

Advances in Pulmonary Hypertension CME Section

Program Overview

Pulmonary arterial hypertension (PAH), an incurable disease, is characterized by medial hypertrophy, intimal fibrosis, and *in situ* thrombi in small muscular pulmonary arteries. PAH was considered a rapidly fatal illness with a median survival of 2.8 years in the 1980s when no proven therapies were available. Since then the treatment of this disease has made tremendous advances, and the last 10 years have seen the discovery of new medications that have positively influenced the prognosis and survival of PAH patients.

This self-study activity is based on three articles that review the latest information on new treatments, combinations of therapies, and data from phase 1 and 2 clinical trials.

This activity is jointly sponsored by the University of Michigan Medical School and the Pulmonary Hypertension Association and supported by an unrestricted education grant from Actelion Pharmaceuticals US, Inc., Encysive Pharmaceuticals, Inc., Gilead Sciences, Inc., Pfizer, Inc., and United Therapeutics Corporation.

Target Audience

This self-study activity is appropriate for cardiologists, pulmonologists, and rheumatologists and other physicians who treat patients with pulmonary hypertension.

Learning Objectives

Upon completion of this activity participants will be able to:

- Describe the 2007 ACCP consensus guidelines for evidence-based treatment of PAH of WHO class II, III, and IV and be able to apply them to PAH patients.
- Summarize controversial areas in the 2007 ACCP guidelines, and recent PAH clinical trial data that were not included in the guidelines.
- Discuss the rationale and emerging evidence supporting combination therapy for PAH.
- Summarize the nature of ongoing phase 2 and 3 PAH clinical trials.

Self-Assessment Examination

See pages 243 and 244 for self-assessment questions, answer key, and evaluation form.

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Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Michigan Medical School and the Pulmonary Hypertension Association. The University of Michigan is accredited by the ACCME to provide continuing medical education to physicians.

Credit Designation

The University of Michigan Medical School designates this activity for a maximum of 2.0 AMA PRA Category 1 credits™. Physicians should claim credit commensurate with the extent of their participation in the activity.

Instructions for Earning Credit

This activity is a self-study program; a self-assessment examination is included on page 243 to help physicians review important points. A form is also included on page 244 for physicians to evaluate the CME activity. Completion of this activity involves reading the journal and completing the self-assessment examination and evaluation form, which may take up to 2 hours. Credits for this self-study program are available from May 1, 2008 through May 1, 2009. There is no fee for this program.

Please note that this self-study program may also be viewed online at: <http://www.cme.med.umich.edu>

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Sponsorship

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Disclosures

The Accreditation Council for Continuing Medical Education and the Association of American Colleges have standards and guidelines to ensure that individuals participating in CME activities are aware of relationships between authors and commercial companies that could potentially affect the information presented. The University of Michigan Medical School follows these national policies to ensure balance, independence, objectivity, and scientific rigor in all its CME activities. Each author was asked to complete a disclosure information form for this activity. Disclosures are reported below.

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Evidence-based Medical Management of Pulmonary Hypertension 2008: Review of Updated 2007 ACCP Guidelines



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During the past decade remarkable advances have been made in the understanding, diagnosis, and clinical management of pulmonary arterial hypertension (PAH). Each of these issues was carefully addressed in the American College of Chest Physicians (ACCP) guidelines document published in 2004.¹ This document described a number of new therapeutic classes, several of which were undergoing active investigation. A number of important clinical trials have since been published; and the ACCP has recently published updated recommendations on the medical management of PAH based on this new information.² These guidelines incorporate the latest clinical trials through September 2006, highlight newly approved therapeutic agents for PAH, and provide treatment strategies that include combination therapy. Recommendations for therapeutic strategies remain largely based on the patient's functional class. The strength of evidence utilizes the same grading system as in the 2004 ACCP guidelines for PAH.^{1,2} The goal of this article is to review the important studies leading to the latest recommendations with regard to disease-specific PAH therapy, as well as to update the reader on trials published since that time.

Calcium Channel Antagonists

The utility of oral calcium channel blockers (CCBs) in PAH remains very limited. No randomized controlled trials (RCT) have studied the use of CCBs in PAH. The subsets of patients that appear to benefit from CCBs are those who have shown an acute response to vasoreactivity testing during right heart catheterization. Sitbon et al retrospectively evaluated 557 consecutive patients with idiopathic PAH who underwent acute vasodilator testing.³ Responders were

defined by a greater than 20% decrease in mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Acute responders were treated with oral CCBs and followed every 3 to 6 months. Patients were classified as long-term CCB responders if their functional class was I or II after 1 year of therapy without adding additional medications for PAH. Of the 70 acute responders to vasoreactivity testing, 38 patients remained responsive to CCBs after 1 year; and this represented less than 7% of the total cohort. The long-term CCB responders had a lower mean PAP of 33 ± 8 mmHg (\pm SD) at baseline compared with the CCB failure group. Given these findings, the definition of acute vasoreactivity response was redefined as a decrease in mean PAP ≥ 10 mmHg to ≤ 40 mmHg with an increased or unchanged cardiac output. This important study suggests that only a small subset of patients will benefit from oral CCBs. No major change was made to the 2007 ACCP guidelines for use of oral CCBs compared with the 2004 guidelines, as shown in **Table 1**.^{1,2} Empiric CCB therapy is never recommended.

Phosphodiesterase Inhibitors

Nitric oxide stimulation of vascular endothelium increases cyclic guanosine 3'-5' monophosphate (cGMP) levels and results in vasorelaxation. Phosphodiesterase type 5 (PDE5) rapidly breaks down cGMP. In the pulmonary vasculature, PDE5 is highly expressed and its inhibition can sustain the vasodilatory effect of NO. Inhibitors of PDE5 such as sildenafil have vasodilatory effects in the pulmonary vasculature in patients with PAH.

Sildenafil has been reported to improve functional class and exercise tolerance in both observational and randomized clinical studies.^{4,5} The Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study randomized 278 functional class II-IV patients with idiopathic PAH or PAH secondary to connective-tissue disease or previously repaired congenital shunts to 12 weeks of either placebo or sildenafil (20, 40, or 80 mg three times daily).⁶ The sildenafil group had improvements in 6-minute walk test distance (6MWD), functional class, and mean PAP with all three dosages compared with placebo. In an open-label extension of sildenafil

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Table 1. Overview of Updated ACCP Guidelines on Medical Therapy for PAH

Recommendation	Level of Evidence	Net Benefit	Grade of Recommendation
<i>Calcium channel blockers (CCBs)</i>			
Acute responders to vasoreactivity testing, defined as fall in mean PAP \geq 10 mmHg to \leq 40 mmHg with increased or unchanged cardiac output, and absence of right heart failure may be treated with oral CCBs, with careful reassessment:			
1. Idiopathic PAH	low	substantial	B
2. Secondary PAH from underlying conditions	expert opinion	intermediate	E/B
<i>Sildenafil</i>			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. II or III	good	substantial	A
2. IV	low	indeterminate	C
<i>Intravenous epoprostenol</i>			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. III or IV	good	substantial	A
<i>Treprostinil</i>			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. II			
a. Subcutaneous or intravenous	low	small/weak	C
2. III or IV			
a. Subcutaneous	fair	intermediate	B (III) C (IV)
b. Intravenous	low	intermediate	C (III and IV)
<i>Inhaled iloprost</i>			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. III	good	intermediate	A
2. IV	fair	intermediate	B
<i>Bosentan</i>			
Patients who are not candidates or in whom CCB therapy has failed can initiate long-term therapy for the following functional class:			
1. III	good	substantial	A
2. IV	fair	intermediate	B

Strength of Recommendation Scale: A, strong; B, moderate; C, weak; D, negative; I, inconclusive; E/X, expert opinion only/consensus

at mostly 80 mg tid to one year, 86% of patients continued to receive sildenafil monotherapy and had improvements in their 6MWD. The Food and Drug Administration (FDA) subsequently approved sildenafil for treatment of PAH at a dose of 20 mg three times daily. The 2007 ACCP guideline recommendations for sildenafil therapy are shown in **Table 1** and are different from the 2004 ACCP guidelines.^{1,2} It is listed as a therapy in patients with functional class II-IV PAH.² The majority of patients in the SUPER trial were in functional class II or III, and these patients now have the strongest evidence for benefit.⁶ The updated ACCP guideline graded sildenafil data the highest quality for functional class II or III, while class IV patients received a substantially lower grade.²

Tadalafil is another PDE5 inhibitor reported in an observational study to benefit patients with PAH.⁷ A phase 3 clinical trial recently finished enrollment.⁸ Tadalafil was not discussed in the 2007 ACCP guidelines.

Prostanoids

Prostacyclin is a potent vasodilator produced in the vascular endothelium. Several methods to administer exogenous prostacyclin analogues (referred to as prostanoids) exist. Epoprostenol is an intravenous, potent, short-acting vasodilator with a half-life of 3 to 6 minutes that has been well studied in randomized trials of idiopathic PAH⁹ and in patients with PAH secondary to scleroderma and found to be efficacious in both groups.¹⁰ The long-term efficacy of intra-

Table 2. Prostanoid Studies in PAH

Trial Name	Follow-up Testing	Enrolled Patients	Drug	Change in meters for mean 6MWD from baseline			Change in mmHg in mean PAP from baseline			Change in dyne-s-cm ⁻⁵ in mean PVR from baseline		
				Treated	Placebo	P	Treated	Placebo	P	Treated	Placebo	P
<i>Randomized Trials</i>												
Barst et al ⁹	12 wk	81	IV epoprostenol	32*	-15	<.003	-4.8±1.3	1.9±1.6	<.002	-272±56	120±96	<.00
Badesch et al ¹⁰	12 wk	111	IV epoprostenol	63.5*	-36	<.001	-5.0±1.1	0.94±1.1	NR†	-366±61	74±45	NR†
Simonneau et al ¹⁴	12 wk	470	SC treprostinil	10‡	0	<.006	-2.3±0.5	0.7±0.6	.0002	NR	NR	NR
Olschewski et al ²⁰	12 wk	203	inhaled iloprost	~16§	~-20§	.004	-4.6±9.3	-0.2±6.9	<.001	-239±279	96±322	<.001
<i>Observational Studies</i>												
McLaughlin et al ¹¹	17±15mo	162	IV epoprostenol	215	NA	<.0001	-8.0¶	N/A	<.0001	-520¶	NA	<.0001
Sitbon et al ¹²	3 mo	178	IV epoprostenol	125	NA	<.001	-7.0¶	NA	<.0001	NR	NR	NR
Kuhn et al ¹³	1 year	49	IV epoprostenol	73\\	NA	.078	-8¶\\	NA	<.001	-528¶\\	NA	<.001
Tapson et al. ¹⁶	12 wk	14	IV treprostinil	82	NA	.001	-4.2±1.6	NA	.03	-752±152	NA	.001
Opitz et al. ²¹	12 wk	48	inhaled iloprost	NR	NR	NR	1.0¶	NA	.41	130	NA	.12

* trial compared IV epoprostenol plus conventional therapy versus conventional therapy alone

† P values not reported yet confidence intervals did not cross zero, thus implying statistical significance

‡ median change for 6MWD reported

§ actual values for 6MWD not reported; absolute change in 6MWD between groups was 36.4 m; values are estimated from graph for 6MWD

¶ ± values not reported for change from baseline

\\ values listed are only for the patients with idiopathic PAH, of whom only 37 underwent right heart catheterization

6MWD = 6-minute walk test distance; IV = intravenous; NA = not applicable; NR - not reported; PAP = pulmonary artery pressure;

PVR= pulmonary vascular resistance; sc = subcutaneous

venous epoprostenol has been evaluated in several observational studies¹¹⁻¹³ of class III or IV idiopathic PAH patients (Table 2). Based on the RCT and observational studies, intravenous epoprostenol appears to benefit survival in functional class III and IV idiopathic PAH patients. Epoprostenol is FDA-approved for use in patients with idiopathic PAH and PAH secondary to the scleroderma spectrum of disease. The most common complication with intravenous epoprostenol remains line-related infections and possible sepsis.⁹⁻¹²

Treprostinil is another prostacyclin analogue, previously approved for subcutaneous administration and now available for intravenous therapy. It has a longer half-life (4.5 hours) than prostacyclin and its stability obviates the need for refrigeration. In a 12-week double-blind trial, 470 functional class II-IV patients with idiopathic PAH or PAH secondary to congenital systemic-to-pulmonary shunts or connective tissue disease were randomized to continuous subcutaneous treprostinil versus placebo.¹⁴ 6MWD and mean PAP improved with treprostinil (Table 2). The most common adverse event was infusion site pain (85% in the treprostinil group). An open-label extension of this study followed 860

patients for 4 years.¹⁵ Among the 15% of patients who continued to receive subcutaneous treprostinil alone, survival at 1, 2, 3, and 4 years was 88%, 79%, 73%, and 70%. Site pain was the most common adverse event (92% of patients) causing a significant number of patients to drop out.

Because of the high frequency of site pain limiting subcutaneous administration, treprostinil administered intravenously was studied in a 12-week open-label prospective trial of 16 functional class III and IV patients with idiopathic PAH and PAH due to connective tissue disease or congenital heart disease.¹⁶ In the 14 patients who completed the trial, 6MWD, mean PAP, and PVR improved from baseline (Table 2). Similar results were found in an open-label trial transitioning 31 class II and III patients from intravenous epoprostenol to intravenous treprostinil.¹⁷ The effects on quality of life are currently being evaluated in patients switched from intravenous epoprostenol to intravenous treprostinil.¹⁸ The long-term efficacy of intravenous treprostinil in functional class II-IV patients is still being evaluated. The strength of evidence in the updated ACCP guidelines does not exceed intravenous epoprostenol in functional class III

Table 3. Endothelin Receptor Antagonist Studies in PAH

Trial Name	Follow-up Testing	Enrolled Patients	Drug	Change in meters for mean 6MWD from baseline			Change in mmHg in mean PAP from baseline			Change in dyne-s-cm ⁻⁵ in mean PVR from baseline		
				Treated	Placebo	P	Treated	Placebo	P	Treated	Placebo	P
<i>Randomized Trials</i>												
Channick et al ²³	12 wk	32	bosentan	77	-15	.0097	-1.6±1.2	5.1±2.8	0.013	-223±56	191±74	<.001
Rubin et al ²⁵	16 wk	213	bosentan, combined*	36	-8	<.001	NR	NR	NR	NR	NR	NR
Galie et al ³⁰	12 wk	64	ambrisentan	36†	NA	<.0001	-5.2±6.3†	N/A	<0.05	-226±202†	N/A	<.05
Barst et al. ³²	12 wk	178	sitaxsentan 100 mg	22	-13	<.01	-3±8	0±8	NS	-221±422	49±244	<.001
			300 mg	20		<.01	-5±11		<0.01	-194±333		<.001
Barst et al ³³	18 wk	247	sitaxsentan 50 mg	17.8	-6.5	.07	NR	NR	NR	NR	NR	NR
			100 mg	25		.03						
<i>Observational Studies</i>												
Provencher et al ²⁷	16 wk	‡	bosentan	42	NA	.003	-3§	NA	0.012	NR	NR	NR

* data for 6MWD are for combined bosentan group, which included patients receiving 125 mg or 250 mg twice daily

† reported values are for four combined doses of ambrisentan

‡ 99 patients had 6MWD testing at 16 weeks; 73 patients had right heart catheterization measurements

§ ± values not reported for change from baseline

6MWD = 6-minute walk test distance; NA = not applicable; NR = not reported; NS = not significant; PAP= pulmonary artery pressure; PVR = pulmonary vascular resistance

or IV patients, as shown in **Table 1**. The subcutaneous form has been given a higher evidence grade than the intravenous form.² A new inhaled form of treprostinil currently being investigated was not discussed.¹⁹

Iloprost is a prostacyclin analogue with a half-life of 25 minutes available in intravenous, subcutaneous, and inhaled forms. The last has been studied the most extensively. A 12-week trial randomized 203 functional class III or IV patients with idiopathic PAH or PAH associated with appetite suppressants, chronic thromboembolic disease, or connective tissue disease to inhaled iloprost or placebo.²⁰ The primary endpoint, defined as a ≥10% improvement in 6MWD and an improvement in functional class, was reached in 16.8% of patients in the iloprost group compared with 4.9% in the placebo group. Improvements in 6MWD, mean PAP, and PVR were also seen (**Table 2**). In a prospective open-label study of 76 functional class II-IV patients with idiopathic PAH, only a minority of patients could be stabilized with inhaled iloprost monotherapy during a follow-up period of up to 5 years.²¹ In general, inhaled iloprost appears to be an effective treatment in patients with functional class III and IV PAH but, as with oral agents, it was not recommended as first-line therapy in class IV patients. For inhaled iloprost, the strength of evidence in the 2007 ACCP guidelines is slightly higher compared with the 2004 recommendation (**Table 1**).^{1,2}

Endothelin Receptor Antagonists

Patients with PAH have increased lung expression of endothelin-1 (ET-1) and blood levels have been correlated

with disease severity.²² ET-1 is a potent vasoconstrictor and may contribute to smooth muscle hypertrophy. Endothelin receptor antagonists are designed to halt the effects of ET-1 and offer another pharmacologic class for the treatment of PAH.

Bosentan was the first oral endothelin receptor antagonist studied in PAH. A double-blind, placebo-controlled study of 32 class III or IV patients with idiopathic PAH or PAH associated with scleroderma demonstrated significant improvement in 6MWD, PAP, and PVR at 12 weeks (**Table 3**).²³ An open-label observational study involving 29 of the original 32 patients demonstrated persistent improvements in 6MWD, PVR, and functional class.²⁴

The Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) randomized 213 functional class III or IV patients with idiopathic PAH or PAH associated with connective tissue disease to placebo or bosentan.²⁵ At 16 weeks, 6MWD improved with bosentan (**Table 3**). Functional class improved to II in 38% of patients receiving 250 mg.

McLaughlin et al examined the long-term efficacy of bosentan in a paper combining two placebo-controlled trials.²⁶ Survival at 1 and 2 years was 96.4% and 88.5%, compared with predicted survival of 69.2% and 57.3% without targeted therapy. Of the patients who were alive at 1 and 2 years, 78% and 55% were receiving bosentan monotherapy. The most common adverse effect was elevated hepatic transaminases at more than three times the upper limit of normal in 14.9% of patients.

A retrospective analysis of 103 consecutive patients of functional class III or IV idiopathic PAH treated with bosentan

tan showed improvements in 6MWD and PAP at 16 weeks (**Table 3**).²⁷ After 24 ± 15 months, prostanoid therapy had been initiated in 44% of patients. Survival at 1 and 2 years was 90% and 87%, compared with predicted survival without targeted therapy of 63% and 45%. Long-term survival was assessed in a cohort of 139 functional class III patients with idiopathic PAH treated with bosentan therapy and compared with 346 historical controls treated with intravenous epoprostenol.²⁸ Survival for the bosentan cohort was 97% and 91% at 1 and 2 years, compared with 91% and 84% in the epoprostenol cohort.

A European study randomized 185 functional class II patients to bosentan or placebo for 6 months.²⁹ A significant 23% reduction in mean PVR was seen, as well as a trend toward improvement in 6MWD. Death, hospitalization, or symptomatic progression was significantly delayed with bosentan (3% vs 11% with placebo). This study has not been formally subjected to peer review. The updated ACCP guideline recommendations regarding bosentan are shown in **Table 1** and did not change from the previous guidelines, finding bosentan's most evidence-based role in monotherapy for class III patients.^{1,2}

Ambrisentan is a second endothelin receptor antagonist recently approved for treatment of PAH. However, publication of the pivotal clinical trials and its subsequent FDA approval had not occurred before the final drafting of the 2007 ACCP guidelines. Ambrisentan was discussed in the guideline text based on a single available clinical trial of 64 functional class II or III patients with idiopathic PAH or PAH associated with connective tissue disease, anorexigen use, or HIV infection, where improvements in functional class, 6MWD, mean PAP, and PVR after 12 weeks of therapy appeared promising (**Table 3**).³⁰ Long-term efficacy of ambrisentan from continuation studies was also not available before the 2007 guidelines were finalized.³¹ Ambrisentan was listed as an investigational agent in the 2007 ACCP guidelines.² Broadly interpreting the Summary of Recommendations in the guidelines, ambrisentan could be considered as an alternative endothelin receptor antagonist for patients with functional class III PAH.

Sitaxsentan is an endothelin receptor antagonist that has not yet been approved for treatment of PAH in the United States, though it has been approved in other countries. However, publication of the pivotal clinical trials and regulatory approval outside the United States had not occurred before the final drafting of the 2007 ACCP guidelines. Sitaxsentan was discussed in the guideline text based on available clinical trials. The first was a randomized study of 178 functional class II and III patients with idiopathic PAH or PAH secondary to connective tissue disease or congenital heart disease receiving 12 weeks of placebo or sitaxsentan (STRIDE-1).³² The second was a trial of 247 functional class II-IV patients with idiopathic PAH or PAH secondary to connective tissue disease or congenital heart disease who were randomized to receive placebo, two different sitaxsentan doses, or open-label bosentan (STRIDE-2).³³ At 18 weeks, 6MWD improved in all treatment groups (**Table 3**). Functional class improved or was unchanged in 98% of patients receiving 100 mg sitaxsentan, compared with 87%

of patients receiving placebo, yet no difference was seen with the 50 mg sitaxsentan group or open-label bosentan compared with placebo.³⁴ A recent trial examining sitaxsentan benefit and tolerance in patients who discontinued bosentan because of hepatotoxicity was also not available for review by the time of guideline submission. Since it was only in clinical trials at the time of review, there were no ACCP guideline recommendations on the use of sitaxsentan.

Future Directions in Medical Management

The 2007 ACCP guidelines on the medical management of PAH are largely based on trials that studied the various agents as monotherapies.² The medical management of PAH worldwide is fast-moving and is often quite different among practitioners from the functional class-based approach using only pre-2007 approved drugs that is emphasized in the ACCP guidelines. The guidelines are most important in determining which pharmacologic class is the best option for initial therapy, yet many patients may need additional therapies to halt the progressive nature of PAH. Combination therapy for PAH is an important and exciting area of current research for the management of PAH, and is reviewed elsewhere in this issue of *Advances in Pulmonary Hypertension*.

ACCP Treatment Algorithm

The ACCP provided a treatment algorithm for PAH in the 2007 ACCP guidelines. As medical management in PAH is shifting in some regions toward initiation of therapy in less symptomatic patients, and toward early combination therapy,³⁵ this paradigm was acknowledged in the treatment algorithm as a consideration.

Conclusions

PAH is a progressive disorder that carries a poor prognosis without pharmacologic intervention. The pace at which the medical therapies for PAH are evolving is rapid. Since the 2007 revision of the ACCP guidelines, several important trials have already been published that will shape future guidelines. Although the medical management of PAH may be shifting toward combination therapy, a large gap of knowledge exists regarding the efficacy and safety of combination therapy, including drug interactions. The costs associated with advanced therapeutic treatment strategies should also be carefully assessed, but were not assessed in either the 2004 or the 2007 ACCP treatment guidelines. Further studies on medical therapies for nonidiopathic PAH are also needed. Using specific treatment goals to guide therapeutic decision-making may be the most rational approach in today's PAH practice. The advances in medical therapies for PAH outlined by the 2007 ACCP guidelines offer an exciting opportunity for physicians to employ evidence-based medicine in a manner that will improve quality of life and survival for PAH patients. ■

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Phase 2 and 3 Clinical Trials in Pulmonary Arterial Hypertension



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Pulmonary arterial hypertension (PAH), an incurable disease, is characterized by medial hypertrophy, intimal fibrosis, and in situ thrombi in small muscular pulmonary arteries.¹ PAH was considered a rapidly fatal illness with a median survival of 2.8 years in the 1980s when no proven therapies were available.² Since then the treatment of this disease has made tremendous advances and the last 10 years have seen the discovery of new medications that have positively influenced the prognosis and survival of PAH patients.^{2,3}

Advances in PAH therapy were made possible by conducting randomized controlled trials (RCTs) designed to demonstrate efficacy, safety, and/or survival benefit. Currently six agents targeting three major pathways implicated in the pathogenesis of PAH are FDA approved and also approved for use outside of the United States. These include the prostacyclin agonists epoprostenol,⁴ treprostinil,⁵ and iloprost⁶; the endothelin receptor antagonists (ETRA) bosentan⁷ and ambrisentan⁸; and the phosphodiesterase-5 (PDE5) inhibitor sildenafil.⁹ Ongoing, yet to be reported phase 2 and 3 clinical trials in PAH are numerous, are outlined in **Table 1**, and are registered at ClinicalTrials.gov. This article focuses on a review of ongoing monotherapy trials (ongoing combination therapy trials are reviewed elsewhere in this issue of *Advances in Pulmonary Hypertension*).

Endothelin Receptor Antagonists

Endothelin-1, a potent vasoconstrictor, acts as a mitogen, induces fibrosis, and leads to the proliferation of vascular smooth-muscle cells. The effects of endothelin-1 are mediated through the activation of ET_A and ET_B receptors. Differential activation of ET_A and ET_B receptors leads to the vasoconstricting and vascular proliferative actions of endothelin-1. Ambrisentan is an ETRA that has a higher affinity for ET_A receptors. Two recent clinical trials (ARIES 1 and ARIES 2) have shown improvement in placebo-corrected 6-minute walk test distance (6MWD)¹⁰ and ARIES 2 documented delayed clinical worsening as compared with placebo. The long-term extension

Key Words—Pulmonary arterial hypertension; endothelin receptor antagonists; prostanoids; tyrosine kinase inhibitor.

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study of ARIES 1 and ARIES 2 showed a sustained benefit on 6MWD, WHO functional class, and Borg dyspnea index.¹¹ Patients with idiopathic PAH and PAH associated with collagen vascular disease, anorexigen use, and HIV infection were enrolled in these studies.

ARIES III

Ambrisentan, a selective ETRA, demonstrated improvement in 6MWD and time to clinical worsening in randomized clinical trials. Ambrisentan was recently FDA approved for WHO Diagnostic Group I PAH patients of NYHA/WHO functional class II and III. An ongoing open-label study will determine the safety and efficacy of ambrisentan in PH populations that are not classically included in the RCTs to date. These include patients with congenital heart defects, and PAH associated with HIV infection, interstitial lung disease, and chronic obstructive pulmonary disease (the later two being WHO Diagnostic Group 3 and 4 populations). This 24-week study will enroll treatment-naïve patients and those receiving stable doses of prostanoids or PDE5 inhibitors. In treatment-naïve subjects addition of prostanoid therapy at week 12 will be allowed according to pre-defined clinical criteria. An option to add sildenafil after week 28 of ambrisentan monotherapy is included. The primary objective of this study is to evaluate the effect of ambrisentan on exercise capacity. Secondary objectives are the effects on other clinical parameters, safety, efficacy, and tolerability, as well as long-term effects and survival. The study may broaden the use of ambrisentan.

Prostanoids

Prostacyclin is the main product of arachidonic acid in the vascular endothelium. By the production of cyclic adenosine monophosphate, prostacyclin promotes pulmonary vascular relaxation and inhibits growth of smooth-muscle cells. In addition, prostacyclin is a powerful inhibitor of platelet aggregation.

FREEDOM Study

A sustained-release approach to prostacyclin delivery uses an osmotic tablet technology to deliver oral treprostinil diethanolamine. The pharmacokinetic data indicate that sustained plasma concentrations of treprostinil were delivered over approximately 8 to 10 hours following twice-daily administra-

Table 1. Ongoing Phase 2 and 3 Clinical Trials in Pulmonary Arterial Hypertension

Current Studies	Study Duration	6MWD Criteria	Brief Description
ARIES III (ambrisentan)	24 weeks	150-450 m	Open-label study in PAH related to Eisenmenger syndrome, lung disorder, and CTED
FREEDOM (oral treprostinil diethanolamine)	12 and 16 weeks	100-400 m	RCT in iPAH, fPAH, PAH related to CVD, HIV, and repaired congenital shunts
PHIRST-1 and -2 (oral tadalafil)	16 and 52 weeks	150-450 m	RCT followed by open-label extension in iPAH, PAH related to CVD, anorexigen use, repaired congenital shunt, and unrepaired atrial septal defect
Low-dose sildenafil	12 weeks	100-450 m	RCT in iPAH, PAH related to CVD and repaired congenital shunt
Serotonin transporter inhibitor (escitalopram)	16 weeks	50-480 m	RCT in iPAH, fPAH, PAH related to CVD, HIV, congenital shunt, and anorexigen use
Tyrosine kinase inhibitor (imatinib mesylate)	6 months	—	RCT in iPAH, fPAH, and PAH related to systemic sclerosis
Acetylsalicylic acid and simvastatin	6 months	none	RCT in iPAH, fPAH, PAH associated with CVD, HIV, congenital shunt, and anorexigen use
Epoprostenol and sildenafil	Long-term	100-450 m	Open-label extension study in iPAH, PAH related to CVD, repaired congenital shunt, and anorexigen use

CTED = chronic thromboembolic disease; CVD = collagen vascular disease; fPAH = familial pulmonary arterial hypertension; iPAH = idiopathic pulmonary arterial hypertension; RCT = randomized controlled trial; 6MWD = 6-minute walk test distance.

tion with a regular meal. A high fat and high calorie meal extends the duration of plasma concentration to 10 to 12 hours on average. In vitro and preliminary data suggest no significant interaction between UT-15C and sildenafil and bosentan, and UT-15C was also shown not to inhibit or induce CYP450. The starting dose suggested was 0.5 mg twice daily, with gradual dose escalation. Adverse events experienced with UT-15C are typically those associated with prostacyclin and include headache, flushing, jaw pain, nausea, and emesis. This study will potentially result in the availability of an oral prostacyclin agent that could obviate the need for an intravenous or subcutaneous indwelling catheter and continuous infusions. This option would positively impact patients without the necessary support or manual dexterity to manage infusion pumps and/or mix medication.

Oral prostacyclin (treprostinil diethanolamine, UT-15C), an analogue of treprostinil, is being evaluated as a therapeutic agent in a multicenter RCT. This study will determine the safety and efficacy of UT-15C in PAH subjects who remain symptomatic despite being treated with bosentan or sildenafil or both.

There are two arms of the trial, one enrolling treatment-naïve subjects for a 12-week study, and the other recruiting subjects who are receiving an ETRA and/or a PDE5 inhibitor for a 16-week study. Adult subjects receiving an ETRA and/or a PDE5 inhibitor for 90 days and on a stable dose for at least 30 days before enrolling are eligible. The primary objective for this RCT is a change in 6MWD from baseline. A substudy is evaluating biomarker levels and genetics of the enrolled subjects. Patients with idiopathic or familial PAH, or PAH related to repaired congenital disorders, collagen vascular disease, or HIV infection are eligible. Patients who complete the study are eligible to enroll in a 1-year extension study to determine the safety/efficacy of this drug and the effects on exercise capacity.

TRIUMPH Study

An inhaled form of prostacyclin (treprostinil) was evaluated in a 12-week RCT in patients who remained symptomatic during bosentan or sildenafil therapy. The primary objective was the change in 6MWD from baseline to week 12. The secondary objectives

were changes in NYHA functional class, Borg dyspnea score, signs and symptoms of PAH, quality of life, and time to clinical worsening. The dosing regimen is to take the nebulized medication or placebo four times—on awakening, at midday, in the evening (dinnertime), and at bedtime. After completing the 12-week study, patients have an option to enroll in an open-label extension study.

Preliminary results of this study were announced on November 1, 2007, and showed that the study met its primary efficacy endpoint of 6MWD at 12 week measured at peak exposure after inhalation of treprostinil relative to baseline. These results demonstrates an improvement in median 6MW distance by approximately 20 meters ($P < .0006$) as compared to patients receiving placebo. The secondary efficacy measures such as Borg dyspnea score, NYHA functional class, and time to clinical worsening did not differ between treprostinil and placebo. The full results of this study are not yet published. Use of an inhaled prostacyclin with a longer half-life in symptomatic PAH patients may have a positive impact on patient compliance.

Phosphodiesterase Type 5 Inhibitors

PDE5 inhibitors block the breakdown of cyclic guanosine monophosphate in the vascular endothelium, resulting in increased activity of endogenous nitric oxide that enhances pulmonary vasodilation. Tadalafil is a long-acting PDE5 inhibitor with a mean half-life of 17.5 hours and a once-daily dosing regimen. Tadalafil is rapidly absorbed orally and has no food interaction. The side-effect profile is similar to that of other PDE5 inhibitors.

PHIRST-1 and -2 Studies

A long-acting PDE5 inhibitor, tadalafil, was tested in a RCT as therapy for PAH. Eligible subjects were those with idiopathic PAH or PAH related to collagen vascular disease, anorexigen use, repaired congenital shunt and unrepaired atrial septal defect with oxygen saturation of 88% or greater on room air. The primary endpoint was a change in 6MWD from baseline and secondary measures included WHO functional class, cardiopulmonary hemodynamic, quality of life measures, and Borg dyspnea score change from baseline to Week 16, and time to the first occurrence of clinical worsening. Clinical worsening was defined as death, lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new PAH therapy (eg, prostacyclin or analog, endothelin receptor antagonist, PDE5 inhibitor), or worsening of WHO functional class. The 16-week study has closed (the extension study is ongoing). An ongoing 52-week open-label study followed the 16 week RCT to determine the long-term safety and efficacy of tadalafil. During the extension phase, subjects will receive 40 mg of tadalafil and subjects who complete the 52-week extension study will continue to receive the study medication till the medication is approved. This study may add a long-acting PDE5 inhibitor to the armamentarium to treat PAH.

Low-Dose Sildenafil Study

A current multicenter RCT is evaluating the dose response of 1 mg, 5 mg, and 20 mg tid sildenafil in a 12-week study. The primary objective is to determine the dose response for 1 mg, 5 mg, and 20 mg sildenafil in PAH subjects in 12 weeks. Other objectives of the study are the safety and tolerability of sildenafil and the effects of sildenafil on brain natriuretic peptide (BNP) levels and on annular plane systolic excursion on echocardiography. Patients with idiopathic PAH, PAH associated with connective tissue disease, and PAH associated with repaired congenital heart defect will be eligible.

The rationale for this study is based on the results of the SUPER-1 trial in which the 20 mg, 40 mg, and 80 mg doses of sildenafil showed little evidence of dose response relationship and protein kinase analyses suggested that the 20 mg dose was at the plateau of the dose response curve.⁹ Although the SUPER-1 data indicated that there was improvement in hemodynamics with higher sildenafil dosing, it did not reach statistical significance.⁹ The low-dose sildenafil study would help define whether a lower sildenafil dose may be as efficacious as the FDA-approved sildenafil dose of 20 mg.

Serotonin Transporter Inhibitor Study

Escitalopram

A multicenter RCT will determine the efficacy of a serotonin

transporter inhibitor (STI), escitalopram, on 6MWD in a 16-week study. The other objectives are changes in hemodynamics, improvement in NYHA functional class, dyspnea and quality of life, and efficacy in reducing hospitalization for PAH exacerbations and treatment intensification, including initiation of intravenous therapy. Adult subjects of both genders meeting the WHO hemodynamic PAH criteria and having idiopathic PAH, familial PAH, or PAH associated with repaired congenital defect or collagen vascular disease, appetite suppressant use, or HIV infection are eligible. The inclusion criteria include a 6MWD between 40% and 80% of typical PAH values (approximately 50 to 480 m). This study will help determine the efficacy of STI as another therapeutic agent in PAH.

The pathogenesis of PAH is characterized by vasoconstriction, hyperplasia, and proliferation of pulmonary artery smooth muscle cells that leads to vascular remodeling.^{12,13} In this regard, serotonin is a pulmonary vasoconstrictor and a smooth muscle mitogen implicated in the pathogenesis of PAH. In rats, hypoxic vasoconstrictor responses of the pulmonary vasculature were potentiated by serotonin.¹⁴ Serotonin has been shown to induce sustained calcium entry in the small intrapulmonary artery of rats.¹⁵ Serotonin is transported into the numerous cells by the serotonin transporter. Serotonin transporter expression is increased in pulmonary vascular smooth muscles cells in patients with PAH.¹⁶ Mice deficient in the transporter gene were protected from hypoxic-induced pulmonary vasoconstriction.¹⁷ A highly selective STI, fluoxetine, has been shown to protect against monocrotaline-induced pulmonary hypertension¹⁸ and abrogate hypoxic-induced vascular remodeling in rats.¹⁹ These data suggest a role for STIs in the treatment of PAH.

Tyrosine Kinase Inhibitor Study

Imatinib Mesylate

This RCT is recruiting PAH subjects to determine the safety and efficacy of imatinib mesylate, a tyrosine kinase inhibitor, in a 6-month study. Eligible subjects are those with idiopathic PAH, familial PAH, or PAH associated with systemic sclerosis. Excluded subjects include those receiving PDE5 inhibitors or inhaled nitric oxide, and those with preexisting lung disease, congenital heart disease including pulmonary artery stenosis, valvular heart disease, and chronic thromboembolic disease. The primary objectives are safety and tolerability of the drug as well as efficacy measured by improvement in the 6MWD. Secondary objectives are improvement in WHO functional class and Borg dyspnea score, changes in hemodynamic, time to clinical worsening, and plasma biomarker levels.

Platelet-derived growth factor (PDGF) is shown to be upregulated in lungs from PAH patients as compared with healthy controls.²⁰ In animal studies, the PDGF antagonist imatinib mesylate completely reversed vascular remodeling, improved hemodynamics, and reduced mortality.²¹ A case report described the compassionate use of imatinib mesylate in a PAH patient awaiting lung transplant who was receiving inhaled prostacyclin, ETRA, and a PDE5 inhibitor. The patient responded to treatment with imatinib with improvement in 6MWD, hemodynamics, and functional class.²² Another recent report described a PAH patient receiving epoprostenol infusion with refractory right-heart failure who responded to imatinib mesy-

late with marked clinical improvement.²³ Hence, it was a logical progression that the investigation of this drug would be undertaken in an RCT. The results of this study are eagerly awaited and have the potential to add another class of agent to treat PAH.

Combination Studies

ASA and Simvastatin

An RCT is enrolling PAH subjects to test aspirin and simvastatin as a combination in a 6-month study. Eligible subjects are those with idiopathic PAH, familial PAH, and PAH associated with collagen vascular disease, HIV infection, congenital shunts, or anorexigen use. The enrollment criteria include mild lung disease, and no walk distance criteria except the ability to perform the 6-minute walk test. The main exclusion criteria include sickle cell disease, kidney failure, initiation of other PAH therapy within 3 months, current therapy with a statin, or use of drugs that are metabolized by the CYP450 pathway. Other exclusion criteria are bleeding diathesis, anemia, severe thrombocytopenia, and intracranial or gastrointestinal bleed.

Antiproliferative and proapoptotic effects of statins on smooth muscle cells occur by the inhibition of ras and rho GTPase activities. Simvastatin, a 3-hydroxy-3-methyl-glutaryl-coenzyme A-reductase inhibitor (statin), has been shown to attenuate vascular injury and remodeling in a monocrotaline-pneumonectomy model of PAH.²⁴ An observational open-label study showed that simvastatin was well tolerated by PAH subjects without any adverse events and that it may have a role in reversing vascular remodeling.²⁵ These data suggest that statins may play an important role in the pathogenesis of PAH.

In addition to medial hypertrophy and intimal fibrosis, PAH is associated with thrombi in situ in small muscular pulmonary arteries.¹ The increased platelet aggregation may be due to abnormal arachidonic acid metabolism, as shown by an elevated urinary metabolite of thromboxane (TXA₂) and a reduced urinary metabolite of prostacyclin (PGI₂) in PAH.^{26,27} Aspirin inhibits platelet aggregation and inactivates cyclooxygenase (COX) that catalyzes the first step of TXA₂ synthesis. Therefore, inhibition of COX would inhibit thromboxane production. Another study showed that the combination of clopidogrel and acetylsalicylic acid effectively reduced thromboxane metabolites without affecting prostacyclin. This study is promising but it remains to be seen whether combining acetylsalicylic acid and a statin would prove to be beneficial in treating PAH.

Epoprostenol and Sildenafil

A multicenter, long-term, open-label extension study is under way to determine the safety of sildenafil when used in combination with intravenous epoprostenol in subjects who completed the initial 16-week RCT. The 16-week RCT was undertaken to determine the effect on exercise capacity of optimized doses of sildenafil (20, 40, 80 mg tid) compared with placebo when combined with intravenous epoprostenol. The secondary objectives of the RCT were to assess the safety and tolerability of optimized doses of oral sildenafil in combination with intravenous prostacyclin, to assess the pharmacokinetic parameters, and the survival status of subjects who participated in the study. The extension phase will assess the long-term safety of the optimized treatment regimen of oral sildenafil and intra-

venous epoprostenol. Other objectives are to determine the treatment effect and number of patients who have increased, decreased, or stopped intravenous epoprostenol. This study will help elucidate the benefits of combining prostacyclin analogues and PGE5 inhibitors in treating PAH. In addition, the optimal dose of sildenafil in combination with stable doses of intravenous epoprostenol may be better defined.

Summary

Treatment of PAH has undergone rapid advances as emerging therapies are tested in clinical trials to treat this fatal disease. Well-designed RCTs have led to the approval of multiple current drugs by the FDA and other regulatory agencies. These RCTs tested therapies targeting well-known pathways involved in the pathophysiology of PAH. Ongoing RCTs are testing agents and combination therapies targeting not only recognized but also novel pathways in PAH. These RCTs will potentially lead to new therapeutic strategies to treat this lethal disorder. ■

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Combination Therapies in Pulmonary Arterial Hypertension



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Introduction

Despite recent advances in the identification of therapeutic targets and the development of novel medications, pulmonary arterial hypertension (PAH) remains a debilitating and progressive condition. Currently available therapies improve functional capacity and quality of life and may improve survival. However, the vast majority of patients are left with severe functional limitations in their daily activities. The pathophysiology of PAH is complex, involving in part imbalances in endogenous mediators that promote vasoconstriction and cell proliferation in the pulmonary vasculature. The mechanisms promoting these pathologic effects involve multiple pathways. In light of this complexity, it is not surprising that many of the therapies employed in PAH do not completely reverse the pathologic changes. Just as systemic hypertension is currently being treated with multiple agents from different classes, patients with PAH may benefit from combination therapy, making this approach appealing in concept.

The goal of combination therapy is aimed at maximizing therapeutic efficacy while limiting toxicity and drug-drug interactions. Endpoints, such as improvement in functional capacity as measured by improvements in New York Heart Association (NYHA) functional class, 6-minute walk test distance, and pulmonary hemodynamics, have been employed to help establish treatment efficacy in monotherapy trials. These same endpoints are being employed in trials of combination therapy. However, there remain many important unanswered questions regarding this approach. For example, what combination of available treatments is most efficacious? Are certain forms of PAH more likely to respond to a particular combination of medications? What are the pharmacologic interactions, safety profiles, and cost-effectiveness of various combinations? Among the physiologic pathways involved in the development and progression of PAH,

three currently have targeted therapies and are therefore being pursued in PAH combination therapy trials.

1) *The prostacyclin pathway.* Prostacyclin is a potent pulmonary vasodilator. It stimulates cyclic adenosine monophosphate (cAMP) production, resulting in vascular smooth muscle cell relaxation and inhibition of smooth muscle cell growth. It may prevent pulmonary vascular remodeling.¹ A deficiency of prostacyclin in the lungs of patients with PAH confirmed the relevance of prostacyclin analogues as a treatment.² Epoprostenol intravenously, treprostinil via intravenous or subcutaneous infusion, and iloprost as an inhalational agent are the currently available prostanoids in the United States.

2) *The endothelin-1 (ET-1) pathway.* ET-1 is a potent pulmonary vasoconstrictor. Increased levels of ET-1 have been detected in the lung vasculature of patients with PAH. Blocking this pathway using either nonselective or selective ET-1 receptor antagonists (ETRAs) has proved beneficial in the treatment of PAH. Bosentan is a nonselective ET-1 receptor antagonist and was the first oral therapy approved by the Food and Drug Administration (FDA) for the treatment of PAH.³ Ambrisentan, a selective ET-1 receptor antagonist, was more recently approved for this indication.

3) *The nitric oxide pathway.* Nitric oxide enhances the production of cyclic guanosine monophosphate (cGMP), which has actions similar to those of cAMP.⁴ cGMP is inactivated by the phosphodiesterase family of enzymes. Phosphodiesterase-5 (PDE5) is abundant in the lung vasculature and PDE5 inhibition by agents such as sildenafil prevents the breakdown of cGMP,⁵ resulting in pulmonary vasodilation.⁶ Sildenafil has been approved by the FDA for the treatment of PAH.

Combination therapies can be viewed either as the use of two or more therapies started concomitantly or as add-on therapy, where the second (or third) agent is added to a previously established therapy. The addition of another medication may occur in the setting of patient deterioration or in the scenario of a stable patient who has not had “adequate” improvement with monotherapy. To date, the vast majority of published studies have examined the efficacy of add-on therapies.

Key Words—Prostanoids; endothelin receptor antagonists; PDE5 inhibitors; goal-directed therapy.

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Table 1. Prostanoids Plus Endothelin Receptor Antagonist Combination Trials

Combination	Study Design	Number of Patients	Dosing	Results	P value
Bosentan + iloprost/beraprost ³⁰	OL	20	Bosentan 125 mg bid + Prostanoid, maximal tolerated dose	6MWD + 45 m Exercise testing parameters	< .05 < .05
Bosentan + epoprostenol (BREATHE-2) ³¹	RCT	33	Bosentan 125 mg bid + Epoprostenol 12-16 ng/kg/min	PVR -36% vs -23% 6MWD NYHA FC	NS NS NS
Bosentan + iloprost (COMBI) ¹¹	RCT	40	Bosentan 125 mg bid + Iloprost 5 mcg 6 times daily	6MWD TCW Functional Class	NS NS NS
Bosentan + iloprost (STEP) ¹⁰	RCT	67	Bosentan 125 mg bid + Iloprost 5 mcg up to 6 times daily	6MWD + 26 m Delayed TCW	.051 .022
Bosentan + prostanoids ¹²	OL	16	Bosentan 125 mg bid + Iloprost intravenous or inhaled; or Beraprost	6MWD + 42 ± 66 m Tei index improved	< .001 <.001

NYHA FC = New York Heart Association functional class; OL = open label; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; 6MWD = 6-minute walk test distance; Tei index = echocardiographic index of right ventricular function; TCW = time to clinical worsening.

Current Studies of Combination Therapy

Prostanoids and ET-1 Receptor Antagonists

Results from early animal studies suggest that this combination is effective in the treatment of PAH.⁷ Early observational and unblinded clinical studies examining this combination were also encouraging (Table 1). The addition of bosentan in an open-label fashion was studied in 20 PAH patients stable on either inhaled iloprost or oral beraprost (maximum tolerated dose).⁸ This regimen was well tolerated and resulted in significant improvement in 6-minute walk test distance (6MWD), as well as in parameters of exercise testing (maximal oxygen consumption, anaerobic threshold, oxygen pulse, ventilatory efficiency, and peak systolic blood pressure during exercise). However, the first placebo-controlled trial of this combination of medications raised questions about their efficacy together. BREATHE-2 was a 16-week, double-blinded, randomized, placebo-controlled prospective trial examining the efficacy of adding oral bosentan at the initiation of intravenous epoprostenol therapy.⁹ Intravenous epoprostenol therapy was started in 33 PAH patients (idiopathic PAH or connective tissue disease-related PAH). Two days later they were randomized to receive either oral bosentan or placebo. The target dosage of epoprostenol at week 16 was 12 to 16 ng/kg/min and the target dosage of bosentan was 125 mg bid. In patients receiving the combination, hemodynamic improvement was

The goal of combination therapy is aimed at maximizing therapeutic efficacy while limiting toxicity and drug-drug interactions. Endpoints, such as improvement in functional capacity as measured by improvements in New York Heart Association (NYHA) functional class, 6-minute walk test distance, and pulmonary hemodynamics, have been employed to help establish treatment efficacy in monotherapy trials. These same endpoints are being employed in trials of combination therapy.

not significant in comparison with placebo and epoprostenol; nor was there significant improvement in functional class or exercise capacity. Leg edema was encountered more frequently in the group receiving bosentan (27% vs 9% with placebo). In addition, three deaths occurred during the course of the study; all were in the combination arm. This study, however, was not powered to detect differences in survival, and the survival difference was of concern but not statistically significant.

In the recent multicenter, placebo-controlled STEP trial, iloprost or placebo was added to treatment in 67 PAH patients in New York Heart Association (NYHA) functional class III or IV whose condition was clinically stable with bosentan.¹⁰ The primary endpoint of this study was the postinhalation 6MWD. The 6MWD significantly improved by 26 m (placebo-adjusted) at week 12 in patients receiving combination therapy. NYHA functional class, time to clinical worsening, and postinhalation hemodynamics also were significantly improved.

The combination of inhaled iloprost and bosentan appeared to be safe and well tolerated. These data were sufficient for the FDA to approve iloprost as an add-on therapy in patients receiving bosentan. In the COMBI multicenter trial, Hoepfer et al studied patients with idiopathic PAH stable on bosentan to whose regimen iloprost or placebo was added.¹¹ The investigators planned to enroll 72 patients, but the study was terminated early because the interim analysis of 40

Table 2. Ongoing Clinical Trials of Combination Add-on Therapies

	Initial Therapy	Added Therapy	Number of Patients	Study Duration	Primary Endpoint
FREEDOM-C	Bosentan and/or sildenafil	Treprostinil	300	16 weeks	6 MWD
TRIUMPH-1	Bosentan	Treprostinil	150	12 weeks	6 MWD
PACES (extension)	Epoprostenol	Sildenafil	264	Long-term	6 MWD
VISION	Sildenafil	Iloprost	180	16 weeks	6 MWD
PHIRST	Naïve or bosentan	Tadalafil	400	16 weeks	6 MWD
Pfizer	Bosentan	Sildenafil	106	12 weeks	6 MWD
COMPASS-2	Sildenafil	Bosentan	180	Event driven	6 MWD Morbidity/mortality events
COMPASS-3	Bosentan	Sildenafil	100	12 weeks	6 MWD

6MWD = 6-minute walk test distance.

patients did not demonstrate efficacy. Interestingly, as in the STEP trial, the 3 patients whose condition showed significant deterioration in all objective outcomes were in the combination arm. Lastly, in an open-label trial, the addition of bosentan was studied in 16 PAH patients stable on inhaled iloprost or intravenous iloprost or oral beraprost.¹² The combination significantly improved the average 6MWD as well as echocardiographic indices of right ventricular function. Nine patients had an improvement in functional class. Effects were sustained at over 6 months.

Two multicenter trials are currently being conducted to analyze the combination of an ETRA with a prostacyclin analogue (**Table 2**). TRIUMPH-1 is a 12-week placebo-controlled trial that is enrolling PAH patients stable on bosentan in whom placebo or inhaled treprostinil qid is added. In the second trial, FREEDOM-C, PAH patients who are receiving bosentan and/or sildenafil will have oral treprostinil added in escalating doses. Although both of these studies have as their main goal the establishment of efficacy for inhaled or oral treprostinil in the combination treatment of PAH, the results of these trials will also shed light on the safety of combining these therapies with ETAs.

Prostanoids and PDE5 Inhibitors

There is experimental evidence of a costimulatory cross-talk between the cAMP and cGMP pathways, including certain animal models of PAH. The combination of sildenafil and beraprost in monocrotaline-induced pulmonary hypertension in rats attenuated the development of pulmonary hypertension and pulmonary vascular remodeling to a greater degree

than did either drug alone.¹³ Animal survival improved and increases in plasma cAMP and cGMP levels were noted. Acute clinical hemodynamic studies and short-term trials in patients have demonstrated potentiation of the vasodilator actions of prostacyclins by sildenafil, thus holding promise for this combination (**Table 3**).

Ghofrani et al¹⁴ administered inhaled iloprost and sildenafil to 30 patients with severe PAH or chronic thromboembolic pulmonary hypertension. The combination was more potent than either agent alone. Sildenafil extended the duration of iloprost effects beyond 3 hours, suggesting that less frequent dosing of iloprost might be possible. In an open-label study Kuhn et al administered 50 mg of sildenafil (one dose) to 8 patients with PAH receiving long-term epoprostenol therapy.¹⁵ They observed improvements in mean pulmonary artery pressure (mPAP), cardiac output, and pulmonary vascular resistance (PVR), suggesting that sildenafil remains a potent acute pulmonary vasodilator in patients receiving chronic epoprostenol therapy.

In an acute vasodilation study in 5 patients with PAH, the combination of oral sildenafil with inhaled iloprost was superior to iloprost alone.¹⁶ Similarly, addition of sildenafil to oral beraprost in 6 patients with moderate to severe PAH produced improvements in mPAP and PVR when compared with beraprost alone.¹⁷ In 14 PAH patients showing clinical deterioration with inhaled iloprost, add-on therapy with sildenafil reversed the deterioration, significantly increasing the 6MWD and functional class; these improvements were sustained after 9 to 12 months of combination therapy.¹⁸

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Table 3. Prostanoids Plus PDE5 Inhibitor Combination Trials

Combination	Study Design	Number of Patients	Dosing	Results	P value
Iloprost + sildenafil vs inhaled NO ¹⁴	Acute, OL	30	Iloprost 2.8 mcg, then sildenafil 12.5 mg or 50 mg after 1 hour, or inhaled NO	PVR -44.2% vs 14.1% with inhaled NO	
Iloprost + sildenafil ¹⁶	Acute, OL	5	Iloprost 8.5-10.5 mcg, then sildenafil 25 mg after 30 min	mPAP -13.8 mmHg vs 8.4 mmHg	.009
Beraprost + sildenafil ¹⁷	Short-term, OL	6	Beraprost 40 mcg -day 1; beraprost 40 mcg + sildenafil 25 mg, days 2-6	2.2 x reduction in mPAP 1.6 x reduction in PVR	< .05
Epoprostenol + sildenafil ³²	Acute OL	8	Epoprostenol average 25.7 ng/kg/min + sildenafil 50 mg once	mPAP -10% PVR -13%	.05 NS
Iloprost + sildenafil ¹⁸	Long-term, OL	14	Iloprost up to 9x/day + sildenafil 25-50 mg tid	6MWD + 90 m at 3 months	.002
Treprostinil sq + sildenafil ¹⁹	Long-term, OL		Treprostinil 35-90 ng/kg/min + sildenafil 50 mg tid	Treadmill time + 42%	.049
Prostanoids + sildenafil ²⁰	Long-term, OL	20		6MWD +79 m (1 year) + 105 m (2 years) NYHA FC improved	<.05
Epoprostenol + sildenafil PACES ²¹	16 weeks, RCT	267	Epoprostenol + sildenafil 80 mg tid	6MWD +26 m TCW delay	.0088 .012

mPAP = mean pulmonary artery pressure; NO = nitric oxide; NYHA FC = New York Heart Association functional class; OL = open label; PDE5 = phosphodiesterase 5; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; 6MWD = 6-minute walk test distance; TCW = time to clinical worsening.

More recently, Gomberg-Maitland et al¹⁹ reported on an open-label study in which 9 stable PAH patients in NYHA functional class II-IV on stable doses of subcutaneous treprostinil had sildenafil added to their regimen. After 12 weeks, patients had significant improvement in their treadmill exercise capacity. Lastly, in a retrospective study, 20 patients with severe PAH who showed clinical deterioration on prostanoid therapy (8 subcutaneous, 7 intravenous, and 5 inhaled) had sildenafil added to their regimen.²⁰ The 6MWD, functional class, and echocardiographic parameters of right ventricular function improved significantly, and the beneficial effects lasted more than 24 months.

These combination studies, albeit reporting on a limited number of patients in mostly open-label studies, suggested that PDE5 inhibitors improve pulmonary hemodynamics and symptoms in PAH patients receiving prostanoid therapy. A large multicenter, double-blind, randomized trial (PACES) of this combination awaits publication. This trial enrolled patients stable on epoprostenol and randomized them to the addition of placebo or sildenafil titrated to tolerance up to 80 mg three times daily. Preliminary results reported in an

abstract at the American Thoracic Society meeting in May 2007 demonstrated an average of 26 meters improvement in 6MWD at week 16 in the combination therapy arm as well as a delay in time to clinical worsening.²¹

ETRA and PDE5 Inhibitors

The combination of oral therapies is an attractive option to both clinicians and patients as it avoids the disadvantages of infusion therapies (Table 4). A few reports have addressed the significant pharmacologic interactions between sildenafil and bosentan. In a recent study, 51 healthy volunteers completed a randomized, double-blind, placebo-controlled, parallel group study with three arms (sildenafil 80 mg three times daily, bosentan 125 mg twice daily, and sildenafil plus bosentan) for 18 days.²² On day 16, bosentan decreased maximum plasma concentration of sildenafil by 55%, while sildenafil increased bosentan concentration by 42%. Despite this pharmacokinetic interaction, the combination of sildenafil and bosentan was well tolerated.

Another pharmacologic study assessed the combination of bosentan with sildenafil in 10 patients with PAH.²³

Table 4. Endothelin Receptor Antagonists Plus PDE5 Inhibitor Trials

Combination	Study Design	Number of Patients	Dosing	Results	P value
Bosentan + sildenafil ²⁵	OL	25	Bosentan 125 mg bid + sildenafil 20-100 mg tid	6MWD + 46 m in idiopathic PAH NYHA FC improved in 5/13 with idiopathic PAH	.05 NS
Bosentan + sildenafil ²⁴	OL	9	Bosentan 125 mg bid + sildenafil 25-50 mg tid	6MWD + 115 m VO2 max + 3.4 mL/min/kg	< .007 .006
Bosentan + sildenafil ²⁷	Post-marketing surveillance	4,996	Bosentan alone vs bosentan + sildenafil	Safety reports similar	

OL = open-label; 6MWD = 6-minute walk test distance; NYHA FC = New York Heart Association functional class.

Bosentan was given at a dosage of 62.5 mg twice daily for 1 month, then at 125 mg twice daily for the second month. Sildenafil 100 mg was given before the first bosentan dose and at the end of each month of bosentan treatment. Treatment with bosentan 62.5 mg twice daily was associated with a twofold increase in sildenafil clearance. Increasing the dose of bosentan to 125 mg twice daily led to a further increase in sildenafil clearance, demonstrating that bosentan decreases the plasma concentration of sildenafil in PAH patients.

Although these short-term pharmacologic studies proved safe, there is a theoretical concern of increased liver toxicity from elevated bosentan levels in patients taking a combination of these medications. We know from the BREATHE-1 study that bosentan at 250 mg twice daily is associated with a higher risk of liver toxicity than is the currently approved dose (125 mg twice daily).³ Therefore, patients taking the combination of bosentan and sildenafil should be carefully monitored for evidence of liver toxicity.

In a small study of idiopathic PAH patients, bosentan was employed as add-on therapy in those whose condition was clinically deteriorating with sildenafil monotherapy.²⁴ The combination was well tolerated, 6MWD improved significantly, and patients remained stable throughout the median follow-up of 9 months. A retrospective study analyzed 25 patients with idiopathic PAH or PAH related to scleroderma who were receiving bosentan but who required addition of sildenafil because of clinical deterioration.²⁵ In this small cohort, only idiopathic PAH patients showed an improvement in average 6MWD with the addition of sildenafil, with 5 of the 13 idiopathic PAH patients showing improvement in NYHA functional class, while scleroderma patients did not have significant improvement with combination therapy. This result emphasizes the difficulties of treating patients with scleroderma-associated PAH. Preliminary results from

the EARLY trial²⁶ were reported for 29 patients with mild PAH (functional class II) receiving sildenafil in whom bosentan was added. Addition of bosentan improved PVR by 20% and delayed time to clinical worsening, although there was no significant improvement in the 6MWD. In a prospective, Internet-based, postmarketing surveillance study required by the European regulatory authorities for assessing the safety of bosentan in PAH patients, of almost 5000 PAH patients who were captured over 30 months, 218 patients received sildenafil in addition to bosentan.²⁷ Combination therapy appeared to be well tolerated in this subgroup; their safety data were similar to those for bosentan alone.

There are three ongoing clinical trials looking at the sildenafil and bosentan combination from which data are not yet available (Table 2).

Goal Directed Therapy

There is debate among PAH specialists as to whether combination therapy should be reserved for patients whose condition deteriorates (add-on therapy) or should be started up front. This paradigm resembles the “induction” therapy used in cancer treatment, followed by maintenance therapy with one or more agents once patients have improved. Both approaches have theoretical advantages and disadvantages. In the add-on therapy approach, physicians must follow their patients very closely to avoid a delay in initiating more aggressive therapy should patients not improve or worsen. A lack of improvement in functional class with treatment and development of class IV symptoms are both associated with a very poor prognosis. However, employing an up-front combination regimen may expose patients to unnecessary drug-drug interactions, toxicity, and higher costs.

An interesting study conducted in Europe adopted a rigorous algorithm employing the approach of add-on therapy. In this “goal directed” trial, Hoepfer et al enrolled 123 con-

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secutive PAH patients.²⁸ Goals of therapy included improvement in 6MWD to more than 380 meters, peak systolic blood pressure greater than 120 mmHg during exercise testing, and a peak VO_2 greater than $10.4 \text{ mL} \times \text{min}^{-1} \times \text{kg}^{-1}$. Patients were evaluated every 2 to 6 months. If the goals of therapy were not met, another therapy was added and the patient was reassessed. Therapies were instituted in the following order: bosentan, sildenafil, inhaled iloprost, and transition to intravenous iloprost, then referral for urgent lung transplantation as a last resort. At entry to the study 98 patients were in functional class III and 25 patients were in class IV. Using this algorithm, reported survival was 93%, 83%, and 79.9% at 1, 2, and 3 years, respectively. This was an improvement in survival compared to pre-2000 era historical PAH controls at the same center. It is important to note that monotherapy failed in 43% of patients in this study, 16% required three-drug combination therapy, and 5% were treated with intravenous prostanoids after triple therapy failed.

Where Are We Now?

The studies discussed above all have made important contributions toward our understanding of the treatment of patients with PAH. As a whole they suggest that combination therapy is well tolerated and may be beneficial in certain groups of patients. Randomized controlled trials have demonstrated the efficacy of an intravenous prostacyclin analog combined with a PDE5 inhibitor (PACES) and an inhaled prostanoid combined with an ETRA (STEP) as add-on therapies. However, a combination of an intravenous prostanoid and an ETRA started concomitantly (BREATHE 2) did not demonstrate efficacy. While the data on combination therapies are still in their infancy, PAH physicians are faced with the practical dilemma of how to treat patients who do not improve significantly or who deteriorate with monotherapy. Preliminary results from the REVEAL registry, presented at the American College of Chest Physicians meeting in October 2007 provided a glimpse of current clinical practice in the United States.²⁹ Among the first 1226 PAH patients enrolled, only 47% were being treated with monotherapy (bosentan 13%; sildenafil 13%; intravenous epoprostenol 8%; sitaxsentan 2%; and calcium channel blockers 4%). A significant percentage (36%) are receiving two-drug combination therapy (intravenous epoprostenol plus sildenafil 8%; bosentan plus sildenafil 8%; bosentan plus epoprostenol 3%; bosentan plus inhaled iloprost 3%; and sildenafil plus inhaled iloprost 2%), and 9% receive three or more PAH-specific medications. Therefore, in the absence of rigorous evidence supporting multidrug therapy, a diverse array of combination strategies has emerged into clinical practice.

It is clear that there remain significant shortcomings in our understanding of the use of combination therapy in PAH. Most of the available trials to date have included only small numbers of patients. Many of these trials were open label and not randomized. The potential for publication bias

exists, as negative studies are less likely to be published. A number of questions remain unanswered as we strive to improve outcomes with PAH treatment.

The Future of Combination Therapy

Because PAH is a rare disease, it is difficult to adequately power therapeutic trials to evaluate significant morbidity or mortality differences between various drug therapies. At this point, it is premature to either dismiss or strongly favor any one combination of therapies over another. Careful design of future trials testing these comparisons is vital. We hope that the future will provide the answers as to which combinations are most effective, the appropriate timing of combination therapy, the identification of subgroups of patients who may respond to particular combinations, as well as establishing the cost-effectiveness of various combination therapies. ■

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Self-Assessment Examination

See answer key on next page

1. Which of the following statements is correct?

- a. An acute vasoreactivity response is defined as a decrease in mean PAP ≥ 10 to ≤ 40 mm Hg with an unchanged or increased cardiac output
- b. Calcium channel blockers may be considered in patients with an acute response to vasoreactivity testing
- c. Tadalafil was not included in the 2007 ACCP guidelines
- d. The strongest evidence for benefit with sildenafil monotherapy is in functional class II and III patients
- e. All of the above

2. All of the following statements about prostanoid therapy are true except:

- a. Epoprostenol likely improves survival in functional class III and IV patients
- b. The most common adverse effect of intravenous poprostenol use is site pain
- c. Though subcutaneous treprostinil is beneficial in functional class III and IV patients, its use is limited by its most common adverse effect
- d. Long-term efficacy of intravenous treprostinil is still being evaluated
- e. The most common adverse effect of intravenous poprostenol is line-related infection

3. Which of the following statements about endothelin receptor antagonists is false?

- a. Bosentan monotherapy appears to be most beneficial in functional class III patients
- b. Sitaxsentan is not considered in the 2007 ACCP guidelines
- c. Ambrisentan may be considered as an alternative endothelin receptor antagonist for patients in functional class III
- d. Hepatotoxicity is the most common severe adverse effect of endothelin receptor antagonists
- e. None of the above

4. The oral prostacyclin form is being tested in a randomized controlled trial as PAH therapy. The primary objective of this study is to determine which of the following?

- a. safety and efficacy of this agent
- b. effect on biomarker profile
- c. change in 6-minute walk test distance
- d. effects on exercise capacity and time to clinical worsening

5. The rationale for testing low-dose sildenafil in a randomized controlled trial is based on which of the following?

- a. lack of evidence of a dose-response relationship
- b. improvement in hemodynamics at higher sildenafil doses
- c. need for lower doses of sildenafil
- d. cost of the drug

6. Inclusion criteria for the randomized controlled trial testing escitalopram, a serotonin transporter inhibitor, do not include which of the following?

- a. PAH associated with connective tissue disease
- b. familial PAH
- c. PAH associated with HIV infection
- d. chronic thromboembolic disease
- e. PAH associated with repaired congenital defect

7. The doses of tadalafil, a phosphodiesterase-5 inhibitor, used in a recent randomized controlled trial were 2.5 mg, 10 mg, 20 mg, and 40 mg. The mechanism of action of this class of drug does not include which of the following?

- a. increase in intracellular calcium and inhibition of platelet aggregation
- b. blocking the breakdown of cyclic guanosine monophosphate
- c. increase in endogenous nitric oxide activity

8. Among the three possible combination therapies for PAH, which of the following did not demonstrate efficacy in a randomized controlled trial?

- a. an intravenous prostacyclin and a phosphodiesterase-5 inhibitor
- b. an inhaled prostanoid and an endothelin-1 receptor antagonist (ETRA)
- c. an intravenous prostanoid and an ETRA

9. Regarding the initial patients reported in the REVEAL database, which of the following is false?

- a. more than 75% of patients were receiving monotherapy for PAH
- b. data were available for more than 100 patients
- c. most patients were receiving combination therapy

10. Pharmacologic studies revealed that there is interaction between sildenafil and bosentan. Which of the following statements regarding this interaction is true?

- a. sildenafil decreases bosentan levels and bosentan increases sildenafil levels
- b. bosentan decreases sildenafil levels and sildenafil increases bosentan levels
- c. sildenafil decreases bosentan levels and bosentan decreases sildenafil levels
- d. sildenafil increases bosentan levels and bosentan increases sildenafil levels

