3].

WHO Group 1 PH, pulmonary arterial hypertension (PAH), is rare, with a prevalence between 15 and 26 per million people [4,5]. However, it is also the most studied category of PH, likely due to the clarity of the phenotype compared with other categories of PH. Idiopathic PAH has a multifactorial pathobiology, which involves components of vasoconstriction, proliferation, inflammation and thrombosis in the pulmonary vessels.

© 2013 Future Medicine Ltd

*Author for correspondence: juliod@uic.edu.

Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Included in WHO Group 1 is familial PAH, of which approximately 80% of cases are associated with mutations in the *BMPR2* gene [6]. However, since reduced function of *BMPR2* is neither necessary nor sufficient to cause PAH, disease development may require a 'double hit' from genetic mutations and environmental factors, such as drugs, viruses or toxins [7]. Interestingly, a recent study suggests that alternative *BMPR2* splicing may explain the low penetrance of PAH in patients with *BMPR2* mutations [8]. Other rarer mutations associated with PAH development have been reported in the hereditary hemorrhagic telangiectasia-associated gene *ALK1* [9]. Overall, PAH involves endothelial dysfunction in the pulmonary arteries characterized by an imbalance between endothelium-derived vasodilators, such as nitric oxide (NO), and vasoconstrictors, such as endothelin-1 (ET-1) [10,11]. As the disease progresses, vascular remodeling occurs, which includes inflammation, cell proliferation and vascular fibrosis – ultimately leading to right ventricular hypertrophy and failure.

WHO Group 2 PH is associated with pulmonary venous hypertension, or post-capillary PH, stemming from elevated left heart filling pressures. Group 2 PH is defined not only by a mean PAP (mPAP) ≥ 25 mmHg, but also by an elevated pulmonary capillary wedge pressure ≥ 15 mmHg. This is also the most common form of PH, with studies estimating its presence in 60–90% of heart failure patients [12–15]. While many of these patients have only mild elevations in PAP, approximately half have PAPs that are disproportionately higher than expected from their left arterial pressure, with greatly increased peripheral vascular resistance (termed 'out of proportion' PH) [12,15]. This increase in PAP is associated with significantly poorer outcomes, with one study estimating that heart failure patients with a very high PAP possess a greater than twofold increased risk of death compared with those with normal PAP [16].

WHO Group 3 PH is associated with underlying hypoxic lung disease, most commonly chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Traditionally, PH in COPD is thought of as common, usually mild, and is of questionable clinical relevance. However, inconsistencies in definition, multiple causes of onset and the fact that most COPD patients do not routinely undergo RHCs make it difficult to identify its true prevalence. In addition, COPD patients with out of proportion PH are at increased risk of mortality, with a nearly 50% decline in 5-year survival [17]. A prognosis of PH in ILD may be even worse, particularly in idiopathic pulmonary fibrosis (IPF), as PH in these patients was associated with a fivefold greater 1-year mortality rate [18]. While Group 3 PH patients may benefit from targeted therapy for PH, no large randomized controlled trials currently exist addressing long-term effects of drugs targeting PH in this patient population [19].

WHO Group 4 PH includes chronic thromboembolic PH (CTEPH), which is defined as mPAP ≥ 25 mmHg that persists for longer than 6 months after diagnosis of pulmonary embolism. It is somewhat rare, being found in approximately 4% of pulmonary embolism patients [20]. However, estimation of prevalence and study of its pathogenesis is difficult because many patients have no documented history of acute PE and develop PH that is only diagnosed as CTEPH in retrospect. This type of PH can be curable with pulmonary thromboendarterectomy. However, for those with inoperable disease, limited evidence suggests vasodilators used in PAH may provide some transient benefit [21].

WHO Group 5 PH consists of multiple miscellaneous etiologies, most of which are not well studied. The most common of these in western countries is likely sarcoidosis. The prevalence of PH in sarcoidosis has been estimated as high as 28% overall and 74% in advanced sarcoidosis awaiting lung transplant [22]. The etiology of PH in this disease setting is not well understood, but may potentially involve pulmonary fibrosis or formation

of vascular flow-inhibiting granulomas [23]. Limited research exists investigating the treatment of PH in sarcoidosis, but the few retrospective studies that exist in the literature suggest that vasodilators used in PAH may provide some benefit [24,25].

The main goals of treatment in all forms of PH include improvement in the patient's symptoms, quality of life and survival. Importantly, this includes slowing the progression of, or even preventing, right heart failure. Objective measurements of treatment response include improvement in WHO Functional Class (which mirror New York Heart Association functional classes in heart failure), exercise capacity (6-min walk distance [6MWD], cardiopulmonary exercise test and treadmill test), hemodynamics obtained from RHC and survival. However, few current drugs have been shown to decrease mortality and while many treatments show improvement in 6MWD, this measurement possesses significant variability, and does not appear to correlate well with mortality or hospitalization [26,27]. Recently, the use of 6MWD as a primary end point in PH treatment studies has been questioned [28,29].

Treatment data in WHO Groups 2–5 PH are much less abundant than in PAH, as no therapies are approved for the treatment of these groups. Currently, three drug classes have been US FDA-approved for chronic treatment of PAH: prostacyclin analogs, endothelin receptor antagonists (ERAs) and phosphodiesterase type 5 (PDE5) inhibitors (**Table 1**). Due to a lack of convenient, effective treatments available for PH, new treatments are being developed to potentially reverse pulmonary vascular remodeling and improve outcomes in patients. Because of the heterogeneity in PH etiology and presentation, this disease provides an excellent opportunity for personalized medicine. Pharmacogenomics can be a useful tool to assist in personalization of PH treatment [30].

Prostacyclin analogs

Pharmacology

Prostacyclin, a naturally occurring prostaglandin synthesized from arachidonic acid, is a potent vasodilator with antiplatelet and anti-proliferative effects that increases intracellular cAMP [31,32]. Prostacyclin synthase, the enzyme responsible for the formation of prostacyclin, may be deficient in the pulmonary endothelium of some patients with severe PH, resulting in excessive vasoconstriction and platelet aggregation [33]. Prostacyclin analogs as a class exert their effects by promoting direct arterial vasodilation and inhibiting platelet aggregation. Three prostacyclin analogs are FDA-approved for the treatment of PAH: epoprostenol, treprostinil and iloprost.

Epoprostenol directly vasodilates the pulmonary and systemic arterial vasculature, which reduces ventricular afterload, pulmonary vascular resistance and platelet aggregation, and increases cardiac output (CO) [34–36]. Epoprostenol is rapidly hydrolyzed both spontaneously and enzymatically in the blood, causing a half-life of less than 6 min, and necessitating continuous intravenous (iv.) delivery [37,38]. Because of its potent vasodilatory properties and narrow therapeutic index, abrupt withdrawal or large dose changes can result in serious rebound symptoms or possibly death [39]. Epoprostenol infusion requires the placement of a central venous catheter, thus users are also susceptible to the risk of serious complications such as sepsis and administration errors [40,41]. Reconstituted preparations of regular epoprostenol are temperature-sensitive and require the continuous use of ice packs during administration; however, a heat-stable formulation is now available and can be infused at controlled room temperature for up to 24 h [39,42].

Treprostinil is a prostacyclin analog with improved drug stability and is available as a sterile solution for subcutaneous (sc.) or iv. infusion, and as a solution for inhalation [43,44].

Because of its stability at room temperature and longer half-life of 4 h, treprostinil can be administered intravenously at low infusion rates with the use of miniature pumps, but carries similar safety concerns to epoprostenol and should be started only by an experienced clinician [40,41,45,46]. The inhaled formulation is administered in four inhalation sessions per day and requires the use of a specially-designed inhalation system [43]. Treprostinil is primarily metabolized by cytochrome P450 (CYP)2C8 in the liver and its metabolites are renally excreted, so clearance may be affected by hepatic impairment. Additive effects can occur if used with anti-hypertensives or -coagulants, and strong inducers or inhibitors of CYP2C8 may affect exposure levels to treprostinil [43,44].

Iloprost is a synthetic prostacyclin analog that is available in the USA as a solution for inhalation. With a half-life of only 20–30 min, it requires 6–9 inhalation sessions throughout the day using a specially approved inhalation system. Iloprost is metabolized via β -oxidation and its metabolism is not significantly affected by liver enzymes. Drug interactions are similar to other prostacyclin analogs with the potential to increase hypotensive effect and platelet inhibition [47].

Clinical use

The benefit of epoprostenol in the treatment of PAH was first observed in an open-label, randomized, controlled clinical trial that compared the use of continuously infused epoprostenol plus conventional treatment with conventional treatment alone for 12 weeks in 81 patients with PAH [48]. The prostacyclin group was titrated to a very low mean dose of 9.2 ng/kg/min. Epoprostenol treatment demonstrated a significant improvement in 6MWD, functional class and hemodynamics at 12 weeks compared with standard treatment alone. Importantly, epoprostenol treatment conferred a survival benefit in this study. However, serious complications were also observed, including catheter site infection or bleeding, and continuous infusion interruption (which, as previously mentioned, can be serious with this drug). Similar results including improvement in symptoms and hemodynamics were found in a study of iv. epoprostenol for PH due to scleroderma; however, the survival benefit was not replicated [49].

Treprostinil was initially approved for use via sc. administration. In a 12-week, double-blind, placebo-controlled trial, 470 WHO Group 1 PH patients were randomized to receive either treprostinil at a very low mean dose of 9.3 ng/kg/min or placebo via continuous sc. infusion [50]. Improvements in 6MWD, Borg Dyspnea Score, mPAP, peripheral vascular resistance (PVR), cardiac index and mean right atrial pressure were observed in the treprostinil group compared with placebo. iv. treprostinil demonstrated clinical benefit versus placebo in the TRUST trial, a double-blind, randomized, controlled trial of 44 patients with PAH [51]. All participants received continuous infusions of either treprostinil (mean dose: 72 ng/kg/min) or placebo via central venous catheter, and both symptomatic and hemodynamic measures significantly improved in the treprostinil group compared with placebo, with a trend towards an improvement in survival. However, this study was terminated early due to the occurrence of serious adverse events and catheter-related complications. Inhaled treprostinil was assessed for effectiveness when added to oral treatment with either sildenafil or bosentan in 235 patients with WHO functional class III or IV PAH [52]. Patients were randomized to receive either inhaled treprostinil 54 μ g or placebo in four inhalation sessions per day, with 70% of patients on background bosentan therapy. The treprostinil group demonstrated an improvement in 6MWD compared with the placebo group at 6 and 12 weeks.

The AIR study was the first to demonstrate the effectiveness of intermittent dosing of an inhaled prostacyclin analog for the treatment of PAH [53]. In this study, 203 patients with WHO functional class III or IV PAH or CTEPH were randomized to receive either inhaled

placebo or iloprost 2.5 or 5 µg, 6–9 times per day for 12 weeks. Significantly more patients receiving iloprost achieved the primary combined end point (10% improvement in 6MWD, improvement in functional class and absence of deterioration or death) versus placebo. In the STEP trial, the addition of inhaled iloprost to stable oral therapy with bosentan improved 6MWD and WHO functional class, and delayed time to clinical worsening versus bosentan with inhaled placebo [54].

Research into prostacyclin analogs for the treatment of WHO Group 2 PH has been limited, likely due to the early termination of the FIRST trial [55]. This study investigated epoprostenol in patients with congestive heart failure and not only showed no improvement in symptoms, but also an increased mortality rate with epoprostenol, which led to its early termination, and consequently a contraindication in this group.

The use of prostacyclins in WHO Group 3 PH is controversial. Initial improvements in PVR and CO were detected with epoprostenol in COPD-related acute respiratory failure. However, these improvements were not sustained over the study period and, importantly, a worsening in oxygenation was observed [56]. Conversely, iloprost improved gas exchange and exercise tolerance in a short-term study of 10 patients with PH secondary to COPD [57]. But, since these patients only received two doses of iloprost, long-term benefits cannot be determined. In a more long-term retrospective study, both epoprostenol and bosentan improved symptoms in patients with PH associated with ILD, but the benefits were not sustained within 1 year of treatment [58].

Both iv. treprostinil and epoprostenol have demonstrated benefit in inoperable CTEPH (WHO Group 4). In a retrospective analysis of 27 patients with inoperable distal CTEPH, long-term epoprostenol was associated with improved exercise tolerance and hemodynamics [59]. In another retrospective study, treprostinil was associated with an improvement in symptoms, hemodynamics and long-term survival in 31 patients with inoperable CTEPH compared with a control group [60]. In WHO Group 5 PH, data are scarce. In a small study of PH secondary to sarcoidosis, five patients initiated on iv. epoprostenol experienced a sustained improvement in symptoms for an average of 29 months [24].

Adverse effects of prostacyclins are predominantly related to their vasodilatory action such as hypotension, headache, diarrhea, nausea, flushing and dizziness. Due to their antiplatelet effects, they can also cause thrombocytopenia and because of their method of delivery, bacteremia, catheter thrombus, site pain, throat irritation, and cough can occur. Other adverse events of unknown etiology, but common to this drug class, are leg and jaw pain.

Pharmacogenomics

Very little exists in the literature describing pharmacogenomic research involving prostacyclin analogs. However, the gene encoding the prostacyclin receptor (*PTGIR*) is an intriguing candidate gene. One study demonstrated that several rare variants of *PTGIR* decreased binding affinity to iloprost, as well as causing defective cAMP production [61]. Variation at the prostacyclin receptor could also inhibit thrombosis formation and cellular proliferation through insufficient cAMP signaling, and was associated with an acceleration of cardiovascular disease in patients with cardiovascular risk factors [62–64]. Whether any of these rare variants have a clinical effect on prostacyclin analog response is yet to be determined.

ERAs

Pharmacology

ET-1 is an amino acid peptide with potent vasoconstrictive and mitogenic properties [65]. It is produced in the endothelium, and binds primarily to one of two G-protein coupled receptors, ET_A and ET_B, on vascular smooth muscle and endothelial cells [66]. The ET_A receptor is responsible for vasoconstriction, while the ET_B receptor produces vasodilation through the release of NO and prostacyclin [65,67]. Overexpression of ET-1 and prolonged interaction with the ET_A receptor leads to an increased state of vasoconstriction, and has chronic hypertrophic and antiapoptotic effects [66]. ET-1 concentrations are elevated in patients with PAH and serve as an important therapeutic target for ERAs [68,69].

Bosentan, the first ERA approved in the USA, is a dual ET_A/ET_B receptor antagonist with slightly higher affinity for the ET_A receptor. The terminal half-life of bosentan is approximately 5 h and, thus, is dosed orally twice daily. It undergoes extensive hepatic metabolism by CYP2C9 and CYP3A4, hence strong inhibitors of these enzymes may lead to elevated plasma concentrations of bosentan [70,71]. Because it is also an inducer of CYP3A4 and CYP2C9, bosentan may decrease concentrations of drugs metabolized by these enzymes, including itself [72–74]. Additionally, bosentan is a substrate of organic anion transporting polypeptides (OATPs), so strong inhibitors (such as cyclosporine A and glyburide) are contraindicated for use with bosentan because of their ability to cause elevated bosentan exposure [75,76].

Ambrisentan is an ERA that has a >4000-fold increased selectivity for the ET_A versus ET_B receptor type. It has an effective half-life of 9 h, requiring once-daily oral administration and is predominantly metabolized by CYP3A4, CYP2C19 and uridine 5'-diphosphate glucuronosyltransferases. Consequently, drugs such as cyclosporine A and ketoconazole can both cause increased ambrisentan plasma concentrations [77].

Clinical use

Multiple early studies demonstrated the benefit of bosentan in the treatment of WHO Group 1 PAH. The largest was the BREATHE-1 trial, where 213 WHO functional class III or IV patients were randomized to placebo or bosentan 62.5 mg twice daily for 4 weeks, followed by either bosentan 125 mg twice daily or 250 mg twice daily for 16 weeks [78]. In the combined treatment groups, bosentan improved 6MWD and symptoms of PAH, and increased time to clinical worsening. While bosentan 125 mg was well tolerated, the 250-mg group experienced a significantly higher frequency of adverse events, including abnormal liver function tests. The EARLY trial assessed the impact of bosentan therapy versus placebo in 168 patients with milder WHO Functional Class II symptoms for 6 months [79]. Improvement in 6MWD from bosentan treatment was not significantly different compared with placebo. However, an improvement in PVR and time to clinical worsening was observed, suggesting that early intervention with bosentan could be beneficial.

The efficacy of ambrisentan was demonstrated in the concurrent ARIES-1 and -2 trials [80]. ARIES-1 randomized 202 patients with PAH to either placebo or ambrisentan 5 mg, or 10 mg once daily, and ARIES-2 randomized 192 PAH patients to ambrisentan 2.5 mg or 5 mg once daily for a total of 12 weeks. All individual treatment groups achieved an improvement in 6MWD and the combined group achieved a significant improvement in time to clinical worsening.

As with other PAH-targeted therapies, research is limited on the use of ERAs for PH related to WHO Groups 2–5. Studies have been particularly limited on WHO Group 2 PH, partly because the current literature indicates that ERAs are not beneficial in heart failure patients,

making them weak candidates for the treatment of WHO Group 2 PH. The VERITAS trial studied the short-acting iv. ERA tezasetan (not currently available in the USA) in 1435 patients with acute heart failure symptoms, but no benefit was found compared with placebo [81]. Bosentan was also evaluated for the treatment of severe congestive heart failure and, like tezasetan, was not associated with symptom improvement [82]. In fact, the study was terminated early due to a short-term increased risk of worsening heart failure in the treatment group. However, a recent retrospective evaluation of 85 patients with end-stage heart failure and PH awaiting cardiac transplant found that bosentan was associated with more patients meeting hemodynamic thresholds for transplantation, as well as a reduced 1-year mortality rate compared with controls [83]. Nonetheless, based on the available evidence, the use of ERAs in WHO Group 2 cannot be supported and may present a risk of worsening symptoms.

Studies of ERAs in WHO Group 3 have been similarly discouraging. Bosentan showed no improvement in exercise capacity compared with placebo and also caused a worsening in hypoxemia and functional class in patients with PH associated with severe COPD [84]. In addition, in an analysis of gas exchange in 12 patients with IPF, bosentan did not provide any clinical improvement in the primary combined end point (gas exchange on day 1; oxygen saturation and minute ventilation on day 14) [85]. Most recently, the ARIES-3 study evaluated the use of ambrisentan in a variety of PH etiologies including a subset of non-PAH patients, such as chronic hypoxia, CTEPH, sarcoidosis and others [86]. No difference in 6MWD was observed in this subgroup after 24 weeks of treatment.

In WHO Group 4-related PH, the BENEFIT trial randomized 157 patients with inoperable CTEPH to receive either bosentan or placebo for 16 weeks [87]. While no improvement in exercise capacity was demonstrated, a significant improvement in PVR was observed. Likewise, one study investigated ERAs in WHO Group 5 PH – a prospective, open-label trial of ambrisentan in 21 patients with PH associated with sarcoidosis [88]. Patients received ambrisentan 5 mg daily for 4 weeks, then 10 mg daily for 20 weeks. No significant benefit was found in exercise tolerance and over half of the patients did not complete the study. However, given the small sample size and high attrition rate, little can be concluded from this study.

Common adverse events associated with ERAs include headache, flushing, peripheral edema, nasal congestion, sinusitis and elevated liver enzymes. More serious adverse events include anemia, heart failure exacerbation, birth defects and hepatotoxicity. Both bosentan and ambrisentan are rated pregnancy category X by the FDA. Additionally, they are both subject to the FDA's program for Risk Evaluation and Mitigation Strategies and are available only through restricted access programs to ensure safe use of the medications by minimizing the risk of fetal exposure, as well as (specifically for bosentan) to minimize the risk of hepatotoxicity [75,89].

Pharmacogenomics

The endothelin pathway and endothelial dys-function offer multiple opportunities for research of genetic polymorphisms due to the multistep process in ET-1 activation and dual receptor interactions. Pharmacogenomic research involving ERAs is scarce, despite studies showing differential responses to the drug class based on race and gender [90]. Candidate genes do exist with this drug class, as a His323His variant in the endothelin ET_A receptor, the major site of action for ERAs, has been associated with PAH [91]. Additionally, because of the ability of bosentan (and to a lesser extent, ambrisentan) to induce CYP3A4, ABCB1, ABCB11 and, to a lesser extent, some OATPs, variation in any of these genes could greatly magnify potential drug interactions with bosentan [92].

PDE5 inhibitors

Pharmacology

Two important features of PAH are increased expression of the vasoconstrictor PDE5 and decreased production of the vasodilator nitric oxide in the pulmonary vasculature [93]. PDE5 is an enzyme abundantly expressed in the lungs that hydrolyzes cGMP, a second messenger of the NO pathway within the lungs. PDE5 inhibitors prevent the hydrolysis of cGMP, which has vasodilatory and antiproliferative effects on the pulmonary vasculature [93]. The two PDE5 inhibitors FDA-approved for treatment of PAH in the USA are sildenafil and tadalafil.

Sildenafil has high selectivity for PDE5 versus PDE2, 3 and 4 [94]. However, selectivity is decreased towards PDE6 and 1, which can increase cAMP, and may explain some of sildenafil's antiproliferative effects [95]. Sildenafil has a half-life of approximately 4 h, requiring dosing three-times daily. Limited food interactions exist with sildenafil; however, absorption and extent of systemic exposure (area under the curve [AUC]) is reduced when given with a high-fat meal [96]. Sildenafil is somewhat metabolized by CYP2C9, but is predominantly metabolized by CYP3A4 into an *N*-desmethyl metabolite that also has some PDE5 inhibitory activity [97]. Thus, drug interactions can occur with CYP3A4 inhibitors such as erythromycin, saquinavir or ritonavir [98,99]. Importantly, pharmacokinetic studies have shown that sildenafil AUC decreases approximately 50% when coad-ministered with bosentan, a known inducer of CYP3A4 [100].

Similar to sildenafil, tadalafil is highly selective for PDE5 compared with 1–4 and 7–10. Because of its long half-life (17 h), tadalafil is usually dosed once daily. Tadalafil pharmacokinetics are not affected by food or alcohol consumption, and it is primarily metabolized by CYP3A4 to inactive metabolites. Thus, known inducers of CYP3A4 such as rifampin, phenytoin and carbamazepine, and inhibitors such as ketoconazole, ritonavir and erythromycin could affect plasma concentrations of tadalafil [101].

Clinical use

The pivotal trial that established sildenafil as a treatment for WHO Group 1 PH was the SUPER trial [102]. SUPER enrolled WHO functional class II and III PAH patients, who were randomized to receive placebo or sildenafil 20, 40 or 80 mg three-times daily for 12 weeks. Compared with placebo, sildenafil improved 6MWD, mPAP, and WHO functional class, all in a dose-dependent fashion. However, incidence of clinical worsening did not differ with sildenafil therapy. Based on the results of SUPER, the FDA-recommended dose for treatment of PAH is 20 mg three-times daily.

Sildenafil has also been tested in combination with other PAH medications. In the PACES trial, patients on long-term iv. epoprostenol were randomized to receive either placebo or sildenafil 20 mg three-times daily, which was titrated to 40 or 80 mg three-times daily [103]. An additional improvement in 6MWD and longer time to clinical worsening were observed with the addition of sildenafil treatment. This study suggests that combination therapy may be beneficial in some patients. One recent study investigated sildenafil in patients with PH associated with sickle cell disease, but was halted early due to an increased incidence of hospitalization for pain in the sildenafil group [104].

Tadalafil showed benefit in PAH in the PHIRST trial [105]. This trial enrolled 405 PAH patients (a majority were WHO functional class II and III) and randomized them to placebo or tadalafil 2.5, 10, 20, or 40 mg daily for 16 weeks. Compared with placebo, tadalafil 10, 20 and 40 mg significantly improved 6MWD in a dose-dependent manner, while improvement in WHO functional class did not significantly differ at any dose. Only the 40-

mg dose improved incidence and time to clinical worsening. Of note, approximately half of the enrolled patients were also on bosentan and 6MWD improvement in this subset of patients only trended towards significance. Based on the results of this trial, the FDA-recommended dose for treatment of PAH is 40 mg daily.

While a majority of the research with PDE5 inhibitors has been completed in patients with WHO Group 1 PH, disease improvement has also been observed in WHO Groups 2, 3 and 4. In Group 2 PH, the use of vasodilators could theoretically cause pulmonary edema when administered to patients with elevated LV filling pressures. However, this may be offset if administered with concomitant treatments that reduce LV afterload and filling pressures [19]. A recent clinical pilot study investigated 1 year of sildenafil treatment (50 mg three-times daily) in 44 patients with WHO Group 2 PH associated with left heart diastolic dysfunction [106]. Improvements were found not only in mPAP and pulmonary capillary wedge pressure, but also RV function, pulmonary function and quality of life. Additionally, a retrospective case-control study in patients with PH associated with advanced heart failure awaiting transplant indicated that sildenafil reduced PVR and improved New York Heart Association functional class and post-transplant survival [107]. A large, randomized, placebo-controlled trial is currently underway to more clearly establish the therapeutic benefits of sildenafil treatment in patients with WHO Group 2 PH [108].

At this point, the data do not support the use of PDE5 inhibitors in patients with WHO Group 3 PH. In patients with COPD, one small clinical study found that a single dose of sildenafil improved mPAP, but also impaired gas exchange, which decreases arterial oxygenation [109]. Impaired gas exchange with sildenafil was confirmed in a recent study of COPD patients without PH [110]. However, other small studies of sildenafil in COPD patients both with and without PH failed to detect any changes in stroke volume, CO or exercise capacity, as well as observing no changes in oxygenation [111,112]. In ILD, small clinical studies indicate that sildenafil causes preferential pulmonary vasodilation, as well as increasing 6MWD [113,114]. However, unlike in COPD, sildenafil may improve gas exchange in this patient population [114].

In WHO Group 4 patients with inoperable CTEPH, one study found that 3 months of sildenafil treatment (50 mg three-times daily) significantly reduced pulmonary vascular resistance and increased 6MWD [115]. Lastly, in patients with sarcoidosis (WHO Group 5), a small retrospective study showed that sildenafil improved mPAP and PVR [116].

Compared with prostacyclin analogs and ERAs, PDE5 inhibitors tend to be well tolerated. Adverse effects appear to be similar in sildenafil and tadalafil [102,105]. The most common effects include headache, dyspepsia, flushing, visual impairment and nasal congestion [117]. Due to the concern regarding severe hypotension, PDE5 inhibitors should not be used with nitrates. More serious, but rare adverse effects include retinal vascular disease, myocardial infarction and nonarteritic ischemic optic neuropathy [118,119].

Pharmacogenomics

While not numerous, more pharmacogenetic studies exist in PDE5 inhibitors than in other PH medications and almost exclusively in sildenafil. Most of the pharmacogenetic research carried out with sildenafil relates to its use in erectile dysfunction (ED). However, some of these data can be extrapolated to sildenafil's use in PH, as its mechanism of vascular smooth muscle vaso-dilation is similar in both diseases. Thus, many of the genetic associations found in ED response indicate strong candidates for research in PH.

A T-1142G polymorphism in the *PDE5* promoter region was not found to be associated with sildenafil response in ED patients [120]. However, because no evidence exists in the

literature that other polymorphisms in the gene have been studied, *PDE5* cannot be completely ruled out as a candidate gene. A key effector in the NO–cGMP pathway is endothelial NO synthase (eNOS). In two separate studies, the 4a variable number tandem repeat in intron 4 of *NOS3* (the gene that encodes eNOS) was associated with better ED response to sildenafil [121,122]. A separate group replicated this variable number tandem repeat association and also found an association between C allele in T-786C and good response to sildenafil [122]. A retrospective study suggests that variation in *GNB3*, a gene that encodes a key component of intracellular signal transduction in G-protein-coupled receptors, affects sildenafil response in ED [123]. However, the number of patients with the response-affecting variant was small and this finding is yet to be replicated in the literature.

Since *CYP2C9* is responsible for approximately 20% of sildenafil metabolism, potential polymorphisms in *CYP2C9* could affect sildenafil response. However, when heterozygotes were tested retrospectively in a sildenafil pharmacokinetic study, nonsignificant increases in AUC were observed [124]. It is important to note, however, that none of these subjects were homozygous genetic variants, which is often associated with a much greater decrease in *in vivo* enzyme activity. Thus, pharmacogenetic effects of *CYP2C9* on sildenafil pharmacokinetics cannot be ruled out.

Other therapies

While not FDA-approved, high-dose calcium channel blockers have been used for years to treat a rare subset of idiopathic PAH patients who demonstrate an acute vasodilator response measured during RHC; currently this is recognized as a drop of at least 10 mmHg in mPAP, resulting in an mPAP of 40 mmHg or less [125,126]. Even in this small group of vasodilator responders, only about half display long-term improvement with calcium channel blocker treatment [127]. Unlike calcium channel blockers, inhaled NO is FDA-approved for the treatment of PAH, but only in neonates and is suggested for only short-term use. Although not evaluated in randomized controlled trials, diuretics, supplemental oxygen and oral anticoagulants have also been used for years as supportive care.

Future treatments

As none of the currently available therapies are known to reverse progression or cure PH, significant effort is being expended in the search for new treatments. One method of exploring new therapies is repurposing drugs currently on the market for another indication. For instance, HMG-CoA reductase inhibitors (statins) have been shown to have pleiotropic anti-inflammatory and -proliferative effects, properties that would be useful to treat PH [128,129]. However, a small clinical trial of aspirin and simvastatin, or simvastatin alone in patients with PAH found no significant difference in 6MWD compared with placebo [130]. However, no hemodynamics were measured and, as mentioned above, 6MWD is questionable as an accurate surrogate outcome. Another example is valproic acid, which has pleiotropic histone deacetylase (HDAC) activities. HDAC inhibition suppresses pulmonary smooth muscle cell proliferation and may reduce PAP to a greater degree than tadalafil [131]. Valproic acid, via its HDAC-inhibiting mechanism, improved hemodynamics in a hypoxic rat PH model and decreased human pulmonary smooth muscle proliferation *in vitro* [132]. However, HDAC inhibitors may adversely affect right ventricular remodeling, as valproic acid caused increased right ventricular dilation and trends towards increased fibrosis in pulmonary artery-banded rats [133].

Because the pathogenesis of PAH includes a proliferative component similar to neoplasia, repurposing the tyrosine kinase inhibitors imatinib, sorafenib and nilotinib may serve an important role in preventing, and possibly reversing, pulmonary vascular remodeling [134–

137]. First demonstrated in multiple smaller studies, imatinib improved 6MWD, PVR and mPAP, and the Phase III IMPRES study showed it was also beneficial in treatment-refractory PAH patients when added to standard therapies [138–141]. Nilotinib, which may offer an improved adverse event profile with a similar effect, is currently undergoing Phase II studies [201]. Additional medications in early stages of investigation for PH include losartan, targeting upregulated renin–angiotensin–aldosterone system activity, and selective serotonin reuptake inhibitors, which have shown mixed results [142–144].

In addition to repurposing drugs approved for other indications, new forms of currently approved PAH medications are being developed to improve ease of use. Macitentan, a new oral dual ERA with high lipophilicity and slow receptor dissociation properties, demonstrated a reduction in mortality and morbidity events compared with placebo in the Phase III SERAPHIN trial [145]. It also reduced risk of death and hospitalization due to PAH, and improved 6MWD and functional class at 6 months. A new drug application was submitted to the FDA in late 2012.

A new drug application for an orally administered formulation of treprostinil was denied by the FDA in 2012 after only one of three Phase III studies met the primary end point of improvement in 6MWD [146,202]. Likewise, a modified formulation of beraprost sodium, an oral prostacyclin available outside of the USA, demonstrated insufficient efficacy in preliminary Phase II studies [203,204].

Another approach to developing new therapies is through the development of novel drug entities, which exert effects on new areas of the PH development pathway. Selexipag is an oral prostaglandin IP receptor agonist that was effective in reducing PVR in a Phase II study and is currently undergoing Phase III trials [147,205]. In addition, early clinical trials of riociguat, a soluble guanylatecyclase stimulator that increases sensitivity to NO, suggest it is well tolerated and improves hemodynamics and 6MWD in patients with PAH, CTEPH, and ILD [148,149]. Because the Rho–Rho-kinase pathway regulates cellular functions such as contraction and proliferation, the Rho-kinase inhibitor fasudil may be a potential future treatment, as small uncontrolled studies indicate that it improves hemodynamics in multiple forms of PH [150,151]. Sapropterin, the optically active form of tetrahydrobiopterin (a cofactor for NO synthesis), showed an improvement in 6MWD in a small uncontrolled study of PAH and inoperable CTEPH patients [152]. A Phase I study of sapropterin as an adjunct treatment for PAH is underway [206]. Terguride, a serotonin receptor antagonist, is also being investigated as a PAH treatment, as serotonin has been implicated in proliferation of arterial smooth muscle cells [153]. Other pathways being explored, which could soon yield promising future therapeutic targets, include hypoxic pulmonary vasoconstriction, regulation of voltage-gated potassium channels and offsetting of dysregulated endoplasmic reticulum in the pulmonary arteries [154–157].

Recently, gene therapy has become another novel therapeutic method under investigation for the treatment of PH. Delivery of prostacyclin synthase, eNOS and BMPR2 each significantly diminish progression to right heart failure in rodent PH models [158–160]. In addition, knockdown of tryptophan hydroxylase, the enzyme responsible for most non-CNS serotonin bio-synthesis, appears to diminish the development of hypoxia-induced PH in rats [161]. However, studies using gene therapy to treat PH in humans have not yet been reported. If these gene therapies come to market, pharmacogenomics could be a very useful tool for determining patients with genetic mutations affecting activity of these proteins, thus making them much stronger candidates for deriving benefit from the gene therapy.

Conclusion

Although WHO Group 1 PH is rare, the majority of research has been done in this group, yielding three pharmacological classes available for its treatment: PDE5 inhibitors, prostacyclin analogs and ERAs. However, the treatments available are not ideal. The only drug class that has displayed a mortality benefit, prostacyclin analogs, has a poor side-effect profile and requires difficult to use parenteral delivery methods. New treatments (including an oral prostacyclin analog) are under investigation and range from repurposed drugs that are used to treat other diseases, to treatments targeting novel pathways, to gene therapy.

Surprisingly, much less research has been carried out on the more common WHO Group 2 and 3 categories, or the rarer WHO Group 4 and 5 categories of PH. What research has been done, however, indicates that the current medication classes approved for WHO Group 1 are not appropriate for all categories of PH (**Table 2**). Pharmacogenomics, which could help personalize therapy in PH, has not been extensively explored in any of the drug classes currently available. In order to improve the treatment of this disease, pharmacogenomic research in PH should be expanded.

Future perspective

Despite survival in patients with PH nearly doubling over the past 20 years, mortality remains high [2,162]. This likely stems from the complicated and poorly understood pathogenesis of these categories of PH. Improved understanding of the disease process in all types of PH should lead to the development of more numerous and efficacious treatment options, particularly those with the ability to actively reverse pulmonary vascular remodeling.

Because of the heterogeneity of PH etiology, personalized approaches will likely be needed for successful treatment. Thus, PH is an excellent target for personalized medicine research. Pharmacogenomics could be a valuable tool in determining patient characteristics that would assist in choosing the best treatment for each individual patient. In the upcoming years, research into the genetics and epigenetics underlying PH pathogenesis and drug response should increase, yielding more effective treatment strategies, which should continue to decrease mortality in this disease.

Acknowledgments

RF Machado has received institutional grants from Actelion and United Therapeutics, and has served as a consultant for Gilead. His contribution to this article was supported by NIH grants R01HL111656 and K23HL098454.

References/Websites

Papers of special note have been highlighted as:

■ of interest

■■ of considerable interest

1. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur. Respir. J.* 2007; 30(6):1103–1110. [PubMed: 17804449]
2. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest.* 2012; 142(2):448–456. [PubMed: 22281797]

3. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J. Am. Coll. Cardiol.* 2009; 54(Suppl. 1):S43–S54. [PubMed: 19555858]
4. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am. J. Respir. Crit. Care Med.* 2006; 173(9):1023–1030. [PubMed: 16456139]
5. Peacock AJ, Murphy NF, McMurray JJ, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur. Respir. J.* 2007; 30(1):104–109. [PubMed: 17360728]
6. Machado RD, Aldred MA, James V, et al. Mutations of the TGF-beta type II receptor BMPR2 in pulmonary arterial hypertension. *Hum. Mutat.* 2006; 27(2):121–132. [PubMed: 16429395]
7. Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. *N. Engl. J. Med.* 2009; 361(19):1864–1871. [PubMed: 19890129]
8. Cogan J, Austin E, Hedges L, et al. Role of BMPR2 alternative splicing in heritable pulmonary arterial hypertension penetrance. *Circulation.* 2012; 126(15):1907–1916. [PubMed: 22923426]
9. Trembath RC, Thomson JR, Machado RD, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. *N. Engl. J. Med.* 2001; 345(5):325–334. [PubMed: 11484689]
10. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N. Engl. J. Med.* 1995; 333(4):214–221. [PubMed: 7540722]
11. Rubens C, Ewert R, Halank M, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. *Chest.* 2001; 120(5):1562–1569. [PubMed: 11713135]
12. Schwartzberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *J. Am. Coll. Cardiol.* 2012; 59(5):442–451. [PubMed: 22281246]
13. Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J. Am. Coll. Cardiol.* 2001; 37(1):183–188. [PubMed: 11153735]
14. Willens HJ, Kessler KM. Severe pulmonary hypertension associated with diastolic left ventricular dysfunction. *Chest.* 1993; 103(6):1877–1883. [PubMed: 8404117]
15. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J. Am. Coll. Cardiol.* 2009; 53(13):1119–1126. [PubMed: 19324256]
16. Bursi F, Mcnallan SM, Redfield MM, et al. Pulmonary pressures and death in heart failure: a community study. *J. Am. Coll. Cardiol.* 2012; 59(3):222–231. [PubMed: 22240126]
17. Oswald-Mammoser M, Weitzenblum E, Quoix E, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest.* 1995; 107(5):1193–1198. [PubMed: 7750305]
18. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest.* 2006; 129(3):746–752. [PubMed: 16537877]
19. Hoeper MM, Barbera JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J. Am. Coll. Cardiol.* 2009; 54(Suppl. 1):S85–S96. [PubMed: 19555862]
20. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N. Engl. J. Med.* 2004; 350(22):2257–2264. [PubMed: 15163775]
21. Condliffe R, Kiely DG, Gibbs JS, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* 2008; 177(10):1122–1127. [PubMed: 18292468]
22. Shigemitsu H, Nagai S, Sharma OP. Pulmonary hypertension and granulomatous vasculitis in sarcoidosis. *Curr. Opin. Pulm. Med.* 2007; 13(5):434–438. [PubMed: 17940490]
23. Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. *Am. J. Respir. Crit. Care Med.* 2011; 183(5):573–581. [PubMed: 21037016]

24. Fisher KA, Serlin DM, Wilson KC, Walter RE, Berman JS, Farber HW. Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment. *Chest*. 2006; 130(5): 1481–1488. [PubMed: 17099027]
25. Barnett CF, Bonura EJ, Nathan SD, et al. Treatment of sarcoidosis-associated pulmonary hypertension. A two-center experience. *Chest*. 2009; 135(6):1455–1461. [PubMed: 19118270]
26. Macchia A, Marchioli R, Tognoni G, et al. Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *Am. Heart J*. 2010; 159(2):245–257. [PubMed: 20152223]
27. Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J. Am. Coll. Cardiol*. 2012; 60(13):1192–1201. [PubMed: 22995024]
28. Rubin LJ. The 6-minute walk test in pulmonary arterial hypertension: how far is enough? *Am. J. Respir. Crit. Care Med*. 2012; 186(5):396–397. [PubMed: 22942342]
29. Rich S. The 6-minute walk test as a primary endpoint in clinical trials for pulmonary hypertension. *J. Am. Coll. Cardiol*. 2012; 60(13):1202–1203. [PubMed: 22995025]
30. Said SI, Hamidi SA. Pharmacogenomics in pulmonary arterial hypertension: toward a mechanistic, target-based approach to therapy. *Pulm. Circ*. 2011; 1(3):383–388. [PubMed: 22140628]
31. Geraci MW, Gao B, Shepherd DC, et al. Pulmonary prostacyclin synthase overexpression in transgenic mice protects against development of hypoxic pulmonary hypertension. *J. Clin. Invest*. 1999; 103(11):1509–1515. [PubMed: 10359560]
32. Tahara N, Kai H, Niiyama H, et al. Repeated gene transfer of naked prostacyclin synthase plasmid into skeletal muscles attenuates monocrotaline-induced pulmonary hypertension and prolongs survival in rats. *Hum. Gene Ther*. 2004; 15(12):1270–1278. [PubMed: 15684702]
33. Tudor RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am. J. Respir. Crit. Care Med*. 1999; 159(6): 1925–1932. [PubMed: 10351941]
34. Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. *N. Engl. J. Med*. 1987; 317(7):397–403. [PubMed: 3302704]
35. Kiernan FJ, Kluger J, Regnier JC, Rutkowski M, Fieldman A. Epoprostenol sodium (prostacyclin) infusion in acute myocardial infarction. *Br. Heart J*. 1986; 56(5):428–432. [PubMed: 3539163]
36. Ashby B. Comparison of Iloprost, Cicaprost and prostacyclin effects on cyclic AMP metabolism in intact platelets. *Prostaglandins*. 1992; 43(3):255–261. [PubMed: 1378640]
37. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature*. 1976; 263(5579):663–665. [PubMed: 802670]
38. Moncada S, Vane JR. Prostacyclin and blood coagulation. *Drugs*. 1981; 21(6):430–437. [PubMed: 7018874]
39. Flolan, package insert. GlaxoSmithKline; NC, USA:
40. Kingman MS, Tankersley MA, Lombardi Set al. Prostacyclin administration errors in pulmonary arterial hypertension patients admitted to hospitals in the United States: a national survey. *J. Heart Lung Transplant*. 2010; 29(8):841–846. [PubMed: 20430649]
41. Kallen AJ, Lederman E, Balaji A, et al. Bloodstream infections in patients given treatment with intravenous prostanooids. *Infect. Control Hosp. Epidemiol*. 2008; 29(4):342–349. [PubMed: 18462147]
42. Veletri®, package insert. Actelion Pharmaceuticals US Inc.; CA, USA:
43. Tyvaso®, package insert. United Therapeutics Corp.; NC, USA:
44. Remodulin®, package insert. United Therapeutics Corp.; NC, USA:
45. Tapson VF, McLaughlin VV, Gombert-Maitland M, et al. Delivery of intravenous treprostinil at low infusion rates using a miniaturized infusion pump in patients with pulmonary arterial hypertension. *J. Vasc. Access*. 2006; 7(3):112–117. [PubMed: 17019662]
46. Laliberte K, Arneson C, Jeffs R, Hunt T, Wade M. Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and

- subcutaneous route to normal volunteers. *J. Cardiovasc. Pharmacol.* 2004; 44(2):209–214. [PubMed: 15243302]
47. Ventavis®, package insert. Actelion Pharmaceuticals US Inc.; CA, USA:
 48. ■■■ Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N. Engl. J. Med.* 1996; 334(5):296–301. [PubMed: 8532025] [First study to demonstrate survival associated with treatment and identify performance of the 6-min walk test at baseline as an independent predictor of survival.]
 49. Badesch DB, Tapson VF, Mcgoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann. Intern. Med.* 2000; 132(6):425–434. [PubMed: 10733441]
 50. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am. J. Respir. Crit. Care Med.* 2002; 165(6):800–804. [PubMed: 11897647]
 51. ■■■ Hiremath J, Thanikachalam S, Parikh K, et al. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J. Heart Lung Transplant.* 2010; 29(2):137–149. [PubMed: 20022264] [Measured plasma biomarkers that may be associated with disease progression.]
 52. Mclaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J. Am. Coll. Cardiol.* 2010; 55(18):1915–1922. [PubMed: 20430262]
 53. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N. Engl. J. Med.* 2002; 347(5):322–329.
 54. Mclaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am. J. Respir. Crit. Care Med.* 2006; 174(11):1257–1263. [PubMed: 16946127]
 55. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am. Heart J.* 1997; 134(1):44–54. [PubMed: 9266782]
 56. Archer SL, Mike D, Crow J, Long W, Weir EK. A placebo-controlled trial of prostacyclin in acute respiratory failure in COPD. *Chest.* 1996; 109(3):750–755. [PubMed: 8617086]
 57. Dernaika TA, Beavin M, Kinasevitz GT. Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. *Respiration.* 2010; 79(5):377–382. [PubMed: 19786728]
 58. Minai OA, Sahoo D, Chapman JT, Mehta AC. Vaso-active therapy can improve 6-min walk distance in patients with pulmonary hypertension and fibrotic interstitial lung disease. *Resp. Med.* 2008; 102(7):1015–1020.
 59. Cabrol S, Souza R, Jais X, et al. Intravenous epoprostenol in inoperable chronic thromboembolic pulmonary hypertension. *J. Heart Lung Transplant.* 2007; 26(4):357–362. [PubMed: 17403477]
 60. Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. *J. Thromb. Haemost.* 2007; 5(3):483–489. [PubMed: 17319903]
 61. ■■■ Stitham J, Stojanovic A, Hwa J. Impaired receptor binding and activation associated with a human prostacyclin receptor polymorphism. *J. Biol. Chem.* 2002; 277(18):15439–15444. [PubMed: 11854299] [Showed the potential importance of pharmacogenomics in pulmonary hypertension by demonstrating that rare variants in the prostacyclin receptor can affect receptor response to iloprost.]
 62. Fetalvero KM, Shyu M, Nomikos AP, et al. The prostacyclin receptor induces human vascular smooth muscle cell differentiation via the protein kinase A pathway. *Am. J. Physiol.* 2006; 290(4):H1337–H1346.
 63. Arehart E, Stitham J, Asselbergs FW, et al. Acceleration of cardiovascular disease by a dysfunctional prostacyclin receptor mutation: potential implications for cyclooxygenase-2 inhibition. *Circ. Res.* 2008; 102(8):986–993. [PubMed: 18323528]

64. Mohite A, Chillar A, So SP, Cervantes V, Ruan KH. Novel mechanism of the vascular protector prostacyclin: regulating microRNA expression. *Biochemistry*. 2011; 50(10):1691–1699. [PubMed: 21250659]
65. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*. 1988; 332(6163):411–415. [PubMed: 2451132]
66. Penna C, Rastaldo R, Mancardi D, et al. Effect of endothelins on the cardiovascular system. *J. Cardiovasc. Med*. 2006; 7(9):645–652.
67. Khalil RA. Modulators of the vascular endothelin receptor in blood pressure regulation and hypertension. *Curr. Mol. Pharmacol*. 2011; 4(3):176–186. [PubMed: 21222646]
68. Galie N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. *Cardiovasc. Res*. 2004; 61(2):227–237. [PubMed: 14736539]
69. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J. Am. Coll. Cardiol*. 2004; 43(Suppl. 12):S13–S24.
70. Dingemans J, van Giersbergen PL. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin. Pharmacokinet*. 2004; 43(15):1089–1115. [PubMed: 15568889]
71. van Giersbergen PL, Halabi A, Dingemans J. Single- and multiple-dose pharmacokinetics of bosentan and its interaction with ketoconazole. *Br. J. Clin. Pharmacol*. 2002; 53(6):589–595. [PubMed: 12047483]
72. van Giersbergen PL, Treiber A, Schreiner R, Dietrich H, Dingemans J. Inhibitory and inductive effects of rifampin on the pharmacokinetics of bosentan in healthy subjects. *Clin. Pharmacol. Therapeut*. 2007; 81(3):414–419.
73. Dingemans J, Schaarschmidt D, van Giersbergen PL. Investigation of the mutual pharmacokinetic interactions between bosentan, a dual endothelin receptor antagonist, and simvastatin. *Clin. Pharmacokinet*. 2003; 42(3):293–301. [PubMed: 12603176]
74. Weber C, Schmitt R, Birnboeck H, et al. Multiple-dose pharmacokinetics, safety, and tolerability of bosentan, an endothelin receptor antagonist, in healthy male volunteers. *J. Clin. Pharmacol*. 1999; 39(7):703–714. [PubMed: 10392325]
75. Tracleer (bosentan) Risk Evaluation Mitigation Strategy (REMS). Actelion Pharmaceuticals US, Inc.; CA, USA: 2010.
76. Treiber A, Schreiner R, Hausler S, Stieger B. Bosentan is a substrate of human OATP1B1 and OATP1B3: inhibition of hepatic uptake as the common mechanism of its interactions with cyclosporin A, rifampicin, and sildenafil. *Drug Metab. Dispos*. 2007; 35(8):1400–1407.
77. Letairis®, package insert. Gilead Sciences, Inc.; CA, USA:
78. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N. Engl. J. Med*. 2002; 346(12):896–903. [PubMed: 11907289]
79. Galie N, Rubin L, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet*. 2008; 371(9630):2093–2100. [PubMed: 18572079]
80. Galie N, Olschewski H, Oudiz RJ, et al. 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. *Circulation*. 2008; 117(23):3010–3019. [PubMed: 18506008]
81. McMurray JJ, Teerlink JR, Cotter G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA*. 2007; 298(17):2009–2019. [PubMed: 17986694]
82. Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. *J. Cardiac Fail*. 2005; 11(1):12–20.
83. Hefke T, Zittermann A, Fuchs U, Schulte-Eistrup S, Gummert JF, Schulz U. Bosentan effects on hemodynamics and clinical outcome in heart failure patients with pulmonary hypertension awaiting cardiac transplantation. *Thorac. Cardiovasc. Surg*. 2012; 60(1):26–34. [PubMed: 21432755]
84. Stolz D, Rasch H, Linka A, et al. A randomised, controlled trial of bosentan in severe COPD. *Eur. Respir. J*. 2008; 32(3):619–628. [PubMed: 18448495]

85. Gunther A, Enke B, Markart P, et al. Safety and tolerability of bosentan in idiopathic pulmonary fibrosis: an open label study. *Eur. Respir. J.* 2007; 29(4):713–719. [PubMed: 17215312]
86. Badesch DB, Feldman J, Keogh A, et al. ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. *Cardiovasc. Therapeut.* 2012; 30(2):93–99.
87. Jais X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension), a randomized, placebo-controlled trial. *J. Am. Coll. Cardiol.* 2008; 52(25):2127–2134. [PubMed: 19095129]
88. Judson MA, Highland KB, Kwon S, et al. Ambrisentan for sarcoidosis associated pulmonary hypertension. *Sarcoidosis Vasc. Diffuse Lung Dis.* 2011; 28(2):139–145.
89. Letairis® (ambrisentan) Risk Evaluation and Mitigation Strategy (REMS). Gilead Sciences, Inc.; CA, USA: 2012.
90. Gabler NB, French B, Strom BL, et al. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. *Chest.* 2012; 141(1):20–26. [PubMed: 21940766]
91. Calabro P, Limongelli G, Maddaloni V, et al. Analysis of endothelin-1 and endothelin-1 receptor A gene polymorphisms in patients with pulmonary arterial hypertension. *Intern. Emerg. Med.* 2012; 7(5):425–430. [PubMed: 21773759]
92. Weiss J, Herzog M, Haefeli WE. Differential modulation of the expression of important drug metabolising enzymes and transporters by endothelin-1 receptor antagonists ambrisentan and bosentan in vitro. *Eur. J. Pharmacol.* 2011; 660(2–3):298–304. [PubMed: 21501604]
93. Wharton J, Strange JW, Moller GM, et al. Antiproliferative effects of phosphodiesterase type 5 inhibition in human pulmonary artery cells. *Am. J. Respir. Crit. Care Med.* 2005; 172(1):105–113. [PubMed: 15817798]
94. Gupta M, Kovar A, Meibohm B. The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J. Clin. Pharmacol.* 2005; 45(9):987–1003. [PubMed: 16100293]
95. Schermuly RT, Pullamsetti SS, Kwapiszewska G, et al. Phosphodiesterase 1 upregulation in pulmonary arterial hypertension: target for reverse-remodeling therapy. *Circulation.* 2007; 115(17):2331–2339. [PubMed: 17438150]
96. Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br. J. Clin. Pharmacol.* 2002; 53(Suppl. 1):S5–S12.
97. Muirhead GJ, Rance DJ, Walker DK, Wastall P. Comparative human pharmacokinetics and metabolism of single-dose oral and intravenous sildenafil. *Br. J. Clin. Pharmacol.* 2002; 53(Suppl. 1):S13–S20.
98. Muirhead GJ, Wulff MB, Fielding A, Kleinermaans D, Buss N. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br. J. Clin. Pharmacol.* 2000; 50(2):99–107. [PubMed: 10930961]
99. Muirhead GJ, Faulkner S, Harness JA, Taubel J. The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil in healthy volunteers. *Br. J. Clin. Pharmacol.* 2002; 53(Suppl. 1):S37–S43.
100. Paul GA, Gibbs JS, Boobis AR, Abbas A, Wilkins MR. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br. J. Clin. Pharmacol.* 2005; 60(1):107–112. [PubMed: 15963102]
101. Adcirca, package insert. Eli Lilly and Company; IN, USA:
102. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N. Engl. J. Med.* 2005; 353(20):2148–2157. [PubMed: 16291984]
103. Simonneau G, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann. Int. Med.* 2008; 149(8):521–530. [PubMed: 18936500]
104. Machado RF, Barst RJ, Yovetich NA, et al. Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. *Blood.* 2011; 118(4):855–864. [PubMed: 21527519]
105. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation.* 2009; 119(22):2894–2903. [PubMed: 19470885]

- 106■. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation*. 2011; 124(2):164–174. [PubMed: 21709061] [Showed hemodynamic improvement in patients with pulmonary hypertension associated with diastolic dysfunction (a group of patients where no successful treatments have been found).]
107. Reichenbach A, Al-Hiti H, Malek I, et al. The effects of phosphodiesterase 5 inhibition on hemodynamics, functional status and survival in advanced heart failure and pulmonary hypertension: a case-control study. *Int. J. Cardiol*. 2012 pii: S0167-5273(12)01180-1.
108. Cooper TJ, Guazzi M, Al-Mohammad A, et al. Sildenafil in Heart Failure (SILHF). An investigator-initiated multinational randomized controlled clinical trial: rationale and design. *Eur. J. Heart Fail*. 2012; 15(1):119–122. [PubMed: 23097067]
109. Blanco I, Gimeno E, Munoz PA, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Am. J. Respir. Crit. Care Med*. 2010; 181(3):270–278. [PubMed: 19875684]
110. Lederer DJ, Bartels MN, Schluger NW, et al. Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. *COPD*. 2012; 9(3):268–275. [PubMed: 22360383]
111. Rietema H, Holverda S, Bogaard HJ, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur. Respir. J*. 2008; 31(4):759–764. [PubMed: 18094009]
112. Holverda S, Rietema H, Bogaard HJ, et al. Acute effects of sildenafil on exercise pulmonary hemodynamics and capacity in patients with COPD. *Pulm. Pharmacol. Ther*. 2008; 21(3):558–564. [PubMed: 18342559]
113. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest*. 2007; 131(3):897–899. [PubMed: 17356110]
114. Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet*. 2002; 360(9337):895–900. [PubMed: 12354470]
115. Reichenberger F, Voswinckel R, Enke B, et al. Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension. *Eur. Respir. J*. 2007; 30(5):922–927. [PubMed: 17690123]
116. Milman N, Burton CM, Iversen M, Videbaek R, Jensen CV, Carlsen J. Pulmonary hypertension in end-stage pulmonary sarcoidosis: therapeutic effect of sildenafil? *J. Heart Lung Transplant*. 2008; 27(3):329–334. [PubMed: 18342757]
117. Revatio, package insert. Pfizer Labs; NY, USA:
118. Hazell L, Cornelius V, Wilton LV, Shakir SA. The safety profile of tadalafil as prescribed in general practice in England: results from a prescription-event monitoring study involving 16 129 patients. *BJU Int*. 2009; 103(4):506–514. [PubMed: 18990133]
119. Margo CE, French DD. Ischemic optic neuropathy in male veterans prescribed phosphodiesterase-5 inhibitors. *Am. J. Ophthalmol*. 2007; 143(3):538–539. [PubMed: 17317413]
120. Salvi F, Sarzani R, Giorgi R, et al. Cardiovascular effects of sildenafil in hypertensive men with erectile dysfunction and different alleles of the type 5 cGMP-specific phosphodiesterase (PDE5). *Int. J. Impot. Res*. 2004; 16(5):412–417. [PubMed: 15175637]
121. Paskircioglu L, Atac FB, Erdem SR, Deveci S, Verdi H, Ozkardes H. The association between intron 4 VNTR, E298A and IVF 23+10 G/T polymorphisms of eNOS gene and sildenafil responsiveness in patients with erectile dysfunction. *Int. J. Impot. Res*. 2007; 19(2):149–153. [PubMed: 16871271]
122. Muniz JJ, Lacchini R, Rinaldi TO, et al. Endothelial nitric oxide synthase genotypes and haplotypes modify the responses to sildenafil in patients with erectile dysfunction. *Pharmacogenomics J*. 2011; 13(2):189–196. [PubMed: 22064666]
123. Sperling H, Eisenhardt A, Virchow S, et al. Sildenafil response is influenced by the G protein beta 3 subunit GNB3 C825T polymorphism: a pilot study. *J. Urol*. 2003; 169(3):1048–1051. [PubMed: 12576843]
124. Jetter A, Lazar A, Schomig E, Fuhr U, Kinzig-Schippers M, Sorgel F. The CYP2C9 genotype does not influence sildenafil pharmacokinetics in healthy volunteers. *Clin. Pharmacol. Therapeutics*. 2005; 78(4):441–443.

125. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N. Engl. J. Med.* 1992; 327(2):76–81. [PubMed: 1603139]
126. Mclaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J. Am. Coll. Cardiol.* 2009; 53(17):1573–1619. [PubMed: 19389575]
127. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation.* 2005; 111(23):3105–3111. [PubMed: 15939821]
128. Carlin CM, Celnik DF, Pak O, Wadsworth R, Peacock AJ, Welsh DJ. Low-dose fluvastatin reverses the hypoxic pulmonary adventitial fibroblast phenotype in experimental pulmonary hypertension. *Am. J. Resp. Cell Mol. Biol.* 2012; 47(2):140–148.
129. Ali OF, Growcott EJ, Butrous GS, Wharton J. Pleiotropic effects of statins in distal human pulmonary artery smooth muscle cells. *Resp. Res.* 2011; 12:137.
130. Kawut SM, Bagiella E, Lederer DJ, et al. Randomized clinical trial of aspirin and simvastatin for pulmonary arterial hypertension: ASA-STAT. *Circulation.* 2011; 123(25):2985–2993. [PubMed: 21593252]
131. Cavaasin MA, Demos-Davies K, Horn TR, et al. Selective class I histone deacetylase inhibition suppresses hypoxia-induced cardiopulmonary remodeling through an antiproliferative mechanism. *Circ. Res.* 2012; 110(5):739–748. [PubMed: 22282194]
132. Zhao L, Chen CN, Hajji N, et al. Histone deacetylation inhibition in pulmonary hypertension: therapeutic potential of valproic acid and suberoylanilide hydroxamic acid. *Circulation.* 2012; 126(4):455–467. [PubMed: 22711276]
133. Bogaard HJ, Mizuno S, Hussaini AA, et al. Suppression of histone deacetylases worsens right ventricular dysfunction after pulmonary artery banding in rats. *Am. J. Respir. Crit. Care Med.* 2011; 183(10):1402–1410. [PubMed: 21297075]
134. Hatano M, Yao A, Shiga T, Kinugawa K, Hirata Y, Nagai R. Imatinib mesylate has the potential to exert its efficacy by down-regulating the plasma concentration of platelet-derived growth factor in patients with pulmonary arterial hypertension. *Int. Heart J.* 2010; 51(4):272–276. [PubMed: 20716845]
135. Duggan N, Bonneau O, Hussey M, et al. Comparison of effects of imatinib and nilotinib in a rodent model of pulmonary arterial hypertension. *Am. J. Respir. Crit. Care Med.* 2010; 181:A6304.
136. Voelkel NF, Cool C, Lee SD, Wright L, Geraci MW, Tudor RM. Primary pulmonary hypertension between inflammation and cancer. *Chest.* 1998; 114(Suppl. 3):S225–S230.
137. Gomberg-Maitland M, Maitland ML, Barst RJ, et al. A dosing/cross-development study of the multikinase inhibitor sorafenib in patients with pulmonary arterial hypertension. *Clin. Pharmacol. Therapeut.* 2010; 87(3):303–310.
138. Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. *N. Engl. J. Med.* 2005; 353(13):1412–1413. [PubMed: 16192491]
139. Ghofrani HA, Morrell NW, Hoeper MM, et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *Am. J. Respir. Crit. Care Med.* 2010; 182(9):1171–1177. [PubMed: 20581169]
140. Patterson KC, Weissmann A, Ahmadi T, Farber HW. Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann. Intern. Med.* 2006; 145(2):152–153. [PubMed: 16847299]
141. Hoeper, M.; Barst, R.; Galié, N., et al. Imatinib in pulmonary arterial hypertension, a randomized, efficacy study (IMPRES).. *European Respiratory Socceity Amsterdam 2011 Annual Congress*; Amsterdam, The Netherlands. 24–28 September 2011; (Abstract 413)
142. Kawut SM, Horn EM, Berekashvili KK, et al. Selective serotonin reuptake inhibitor use and outcomes in pulmonary arterial hypertension. *Pulm. Pharmacol. Therapeut.* 2006; 19(5):370–374.

143. Shah SJ, Gomberg-Maitland M, Thenappan T, Rich S. Selective serotonin reuptake inhibitors and the incidence and outcome of pulmonary hypertension. *Chest*. 2009; 136(3):694–700. [PubMed: 19349384]
144. de Man FS, Tu L, Handoko ML, et al. Dysregulated renin–angiotensin–aldosterone system contributes to pulmonary arterial hypertension. *Am. J. Respir. Crit. Care Med*. 2012; 186(8):780–789. [PubMed: 22859525]
145. Rubin L, Pulido T, Channick R, et al. Effect of macitentan on morbidity and mortality in pulmonary arterial hypertension (PAH): results from the SERAPHIN Trial. *Chest*. 2012; 142:A1026–A1026.
146. Tapon VF, Torres F, Kermeen F, et al. 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. *Chest*. 2012; 142(6):1383–1390. [PubMed: 22628490]
147. Simonneau G, Lang I, Torbicki A, et al. Efficacy, safety and tolerability of ACT-293987, a novel oral, non-prostanoid, prostaglandin I₂ (IP) receptor agonist: results from a Phase IIa study in pulmonary arterial hypertension (PAH). *Am. J. Respir. Crit. Care Med*. 2010; 181:A2515.
148. Hoeper MM, Halank M, Wilkens H, et al. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. *Eur. Respir. J*. 2013; 41(4):853–860. [PubMed: 22936711]
149. Ghofrani HA, Hoeper MM, Halank M, et al. Riociguat for chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension: a Phase II study. *Eur. Respir. J*. 2010; 36(4):792–799. [PubMed: 20530034]
150. Kojonazarov B, Myrzaakhmatova A, Sooronbaev T, Ishizaki T, Aldashev A. Effects of fasudil in patients with high-altitude pulmonary hypertension. *Eur. Respir. J*. 2012; 39(2):496–498. [PubMed: 22298615]
151. Fujita H, Fukumoto Y, Saji K, et al. Acute vasodilator effects of inhaled fasudil, a specific Rho-kinase inhibitor, in patients with pulmonary arterial hypertension. *Heart Vessels*. 2010; 25(2):144–149. [PubMed: 20339976]
152. Robbins IM, Hemnes AR, Gibbs JS, et al. Safety of sapropterin dihydrochloride (6r-bh4) in patients with pulmonary hypertension. *Exp. Lung Res*. 2011; 37(1):26–34. [PubMed: 21077779]
153. Dumitrascu R, Kulcke C, Konigshoff M, et al. Terguride ameliorates monocrotaline-induced pulmonary hypertension in rats. *Eur. Respir. J*. 2011; 37(5):1104–1118. [PubMed: 20947677]
154. Dromparis P, Paulin R, Stenson TH, Haromy A, Sutendra G, Michelakis ED. Attenuating endoplasmic reticulum stress as a novel therapeutic strategy in pulmonary hypertension. *Circulation*. 2013; 127(1):115–125. [PubMed: 23149668]
155. Li J, Long C, Cui W, Wang H. Iptakalim ameliorates monocrotaline-induced pulmonary arterial hypertension in rats. *J. Cardiovasc. Pharmacol. Therapeut*. 2013; 18(1):60–69.
156. Perez-Vizcaino F, Cogolludo A, Moreno L. Reactive oxygen species signaling in pulmonary vascular smooth muscle. *Resp. Physiol. Neurobiol*. 2010; 174(3):212–220.
157. Ward JP, Mcmurtry IF. Mechanisms of hypoxic pulmonary vasoconstriction and their roles in pulmonary hypertension: new findings for an old problem. *Curr. Opin. Pharmacol*. 2009; 9(3):287–296. [PubMed: 19297247]
158. Kanki-Horimoto S, Horimoto H, Mieno S, et al. Implantation of mesenchymal stem cells overexpressing endothelial nitric oxide synthase improves right ventricular impairments caused by pulmonary hypertension. *Circulation*. 2006; 114(Suppl. 1):I181–I185. [PubMed: 16820570]
159. Reynolds AM, Holmes MD, Danilov SM, Reynolds PN. Targeted gene delivery of BMPR2 attenuates pulmonary hypertension. *Eur. Respir. J*. 2012; 39(2):329–343. [PubMed: 21737550]
160. Kataoka M, Kawakami T, Tamura Y, et al. Gene transfer therapy by either type 1 or type 2 adeno-associated virus expressing human prostaglandin i₂ synthase gene is effective for treatment of pulmonary arterial hypertension. *J. Cardiovasc. Pharmacol. Therapeut*. 2013; 18(1):54–59.
161. Morecroft I, White K, Caruso P, et al. Gene therapy by targeted adenovirus-mediated knockdown of pulmonary endothelial Tph1 attenuates hypoxia-induced pulmonary hypertension. *Mol. Ther*. 2012; 20(8):1516–1528. [PubMed: 22525513]

162. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann. Intern. Med.* 1991; 115(5):343–349. [PubMed: 1863023]
201. Efficacy, safety, tolerability and pharmacokinetics (PK) of nilotinib (AMN107) in pulmonary arterial hypertension (PAH). <http://clinicaltrials.gov/ct2/show/NCT01179737>
202. United Therapeutics Corporation. UT-15C treprostinil diethanolamine sustained release tablets (oral treprostinil). www.unither.com/oral-treprostinil-for-pah
203. A multi-center, open-label, multiple dose, dose finding study exploring the safety and tolerability of beraprost sodium modified release in PAH patients. <http://clinicaltrials.gov/ct2/show/NCT00781885>.
204. United Therapeutics Corporation. BPS for PAH. www.unither.com/bps-for-pah
205. ACT-293987 in pulmonary arterial hypertension. <http://clinicaltrials.gov/ct2/show/NCT01106014>
206. 6R-BH4 pulmonary arterial hypertension study. www.clinicaltrials.gov/ct2/show/NCT00435331

Box 1. Clinical classification of pulmonary hypertension

- Group 1: pulmonary arterial hypertension
 - Idiopathic
 - Heritable
 - Drug- and toxin-induced
 - Disease-associated (connective tissue disease, HIV, portal hypertension, congenital heart disease, schistosomiasis and chronic hemolytic anemia, including sickle cell disease)
 - Persistent pulmonary hypertension of the newborn
- Group 1': pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
 - Hemangiomatosis
- Group 2: pulmonary hypertension due to left heart disease
 - Systolic dysfunction
 - Diastolic dysfunction
 - Valvular disease
- Group 3: pulmonary hypertension due to lung diseases and/or hypoxia
 - COPD
 - Interstitial lung disease
 - Other restrictive and obstructive pulmonary diseases
 - Sleep-disordered breathing
 - Alveolar hypoventilation disorders
 - Chronic high-altitude exposure
 - Developmental abnormalities
- Group 4: chronic thromboembolic pulmonary hypertension
- Group 5: pulmonary hypertension with unclear multifactorial mechanisms
 - Hematologic disorders
 - Systemic disorders (sarcoidosis)
 - Metabolic disorders (thyroid disease and Gaucher's disease)
 - Others (tumoral obstruction and chronic renal failure on dialysis)

COPD: Chronic obstructive pulmonary disease.

Data taken from [3].

Executive summary

Background

- Pulmonary hypertension (PH) is a progressive disease that is classified by the WHO into five broad categories, each with a different etiology and pathogenesis, but all involving a mean pulmonary artery pressure of 25 mmHg or greater.
- Three drug classes are FDA-approved for chronic treatment of WHO Group 1 PH (pulmonary arterial hypertension), whereas no drugs have been approved for Groups 2–5.

Current treatments

- Prostacyclin analogs are the only drug class that have demonstrated a mortality benefit in pulmonary arterial hypertension, but are plagued by a poor side-effect profile and inconvenient non-oral dosage forms.
- Endothelin receptor antagonists can be administered orally, but have not yet demonstrated mortality benefits and have a moderate side-effect profile.
- Phosphodiesterase type 5 inhibitors are administered orally and have a more acceptable side-effect profile; however, they also have yet to demonstrate a mortality benefit.
- Because of the heterogeneity of PH presentation, pharmacogenomics could help identify the best treatment for individuals; however, while little pharmacogenomic research has been done on phosphodiesterase type 5 inhibitors, almost none has been undertaken on endothelin receptor antagonists or prostacyclin analogs.

Future treatments

- New treatments are being developed and include repurposed drugs, including tyrosine kinase inhibitors, statins and valproic acid. New drug entities are also under development including prostaglandin receptor agonists, guanylate cyclase stimulators and gene therapy.

Table 1

Summary of FDA-approved drug classes for treatment of pulmonary arterial hypertension.

Drug class	Mortality benefit shown?	Side-effect profile	Dosage forms available (dosing interval)	Pharmacogenomic data available
Prostacyclin analogs	Yes	Poor	Inhalation (2–6 h) sc. infusion (continuous) iv. infusion (continuous)	Minimal
ERAs	No	Moderate	Oral (12–24 h)	Minimal
PDE5 inhibitors	No	Good	Oral (8–24 h)	Some

ERA: Endothelin receptor antagonist; iv.: Intravenous; PDE5: Phosphodiesterase type 5; sc.: Subcutaneous.

Table 2

Treatment effects of current pulmonary arterial hypertension drug classes in all categories of pulmonary hypertension.

Drug class	WHO PH Classification (strength of evidence) [†]				
	<i>Group 1</i>	<i>Group 2</i>	<i>Group 3</i>	<i>Group 4</i>	<i>Group 5</i>
ERAs	Beneficial (strong)	Harmful (weak)	Neutral (weak)	Neutral (moderate)	Unknown
PDE5 inhibitors	Beneficial (strong)	Beneficial (weak)	Harmful (weak)	Beneficial (weak)	Unknown
Prostacyclin analogs	Beneficial (strong)	Harmful (moderate)	Neutral (weak)	Beneficial (weak)	Unknown

ERA: Endothelin receptor antagonist; PDE5: Phosphodiesterase type 5; PH: Pulmonary hypertension.

[†] Strong: multiple randomized clinical trials agree; Moderate: one clinical trial completed or multiple trials conflict; Weak: only small or nonrandomized trials available; Unknown: not enough data to determine benefit.