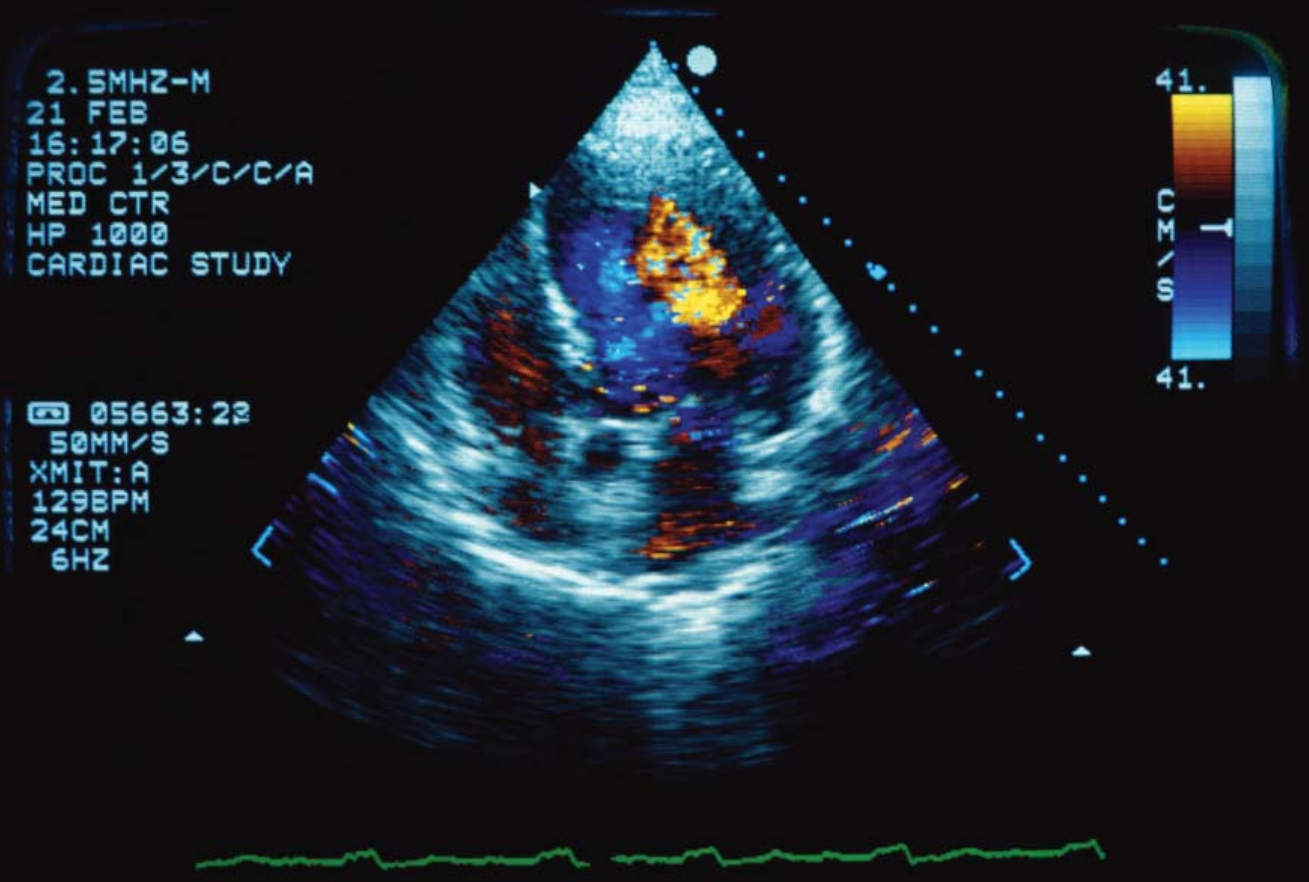
October 2009

Scleroderma Spectrum

a clinical newsletter for medical professionals



Inside This Issue:

Annual ECHO Screening for Pulmonary Hypertension in Scleroderma

SCLERODERMA FOUNDATION

Lowering Mortality in Systemic Sclerosis (Scleroderma)

The Importance of Annual ECHO Screening for Pulmonary Hypertension

Scleroderma and Pulmonary Arterial Hypertension: Call to Action

Pulmonary arterial hypertension (PAH) is one of the most debilitating and deadly conditions associated with scleroderma, yet it often goes undetected until it has significantly progressed in severity. Because of this dangerous and often silent comorbidity, physicians are recommended to screen every patient who has newly diagnosed or existing systemic sclerosis (SSc) with an echocardiogram to help identify mild to moderate PAH before patients display signs or symptoms. The early diagnosis of PAH through yearly screenings and initiation of treatment earlier in the course of the disease may improve the quality of life and extend survival for scleroderma patients. The earlier PAH is diagnosed in SSc patients, the better patients will respond to a variety of drug therapies approved to treat PAH.[1]

About Pulmonary Arterial Hypertension

PAH is defined as a mean pulmonary artery pressure (PAPm) $\geq$ 25 mm Hg with a pulmonary capillary wedge pressure $\leq$ 15 mm Hg measured by cardiac catheterization. It is a disorder that may occur either in the setting of a variety of underlying medical conditions or as a disease that uniquely affects the pulmonary circulation. Irrespective of its etiology, PAH is a serious and often progressive disorder that results in right ventricular dysfunction and impairment in activity tolerance, and may lead to right-heart failure and death. The pathogenesis of PAH is complex and incompletely understood, but includes both genetic and environmental factors that alter vascular structure and function.[2]

PAH is a common complication of SSc that significantly increases the chances of patient mortality. PAH is more common in patients with the limited form of SSc, formerly called CREST syndrome, while diffuse scleroderma is more often associated with pulmonary fibrosis.[3] Studies suggest seven of every twelve patients with SSc in the United States have or will develop PAH.[4] SSc patients who have an increased risk for developing PAH are postmenopausal females and those with more severe Raynaud's phenomena and digital ulcers.[5]

The Clinical Reality of PAH in Systemic Sclerosis

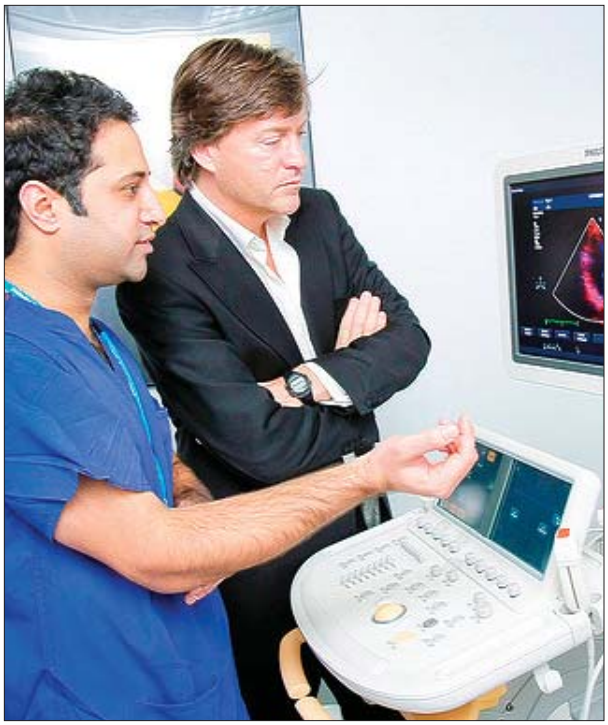
PAH is frequently misdiagnosed and has often progressed to an advanced stage by the time it is accurately diagnosed.[6] Because SSc compromises the function of one or more organ systems, patients tend to be treated primarily by rheumatologists and secondarily by specialists who treat their particular form of involvement, including cardiologists, nephrologists, gastroenterologists, pulmonologists, and dermatologists. With such a broad spectrum of healthcare professionals engaged in the treatment of SSc, a tremendous need exists to educate clinicians about the risks of PAH and the necessity for annual echocardiograms. In addition, healthcare professionals need to understand the importance of referring their patients to pulmonologists or cardiologists, preferably at specialized pulmonary hypertension centers to receive the proper screening for PAH.[7] Increasing awareness among targeted healthcare professionals about the need to screen for—and treat—PAH in its early stages can improve patient outcomes.[8]

Why Annual Screening is Critical for Patients with Systemic Sclerosis

PAH is the most common cause of death in patients with SSc.[9] Physicians should be aware that SSc patients can have significant pulmonary involvement from their disease before signs and symptoms of PAH appear. In a prospective and retrospective analysis of 50 community rheumatology practices, 13 percent of scleroderma patients had undiagnosed PAH. Eighty-five percent of these undiagnosed patients presented with symptoms suggesting late-stage disease.[10]

Dyspnea and decreased exercise tolerance appear to be the earliest and most common symptoms of PAH, but these symptoms are nonspecific with about 60 percent of scleroderma patients experiencing them as a result of a variety of conditions, including anemia, interstitial lung disease, heart failure, deconditioning, or PAH.[11] Annual screening with echocardiography offers the best opportunity to identify which patients may have PAH.

Patients with SSc also experience the worst outcomes of any category of patients with PAH, and scleroderma patients with PAH experience worse outcomes than scleroderma patients without PAH. Approximately 25 percent of all causes of death in one population of scleroderma patients was found to be pulmonary-related (PAH and/or pulmonary fibrosis).[12] In a retrospective study, 106 patients with scleroderma and PAH were matched against 106 patients without PAH in terms of scleroderma subtype, age of disease onset, disease



duration from initial visit, and date of initial visit. Results showed only 10 percent of patients with scleroderma and PAH survived five years, compared with 80 percent of scleroderma patients without PAH.[13]

Because the initial stage of PAH is often clinically silent without symptoms and because patients with SSc and PAH experience such poor outcomes, numerous medical organizations have urged over the past decade that screening be conducted at regular intervals.[14]

Screening and Diagnosing PAH in Patients with Systemic Sclerosis

Right-heart catheterization remains the gold standard for confirming a diagnosis of PAH, but the echocardiogram is the most practical and reliable noninvasive tool to survey for disease, with an estimated sensitivity of 90 percent.[15] Echo can show right ventricular hypertrophy and dysfunction, right heart chamber dilation, and paradoxical movement of the septum.

Because of the high prevalence of PAH among SSc patients, medical guidelines suggest annual echocardiograms and, if necessary, right-heart catheterizations to detect the condition as early as possible. Unfortunately, many healthcare professionals are not aware of the importance of annual screenings in improving outcomes.[16] Two-dimensional echocardiography with Doppler flow studies is the most useful imaging modality in patients with suspected PAH. If PAH is present, further evaluation may include assessment of oxygenation, high-resolution computed tomography of the chest, ventilation-perfusion lung scanning and cardiac catheterization.[17] ACCP Guidelines indicate that yearly pulmonary function testing should be done along with echocardiography as a screening tool because a disproportionate drop in DLCO out of proportion to FVC predicts who goes on to develop PH.

PAH is defined by using cardiac catheterization data showing either a resting mean pulmonary artery pressure (PAP) > 25 mmHg or an exercise-induced mean PAP > 30 mmHg with an associated pulmonary capillary or left atrial pressure < 15 mmHg.[18]

A consensus of expert opinion suggests that all patients with SSc should get an echocardiogram regardless of their symptoms and regardless of the suspicion of whether they have interstitial lung disease or PAH. Annual screening with echocardiography will provide a baseline of a patient's function. Waiting to perform diagnostic studies until patients develop dyspnea or edema will result in a cohort of patients who will be diagnosed with advanced heart failure.[19]

Functional Assessment: A Critical Tool for Patients with PAH

In 1998, the World Health Organization (WHO) convened a World Symposium on Primary Pulmonary Hypertension in Evian, France, to establish annual echocardiogram screening guidelines for patients with SSc and to revise the functional classification system for PAH, which is a critical element of patient assessment. Functional classification is strongly predictive of mortality, and is an important factor in the choice of PAH therapy.[21]

The WHO functional classification system recognizes the importance of near syncope and syncope in the symptom complex of these patients. Syncope is gener-

Major Signs and Symptoms

Most people with systemic sclerosis and PAH will not experience symptoms until their disease is advanced and prognosis is poor. The major symptoms in patients with moderate to severe PAH are dyspnea on exertion, fatigue, syncope, anginal chest pain, hemoptysis and Raynaud's phenomenon. Major signs are jugular vein distention, prominent right ventricular impulse, accentuated pulmonic valve component (P2), right-sided third heart sound (S3), tricuspid insufficiency murmur, hepatomegaly and peripheral edema.[20]

ally thought to carry a grave prognosis in patients with PAH. For this reason, PAH patients who have experienced a syncopal episode are generally assigned to WHO Functional Class IV (although this is not explicitly stated in the WHO functional classification system).[22]

Treating PAH in Patients with Systemic Sclerosis

PAH is a chronic and incurable disease, however, earlier diagnosis combined with new treatments can significantly improve the prognosis of patients with PAH. Recent data indicate that the length of survival is continuing to improve, with some patients able to manage the disorder for 15 to 20 years, or even longer. [24]

Treatment is divided into treating the underlying disease process and management of PAH sequelae. Managing complications of PAH include using diuretics to treat symptoms of volume overload and continuous oxygen therapy for patients with hypoxia. Anticoagulation, reported effective in idiopathic PAH (IPAH), is also recommended in scleroderma-associated PAH to prevent in situ thrombosis, but anticoagulation is often contraindicated due to the risk of gastrointestinal bleeding that frequently occurs in scleroderma patients.[25]

Cardiac catheterization can help guide treatment. During cardiac catheterization, patients with idiopathic PAH demonstrating an improvement in their pulmonary artery pressure following a vasodilator challenge, such as with inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol can benefit from long-term treatment with calcium channel blockers. Unfortunately, scleroderma patients rarely respond to this challenge, and treatment with calcium channel blockers has limited benefit. In recent years, other vasodilatory medications have proven helpful for managing scleroderma associated pulmonary arterial hypertension.[26]

In the past decade, there has been significant progress in the development of new therapies for the treatment of PAH.[27] Current treatment options fall into three categories: Endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclins:

- **Endothelin Receptor Antagonists**

  a) Bosentan and ambrisentan are oral endothelin receptor antagonists (ERA). ERAs are a class of drugs that prevent the constriction or narrowing of blood vessels thereby enhancing blood flow through the pulmonary circulation. Bosentan is currently approved for treatment of patients with Functional Class III and IV PAH, and ambrisentan is approved for the treatment of Class II and III patients. Oral ERA therapies are more easily administered than chronic intravenous epoprostenol or subcutaneously infused therapies. However, because of the potential for liver injury with ERAs, monthly blood tests are required while receiving treatment. Bosentan is likely to produce major birth defects if used by pregnant women. In order to prevent pregnancy, monthly pregnancy tests are required while taking ERAs. Other side effects of bosentan therapy may include headache, flushing, edema (fluid retention), and anemia. The most common side effect of ambrisentan is headache. Patients face the risk of developing liver function abnormalities on ERAs.[28]

- **Phosphodiesterase type 5 inhibitors**

  a) Sildenafil is approved as a three time a day oral PAH treatment. Sildenafil has been shown to improve exercise capacity, pulmonary artery pressure, and Functional Class in patients with PAH.

World Health Organization functional assessment classification[23]

Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Potential side effects include flushing, dyspepsia, visual changes, and nosebleeds. It is approved for Class II and III patients.

b) Tadalafil was approved in 2009 as a once-daily oral therapy for the treatment of PAH, and is indicated to improve exercise ability in Class II and III. Side effects include headache, stomach upset, back pain, muscle pain, nasal stuffiness, flushing, pain in arms or legs, dizziness, or vision change.

- **Prostacyclins**

  a) Epoprostenol is a potent vasodilator, given by a constant intravenous infusion. This requires an indwelling central venous catheter and an infusion pump. Clinical benefits in patients with PAH occurring in association with scleroderma include improvement in exercise capacity and hemodynamics. Common side effects of epoprostenol therapy include headache, flushing, jaw pain with initial chewing, diarrhea, and foot/bone pain. Other side effects include the potential for serious infection associated with the catheter. Chronic intravenous epoprostenol has been approved by the FDA for the treatment of patients in Functional Class III and IV PAH related to scleroderma.

  b) Treprostinil. Due to the complexity of chronic intravenous epoprostenol therapy, studies have since been undertaken with various analogues of prostacyclin being administered via the subcutaneous, oral, and inhaled routes. Continuous subcutaneous infusion of treprostinil resulted in a slight improvement in exercise capacity, which was greater in sicker patients, and was dose-related.[29] The use of subcutaneous treprostinil may often be limited by infusion site pain and redness. Intravenous treprostinil is approved by the FDA for treatment of patients in Functional Class II, III, and IV PAH. More recently the FDA approved an inhaled form of treprostinil to increase walk distance in patients with NYHA Class III symptoms associated with WHO Group I PAH, which includes multiple etiologies such as idiopathic and familial PAH as well as PAH associated with scleroderma and congenital heart disease.[30]

  c) Iloprost, a prostanoid medication delivered by inhalation 6–9 times per day, improved a composite measure of exercise capacity and Functional Class, in the absence of clinical deterioration or death. Inhaled iloprost has been approved by the FDA for treatment of patients with Functional Class III and IV PAH.

- **Combination Therapy**

  a) Today, many PAH patients are on combination therapy. For example, inhaled iloprost has been studied in patients who remain symptomatic while on stable bosentan therapy for at least three months.[31] There was a borderline significant improvement in exercise capacity, and improvement in Functional Class. Combination therapy appeared safe and well tolerated. The safety and efficacy of combination therapies have been examined in small studies, which found that prostanoids plus an endothelin receptor antagonist (bosentan) can improve hemodynamics, exercise capacity, and Functional Class in children and adults.[32] Combination therapy with prostacyclin analogues and the PDE5 inhibitor sildenafil also have shown positive results. One study showed sildenafil is a safe and effective rescue agent for waning clinical responses to inhaled iloprost.[33] Studies of sildenafil plus treprostinil and of sildenafil plus epoprostenol confirm the combination is well-tolerated, safe, and significantly improves 6-minute walk distance.[34]

Challenges and Considerations

PAH screening with echocardiography is considered standard of care for SSc patients based on American College of Chest Physicians guidelines, however, reimbursement will depend on the insurer. Physicians should forward as much supporting documentation/evidence to the insurance company as possible to support why this was the recommended screening.[35]

Conclusion

PAH is a common and serious disease in patients with SSc and it is a major cause of their deaths. A number of medical therapies are now approved and available for treating systemic scleroderma patients who are diagnosed with PAH. Because signs and symptoms of PAH often do not appear in patients until the disease is in advanced stages, physicians should follow recommendations to screen their scleroderma patients for PAH. Annual screening with an echocardiogram can identify patients with mild to moderate PAH. Providing medical treatment for PAH earlier in the course of its development may improve the patient's quality of life and may reduce the risk of mortality.

[1] Galie N, et al, Lancet (2008); 371:2093-2100

[2] Badesch, David B, MD, FCCP, et al, (2007). "Medical Therapy for Pulmonary Arterial Hypertension: Updated ACCP Evidence-Based Clinical Practice Guidelines." *Chest*, June 2007; Volume 131 No. 6. Retrieved from http://www.chestjournal.org/content/131/6/1917.full?sid=0abc21d6-019d-4cbb-aa6c-c047b2ec20dd

[3] http://www.scleroderma.org/medical/pulmonary_articles/Preston2006-1.shtm

[4] Scleroderma Foundation Fact Sheet; Haculla E, et al, Arth & Rheum, 2005; Mukerjee D, et al, Ann Rheum 2003; Mukerjee D, et al, Rheum 2004.

[5] http://www.scleroderma.org/medical/pulmonary_articles/Preston2006-1.shtm

[6] Pulmonary Hypertension Association. What is PH? Retrieved from http://www.phassociation.org/learn/what-is-PH/

[7] Scleroderma Foundation (2008). The Echo Campaign: A Pulmonary Arterial Hypertension (PAH) Physician Outreach and Education Program. Retrieved from http://www.echossc.org/SDFLib001.html

[8] Galie N, et al (2008). "Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial." *Lancet* 2008; 371:2093-2100

[9] Pulmonary Hypertension Association (2008). Virginia D. Steen, MD: "Pushing the Envelope of Research, Redefining the Link Between Scleroderma and PAH." *Advances in Pulmonary Hypertension*, Volume 7 No. 2. Retrieved from http://www.phassociation.org/Medical/Advances_in_PH/summer2008/ProfileVirginiaSteen.pdf; Shanahan, Joseph C. MD, (2007). "Early Diagnosis of PAH in Systemic Sclerosis: How Do We Recognize the Warning Signs?" Retrieved from http://cme.medscape.com/viewarticle/549601_2

[10] Wigley Frederick MD, et al (2005). "The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary healthcare level of community-based rheumatologists (the UNCOVER study)." *Arthritis Rheum*. 2005;52:2125–32. Retrieved from http://www.tracleer.com/default.asp?page=AtRisk_Uncover

[11] Wigley, Frederick MD, Nanda, Shikha MD, Bsc (2005). Scleroderma and Pulmonary Arterial Hypertension: Definition. Retrieved from http://cme.medscape.com/viewarticle/501603_2

[12] Steen V. (2004). "Changes in causes of death in systemic sclerosis over the past 30 years." Program and abstracts of the American College of Rheumatology 68th Annual Scientific Meeting; October 16-21, 2004; San Antonio, Texas. Abstract 1052. Retrieved from http://cme.medscape.com/viewarticle/501603_6)

[13] Hachulla E, Coghlan JG. (2004) "A new era in the management of pulmonary arterial hypertension related to scleroderma: endothelin receptor antagonism." *Ann Rheum Dis.* 2004;63:1009-1014. Retrieved from http://cme.medscape.com/viewarticle/501603_6)

[14] Wigley, Frederick MD (2005). Scleroderma and Pulmonary Arterial Hypertension:Clinical Presentation. Retrieved from http://cme.medscape.com/viewarticle/501603_4

[15] Denton CP, et al (1997). "Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis." *Br J Rheumatol*. 1997;36:239-243.

[16] Scleroderma Foundation (2008). The Echo Campaign: A Pulmonary Arterial Hypertension (PAH) Physician Outreach and Education Program. Echo Campaign Fact Sheet

[17] Nauser, Trenton D MD and Stites, Steven W MD (2001). "Diagnosis and Treatment of Pulmonary Hypertension." *American Family Physician* 2001;63:1789-98,1800. Retrieved From http://www.aafp.org/afp/20010501/1789.html

[18] Wigley, Frederick MD, Nanda, Shikha MD, Bsc (2005). Scleroderma and Pulmonary Arterial Hypertension: Definition. Retrieved from http://cme.medscape.com/viewarticle/501603_2

[19] Shanahan, Joseph C. MD, (2007). "Early Diagnosis of PAH in Systemic Sclerosis: How Do We Recognize the Warning Signs?" Retrieved from http://cme.medscape.com/viewarticle/549601_2

[20] Nauser, Trenton D MD and Stites, Steven W MD (2001). "Diagnosis and Treatment of Pulmonary Hypertension." *American Family Physician* 2001;63:1789-98,1800. Retrieved From http://www.aafp.org/afp/20010501/1789.html

[21, 22, 23] Mathier, Michael A. MD FACC (2006). "The Classification of Pulmonary Arterial Hypertension." Retrieved from http://cme.medscape.com/viewarticle/544175

[24] Pulmonary Hypertension Association. What is PH? Retrieved from http://www.phassociation.org/learn/what-is-PH/

[25] Wigley, Frederick MD, Nanda, Shikha MD, Bsc (2005). "Scleroderma and Pulmonary Arterial Hypertension: Treatment." Retrieved from http://cme.medscape.com/viewarticle/501603_7

[26] Wigley, Frederick MD, Nanda, Shikha MD, Bsc (2005). "Scleroderma and Pulmonary Arterial Hypertension: Treatment." Retrieved from http://cme.medscape.com/viewarticle/501603_7

[27] Scleroderma Foundation (2008). Pulmonary Hypertension. Retrieved from http://www.scleroderma.org/pdf/Medical_Brochures/Pulmonary.pdf

[28] AHFS Drug Information (2009) Ambrisentan. American Society of Health-System Pharmacists. Retrieved from http://www.ahfsdrug-information.com/

[29] Simonneau, G et al, *Am J Resp Crit Care Med*, 2002; 165:800-804 & Oudiz R, et al, *Chest* 2004; 126:420-427.

[30] United Therapeutics Corporation (2009) "FDA Approves TYVASO (Treprostinil) Inhalation Solution for the Treatment of Pulmonary Arterial Hypertension" [Press Release] Retrieved from ttp://news.prnewswire.com/ViewContent.aspx?ACCT=109&STORY=/www/story/07-30-2009/0005069209&EDATE=

[31] Park, Myung H. MD FACC (2008). "Using Combination Therapies in the Treatment of Pulmonary Arterial Hypertension: What's on the Horizon?" Retrieved from http://cme.medscape.com/viewarticle/576212

[32] *Eur Respir J*. 2004;24:353-359; *J Am Coll Cardiol*. 2005;46:697-704

[33] *J Am Coll Cardiol.* 2003;42:158-164

[34] Simonneau, G. et al(2005). *Am J Cardiol.* 2005;96:1334-1336; *Ann Intern Med.* 2008;149:521-530.

[35] *Chest* 2004;126;4S-6S

This is a publication of the Scleroderma Foundation and is made possible by an unrestricted educational grant from Pfizer, Inc.

The Scleroderma Foundation Physician Membership Program

Helping physicians and academics keep in touch with what is happening in scleroderma research.

Due to increasing interest and an ever-widening field of inquiry in scleroderma research, the Scleroderma Foundation has created a Physician Membership Program (PMP).

"It was not many years ago that scleroderma research was being done by a relatively small group of investigators," said Dr. John Varga, the Chair of the Scleroderma Foundation Medical Advisory Board. "Today, however, we see advances in scleroderma and diseases related to it spreading over an increasingly wide area. Along with progress comes change. It is more difficult to stay in touch with studies and research than ever before."

The PMP is meant to help researchers and clinicians by providing a one-stop shop where they can learn the latest about what is happening with scleroderma treatment and research in addition to having access to a wide variety of resources.

The PMP is helpful to doctors who specialize in several fields that overlap with the symptoms of scleroderma. These fields include rheumatology, dermatology, gastroenterology, pulmonologists, pediatricians, and family practitioners.

Physician members receive articles, pamphlets and Scleroderma Information Packets at no charge; a complete listing on the Physician Member section of the Foundation's high visibility Web site; discounts for the national patient conference and special events; periodic eLetter updates about new or advancing research; and five copies of our quarterly magazine, the *Scleroderma Voice*.

Physician Membership Program Application Form

Name (with suffixes): _____

Title: _____

Institutional Affiliation: _____

Professional Address: _____

City: _____

State: _____

ZIP Code: _____

Areas of Medical Specialty: _____

_____

Office Phone: _____

Fax: _____

E-mail: _____

Web site/Homepage: _____

Board Certification(s): _____

☐ I do not wish to be listed in the Physician Member section of your Web site.

Domestic physician membership in the Scleroderma Foundation is $150 annually. International membership is $200 U.S. annually. This fee provides members with the benefits described in the Physician Membership brochure and other benefits that may be added in the future. The Scleroderma Foundation is a U.S. 501(c)3 nonprofit organization. As such your membership fee is tax deductible to the full amount permitted by U.S. law.

Method of Payment

☐ Check enclosed. Please make checks payable to Scleroderma Foundation PMP

☐ Credit Card (circle one)
Visa Mastercard AMEX

Account Number:

|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|

Expiration Date: _____

Signature: _____

Please tear off this flap and mail to the Scleroderma Foundation, 300 Rosewood Drive, Suite 105, Danvers, MA 01923.

SCLERODERMA FOUNDATION
SUPPORT · EDUCATION · RESEARCH

300 Rosewood Drive
Suite 105
Danvers, MA 01923

ADDRESS SERVICE REQUESTED

NON PROFIT ORG.
U.S. POSTAGE
PAID
BOSTON, MA
PERMIT NO. 54162

Scleroderma Foundation
300 Rosewood Drive
Suite 105
Danvers, MA 01923
800-722-HOPE
www.scleroderma.org
www.echossc.org