PHA’s 10th International Conference and Scientific Sessions
The Scientific Leadership Council of the Pulmonary Hypertension Association

The scientific program of the Pulmonary Hypertension Association is guided by the association’s Scientific Leadership Council. The Council includes the following health care professionals.

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Program Description

The mission of Advances in Pulmonary Hypertension is to serve as the premiere forum for state of the art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2008 Dead Sea press conference of the World Health Organization Classification serves as a guide to categories of pulmonary hypertension addressed in Advances in Pulmonary Hypertension. While focusing on WHO Group 1 PAH, the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, pulmonary embolic hypertension; Group 5, miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions. In addition, a special section in selected issues entitled “Profiles in Pulmonary Hypertension” recognizes major contributors to the field and serves as an inspiring reminder of the rich and collegial history of dedication to advancing the field.

Objectives

• Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.

• Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

• Recognize and preserve the rich history of individuals who have made major contributions to the field via dedication to patient care, innovative research, and furthering the mission of the PH community to cure pulmonary hypertension.

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Rochester, Minnesota

The mission of the Scientific Leadership Council is to provide medical and scientific guidance and support to the PHA for:

• Developing and disseminating knowledge for diagnosing and treating pulmonary hypertension.

• Advocating for patients with pulmonary hypertension.

• Increasing involvement of basic and clinical researchers and practitioners.

More information on PHA’s Scientific Leadership Council and associated committees can be found at www.PHAAssociation.org/SLC
This past summer, medical experts, patients, and their caregivers came together at the PHA’s 10th International Conference and Scientific Sessions to learn about advances in the diagnosis and management of pulmonary hypertension. At the PHA conference, there is “something for everyone” and the scientific sessions are always highly attended as investigators provide their latest updates in the field of pulmonary vascular disease. This year, Todd Bull, MD, along with his scientific sessions committee, built these sessions around the theme of the genetics of pulmonary hypertension. As Guest Editor, Karen Fagan, MD, then tracked down many of the scientific session conference speakers and asked them to summarize their lectures in this edition of Advances. Authors cover topics ranging from genetic mechanisms of disease to the future of basic science research in the current funding climate and under the NHLBI strategic plan for lung vascular research. In this issue, John Newman, MD, describes a phased approach at his institution for studying genetic mechanisms of PAH with a current focus on investigating other intracellular pathways that may influence the development of pulmonary hypertension. In conjunction with the science, Ghazwan Butrous, MD, provides a look at the global impact of pulmonary vascular disease with a call to action for attention to this problem in developing countries.

For those who missed the conference, this issue of Advances in Pulmonary Hypertension offers an opportunity to catch up on the latest science. In addition to these topics, current and past issues of Advances can also be found online on PHA’s Online University along with other coverage of the amazing conference. Just go to www.phassociation.org for a wealth of information for you and your patients.

Erika Berman Rosenzweig, MD
Director, Pulmonary Hypertension Center
Columbia University, College of Physicians and Surgeons

As the PHA International Conference continues to grow with record-breaking attendance for patients, caregivers, and medical professionals, so have the Scientific Sessions. The 2012 Scientific Sessions marks the 7th time scientists and medical professionals have gathered at the International Conference to hear the latest scientific advances in the field. This year proved no exception under the leadership of Dr Todd Bull. The theme was “Genetics of Pulmonary Hypertension,” with talks focused on continuing efforts to understand BMPR2 mutations in PAH, other genetic contributors important in development of PAH such as microRNAs, genes that cause HHT, and PAH as a systemic disease. The events were started by a resounding call to arms by Dr Ghazwan Butrous, who spoke at the PHCR dinner the night before on “The Global Spectrum of Pulmonary Hypertension and its Forgotten Impact in the Developing World.”

Continuing with the focus of developing the next generation of PAH physicians and scientists, the presentation of the best clinical and basic science abstracts by junior investigators is always a highlight, as is the update from the NHLBI focusing on PH-related research initiatives and opportunities. The day concluded with the largest poster session to date where researchers were able to present their current research and obtain feedback and encouragement.

Finally, the research room was extremely busy this year with more than 250 patients, caregivers, and other volunteer participants in a number of research projects. Response was so great that several investigators ran out of supplies before they ran out of willing participants! Perhaps we will see the results of this work at the next Scientific Sessions in 2014.

This issue of Advances provides summaries of many of the talks as well as a roundtable discussion about the recent meeting. Also are abstracts from the most promising young investigators in the PH field. For those who didn’t attend, and for those who did, these articles and discussions are highlighting many of the areas where our understanding of PH is headed toward more effective treatments and eventually a cure.

Karen A. Fagan, MD
Associate Professor of Medicine and Pharmacology
University of South Alabama
ADCIRCA® (tadalafil) tablets is a phosphodiesterase 5 inhibitor (PDE-5i) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

**ADCIRCA once-daily opens up possibilities**

Proven PDE-5 inhibition that can help patients with PAH be more active

- The only once-daily PDE-5 inhibitor for PAH¹
- 33-meter placebo-adjusted mean improvement in 6MWD at 16 weeks¹
- A $20 co-pay for eligible patients on commercial/private insurance plans*"**
- The most common adverse event with ADCIRCA is headache. Other common adverse events include myalgia, nasopharyngitis, flushing, respiratory tract infection, extremity pain, nausea, back pain, dyspepsia, and nasal congestion

*This assistance program is not valid for prescriptions reimbursed under Medicare, Medicaid, TRICARE, state pharmaceutical assistance programs, or other federal or state programs. This assistance program is not valid for patients in the state of Massachusetts with prescription drug coverage.

**Important Safety Information**

**CONTRAINDICATIONS**

- ADCIRCA should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure
- Patients with a known serious hypersensitivity to tadalafil should not take ADCIRCA

**WARNINGS AND PRECAUTIONS**

- If a patient experiences anginal chest pain after taking ADCIRCA they should seek immediate medical attention
- Phosphodiesterase 5 inhibitors (PDE-5i), including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing ADCIRCA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of ADCIRCA to these patients is not recommended
- The use of ADCIRCA with alpha blockers, blood pressure medications, and alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (fainting)
- Tadalafil is metabolized predominantly by CYP3A in the liver. Use of ADCIRCA with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on ADCIRCA therapy that require treatment with ritonavir, ADCIRCA should be discontinued at least 24 hours prior to starting ritonavir. For patients on ritonavir therapy that require treatment with ADCIRCA, start ADCIRCA at 20 mg once a day. Use of ADCIRCA with potent inducers of CYP3A, such as rifampin, should be avoided
- The use of ADCIRCA is not recommended for patients with severe renal or hepatic impairment. Please see full prescribing information for dosing recommendations for patients with mild to moderate renal or hepatic impairment
- ADCIRCA contains the same ingredient (tadalafil) as Cialis, which is used to treat erectile dysfunction (ED). The safety and efficacy of combinations of ADCIRCA with Cialis or other PDE-5 inhibitors have not been studied. Therefore, the use of such combinations is not recommended
- In rare instances, men taking PDE-5 inhibitors (including tadalafil) for ED reported a sudden decrease or loss of vision or hearing, or an erection lasting more than four hours. A patient who experiences any of these symptoms should seek immediate medical attention

**ADVERSE REACTIONS**

- The most common adverse event with ADCIRCA is headache (42% ADCIRCA vs 15% placebo). Other common adverse events (reported by ≥9% of patients on ADCIRCA and more frequent than placebo by 2%) include myalgia (14% vs 4%), nasopharyngitis (13% vs 7%), flushing (13% vs 2%), respiratory tract infection (13% vs 6%), extremity pain (11% vs 2%), nausea (11% vs 6%), back pain (10% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)

ADCIRCA is a registered trademark of Eli Lilly and Company, 2011.


www.adcirca.com
877-UNITHER

Please see brief summary of Full Prescribing Information on following page. Please see Full Prescribing Information and Patient Information available at www.adcirca.com, or call 1-800-545-5979.
ADICIRA® (tadalafil) tablets

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on ADICIRA (tadalafil). Please review the full prescribing information prior to prescribing ADICIRA.

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension: ADICIRA is indicated for the treatment of pulmonary arterial hypertension (PAH) WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue disease (23%).

CONTRAINDICATIONS

Concomitant Organic Nitrates: Do not use ADICIRA in patients who are using any form of organic nitrate, either regularly or not regularly, due to the potent vasodilating effect of nitrates. Avoid use of ADICIRA with any of the organic nitrates, including isosorbide dinitrate and isosorbide mononitrate. In patients with severe renal impairment, the use of organic nitrates may further reduce renal function, including renal vasoconstriction. The use of ADICIRA and organic nitrates may result in profound hypotension and/or fatal cardiovascular collapse.

CYP3A — For patients chronically taking potent inducers of CYP3A such as ritonavir, do not use ADICIRA. Potent Inducers of CYP3A — For patients taking potent inhibitors of CYP3A, such as ritonavir, avoid use of ADICIRA. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Other Potent Inducers of CYP3A — Tadalafil is metabolized predominately by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole and itraconazole, avoid use of ADICIRA. Potent Inducers of CYP3A are found in the core medications prescribed for chronic hepatitis C, such as telaprevir and boceprevir. Prolonged Erection: There have been rare reports of prolonged erections greater than 4 hours and priapism (painful or non-painful erosion of the corpora cavernosal and/or corpora spongiosa). Use in Patients with PDE5 inhibitors — It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Use in Patients with ED — Use of PDE5 inhibitors in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended. Use in Patients with PDE5 inhibitors and alpha blockers may be affected by other factors.

ADVERSE REACTIONS

Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis. See Table 1 for a list of adverse events occurring more frequently than with placebo. Allergic reactions include angioedema, angina, chest pain, dyspepsia, dysphagia, flushing, headache, hypotension, and nasal congestion. Angioedema has been reported in patients taking ADICIRA and concomitantly treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Angioedema has also been reported after sexual activity and may be a sign of non–arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors.

Ophthalmologic events may occur in patients taking ADICIRA with or without concomitant use of Ritonavir. These events have been identified during post-approval use of tadalafil. These events have been included for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are voluntarily reported from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. Cardiovascular and cerebrovascular events — Serious cardiovascular events, including myocardial infarction, sudden cardiac death, stroke, chest pain, palipitations, and tachycardia, have been reported postmarketing in temporal association with the use of tadalafil. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient’s underlying cardiovascular disease, to a combination of these factors, or to other factors. Body as a whole — Hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, and exfoliative dermatitis. Nervous — Migraine, seizure and seizure disorder, and transient global amnesia. Ophthalmologic — Visual field defect, retinal vein occlusion, and retinal artery occlusion. Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, and retinal artery or retinal vein disease. Nonsmoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Urogenital — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have played a role in the adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or other factors.

Potent Inducers of PDE5 (e.g., ketoconazole and itraconazole) may be affected by other factors.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

— Hypotension
— Pain
— Priapism
— Visual field defect

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. Use in Renal Impairment: In patients with mild to moderate renal impairment — Start dosing at 20 mg once daily. Increase the do
are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiated the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Alpha-Blockers — PDE5 inhibitors, including ADCIRCA, and alpha–adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin. Antihypertensives — PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amiloride, angiotensin II receptor blockers, bendrofumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. Alcohol — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations. Potential for Other Drugs to Affect ADCIRCA: Ritonavir — Ritonavir initially inhibits and later induces CYP3A, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir. Other Potent Inhibitors of CYP3A — Tadalafil is metabolized predominantly by CYP3A in the liver. In patients taking potent inhibitors of CYP3A such as ketoconazole, and itraconazole, avoid use of ADCIRCA. Potent Inducers of CYP3A — For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCIRCA. Potential for ADCIRCA to Affect Other Drugs: Cytochrome P450 Substrates — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan). Aspirin — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin. P-glycoprotein (e.g., digoxin) — Coadministration of tadalafil (40 mg once daily) for 10 days did not significantly alter digoxin pharmacokinetics in healthy subjects. USE IN SPECIFIC POPULATIONS Pregnancy: Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of fetal harm. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed. Non-teratogenic effects — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance. Nursing Mothers: It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman. Pediatric Use: Safety and effectiveness of ADCIRCA in pediatric patients have not been established. Geriatric Use: Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered. Renal Impairment: For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis. Hepatic Impairment: Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients. OVERDOSAGE Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination. Marketed by Lung Rx, LLC, a wholly owned subsidiary of United Therapeutics Corporation. Rx only April 2011 www.adcirca.com
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Important Safety Information
Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with α-blockers as both are vasodilators with blood pressure lowering effects.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%). Co-administration of REVATIO with potent CYP3A4 inhibitors, eg, ketoconazole, itraconazole, and ritonavir, is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Please see Brief Summary on the following pages.
Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil.

It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established. In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo.

REVATIO contains sildenafil, the same active ingredient found in VIAGRA®. Combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Patients taking REVATIO should not take VIAGRA or other PDE5 inhibitors.

Patients with the following characteristics did not participate in the preapproval clinical trial: patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months, unstable angina, hypertension (BP >170/110), retinitis pigmentosa, or patients on bosentan. The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration. In these patients, physicians should prescribe REVATIO with caution.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events of Revatio injection were similar to those seen with oral tablets.

The most common side effects of REVATIO (placebo-subtracted) as an adjunct to intravenous epoprostenol were headache (23%), edema (14%), dyspepsia (14%), pain in extremity (11%), diarrhea (7%), nausea (7%), and nasal congestion (7%).

**Indication**

REVATIO is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.
REVATIO® (SILDENAFIL)

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: REVATIO® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and delay clinical worsening. Delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV; symptoms and efficacy of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

DOSEAGE AND ADMINISTRATION

Pulmonary Arterial Hypertension (PAH)

REVATIO Tablets

The recommended dose of REVATIO is 20 mg three times a day (TID). REVATIO tablets should be taken approximately 4-6 hours apart, with or without food.

In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Dosages lower than 20 mg TID were not tested. Whether dosages lower than 20 mg TID are effective is not known.

REVATIO Injection

REVATIO injection is for the continued treatment of patients with pulmonary arterial hypertension (PAH) who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication. The recommended dose is 10 mg (corresponding to 12.5 mL) administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight.

A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

CONTRAINDICATIONS

Do not use REVATIO in patients taking organic nitrates in any form, either regularly or intermittently. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates.

Hypersensitivity Reactions

REVATIO is contraindicated in patients with a known hypersensitivity to sildenafil or any component of the tablet.

Rare cases of hypersensitivity have been reported in association with the use of sildenafil including anaphylactic reaction/shock events and anaphylactoid reaction. The majority of reported events were non-serious hypersensitivity reactions.

WARNINGS AND PRECAUTIONS

Cardiovascular Effects

REVATIO has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Before prescribing REVATIO, carefully consider whether patients with certain underlying conditions could be adversely affected by such vasodilatory effects (e.g., patients with resting hypotension [BP < 90/50], fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction).

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of REVATIO to patients with veno-occlusive disease, administration of REVATIO to such patients is not recommended. Should signs of pulmonary edema occur when REVATIO is administered, consider the possibility of associated PVOD.

As there are no controlled clinical data on the safety or efficacy of REVATIO in the following groups, prescribe with caution:

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with coronary artery disease causing unstable angina;
- Patients with a known history of bleeding (e.g., hemophilia, platelet dysfunction); or
- Patients currently on bosentan therapy.

Use with Alpha-blockers

PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly, leading to symptomatic hypotension. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension (71%) or pulmonary hypertension associated with connective tissue disease (25%). The efficacy of REVATIO has not been adequately evaluated in patients taking bosentan concurrently.

Use with Ritonavir and Other Potent CYP3A Inhibitors

Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of REVATIO with VIAGRA or other PDE5 inhibitors have not been studied. Inform patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

Prolonged Erection

Use REVATIO with caution in patients with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease) or in patients who have conditions, which may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Pulmonary Hypertension Secondary to Sickle Cell Anemia

In a small, prematurely terminated study of patients with PH secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received REVATIO than by those randomized to placebo. The effectiveness of REVATIO in pulmonary hypertension (PH) secondary to sickle cell anemia has not been established.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension [see Warnings and Precautions]
- Vision loss [see Warnings and Precautions]
- Pneumonia [see Warnings and Precautions]
- Cholecystitis [see Warnings and Precautions]
- Nephrolithiasis [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Sildenafil-treated patients with a concomitant oral vitamin K antagonist (9% versus 2% in placebo) had a significantly higher rate of hemorrhage. Safety data were obtained from the 12 week, placebo-controlled clinical study and an open-label extension study in 277 treated patients with pulmonary arterial hypertension. Doses up to 80 mg TID were studied.

The overall frequency of discontinuation in REVATIO-treated patients at the recommended dose of 20 mg TID was 3% and was the same for the placebo group.

In the placebo-controlled trial in pulmonary arterial hypertension, the adverse drug reactions that were reported by at least 3% of REVATIO patients treated at the recommended dosage (20 mg TID) and were more frequent in REVATIO patients than placebo patients, are shown in Table 1. Adverse events were generally transient and mild to moderate in nature.

Table 1. REVATIO All Causality Adverse Events in ≥ 3% of Patients and More Frequent (> 1%) than Placebo

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo (n=70)</th>
<th>Revatio 20 mg TID (n=69)</th>
<th>Placebo-Subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Dryness</td>
<td>13</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Edema</td>
<td>1</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Genital pain</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

nos: Not otherwise specified
Decreases in and Loss of Vision

The incidence of eye disturbances reported was mild and transient, and were predominately colorblurring to vision, but also increased sensitivity to light or blurring vision. The incidence of retinal hemorrhage at the recommended sildenafil 20 mg TID dose was 1.4% versus 0% placebo and for all sildenafil doses studied was 1.8% versus 0% placebo. The incidence of eye hemorrhage at both the recommended dose and all doses studied was 1.4% for sildenafil versus 1.4% for placebo. The patients experiencing these events had risk factors for hemorrhage including concurrent anticoagulant therapy.

In a placebo-controlled fixed dose titration study of REVATIO (starting with recommended dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID) as an adjunct to intravenous epoprostenol in pulmonary arterial hypertension, the adverse events that were reported were more frequent than in the placebo arm (>4% difference) are shown in Table 2.

Table 2. REVATIO-Epoprostenol Adverse Events More Frequent (> 6%) than Placebo

<table>
<thead>
<tr>
<th>AVERSE EVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Placebo (n=70)</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Edema*</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Pain in extremity</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Nasal congestion</td>
</tr>
</tbody>
</table>

*includes peripheral edema

REVATIO Injection

REVATIO injection was studied in a 66-patient, placebo-controlled study at doses targeting plasma concentrations between 10 and 500 ng/mL (up to 8 times the exposure of the recommended dose). Adverse events in PAH patients were similar to those seen with oral tablets.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sildenafil (marketed for both PAH and erectile dysfunction). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

Decreases in and Loss of Vision

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio (“crowded disc”), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors [see Warnings and Precautions].

Loss of Hearing

Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including REVATIO. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of REVATIO, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors [see Warnings and Precautions].

Other Events

The following list includes other adverse events that have been identified during postmarketing use of REVATIO. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system: Seizure, secure recurrence

DRUG INTERACTIONS

Notations

Concomitant use of REVATIO with nitrates in any form is contraindicated [see Contraindications].

Ritonavir and other Potent CYP3A4 Inhibitors

Concomitant use of REVATIO with ritonavir and other potent CYP3A4 inhibitors is not recommended [see Warnings and Precautions].

Alpha-Blockers

Use caution when co-administering alpha-blockers with REVATIO because of additive blood pressure-lowering effects [see Warnings and Precautions].

In drug-drug interaction studies, sildenafil (25 mg, 50 mg, or 100 mg) and the alpha-blocker doxazosin (4 mg or 8 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, were observed. Mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were also observed. There were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

Amiodarone

When sildenafil 100 mg oral was co-administered with amiodarone, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m² basis, 32- and 68-times, respectively, the recommended human dose (RHD) of 20 mg TID. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m² basis). There are, however, no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The safety and efficacy of REVATIO during labor and delivery has not been studied.

Nursing Mothers

It is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when REVATIO is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of sildenafil in pediatric pulmonary hypertension patients have not been established.

Geriatric Use

Clinical studies of REVATIO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

No dose adjustment for mild to moderate impairment is required. Severe impairment has not been studied.

Renal Impairment

No dose adjustment is required (including severe impairment ClCr < 30 mL/min).

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but rates and severities were increased. In cases of overdose, standard supportive measures should be adopted as required.

Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for up to 24 months at 60 mg/kg/day, a dose resulting in total systemic exposure (AUC) to unbound sildenafil and its major metabolite 33 and 27 times, for male and female rats respectively, the human exposure at the RHD of 20 mg TID. Sildenafil was not carcinogenic when administered to male and female mice for up to 21 and 18 months, respectively, at doses up to a maximally tolerated level of 10 mg/kg/day, a dose equivalent to the RHD on a kg/m² basis. Sildenafil was negative in vitro bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and in vitro human lymphocytes and in vivo mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the RHD of 20 mg TID.

PATIENT COUNSELING INFORMATION

• Inform patients of contraindication of REVATIO with regular and/or intermittent use of organic nitrates.

• Inform patients that sildenafil is also marketed as VIAGRA for erectile dysfunction.

• Advise patients taking REVATIO not to take VIAGRA or other PDE5 inhibitors.

• Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking REVATIO. Such an event may be a sign of NAION.

• Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking REVATIO. These events may be accompanied by tinnitus and dizziness.

RX only

Revised: March 2011

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Join the PH Professional Network (PHPN) to connect with your PH-treating peers who share your commitment to caring for PH patients and changing the history of this disease.

As a member of PHPN, you will:

- Have the opportunity to ask questions about PH clinical care and engage in active conversations about topics in PH with your peers on the PHPN Email Group.
- Get involved and boost your CV by joining one of PHPN’s project-driven committees.
- Share your expertise or benefit from someone else’s through the PHPN Mentor Program.
- Be welcome to attend the PH Professional Network Symposium, where you can advance your PH knowledge, network with others in the field, and attend sessions by the foremost experts in PH care. CE credits available.

Stay informed with *PH Pulse*, PHPN’s exclusive quarterly newsletter; a free copy of *Pulmonary Hypertension: A Patient’s Survival Guide* and a subscription to PHA’s monthly e-newsletter, *PH Roundup*, which highlights the most current PH opportunities and findings in the field.

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Join **PH CLINICIANS AND RESEARCHERS**

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Share your commitment to advance the study and treatment of pulmonary hypertension. Become a member of PHA’s PH Clinicians and Researchers (PHCR) and connect with hundreds of PH-treating colleagues.

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- Have the opportunity to ask questions about PH cases, participate in case study discussions, and engage in active conversations about topics in PH with expert clinicians and researchers on the PHCR Email Group.
- Share your expertise and build your CV. Speak at a PHA program, host a Building Medical Education in PH event, or get involved with one of PHA’s project-driven committees to advance PH.
- Receive a registration discount to attend PHA’s biennial International PH Conference and Scientific Sessions.

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We’ve Come—and Are Going—a Long Way...  

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A s I stepped out of the taxi at the entrance of the Renaissance Hotel at the PHA’s 10th International Conference, I ran into a couple of mothers of former patients of mine. The last conference I attended was in 2008, so this felt like a homecoming for me. They asked me: “Have you seen the girls?” The girls they were referring to were their 2 daughters plus 5 of their friends. All had pulmonary hypertension (PH) and had become friends through their shared experience of living with the disease. When I started treating PH patients 10 years ago, these girls were aged 7-15 years. I turned around, and there they were—“my girls” (as I would always think of them), now 17-25 years old. They are beautiful young women living fulfilling lives; they are college and nursing students, wives—even a mom among them.  

We have come so far in this fight, and seeing my former patients made me think back to when I first started working in PH in 2002. At that time, Flolan and Tracleer were the only 2 therapies approved for the treatment of PH. Since then we have added 7 more therapies to our armamentarium in various forms, with additional therapies currently under clinical investigation. With the advent of additional therapies came the questions: Is monotherapy or combination therapy more effective? Is up-front combination therapy better than add-on therapy? Clinical trials are currently underway geared toward trying to answer these very questions. Registries such as REVEAL and TOPP are helping bridge the gap between science and clinical practice. These registries allow practitioners access to invaluable information that will help guide the future of PH treatment and perhaps lead us in the direction of a cure. In addition, more and more clinical trials are looking at appropriate dosing for the pediatric population. A lot has happened in the last 10 years and the PHA conference has continued to grow and expand, providing patients with the most up-to-date information available and a chance to meet up with old and new “PHriends.”  

The theme of this year’s conference, The Power of One: From a Kitchen Table to Around the World, was a powerful message for all the attendees. What started with 4 women at a kitchen table has evolved into a community of 30,000 from all over the world working toward the same goals. The patient- and family-led sessions are a true testament to the patients and their caregivers working together to advocate for themselves and their loved ones. Not letting PH define you was a message that wound its way through many of the sessions. Sessions titled 9 to 5 With PH; School and PH; and PH Goes to College addressed working or attending school with PH, and provided tips and lively discussions for how to be successful while managing your PH. A parent of a newly diagnosed 6-year-old told me she attended the PH Goes to College session because it brought her hope that one day her own child would be attending college. She left armed with the knowledge that there is life after a diagnosis of PH. Family Affair was an important session that highlighted the message that having PH doesn’t preclude you from having a family. It is well known in the PH community that pregnancy should be avoided; unfortunately, upon hearing this many patients think that being a parent is not an option for them. During the session the many avenues available were discussed, and valuable information was provided for all in attendance.  

As medical professionals in the field of PH, we are often so focused on treating our patients, finding new therapies, or searching for a cure that we can lose sight of what some of the other issues for our patients might be. Attending patient-/family-led sessions gives medical professionals the opportunity to learn from patients and to see beyond their therapies and hear about their other core concerns.  

I had the privilege to speak at a medically led session titled New Medical Therapy for Children With PH. The session discussed targeted therapies for children with pulmonary arterial hypertension (PAH) and how they work, combination therapies, and pediatric studies currently underway. It was well attended with many familiar faces and many new faces. As a panel we really wanted to have an interactive discussion with the families, so we allowed the audience to guide the course of the discussion. What evolved was an honest and robust discussion among the panel members and the families about how we can move the field of pediatric PH forward. Everyone was interested in new research on the horizon, where we thought the field was heading, and my favorite question: “How can we help?” We discussed fundraising and donating to pediatric research funds, and the importance of participating in clinical trials. One father shared that his young daughter had recently been diagnosed—within weeks of the conference—and really wanted to know what he could do to help. Someone in the audience answered first by welcoming him to the conference and the PH family, and assured him that everyone here is available to help him and his family through their journey. This person then said, “If you really want to help, you can start today by going over to the research room at the end of this session to give a blood sample.” With that one invitation, I watched after the session as a whole group of families walked over together to the research room to provide blood samples. One small suggestion led to a collective movement: the power of one, indeed.

Correspondence: dm2069@columbia.edu
**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 evidence-based therapies were available. Since then the treatment of this disease has made tremendous advances, and in the last 10 years the discovery of new medications have positively influenced the prognosis and survival of patients with PAH.

This self-study activity is based on 7 articles that summarize presentations at PHA’s 10th International Pulmonary Hypertension Conference and Scientific Sessions in Orlando June 22-24, 2012.

**Target Audience:** This self-study activity is appropriate for cardiologists, pulmonologists, rheumatologists, and other physicians who treat patients with PH.

**Learning Objectives:** Upon completion of this activity, participants will be able to:

1. Define the global burden of pulmonary hypertension.
2. Define the cellular metabolic changes seen in the development of PAH.
3. Describe the effects of altered cellular metabolism on BMPR2 signaling.
4. Outline the hypothesis regarding PAH as a systemic disease.

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**Self-Assessment Examination:**

This issue of Advances in Pulmonary Hypertension does not provide CME credits. A quiz, answer key, evaluation form, and answers appear on pages 133 and 134 so you may assess yourself regarding your accomplishment of the learning objectives for these articles. For CME opportunities from other PHA programs, go to http://www.phaonlineuniv.org/.

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To ensure balance, independence, objectivity, and scientific rigor in all its educational activities, all faculty participating in this activity are expected to disclose to the audience any financial interest or other potential conflict. Each author was asked to complete a disclosure information form for this activity. Disclosures are reported below:

Dr. Fagan has served as a consultant/advisory board member/or on the steering committee for Gilead, Pfizer, Novartis, and Bayer. She has been on the speaker’s bureau for Gilead, Simply Speaking, and PHA. She has received institutional grants/research support from Bayer Healthcare, Actelion Pharmaceuticals, and Gilead.

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The Global Challenge of Pulmonary Vascular Diseases and its Forgotten Impact in the Developing World

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THE SITUATION: AN OVERVIEW
Pulmonary vascular diseases (PVDs) are a heterogeneous family of ailments. They include conditions such as pulmonary arterial hypertension (PAH), pulmonary venous hypertension, PVDs secondary to lung diseases, and many other conditions. This has been very well documented in the Dana Point classifications.1

Clinically, we tend to concentrate on arterial hypertension, as it is the only class for which we have approved therapy. At least at present, we do not consider clinically the pulmonary vascular complications of other conditions. For example, we don’t do that with heart failure or chronic obstructive pulmonary disease (COPD) despite knowing that, especially in advanced stages of the disease, the pulmonary vascular complications will have a significant impact on prognosis. However, things are likely to change in the future, in particular if a new therapy is approved. Thus, at present the real impact of PVD is not very well documented globally, not only in the developed world but also in the developing world. However, the interest in considering the pulmonary vascular complications of many conditions is growing, which is why we must start planning to assess the full clinical challenge globally.

We are gaining some insight into the distribution of patients with PAH in various databases in the developed world such as REVEAL, COMPERA, and other local registries in Europe and the United States. These are not epidemiological studies, but are mainly an assessment of patients cared for in specialized centers. Therefore, the epidemiological picture of PAH in the West is still far from being fully realized—let alone in developing countries. It is currently a serious challenge to truly estimate the impact of PVDs globally, as we are left with no tools other than speculations and intelligent guesswork. Hopefully this brief article will be viewed as a catalyst to stimulate more coherent works, more thoughtful and well-organized epidemiological studies.

The figures put forth here are controversial, and will likely be considered provocative. However, it seems justified, as these figures may be the best available tool in our arsenal to stimulate more discussion and to prompt further research to meet this global challenge.

TOOLS, METHODS, AND GLOBAL ESTIMATES
The method we have used to assess the global impact of PVDs in the world is very simple. We have tried to assess the proportion of patients who are likely to develop PVDs of various clinical conditions from the published data. This will help us to predict the potential prevalence of PVDs in these conditions globally, based on the global number of patients affected. This is a controversial method, as it could be considered subject to too much guesswork; but at present it appears to be the only method available, due to the scarcity of hard data. It is to be hoped that future studies will be able to confirm or refute the picture painted by our estimate.

Various studies estimate that there are around 40,000-50,000 patients with PAH in Europe, and likely the same number in the US, although not all of them have been treated as shown in the unpublished data from large databases mentioned above. Obviously, this number will increase; we estimate about 2 million patients with PVD secondary to left heart failure. The picture in the COPD and lung diseases is more confusing and has less clarity, although one French study2 suggests that about 5%-13.5% of patients with COPD have some form of significant PVD. On this basis we estimate about 1 million people in the developed world with COPD have PVDs. If we use this to chart the distribution of PVDs in the developed world, we will see that the majority is due to lung diseases and heart failure, and only a very small proportion of this is due to PAH.

The developing world is faced with 2 major issues: first, there are no patient-based studies; and secondly, we know there are various clinical conditions that are not prevalent in the developed world, which may contribute to PVD. We believe that infectious diseases are among the most important contributors to PVDs.

One example is schistosomiasis. It is well documented to be a culpable cause of PVD, but at present we do not know the real incidence or prevalence of PVD associated with schistosomiasis. The most recently available data come from Brazil, where it was estimated that 2%-8% of patients may have some form of PVD secondary to schistosomiasis.3,4 However, Brazil is one of the countries that has a very good schistosomiasis control program, and its clinical care is far superior in comparison to many developing coun-
tries. This is especially true when compared to Africa, which houses 80% of global schistosomiasis patients, and has far worse disease control than Brazil. In addition, many other comorbidities complicate the picture in Africa. Two hundred million people are suffering from schistosomiasis worldwide according the World Health Organization (WHO), and if we take the 2%-8% estimate to be true, we can expect 4 to 16 million people globally to have schistosomiasis-related PVD.

The second prevalent infectious disease condition is HIV, which is recognized for its ability to cause PAH. The best estimate of PAH in HIV is about 0.5%-4% of patients, and taking into consideration the number of patients suffering from HIV worldwide, we estimate about 170,000 to 1 million patients suffer from pulmonary hypertension secondary to HIV.

Another problem present in the developing world is the hemoglobinopathies, and other forms of hemolytic anemia, specifically sickle cell anemia. Sickle cell anemia has been thoroughly discussed in the West, but the current estimates of PVDs in patients with sickle cell anemia could be around 6% to 10%. Taking into consideration that there are about 55 million patients suffering from sickle cell anemia worldwide, we estimate a number of 3 to 6 million patients suffering from pulmonary hypertension secondary to sickle anemia globally.

Another condition found predominantly in the developing world is the issue of high altitude. We know that nearly 140 million people worldwide live in high-altitude locations. The real incidence of PVDs in these conditions varies due to geographic and genetic distribution. Generally, we believe around 5% to 18% of patients in these locations may have clinically significant PVDs, which means 7 to 25 million high-altitude inhabitants may suffer from some sort of PVD.

When considering other cardiac conditions, we cannot dismiss rheumatic heart diseases. Although these are decreasing, they are still an important part of any cardiology practice in the developing world. This is particularly true due to the delay in clinical intervention of mitral valve diseases and aortic valve diseases. For example, in India and Africa pulmonary hypertension is found in about 72% of patients with rheumatic mitral diseases. Although this is a curable and reversible condition, particularly with valve replacement or valvuloplasty, it recognizably carries an important clinical risk even postoperatively. Taking into account that 1.5-2.5 million people suffer from rheumatic heart disease, and assuming that 10%-70% of patients have some form of PVD, we would estimate that 0.25 million to 1.4 million patients may have some form of pulmonary vascular complications secondary to rheumatic heart diseases.

Similarly, congenital heart diseases are an important contributor to PVDs, and the best estimate for the proportion of PAH comes from the CONCOR study and is estimated to be at least 4.2%. Although this varies according to the cardiac lesions, if we consider that 24.5 million people are affected by congenital heart disease worldwide, we can expect about 1 million patients to be suffering from PVD secondary to congenital heart disease. Heart failure and COPD are also significant contributors to cardiopulmonary diseases in the developing world, and this will contribute significantly to the PVD globally.

In summary, PVD in the developed world shows a very different picture compared to the developing world. The number of the global population living in the developing world is about 6 billion vs 1 billion in the developed world. Based on the speculative calculations presented here and accounting for population numbers, it seems that the prevalence of PVDs is 6 times per billion of the population higher in the developing world vs the developed world.

CONCLUSION

PVDs are still an unrecognized sequel of many diseases that are found in the developed world, and are far more prevalent in the developing world. A real effort is necessary to study this reality from an epidemiological and clinical point of view.

References

Update From the NHLBI: Lung Vascular and Pulmonary Hypertension Research

NIH Mission
The National Institutes of Health (NIH), a part of the US Department of Health and Human Services, is the nation’s biomedical research agency. The NIH is the largest source of funding for biomedical research in the world, funding thousands of scientists in universities and research institutions. The NIH’s mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. The NIH is composed of 27 institutes and centers, each with a specific mission, often focusing on particular diseases or body systems. The National Heart, Lung, and Blood Institute (NHLBI) is one of the component institutes, whose mission is to provide global leadership for research, training, and education programs that promote the prevention and treatment of heart, lung, and blood diseases. The Division of Lung Diseases (DLD) within the NHLBI is responsible for administration of the extramural grant and contract portfolio in lung diseases research, which includes diseases of the airways, lung tissues, including the interstitial compartments and cells, the lung vascular systems, and sleep. Additional information about the NIH and its mission, its collections of institutes and centers, and the DLD can be found by accessing the following Web site and its associated links: http://www.nih.gov/index.html.

Five areas of promise for advancing biomedical research are currently identified by the NIH.1 The NHLBI strategic plan is aligned to these 5 areas, which include: 1) capitalizing on high-throughput technologies, 2) fostering translational medicine, 3) performing research beneficiary to the cause of US health care reform, 4) performing research focused on global health, and 5) improving the research base by reinvigorating and empowering the biomedical research community. NHLBI-sponsored research programs and initiatives are designed to foster ongoing efforts in these areas of promise specific to heart, lung, and blood diseases. Programs and initiatives originating from within the DLD likewise align to the strategic plan and goals of the NHLBI and NIH. Furthermore, the DLD strategic plan for advancing lung disease research involves a multidisciplinary approach to program development to generate support mechanisms for the lung investigatory community.

The NHLBI currently supports a robust program in lung vascular and pulmonary hypertension (PH) research. The NHLBI funded approximately $32.9 million in fiscal year 2010 and $37.2 million in fiscal year 2011 in PH and related research projects. The NHLBI supports basic science in lung vascular biology and disease with projects that: 1) discover and define lung vascular biology and factors contributing to development of lung vascular disease; 2) focus on cellular, molecular, and genetic factors contributing to PH pathogenesis including high-throughput, technology-based projects; 3) advance the paradigm of PH as a vasculoproliferative disease; and 4) define right ventricular biology and pathophysiology in the context of lung vascular function and disease. In addition, translational projects are: 1) advancing diagnostics, therapeutics, and disease monitoring; 2) testing novel hypotheses of disease etiology using human tissues; and 3) identifying novel endpoint measures for use in clinical trials.

ACTIVITIES IN LUNG VASCULAR RESEARCH
While the breadth of the entire NIH portfolio cannot be presented in this article, the following are selected examples of NHLBI-supported research projects.

The NHLBI continues to build off the strategic plan for lung vascular research in order to identify priority areas for future activities.2 The NHLBI has implemented programs in response to the strategic plan. These include: 1) Utilization of a Human Lung Tissue Resource for Vascular Research, and 2) the Pulmonary Vascular-Right Ventricular Axis Research Program (PV-RV); both are designed to fill gaps in pulmonary vascular disease (PVD) translational research. Researchers supported by the Lung Tissue Resource Program have the opportunity to leverage tissues and cells comprised in a biorepository supported by the Pulmonary Hypertension Breakthrough Initiative (PHBI). This program also introduces young investigators to lung vascular translational research, and presents an opportunity to test mechanistic hypotheses derived from animal models in human specimens. Researchers supported by the PV-RV are better defining the relationship between the "sick" lung vasculature and its impact on right heart function and failure. This program brings together multi-

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disciplinary teams of investigators who are studying questions such as: 1) how does infant and childhood lung vascular disease affect lung vascular and right heart function in later life? 2) Can stem cells treat lung vascular and right heart disease? 3) Are beta-blockers effective in treating right heart disease? 4) What are ideal noninvasive measures for diagnosing and monitoring right heart disease in adults and children who have PVD? Both the Lung Tissue Resource Program and the PV-RV are very early in their progress.

In addition to the translational programs, the NHLBI held a workshop in August 2011, to focus on 21st century clinical research priorities in PVD. Experts with diverse experience in pediatric and adult PH clinical research, as well as experts from other fields reviewed the state of scientific knowledge forming the basis for current treatment of children and adults with PVD. Recommendations on how to fill gaps in clinical research included: 1) improved methods of phenotyping to identify subjects for appropriate PVD clinical studies; 2) validation of new, meaningful endpoints; and 3) priorities for specific clinical research needed to advance care of patients with various subsets of PVD from childhood through adulthood. The recommendations from this workshop will help to inform future activities and research opportunities.

As a final example, the NHLBI recently supported an investigator-initiated resource in PVD, the “National Biological Sample and Data Repository for Pulmonary Arterial Hypertension (PAH).” This resource will significantly enhance the conduct of basic, translational, and clinical research for PAH, and the biological samples collected and genetic data generated from these samples will enable unprecedented hypothesis-driven science for all forms of PH. This resource represents collaboration between academic PH centers to leverage an industry-sponsored patient registry (the REVEAL registry). Upon full implementation, the resource will collect and maintain biologic material from no less than 2500 World Health Organization (WHO) Group 1 PAH patients, including total genomic lymphocyte DNA; EBV transformed peripheral blood lymphocytes and plasma; and genome-wide SNP genotype data and BMPR2/ALK1 sequence/MLPA data. All biological samples, clinical data, as well as the SNP genotype and sequencing data for the patients will be made available to the entire scientific community.

For a comprehensive summary of PH-related research ongoing at the NIH, please utilize the NIH Research Portfolio Online Reporting Tools (RePORT) to obtain reports, data, and analyses of NIH research activities (http://report.nih.gov).

CONCLUSION

Advances in treating PH patients have come as a result of collective efforts by physicians, scientists, patient advocacy, pharmaceutical companies, and public and private grant-awarding agencies. NHLBI-supported basic science research on the physiologic and cellular mechanisms responsible for pulmonary vascular tone regulation and abnormal vasoconstriction have been important in identifying the therapeutic potential of the drugs now in clinical practice for PAH. However, a new era in our understanding of PH pathogenesis is emerging, and with this new understanding novel challenges and exciting research opportunities will arise. The NHLBI will strive to work with and support the research community to meet the challenges ahead.

References
After years of effort, investigators at Vanderbilt and Columbia found the gene for heritable pulmonary hypertension (PH) nearly simultaneously in the year 2000. \textsuperscript{1,2} Mutations in the so-called bone morphogenetic protein receptor type 2 (BMPR2) are now known to be responsible for about 75\% of cases of heritable pulmonary arterial hypertension (PAH). \textsuperscript{3} In the other 25\% of families, either the mutation remains unknown, or it is in the ALK-1 or endoglin genes, SMAD 8 or caveolin 1.\textsuperscript{4} Undoubtedly, other rarer mutations that cause disease will be found. In most registries, known heritable PAH accounts for about 6\% of the population enrolled, so 6 out of every 100 cases.\textsuperscript{5,6} However, surveys of mutation status in idiopathic PAH have revealed a prevalence of about 10\%-20\% of BMPR2 mutation carriers.\textsuperscript{7} Thus, as shown in Figure 1, the number of patients with the gene raising the risk of PH is in the idiopathic group, and these actually outnumber the known family cases. One of the scientists vital to the discovery of BMPR2 mutations, William Nichols, PhD, at the University of Cincinnati, now has National Institutes of Health (NIH) funding to obtain DNA and RNA from a large number of patients with idiopathic PAH from multiple centers, to discover the actual prevalence of BMPR2 mutations in a USA cohort, and to look for other genetic associations with PH.

The next phase in our journey with heritable PAH was to look for genetic/genomic associations that might help explain the incomplete penetrance of BMPR2 mutations. For many years, based on discussions at the Evian World Health Organization (WHO) Pulmonary Hypertension Conference, the penetrance of the BMPR2 gene has been estimated to be about 20\%. This means that having the mutation is not enough, and that environmental, genetic, or biological differences must have a role. Newer data from the Vanderbilt PAH Registry suggests that the penetrance is about 27\%, with a 3:1 female to male ratio, giving females about a 42\% penetrance and males 14\%.\textsuperscript{8} Nonetheless, the reduced penetrance gave rise to several years of difficult experiments designed to discover a major second gene that might explain penetrance. Although multiple genes were discovered to have a minor role, no major gene has been found. Genes that have been found to possibly have influence on the likelihood of disease include serotonin transporter, Cyp, angiotensin converting enzyme, and nitric oxide synthase. Undoubtedly, a large number of interacting gene products will have major influence on the development of PAH. Part of the problem is that PAH is not one disease and therefore does not have one etiology. This is a very complex problem to address. It also must include epigenetic and other somatic gene modifications that are not discoverable by germline approaches. The problem is summarized in Figure 2. Although basic important work is progressing on mechanisms that regulate BMPR2 expression and function, the modifier gene approach must await newer modalities such as whole exome and genome sequencing to discover rare variants that may influence development of pulmonary vascular disease. This approach will also discover rare variants that have a Mendelian effect on the development of PH in families that remain with undiscovered mutations.

The current thrust of our work is along 4 lines. The first is the study of the gender difference and sex hormones in PH. The greatest risk for development of either idiopathic or heritable PH is female gender, 3:1 over males. Eric Austin in our laboratory is studying estrogen metabolites and the role of cytochrome enzymes in determining circulating levels of estrogen metabolites and their impact on PH risk. Others are following similar experimental approaches. These studies will certainly yield insights into development of PH and perhaps lead to preventive or management therapies.

\textbf{Key Words—} BMPR2, genetics, heritable pulmonary hypertension, idiopathic pulmonary hypertension

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The second set of experiments is to determine the relationship of insulin resistance and PAH. These experiments are driven by the increasing recognition that hyperglycemia and features of the metabolic syndrome are common in PAH. Either the pulmonary circulation is remodeled or primed for vascular damage by insulin resistance/hyperglycemia, or PAH may lead to metabolic abnormalities. These experiments are led by Anna Hemnes.

The third approach is to determine how BMPR2 expression is regulated. Because of the increasing data that BMPR2 is downregulated in all form of PAH, Rizwan Hamid in our group is performing experiments to determine the role of splice variants, the role of the normal wild-type allele in PAH, and he is beginning to explore the possibility of stimulating BMPR2 expression to normalize the vasculature in PAH or those at risk of PAH.

Finally, James West is heading a translational study looking at the enzyme ACE2. Preliminary data show that ACE2, which converts angiotensin 2 to angiotensin 1-7 is protective in the mouse model of BMPR2-driven PAH, and normalizes cell culture function of cytoskeletal abnormalities. A ngiotensin 1-7 is an antiproliferative protein that has generally opposite effects of angiotensin 2. These studies will include a small Phase II human trial.

Thus, our journey at Vanderbilt can be divided into 3 phases. The first was the struggle to identify the genetic mechanism for inherited PH. The second was to assess associations with genes that might influence BMPR2 expression as full-blown clinical PH. The third, current phase is the study of intracellular pathways that are intimately involved in PH. These pathways are sex hormones, glucose metabolism, and neurohumoral effects of the angiotensin system. In addition we continue to investigate what regulates BMPR2 expression in hopes of ultimately modifying it to treat disease.

References
Knowing that a mutation in the bone morphogenetic protein receptor type 2 (BMPR2) gene is present in most patients with a hereditary form of pulmonary hypertension (PH) has allowed us to propose therapies that might be of value in patients with all forms of PH. The premise is based on evidence from cultured cells and experimental animals. Taken together, these studies indicate that dysfunction of BMPR2 and related genes leads to an adverse response of the pulmonary circulation to injury, and that this can cause the progressive elevation in pulmonary arterial (PA) pressure and right heart failure in patients with PA hypertension (PAH).

The adverse response to injury is manifest as rarefaction of the pulmonary arteries seen on the angiogram (Figure 1). This is caused by loss of the most distal arteries, attributed at least in part to programmed cell death of the endothelial cell lining. As a consequence, at least in part because of dysfunction of the remaining endothelial cells in small and larger arteries, there is an expansive proliferation of cells that have features of smooth muscle, and this culminates in progressive occlusion of the lumen of the vessel. The origin of these smooth muscle-like cells can be endothelial cells, fibroblasts, or even inflammatory cells. A further feature related to dysfunction of the endothelial and other cells of the vessel wall is the abnormal recruitment of inflammatory cells that contribute further to the adverse response to injury. They do so both by releasing factors that amplify proliferation, and also by contributing to factors that cause elastic fibers to degrade.

Figure 1: The adverse response to injury is manifest as rarefaction of the pulmonary arteries seen on the angiogram, and this results from loss of the most distal arteries by programmed cell death of the endothelial cell lining. As a consequence, at least in part because of dysfunction of the endothelial cells in larger arteries, there is an expansive proliferation of cells that have features of smooth muscle that culminate in progressive occlusion of the lumen of the vessel. Another feature related to dysfunction of the endothelium of the vessel wall is the abnormal recruitment of inflammatory cells that contribute further to the adverse response to injury. They do so both by releasing factors that amplify proliferation, and also by contributing to factors that cause elastic fibers to degrade.

While BMPR2 mutations are present in >70% of familial and 25% of sporadic cases of idiopathic PAH, dysfunction of the BMPR2 receptor alone is insufficient to cause PAH, but may be necessary to allow it to develop in response to one or more injurious perturbations of the pulmonary circulation. Moreover, patients without a mutation and PAH and experimental models of PAH show low expression levels of BMPR2. The focus on BMPR2 signaling is important because of the protective nature of this pathway. BMPR2 signaling has been shown to be
critical in preventing adverse remodeling by promoting survival of pulmonary arterial endothelial cells, and doing so can prevent damage or facilitate regeneration of damaged microvessels. BMPR2 signaling also inhibits pulmonary arterial smooth muscle cell proliferation in response to growth factors that are liberated by elastases in response to injury and inflammation, and conversely BMP signaling has the opposite effect on endothelial cells in sustaining the survival of endothelial cells and the regeneration of the microvessels in response to injury. Both processes involve PPARγ, but in smooth muscle cells a target is apolipoprotein E, and in endothelial cells a target is apelin. Apelin also inhibits smooth muscle cell proliferation, as do nitro-fatty acids that regulate PPARγ in both cell types.

The BMPR2 receptor has been found to direct transcription factors to turn on target genes that protect the vessel wall, and reasoning suggests that knowing what those factors and target genes are will ultimately allow us to replace them, and therefore, to rescue dysfunction of the BMPR2 receptor and to either arrest or reverse the disease process.

It has been shown that when there is injury to the vessel wall, an enzyme that degrades elastin, an elastase, releases growth factors that are normally stored in the matrix surrounding the cells of the vessel wall. One of the most potent of these growth factors is platelet-derived growth factor (PDGF). It binds to its receptor on the surface of smooth muscle cells and activates a signaling messenger called pERK to induce expression of genes that make cells proliferate. But when BMPR2 is functional, it counteracts this pathway by directing a molecule called PPARγ to the nucleus. PPARγ can block the pERK signal, and it induces expression of genes that prevent cell division (cell cycle inhibitors called p27 and p21). Another gene that responds to PPARγ is apolipoprotein E, and the apolipoprotein E protein blocks the PDGF receptor. In adipocytes (fat cells) PPARγ produces a molecule called adiponectin that sequesters PDGF (Figure 3). So now the growth factor is incapacitated, the receptor is incapacitated; the signal is blocked and replaced by signals that inhibit the cell from dividing. In cultured cells PPARγ has been shown to be pivotal in directing BMPR2’s ability to prevent proliferation. When smooth muscle cells are stimulated to divide by the growth factor PDGF, they stop dividing when you activate BMP signaling. However, when PPARγ is incapacitated by an inhibitor, this protective advantage is lost.

It follows that a mouse genetically engineered not to produce PPARγ in smooth muscle cells will spontaneously develop PAH. The pressure in the right ventricle is elevated, the right side of the heart hypertrophies, and the small vessels become abnormally thick walled, and there is right ventricular hypertrophy. Mice that lack a protective target of PPARγ namely apolipoprotein E, also develop spontaneous PAH, but only as they age. However, if these mice are fed a high-fat diet they develop PAH earlier. This PAH can be reversed by treating the mice with an activator of PPARγ, a drug that is used to treat metabolic syndrome.

Because PPARγ activation is used to treat metabolic syndrome (also known as insulin resistance or Type 2 diabetes), our studies suggested that there may be a high incidence of this complication in patients with PAH and dysfunctional PPARγ activation. Indeed, further studies by our group showed that women with PAH are twice as likely to have metabolic syndrome than the general population of women. In addition, if you divide the women with PAH into the group that has insulin resistance or Type 2 diabetes, our studies suggested that there may be a high incidence of this complication in patients with PAH and dysfunctional PPARγ activation. Indeed, further studies by our group showed that women with PAH are twice as likely to have metabolic syndrome than the general population of women.

This was tested in pulmonary arterial smooth muscle cells from mice that were engineered to only express half the amount of BMPR2, and from a patient with a mutation in BMPR2. In both cases,
the profound increase in pulmonary arterial smooth muscle cell number in response to a growth factor could not be prevented by activating the receptor because it was deficient. However, when we activated PPARγ, we could rescue the dysfunction of the receptor and inhibit the proliferative response to a growth factor.14

We also showed that the BMPR2 counteracts endothelial vulnerability to injury, allowing these cells to recover and regenerate.13 In endothelial cells, BMPR2 also activates PPARγ, but PPARγ now forms a complex with another transcription factor called beta-catenin and together they induce expression of genes that regulate endothelial cell survival and angiogenesis.25 Prominent among these genes is apelin, a small protein that others have shown can promote endothelial health (Figure 4). It was interesting that synthetic drugs used to treat metabolic syndrome were not effective in activating PPARγ in endothelial cells because they disrupted its interaction with beta-catenin. However endogenous activators of PPARγ (those that the cells produce) such as nitro-fatty acids26 were highly effective in inducing PPARγ activity and inducing the production of apelin by pulmonary arterial endothelial cells.25 In fact, we were able to show that in mice that develop PAH because they lack PPARγ in endothelial cells, administration of apelin could reverse the pathology. Apelin not only promotes endothelial cell survival, but it is a protein that is released by endothelial cells and has beneficial effects in preventing smooth muscle cell proliferation in response to growth factors (Figure 5). Thus, it can rescue BMPR2 dysfunction in endothelial or smooth muscle cells.

In addition, loss of BMPR2 activity is proinflammatory in smooth muscle cells17 and some data show that the same is true in endothelial cells. Agents that rescue BMPR2 dysfunction, such as apelin or endogenous nitro-fatty acids, are also known for their antiinflammatory properties, thus further protecting the vessel wall.27

Finally, we have embarked on a strategy that searches drug libraries for an agent that will have as an “off-target” effect the added benefit of activating

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**Figure 3:** This is a schema showing that when there is injury to the vessel wall, there is elastase activity and release of PDGF, inducing a signaling messenger called pERK. This is a factor that facilitates cell proliferation. To counteract this process, BMPR2 directs PPARγ to the nucleus. PPARγ can block the pERK, and it also induces genes that prevent cell division (cell cycle inhibitors p27 and p21). PPARγ also induces production of a gene product, apolipoprotein E. This protein blocks the PDGF receptor. In adipocytes PPARγ induces production of adiponectin, a protein that sequesters the growth factor, PDGF.

**Figure 4:** This is a schema showing that in pulmonary arterial endothelial cells, BMPR2 signaling induces a complex between PPARγ and beta-catenin. Nitro-fatty acids that are released from mitochondrial membranes by reactive oxygen species can also promote the interaction between PPARγ and beta-catenin and rescue dysfunction of BMPR2 by inducing the target endothelial cell survival gene, apelin.
Apelin should be able to help regenerate normal microvessels and reverse occlusive neointimal formation by inducing apoptosis of abnormal smooth muscle-like cells, and may therefore be a promising therapy for PAH.

References


Pathogenesis of Pulmonary Arterial Hypertension: Clues From Patients and Animal Models of Hereditary Hemorrhagic Telangiectasia

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Hereditary hemorrhagic telangiectasia (HHT) is a vascular disease characterized by multiple focal telangiectases and arteriovenous malformations (AVMs) in the pulmonary, hepatic, and cerebral microcirculations. These fragile structures are low-pressure conduits that can affect local tissue blood flow, and their potential rupture in vital organs can lead to internal hemorrhage, anemia, and death. Patients with HHT1 and HHT2 display very similar vascular lesions, but diverge with respect to organ involvement, where a higher prevalence of pulmonary AVMs (PAVMs) is seen in HHT1.

Mutations in the endoglin (ENG) and activin-like kinase 1 receptor (ACVLR1, ALK1) genes leading to haploinsufficiency are the underlying causes of HHT type 1 and HHT type 2, respectively. Recent findings indicate that individuals harboring mutations in ENG or ACVLR1 can also present with varying degrees of pulmonary arterial hypertension (PAH) and/or HHT, suggesting that these diseases share defects in common or related signaling pathways. ENG is a 180kD homodimeric transmembrane glycoprotein that is mostly expressed on endothelial cells and acts as an ancillary receptor for several transforming growth factor-beta (TGF-β)superfamily ligands, including bone morphogenetic proteins (BMPs). It can be found in both TGF-β and BMP receptor complexes such as TGF-β receptor 2 (TβRII)/ALK1 and BMPR2/ALK1. ENG physically interacts with ALK1 and regulates its activity within these complexes. Both ENG-null (ENG-/-) and ALK1-null (ALK1-/-) mice die at mid-gestation (E9.5) from severe cardiovascular defects, while heterozygous mice are viable and serve as valuable models to study HHT.

In PAH, endothelial dysfunction and the characteristic loss of peripheral capillaries are believed to precede the muscularization and remodeling of pulmonary arteries. The activity of the endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) bioavailability are critical determinants of normal endothelial and vascular function, which are perturbed in patients with PAH and in many animal models of this disease. For example, eNOS activity is reduced in hypoxia-induced pulmonary hypertension as a result of impaired association of eNOS with its allosteric activator, heat shock protein 90 (Hsp90). These changes in eNOS activation lead to increased eNOS-derived reactive oxygen species (ROS) production instead of NO in endothelial cells, and have been observed in an animal model of persistent pulmonary hypertension of the newborn. In response to a stimulus, eNOS activity is termed uncoupled when eNOS fails to efficiently couple the conversion of its substrate, L-arginine, to NO and instead produces superoxide (O2·-; generally measured as ROS). Conditions that cause eNOS uncoupling include: 1) substrate (L-arginine) and/or co-factor (tetrahydrobiopterin, BH4) deficiencies, and 2) the impaired ability of eNOS to bind Hsp90.

ENG and ALK1 are expressed on endothelial cells of the distal pulmonary vasculature. ENG resides in endothelial caveolae, associates with eNOS, and facilitates eNOS activation by acting as a scaffolding protein, bringing cytoplasmic Hsp90 into close proximity with caveolar eNOS, and thus resulting in normal NO production. ENG-deficient endothelial cells have reduced eNOS/Hsp90 association during agonist-induced activation and produce increased eNOS-derived ROS instead of NO. Interestingly, adult ENG-/- mice spontaneously acquire signs of PAH, including increased right ventricular systolic pressure (RVSP), muscularization of pulmonary arteries, and pruning of distal vessels. The onset of PAH in these mice is developmentally regulated and due to uncoupled eNOS activity acquired in adulthood. Treatment of adolescent ENG-/- mice with the antioxidant Tempol prevents the onset and progression of PAH. More recently, it has been shown that adult ALK1-/- mice also acquire signs of PAH due to uncoupled eNOS activity, providing further support that a common defective pathway involving ENG/ALK1/eNOS may be critical for the spontaneous onset and progression of PAH. More specifically, ENG links TGF-β/BMP receptors including ALK1 to the eNOS activation complex. Its reduction renders eNOS unresponsive to the regulation of its phosphorylation status by TGF-β/BMP signals, leading to constitutive endothelial eNOS-derived oxidative stress.

While both ENG-/- and ALK1-/- mice acquire signs of PAH in adulthood via similar mechanisms, it is important to note that ALK1-/- mice display a more severe phenotype. This has also been observed in humans harboring ALK1 mutations who tend to have a greater prevalence and severity of PAH compared to those with ENG mutations. Interestingly, PAVMs are more prevalent in HHT1.
(ENG mutation) than in HHT2 (ALK1 mutation) patients (48% vs 5%). These low-resistance structures may serve to alleviate overall pulmonary vascular resistance (PVR) and thus mask the severity and attenuate the progression of PAH in patients with ENG mutations. Indeed, patients with ENG mutations presenting with PAH typically have lower PVR than those with ALK1 mutations. Moreover, in some of these cases, the increased pulmonary arterial pressure has eventually normalized with the appearance of PAVMs. These studies suggest that ENG mutations are a predisposing factor to PAH, and that PAVMs in HHT1 may result from abnormal vascular remodeling under high local pressure conditions, which may in turn serve to alleviate PVR. Manifestations of PAH and/or HHT may be influenced by genetic and environmental modifying factors that specifically affect the integrity of the ENG+/− pulmonary vasculature and its ability for normal remodeling/repair under elevated intra-vascular pressure.

In summary, TGF-β/BMP signaling and eNOS activity are critical determinants of normal endothelial function and survival, which may be perturbed in PAH patients and in many animal models of this disease. ENG links certain TGF-β/BMP receptors to the eNOS activation complex, and that adult ENG+/− and ALK1+/− mice spontaneously develop signs of PAH due to increased pulmonary endothelial oxidative stress and reduced NO bioavailability. A growing number of studies suggest a close association between PAH and HHT, and current experimental systems may provide a means to define the specific determinants in the pathogenesis of AVMs from those that underpin vascular remodeling leading to PAH. Moreover, the identification of novel factors that can regulate the level/activity of ENG, ALK1, and their associated signaling pathways irrespective of inborn mutations in TGF-β/BMP receptors may represent novel biomarkers of disease and potential therapeutic targets in the onset and progression of PAH.

References
Pulmonary Arterial Hypertension As a Systemic Disease

Group 1 pulmonary arterial hypertension (PAH) has historically been thought of as a disease of the lungs, which causes adaptive or maladaptive changes to the heart. Recent data, however, have suggested that the molecular defects that lead to PAH are found throughout the body, and that PAH might be more properly considered a systemic disease whose primary pathologic manifestations are in the lungs. These include changes in metabolism, right ventricular (RV) adaptation to stress, intracellular shuttling, and immune function.

The most well studied of these systemic changes are alterations in metabolism. Measurements in human patients—both idiopathic and heritable—indicating systemic metabolic abnormalities include increased insulin resistance, an increase in chronic high blood sugar, increased glucose consumption for the same energy production, and increased oxidative stress. We examined these metabolic defects using culture of pulmonary microvascular endothelial cells, either control or with different mutations of the heritable PAH gene, bone morphogenetic protein receptor type 2 (BMPR2). Using an overlay of GC/mass spec analysis of small molecule metabolites with gene expression arrays, we found that there are broad metabolic defects on a cellular level. These include not just an increase in glycolysis and decreased TCA cycle metabolism, but also decreased fatty acid and carnitine metabolism and a failure of anaplerosis. These changes may indicate that suppression of signaling through BMPR2 causes a shift from normal energy metabolism toward a state in which metabolic intermediates are shunted to the production of proteins and fats needed for rapid proliferation. These defects are probably associated with cause, not just correlated: when BMPR2 mutant mice are metabolically stressed, either using hyperoxia or by using high-fat diet to exacerbate insulin resistance, there is nearly a doubling of disease penetrance, while using metformin to reduce insulin resistance as preventive in mice slows development of disease. Metabolic defects are thus found in patients, predate and modulate disease in mice, and are consistent with a shift geared toward sustaining proliferation.

RV adaptation or failure is the primary determinant of survival in PAH patients. Recent data suggest that the RV is not passively responding to increased resistance to the lungs, but rather that many of the determinants of disease in the lungs have a direct impact on the heart. Examination of the RV from heritable PAH patients shows significant lipid accumulation within the cardiomyocytes; this lipid accumulation does not occur when the RV is under stress in idiopathic dilated cardiomyopathy. Epidemiologic data suggest that heritable PAH patients fare worse in survival than idiopathic patients with comparable hemodynamic characteristics. Based on evidence primarily derived from studies of BMPR2 mutant mice, we believe that the human data are best explained as follows. The heart under stress substantially shifts to lipid oxidation for energy. However, because of the metabolic defects discussed above, this shift does not occur properly in BMPR2 mutant hearts, and so the RV does not respond correctly to load stress—dilating and failing rather than remodeling.

BMPR2 mutation or suppression also results in substantial defects in intracellular trafficking. BMPR2 directly interacts with and regulates Src phosphorylation, the actin organization regulator LIMK, and the microtubule motor DYNLT1. BMPR2 mutation thus causes defects in microtubule and caveolin-based trafficking. In BMPR2 mutant mice, caveoli appear mislocalized, with increased internalized caveoli and very few associated with the cell surface, in a pattern nearly identical to that seen in skin biopsies from human heritable PAH patients with mutations in the scaffold attachment region of Cav1. In addition, there appears to be a broad failure in trafficking of steroid hormone receptors. BMPR2 expression level is one of the strongest determinants of glucocorticoid sensitivity in healthy humans, and when mutated it produces an odd mixture of steroid insensitivity and constitutive activation. The same is true of estrogens: estrogen receptor trafficking is defective in BMPR2 mutant cells and mice, resulting in relative insensitivity and perhaps forcing signaling into deleterious alternative estrogen signaling pathways. All of these defects are found throughout the body.

BMPR2 mutation also appears to cause chronic inflammatory problems, at least in mice. Grunig et al found that BMPR2 mutant mice had a nearly 10-fold increase in lung lymph node cellularity, while Monceaux et al found that BMPR2 mutant mice had a doubling of the number of lymphatic ducts, indicative of a chronic

Key Words—BMPR2, heritable PAH, idiopathic PAH, metabolic defects, pulmonary arterial hypertension
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need for clearance of inflammatory cells. BMPR2 mutant mice also appear to have alterations in the types of cells released from the bone marrow and in the activation state of monocytes and macrophages that predate development of disease. These defects have been difficult to directly test in patients, because it is difficult to distinguish cause from effect when disease has developed.

In conclusion, idiopathic and heritable PAH patients have multiple alterations in metabolic, trafficking, and heart function, which appear to be causal for or exacerbate disease, and are found throughout the body. Particularly for heritable patients, this is not surprising: the mutation is expressed throughout the body. These manifestations of disease outside the lung are important indicators of molecular mechanisms of disease, and may be important to treatment.
Understanding the Molecular Origins of Pulmonary Hypertension: Role of MicroRNAs

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Pulmonary arterial hypertension (PAH) is a disease of the pulmonary vasculature, defined by an elevated pulmonary vascular resistance, leading to right heart failure and premature death. The cause remains unknown and available treatments are limited. PAH is characterized by enhanced pulmonary artery smooth muscle cell (PASMC) and pulmonary artery endothelial cell (PAEC) proliferation and suppressed apoptosis within the pulmonary artery wall. It has been shown that this phenotype is associated with mitochondrial hyperpolarization and enhanced glycolysis over glucose oxidation (Warburg effect), which are sustained over time by the activation of the transcription factors HIF-1 and NFAT. Nonetheless, the mechanisms accounting for these abnormalities remain unknown. A common feature to all vascular remodeling processes is that in early stages of the disease, a significant increase in oxidative stress and inflammatory processes are observed, causing irreversible DNA damage and cell death.

Despite the sustained environmental stress in PAH, hyperproliferative and apoptosis-resistant PASMC and PAEC populations will emerge over time, resulting in distal pulmonary artery remodeling. We have evidence that the survival of these cells is associated with an efficient activation of poly(ADP-ribose) polymerases (PARP), a predominant mechanism involved in DNA repair. Indeed, PARP activation under stress conditions regulates cell survival and cell death. Moreover, PARP-1 interacts with several mitochondrial and metabolic enzymes implicated in the Warburg effect and promotes NFAT and HIF-1 activation. Recently, PARP inhibition has been shown to be an efficient treatment to reverse carotid stenosis, a vascular disease that shares several similarities with PAH. Moreover, PARP inhibition has been shown to decrease endothelial cell proliferation. More recently, we observed that pharmacological inhibition of PARP activity reverses PAH in cells and animals. These constitute a strong basis to propose that PARPs are implicated in the etiology of PAH, especially in the dysregulation of the mitochondria/metabolic/NFAT/HIF-1 axis.

Because intervening in established PAH is more relevant clinically since most patients with PAH present late, we will focus our research program on the role of PARP activation in hyperproliferative and apoptosis-resistant cells.

Key Words—pulmonary arterial hypertension, pulmonary artery endothelial cell, pulmonary artery smooth muscle cell, pulmonary vascular resistance
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1. Which of the following represents an important risk factor for pulmonary hypertension in the developing world?
   a. High-altitude resistance
   b. Infectious diseases (HIV, parasites, bacteria)
   c. Heart disease
   d. COPD
   e. All of the above

2. Hereditary hemorrhagic telangiectasia associated PAH may involve which of the following cell signaling pathways?
   a. TGFβ
   b. Activin-like kinase 1
   c. Nitric oxide
   d. Both a and b
   e. a, b, and c

3. The percentage of patients with BMPR2 mutations in idiopathic PAH is estimated to be approximately:
   a. 6%
   b. 20%
   c. 50%
   d. 70%

4. The Warburg effect is seen when cells preferentially use glycolysis over glucose oxidation as a source of cellular energy.
   a. True
   b. False

5. PPARγ (proliferating peroxisome) activation is used to treat insulin resistance and may provide a new therapeutic modality for PAH by:
   a. Lowering blood glucose
   b. Restoring normal BMPR2 signaling
   c. Weight loss
   d. Inhibiting endothelin-1 signaling

6. In humans with PAH, metabolic changes have been observed including which of the following:
   a. Decreased oxidative stress
   b. Insulin resistance
   c. Hypoglycemia
   d. None of the above

7. High fat diets increase the penetrance of PAH in BMPR2 mutant mice or the development of PAH in apolipoprotein E deficient mice:
   a. True
   b. False

8. The total number of patients with BMPR2 mutations is highest in which group of patients:
   a. Idiopathic PAH
   b. Heritable PAH
   c. Associated PAH
   d. PVOD

9. The DNA-repair enzyme, poly-ADP-ribose polymerases (PARP), is activated in PAH cells with enhanced proliferation and survival:
   a. True
   b. False
The Genetics of Pulmonary Hypertension

While most issues of Advances in Pulmonary Hypertension provides up to 2 hours of CME credit, because credit was available at the 10th International Pulmonary Hypertension Conference and Scientific Sessions, this issue does not offer credit. To test your understanding of the material in this issue, you may quiz yourself using the questions on the preceding page and check your answers below. Watch for CME opportunities in future issues of Advances or go to http://www.phaonlineuniv.org/ for other CME programs from the Pulmonary Hypertension Association.

Self-Assessment Answers

1. e. All of the above
2. e. a, b, and c
3. b. 20%
4. a. True
5. b. Restoring normal BMPR2 signaling
6. b. Insulin resistance
7. a. True
8. a. Idiopathic PAH
9. a. True

Evaluation of Activity

Poor Satisfactory Excellent

1. Extent to which objectives were met

   1 2 3 4 5

2. How would you rate the course overall

   1 2 3 4 5

3. How helpful was the information presented

   1 2 3 4 5

4. Was the activity free of commercial bias? Yes No

5. After participating in this activity, do you anticipate changing any of your patient care practices? Yes No

   If yes, what do you plan to change? ________________

6. Do you foresee any barriers to change? Yes No

   If yes, what? ________________________________

Additional comments about this self-study activity:

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__________________________________________

__________________________________________

Suggestions for future topics:

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* Please send evaluation form to: Medical Services, Pulmonary Hypertension Association, 801 Roeder Road, Suite 1000, Silver Spring, MD 20910-4496
Pulmonary Hypertension Roundtable

Perspectives on PHA’s 10th International PH Conference

As a way to integrate the presentations at PHA’s June scientific sessions with clinical practice, Guest Editor Karen Fagan, MD, convened a group of attendees to discuss their experience in Orlando. The discussants included Todd Bull, MD, Associate Professor, Medical Director, Anschutz Intensive Care Unit, University of Colorado, Aurora, Colorado; Anna Hemnes, MD, Assistant Director, Center for Adult Pulmonary Vascular Disease, Vanderbilt University, Nashville, Tennessee; C. Gregory Elliott, MD, Professor of Medicine, University of Utah and Medical Director, Pulmonary Hypertension Center, Intermountain Medical Center, Murray, Utah; Vinicio A. de Jesus Perez, MD, Assistant Professor in Medicine and Staff Physician, Wall Center Adult PH Clinic, Stanford University Medical Center, Palo Alto, California; and Paul B. Yu, MD, PhD, Brigham and Women’s Hospital, Boston, Massachusetts.

Dr Fagan: Thank you for joining us. Welcome to this roundtable. The focus of this discussion is to allow us to talk a little about the recent international conference, but specifically, the scientific sessions. New this year is also to talk about the research room, both from the current research room, and also some perspective on biomedical research performed as part of the meeting. What I’d first like to do is to congratulate Todd and the rest of the members of the committee on really a lovely program. I think that it really allowed us to focus in a lot of different, creative ideas as it relates to pulmonary hypertension and future directions. And so Todd, I know that you worked with your committee and came up with this year’s theme. Do you want to describe that theme to the rest of us again?

Dr Bull: Thanks, Karen. Our theme for the 10th PHA International Conference Scientific Sessions was the genetics of pulmonary hypertension. I also want to extend my thanks to those that helped put this together, and I’ll briefly throw the names out there. It was Aaron Waxman, Anna Hemnes, Charlie Burger, Troy Stevens, and James White. We kicked around a bunch of different ideas from the standpoint of pulmonary hypertension. And our first decision was that we wanted to come up with a theme, to try to focus our discussions around a central topic. With the time that had passed since the discovery of the BMPR2 mutations in 2000, and all the new directions this research has taken since that time, all the evolving data in the area of genetics, genomics, epigenetics, and pulmonary hypertension, we decided that the genetics of pulmonary hypertension would be a great area to explore. Underlying this idea is the realization that at some level all diseases are genetic in their development, genetic in their progression. Our ability to understand the interaction of the individual’s genes with the environment will drive new developments in terms of therapies and some of the ultimate developments in terms of therapies down the road. For example, why do some HIV patients develop PH while others do not? Similarly, why do some scleroderma patients get PH and some patients liver disease? And so, it was with that idea that we decided on an underlying or overlying theme for the conference. We then set about finding the speakers that we thought could really show us not just where we’ve been (which is what Dr. Newman focused on in his talk), but where we are going, which is what the rest of the speakers ended up discussing.

Dr Fagan: Well, I think that you put together a lovely program. Anna, do you want to talk about what it was like to participate on the committee and some of the thought process that you and the committee contributed to?

Dr Hemnes: I thought it was a great committee to be a part of. There was a lot of discussion about what the best research was and how we could make it accessible to people who were attending the conference, and how to increase our knowledge about where genetics was bringing us in pulmonary hypertension. I really enjoyed working with the other committee members in thinking about how to put the best conference that we could together. And probably one of the most enjoyable things was reviewing the abstracts and seeing some of the science that is going on around the country and internationally. There were several abstracts that I recall being from international groups, which really demonstrated the draw of the conference. So that was a particularly enjoyable part of the committee.

Dr Fagan: Well, I think that this was a record setting year for numbers of abstracts presented, as well, is that correct, Todd?

Dr Bull: I’ll have to check back to see our final count, but we had a record number—well over 100 in total. We had hit really above our target number going into it. And really some great, great abstracts. So I would agree with Anna that it was fun. We had great abstracts on genetics, genomics, and epigenetics, but also great abstracts on many other topic areas important to PH. A number of abstracts were selected for presentation dur-
of evolving interest in PH. The conference was a great opportunity to look at these mutations from different angles than we have in the past. That is just one example of the great things that came out of some of these talks.

**Dr Hemnes:** I think the other exciting thing was the hereditary hemorrhagic telangiectasia data and how it intersects with BMPR2 mutation. The ability to bring top-notch scientists together and talk about how their own research, in what seem like pretty disparate fields, actually intersects pretty closely was a really nice opportunity, and something that I think the conference brought to the forefront pretty well.

**Dr Bull:** I definitely agree with Anna. That was a nice look into a rare disease, but then how it comes back across to what the bigger picture is here...

**Dr Fagan:** I thought he had a very interesting perspective. And I think one of the things that the scientific sessions originally did and continue to do is to bring in experts in areas that are related to PH, to inform us and to help us identify other avenues that need further investigation or other areas that are complementary to what we’re doing that by working together, we can advance multiple fields. I think the scientific sessions have always done a really lovely job of that. Greg and Paul, you’ve both been a little quiet. I want to switch over a little bit to talk about the research room. And Paul, I invited you as this year’s chair of the research room activities. And Greg, obviously as the founder, so to speak, of clinical research at the PHA meeting, to kind of bring your perspective in. Paul, if you could tell us a little bit about the research room this year and the success of that, I think that all of us would like to hear about how well the program ran this year.

**Dr Yu:** Thanks, Karen. This is a neat thing to be able to sort of look back at how the research room has grown, especially with Greg’s perspective of having been there at the very first research room. Was it in 1994?

**Dr Elliott:** Paul, that research room wasn’t much, I can tell you.

**Dr Fagan:** The card table, the research card table.

**Dr Elliott:** But the investigators were highly motivated. And I still remember to this day, David Badesch, MD, coming with little pieces of filter paper to collect samples. I think these were for ACE genotyping that he was doing. And Jane Morse, MD, needed...
help with phlebotomy. So we drew the blood samples for her. I was told that one sample was from a family that helped her team at Columbia find the BMPR2 gene mutations. So, back then, we were just kind of finding our own way. And luckily, the patients and families were incredibly supportive. And I think Todd Bull, MD, coined the phrase “stick it to PH” for the blood drawing.

Dr Bull: I wish I could take credit for that, Greg. That was actually one of the patients who came up with that. And then we thought it was such a great idea, we should get it on a sticker. She’s one of the organizing committee members. Again, PHA being all about patients, at its origin, patients helping drive this forward, that’s a nice example of that. So we came up with the sticker, “Stick it to PH,” which the people that then participated in the research room could wear sort of proudly for helping us with this work.

Dr Elliott: It really is one place where physicians, scientists, patients, and clinicians all come together. I think the research room has always been a tangible way for the community to organize and advance our scientific knowledge. This year I was so impressed at how well organized it was and how well people were interacting with each other. In 1994 I had no idea whatsoever that we’d ever end up with anything quite as great as what you have done.

Dr Fagan: And with that actually, Paul, I’m going to ask you to just give us a little bit of a summary about the research room. And like the abstract submissions, I understand it was a record-setting participation, not just with patients, but also with investigators. Is that correct?

Dr Yu: Yes, that’s right. We had more interest from investigators than in years past. There were 4 or 5 groups that returned from 2010 to continue their studies. They were interested in following patients with some continuity, as well as recruiting new patients. And then we had some interesting new groups join the research room effort, for a total of 9 groups. So there’s been a steady progression in terms of number of groups interested in participating, as well as the patients participating themselves. We had people doing quality-of-life studies, looking at correlations between exercise function and markers of depression. We had people doing actual sorting of progenitor cells, circulating endothelial progenitor cells right there in the room. We had people doing some very interesting proteomics, some very interesting genetic studies, as they’ve done since the beginning of this research room. So I was impressed with the increased diversity in the types of research and the research methods that were being pursued in the room this year. We’ve tried to be as inclusive as possible in accommodating both numbers of groups, and types of activity. The only real constraints are that some exercise or walking studies aren’t considered to be safe for this setting, but any other imaging, questionnaire, or phlebotomy study that has been proposed has usually been accommodated one way or another.

Dr Bull: I just want to compliment Paul on getting this all organized. It’s always a tricky thing making sure everyone’s got their IRBs in place. That we’re drawing the appropriate amount of blood from people, that the consent forms are being filled out appropriately. Then trying to organize, the appropriate infrastructure in terms of centrifuges, phlebotomy equipment, etc. In 2010, we had a broken centrifuge show up. And then actually Paul, at that point, somehow managed to finagle another centrifuge at the last minute. Anyway, it is no easy task.

Dr Yu: No, that was fun. There’s a lot of troubleshooting on the day, no matter how much planning we tried to do ahead of time to make it as smooth as we could from the patient’s perspective, the participants, as well as for the investigators, things always happen. And, I wish I could say this year was perfect. We still had some issues. As the scope of the effort has grown, as we’ve had more patients interested and had more investigators, and the potential for things to get out of hand is always there. This year the proactiveness of the PHA staff and the other people on the research room committee helped a lot. And this is to say that we still have a lot of aspects that we’d like to work on, because we think that this effort will continue to grow. We’ve had some nice constructive and critical feedback from the patients who participated, and some of the board members, who felt that, even though we’ve made strides, we could make the experience better from the patients’ perspective. But from the investigators’ and researchers’ perspective, I think we all agree that there’s nothing quite like the experience of reaching out across the table and talking to people who live with this disease, or who have family members with this disease. To me, nothing quite encapsulates the whole interface between investigators, physicians, and patients that is the philosophy of the PHA scientific sessions the way the research room does.

Dr Fagan: I was very lucky in that we were able to bring some projects to the research room from our institution. And we brought the graduate students who were working on these projects. And for those...
working on a PhD in basic medical sciences the profound interaction they had with the patients and their family members and other people willing to volunteer to provide specimens to them was great. Each and every one of them came back and reported in their respective lab meetings the profound impact that this type of interaction has on them as a scientist—and that it’s no longer a theoretical situation that people find themselves in. These are real people with real faces and real names, and real stories to tell. I’ve personally experienced that in the meeting—even though I get that interaction clinically all the time; somehow it brings that to a much more heightened awareness. Maybe just the sheer volume of patients does that.

Greg, I was wondering; again thinking back to maybe the shoebox that you sat on to collect blood samples, not as long ago as all of us would like to imagine, and I was wondering if you, as you looked at the meeting, including the genetics story that came out of this. And I was wondering if you, as you looked at the research room this time, what were some of the things that you were thinking about in terms of where the research room has ended up now?

**Dr Elliott:** Well, I think first Paul said it correctly. I think when we started, it really was an idea. I mean, the history, as briefly as I can tell it, is that I heard that there was someone in Chicago named Judy Simpson who was planning a patient conference. And I thought, that’s interesting because I’m interested in collecting DNA from patients with pulmonary hypertension. And the pace at which I can collect here in Utah is pretty slow. But maybe if I went to this meeting, I could find some patients with this rare disorder and collect more samples. So I called Judy Simpson, and Judy was incredibly cautious. She said, “Can I get back to you?” And then I’d since learned that she called Al Fishman, MD, and Lew Rubin, MD, to check and see if I was a legitimate person to talk to. And luckily, they said yes. And then it went forward from there. I had a fellow, Gary Alexander, MD, working with me at the time. Gary agreed to come with me. We packed up all our tubes and headed to Stone Mountain, Georgia. And in one weekend, we collected 40 DNA samples from patients with PPH and accessed their records to confirm the diagnosis. I said it would have taken me 8 years of work in Utah to do what I did in that one weekend. So that was the beginning. And then we came back every 2 years—I think we skipped one conference because I didn’t have the resources. But we came back and added to our pool. And I just sent off to Wendy Chung a map of the United States, showing that we have DNA samples for patients from all over the country.

In the meantime, investigators have come with other questions. That’s been very rewarding to me. We’ve seen a lot of projects. And I think I’ve also seen people interacting and sharing their ideas there, which I think is terrific. So those are the things I’ve liked.

**Dr Fagan:** So Anna, I know you’re someone who has done basic science research and translational and clinical research, in addition to caring for patients with PH. What are some things that you think that the research room might be able to do in the future that might be good? Are there ideas that you have about other things besides questionnaires, samples, things that you think as an investigator would be something interesting to do there?

**Dr Hemnes:** Gosh, there are so many things that I don’t know how to start. I guess the samples are really a particularly unique thing that are available at the PHA, because there’s such a large number of patients with a rare disease together at one place. So I don’t want to discredit that. But there are certainly many different kinds of research that are available. For instance, questionnaires about quality of life and pulmonary hypertension, and how drug therapy has affected quality of life for patients come to mind. I think looking at exercise capacity, using some of the newer techniques, like the Shape heart failure device may be an option. So perhaps bringing some of the ideas that people have had, that have only been able to study at their local centers, to the research room in the future may be a venue to broaden that research applicability and enhance knowledge. And, in particular, the participation of various subtypes of patients with pulmonary hypertension may allow greater comparison of different subtypes, really enhancing research in patient samples, as well as outcomes research and also quality of life, which I think also would be interesting.

**Dr de Jesus:** I would like to add to that. One of the things that I think cannot be overlooked is that, in addition to the patients themselves, we may also have access to their immediate families. Affordable complete genome sequencing will soon be a reality and we will be asked to provide input on variants that could have potential roles in PH development. The genetic information obtained from family members may facilitate interpretation of a patient’s genetic data and could help us elucidate the impact of some of these genetic variants in disease development.

**Dr Bull:** Y’eh, that’s great, Vinicio. I think that’s an important point to add up. And then one thing I want to throw out that Greg Elliott and I have talked about in the past, and that I know Paul has talked about, is...
that it’s such an amazing opportunity, being allowed to work with the patients at the PHA, who give so much of their time, that I wonder if we can come up with even smarter ways of approaching it in terms of collaboration. One thing Greg and I had discussed once was trying to get a planning meeting of the participating investigators well before the next PHA meeting to try to figure out where our interests come together, and then come up with projects that attack this at multiple levels. For example, coordinate the efforts of the investigators doing DNA work versus those doing RNA work and those interested in circulating factors, and coordinate the efforts. One of the things that becomes very difficult with projects such as this is getting the phenotypic data after you have gotten the sample, because it involves requesting clinical data from multiple institutions from around the country. If there were some way to get this data once and share it among all the investigators, it would make these projects much easier. I think it would be something worth exploring now. In the modern age of IRBs that becomes in some ways a difficult thing to contemplate. But at the same time, could the PHA, for example, serve as the clearinghouse for the data that then lets multiple groups access it. These are the sort of things that I think could really ramp up our ability to use this incredible resource in more effective ways.

**Dr Elliott:** Well, Todd, I am glad you brought that up. I was going to bring it up if you hadn’t. And I’ve always viewed that as what I call an unrealized opportunity. I think there really is an opportunity that goes beyond the conference. And I think the conference is such an intense activity that if there were funds somewhere available to bring the investigators of the research room together, as you said, before the meeting, and to have a little more of an organizational structure to allow for integration, then I think even more could be accomplished.

**Dr Hemnes:** I would also agree with that and say that it’s possible now in the electronic age that some of those interactions with patients don’t even necessarily have to happen in the context of the conference. And that people who are interested in participating in research protocols may sign themselves up to some sort of database that’s sponsored by the PHA ideally, or another organization, as people who are willing to be contacted for research purposes. And many blood samples, or even other types of samples, could be collected remotely, so that some of the real riches of the research room in terms of patient benefit and research knowledge could be extended beyond just this once-every-two-year opportunity. A sort of a pie-in-the-sky dream, but why not dream big?

**Dr Fagan:** There’s no reason to say that that couldn’t happen. And indeed, there are companies out there that sell database access, where people can input data and things like that. And certainly, the PHA has been looking at those, because of the concerns raised there. In just the last couple of minutes, what I thought I might do is switch gears just a wee bit. And one of the things that I can say from my personal experience with the PHA International Conference and Scientific Sessions is the focus of the meetings have been on trying to engage young physicians and young scientists in an enthusiastic career in pulmonary hypertension research. I think that one of the things that the meeting does, and again because of its uniqueness, is to really inspire those types of experiences. And I know, Vinicio, I’m going to pick on you a bit, since this was your first time at the meeting, to ask you to say a little bit about how you think that the meeting is moving you forward a bit in your interest in pulmonary hypertension.

**Dr de Jesus:** The PHA international meeting was a great opportunity to meet with mentors and colleagues who were excited to share knowledge and experience with a young clinician scientist such as myself. Also, it is a great platform to interact with people who are at my stage of career development, and exchange experiences that go beyond just what we’re doing in the lab to include the challenges that we face in our clinical PH practices. As far as the science, I was clearly blown away. In the end, I felt that I had a good idea of where I would like to be as the field evolves over the next decade. It is my goal to become a better scientist and to learn how to fit a mentor role in my career, as exemplified by the rest of the colleagues in the meeting, such as Greg, Karen, and Todd, among others. I certainly hope to continue my current career track and contribute as much as they have in the coming years.

**Dr Yu:** Well, it’s been pretty amazing actually to see the meeting grow, both in the scientific sessions, as well as the research room, over the past 3 or 4 meetings that I’ve been to. I was a trainee at the first 2 meetings that I went to, and I was blown away then. And I didn’t anticipate that it would grow as much as it has. The scientific programs have gotten better and better, in participation, breadth of research topics, and ambition. I agree with Vinicio that the quality and the scope of the science that’s presented there is just amazing. From the perspective of anybody who’s

*The ability to bring top-notch scientists together and talk about how their own research, in what seem like pretty disparate fields, actually intersects pretty closely was a really nice opportunity . . . .*

Dr Hemnes
interested in pulmonary vascular disease, there’s pretty much something for everybody, even though there was a well-defined theme at this year’s meeting. And the research room has been really fun to be a part of. Since I think I was introduced to it by Greg Elliott, I think 4 years ago, it’s done many of the things that he’s talked about in terms of exposed me to mentors in the field, to thought leaders in the field; it has exposed me to science and has led to really nice collaborations with people scientifically—and friendships, as well, beyond the collaboration. So I’m very grateful for a lot of that.

Dr Fagan: I’m going to pose the same question to the rest of the panel. Greg, don’t think you’re off the hook (laughter). Todd, do you want to go next?

Dr Bull: Similar to Paul, I attended my first conference as a fellow and was—I remember thinking to myself—what an unusual conference. I’d never heard of patients going to the same conference as the physicians. And I came out of that conference saying to myself, what an amazing idea. Why doesn’t every organization do something like this? And similar to you, Karen, I come away from it re-inspired, even though I take care of patients all the time with pulmonary hypertension, there’s something unique about that conference in terms of refocusing you on why you do what you do, and what’s so important about it, and why it matters so much to so many people. There’s nothing else quite like it I have to say.

Dr Elliott: I guess what I’d say first is, first, well said, both you and Paul. I think you’re right, it’s always—it gives back to us more than we ever—at least to me, it’s given back to me more than I’ve ever been able to give to the community. So I really have valued the conference. Historically, it might interest you to know that that first conference at Stone Mountain was purely a patient-driven conference. And it was because Judy, I think, and perhaps others were willing to have some good physician advisors, I think, to welcome us in as scientists. I remember once they gave the green light for research, then we came a little early, and I met with a number of colleagues. I think Jim Loyd was there. And I don’t remember if John was. And we talked about what we were going to do with research and basically said, if any of you want to do this, too, we’ve partitioned off a room. And I think that’s when James stepped forward and Dave Badesch, to the best of my recall, that first room just had the 3 of us in it. But there was no scientific session. And the first stab at a scientific session I think I was a program chair or something. And I invited Ted Lowe from the University of Utah to come talk about advances in cystic fibrosis and the genetics and some of his work with survival curves. Ted was probably the mathematical modeler. And that was sort of a seminal event. And it really had come because somebody said, why would physicians and scientists come all this way to a conference that’s purely patients? And so you can see, it really—I think it grew out of ideas that good people had. And what we’ve seen is, it is a lot condensed into the conference, including great scientific sessions on the front end. And then, the sessions for patients and families and caregivers and the PH community, locked arm in arm with the research room. So, it really has evolved where it is. And it’s evolved because people have had good ideas and been willing to work, do the work to see them through.

Dr Hemnes: I would say it was only my second scientific session that I’ve ever been to. But both times I’ve been, I’ve been inspired by 2 things. First is the enthusiasm of the patients for what we’re doing and for their interest in research. And really on a more personal level, for finding a cure for this terrible disease. And that’s brought a lot of personal meaning to my own research. And the second thing that inspired me was the tremendous quality of science that’s being done by our colleagues and it’s inspired me to raise up my own science. So on both levels, I really love the meeting because of the unique interaction of patients and researchers and caregivers all together, it can’t be found anywhere else.

Dr Bull: The one thing that Paul remembered to do and I’ve neglected to do was to really thank the PHA for their outstanding work in putting this together. I mean, we obviously had work to do, but it only comes together just because they’ve organized it and keep us on task and then really do all the things that need to happen to make it—just to make it occur. So, Rino and his staff never cease to amaze me at how well they can put this sort of thing together and keep them rolling.

Dr Fagan: I’m going to conclude by just again thanking all of you for participating. I know that we all have busy days and this occurs right in the middle of everyone’s day. But like all of you, I share a commitment to helping the PHA advance its causes for patient advocacy, for research, for education, and ultimately to find a cure. And thank you all for participating in this. And we’re looking with great enthusiasm to the next scientific sessions, which will be chaired by Anna in Indianapolis, and Eric Austin has kindly accepted the position of being the new chair of the research room. I am certain that the sessions and research room will be terrific under their leadership. Thank you all so much.
A record number of abstracts were submitted during the poster sessions at the Conference. The winning abstracts in Basic Science and Clinical Science were presented as oral abstracts during the scientific sessions and are included in this issue of Advances.

**CLINICAL/TRANSLATIONAL SCIENCE:**

**β-2 Adrenergic Receptor Polymorphism and Gene Expression are Associated with Risk of Development of and Disease Severity in Pulmonary Arterial Hypertension Associated with Scleroderma**

Mathai SC, Gao L, Cheadle C, Rafaels N, Berger AE, Grigoryev DN, Barnes KC, Hassoun PM
Johns Hopkins University, Baltimore, Maryland USA

**Background:** Little is known about the role of neurohormonal dysfunction in the pathophysiology of pulmonary arterial hypertension (PAH), particularly with respect to PAH-related to scleroderma (SSc-PAH). Single nucleotide polymorphisms (SNPs) in the β-2 adrenergic receptor (ADBR2) gene have been associated with cardiovascular disease and specifically, risk of development of left heart failure. Similarly, expression of related genes in peripheral blood mononuclear cells (PBMC) has been associated with disease severity in left heart failure. Therefore, we sought to 1) determine whether previously validated SNPs in ADBR2 were associated with the risk of development of PAH in SSc and 2) characterize the gene expression of ADBR2 in treatment-naïve SSc-PAH patients.

**Methods:** 308 SSc patients without PAH and 140 SSc-PAH patients provided blood for genetic analyses. Several SNPs of the ADBR2 gene (n=13), previously demonstrated to have functional significance in cardiovascular disease, were examined for their association with the risk of development of PAH in SSc at the single locus level using PLINK. Fifteen of the SSc-PAH patients, who were treatment-naïve at enrollment, also provided PBMCs for gene expression analyses using Illumina high-density BeadArrays. Pearson correlations between ADBR2 and clinical variables were calculated along with p-values and false discovery rates (FDR).

**Results:** Genetic analyses showed a significant association between the ADBR2 SNP Arg16Gly in the promoter region (rs17778257) and development of PAH in SSc (p=0.03). Gene expression profiles showed a strong positive correlation with ADBR2 expression and cardiac output (r=0.81, p<0.0001, FDR<0.01).

**Conclusions:** Preliminary results in this cohort suggest that functional SNPs in ADBR2 may be associated with the risk of development of PAH in SSc and that gene expression of ADBR2 is associated with disease severity. Given the known associations between ADBR2 and left heart failure, further study is warranted.

**CLINICAL SCIENCE:**

**Living with Pulmonary Hypertension (PH): Unique Insights from an International Ethnographic Study**

Kingman M,1 Hinzmann B,2 Sweet O,3 Vachiery J-L4
1UT Southwestern Medical Center, Dallas, TX, USA; 2Bayer Healthcare Pharmaceuticals, Berlin, Germany; 3Ipsos MORI, London, UK; 4Hôpital Erasme, Brussels, Belgium

**Background:** Despite the widespread use of quality of life (QoL) assessments in PH research, large gaps remain in our awareness of how patients perceive their disease. This study utilized ethnography, a unique qualitative research methodology based on participant-led observations, to acquire a better understanding of the patient’s perspective of QoL, disease management, and the patient–healthcare professional (HCP) relationship in PH.

**Methods:** Patients were recruited through HCPs and patient associations. They were included if they were aged ≥18 years, had been diagnosed with pulmonary arterial hypertension (PAH) or chronic thromboembolic PH (CTEPH) for ≥6 months, and were receiving PAH-specific medication. The study used interviews and observations to assess real-life patterns of behavior. Patients completed diaries before being interviewed to gauge the emotional impact of living with PH. The researcher then observed the patient in their home for up to 6 hours, capturing the environment, interactions, and activities of everyday life. A total of 140 hours of footage were independently reviewed and analyzed by several ethnographers within the research team. The data were cut thematically and analyzed for behavioral themes including: daily routines, impact on lifestyle, future outlook, information and support sources, medication practicalities, compliance, and emotional attachment to therapy. These observations were then compared with stated patient responses.

**Results:** In total, 39 patients with PH (PAH=34, CTEPH=5; NYHA FC I=2, II=14, III=17, IV=6; 29 females; age range 19–91 years) were enrolled from 7 countries across 4 continents. In addition to the severe limitations imposed by the disease on patients’ lifestyles, a striking outcome of the study was the reported secrecy surrounding PH. Many patients had a poor understanding of PH and found their ‘invisible’ disease difficult to explain to others. Feelings of insecurity, isolation, and depression were regularly reported, with many patients admitting to hiding their symptoms. The majority recalled the pre-diagnosis phase of PH as being defined by feelings of anxiety and a fear of being judged as lazy or unfit. Following diagnosis, access to medication played an integral role in their lives, providing symptomatic relief and improving QoL.
Thus, compliance with, and emotional attachment to, medication were observed to be high. The marked improvement in symptoms after initiation of therapy made assessment of disease progression more difficult as patients tended to compare their QoL against a pre-treatment level and were less aware of ongoing subtle changes. In terms of disease coping strategies, patients fell into 2 categories: solution-seekers who developed tactics to cope with PH on a daily basis; or disease-dominated who had a greater dependency on caregivers and a more passive attitude toward PH. Regardless of the strategy adopted, patients stated that extensive planning and adherence to daily routines were required in everyday life. Many patients were unaware of, and reluctant to discuss, their prognosis. The enforced dependency on caregivers who followed diagnosis was an aspect of PH that patients were unprepared for, and the majority appreciated personal contact with expert PH HCPs.

Conclusions: This study provides a unique real-life insight into PH from the patient’s perspective, uncovering a number of findings that would not typically be revealed by other qualitative approaches. It highlights the secrecy surrounding PH, the difficulties in describing the disease, and the challenges in assessing disease progression. A more tailored dissemination of information and a simple and understandable definition of PH may prove beneficial to patients. A greater appreciation by HCPs and caregivers of how patients perceive their disease and their QoL has the potential to improve PH management.

BASIC SCIENCE:

Pulmonary Arterial Hypertension Induces Gene Expression Changes in the Right Ventricle in Advance of Right Ventricular Failure that Are More Severe in Female Rats

Ahmad F,1 Sembrat JC,1 Rajkumar R,1 Huang X N,1 White R J2
1University of Pittsburgh, Pennsylvania, USA; 2University of Rochester, New York, USA

Background: Right ventricular (RV) failure is the leading cause of morbidity and mortality in patients with pulmonary arterial hypertension (PAH), and females represent up to 75% of patients with PAH. However, most animal models of PAH focus on male rats precluding an analysis of sex-specific changes in RV adaptation or dysfunction. We analyzed genome-wide mRNA expression patterns in the RV of both female and male rat models of severe PAH to determine whether changes occur prior to the onset of RV failure, whether these changes resemble those characteristic of left ventricular (LV) failure, and whether there are sex-specific biological differences in RV failure.

Methods: 6 week-old female and male rats underwent left pneumonectomy or sham surgery followed by 50 mg/kg MCT 7 days later to induce severe, neointimal PAH. Rats underwent transthoracic echocardiography and continuous ambulatory invasive right heart hemodynamic monitoring. Cardiac tissue was harvested and RNA expression profiles were generated by microarrays from female (n=3) and male (n=4) rats with PAH 10 days following MCT, and from female (n=4) and male (n=4) control rats.

Results: Experimental rats exhibited significantly elevated pulmonary pressures but grossly normal RV size and function prior to sacrifice. 195 genes were differentially expressed in the RV of rats with PAH relative to normal control rats. These genes were involved in calcium signaling, myocyte contraction, mitochondrial function, extracellular matrix remodeling, cell proliferation, and cell membrane and cytoskeleton structure. Expression changes in Emp3, Fn1, Hspb1, Mgp, S100a4 and Timp1 were confirmed by real-time quantitative PCR in RV. Expression of these genes was unchanged in the LV. In general, female PAH rats exhibited more extreme gene expression changes than male PAH rats.

Conclusions: We have documented gene expression changes in RV of rats with PAH prior to the appearance of significant RV enlargement. These changes resemble those occurring in LV failure but appear to be more severe in female relative to male rats.

BASIC SCIENCE:

Mechanobiological Feedback Amplification of Vascular Remodeling in Pulmonary Arterial Hypertension is Modulated by COX-2-Derived Prostanoids

Liu F,a Suárez Velandia M,b Ifedigbo E,b Marinkovic A,a Liu X,b Tschumperlin DJ,a Fredenburgh LEb
aMolecular and Integrative Physiological Sciences, Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA; bDivision of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women’s Hospital, Boston, MA, USA

Background: Recent studies suggest that increased pulmonary arterial stiffness contributes significantly to increased right ventricular afterload and is associated with increased mortality in pulmonary arterial hypertension (PAH) patients, however the role of PA stiffening in the pathogenesis of PAH has not yet been fully elucidated.

Methods: Male Sprague-Dawley rats were treated with SU5416 (20 mg/kg) or vehicle subcutaneously and exposed to hypoxia (10% FiO2) for three weeks followed by re-exposure to normoxia for 2, 5, or 10 weeks (for a total of 5, 8, and 13 weeks). Lungs were harvested and pulmonary arteries were mechanically characterized using atomic force microscopy (AFM) microindentation. Human PASM C were cultured on synthetic polyacrylamide substrates of defined stiffness spanning a shear modulus range of 0.1 to 25.6 kPa.

Results: SU5416/hypoxia-exposed rats developed dramatic increases in right ventricular systolic pressure (58 ± 2.5 vs. 22 ± 1 mm Hg) and Fulton’s index (0.63 ± 0.04 vs. 0.14 ± 0.04) compared with controls, as well as marked pulmonary vascular remodeling. SU5416/hypoxia-exposed rats developed significant increases in stiffness in pulmonary arteries <100 μm (1.26 ± 0.8 kPa) compared with controls at 5 weeks, with progressive and sustained increases in PA stiffness at 8 and 13 weeks. Interestingly, pulmonary arteries >100 μm demonstrated no increase in stiffness early following SU5416/hypoxia, however subsequently developed significant increases in...
shear modulus at 8 weeks (2.8 ± 2.5 kPa) and 13 weeks (3.1 ± 1.1 kPa) compared with controls. PASMC grown on substrates that span this stiffness range demonstrated exaggerated contractility and enhanced matrix deposition with increasing substrate stiffness, as well as increased proliferation, decreased apoptosis, and reduced cyclooxygenase-2 (COX-2)-derived prostanoid expression. Treatment with iloprost, a PGJ2 analog, significantly attenuated stiffness-dependent increases in PASMC proliferation, matrix deposition, and contractility. Furthermore, increased matrix stiffness led to a significant reduction in COX-2 promoter activity in transiently transfected PASMC grown on substrates of pathologic stiffness.

**Conclusions:** Our results demonstrate that matrix remodeling in the pulmonary arterial wall fundamentally biases cellular behavior towards progressive vascular remodeling via previously unrecognized effects of matrix stiffening and suggest a central role for COX-2 in orchestrating stiffness-driven amplification of vascular remodeling.
Connect Patients with Support Resources
PHA offers ongoing education and information for patients and caregivers at every stage of their PH journey. We now provide resources to help your patients and caregivers cope with the mental, emotional, social and spiritual components of living with PH. To download your free guide, visit www.PHAssociation.org/Coping.

First Pediatric PH Research Program Funded
The Pulmonary Hypertension Association is pleased to announce that the Robyn Barst Pediatric Research and Mentoring Fund has hit its initial funding goal to begin operations. This is the first pediatric research fund established to support pediatric research in pulmonary hypertension. Grant procedures are currently being developed and when complete will be posted on the PHA website at www.PHAssociation.org/BarstFund. More detailed information will also appear in the next issue of Advances in Pulmonary Hypertension.

PHA Online University Webinar Archives
View the archive of previous webinars on PHA Online University. Recent additions include:

- **Palliative Care and PH**
  Winifred Teuteberg, MD, University of Pittsburgh, Pittsburgh, PA
  Sept. 2012

- **Working with a Social Worker**
  Allyson Rupp, LCSW, Stanford Hospitals and Clinics, Stanford, CA

- **Understanding Compassion Fatigue**
  Crystal Weber, RN, Duke University, Durham, NC
  Nov. 2012

To view these and more visit www.PHAOnlineUniv.org/WebinarArchive.

Global PHCR Memberships
In an effort to increase global membership in PH Clinicians and Researchers (PHCR) and foster the sharing of ideas around the world, PHA is offering free first-year memberships for non-US physicians, researchers, residents, and fellows interested in PH. Benefits of PHCR membership include case-based learning opportunities by top PH specialists, access to an email group of a growing number of PHCR members, inclusion in PHA’s Find A Doctor Directory, and more. For medical professionals in countries that have a gross national income per capita of less than $5000 USD, PHCR memberships may be renewed at no cost each year. Learn more at www.PHAssociation.org/PHCR.

Calendar of PH Activities

To have your event for PH health care providers considered for listing in future issues of *Advances in Pulmonary Hypertension*, send your announcement to brianar@PHAssociation.org.

**Society of Critical Care Medicine Critical Care Congress**
January 19-23, 2013
San Juan, Puerto Rico
www.sccm.org

**American College of Cardiology ACC.13**
March 9-11, 2013
San Francisco, California
www.cardiosource.org

**International Society for Heart and Lung Transplantation 33rd Annual Meeting and Scientific Sessions**
April 24-27, 2013
Montréal, Québec, Canada
www.ishlt.org

**American Thoracic Society International Conference**
May 17-22, 2013
Philadelphia, Pennsylvania
www.thoracic.org

**European Respiratory Society Annual Congress 2013**
September 7-11, 2013
Barcelona, Spain
www.ersnet.org

**2013 PH Professional Network Symposium**
September 26-28, 2013
Arlington, Virginia
www.PHAssociation.org

**European Society of Intensive Care Medicine Annual Congress**
October 5-9, 2013
Paris, France
www.esicm.org

**CHEST 2013**
October 26-31, 2013
Chicago, Illinois
www.chestnut.org

**American Heart Association Scientific Sessions 2013**
November 16-20, 2013
Dallas, Texas
www.americanheart.org
LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%). Clinical worsening is defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape.1

LETAIRIS is contraindicated in pregnancy. Please see accompanying brief summary of full prescribing information, including boxed WARNING on the risk of serious birth defects.

Reference: 1. LETAIRIS [Prescribing Information]. Foster City, Calif: Gilead Sciences, Inc; February 2012.
Letairis® (ambrisentan) 5 mg and 10 mg Tablets, for oral use

brief summary of full prescribing information. See full prescribing information. Read it only.

**BOXED WARNING: CONTRAINDICATED IN PREGNANCY**

Do not administer Letairis to a pregnant woman because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see Contraindications). Pregnancy must therefore be excluded before the initiation of Letairis and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or Lng 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests (see Warnings and Precautions). Because of the risk of birth defects, Letairis is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Letairis Education and Access Program (LEAP). As a component of the Letairis REMS, prescribers, patients, and pharmacies must enroll in the program (see Warnings and Precautions).

INDICATIONS AND USAGE: Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (IPAH) or PAH associated with connective tissue disease (CTD).

**DOSAGE AND ADMINISTRATION:** Healthcare professionals who prescribe Letairis must enroll in the restricted program called LEAP and must comply with the required monitoring to ensure safe use of Letairis (see Warnings and Precautions). Adult Dosing: Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated. Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH). Women of Childbearing Potential: Initiate treatment with Letairis in women of childbearing potential only after a negative pregnancy test (see Contraindications, Warnings and Precautions).

**CONTRAINDICATIONS:** Pregnancy: Letairis may cause fetal harm when administered to a pregnant woman. Ambrisentan was teratogenic at oral doses of ≥5 mg/kg/day in rats and ≥7 mg/kg/day in rabbits; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hard and soft palate, malfunction of the heart and great vessels, and failure of formation of the thymus and thyroid. Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of Letairis in pregnant women. Letairis is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with Letairis and prevented during treatment and for one month after stopping treatment (see Dosage and Administration, Warnings and Precautions).

**WARNINGS AND PRECAUTIONS:** Letairis Education and Access Program (LEAP): Because of the risk of birth defects, Letairis is available only through a restricted program called the Letairis Education and Access Program (LEAP). Required components of LEAP: Healthcare professionals who prescribe Letairis must complete the LEAP Prescriber Enrollment and Agreement Form, enroll in the program, and comply with the REMS requirements. To receive Letairis, all patients must complete a patient enrollment form and be re-enrolled annually by their prescriber. For women of childbearing potential, (1) a pregnancy test must be ordered and reviewed by the prescriber prior to initiation of LETAIRIS treatment and monthly during treatment, (2) she must agree to be contacted prior to each shipment to confirm that a pregnancy test was completed, (3) she must agree to be counseled on the requirements of the REMS program and the risks of LETAIRIS, and (4) she must agree to be contacted by Glaxo if she becomes pregnant while on LETAIRIS or within 30 days of treatment discontinuation. Pharmacies that dispense Letairis must enroll in the program and agree to comply with the required monitoring to ensure safe use of Letairis as this effect has been seen consistently when it is administered to animals (see Contraindications, Warnings and Precautions). Further information is available at www.letairis.com or 1-866-644-LEAP (5327).

**Fluid Retention:** Peripheral edema is a known class effect of endothelin receptor antagonists, and also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg LETAIRIS compared to placebo (see Adverse Reactions). Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients. In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks of starting LETAIRIS. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure. If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as LETAIRIS or underlying heart failure, and the possible need for specific treatment or discontinuation of LETAIRIS therapy. Pulmonary Veno-occlusive Disease: If patients develop acute pulmonary edema during initiation of therapy with vasoconstricting agents such as LETAIRIS, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed LETAIRIS should be discontinued. Letairis is contraindicated in patients with pulmonary veno-occlusive disease. Letairis is contraindicated in patients with a prior history of LETAIRIS use, and for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for LETAIRIS (5%; 13/261 patients). During 12-week controlled clinical trials, the incidence of anemia was >3% in normal limit of ULN (0%) were 0% on LETAIRIS and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause. Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities: In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to anemia or thromboembolic events were treated with LETAIRIS. Prior elevations (e.g., angioedema, rash), nausea, and vomiting. Elevations of liver amiotransferases (ALT, AST) have been reported with LETAIRIS use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of amiotransferases, hepatotoxicity, and other types of liver failure (see Adverse Reactions).

**DRUG INTERACTIONS:** Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine (see Clinical Pharmacology).

**Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Safety data for LETAIRIS were obtained from two 12-week, placebo-controlled studies in patients with pulmonary arterial hypertension (PAH) (ARIES-1 and ARIES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily. The exposure to LETAIRIS in these studies ranged from 1 day to 4 years (n=48 for at least 6 months and n=343 for at least 1 year). In ARIES-1 and ARIES-2, a total of 261 patients received LETAIRIS at doses of 2.5, 5, or 10 mg once daily and 122 patients received placebo. The adverse reactions that occurred in >3% of patients receiving LETAIRIS but not receiving placebo are shown in Table 1.

<table>
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<tr>
<th>Table 1 Adverse Reactions with Placebo-Adjusted Rates &gt;3%</th>
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<td>Periph edema</td>
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<td>Nasal congestion</td>
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<td>Sinusitis</td>
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<td>Flushing</td>
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</table>

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent. Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<55 years) receiving LETAIRIS (19%, 29/150) or placebo (13%, 13/104), and was greater in elderly patients (>65 years) receiving LETAIRIS (29%; 16/55) compared to placebo (4%; 4/128). The results of such subgroup analyses must be interpreted cautiously. The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for LETAIRIS (25%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for LETAIRIS (5%; 13/261 patients). During 12-week controlled clinical trials, the incidence of anemia or thromboembolic elevations >3x upper limit of normal (ULN) were 0% on LETAIRIS and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause. Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities: In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to anemia or thromboembolic events were treated with LETAIRIS. Prior elevations (e.g., angioedema, rash), nausea, and vomiting. Elevations of liver amiotransferases (ALT, AST) have been reported with LETAIRIS use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of amiotransferases, hepatotoxicity, and other types of liver failure (see Adverse Reactions).
USE IN SPECIFIC POPULATIONS: Pregnancy Category X (see Contraindications). Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using acceptable methods of contraception. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS (ambrisentan) [see Warnings and Precautions]. Nursing Mothers: It is not known whether ambrisentan is excreted in human milk. Breastfeeding women receiving LETAIRIS are not recommended. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testis size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (low, mid, high dose, respectively) the maximum oral human dose of 10 mg on a mg/m² basis. Pediatric Use: Safety and effectiveness of LETAIRIS in pediatric patients have not been established. Geriatric Use: In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (age ≥65 years) showed less improvement in walk distances with LETAIRIS than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients. Renal Impairment: The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan [see Clinical Pharmacology]. Dose adjustment of LETAIRIS in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated. Hepatic Impairment: Pre-existing hepatic impairment: The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan [see Clinical Pharmacology]. LETAIRIS is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of LETAIRIS in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients. Elevation of Liver Transaminases: Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure [see Adverse Reactions]. In patients who develop hepatic impairment after LETAIRIS initiation, the cause of liver injury should be fully investigated. Discontinue LETAIRIS if aminotransferase elevations >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded. 

OVERDOSAGE: There is no experience with overdosage of LETAIRIS. The highest single dose of LETAIRIS administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdose could potentially result in hypotension that may require intervention.

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Medication Guide). LETAIRIS (Education and Access Program (LEAP); Advise the patient that LETAIRIS is available only through a restricted program called LEAP. As a component of LEAP, prescribers must review the contents of the LETAIRIS Medication Guide and the LETAIRIS Patient Enrollment Guide before initiating treatment with LETAIRIS. Inform the patient that LETAIRIS is available only from Certified Specialty Pharmacies enrolled in LEAP. Provide patients with a list of Certified Specialty Pharmacies. As a component of LEAP, Certified Specialty Pharmacies must provide a copy of the Medication Guide to patients or caregivers each time LETAIRIS is dispensed. Patients must be instructed to read the Medication Guide each time they receive LETAIRIS because new information may be available. In addition, Certified Specialty Pharmacies must contact patients before each shipment to confirm that the patient will be available to receive the LETAIRIS shipment, and, in the case of women of childbearing potential, to confirm that a pregnancy test has been completed. Patients must complete a patient enrollment form and be re-enrolled annually by their prescribers using the LEAP Patient Enrollment and Consent form to confirm that they understand the risks of LETAIRIS. Patients may be asked to participate in a survey to evaluate the effectiveness of LEAP. Pregnancy: Instruct patients that the risks associated with LETAIRIS include serious birth defects if used by pregnant women. Educate and counsel women of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception: one hormone method and one barrier method, or two barrier methods where one method is the male condom. Acceptable hormone methods include progesterone implants, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring. Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom. Partner’s vasectomy must be used along with a hormone method or a barrier method. Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure [see Boxed Warning, Contraindications]. Instruct patient to immediately contact their physician if they suspect they may be pregnant. Hematological Change: Patients should be advised of the importance of hemoglobin testing. Administration: Patients should be advised not to split, crush, or chew tablets. GS22-081-009

For detailed information, please see full prescribing information. To learn more: call 1-800-GILEAD-5 (Option 2) or visit www.letairis.com. Manufactured and marketed by: Gilead Sciences, Inc., Foster City, CA 94404, USA © 2013 Gilead Sciences, Inc. All rights reserved. ABS11631 February 2012. LETAIRIS is a registered trademark of Gilead Sciences, Inc. Gilead and the Gilead logo are trademarks of Gilead Sciences, Inc. Other brands noted herein are the property of their respective owners.

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- One-time use of PHA’s mailing list of medical professionals
- Advertising support through PHA’s publications and online communities
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- PHA staff to exhibit and/or speak at event (pending invitation and availability)

To partner with PHA in Building Medical Education in PH for your upcoming CME event, please contact 240-485-0776 or BME@PHAssociation.org.

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To view a full list of education opportunities for medical professionals, visit: www.PHAOnlineUniv.org/Calendar
INDICATION
Tyvaso is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

IMPORTANT SAFETY INFORMATION
- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System.
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants.
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8 such as gemfibrozil or inducers such as rifampin are added or withdrawn.
- Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women.
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope.

Adverse events
- The most common adverse events seen with Tyvaso in ≥4% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope.

STUDY DESIGN: TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients (N=125) with PAH who were receiving a stable dose of bosentan or sildenafil for 3 months before study initiation. Patients were administered either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Primary endpoint was change in 6MWD at 12 weeks. Secondary endpoints included time to clinical worsening, Borg dyspnea score, NYHA functional class, trough 6MWD at week 12 (obtained at least 4 hours after study drug administration), peak 6MWD at 6 weeks, quality of life as measured by the MLWHF questionnaire, and PAH signs and symptoms.

References:

For PAH (WHO Group 1) patients on oral monotherapy
ONLY inhaled prostacyclin analogue approved for 4x-daily dosing
Short treatment sessions: just 2 to 3 minutes each

Adverse events
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References:
BRIEF SUMMARY

The following is a brief summary of the full prescribing information for TYVASO® (treprostinil) Inhalation Solution. Please review the full prescribing information prior to prescribing TYVASO.

INDICATIONS AND USAGE
TYVASO is a prostanoyl vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

CONTRAINdications
None.

WARNINGS AND PRECAUTIONS

Patients with Pulmonary Disease or Pulmonary Infections–The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Risk of Symptomatic Hypotension–Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension.

Patients with Hepatic or Renal Insufficiency–Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

Risk of Bleeding–Since TYVASO inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

Effect of Other Drugs on Treprostinil–Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions:

• Decrease in systemic blood pressure — Bleeding

Adverse Reactions Identified in Clinical Trials–Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In a 12-week placebo-controlled study (TRUMP II) of 225 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions to TYVASO included: cough and throat irritation; headache; gastrointestinal effects; muscle, jaw or bone pain; flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

Table 1: Adverse Events in ≥4% of PAH Patients Receiving TYVASO and More Frequent* than Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TYVASO n = 115</th>
<th>Treatment n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>62 (54)</td>
<td>35 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (41)</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Throat Irritation/Pharyngolaryngeal Pain</td>
<td>29 (25)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (19)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Flushing</td>
<td>17 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (6)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*More than 3% greater than placebo

The safety of TYVASO was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial. Adverse Events Associated with Route of Administration–Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO); however, some of such studies have been conducted with orally (treprostinil diltetanolamine) and subcutaneously administered treprostinil (Remodulin®). Pharmacodynamics–Antithromtensive Agents or Other Vasodilators–Concomitant administration of TYVASO with diuretics, antithromtensive agents or other vasodilators may increase the risk of symptomatic hypotension. Anticoagulants–Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics–Bosentan–In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diltetanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed. Additionally, treprostinil does not inhibit cytochrome P450 (CYP) 2C8, 2C9, 2C19, 3A4 and 3A5. In a randomised study with an oral formulation of treprostinil (treprostinil diltetanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed. Effect of Cytochrome P450 Inhibitors and Inducers–In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2B1, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP3A4, and CYP3A. Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diltetanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both Cmax and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8. Effect of Other Drugs on Treprostinil–Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 mg/kg/min.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B–There are no adequate and well controlled studies with TYVASO in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Animal reproduction studies are not always predictive of human response; TYVASO should be used during pregnancy only if clearly needed.

Labor and Delivery–No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

Nursing Mothers–It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

Pediatric Use–Safety and effectiveness in pediatric patients have not been established. Clinical studies of TYVASO did not include patients younger than 18 years to determine whether they respond differently from older patients.

Geriatric Use–Clinical studies of TYVASO did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

Patients with Hepatic Insufficiency–Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptake slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency.

Patients with Renal Insufficiency–No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent.

OVERDOSE

In general, symptoms of overdose with TYVASO include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.
Helping a patient apply for Social Security Disability (SSD) benefits?

Get provider-specific tips at

PHA Online University:

www.PHAOnlineUniv.org/Insurance

You can also find:

- Templates to help you draft successful appeal letters
- A training video on PH for SSA adjudicators
- Webinars including “The Dish on Disability”

Quick Tip:
Review your patient’s work history for the past 15 years. They will likely be considered disabled if they cannot do the least strenuous job they’ve done in the past 15 years.

The Pulmonary Hypertension Association invites nurses, PAs, NPs and other health professionals to attend the

2013 PH Professional Network Symposium

The Power of Teamwork:
10 Years of Professional Collaboration in PAH

An educational and networking event for

PH-treated health professionals

September 26 – 28, 2013
Crystal Gateway Marriott
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2013 Symposium Highlights:

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- Be welcome to attend the **PH Professional Network Symposium**, where you can advance your PH knowledge, network with others in the field, and attend sessions by the foremost experts in PH care. CE credits available.

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Sometimes symptoms indicate asthma or COPD. But sometimes they don’t.

When learning to diagnose, doctors are taught that hoof beats suggest horses, not zebras. But a rare disease like pulmonary hypertension is like a zebra among horses.

Those expecting common diseases often overlook the zebras. As a result, many PH patients have been misdiagnosed repeatedly before getting the treatment they need. Even worse, almost three-quarters of patients have advanced PH by the time they are diagnosed.

The Pulmonary Hypertension Association is taking unprecedented action to change that. Our Sometimes it’s PH campaign promotes early diagnosis among primary and specialty care providers. Join us.

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Program Announcement:

New Application Deadline: June 12, 2013  
Resubmission Deadline: July 12, 2013  
New Application Deadline: October 12, 2013  
Resubmission Deadline: November 12, 2013

Pulmonary Hypertension Association (PHA)  
National Heart, Lung, and Blood Institute (NHLBI)

Jointly Sponsored

Mentored Clinical Scientist Development Award (K08) &  
Mentored Patient-Oriented Research Career Development Award (K23)

PURPOSE: K08
- To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
- To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
- To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
- To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

PURPOSE: K23
- To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
- To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
- To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
- To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

MECHANISM:
Awards in response to the program announcement will use the National Institutes of Health (NIH) K08 or the K23 mechanism.

FUNDING:*  
The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2013.

FOR MORE INFORMATION:  
Visit: www.PHAssociation.org/MedicalProfessionals/Research

* Restrictions apply. Please see complete announcement at the website listed above.