

PULMONARY HYPERTENSION IN SCLERODERMA



**SCLERODERMA
FOUNDATION**

SUPPORT • EDUCATION • RESEARCH

PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is high blood pressure in the blood vessels of the lungs. If the high blood pressure in the lungs is due to narrowing of the pulmonary arteries, it is known as pulmonary arterial hypertension (PAH). When the blood pressure inside the pulmonary vessels is high, the right side of the heart has to pump harder to move blood into the lungs to pick up oxygen. This can lead to failure of the right side of the heart. Patients with scleroderma are at increased risk for developing PH from several mechanisms. Frequently patients with scleroderma have multiple causes of their PH.

Patients with limited cutaneous scleroderma (formerly known as CREST syndrome) are more likely to have PAH than those patients with diffuse cutaneous systemic sclerosis. It is not known what causes PAH in this group of patients. It may be the same processes that cause damage to small blood vessels in the systemic circulation. The lining cells of the blood vessels (endothelial cells) are injured and excessive material is laid down inside the blood vessel walls. The muscle that constricts the blood vessel may overgrow and narrow the blood vessel.

Other scleroderma patients have PH because they have significant scarring. This reduces the blood oxygen level, which in turn, may cause a reflex increase in blood pressure in the pulmonary arteries.

WHAT ARE THE SYMPTOMS OF PH?

Patients with mild PH may have no symptoms. Patients with moderate or severe PH usually notice shortness of breath (dyspnea), especially with exercise. Patients may also notice unusual chest pains and symptoms of right-sided heart failure, such as worsening shortness of breath and swelling of the feet and legs. Other symptoms that patients cite include a cough, light headedness or fainting, palpitations (heart racing or fluttering), and swelling.

WHAT TESTS MIGHT BE DONE TO DIAGNOSE PH?

In a patient with scleroderma, the development of unexplained shortness of breath should lead to consideration of possible PH.

A laboratory clue that a patient might have PH is a reduced diffusing capacity (DLCO) on pulmonary function tests (PFTs). The diffusing capacity measures the ability of gas to move from the air, across the lung tissue and blood vessel wall, into the blood. In the absence of interstitial lung disease (ILD), if the diffusing capacity is less than 50 percent of its predicted value, this is a clue that PH may be present. The test most commonly used to diagnose PH is the echocardiogram. It can estimate the pulmonary artery pressure fairly well in most patients in a noninvasive manner.

The physician may order a cardiac catheterization to measure the actual pressure in the pulmonary arteries. This invasive test is done to more accurately measure the pressures in the lung blood vessels; to assess the blood flow generated by the heart (the cardiac output); to exclude an underlying leak or shunt contributing to the PH; to assess the function of the left side of the heart; and possibly to assess the patient's responsiveness to vasodilator therapy. The results of this test may change the therapy prescribed by the physician.

An exercise test known as the six-minute walk test is often helpful in assessing exercise capacity in patients with PH. In addition, a Functional Class is often assigned to patients based on their activity tolerance, ranging from Class I to IV (with I being mildest and IV the most severe).

WHAT IS THE TYPICAL COURSE OF PAH IN SCLERODERMA?

It was previously thought that the development of PAH in patients with scleroderma was always associated with a poor prognosis. However, ongoing educational efforts regarding the risk of PAH in scleroderma has led to earlier diagnosis. Within the last few years, the echocardiogram has been widely used to identify mild or moderate PAH in scleroderma patients.

The natural course of mild or moderate PAH in

scleroderma patients is unknown. It is possible that mild or moderate PAH will persist unchanged for long periods of time. However, if a patient develops severe PAH and right-sided heart failure, the prognosis may be poor.

WHAT IS THE TREATMENT OF PAH?

Supplemental oxygen, anticoagulation (blood thinners), and diuretics are often important parts of treatment for PAH. If the oxygen level at rest, with exercise, or during sleep is low, home oxygen therapy may be given. The decision to treat with anticoagulation is made on an individual basis by the patient and their physician, based on the potential risk of bleeding.

Calcium channel blockers (such as diltiazem, nifedipine, or amlodipine) can help a small proportion/percentage of patients. Such treatment is successful in only a minority of scleroderma patients with PAH.

PAH SPECIFIC MEDICATIONS

The past decade has seen seven new drugs for treating PAH: epoprostenol (Flolan®), treprostinil (Remodulin®), bosentan (Tracleer®), ambrisentan (Letairis®), sildenafil (Revatio®), iloprost (Ventavis®), and tadalafil (Adcirca®). Each will be briefly reviewed below. Additional drugs have been approved in other countries and are pending approval by the FDA for usage in the U.S.

Epoprostenol

Epoprostenol (Flolan®) is a potent vasodilator, which must be given by a constant intravenous infusion. This requires an indwelling central venous catheter and an infusion pump. In a multicenter, randomized, controlled clinical trial of chronic intravenous epoprostenol, in patients with PAH occurring in association with scleroderma, there was improvement in exercise capacity and hemodynamics. A survival benefit was not seen in this population over the period of study, but the study was not designed to detect a difference in survival. 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.

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 (under the skin), oral, and inhaled routes. Continuous subcutaneous infusion of treprostinil (Remodulin®) resulted in a slight improvement in exercise capacity, which was greater in sicker patients, and was dose-related. The use of subcutaneous treprostinil may be limited, often by infusion site pain and redness. Treprostinil has more recently been approved by the FDA for intravenous delivery, and the drug is approved for the treatment of patients in Functional Class II, III, and IV PAH.

Bosentan

Endothelin receptor antagonists (ERAs) have recently garnered attention in the treatment of PAH. Bosentan (Tracleer®) is an oral endothelin receptor antagonist. In a pilot study, bosentan was shown to improve exercise capacity and cardio-pulmonary hemodynamics in patients with Functional Class III and IV PAH. A larger international study (the BREATHE-1 study) confirmed improvement in exercise capacity and showed a reduction in clinical worsening. While oral bosentan therapy is clearly simpler than chronic intravenous epoprostenol or subcutaneously infused treprostinil, there is a potential for liver injury with bosentan, and monthly blood tests are required while receiving treatment. Bosentan is likely to produce major birth defects if used by pregnant women. Pregnancy must be prevented, and monthly pregnancy tests are required while taking bosentan.

Ambrisentan

Ambrisentan (Letairis®), like bosentan, is a FDA-approved ERA treatment for patients with pulmonary arterial hypertension. To be taken once daily for patients in Functional Class II or III, this drug

has shown improvement in exercise capacity and reduction of clinical worsening. Similar to bosentan, ambrisentan should not be taken by pregnant women, or women thinking of becoming pregnant. Other side effects may include edema and nasal congestion.

Sildenafil

Sildenafil was previously approved for the treatment of erectile dysfunction under the trade name of Viagra®. It has now been approved for the treatment of PAH as well, under the trade name of Revatio®. Sildenafil has been shown to improve exercise capacity, pulmonary artery pressure, and Functional Class in patients with PAH. Potential side effects include flushing, dyspepsia, visual changes, and nosebleeds.

Tadalafil

Tadalafil (Adcirca®) was approved in 2009 as a once-daily oral therapy for the treatment of PAH, and is indicated to improve exercise ability in WHO Group I (World Health Organization). Side effects include headache, stomach upset, back pain, muscle pain, stuffy or congested nose, flushing, pain in arms or legs, or vision change.

Iloprost

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. More recently, inhaled iloprost has been studied in patients who remain symptomatic while on stable bosentan therapy for at least three months. There was a borderline significant improvement in exercise capacity, and improvement in Functional Class. Combination therapy appeared to be safe and well tolerated. Inhaled iloprost has been approved by the FDA for treatment of patients with Functional Class III and IV PAH.

LUNG TRANSPLANTATION

Lung transplantation is reserved for patients with severe PH who do not respond to aggressive medical therapy. Due to the relatively high operative and perioperative risks, as well as the significant

long-term risks of infection and rejection, lung transplantation should not be considered as first-line therapy or a cure for PH. Whether single-lung, bilateral-lung, or heart-lung transplantation is the procedure of choice is still the subject of controversy. Some experts tend to prefer bilateral-lung transplantation for patients with PH, and reserve heart-lung transplantation for patients with PH occurring in association with uncorrectable congenital heart disease, or patients having significant left ventricular dysfunction or valvular disease. Not all patients are suitable candidates for lung transplantation. Gastroesophageal reflux disease (GERD), or esophageal dysmotility occurs frequently in scleroderma, and may be a reason not to attempt lung transplantation due to the risk of aspiration.

PUTTING IT ALL TOGETHER

Pulmonary hypertension is not the only type of lung disease that can occur in association with scleroderma. Interstitial lung disease (ILD), also called pulmonary fibrosis, is another serious complication. Please contact the Scleroderma Foundation for information on pulmonary fibrosis.

It is important to note that patients can have significant pulmonary involvement from their scleroderma before signs and symptoms appear. Therefore, it is important to have routine screening for possible pulmonary involvement, in particular pulmonary arterial hypertension and interstitial lung disease.

Due to the complexity of the diagnosis and treatment of scleroderma lung disease, strong consideration should be given to referral of patients to physicians with expertise in scleroderma, interstitial lung disease, and PH. This requires close collaboration between you, your rheumatologist, pulmonologist, and cardiologist.

Please note that this brochure is provided for educational purposes only. It is not intended to substitute for informed medical advice.

The Scleroderma Foundation wishes to thank Kristin Highland, M.D., Richard Silver, M.D., and David Badesh, M.D., for their input on this brochure.

BECOME A MEMBER OF THE SCLERODERMA FOUNDATION

When you become a member of the Scleroderma Foundation, you support the organization's mission of support, education and research. Your donation helps pay for programs in each of those three areas, including:



- Funding an average of \$1 million in original research grants awarded to investigators annually.
- Helping patients and their families cope with scleroderma through mutual support groups, physician referrals and the National Patient Education Conference.
- Promoting public education of the disease through publications, seminars, patient education events and publicity campaigns.

As a member of the Scleroderma Foundation, you will receive:

- Our quarterly magazine, the "Scleroderma VOICE." The magazine includes updates on the latest scleroderma research and treatments, positive and uplifting stories from patients living with the disease; and tips about how to manage living with scleroderma.
- Information and educational offerings from your local chapter.
- Discounted registration fees to the annual National Patient Education Conference.

Please consider joining the Scleroderma Foundation today. A membership form is attached on the reverse side of this panel.

To become a member of the Scleroderma Foundation, fill out this form, tear at perforation and send with your check or credit card information to:

Scleroderma Foundation
Attn: Donations
300 Rosewood Drive, Suite 105
Danvers, MA 01923

I would like to become a member and help support the Scleroderma Foundation's efforts to improve the lives of those with scleroderma, and to assist in the search for a cause and cure. Enclosed please find my check (or credit card information) in the amount of \$_____.

Donations of \$25 or more can be acknowledged as members (\$35 or more for international members).

- I am not interested in members benefits.
- However, I would like to make a contribution in the amount of \$_____.

Name: _____

Address: _____

City: _____

State/ZIP: _____

Country: _____

Telephone: _____

Email: _____

Credit Card: _____

Credit Card No.: _____

(Circle One:   )

Exp. Date: _____

Name on Card: _____

OUR THREE-FOLD MISSION IS SUPPORT, EDUCATION AND RESEARCH

Support: To help patients and their families cope with scleroderma through mutual support programs, peer counseling, physician referrals, and educational information.

Education: To promote public awareness and education through patient and health professional seminars, literature, and publicity campaigns.

Research: To stimulate and support research to improve treatment and ultimately find the cause of and cure for scleroderma and related diseases.



Funding for this brochure was provided by an unrestricted educational grant from Actelion Pharmaceuticals USA, Inc.



Rev. 2

A publication of
Scleroderma Foundation
300 Rosewood Drive, Suite 105
Danvers, MA 01923

800-722-HOPE (4673)

www.scleroderma.org

 www.facebook.com/sclerodermaUS

 www.twitter.com/scleroderma