Pharmacotherapy for Idiopathic Pulmonary Arterial Hypertension During the Past 25 Years

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Objective. To review the current pharmacotherapy for idiopathic pulmonary arterial hypertension (IPAH).

Methods. A search of the primary literature was conducted by using MEDLINE, the National Institutes of Health medical research Web site (www.clinicaltrials.gov), and the United States Food and Drug Administration's Center for Drug Evaluation and Research Web site (www.fda.gov/cder).

Results. Until the early 1980s, conventional therapy for IPAH consisted of anticoagulation, diuretics, digitalis extracts, and supplemental oxygen, yet the 5-year mortality rate remained at 66%. Calcium channel blocker therapy was introduced with the hope that it would improve survival in patients with IPAH, but it was found to be effective in only approximately 25% of patients. In 1996, intravenous epoprostenol was the first drug to show long-term benefit on hemodynamics, exercise capacity, and survival. However, administration of epoprostenol requires a permanently indwelling central venous catheter, and tachyphylaxis is common, necessitating continuous dosage escalations. Subsequently, treprostinil, a prostacyclin analog of epoprostenol that can be administered by continuous subcutaneous infusion, was introduced, followed by aerosolized iloprost, a prostacyclin analog for inhalation. An increasing understanding of the multiple pathogeneses of IPAH led to the discovery of another target for drug therapy, and bosentan, an orally administered agent, became the first endothelin-receptor antagonist approved for treatment of IPAH. Most recently, the phosphodiesterase inhibitor, sildenafil, has received approval from the United States Food and Drug Administration for the treatment of IPAH.

Conclusion. Recently developed pharmacotherapies offer greater effectiveness and safety than traditional agents for the treatment of IPAH.

Key words: pulmonary arterial hypertension, IPAH, prostacyclins, endothelin-receptor antagonists, phosphodiesterase inhibitors.

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OUTLINE

As recently as the early 1980s, a diagnosis of idiopathic pulmonary arterial hypertension (IPAH, also known as primary pulmonary hypertension) was tantamount to a death sentence, with a mean survival time after diagnosis of 2.8 years.[1] This is a rare disease, with an incidence of only 1–2 persons/million, but it affects healthy adults in their prime, frequently in the third or fourth decade of life, and occurs in women 3 times more frequently than in men.

For almost a century, since Romberg first described the abnormal pulmonary vasculature findings of IPAH, the only drug therapy that improved survival was anticoagulation with warfarin.[2] Not until the 1980s were three significant advances made in the treatment of IPAH. First, in 1981 the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) established the Patient Registry for the Characterization of Primary Pulmonary Hypertension. This registry facilitated cooperation among 32 medical centers while screening nearly 200 patients to elucidate the clinical and pathologic characteristics of IPAH, opening the door to coordinated scientific scrutiny of this disease.[3, 4] Shortly thereafter, the second advance occurred with the introduction of high-dose calcium channel blockers as therapy for IPAH. Vasodilatory effects in the pulmonary vasculature improved clinical symptoms, reduced pulmonary artery pressure, and caused regression of right ventricular hypertrophy. Unfortunately, this effect was seen in only the 20-30% of patients who exhibited pulmonary vascular responsiveness to acute vasodilator challenge.[5] The acute challenge itself, using agents such as hydralazine, diazoxide, phentolamine, or isoproteronol, posed serious risks due to the potential for prolonged systemic hypotension in patients who were already hemodynamically compromised.[6–8] Therefore, the third seminal event was the successful use of epoprostenol, a synthetic formulation of endogenous prostacyclin, a potent vasodilator, in testing acute pulmonary vascular responsiveness in patients with pulmonary hypertension. Because of its short half-life, epoprostenol offered a safer alternative for vasodilator challenge without the potential for sustained, life-threatening systemic hypotension seen with previously used agents, and it quickly became the reference standard in pulmonary vascular testing.[3, 9]

Recently, at the request of the American College of Chest Physicians, the current body of evidence regarding IPAH was reviewed and summarized, then evaluated by an international panel of experts. The resultant guidelines published in 2004 include recommendations on screening, early detection and diagnosis, and medical and surgical therapies for and prognosis of IPAH, along with grading of the evidence, benefits to the patient, and strength of the recommendations.[10] Although IPAH remains an incurable disease, in the past 2.5 decades, significant advances have been made in our understanding of its pathophysiology, in recently available treatment options for this condition, and, consequently, in the overall prognosis for patients.

Clinical Presentation

Patients with IPAH often have nonspecific symptoms, which confound its recognition and result in a mean length of time from onset of the initial symptoms to diagnosis of approximately 2 years.[4] Initial symptoms include fatigue and shortness of breath. As the disease progresses, additional clinical features may include dizziness or lightheadedness on exertion, peripheral edema, exertional chest pain, and syncope. Clinical signs often include an increase in the pulmonic component of the second heart sound, indicative of elevated pulmonary artery pressure.[4] Radiographic changes such as a prominent central pulmonary artery, and electrocardiographic abnormalities including large P waves, right ventricular hypertrophy, or right axis deviation, are commonly seen.[2, 4] Echocardiography frequently shows enlargement of the right side of the heart, with a reversal of the normal septal curvature. Pressures in the left side of the heart are generally normal, although compression of the left chambers by extreme dilatation of the right chambers can result in decreased left ventricular filling and, consequently, small increases in diastolic pressures.[11]

Diagnosis

A diagnosis of IPAH is essentially a diagnosis of exclusion. If symptoms of pulmonary arterial hypertension (PAH) are present, chest radiography and pulmonary function tests can exclude emphysema, pulmonary or cystic fibrosis, and thoracic cage abnormalities. Echocardiography

will rule out left-sided heart disease, valvular anomalies, and congenital heart disease, whereas ventilation-perfusion scanning and angiography can eliminate the diagnosis of thromboembolic disease. Finally, blood tests such as for antinuclear antibody, rheumatoid factor, human immunodeficiency virus (HIV), hepatitis, and aspartate aminotransferase and alanine aminotransferase levels can rule out causes of pulmonary hypertension such as lupus, scleroderma, rheumatoid arthritis, acquired immunodeficiency syndrome, and liver disease.

The lack of an identifiable cause confers the term "idiopathic" on this condition. Ultimately, although invasive, catheterization of the right side of the heart revealing elevated pulmonary artery pressure, increased right atrial pressure, and a decreased cardiac index provides the final diagnosis. Mortality in IPAH has been shown to correlate directly with the degree of derangement in these three hemodynamic variables.[1] Diagnosis of IPAH follows the American College of Chest Physicians' guideline parameters of mean pulmonary artery pressure greater than 25 mm Hg with a left atrial pressure less than 15 mm Hg. In comparison, the mean pulmonary artery pressure in a healthy adult is approximately 14 mm Hg at rest.

Pathophysiology

In a healthy individual, the right ventricle is a thin-walled muscular pump, and normal pulmonary circulation is a high-flow, low-resistance system. In pulmonary hypertension, however, pulmonary artery pressure and pulmonary vascular resistance are elevated. A consequence of the increased pulmonary artery pressure is right ventricular hypertrophy, progressing eventually to right-sided heart failure. Initially, cardiac output remains normal at rest but is limited during exercise. Right myocardial perfusion may be restricted by increases in right ventricular pressures, resulting in right ventricular ischemia. As the disease progresses, cardiac output becomes compromised even at rest. In addition, tricuspid regurgitation may develop, contributing to heart failure.[11] The three most common causes of death in IPAH are right-sided heart failure, pneumonia, and sudden death caused, individually or in combination, by acute pulmonary embolism, right ventricular ischemia, pulmonary hemorrhage, or arrhythmias due to arterial hypoxia and acidosis.[2, 11]

Cellular Pathology

Idiopathic pulmonary arterial hypertension is the consequence of three characteristic pathologic elements: in situ thrombosis, vasoconstriction, and vascular wall remodeling. In situ thrombosis, evident in most patients, may be associated with a hypercoaguable state, fibrinolytic defects, platelet abnormalities, and injury to the endothelium.[12, 13] Vasoconstriction is thought to be the result of endothelial dysfunction, causing an imbalance in endothelium-derived, vasoactive mediators such as nitric oxide, prostacyclin, thromboxane, and endothelin-1. Studies have shown that patients with IPAH exhibit decreased production of the vasodilator nitric oxide in the pulmonary vasculature, as well as impaired production of prostacyclin, a potent endogenous vasodilator and inhibitor of platelet aggregation.[14, 15] In contrast, production of thromboxane, an ecosanoid that acts to constrict pulmonary blood vessels and enhance platelet aggregation, is increased in IPAH, as is production of endothelin-1, a vasoconstrictive and pro-proliferative peptide in the pulmonary endothelium.[15, 16]

Finally, pulmonary vascular wall remodeling occurs secondary to chronic pulmonary vasoconstriction, resulting in a smaller cross-sectional area and decreased distensibility in pulmonary vessels. In the early stages of IPAH, this remodeling involves smooth muscle hypertrophy, which may be reversed with oral vasodilator therapy such as calcium channel blockers.[17] Later stages of the disease, however, exhibit cellular proliferation and hyperplasia of the intimal, medial, and adventitial layers of small pulmonary arteries and arterioles (Figure 1).[18] Until the introduction of recently approved drug therapies, this late-stage remodeling had been considered to be irreversible by the time a patient presented and IPAH was diagnosed.[18]

Another mechanism of vasoconstriction may be dysfunctional smooth muscle cells in the pulmonary vasculature. Inhibition of voltage-gated potassium channels on these cells increases the influx of calcium and therefore the degree of muscle contraction. In healthy individuals, low levels of oxygen activate these hypoxia-sensitive channels, resulting in vasodilation. In IPAH, however, these potassium channels are turned off. The result is increased intracellular calcium concentrations, leading to vasoconstriction and smooth muscle hypertrophy.[18, 19]

Treatment Options

Literature Search

A MEDLINE search was conducted by coupling the key search term idiopathic pulmonary arterial hypertension with each pharmacologic agent used in the treatment of IPAH. Because most of the advances in treating IPAH have occurred since the NIH patient registry was begun in 1981, the search was limited to the period from January 1981–September 2005. In addition, information regarding upcoming and ongoing IPAH clinical trials was retrieved through searches of the NIH medical research Web site (www.clinicaltrials.gov) and the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research Web site (www.fda.gov/cder).

Identified primary research articles, as well as primary research referenced by IPAH review articles, were examined for relevance to the pharmacotherapy for IPAH. Articles were excluded from the literature review if they pertained to studies of pharmacologic agents in the treatment of conditions other than IPAH (e.g., bosentan for the treatment of systemic hypertension), if the studies were conducted in animals, if the articles were not in English, and if the research was performed in neonatal populations, as this group can be affected by persistent pulmonary hypertension of the newborn, which has a different etiology and treatment options than those of IPAH.

The literature search identified 365 articles, of which 178 met the stated selection criteria and were reviewed. Seventy-five articles were deemed appropriate for use in developing this review. These articles consisted of 56 primary research articles, 5 review articles, 4 case reports, 3 consensus panel statements, 4 package inserts, 1 report, 1 editorial, and 1 letter.

Conventional Therapy

Warfarin has been shown to improve survival in patients with IPAH, resulting in a significant increase in the number of patients surviving to 3 years.[2, 17] Dilated right heart chambers and sluggish pulmonary blood flow, in addition to the characteristic finding of in situ thrombosis in this disease, are indications for anticoagulation in patients with IPAH. Because these patients have

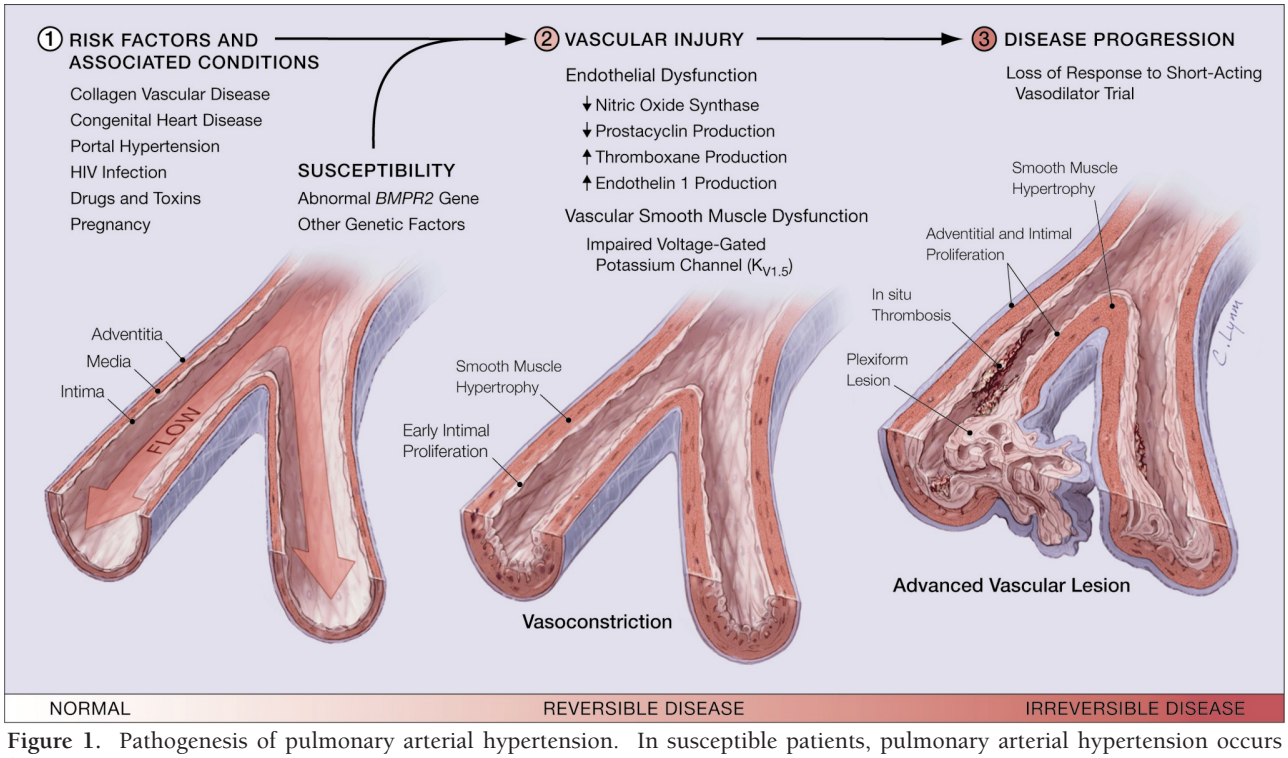

Figure 1. Pathogenesis of pulmonary arterial hypertension. In susceptible patients, pulmonary arterial hypertension occurs from an insult to the pulmonary vascular bed. This insult results in an injury that progresses to produce the characteristic pathologic features. HIV = human immunodeficiency virus; *BMPR2* = bone morphogenetic protein receptor II gene, which is believed to be the gene responsible for the inherited form of the disease. (From reference 18 with permission.)

Table 1. Summary of New Agents for the Treatment of Idiopathic Pulmonary Arterial Hypertension

	Epoprostenol	Bosentan	Treprostinil	Iloprost
Year of FDA approval	1995	2001	2002	2004
Therapeutic category	Prostaglandin (prostacyclin)	Endothelin receptor antagonist	Prostaglandin analog	Prostaglandin analog
Administration route	Intravenous	Oral	Subcutaneous	Inhalation
Indication	NYHA III–IV	NYHA III–IV	NYHA II–IV to improve exercise capacity	NYHA III–IV
Usual dosage	Start at 2 ng/kg/min, then increase by 2 ng/kg/min every 15 min until dose-limiting effects occur (no ceiling dose established)	Start at 62.5 mg b.i.d. for 4 wks, then 125 mg b.i.d.	Start at 1.25 ng/kg/min, then increase by ≤ 1.25 ng/kg/min for 4 wks, then ≤ 2.5 ng/kg/min/wk (little experience with > 40 ng/kg/min)	Start at 2.5 µg 6–9 times/day (no more than q2h), increase to 5 µg if tolerated
Contraindications	Heart failure (left-sided), pulmonary edema	Pregnancy (category X), coadministration with cyclosporine or glyburide	None reported	None reported
Warnings	Abrupt withdrawal should be avoided; must be reconstituted using only sterile diluent supplied by manufacturer	Liver function tests (AST, ALT) must be measured before starting therapy and monthly thereafter	Intended for subcutaneous use only	Intended for inhalation only using the nebulizer systems specified by the manufacturer; monitor for signs of hypotension or pulmonary edema
Adverse effects	Headache, flushing, jaw pain, diarrhea, nausea, rash, musculoskeletal aches (all dose dependent)	Abnormal liver function, anemia, flushing, palpitations, dyspepsia, pruritus	Infusion site pain, infusion site reaction (erythema, rash, or induration), diarrhea, jaw pain, edema, flushing, nausea	Flushing, cough, headache, trismus, insomnia, nausea, hypotension
Drug interactions	Antihypertensive agents, diuretics, and vasodilators (additive effects); anticoagulants (increased risk of bleeding)	Cyclosporine (increased bosentan levels, decreased cyclosporine levels), hormonal contraceptives (decreased contraceptive levels), glyburide (increased risk of elevated liver enzyme levels), ketoconazole and tacrolimus (increased bosentan levels), warfarin (decreased warfarin levels), glipizide, simvastatin, sildenafil (decreased levels of these drugs)	Antihypertensive agents, diuretics, and vasodilators (additive effects); anticoagulants (increased risk of bleeding)	Antihypertensive agents, diuretics, and vasodilators (additive effects); anticoagulants (increased risk of bleeding)

FDA = United States Food and Drug Administration; NYHA = New York Heart Association functional class; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

a compromised pulmonary vasculature with little ability to dilate or recruit unused vessels, even minor pulmonary obstruction by a thrombus can be life threatening. Therefore, unless contraindicated, indefinite therapy with warfarin (goal international normalized ratio [INR] of 1.5–2.5) is recommended in adults and children with right-sided heart failure or a hypercoagulable

Table 1. (continued)

Sildenafil
2005
Phosphodiesterase type-5 inhibitor
Oral
NYHA II–IV to improve exercise ability
20 mg t.i.d.
Coadministration of organic nitrates either regularly or intermittently
Coadministration with ritonavir not recommended; monitor for signs of hypotension; use in patients with pulmonary veno-occlusive disease not recommended
Use with caution in patients with unstable angina, myocardial infarction, stroke, or life-threatening arrhythmias in the last 6 mo; blood pressure > 170/110; retinitis pigmentosa; concurrent bosentan use; concurrent α-blockers; anatomical deformation of the penis or predisposition to priapism
Epistaxis, headache, dyspepsia, flushing, insomnia, erythema
Vitamin K antagonists (increased risk of bleeding), organic nitrates (hypotension), ketoconazole, itraconazole, erythromycin, ritonavir, saquinavir (increased sildenafil levels), bosentan (decreased sildenafil levels)

state with IPAH. Anticoagulation with warfarin also should be considered in children with IPAH without right-sided heart failure or a hypercoagulable state; if such children are younger than 5 years of age, the dosage should be adjusted to maintain a lower target INR.[10]

During diagnostic testing for IPAH, patients are typically given an acute vasodilator challenge with use of a short-acting pulmonary vasodilator (e.g., intravenous epoprostenol, inhaled nitric oxide, or intravenous adenosine). Patients who respond with a decrease in mean pulmonary artery pressure of at least 10 mm Hg over baseline and an increased or unchanged cardiac output are considered responders. For these patients, calcium channel blockers such as nifedipine or diltiazem are an appropriate and effective first-line therapy, in the absence of right-sided heart failure.[17, 18]

Results of a prospective, open-label, parallel-group study showed a 94% 5-year survival rate for responders treated with high-dose calcium channel blockers compared with a 55% survival rate among nonresponders treated with conventional therapy (digoxin, diuretics, and/or warfarin), and a 38% survival rate in the historical control group.[17] Unfortunately, only approximately 25% of all patients with IPAH experience a positive acute vasodilator trial and are able to benefit from high-dose calcium channel blocker therapy. Indeed, in patients with fixed or late-stage IPAH, the only treatment effect of high-dose calcium channel blockers is systemic hypotension, causing a decrease in an already compromised cardiac output, with potentially disastrous consequences. In addition, the high doses of nifedipine (up to 180 mg/day) and diltiazem (up to 720 mg/day) necessary to produce beneficial effects in patients with IPAH, and the nonselectivity of calcium channel blockers for the pulmonary vasculature, may result in dose-limiting systemic hypotension even in patients for whom calcium channel blocker therapy is an option.[10, 17]

Although diuretics can reduce fluid overload associated with right-sided heart failure, the right ventricle is highly dependent on preload. Cautious use of diuretics must be exercised to avoid a deleterious decrease in cardiac output with resultant systemic hypotension, syncope, and renal insufficiency.[10] Various diuretics have been used to treat clinical signs of right-sided heart failure in patients with IPAH, including furosemide, hydrochlorothiazide, metolazone, and bumetanide. A less aggressive, potassium-sparing diuretic such as triamterene, however, may be the preferred agent, particularly in early stages of the disease or with concomitant use of digoxin. In patients not receiving digoxin, spironolactone is an attractive agent because of

its aldosterone-inhibiting properties in the setting of sympathetic nervous system and renin-angiotensin-aldosterone system activation due to increased right-sided heart filling pressure and upstream venous congestion in patients with IPAH.[20] Spironolactone's ability to increase digoxin concentrations, however, may complicate therapy if these drugs are coadministered. Patients requiring additional diuresis can receive low-dose loop diuretics, with dosage titrated to maximum effect, with metolazone added in refractory cases. To tread the line between symptom amelioration and compromised cardiac output, careful monitoring of blood pressure, fluid status, serum electrolyte levels, and renal function is critical.

Limited data suggest that digoxin may be useful in mitigating the negative inotropic effects of calcium channel blockers in the treatment of IPAH, as well as improving cardiac output in patients with IPAH and refractory right ventricular failure.[21] As in left-sided heart failure, however, a long-term survival benefit has never been shown with digoxin therapy in patients with IPAH. If used, serum digoxin concentrations must be carefully monitored due to the increased risk of digoxin toxicity when hypoxemia or diuretic-induced hypokalemia is present. Rhythm disturbances associated with digoxin toxicity are of particular concern in patients with IPAH, as their compromised right ventricular function presents an increased baseline risk for sudden cardiac death.

Because hypoxemia can lead to pulmonary vasoconstriction, supplemental oxygen therapy may provide a degree of pulmonary-specific vasodilation in patients with IPAH. In a recent study, treatment with 100% oxygen provided a significant decrease in mean pulmonary artery pressure and increase in cardiac output.[22] In addition, some patients with IPAH experience significant nocturnal hypoxemia and may benefit from supplemental oxygen therapy at night to help attenuate vasoconstrictive disease progression and provide symptomatic relief. Current recommendations advise use of supplemental oxygen to maintain oxygen saturations of greater than 90% at all times.[10]

Despite conventional medical therapy, IPAH inevitably will progress to New York Heart Association (NYHA) functional class III or IV right-sided heart failure in most patients, necessitating lung or heart-lung transplantation.[23] The paucity of donor organs, however, limits the usefulness of this treatment option, and the reality of the organ distribution system often dictates whether the procedure is a single lung, bilateral lung, or heart-lung transplant. Mortality among patients while waiting on transplant lists is high, and the procedure itself has an in-hospital mortality rate of approximately 15%. Reports of 4-year survival rates vary from 55–100%, and studies show a dramatic reduction in mean pulmonary artery pressure after transplantation, as well as appreciable improvements in quality of life.[24, 25] The rate of survival to transplantation can be improved with atrial septostomy, a surgical procedure that creates a right-to-left shunt in the heart by forming a hole in the atrial septum. This improves cardiac output and can provide a bridge to lung or heart-lung transplantation in patients with end-stage IPAH.[26]

New Agents

Epoprostenol

Epoprostenol is a prostaglandin (or prostacyclin) that activates intracellular adenylate cyclase, causing increased cyclic adenosine 3′,5′-monophosphate (cAMP) concentrations (Table 1). Increased cAMP mediates vasodilation of the pulmonary vasculature, as well as inhibition of platelet aggregation. Synthesized in the body from arachadonic acid through the cyclo-oxygenase pathway, prostacyclin is released by vascular endothelial cells. In patients with IPAH, however, production of prostacyclin is depressed, resulting in impaired pulmonary vasodilation and increased platelet activation.[15]

Epoprostenol initially was used only as a diagnostic agent in acute vasodilator trials, but the focus changed to treatment when it became apparent that continuous intravenous infusion of epoprostenol could provide a life-saving bridge to lung transplantation in patients with IPAH.[18, 27] Eventually its long-term efficacy was proved in clinical trials, and it is now considered a long-term alternative to transplantation. In one study, 70% of lung transplant candidates treated with epoprostenol were removed from the transplant list or transplantation was deferred because of clinical improvement.[27] As a first-line treatment option in patients who do not exhibit a positive response to acute vasodilator challenge and who, therefore, are not candidates for high-dose calcium channel blocker therapy, epoprostenol improves mean pulmonary artery pressure, pulmonary vascular resistance, cardiac output, exercise tolerance, quality of life, and survival.

Table 2. Studies of Epoprostenol in Idiopathic Pulmonary Arterial Hypertension

Design	Duration	Population	No. of Patients	Regimens	Results
Multicenter randomized, parallel groups[28]	8 wks	IPAH only (NYHA II–IV)	11	Epoprostenol + conventional therapy	mPAP ↓ from 58.6 to 49.3 mm Hg (p=0.057[a]) TPR ↓ from 21.6 to 13.9 units (p=0.022[a]) CO ↑ from 3.3 to 3.9 L/min (p=0.020[a]) SMWD ↑ from 246 to 378 m (p=0.011[a])
			12	Conventional therapy	mPAP unchanged at 62.2 mm Hg TPR ↓ from 20.6 to 20.4 units (p=0.960[a]) CO ↑ from 3.5 to 3.9 L/min (p=0.393[a]) SMWD ↑ from 205 to 292 m (p=0.022[a])
Multicenter, open-label, randomized, parallel groups[29]	12 wks	IPAH only (NYHA III–IV)	41	Epoprostenol + conventional therapy	Primary end point: SMWD ↑ from 316 to 348 m (p=0.003[b]) Secondary end points: Mortality = no deaths (p=0.003[b]) mPAP ↓ from 62.0 to 57.2 mm Hg (p=0.002[b]) PVR ↓ from 16.0 to 12.6 mm Hg/L/min (p=0.001[b]) CI ↑ from 2.0 to 2.3 L/min/m^2 ("significant" [no p value given])
			40	Conventional therapy	Primary end point: SMWD ↓ from 272 to 257 m (p=0.003[b]) Secondary end points: Mortality = 8 deaths (p=0.003[b]) mPAP ↑ from 59.0 to 60.9 mm Hg (p=0.002[b]) PVR ↑ from 16.0 to 17.5 mm Hg/L/min (p=0.001[b]) CI ↓ from 2.1 to 1.9 L/min/m^2 ("significant" [no p value given])
Case series[30]	16.7 mo	IPAH only (NYHA III–IV)	27	Epoprostenol dosed per aggressive treatment protocol (mean dose at follow up 40 ng/kg/min) + conventional therapy	mPAP ↓ from 67 to 52 mm Hg (p=0.001[a]) PVR ↓ from 16.7 to 7.9 units (p=0.001[a]) CO ↑ from 3.7 to 6.3 L/min (p=0.001[a]) Exercise time ↑ from 261 to 631 sec (p=0.001[a]) Changes in NYHA class (p=0.001[a]): Patients in NYHA I: ↑ from 0% to 22% Patients in NYHA II: ↑ from 0% to 74% Patients in NYHA III: ↓ from 63% to 4% Patients in NYHA IV: ↓ from 37% to 0%
Case series[31]	12–24 hrs (epoprostenol dosage reduction) with follow-up over 13.6 mo	IPAH only (NYHA III–IV)	12	Epoprostenol mean dose of 98 ng/kg/min (high dose) over 6–24 hrs reduced to 60 ng/kg/min + conventional therapy	mPAP (mm Hg): baseline = 60, high-dose = 45 (p=0.001[a]), low-dose = 46 (p=0.001[a]) PVR (Woods units): baseline = 13, high-dose = 4 (p<0.001[a]), low-dose = 5 (p<0.001[a, c]) CI (L/min/m^2): baseline = 2.2, high-dose = 5.5 (p<0.001[a]), low-dose = 4.0 (p<0.001[a, c])

Several key studies elucidate these findings (Table 2).[28–33]

In 1990, the first controlled study was conducted to investigate the effects of treatment with epoprostenol on pulmonary hemodynamics and exercise tolerance in patients with IPAH.[28] The 8-week trial randomly assigned 11 patients to conventional therapy (warfarin plus digoxin, supplemental oxygen, diuretics, methyldopa nitroglycerin ointment, and/or oral vasodilators such as diltiazem or nifedipine) plus continuously administered intravenous epoprostenol, whereas 12 patients received conventional therapy alone. During the trial, three patients from the conventional treatment group and one patient from the epoprostenol group died. Results from the remaining patients showed significant favorable hemodynamic changes from baseline in the epoprostenol group, including a decrease in total pulmonary resistance of 36%, and an 18% increase in cardiac output. Changes in exercise tolerance, as measured by the distance

Table 2. Studies of Epoprostenol in Idiopathic Pulmonary Arterial Hypertension (continued)

Design	Duration	Population	No. of Patients	Regimens	Results	
Case series[32]	36.3 ± 27.1 mo (mean ± SD)	IPAH only (NYHA III–IV)	162	Epoprostenol + conventional therapy	Actual survival: 1 yr: 87.8% 2 yrs: 76.3% 3 yrs: 62.8%	Predicted survival[d] 1 yr: 58.9% (p<0.001[e]) 2 yrs: 46.3% (p<0.001[e]) 3 yrs: 35.4% (p<0.001[e])
					Remaining results were measured at the end of period 1 (17 ± 15 mo): mPAP ↓ from 61 to 53 mm Hg (p<0.0001[a]) PVR ↓ from 16.7 to 10.2 units (p<0.0001[a]) CO ↑ from 3.41 to 5.05 L/min (p<0.0001[a]) Exercise time ↑ from 217 to 432 sec (p<0.0001[a]) Changes in NYHA classification ↓ from mean of class 3.5 to 2.5 (p<0.001[a])	

CI = cardiac index; CO = cardiac output; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NYHA = New York Heart Association functional class; PVR = pulmonary vascular resistance; SMWD = 6-minute–walk distance; TPR = total pulmonary resistance; ↑ = increase; ↓ = decrease.
Statistically significant differences are defined as p<0.05.
[a]p value for change over baseline.
[b]p value for comparison between treatment groups.
[c]p value for comparison to treatment with high-dose epoprostenol (mean dose of 98 ng/kg/min).
[d]National Institutes of Health registry equation.[1]
[e]p value for comparison between actual survival of patients taking epoprostenol and predicted survival based on National Institutes of Health registry equation.[1, 33]

covered in a 6-minute walk, increased in the epoprostenol group by 54%. In contrast, except for an increased mean 6-minute–walk distance, none of these parameters showed statistically significant changes in the conventional treatment group. Epoprostenol dosages were individualized based on the greatest hemodynamic benefit achieved without significant adverse effects in each patient and were found to require repeated escalation to maintain symptom control. Similar reports of tachyphylaxis have been documented in other trials.[29, 30] Although this study represented only a short-term trial of epoprostenol, it indicated that unambiguous clinical benefits existed over conventional therapy.

A larger, 12-week trial compared intravenous epoprostenol plus conventional treatment with conventional therapy alone in 81 patients with IPAH in NYHA class III or IV.[29] Exercise capacity significantly improved over baseline in 41 patients treated with epoprostenol (mean distance covered during the 6-min walk increased from 316 to 348 m) compared with 40 patients receiving conventional therapy, who experienced a significant decline in exercise capacity (mean 6-min–walk distance decreased from 272 to 257 m). The NYHA class in the epoprostenol group improved in 40% of the patients, was unchanged in 48%, and worsened in 13%. By contrast, NYHA class in the conventional therapy group improved in only 3%, was unchanged in 87%, and worsened in 10% of patients. Significant decreases in the mean pulmonary artery pressure and pulmonary vascular resistance favored patients receiving epoprostenol.

Mortality was evaluated as a secondary end point: eight patients (10%) died during the 12-week study; all were in the conventional treatment group. As previously noted, frequent dosage increases of epoprostenol were necessary to maintain the beneficial effects of therapy. The initial mean ± SD dose of 5.3 ± 0.5 ng/kg/minute was increased to 9.2 ± 0.8 ng/kg/minute by the end of the study. Again, clinical benefits from epoprostenol therapy were recognized, and additional knowledge was being gained, but longer term studies were needed before epoprostenol could offer genuine hope for patients with IPAH.

A separate analysis of the same patient population studied the effects of epoprostenol on echocardiographic measures of right ventricular structure and function.[34] Patients treated with epoprostenol had a significantly smaller increase in right ventricular end-diastolic area (an indication of right ventricular dilatation associated with a loss of contractile function), as well as a significantly lower maximal tricuspid regurgitant jet velocity (reflecting a lower

pulmonary artery systolic pressure), when compared with those receiving conventional therapy. The epoprostenol group also exhibited significantly greater improvement in the eccentricity index in both systole and diastole (indicative of the degree of curvature of the ventricular septum caused by elevated right ventricular pressures and resulting in abnormal left ventricular filling dynamics) compared with the conventional therapy group. This analysis indicated that therapy with epoprostenol could result in beneficial changes in right-sided heart structure and function, in addition to previously shown clinical benefits.

Through the mid-1990s, conventional wisdom suggested that optimal epoprostenol dosing required an aggressive treatment protocol to overcome the inevitable effects of tachyphylaxis. In a case series considering the effectiveness of such an epoprostenol regimen, dosages were increased as soon as tolerance developed or at any time a reduction in adverse effects permitted a dosage increase.[30] The goal was to maintain the 27 study participants at the highest tolerated dose throughout the trial period of 16.7 months. In seven of eight participants who initially exhibited minimal or no response to acute vasodilator challenge, an unexpected 39% reduction in pulmonary vascular resistance was achieved with long-term epoprostenol therapy, indicating that epoprostenol may have the potential to reverse vascular remodeling in addition to possessing vasodilatory properties. In addition, significant decreases of 22% in mean pulmonary artery pressure and 53% in pulmonary vascular resistance, as well as a significantly increased cardiac output of 70% over baseline, were demonstrated.

By 1999, however, it had become apparent that patients may experience adverse effects from being maintained in a state of continually elevated cardiac output during epoprostenol therapy. Although individuals with untreated IPAH typically have reduced cardiac output at presentation, the development of a treatment-induced, long-term high output state could have deleterious effects on cardiac function, resulting in dangerous arrhythmias. In addition, it has been postulated that a persistently elevated cardiac output may, itself, induce tolerance due to neurohormonal activation.[31] Increasing a patient's epoprostenol dosage would overcome this tachyphylaxis until further neurohormonal activation again negated it.

In an attempt to ameliorate these consequences of epoprostenol treatment, another case series evaluated the possible benefits of a more conservative dosage regimen.[31] The study followed 12 patients with IPAH who had been successfully treated with long-term epoprostenol therapy for 39 ± 20 months, as evidenced by an improvement in NYHA rating from class III or IV to class I or II, as well as an average decrease in mean pulmonary artery pressure of 25% and a reduction in pulmonary vascular resistance of 71%. Throughout this initial period of epoprostenol treatment, patients had periodically experienced a return of IPAH symptoms that required dosage escalations. After each dosage increase, patients' symptoms of IPAH were alleviated, but adverse events related to epoprostenol (jaw pain, leg pain, diarrhea, severe flushing) were reported to have worsened. In addition, each patient was found to have a relatively high cardiac output (mean ± SD cardiac index 5.5 ± 1.1 L/min/m^2).

The mean ± SD epoprostenol dose during this period was 98 ± 61 ng/kg/minute. Investigators hypothesized that the dosage of epoprostenol could be tapered downward, under direct hemodynamic monitoring, to a dosage that prevented rebound pulmonary hypertension while achieving the goal of maintaining patients' cardiac index below 4 L/minute/m^2 (upper limit of normal). They successfully accomplished a downward titration in 11 of 12 patients over 6–24 hours, with a mean dose reduction of 39%. Although dyspnea in one patient limited dose reduction, rebound pulmonary hypertension did not occur in any patient, and mean pulmonary artery pressure did not significantly increase (45 ± 12 vs 46 ± 10 mm Hg after reduction).

After initial dose reduction, patients were followed as outpatients over a mean of 13.6 months, during which time further dose reductions were possible in three patients, two patients required no further dosage changes, and six patients required minor increases in dosage. Throughout the follow-up period, all patients reported an improvement in epoprostenol-related flushing, with some study participants also describing a significant reduction in treatment-related leg pain. In addition, patients were able to maintain a lower, more normalized cardiac output, with a significantly reduced rate of tolerance development. The investigators concluded that epoprostenol dosing could be optimized without compromising clinical efficacy, thereby maintaining the patient's cardiac index within normal limits and relieving some of

the adverse effects associated with epoprostenol therapy. Optimal dosing can be monitored during periodic heart catheterizations, with dosage being adjusted based on a target cardiac index of 2.5–4.0 L/minute/m^2.[32]

In a case series from 1991–2001, 162 patients treated with epoprostenol were followed for an average of 36.3 months (range 1–122 mo).[32] The objective of this case series was to determine the long-term effects of epoprostenol on survival in patients with IPAH. All patients were NYHA class III (46%) or IV (54%), despite optimal conventional medical therapy. During the study, 70 patients (43.2%) died, 11 (6.8%) underwent lung or heart-lung transplantation, and 3 (1.9%) elected to discontinue epoprostenol. Researchers realized that, due to the high mortality rate associated with advanced IPAH and the demonstrated short-term efficacy of epoprostenol, it was no longer considered ethical to conduct a long-term randomized trial using epoprostenol. Therefore, study investigators compared survival in this case series with predicted survival determined by a prognostic equation derived from data from the NIH registry. This equation incorporates three key hemodynamic variables in IPAH: mean pulmonary artery pressure, right atrial pressure, and cardiac index.[1, 33] Results from the case series showed a significant improvement in survival among patients treated with epoprostenol (87.8% survival at 1 yr, 76.3% at 2 yrs, and 62.8% at 3 yrs) compared with predicted survival (58.9% at 1 yr, 46.3% at 2 yrs, and 35.4% at 3 yrs).[32]

This large-scale trial provided evidence for the American College of Chest Physicians' guideline recommendation that in patients with IPAH who are in NYHA class III and who are not candidates for calcium channel blocker therapy, epoprostenol should be considered as a first-line treatment alternative, and that in patients in NYHA class IV who are not candidates for calcium channel blocker therapy, epoprostenol should be regarded as the treatment of choice, particularly if their condition is unstable.[10]

Although studies indicate that epoprostenol improves survival and quality of life in patients with IPAH,[29, 32] its use is not without serious limitations. Because epoprostenol is unstable at pH values below 10.5, it is inactivated by the low pH of the stomach and cannot be given orally. In addition, with a half-life of only 3–5 minutes, rapid metabolism in the systemic circulation necessitates administration by continuous intravenous infusion. The delivery system is complex and cumbersome, using a portable infusion pump connected to a permanent, indwelling catheter inserted into either the subclavian or jugular vein. A backup drug delivery system is required in case of pump malfunction because of the risk of rebound pulmonary hypertension, rapid hemodynamic and symptomatic deterioration, and potentially life-threatening pulmonary hypertensive crisis if the epoprostenol infusion is interrupted for even a brief period of time.[28, 32, 35] Patients or caregivers must learn to mix the drug each day, including a backup supply in case of problems, by using an aseptic technique. Because epoprostenol is light and temperature sensitive, the infusion pump and medicine cassette must be placed in a bag containing ice packs to keep the drug cool.

Instruction in sterile technique, catheter care, drug administration, and infusion pump maintenance is critical, as most serious adverse effects of long-term epoprostenol therapy are related to the delivery system and include infusion pump failure, catheter-related infection and/or sepsis, and catheter thrombosis, dislodgment, or perforation. One study reported 119 local infections at the catheter site (0.24/person-yr), 70 episodes of sepsis (0.14/person-yr), 10 tunnel infections (0.02/person-yr), and 72 instances in which the catheter had to be replaced (0.15/person-yr).[32] In the same study, four patients (2.5%) died of sepsis, which may have been related to the catheter, and one patient (0.6%) died after interruption of the epoprostenol infusion. In addition to these medical consequences, there are psychosocial ramifications of epoprostenol therapy, since it commits the patient and their family to a way of life that focuses on ensuring uninterrupted delivery of the drug. The cost of epoprostenol treatment, including the drug as well as pump rental and supplies, can exceed $60,000/year and may be a consideration for some patients contemplating treatment options.

Adverse drug events are frequent and include diarrhea, headache, jaw pain, and cutaneous flushing.[28–31] Other common adverse events are nausea and vomiting, anxiety and nervousness, and muscle pain.[35] In addition, even with careful monitoring, tachyphylaxis can be a common event, requiring frequent dose escalations.

Treprostinil

Treprostinil was approved by the FDA in May 2002 and is indicated for patients with IPAH who

Table 3. Studies of Treprostinil in Idiopathic Pulmonary Arterial Hypertension

Design	Duration	Population	No. of Patients	Regimens	Results
Multicenter, open-label; trial 1[37]	Short-term dose-ranging over 8 hrs	IPAH only (NYHA III–IV)	14	i.v. epoprostenol over 2 hrs, then 90-min washout period, followed by i.v. treprostinil over 4.5 hrs	Maximum dosage: i.v. epoprostenol 6.4 ± 0.8 ng/kg/min i.v. treprostinil 24.6 ± 4.0 ng/kg/min mPAP, PVR, and CO between epoprostenol and treprostinil: NS for all 3 parameters
Multicenter, open-label; trial 2[37]	Short-term dose-ranging over 8 hrs	IPAH only (NYHA III–IV)	25	i.v. treprostinil over 75 min, then 150-min washout period, followed by s.c. treprostinil over 150 min	Maximum dosage: s.c. treprostinil 10 ng/kg/min i.v. treprostinil 10 ng/kg/min i.v. treprostinil: mPAP ↓ 7% from baseline[a] PVR ↓ 23% from baseline[a] CI ↑ 15% from baseline[a] s.c. treprostinil: mPAP ↓ 13% from baseline[a] PVR ↓ 28% from baseline[a] CI ↑ 20% from baseline[a]
Multicenter, double-blind, placebo-controlled, randomized; trial 3[37]	8 wks	IPAH only (NYHA III–IV)	15	s.c. treprostinil + conventional therapy	mPAP from 59.0 to 59.0 mm Hg (p=NS[b]) PVRI ↓ from 24.8 to 20.0 units/m^2 (p=0.065[b]) CI ↑ from 2.3 to 2.7 L/min/m^2 (p=0.065[b]) SMWD ↑ from 373 to 411 m (p=NS[b]) Borg Dyspnea Score ↓ from 3.2 to 3.1 (↓ indicates improvement, p=NS[b])
				s.c. placebo + conventional therapy	mPAP ↓ from 64.0 to 62.0 mm Hg (p=NS[b]) PVRI ↑ from 24.7 to 24.9 units/m^2 (p=0.065[b]) CI from 2.4 to 2.4 L/min/m^2 (p=NS[b]) SMWD ↓ from 384 to 378 m (p=NS[b]) Borg Dyspnea Score ↓ from 3.4 to 2.4 (↓ indicates improvement, p=NS[b])
Multicenter, double-blind, placebo-controlled, randomized[38]	12 wks	IPAH and PAH associated with connective tissue disease or congenital systemic-to-pulmonary shunt (NYHA II–IV)	233	s.c. treprostinil + conventional therapy	Primary end point: SMWD ↑ from 326 to 336 m (p=NS[c])[36] Secondary end points: Death, transplantation, clinical deterioration in 13 patients (p=NS[c]) Dyspnea-Fatigue Rating ↑ from 4.2 to 5.4 (↑ indicates improvement, p=0.0001[c]) mPAP ↓ from 62.0 to 59.7 mm Hg (p=0.0003[c]) PVRI ↓ from 26.0 to 22.5 units/m^2 (p=0.0001[c]) CI ↑ from 2.40 to 2.52 L/min/m^2 (p=0.0001[c])
Same as above[38]	12 wks	Same as above	237	s.c. placebo (vehicle solution without treprostinil) + conventional therapy	Primary end point: SMWD from 327 to 327 m (p=NS[c])[36] Secondary end points: Death, transplantation, clinical deterioration in 16 patients (p=NS[c]) Dyspnea-Fatigue Rating ↓ from 4.4 to 4.3 (↑ indicates improvement, p=0.0001[c]) mPAP ↑ from 60.0 to 60.7 mm Hg (p=0.0003[c]) PVRI ↑ from 25.0 to 26.2 units/m^2 (p=0.0001[c]) CI ↓ from 2.30 to 2.24 L/min/m^2 (p=0.0001[c])

are in NYHA classes II–IV to diminish symptoms associated with exercise (Table 1).[36] A structural analog of prostacyclin, treprostinil exhibits the same mechanism of action (i.e., an increase in cAMP leading to vasodilation of the pulmonary vasculature and inhibition of platelet

Table 3. Studies of Treprostinil in Idiopathic Pulmonary Arterial Hypertension (continued)

Design	Duration	Population	No. of Patients	Regimens	Results
Multicenter, open-label[39]	8 wks	IPAH and PAH associated with portal hypertension, scleroderma, or congenital left-to-right shunt (NYHA III–IV)	8	Transition from i.v. epoprostenol to s.c. treprostinil over 21–96 hrs, with follow-up 6–8 wks after transition	Changes in mean NYHA classification: Baseline: 3.5 Epoprostenol: 2.25 (p= NS[b, d]) Treprostinil: 2.25 (p=NS[b, d]) Changes in SMWD: Epoprostenol: 496 m (p=NS[b, d]) Treprostinil: 486 m (p=NS[b, d])

CI = cardiac index; CO = cardiac output; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NS = not statistically significant; NYHA = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; SMWD = 6-minute–walk distance; TPR = total pulmonary resistance; ↑ = increase; ↓ = decrease.

Statistically significant differences are defined as $p<0.05$.

[a]Data not statistically analyzed.

[b]p value for comparison between treatment groups.

[c]p value for comparison between placebo and treatment groups.

[d]Between-group comparison between 1 week before transition and 6–8 weeks after transition.

aggregation). However, treprostinil is considerably longer acting, with a half-life of 2–4 hours, and is chemically stable at room temperature and a neutral pH.[36] These characteristics permit continuous subcutaneous infusion with a pager-sized microinfusion device and small, self-inserted subcutaneous catheters similar to those used by patients with diabetes mellitus to administer insulin with an insulin pump. Treprostinil comes prepared as a sterile solution intended for administration without dilution. Therefore, many of the risks associated with epoprostenol therapy, such as sepsis, thrombosis, or drug delivery failure, are not associated with treprostinil. Studies comparing epoprostenol with treprostinil, as well as studies crucial to FDA approval of treprostinil, are summarized in Table 3.[37–39]

In a study that consisted of a series of three sequential trials, the feasibility of long-term subcutaneous infusion of treprostinil in patients with IPAH was assessed.[37] The first two trials were multicenter, open-label, cross-over designs; the third was a controlled study. Trial 1 evaluated the short-term effects of intravenous epoprostenol and intravenous treprostinil to determine maximum tolerated doses and comparative efficacy with the same route of administration. Similar increases in cardiac output and similar decreases in mean pulmonary artery pressure and pulmonary vascular resistance were demonstrated. In addition, dose-limiting adverse events (headache, nausea, chest pain, jaw pain, backache, and restlessness) were similar with both treatments.

Trial 2 compared the hemodynamic effects and pharmacokinetics of intravenous treprostinil with those of subcutaneous treprostinil. Results from trial 2 showed similar changes in hemodynamic parameters in both the intravenous and subcutaneous treprostinil groups, suggesting that the favorable effects observed from intravenous treprostinil in trial 1 could be reproduced with subcutaneous administration. The pharmacokinetic data obtained from trial 2 found that the half-life of intravenous treprostinil ranged from 26–42 minutes, compared with 55–117 minutes for subcutaneous treprostinil.

Trial 3 was an 8-week pilot study that compared subcutaneous treprostinil with placebo. Although treprostinil had a favorable effect on hemodynamics and exercise tolerance, none of these effects reached statistical significance. The most common adverse events with subcutaneous treprostinil were infusion-site pain and erythema. In addition, headache, diarrhea, flushing, foot pain, and jaw pain were seen with treprostinil therapy, adverse events that are also common with epoprostenol.

Treprostinil was approved by the FDA based on the results of two controlled studies that enrolled a total of 470 patients (NYHA classes II–IV) with IPAH or PAH associated with connective tissue disease or congenital systemic-to-pulmonary shunts.[36, 40] All subjects received either conventional therapy plus continuous subcutaneous treprostinil or conventional therapy plus continuous infusion of placebo during a 12-week period. The studies were identical in design and were conducted

simultaneously. Results of both studies were analyzed and reported by using individual as well as pooled data, which tended to confound interpretation of study results.[36, 38, 41] The primary end point of the studies was exercise capacity after 12 weeks of treatment. Pooled study results showed a median change from baseline of only 10 m for the treprostinil group, compared with no change in the control group[36]; this treatment effect was not statistically significant. In addition, no difference was noted in the results between the two groups regarding principal reinforcing end points of mortality, lung transplantations, or clinical deterioration.[38, 40] However, the subjectively scored Dyspnea-Fatigue Rating, Borg Dyspnea Score, and composite score for signs and symptoms of pulmonary hypertension, also defined as principal reinforcing end points, improved significantly in the treprostinil group compared with the placebo group.

The secondary end points of mean pulmonary artery pressure, pulmonary vascular resistance index, and cardiac index were significantly improved as well. Ultimately, although the study did not achieve its primary end point, FDA approval was granted based on an improvement in perceived quality of life and a reduction in clinical symptoms, coupled with a lack of safety concerns.[40]

In the current study, a significant difference was noted in the frequency of adverse events with treprostinil compared with placebo.[38] These effects included infusion-site pain, infusion-site reaction (including erythema, induration, or rash), diarrhea, jaw pain, vasodilatation, and edema. Infusion-site pain was the most common adverse effect related to treatment with treprostinil, occurring in 85% of the patients. Eighteen treprostinil-treated participants (8%) discontinued their study treatment due to intolerable infusion-site pain, compared with only one patient in the placebo group. Infusion-site pain was variably relieved by the use of topical cold and hot compresses, topical and oral analgesics, antiinflammatory drugs, and narcotics. In addition, rotation of the infusion site every 3 days rather than every day helped to minimize infusion-site adverse events.[36]

Treprostinil may be an alternative therapy for patients who, although stable while receiving epoprostenol, have experienced life-threatening catheter or delivery system complications or who cannot tolerate dosage escalations. In an open-label study, a cohort of eight such patients was successfully transitioned from intravenous epoprostenol to subcutaneous treprostinil.[39] All of the patients had experienced initial clinical improvement with long-term epoprostenol therapy (3–15 mo), as well as an improvement in NYHA class. The transition to treprostinil was prompted by severe complications of epoprostenol therapy, including recurrent central catheter–related sepsis (five patients); severe headache, jaw pain, abdominal cramping and diarrhea that prevented an increase in epoprostenol dosage in the face of deteriorating clinical condition (one patient); recurrent cerebral air emboli (one patient); and several episodes of syncope related to accidental disconnections of the intravenous line (one patient). Transitions were performed over 21–96 hours in an intensive care or telemetry inpatient setting. The clinical status and NYHA class of all patients were unchanged after the transition from epoprostenol to treprostinil. A 6-minute–walk test was performed in five patients able and willing to participate at 1 week before and 6–8 weeks after transition and showed a nonsignificant change (from 496 ± 45 to 486 ± 29 m). All of the patients experienced pain, swelling, and erythema at the subcutaneous injection site. The pain was rated as moderate-to-severe in 7 patients (88%) and was treated with cold compresses, corticosteroid or nonsteroidal antiinflammatory drug (NSAID) ointments, acetaminophen, or oral NSAIDs. Two patients were treated briefly with acetaminophen-codeine preparations, and two patients received short courses of oral prednisolone 2 mg/kg/day, which appeared to be very effective.

The local infusion-site pain markedly improved after several weeks in all but two patients, but all study participants reported an improved sense of comfort and well being after changing to treprostinil. Follow-up ranged from 4–11 months. In seven patients, clinical state, functional class, and 6-minute–walk distance remained unchanged. One patient, whose clinical condition had been deteriorating while receiving intravenous epoprostenol, continued to deteriorate after the transition despite continually increasing dosages of treprostinil.

These studies indicate that although treprostinil may not be appropriate as first-line therapy for IPAH, patients in NYHA class II or III may consider a trial with treprostinil, particularly if other treatment options have failed. Patients in NYHA class IV should be advised to use intravenous epoprostenol due to the lack of

Table 4. Studies of Iloprost in Idiopathic Pulmonary Arterial Hypertension

Design	Duration	Population	No. of Patients	Regimens	Results
Uncontrolled, open-label, crossover[42]	Short term (10 hrs)	IPAH and PAH associated with CREST syndrome (NYHA III–IV)	6	Oxygen, then nitric oxide, then i.v. prostacyclin (epoprostenol), then inhaled prostacyclin, then inhaled iloprost (washout period sufficient to allow new stable baseline between each agent)	Oxygen (duration of effect NA): mPAP ↓ from 58.2 to 55.2 mm Hg (p=NS[a]), PVR ↓ from 1537 to 1465 dyn•sec•cm^{-5} (p=NS[a]), CO ↑ from 2.76 to 2.78 L/min (p=NS[a]), MAP ↑ from 96 to 97 mm Hg (p=NS[a]) Nitric oxide (duration of effect 2–5 min): mPAP ↓ from 60.4 to 54.2 mm Hg (p<0.05[a]), PVR ↓ from 1578 to 1141 dyn•sec•cm^{-5} (p<0.01[a]), CO ↑ from 2.80 to 3.48 L/min (p<0.05[a]), MAP unchanged at 97 mm Hg i.v. prostacyclin (duration of effect NA): mPAP ↓ from 62.7 to 59.8 mm Hg (p=NS[a]), PVR ↓ from 1551 to 1000 dyn•sec•cm^{-5} (p<0.01[a]), CO ↑ from 2.94 to 4.52 L/min (p<0.01[a]), MAP ↓ from 100 to 87 mm Hg (p<0.01[a]) Inhaled prostacyclin (duration of effect 10–30 min): mPAP ↓ from 62.3 to 50.8 mm Hg (p<0.01[a]) PVR ↓ from 1721 to 1019 dyn•sec•cm^{-5} (p<0.01[a]), CO ↑ from 2.75 to 4.11 L/min (p<0.01[a]), MAP ↓ from 96 to 90 mm Hg (p=NS[a]) Inhaled iloprost (duration of effect 60–120 min)[b]
Uncontrolled, open-label[43]	1 yr	IPAH only (NYHA III–IV)	24	Inhaled iloprost + conventional therapy	SMWD ↑ from 278 to 363 m (p<0.05[a]) mPAP ↓ from 59 to 52 mm Hg (p<0.05[a]) PVR ↓ from 1205 to 925 dyn•sec•cm^{-5} (p<0.05[a]) CO ↑ from 3.8 to 4.4 L/min (p<0.05[a])
Multicenter, placebo-controlled, double-blind, randomized[44]	12 wks	IPAH or scleroderma disease, anorexigen use, or chronic thromboembolic disease (NYHA III–IV)	101	Inhaled iloprost + conventional therapy	Primary composite end point: 16.8% (p=0.007[c]) Secondary end points: Patients with > 10% increase over baseline in SMWD: 37.6% (p=NS[c]) Improvement in NYHA class: 24.8% (p=0.03[c]) Occurrence of clinical deterioration: 4.0% (includes 1 death) (p=0.024[c]) Mahler Dyspnea Index ↑ from 4.14 to 5.56[d] (p=0.015[c]) Hemodynamics: Predose mPAP ↓ from 52.8 to 52.7 mm Hg (p=NS[a]), postdose mPAP↓ from 52.8 to 48.2 mm Hg (p<0.001[a]), predose PVR ↓ from 1029 to 1020 dyn•sec•cm^{-5} (p<0.01[c]), postdose PVR ↓ from1029 to 790 dyn•sec•cm^{-5} (p<0.001[a]), predose CO ↑ from 3.8 to 3.85 L/min (p=NS[a]), postdose CO ↑ from 3.8 to 4.35 L/min (p<0.001[a])

proven long-term mortality benefit with treprostinil.[9]

Iloprost

The possibility of a therapy for IPAH that could be administered directly to the lungs through inhalation has been an attractive concept for many years. Iloprost, an aerosolized analog of epoprostenol, has been studied as a treatment for IPAH for nearly 2 decades. Recently approved by the FDA, it is the only inhalation therapy available (Table 1). Iloprost is a powerful vasodilator, selectively acting on the pulmonary vascular bed through ventilation-matched

Table 4. Studies of Iloprost in Idiopathic Pulmonary Arterial Hypertension (continued)

Design	Duration	Population	No. of Patients	Regimens	Results
Multicenter, placebo-controlled, double-blind, randomized[44] (continued)	12 wks	IPAH or scleroderma disease, anorexigen use, or chronic thromboembolic disease (NYHA III–IV)	102	Inhaled placebo + conventional therapy	Primary composite end point: 4.9% (p=0.007[c]) Secondary end points: Patients with > 10% increase over baseline in SMWD: 25.5% (p=NS[c]) Improvement in NYHA class: 24.8% (p=0.03[c]) Occurrence of clinical deterioration: 13.7% (includes 4 deaths) (p=0.024[c]) Mahler Dyspnea Index ↑ from 4.27 to 4.57[d] (p=0.015[c]) Hemodynamics: mPAP ↓ from 53.8 to 53.6 mm Hg (p=NS[a]), PVR ↑ from 1041 to 1137 dyn•sec•cm^{-5} (p<0.001[a]), CO ↓ from 3.8 to 3.61 L/min (p<0.001[a])

CO = cardiac output; CREST = calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; IPAH = idiopathic pulmonary arterial hypertension; MAP = mean arterial pressure; mPAP = mean pulmonary artery pressure; NA = not applicable; NS = not statistically significant; NYHA = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SMWD = 6-minute–walk distance; ↑ = increase; ↓ = decrease.
Statistically significant differences are defined as p<0.05.
[a]p value for comparison of change over baseline.
[b]Authors reported that iloprost caused nearly identical changes in hemodynamics and gas exchange (further data not shown).
[c]p value for comparison between placebo and treatment groups.
[d]On this 12-point scale, higher scores indicate less dyspnea.

alveolar deposition of the drug, theoretically preventing systemic hypotension. The effects last for 60–120 minutes, which necessitates inhalation using a jet nebulizer 6–9 times/day (without interruption of bed rest at night), with each treatment lasting approximately 10 minutes. Studies following the development of iloprost are detailed in Table 4.[42–44]

In order to compare efficacy, an uncontrolled, open-label study looked at the effects of short-term administrations of oxygen, inhaled nitric oxide, intravenous prostacyclin (epoprostenol), inhaled prostacyclin, and inhaled iloprost in six patients (four with IPAH and two with PAH associated with CREST syndrome [calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia]).[42] All patients were in NYHA class III or IV. Each agent was administered as a single dose followed by a washout period sufficient to allow a return to stable baseline. Hemodynamic measurements were taken before, during, and after administration of each agent.

As expected, hemodynamic variables were only slightly affected by oxygen administration, but inhalation of nitric oxide, an endogenous vasodilator, resulted in marked improvements in mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output, with little impact on systemic arterial pressure. The beneficial effects of nitric oxide, however, ended 2–5 minutes after the dose. Intravenous prostacyclin significantly decreased pulmonary vascular resistance and increased cardiac output, resulting in a modest decline of pulmonary artery pressure but a substantial decrease in mean systemic arterial pressure and an increase in heart rate due to peripheral vasodilation. Inhaled prostacyclin, acting selectively on the pulmonary vascular bed, caused significant improvements in mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output, with only a minimal effect on mean systemic arterial pressure. These beneficial effects lasted 10–30 minutes after the end of the inhaled prostacyclin dose. Finally, in all patients, inhalation of the stable prostacyclin analog iloprost provided nearly identical changes in hemodynamics to those seen with inhaled prostacyclin (data not provided by the study authors), but the iloprost-induced changes were maintained for 60–120 minutes after inhalation.

In another uncontrolled, open-label study, 24 patients with NYHA class III or IV IPAH received inhaled iloprost 6–8 times/day over 1 year to assess long-term changes in exercise capacity and hemodynamics.[43] At 3 months, significant improvements compared with baseline were noted in the mean distance covered during a 6-minute–walk test, as well as in mean pulmonary

artery pressure and pulmonary vascular resistance. These changes were sustained at the end of 12 months, at which time a significant increase compared with baseline was also noted in cardiac output. All hemodynamic measurements were taken before the first iloprost inhalation of the day, suggesting that mechanisms other than vasodilation may contribute to its therapeutic effect, and at all times there was further improvement in these variables immediately after inhalation of iloprost. Treatment was well tolerated by all patients, with reports of flushing, headache, and jaw pain in five patients (21%). Coughing during inhalation was common initially but spontaneously resolved during the first 4 weeks of therapy.

A multicenter, double-blind, randomized study followed 203 patients with IPAH or selected forms of secondary pulmonary hypertension.[44] Patients were randomly assigned to receive either aerosolized iloprost or placebo, in addition to conventional therapy. The primary end point was fairly rigorous and consisted of a composite of a 10% or greater increase in 6-minute–walk distance evaluated 30 minutes after inhalation of the study drug, and improvement of one NYHA class (e.g., from class III to class II), in the absence of clinical deterioration or death during the 12-week study. Secondary end points included each component of the primary end point individually, as well as hemodynamic values, and Mahler Dyspnea Index Scores. During the study, the mean frequency of inhalation was 7.5 times/day. Nine percent of patients received 2.5 µg/inhalation, and 91% received 5 µg/inhalation, corresponding to a median inhaled dose of 30 µg/day. Tolerance did not appear to occur at any time during the study.

The primary end point was met by 17 (16.8%) patients in the iloprost group, compared with just 5 (4.9%) of the placebo group. Of the secondary end points, changes in NYHA class and Mahler Dyspnea Index Scores showed statistically significant differences between treatment groups. Five patients receiving iloprost met the criteria for clinical deterioration (including one death), compared with 12 patients (with four deaths) in the placebo group. Although nearly 40% of iloprost-treated patients increased their 6-minute–walk distance by greater than 10%, more than 25% in the placebo group did as well, rendering the between-group difference statistically insignificant.

The placebo group showed significant worsening in pulmonary vascular resistance and cardiac output at the end of 12 weeks compared with baseline. In the iloprost group, the same parameters were significantly improved compared with baseline. However, even at 12 weeks, hemodynamic measurements preceding the first daily inhalation of iloprost were largely unchanged from baseline, suggesting subtherapeutic concentrations during overnight, drug-free periods, and a potential drawback to inhaled iloprost therapy.

This limitation of treatment with aerosolized iloprost may be ameliorated with the use of other agents in combination with iloprost. Polypharmacy approaches have been investigated with promising results,[45, 46] but larger, long-term studies are indicated. As no studies have yet evaluated the mortality benefits of iloprost, it should be considered second-line therapy, even though its noninvasive, easy administration and relative lack of serious adverse effects may make it an attractive treatment alternative for some patients.

Bosentan

An increasing understanding of the multiple pathogeneses of IPAH led to the discovery of another target for drug therapy, and bosentan was subsequently developed as the first endothelin-receptor antagonist available for IPAH (Table 1). Endothelin-1 is a peptide produced in endothelial cells and vascular smooth muscle cells. It binds to two types of receptors, ET_A and ET_B. When bound by endothelin-1, ET_A receptors located on vascular smooth muscle cells activate phospholipase C, which mediates an increase in intracellular calcium through the inosital 1,4,5-triphosphate pathway, resulting in potent vasoconstriction by the vascular smooth muscle cells.[47, 48] In a parallel cascade of events, endothelin-1 binding to ET_A receptors also leads to cell proliferation and vascular remodeling by increasing concentrations of diacylglycerol, thereby stimulating protein kinase C.[47] Similar to ET_A receptors, some ET_B receptors are located on vascular smooth muscle cells, where they are involved, although to a much lesser extent, in vasoconstriction. However, ET_B receptors are also found in substantial numbers on the vascular endothelium, where they conversely mediate vasodilation through the release of nitric oxide and play a role in the clearance of endothelin-1 from the circulation.[49]

Bosentan is a competitive antagonist of endothelin-1 at both ET_A and ET_B receptors, leading to reductions in vasoconstriction and

Table 5. Studies of Bosentan in Idiopathic Pulmonary Arterial Hypertension

Design	Duration	Population	No. of Patients	Regimens	Results
Multicenter, double-blind, placebo-controlled, randomized[50]	12 wks	IPAH and PAH associated with scleroderma, WHO III	21	Bosentan + conventional therapy	Primary end point (p=0.021[a]): SMWD ↑ from 360 to 430 m (p<0.050[b]) Secondary end points: mPAP ↓ from 54.0 to 52.4 mm Hg (p=0.013[a]) PVR ↓ from 896 to 673 dyn·sec·cm^{-5} (p≤0.001[a]) CI ↑ from 2.4 to 2.9 L/min/m^2 (p<0.001[a]) WHO functional class (p=0.019[a]) Patients in class II ↑ from 0% to 43% (p=0.0039[b]) Patients in class III ↓ from 100% to 57% (p=0.0039[b])
Same as above[50]	12 wks	Same as above	11	Placebo + conventional therapy	Primary end point (p=0.021[a]): SMWD ↓ from 355 to 349 m (p=NS[b]) Secondary end points: mPAP ↑ from 56.0 to 61.1 mm Hg (p=0.013[a]) PVR ↑ from 942 to 1133 dyn·sec·cm^{-5} (p≤0.001[a]) CI ↓ from 2.5 to 2.0 L/min/m^2 (p<0.001[a]) WHO functional class (p=0.019[a]): Patients in class II ↑ from 0% to 9% (p=NS[b]) Patients in class III ↓ from 100% to 73% (p=NS[b]) Patients in class IV ↑ from 0% to 18% (p=NS[b])
Multicenter, double-blind, placebo-controlled, randomized[51]	16 wks	IPAH and PAH associated with connective-tissue disease, WHO III–IV	74	Bosentan 62.5 mg b.i.d. for 4 wks, then bosentan 125 mg b.i.d. + conventional therapy	Primary end point: SMWD ↑ from 326 to 361 m (p<0.01[a]) Secondary end points: Clinical deterioration (death, transplantation, epoprostenol rescue, hospitalization for PAH, atrial septostomy, subject withdrawal) 7% occurrence rate (p=0.01[a]) Borg Dyspnea Score ↓ from 3.3 to 3.2 (↓ indicates improvement, p=0.42[a])
Same as above[51]	16 wks	Same as above	70	Bosentan 62.5 mg b.i.d. for 4 wks, then bosentan 250 mg b.i.d. + conventional therapy	Primary end point: SMWD ↑ from 333 to 387 m (p<0.001[a]) Secondary end points: Clinical deterioration (death, transplantation, epoprostenol rescue, hospitalization for PAH, atrial septostomy, subject withdrawal) 6% occurrence rate (p=0.01[a]) Borg Dyspnea Score ↓ from 3.8 to 3.3 (↓ indicates improvement, p=0.012[a])
Same as above[51]	16 wks	Same as above	69	Placebo + conventional therapy	Primary end point: SMWD ↓ from 344 to 336 m (p<0.001[a]) Secondary end points: Clinical deterioration (death, transplantation, epoprostenol rescue, hospitalization for PAH, atrial septostomy, subject withdrawal) 20% occurrence rate Borg Dyspnea Score ↑ from 3.8 to 4.2 (↑ indicates worsening)

CI = cardiac index; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NS = not statistically significant; WHO = World Health Organization functional class; PAH = pulmonary hypertension; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; SMWD = 6-minute–walk distance; TPR = total pulmonary resistance; ↑ = increase; ↓ = decrease. Statistically significant differences are defined as p<0.05.

[a]p value for comparison between placebo and treatment groups.

[b]p value for comparison of change over baseline.

vascular remodeling. Because it is a nonpeptide, bosentan is not hydrolyzed by peptidases in the systemic circulation and gastrointestinal tract, making oral administration possible. Given the

clinically significant improvements in exercise capacity, functional class, and hemodynamics seen with bosentan, it may be considered a potential first-line treatment option in patients who are not candidates for high-dose calcium channel blocker therapy.[10, 50, 51]

However, bosentan has caused dose-related, reversible hepatic toxicity during clinical trials, with elevated aminotransferase concentrations in as many as 11% of patients.[40, 52] These results are of particular concern in patients with IPAH. Patients frequently have advanced disease at presentation, including compromised hepatic function as a result of right-sided heart failure. The risk of increased hepatic insult has led to implementation of a monitoring program by the manufacturer that requires liver function tests before therapy begins and at monthly intervals. Bosentan is also an FDA category X teratogen, necessitating the exclusion of pregnancy both before therapy begins and monthly thereafter. Information about the potential for liver injury and the contraindication regarding pregnancy are included in a black box warning in the package insert.[52] Finally, bosentan has been shown to cause hypochromic anemia (> 15% decrease in hemoglobin level).[52, 53]

Bosentan has the potential for numerous drug interactions, particularly among cytochrome P450 (CYP) 3A4 and CYP2C9 substrates.[52, 53] Coadministration of cyclosporine (which may increase bosentan concentrations by up to 30-fold) or glyburide (which increases risk of hepatotoxicity) with bosentan is contraindicated, whereas caution is indicated for concomitant use with tacrolimus (which may increase bosentan concentrations), ketoconazole (which may increase bosentan concentrations), and warfarin (which may decrease warfarin concentrations). Although specific drug studies have not been performed to evaluate the effect of bosentan on hormonal contraceptives (including oral, parenteral, transdermal, and implantable forms), many of these drugs are metabolized by CYP3A4, and the possibility of contraceptive failure exists; a second form of birth control should be used at all times by women of childbearing age who are taking bosentan. Additional drug interactions may be the result of bosentan's CYP3A4- and CYP2C9-inducing potential and include drugs primarily metabolized by these CYP enzymes. Examples include glipizide, simvastatin, and sildenafil; such drugs should be monitored clinically during concomitant administration of bosentan.[52–56]

Two critical studies examined the clinical implications of bosentan (Table 5).[50, 51] A 12-week controlled study of bosentan (dosage titrated to 125 mg twice/day) was conducted in 32 patients with IPAH or PAH associated with scleroderma who were in World Health Organization (WHO) functional class III despite optimal medical therapy.[50] A significant increase in walking distance of 70 m was realized in the bosentan group compared with a reduction of 6 m in the placebo group. A significantly greater improvement in WHO functional class was observed in the bosentan group compared with the placebo group. The hemodynamic variables most closely correlated with mortality in patients with IPAH (i.e., mean pulmonary artery pressure, mean right atrial pressure, and cardiac index) showed significantly greater improvement in patients receiving bosentan versus placebo.[1, 50]

Finally, study investigators reported that the frequency of adverse events between groups did not differ significantly. Nine (43%) of 21 patients receiving bosentan experienced an adverse event compared with 7 (64%) of 11 patients in the placebo group. The only information provided regarding the type of adverse events indicated that increases in aminotransferase concentrations were seen in two patients treated with bosentan, but that these increases were asymptomatic and self-limiting. This initial small study provided the first indication that a new drug target could be effectively exploited in the treatment of IPAH. Although secondary end points showed promising evidence for therapy with bosentan, a long-term mortality benefit had yet to be proved.

The Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) was designed to evaluate the effect of bosentan on exercise capacity and WHO functional class in patients with PAH, as well as to compare the efficacy and adverse effect profiles of two different bosentan dosages.[51] This controlled study randomly assigned 213 patients with WHO classes III and IV disease (both primary and associated with connective tissue disease) into three groups: bosentan dosage titrated to 125 mg twice/day, bosentan dosage titrated to 250 mg twice/day, or placebo. At the end of 16 weeks, all patients continued their assigned study drug in a double-blinded manner until the completion of the study period, the day the last enrolled patient finished the assessment at week 16. This second time period lasted up to 12 additional weeks. At the end of the study, all participants were eligible to enter an open-label study of bosentan.

At the end of 16 weeks, the 6-minute–walk test was significantly improved in the bosentan groups compared with the placebo group. The increase was more pronounced in the bosentan 250-mg group than in the 125-mg group (54 vs 35 m, respectively), but the difference between the bosentan treatment groups was not significant. Although patients treated with bosentan exhibited a greater improvement in WHO functional class than that in the placebo group, the significance of this difference was not reported; overall, although 42% of the patients treated with bosentan showed an improvement in functional class, 30% of the placebo group did as well. Finally, with the exception of abnormal hepatic enzymes seen in both bosentan groups, the type and frequency of adverse events were similar among all three treatment groups and most often involved headache, dizziness, cough, and flushing. Study results showed increases in aminotransferase concentrations to greater than 8 times the upper limit of normal in two patients (3%) in the bosentan 125-mg group and five patients (7%) in the bosentan 250-mg group, leading to premature discontinuation of the study drug by three patients.[51]

In addition, in a published letter replying to readers comments,[57] the investigators reported that 10 patients (13.5%) treated with bosentan 125 mg twice/day experienced increases in aminotransferase concentrations of more than 3 times the upper limit of normal. None of these patients elected to withdraw from the study, and bosentan therapy was continued at either the same dosage or at a reduced dosage of 62.5 mg twice/day. Aminotransferase concentrations returned to values that were less than twice the upper limit of normal in 7 of the 10 patients and decreased progressively in the remaining 3 patients. All 10 patients participated in the open-label elective phase of the study.[57]

Although the study's primary end point, an increase in 6-minute–walk distance, was achieved, there are no trials yet that prove a long-term mortality benefit with bosentan therapy, and safety concerns may limit its use. The American College of Chest Physicians' guidelines, however, recommend that patients with IPAH who are in NYHA class III should consider long-term therapy with bosentan as a treatment alternative, and the substantially lessened effect on quality of life with oral bosentan over intravenous epoprostenol must be taken into account in devising a treatment plan.

A recently published subanalysis of the BREATHE-1 trial assessed the effects of bosentan on cardiac structure and function in 85 patients (84% with IPAH, 16% with PAH associated with connective tissue disease) over a 16-week period.[58] In the 56 patients randomly assigned to receive bosentan, echocardiographic results revealed a smaller mean increase in right ventricular end-diastolic area, indicating less contractile function loss, than in patients assigned to placebo, although this change failed to reach statistical significance. A decrease in septal displacement reflected by reduced systolic and diastolic eccentricity indexes was also observed in this group, reflecting lower right ventricular pressures and resulting in improved left ventricular filling dynamics. Doppler measurements included right ventricle ejection time, left ventricle stroke volume, cardiac index, and maximal tricuspid regurgitant velocities, all of which were significantly improved over that of the placebo group, with the exception of maximal tricuspid regurgitant velocity, an indicator of pulmonary artery pressure. These data suggest that bosentan treatment may improve right-sided heart function, but not to an extent that would be expected to reverse structural anomalies.

The BREATHE-2 trial was a double-blind, randomized study of the safety and efficacy of oral bosentan combined with intravenous epoprostenol.[59] Patients received intravenous epoprostenol for 48 hours and were then randomly assigned to receive in addition either bosentan or placebo for 4 months. Results indicated that the combination of bosentan and epoprostenol was well tolerated, and both groups showed an improvement in the primary end point of total pulmonary resistance. However, the change from baseline in total pulmonary resistance did not reach statistical significance between the epoprostenol-placebo and epoprostenol-bosentan groups. Because the two drugs possess different mechanisms of action, the possibility of combining their effects is an attractive treatment option that requires additional research.

Sildenafil

In an attempt to exploit another target for drug therapy, researchers have focused on the nitric oxide pathway. Production of nitric oxide is impaired in patients with IPAH,[14] resulting in decreased production of cyclic guanosine

Table 6. Studies of Sildenafil in Idiopathic Pulmonary Arterial Hypertension

Design	Duration	Population	No. of Patients	Regimens	Results
Case series[64]	3 mo	IPAH or PAH associated with Eisenmenger's syndrome (NYHA II–III)	5	Sildenafil 50 mg q8h + conventional therapy	mPAP ↓ from 70 to 52 mm Hg ($p<0.007$[a]) PVRI ↓ from 1702 to 992 dyn•sec•cm^{-5}•m^{-2} ($p<0.006$[a]) SMWD ↑ from 376 to 504 m ($p<0.0001$[a]) Right ventricular mass[b] ↓ from 290 to 243 g (no p value given[a])
Double-blind, placebo-controlled, randomized, crossover[65]	3 mo	IPAH only (NYHA II–III)	22	Sildenafil or placebo + conventional therapy for 6 wks, then crossover for 6 wks (no washout period) Sildenafil dosing (based on body wt): ≤ 25 kg: 25 mg t.i.d. 26–50 kg: 50 mg t.i.d. ≥ 51 kg: 100 mg t.i.d.	Primary end point: Exercise time (treadmill) ↑ from 475 to 686 sec ($p<0.0001$[c]) Secondary end points: sPAP[d] ↓ from 105 to 98 mm Hg (p=NS[c]) CI[d] ↑ from 2.8 to 3.45 L/min/m^2 ($p<0.0001$[c])
Open-label, non-randomized[66]	8 wks	IPAH only (NYHA III–IV)	15	Sildenafil 50 mg b.i.d. x 4 wks, then 100 mg b.i.d. x 4 wks + conventional therapy	SMWD ↑ from 234 to 377 m at 4wks ($p=0.001$[e]) SMWD ↑ from 377 to 385 m at 8 wks (p=NS[f]) NYHA class ↓ from mean of 3.8 to 2.4 at 4 wks ($p=0.002$[e]) NYHA class ↑ from mean of 2.4 to 2.5 at 8 wks (p=NS[f]) Borg Dyspnea Index ↓ from 8.1 to 4.4 at 4 wks ($p=0.0007$[e]) Borg Dyspnea Index ↑ from 4.4 to 4.7 at 8 wks (p=NS[f])

CI = cardiac index; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NS = not statistically significant; NYHA = New York Heart Association functional class; PAH = pulmonary arterial hypertension; PVRI = pulmonary vascular resistance index; SMWD = 6-minute–walk distance; sPAP = pulmonary artery systolic pressure; ↑ = increase; ↓ = decrease.
Statistically significant differences are defined as $p<0.05$.
[a]p value for change over baseline.
[b]Right ventricular mass measured by magnetic resonance imaging in three patients.
[c]p value for comparison between placebo and treatment groups.
[d]Hemodynamic measurements performed by noninvasive methods (Doppler echocardiography).
[e]p value for comparison between baseline and 4 wks (end of 50-mg dosing period).
[f]p value for comparison between 4 wks (end of 50-mg dosing period) and 8 wks (end of 100-mg dosing period).

monophosphate (cGMP), a potent mediator of vascular smooth muscle relaxation and vasodilation. Although inhaled nitric oxide has been shown to decrease pulmonary vascular resistance,[42] ambulatory delivery is cumbersome. Another strategy is to prolong the circulation of existing cGMP by inhibiting phosphodiesterase type 5, an enzyme that rapidly hydrolyzes cGMP. Because phosphodiesterase type 5 is selective for penile and pulmonary tissue, phosphodiesterase type 5 inhibitors increase cellular concentrations of cGMP in these tissues, causing preferential vasodilation with minimal reductions in systemic blood pressure. Numerous anecdotal reports have described successful treatment of IPAH with the phosphodiesterase type 5 inhibitor sildenafil (Table 1), either singly or in combination with other drugs.[60–63] More recently, studies have been conducted to evaluate the efficacy, safety, and optimal dosage of sildenafil. These are reviewed below and summarized in Table 6.[64–66]

A case series followed five patients with PAH (four with IPAH and one with Eisenmenger's syndrome) who were treated with oral sildenafil 50 mg every eight hours.[64] All patients were NYHA class II or III and received conventional therapy (diuretics, warfarin, and/or calcium channel blockers) in addition to sildenafil. At the end of the 3-month study, NYHA class had improved by one class in every patient. Exercise capacity had increased significantly, as evidenced by a 34% increase in 6-minute–walk distance.

Mean pulmonary artery pressure and pulmonary vascular resistance index decreased 25.7% and 41.5%, respectively, with no significant change in systolic blood pressure. In addition, right ventricular mass, as measured by magnetic resonance imaging in three patients, decreased 16.2%, apparently reversing the pathologic septal shift seen in patients with IPAH. Although this was a small, uncontrolled study, it suggested that due to sildenafil's potential efficacy, simplicity, and safety profile, further controlled studies were warranted.

In a double-blind, randomized, crossover study, 22 patients with IPAH (NYHA class II or III) were randomly assigned to receive either sildenafil or placebo, in addition to conventional therapy.[65] After 6 weeks, each group was given the alternate therapy, with no washout period, for another 6 weeks. Sildenafil dosage was based on body weight: patients weighing 25 kg or less received 25 mg 3 times/day, patients weighing 26–50 kg received 50 mg 3 times/day, and patients weighing 51 kg or greater received 100 mg 3 times/day. The primary end point was the change in exercise capacity, as measured by time (sec) on a treadmill using the Naughton protocol. Secondary end points included changes in cardiac index and pulmonary artery systolic pressure as assessed by Doppler echocardiography. When considering the combined values of both groups, exercise time increased significantly, rising from a mean of 475 seconds at the end of the placebo phase to 686 seconds after 6 weeks of treatment with sildenafil. Likewise, cardiac index significantly improved from 2.80 to 3.45 L/minute/m^2. The decrease in pulmonary artery systolic pressure, however, was not statistically significant. One of the limitations of this study was the absence of a washout period between crossover phases, allowing the sildenafil treatment effect to be carried over into the placebo phase in the sildenafil-first group and effectively blunting the beneficial effect of sildenafil therapy. In spite of this, the study achieved its primary end point. One patient in the placebo-first group died one week after randomization and one patient had syncope at rest while in the placebo phase. In addition, one patient in the sildenafil-first group elected not to continue 1 week after randomization. All other patients tolerated sildenafil therapy well except for minor adverse effects (headache, backache, constipation, and numbness in hands and feet).

A prospective, open-label study also looked at the efficacy and optimal dosage of sildenafil in patients with IPAH.[66] Over an 8-week period, 15 patients with IPAH (NYHA class III or IV) participated in a step-up therapeutic protocol. In addition to conventional therapy, patients received sildenafil 50 mg twice/day during the first 4 weeks and 100 mg twice/day for the next 4 weeks. Primary end points were changes in 6-minute–walk distance, NYHA class, and Borg Dyspnea Index. Results showed significant improvements in all primary end points with sildenafil 50 mg twice/day at 4 weeks. Six-minute–walk distance increased by 61%, NYHA class improved by 58%, and the Borg Dyspnea Index decreased by 45% (lower score means less dyspnea). In all but one patient, increasing the dosage to 100 mg twice/day did not provide any additional clinical benefit.

Based on a priority review of data from a 3-month, randomized, double-blind, placebo-controlled study involving 278 patients, the FDA approved sildenafil for the treatment of IPAH in June 2005. The study participants were patients with IPAH (63%), PAH associated with connective tissue disease (30%), and PAH following surgical repair of congenital heart defects (7%); all patients but one were in NYHA classes II and III.[67] Patients were randomly assigned to receive either placebo or sildenafil 20, 40, or 80 mg 3 times/day. Although full results of the study (Sildenafil Use in Pulmonary Arterial Hypertension [SUPER-1]) have not yet been published, preliminary analyses indicate that the sildenafil groups showed significant improvements in both 6-minute–walk distance and NYHA functional class. Because differences in walk distance were not significant between sildenafil dosage groups, the approved dosage is limited to 20 mg 3 times/day. In addition, initial data from a 1-year, uncontrolled extension of the SUPER-1 study were recently presented at the 2005 International Conference of the American Thoracic Society. Results from SUPER-2 suggest that patients who experienced a treatment benefit at 3 months continued to see this clinical improvement when taking sildenafil long term.[68] Finally, of the 259 patients who elected to participate in the SUPER-2 extension, 96% were still alive at the end of 1 year, suggesting a mortality benefit with long-term sildenafil therapy.[69] A more thorough evaluation of the SUPER-1 and -2 studies must be undertaken before any recommendations can be made;

however, in view of its convenient oral administration and relative safety profile (the most common adverse effects are headache, nasal congestion, and visual disturbances), sildenafil's potential role as monotherapy or adjunctive therapy for IPAH may soon be fully realized.

Investigational Agents

Sitaxsentan

Like bosentan, sitaxsentan is an endothelin-1–receptor antagonist, but unlike bosentan, it is specifically an ET_A-receptor antagonist. By preferentially blocking ET_A receptors, sitaxsentan preserves the vasodilatory and endothelin-1–clearing properties of ET_B receptors, theoretically resulting in less vasoconstriction as well as lower circulating endothelin-1 concentrations. In a small, 12-week, open-label trial involving 20 patients with PAH (8 with IPAH and 12 with PAH secondary to either collagen vascular disease or congenital systemic-to-pulmonary shunts), sitaxsentan significantly improved exercise capacity as measured by the 6-minute–walk distance, as well as mean pulmonary artery pressure and pulmonary vascular resistance index (mean pulmonary vascular resistance/body surface area); there was, however, no significant change in cardiac output.[70] Clinically important adverse events during the trial included anemia, increased prothrombin time or INR, systemic hypotension, pulmonary edema, and asymptomatic increases in serum transaminase levels. At the end of the trial, any study participants who had not deteriorated during the trial were eligible to continue taking sitaxsentan during an extension phase of the study. Unfortunately, at weeks 16 or 17, two patients developed acute hepatitis. One patient immediately discontinued sitaxsentan administration, and serum transaminase levels returned to baseline approximately 9 weeks later. The other patient chose to reduce the dosage of sitaxsentan, but after 3 weeks serum transaminase levels continued to increase. Acute fulminant hepatitis was diagnosed, and despite discontinuation of sitaxsentan administration, the patient died. The extension phase of the trial was terminated early due to these serious adverse events.

Recently, the Sitaxsentan to Relieve Impaired Exercise (STRIDE-1) trial randomly assigned 178 patients with PAH (94 with IPAH, 42 with PAH related to connective tissue disease, and 42 with PAH associated with congenital systemic-to-pulmonary shunts) to receive sitaxsentan 100 mg, sitaxsentan 300 mg, or placebo daily for 12 weeks.[71] The primary end point, percentage of predicted peak oxygen consumption during cycle ergometry, was significantly increased in the 300-mg group only. Secondary end points included 6-minute–walk distance, NYHA class, hemodynamic parameters (mean pulmonary artery pressure, mean right atrial pressure, pulmonary vascular resistance, and cardiac index), and time to clinical worsening (death, epoprostenol rescue, atrial septostomy, or transplantation). Compared with the placebo group, significant improvements were seen in all secondary end points in both the 100- and 300-mg groups, with the exception of mean pulmonary artery pressure, which showed no significant change between the 100-mg group and the placebo group, and time to clinical worsening, in which no differences were seen among any of the three arms of the study.

Adverse events reported by more than 10% of the patients receiving sitaxsentan and occurring more frequently than in the placebo group were headache, peripheral edema, nausea, increased INR or prothrombin time, nasal congestion, and dizziness. However, of greater concern was the high rate of liver enzyme abnormalities, defined as aminotransferase concentrations greater than 3 times the upper limit of normal. Increased liver enzyme levels were found in 10% of the sitaxsentan 300-mg group (6/63), resulting in discontinuation of the study by three patients, compared with 3% of the placebo group (2/59), resulting in discontinuation of the study by one patient, and none of the group receiving 100 mg of sitaxsentan.

Although possibly warranted because of the significant improvements in clinical status demonstrated thus far, future studies evaluating the safety and efficacy of sitaxsentan will require careful monitoring of liver enzyme levels. A phase III trial comparing sitaxsentan and bosentan is planned.

Beraprost

Beraprost is an orally active, chemically stable analog of epoprostenol. It has been approved in Japan for treatment of patients with IPAH, where a multicenter case series study evaluated survival rates in patients receiving beraprost plus conventional therapy (24 patients) compared with patients receiving only conventional therapy (calcium channel blockers, nitrates, digitalis, and diuretics; 34 patients).[72] The results showed significantly higher 1-, 2-, and 3-year survival

rates of 96%, 85%, and 76%, respectively, in the beraprost treatment group, compared with 77%, 47%, and 44% in the group receiving only conventional therapy.

A small, uncontrolled European study involving 13 patients with IPAH and PAH secondary to thromboembolic disease or Eisenmenger's syndrome showed significant improvements over baseline in NYHA class, 6-minute–walk distance, and pulmonary artery pressure with beraprost administration during a 12-month period.[73] More recently, the Arterial Pulmonary Hypertension and Beraprost European Trial (ALPHABET) group conducted a 12-week controlled study in 130 patients with IPAH or PAH associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, or HIV infection.[74] After 12 weeks, the patients treated with beraprost showed significant improvement over the control group in 6-minute–walk distance. A subgroup analysis comprised only of patients with IPAH showed an even greater improvement in the beraprost group compared with placebo. Similarly, IPAH symptoms, as measured subjectively by the Borg Dyspnea Score, improved significantly by -0.94 (a lower score indicates fewer symptoms) in the beraprost group compared with the control group. However, cardiopulmonary hemodynamics showed no significant changes.

A United States study of oral beraprost was conducted over 9 months in 116 patients with IPAH (86 patients) or PAH related to either collagen vascular disease (12 patients) or congenital systemic-to-pulmonary shunts (18 patients).[75] After 6 months, the primary end point of disease progression (death, transplantation, epoprostenol rescue, or > 25% decrease in peak oxygen consumption) was significantly lower with beraprost compared with placebo. However, this treatment effect was not significantly different from placebo at either the 3- or 9-month follow-up evaluations. The beraprost treatment group also performed significantly better on the 6-minute walk at months 3 and 6 but showed no significant difference at the 9-month follow-up. Composite changes in WHO functional class between the beraprost and placebo groups were significant only at the 6-month interval. Hemodynamic variables and quality-of-life indicators were not significantly improved at any time during the study.

The benefits of beraprost seen during early phases of this trial may have dissipated due to an inability to adequately increase the dosage regimen. Dose-limiting adverse events (headache, jaw pain, flushing, and diarrhea) were more common in the beraprost-treated group, although serious adverse events (fatal or life-threatening incidents or events requiring hospitalization) occurred more frequently in the control group.

Conclusion

Advances in understanding the pathophysiology of IPAH have led to the development of several suitable pharmacologic treatment alternatives. Initially, calcium channel blockers were demonstrated to be efficacious in the small percentage of patients with IPAH who exhibit a favorable response to acute vasodilator challenge. Twenty years after the identification of endogenous prostacyclin, intravenous epoprostenol was approved by the FDA and is now a first-line treatment option in patients who are not candidates for calcium channel blocker therapy. Studies have shown that epoprostenol provides long-term benefits in exercise capacity, hemodynamic parameters, and survival.

Treprostinil, a stable prostacyclin analog, is an alternative to intravenous epoprostenol in patients who experience life-threatening catheter or delivery system complications or who cannot tolerate dosage escalations while receiving intravenous epoprostenol. Compared with administration of epoprostenol, administration of subcutaneous treprostinil is considerably less cumbersome and has fewer serious adverse effects related to drug delivery, although a long-term mortality benefit with treprostinil has not yet been proved.

Iloprost is an aerosolized prostanoid recently approved by the FDA for treatment of IPAH. It appears to be safe, effective, and well tolerated and may be considered a long-term treatment alternative. Like treprostinil, however, controlled studies addressing a substantive mortality benefit with iloprost have yet to be completed.

An increasing understanding of the multiple pathogeneses of IPAH led to the discovery of another target for drug therapy, and subsequently the endothelin-receptor antagonist bosentan was approved as the first orally administered drug available to treat IPAH. Although long-term studies on survival have not been completed, bosentan is considered a potential first-line treatment option in patients who do not respond to calcium channel blockers.

Finally, sildenafil is the newest drug available for IPAH, having received FDA approval in 2005. A phosphodiesterase type 5 inhibitor originally marketed for erectile dysfunction, sildenafil brings efficacy, convenience, and cost-effectiveness to the treatment of IPAH.

Indefinite therapy with epoprostenol or bosentan should be considered primary treatment for patients with IPAH who are in NYHA class III, and possibly class II, and are not suitable candidates for calcium channel blocker therapy. Based on current evidence, the benefit of subcutaneous treprostinil, inhaled iloprost, sildenafil, and oral beraprost appears to be less than that of intravenous epoprostenol or oral bosentan. Indefinite treatment with intravenous epoprostenol is the treatment of choice for patients with IPAH who are in NYHA class IV and are not candidates for calcium channel blocker therapy. Second-line alternative, or possibly combination, therapies in this case are bosentan, subcutaneous treprostinil, inhaled iloprost, and sildenafil.[10]

New agents are in various phases of development, and novel uses for existing drugs are being investigated. As our knowledge of the multifactorial pathogenesis of IPAH grows, it is anticipated that additional innovative treatment options will be discovered, promising a new era of hope for patients and the clinicians who care for them.

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