SCLERODERMA FOUNDATION

SUPPORT · EDUCATION · RESEARCH

Dear Friend,

Thank you for your recent inquiry about scleroderma. Our goal is to provide the most up-to-date information available. In addition to providing resources designed to give you a better understanding of scleroderma, we also strive to provide strategies for coping challenges scleroderma causes. As you begin to learn more about scleroderma, it is important to know that its symptoms and the severity of the disease vary greatly from person to person.

Become a Member

You don't have to face scleroderma alone! Becoming a member of the Scleroderma Foundation connects you to a nation-wide family dedicated to supporting those affected by this disease. Together, we are working to find a cure. Membership also ensures that you receive our quarterly magazine, the *Scleroderma Voice*, which contains current and information important to the scleroderma community. In addition, the magazine frequently features news about support groups, patient education programs, physician referrals, peer counseling and much more. Please take a moment to fill out and return the enclosed membership form. Don't miss out on the benefits of membership!

What's Happening in Your Local Area?

The Scleroderma Foundation has a nation-wide network of chapters and support groups that offers numerous opportunities that may be of interest to you. Throughout the country, our chapters and support groups provide educational programs to learn more about the disease; networking opportunities with others affected by scleroderma; events to raise awareness about scleroderma; and ways to raise money to fund some of the most promising scleroderma-related research. You'll find a list of chapters and support groups enclosed. If you live in an area served by a chapter or support group, we urge you to contact them to learn what's happening in your community.

We Are Here for You

We hope that you'll join us in supporting those living with this disease. Whether membership is or isn't your thing, donating to the Scleroderma Foundation contributes to the search for a cure. We encourage you to contact the national office or any of our chapters if we can be of assistance. Much more about the Scleroderma Foundation and the disease can be found at www.scleroderma.org. We believe that you'll find it a valuable resource.

The Scleroderma Foundation is a national support system dedicated to helping each other—and working toward the day when a cure is found. Please join us!

Sincerely yours,

Mary J. Wheatley, IOM, CAE
Chief Executive Officer

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Scleroderma Facts

- Scleroderma is an autoimmune disease with symptoms that may include sensitivity to cold in extremities, thickening of the skin, shortness of breath, difficulty swallowing, joint stiffness and pain and damage to internal organs.
- Autoimmune diseases, which affect more than 50 million Americans, are the third leading cause of death in the United States.
- 300,000 cases of scleroderma are estimated in the United States.
- 80% of scleroderma patients are female.
- Scleroderma typically strikes between the ages of 25 and 55.
- 95% of scleroderma cases begin with Raynaud Phenomenon (hands and feet abnormally sensitive to cold).
- Federal funding for scleroderma research lags behind funding for other diseases of similar prevalence.
- Misdiagnosis is common. It can take three years or more for an individual to be diagnosed and to receive appropriate treatment.
- Medical professionals often lack familiarity with scleroderma or that symptoms may be directly associated with the disease.

The Scleroderma Foundation is here to help!

- The Scleroderma Foundation is a 501(c) (3) national nonprofit organization serving the interests of those affected by scleroderma. The foundation's 20 chapters and more than 160 support groups nationwide help carry out its three-fold mission of support, education and research. The Scleroderma Foundation is the leading nonprofit support of scleroderma research.
- The Scleroderma Foundation has granted more than 20 million in research grants since 1989 and consistently funds a minimum of $1 million in new grants annually.

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Serves New York, Connecticut, Northern New Jersey area

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Visit our online discussion board, please go to:
www.inspire.com/scleroderma-foundation

SCLERODERMA: OVERVIEW AND CAUSES

SCLERODERMA FOUNDATION

SUPPORT · EDUCATION · RESEARCH

SCLERODERMA OVERVIEW

Introduction

Scleroderma is an autoimmune disease which means that it is a condition in which the body's immune system attacks its own tissues. The normal role of the immune system is to provide protection from outside invaders such as bacteria and viruses. In autoimmune disorders, this ability to distinguish foreign from self is compromised. As immune cells attack the body's own tissue, inflammation and damage result. Scleroderma (the name means "hard skin") can vary a great deal in terms of severity. For some, it is a mild condition; for others it can be life-threatening. Although there are medications to slow down disease progression and help with symptoms, right now there is no cure for scleroderma.

TYPES OF SCLERODERMA

There are two main forms of scleroderma: systemic (systemic sclerosis, SSc) that usually affects the internal organs or internal systems of the body as well as the skin, and localized that affects a local area of skin either in patches (morphea) or in a line down an arm or leg (linear scleroderma), or as a line down the forehead (scleroderma en coup de sabre). It is very unusual for localized scleroderma to develop into the systemic form.

SYSTEMIC SCLEROSIS (SSc)

To make matters more confusing, there are two major types of systemic sclerosis or SSc: limited cutaneous SSc and diffuse cutaneous SSc. The difference between limited cutaneous and diffuse cutaneous SSc is the extent of skin involvement. In limited SSc, skin thickening only involves the hands and forearms, lower legs and feet. In diffuse cutaneous disease, the hands, forearms, upper arms, thighs, or trunk are affected. The face can be affected in both forms. The importance of making the distinction between limited and diffuse disease is that the extent of skin involvement tends to reflect the degree of internal organ involvement.

Systemic Sclerosis sine (without) skin thickening refers to the unusual occurrence (only about 5% of all cases) in which there is evidence of internal organ complications of SSc but no skin thickening.

Several clinical features occur in both limited and diffuse cutaneous SSc. Raynaud phenomenon, for example, occurs in both. Raynaud phenomenon is a condition in which the fingers turn pale or blue upon cold exposure, and then become ruddy or red upon warming up usually associated with a numb or tingling sensation in the fingers. These episodes are caused by a spasm of the small blood vessels in the fingers. As time goes on, these small blood vessels become damaged to the point that they may become totally blocked. This can lead to ulcerations of the fingertips. Raynaud phenomenon occurs in almost all (95%) SSc patients with either limited or diffuse disease, and painful finger ulcers can also be seen in both forms.

The esophagus is also affected in almost all SSc patients with loss of the usual movement. As a result, food can "hang up" in the esophagus, and stomach acid can reflux back up into the esophagus, causing heartburn.

Telangiectasias are small red spots that appear on the hands, arms, face, and/or trunk. These are tiny blood vessels in the skin that have widened. They are usually not dangerous in themselves, but are cosmetically unpleasing, particularly if they occur on the face. Some people have telangiectasias in the esophagus, stomach, and bowel that can be a source of bleeding.

People with the diffuse form of SSc are at a greater risk of developing pulmonary fibrosis (scar tissue in the lungs that interferes with breathing, also called interstitial lung disease), kidney disease, and bowel disease.

All patients with SSc should have periodic pulmonary function tests to monitor for the development of pulmonary fibrosis. Symptoms of pulmonary disease include a dry cough and shortness of breath. However, in the early stages there may not be any symptoms at all.

Kidney involvement occurs more frequently in the diffuse than in the limited form of SSc, especially in the first five years after disease onset, and typically takes the form of a sudden increase in blood pressure. As is the case with usual high blood pressure, there are no symptoms at first. However, if undetected and untreated, this high blood pressure can damage the kidneys in a matter of weeks, which is why it is called scleroderma renal crisis. The key to management and prevention of permanent kidney damage is early detection and treatment of high blood pressure with a class of medications called ACE inhibitors.

The risk of extensive gut involvement, with slowing of the movement or motility of the stomach and bowel, is higher in those with diffuse rather than limited SSc. Symptoms include feeling bloated after eating, diarrhea, or alternating diarrhea and constipation.

Calcinosis refers to the presence of calcium deposits in, or just under, the skin. This takes the form of firm nodules or lumps that tend to occur on the fingers or forearms, but can occur anywhere on the body. These calcium deposits can sometimes break out to the skin surface and drain whitish material (described as having the consistency of toothpaste).

Pulmonary hypertension (PH) is high blood pressure in the blood vessels of the lungs. It is totally independent of the usual blood pressure that is taken in the arm. This tends to develop in patients with limited SSc after several years of disease. The most common symptom is shortness of breath on exertion. However, several tests need to be done to determine if PH is the real culprit. If the ultrasound of the heart, called an echocardiogram, is abnormal, then a right heart catheterization should be done to actually measure the pressure in the lung blood vessel (pulmonary artery) and to test for other abnormalities that can cause PH. Because there are now many medications to treat PH, the earlier it is detected and treated, the better the result will be.

LOCALIZED SCLERODERMA

Localized scleroderma is almost always a purely skin condition, and is virtually never associated with the severe and potentially life threatening complications of SSc.

Morphea

Morphea consists of patches of thickened skin that can vary from half an inch to six inches or more in diameter. Some people have only one or a few such patches, while others have multiple ones all over the body. The patches can be lighter or darker than the surrounding skin and thus tend to stand out. Also there is usually a loss of the fatty layer underneath the morphea spots. Morphea, as well as the other forms of localized scleroderma, does not affect internal organs.

Linear scleroderma

Linear scleroderma consists of a line of thickened skin down an arm or leg on one side. The fatty layer under

the skin can be lost, so the affected limb is thinner than the other one. In growing children, the affected arm or leg can be shorter than the other.

Scleroderma en coup de sabre

Scleroderma en coup de sabre is a form of linear scleroderma in which the line of skin thickening occurs on the forehead or elsewhere on the face. In growing children, both linear scleroderma and en coup de sabre can result in distortion of the growing limb or lack of symmetry of both sides of the face.

WHAT CAUSES SCLERODERMA?

The cause of scleroderma is unknown. However, we do understand a great deal about the biological processes involved. In localized scleroderma, the underlying problem is the overproduction of collagen (scar tissue) in the involved areas of skin. In systemic sclerosis, there are three processes at work: blood vessel abnormalities, fibrosis (which is overproduction of collagen) and immune system dysfunction, or autoimmunity.

In systemic sclerosis, the small blood vessels are damaged and become narrowed. This is what is responsible for Raynaud phenomenon and the painful ulcers that can occur on the fingers. This vascular damage also occurs in the internal organs and is responsible for scleroderma renal crisis and PH.

The small arteries are normally capable of constricting (narrowing) or dilating (relaxing) to adjust blood flow to the needs of the body. For example, in very cold weather the blood vessels to the hands and feet narrow in order to maintain central body warmth. However, in SSc the blood vessel loses its normal method of relaxation, becoming prone to episodes of vasospasm (contraction of the muscle wall that closes the vessel). The vessels become overly sensitive to cold temperatures and other stimuli like emotional stress, which results in Raynaud attacks.

The thickened skin in scleroderma is caused by overproduction of collagen, which is the basic component of scar tissue. Abnormal accumulation of collagen is called fibrosis. Collagen is a normal part of skin and many organs. However, in scleroderma the balance of collagen formation and collagen breakdown is altered so that too much collagen builds up.

In localized scleroderma this process is confined to some areas of the skin. In SSc, excess collagen can cause fibrosis in the heart, lungs, and the muscles that line the GI tract.

Collagen is made by fibroblasts (a type of cell that is part of almost every tissue in the body) which can be provoked or activated to make more collagen. Under normal circumstances, the production of a scar is the last step in healing following an injury or an infection, for example, the production of a scar following a cut in the skin. Fibroblasts are activated by the immune system to produce collagen as part of the normal healing process. However, in SSc fibroblasts are activated for no apparent reason. The resulting scar causes tissue damage, decreased flexibility, and malfunction of the organ involved.

The third problem in SSc is the dysregulation of the immune system resulting in an immune attack on the body's own tissues. In patients with early disease, immune cells such as B cells, T cells and macrophages appear to be activated and poised to attack the patient's own tissues. This might be particularly prominent in the skin and the lungs. In addition, the body generates self-directed antibodies called autoantibodies. Some of these autoantibodies are found in several autoimmune diseases, while others are highly specific for scleroderma.

One way to detect activation of the immune system is to find antibodies (proteins made by immune cells, the bullets of our immune army) in the blood that targets the body's own tissue (autoantibodies). A very specific set of autoantibodies is found in scleroderma. These autoantibodies can be thought of as footprints of the scleroderma disease process because they are only made under very specific conditions. At this point, it is still not clear what role, if any, these autoantibodies play in damaging the blood vessels or stimulating collagen overproduction in SSc.

WHO GETS SCLERODERMA?

There are many clues that define susceptibility to develop scleroderma. A genetic basis for the disease has been suggested by the fact that SSc is more common among patients whose family members have other autoimmune diseases (such as lupus). In

rare cases, SSc runs in families, although for most patients there are no other family members affected. Scleroderma may affect some Native Americans and African Americans more severely than Caucasians.

Women are more likely to get SSc. Environmental factors may trigger the disease in the susceptible host. For example, silica exposure (as in coal mining or sand blasting) has been associated with systemic scleroderma and certain drugs can cause scleroderma-like reactions. Localized scleroderma is more common in children, whereas SSc is more common in adults. However, both can occur at any age.

PUTTING IT ALL TOGETHER

Research suggests that the susceptible host for scleroderma is someone with a genetic predisposition to injury from some external agent, such as a viral or bacterial infection or a substance in the environment. In localized scleroderma, the resulting damage is confined to the skin. In SSc, the process causes injury to blood vessels, or indirectly perturbs the blood vessels by activating the immune system. Fibroblasts are activated as part of the response to tissue injury. Interacting networks of immune inflammation and injury from inadequate blood supply drive the process, so it becomes chronic. Collagen made in excess interferes with normal organ function, sometimes leading to organ failure. In many cases, the process goes into remission after some years of activity. Research continues to assemble the pieces of the scleroderma puzzle to identify the susceptibility genes, to find the external triggers and cellular proteins driving fibrosis, and to interrupt the networks that perpetuate the disease.

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

The Scleroderma Foundation thanks Maureen Mayes, M.D., M.P.H., University of Texas/Houston and John Varga, M.D., Northwestern University, for their assistance in the preparation of 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 member 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:_____CVV Code:____

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.

SCLERODERMA FOUNDATION

SUPPORT · EDUCATION · RESEARCH

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OUR MISSION: SUPPORT, EDUCATION AND RESEARCH

SCLERODERMA FOUNDATION

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LISA'S STORY

Lisa Hendricks was just seven years old when her parents noticed she was limping and couldn't lay her hands flat on a table. She hadn't complained of any pain, or showed any signs that the stiffness in her fingers was slowing her down. In fact, she had just started to play the piano and seemed to love it. Yet her parents knew something was wrong.

Suddenly, Lisa was unable to get up from a sitting position. Her parents rushed her to the doctor, who immediately recognized the symptoms of the linear and morphea forms of scleroderma. Two months later, specialists at the University of California, San Francisco, confirmed the diagnosis.

And just like that, in the blink of an eye, Lisa had begun her life with scleroderma.

Lisa has recently finished college and is beginning her career as an elementary school teacher. She volunteers for her church, hangs out with friends and family, and still enjoys playing the piano. She just does it all with scleroderma.

Lisa first found the Scleroderma Foundation while she was doing research online about the disease and support groups that provide resources for patients. What she found in her research was life-changing.

"When you talk to other members of a Scleroderma Foundation support group, you know they understand what you are talking about. It's very comforting," said Lisa, who belongs to the Foundation's support group in Sacramento. "We get together once a month, but really a lot of us are in constant contact. It's like I finally found where I belong."

Support is a critical component of the Scleroderma Foundation's mission, but it isn't the only aspect that drives the organization. The Foundation educates patients, families, medical professionals and the public through awareness campaigns. The organization also works to raise much-needed funds for research to identify the cause, and ultimately a cure, for the disease. These components make up the Foundation's three-fold mission of support, education and research.

"When you talk to other members of a Scleroderma Foundation support group, you know they understand what you are talking about. It's very comforting. We get together once a month, but really a lot of us are in constant contact. It's like I finally found where I belong." – Lisa Hendricks

SUPPORT

Because scleroderma is rare (it is estimated that the disease affects about 300,000 people in the U.S., 80 percent of whom are women), people who are newly diagnosed often worry that they are alone with the disease. While health care providers administer medical therapies to aid a patient's physical wellness, fellow patients play a significant role in the person's mental and physical health.

It is that reason why the Foundation's nationwide network of chapters and support groups exist: to make connections with others living with the disease. Here, people can find a safe and welcoming place to share, to learn, to cry, and to laugh.

Inspire℠ together we're better℠

For patients unable to connect in person, the Foundation has an active online support group through Inspire (www.inspire.com), where people living with scleroderma can chat in a secure environment 24/7. The Foundation also serves the community with support and resources on social media venues, such as Facebook and Twitter.

EDUCATION

Often times, scleroderma is difficult to diagnose because it mimics other diseases. It has many forms and varied symptoms. It is not a condition that easily can be categorized because it is so complex and affects people in such drastically different ways.

We realize the need to provide education to patients, family members, medical professionals and the public to foster a better understanding about scleroderma. We also want to help patients manage and cope with the disease.

The Foundation's national network of chapters and support groups hosts patient education events, including seminars with medical experts that offer patients access to information from some of the top clinicians and researchers working in the field. These events provide members, including patients and their families, the most up-to-date information about scleroderma treatments and research.

Through the Foundation's website (www.scleroderma.org) you can find valuable health information and frequently asked questions about the disease, learn about Foundation activities and events, access chapter and support groups, make a donation, and much more.

The "Scleroderma VOICE," a magazine published quarterly, is a patient/member-friendly tool designed to inform people about important scleroderma issues including research and advocacy. With a worldwide readership, the magazine is the leading publication dedicated to the scleroderma community. It is available to individuals who become members or supporters of the Scleroderma Foundation.

Each year, the Foundation, with the generous support of its sponsors, holds the National Patient Education Conference. This special event brings together scleroderma experts from around the country to lead workshops and panel discussions. The conference offers an invaluable experience for

attendees thanks to the network of people they meet who experience similar physical and emotional feelings, as well as the information they receive from medical and research experts.

Among the most effective tools the Foundation uses to provide education to its members is a weekly online newsletter. The eLetter provides current medical information, news about national and local Foundation events, and helpful articles taken from current sources as well as from its large medical archive.

The Foundation also has a toll-free hotline (1-800-722-HOPE) with a dedicated staff member available to help patients and their families find resources and information near their home.

A final component of education is through public awareness campaigns initiated on a national and local level.

RESEARCH

In addition to providing support and education to patients and promoting awareness, we also are a leading funder of scleroderma-related research. Currently, the Foundation provides at least $1 million per year for research funding – our single largest budgeted expense. Each year, new and established investigators apply to receive a portion of that funding through the Foundation's research program.

A Peer-Review Research Committee, composed of scleroderma experts from around the country, evaluates research proposals using a model based on best practices established by the National Institutes of Health (NIH). The committee determines which proposals receive funding each year through an objective critique and ranking of all applications.

Key to the Foundation's research program is the goal of fostering new research and young investigators. Through the years, the Foundation's research

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:

- We budget at least $1 million annually for research.

- 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 awareness activities.

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.

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Attn: Donations
300 Rosewood Drive, Suite 105
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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 $_____.

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program has provided vital "seed" funding that has allowed new investigators to advance to a level that makes it possible for him or her to receive greater amounts of funding through the National Institutes of Health and other entities. For this reason, the Scleroderma Foundation takes seriously its role as a catalyst to fund and stimulate new research and ideas.

Thanks to recent advances in research and treatment, scleroderma patients now can expect to live longer and more productive lives – with increased hope for the future. A cure for scleroderma, however, remains elusive. Research costs continue to climb. Modern laboratory staff, equipment and supplies are expensive. Laboratories and clinical research programs must look outside their own facilities for financial support.

ADVOCACY

Each area of our mission comes together in the area of advocacy. Our advocates volunteer to carry important messages from the scleroderma community to elected and appointed officials on the state and federal levels. It is our collective goal and hope to educate public officials about the critical need for public funding of scleroderma research.

The Scleroderma Foundation enlists the support of legislators and other decision makers to establish a higher profile for scleroderma and the needs of patients. We work to support broad health care priorities in Washington, D.C., including health insurance reform, and the expansion of federal orphan drug research and development programs.

SUPPORTING THE FOUNDATION

The Scleroderma Foundation, like all charitable organizations, must rely on the generosity of donors who support its three-fold mission. Without the support of its donors, the Foundation cannot fulfill its mission of service to patients, their families and the medical community working to find a cure. It is

the hope of a cure that drives us forward to fund the most promising peer-reviewed medical research. We strive to be a leader in patient education and support services, and a resource for researchers working to eradicate this disease.

In addition to the fundraising efforts conducted by the national organization, the Foundation's network of chapters and support groups engage in a variety of fundraising activities. One such successful program is Stepping Out to Cure Scleroderma. These walk-a-thons held throughout the country bring together thousands of walkers to raise money through pledged donations that support the Foundation's mission.

From volunteering in your local chapter, getting involved in fundraising initiatives, to being an advocate, you can become involved and support our work and mission in numerous ways.

LEARN MORE

For more information about the programs and services of the Scleroderma Foundation, including how you can help, please call 1-800-722-HOPE (4673) or visit www.scleroderma.org.

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.

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Pulmonary Fibrosis in Systemic Sclerosis: Diagnosis and Management

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Pulmonary disease is an important component of systemic sclerosis (SSc). It is estimated that 90% of patients with SSc have some evidence of pulmonary disease[1]. This makes pulmonary disease second only to esophageal disease as the most common manifestation of SSc found on the inside of your body (visceral) component. Moreover, pulmonary involvement portends a poorer prognosis and pulmonary disease is now the leading cause of death amongst patients with SSc with an estimated mortality from pulmonary disease of all causes to be 33%[1]. While multiple pulmonary manifestations have been associated with SSc including pleural effusions[2], bronchiectasis[3], lung neoplasms[4], aspiration pneumonia and drug induced pneumonitis, the most common pulmonary manifestations of SSc include pulmonary hypertension and interstitial lung diseases (ILDs). The significant prevalence of ILD in SSc is reflected in the classification criteria of SSc [2] with the finding providing 2 points towards diagnosis of SSc.

Lung Fibrosis in SSc

Like pulmonary fibrosis of most origins including idiopathic pulmonary fibrosis, the precise molecular events that occur in the pathogenesis of lung fibrosis is not well understood. There is likely a complex interplay between inflammatory[5], antibody production[6-7], oxidative stress and fibrosis occurring in the setting of blood vessel hyperreactivity[8].

Environmental or genetic factors may contribute to the development of ILD in SSc and researchers are actively trying to identify these targets[3]. While environmental triggers have been considered in the pathophysiology of SSc in general and environmental exposures such as polyvinylchloride, and an impurity in one preparation of L-tryptophan have been known to trigger scleroderma like syndromes, there has never been a clearly established environmental link. The lung injury specific to inhalation of inorganic or organic dusts in the environment are termed pneumoconiosis or hypersensitivity pneumonitis, which are not the same as ILD,. There has never been an environmental exposure implicated specific to ILD associated with SSc.

A genetic contribution to scleroderma is supported by observed familial aggregation, ethnic predispositions, gene association studies and genome wide studies[9]. Pedigrees have been described that demonstrate members with SSc as well as members with ILDs not known to be related to SSc in numbers higher than would be expected by chance, suggesting a shared genetic predisposition between SSc, SSc ILD and non SSc[10]. As with all genetic studies, the heterogeneous nature of SSc complicates the detection and interpretation of genetic studies and better characterization of phenotype may aid the understanding of scleroderma in general and the development of ILD specifically[9].

Subsets of Scleroderma associated with ILD

The estimated prevalence of ILD in SSc ranges from 25-90% depending on the methods utilized and the subset of SSc patients evaluated. There are currently no reliable means to consistently predict which SSc patients will develop ILD. There are some clinical predictors that have been associated with a higher prevalence of ILD. These include African-American ethnicity, higher skin score (diffuse cutaneous, dcSSc), muscle inflammation (elevated serum CPK

levels), hypothyroidism, and cardiac involvement[12].

The association between SSc and ILD is strongest in patients who suffer from dcSSc. Patients with diffuse SSc typically develop the ILD early in the course of their disease. However, ILD is also has a well described association with limited skin involvement (lcSSc)[13]. Specific auto-antibodies such as the anti-SCL-70, RNP, anti U11/U12 RNP, anti Th/ To and antihistone antibodies have been reported to be associated with an increased risk of ILD in SSc[14] and others such as anticentromere antibodies are protective[15]. However, these associations are not specific are not absolutely predictive and serologies have low sensitivity[13] limiting the effectiveness of the serologies as a clinical predictor of ILD.

Diagnosis of ILD in SSc

The onset of ILD in scleroderma is often difficult to detect. Factors that may mask the onset of disease include mild lung involvement, musculoskeletal, or hematologic (such as anemia) manifestations of SSc or other comorbid conditions. When studied systematically, approximately 50% of patients with ILD will demonstrate a measurable decline in pulmonary function within the first three years of diagnosis of SSc although many of these patients report no pulmonary symptoms[16]. Once the presence of a pulmonary disease is established, care must be taken to differentiate between ILD and other pulmonary manifestations, specifically pulmonary arterial hypertension (PAH), which may co-exist with ILD or be present in the absence in ILD. Thus, it is clear that correctly identifying and managing ILD in scleroderma is a critical issue in the management of SSc.

There are a number of tests that can be applied to the diagnosis of ILD in SSc. Physical examination can be revealing with the presence of bibasilar crackles, but often times these are subtle or absent early in the disease. Thus, additional testing is required to assess for the presence of ILD in SSc.

Pulmonary Function Testing

Pulmonary function testing (PFTs) are cornerstone tests in the evaluation of dyspnea and for detection of pulmonary involvement in patients with SSc. While not diagnostic of ILD, patients with ILD will demonstrate restriction on lung function testing. Total Lung Capacity (TLC) by means of plethysmography is the most reliable measure of restriction and will confirm the presence of true lung restriction. However, spirometry is more typically utilized in clinical practice provides a good estimation of true restriction. Spirometry provides measures of the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1). In a restrictive lung disease, the FVC should be reduced and the FEV1/FVC ratio should be normal.

The diffusing capacity (DLCO) provides a measure of gas transfer between the air inhaled into the alveoli to the red blood cells in the systemic circulation. The DLCO is one of the most valuable measures in the evaluation of the scleroderma patient as a decreased value may be the earliest signal of lung disease in SSc and is reduced in 70% of SSc patients[17-18]. Moreover, the DLCO correlates most closely with the degree of disease seen on the high resolution computed tomography (HRCT) scan[19]. The DLCO will be reduced in both pulmonary hypertension and ILD. Thus, the DLCO is not

specific for the diagnosis of SSc ILD, but does indicate further evaluation is indicated.

The rate of decline of both the FVC and the DLCO are important prognosticators of survival[16, 19]. The most rapid decline in the FVC occurs within the first three to five years of disease onset[16]. This implies that lung injury is an early event and suggests that frequent monitoring in lung function in early stage disease is important.

High Resolution CT

As with ILDs of all types, the HRCT is the most sensitive and specific modality for detecting and characterizing any ILD present in the setting of SSc. It is more sensitive than chest radiograph and is the imaging technique of choice[20]. The most common radiographic pattern is that of NSIP. Early in the disease, ground glass opacities are prominent in a peripheral distribution and then progress to reticular changes. The classic UIP pattern with bibasilar reticulation, traction bronchiectasis and honeycombing is also observed in patients with SSc but less commonly than NSIP. Honeycombing is seen more frequently in patients with lcSSc than in those with diffuse SSc[21]. Tracheobronchial disease can be seen in patients with an overlap of Sjögren's syndrome, A HRCT is required to make these radiographic distinctions.

The HRCT scan has limited prognostic significance. The finding of ground glass opacities does not universally connote reversible disease or alveolitis and is often fine reticulation below the threshold of CT detection[22]. The extent of ILD seen on HRCT has prognostic significance with those patients demonstrating more than 20% involvement demonstrating increased mortality[23]. There are several computer-aided tools in development to help better understand meaningful change on HRCT scan, but these are mainly research tools. Additionally, the role of low radiation dose HRCT and lung ultrasound for serial monitoring the progression of ILD is also under investigation.

Bronchoalveolar Lavage (BAL)

The role of BAL in patients with SSc ILD is controversial and most often utilized when there is concern about infection, malignancy, or drug toxicity. When a cell count is done on BAL from patients with SSc-associated ILD, elevated numbers of granulocytes may be seen, especially neutrophils and eosinophils. Increased numbers of lymphocytes and mast cells may also be seen[24]. Early studies correlated increased granulocytes in BAL with increased response to immunosuppression presumably because this represented active alveolitis[25-26]. Subsequently, BAL granulocytosis has been shown to correlate with the degree of ground glass opacity seen on HRCT[21] and with more advanced interstitial disease[27]. However, data from the Scleroderma Lung Study suggest that BAL granulocytosis does not add any additional prognostic information to HRCT and pulmonary function measures and is not a predictor of treatment response[27-28]. There is no question that BAL is an important test in the consideration of infection, especially when a patient is taking medications that suppress the immune system.

Biopsy

Similar to radiographic appearances, there are a variety of histologic subtypes found in SSc ILD. NSIP is seen most commonly,

estimated to be the histopathology in 76% of the cases[19]. In this same series, UIP occurred in 11% of the cases and there were rare cases of organizing pneumonia and diffuse alveolar damage. Importantly, the clinical outcome does not correlate with the observed histology[19, 29]. Patients with scleroderma ILD can often experience stabilization after the initial development of their lung disease. These patterns are in stark contrast to idiopathic ILDs where UIP is the most common pathology, the pathologic finding of UIP is associated with a poorer prognosis and stabilization of UIP for decades is rarely seen. Specifically, in a series of 80 patients, survival does not differ between cellular NSIP, fibrotic NSIP and UIP. Thus, histology has no prognostic value. Given this data, there is rarely value to a surgical biopsy in the evaluation of a patient with scleroderma associated ILD. The exception to this may be in cases of an unusual CT pattern, which does not fit a predicted pattern seen in SSc.

Treatment of ILD in SSc

The decision of who requires treatment in the ILD associated with SSc is not always simple. The goals of therapy are to provide an effective agent to a patient in order to prevent progression to fibrosis and to target active inflammation or alveolitis as this may represent a reversible component of the disease. A patient's symptoms of shortness of breath and cough are important. Thus, the appropriate candidates for therapy are those who have symptoms, early stage lung disease, ground glass opacities on CT scan or who are demonstrating progression of disease.

It is notable that therapeutic interventions remain primarily anti-inflammatory in nature as inflammation is still believed to be the primary driver of lung disease progression. This is in contrast to the IPF model where inflammation is felt to be less important than an aberrant fibrotic pathway. Only a small number of drugs have been assessed via randomized controlled studies and few therapeutic options exist for patients with SSc ILD.

Nintedanib

The Food and Drug Administration (FDA) approved the first specific therapy for SSc-ILD, following a randomized, double-blind placebo-controlled trial among patients with ILD associated with SSc that showed that the annual rate of decline in FVC was lower with nintedanib than with placebo. While no clinical benefit of nintedanib was observed for other manifestations of SSc, nintedanib, a tyrosine kinase inhibitor, demonstrated antifibrotic and antiinflammatory effects.

Cyclophosphamide

This drug has been rigorously assessed for use in SSc ILD. In general, there is evidence that it has a small benefit for long stabilization by PFT and breathlessness (PMID 29297205) . The Scleroderma Lung Study (SLS) 28 was a double-blind, 13 center trial of 158 patients with early SSc-associated ILD who demonstrated evidence of active alveolar inflammation with either ground glass opacities on HRCT or increased cellularity on BAL. Patients were randomized to receive either oral cyclophosphamide (≤2 mg/kg) or placebo daily for one year. In this study, the cyclophosphamide group had a smaller decline than the placebo

group (-1.0 versus -2.6 percent predicted). This difference, while small, was statistically significant. This difference was seen at the end of the first year of treatment. In addition, a HRCT scan study was done on a subset of the SLS patients. With comparison of the initial CT scan and follow-up CT scan at one year, less progression of fibrosis was seen in the cyclophosphamide group[30].

Cyclophosphamide is an effective, albeit with small impact, agent for treatment of SSc associated ILD, there are several additional considerations. There is significant toxicity associated with daily oral cyclophosphamide including blood in the urine (hematuria), low blood counts (cytopenias), and malignancies. There is also concern that the response seen at one year is not persistent. While patient's reports of respiratory symptomatology and objective skin improvements were still present at the 24 month SLS follow-up study, the differential improvement in FVC had disappeared[31].

IV administration of cyclophosphamide is less rigorously studied but several uncontrolled studies[32-34] and one randomized trial have been done. In the 45 patient double blind placebo controlled study, there was a trend toward improved FVC in the cyclophosphamide group but this did not achieve statistical significance[35]. Thus, it remains unclear what the true role of IV cyclophophamide might be in the management of SSc related ILD.

Mycophenolate Mofetil

Mycophenolate is an inhibitor of lymphocyte proliferation. This drug has been the subject of retrospective studies and observational studies. These small studies have had mixed results but observed improvements in FVC and DLCO have been documented[36-38]. The second Scleroderma Lung Study (SLS II) compared in a double-blind fashion 142 SSc-ILD patients with 7 years disease duration or less to receive either mycophenolate mofetil (MMF) (n = 69) for 2 years or oral cyclophosphamide (n = 73) for 1 year followed by a year of placebo treatment. This study showed equivalence for both therapies, but MMF was better tolerated.

Rituximab

The monoclonal antibody rituximab depletes B cells that play in the pathogenesis of SSc. In a randomized controlled trial in 14 patients with SSc-ILD, rituximab (4 weekly infusions followed by 4 weekly infusions at 24 weeks) was associated with significant improvement in both FVC(%) and DLCO(%) at 1 year. Case control studies with anti–B-cell therapy were associated with stability or improvement in pulmonary function tests. In these studies, the medication was well tolerated. However, a recent prospective cohort study of 254 patients treated with rituximab compared with 9575 propensity-score–matched patients showed that treated patients did not have significantly different rates of decrease in FVC or DLCO, although they were more likely to have improvement in skin fibrosis. More data is needed to fully evaluate the efficacy of rituximab in SSc-ILD. Currently, there are 2 clinical trials of rituximab in patients with ILD connective tissue disease that are currently recruiting patients (clinical trials.gov: NCT02990286 and NCT01862926).

Intravenous Immunoglobulin

Intravenous Ig (IVIg) is a pooled plasma product that is sometimes used in SSc patients with ILD and inflammatory muscle disease (myositis). It is sometimes used off-label with increasing frequency for refractory cases that have failed to respond to immunosuppression. Although associated with less systemic toxicity and global immunosuppression than traditional agents, IVIg is much more costly.

Corticosteroids

The role of corticosteroids remains unclear in SSC related ILD. In general, these drugs are avoided because of the well-known risk of scleroderma renal crisis. This phenomenon has been well documented[39] and occurs at low prednisone doses with a mean dose of only 7.4 mg in one series[40]. However, in most clinical trials, use of prednisone was permitted with the drug in question. Thus, while monotherapy with glucocorticoids is not recommended, the role that the accompanying prednisone plays in combination with cyclophosphamide, mycophenolate or other therapies remains unknown.

Other therapies

There are a large number of other possible therapies that are under investigation. Beyond the consideration of inflammation as the primary driver of lung fibrosis, other pathways have been targets of study. The anti-fibrotic effects of pirfenidone are under investigation in SLSIII, which is a Phase II multi-center, double-blind, parallel group, randomized and placebo-controlled clinical trial addressing the treatment of patients with active and symptomatic SSc-ILD. Patients who are either treatment naive or only recently started treatment (</= 6 months of prior treatment) will be randomized in a 1:1 assignment to receive either oral mycophenolate mofetil (MMF) and a placebo or a combination of oral MMF and oral pirfenidone, with both regimens administered for 18 months.

Conclusion

ILD in SSc is a common manifestation that is associated with poor prognosis.

Careful evaluation by the clinician is warranted to detect the presence of an ILD and to select patients for consideration of therapy. Factors to consider in the initiation of therapy include early disease, evidence of progression and evidence of alveolitis. Possible side effects of therapy must be weighed against the known benefits. At the current time, nintedanib, cyclophosphamide and mycophenolate mofetil remain the best studied therapeutic agents although alternatives are actively being evaluated. The role of other immunosuppressive agents or other pathways remains undetermined and offer hope for future therapeutic interventions., but there is some evidence for rituximab, tocilizumab, and pirfenidone,. More data is necessary to best understand the role of these agents for SS-related ILD. For some patients with access to specialty centers hematopoietic stem cell transplantation and lung transplantation may be an option. Additional research is needed to determine which patients will benefit from SSc-ILD therapy, how to best measure their treatment response, and long- term management plans after initial therapy in order to optimize outcomes among patients with SSc-

ILD.

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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.

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PULMONARY HYPERTENSION IN SCLERODERMA

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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 leading to increased pulmonary vascular resistance, 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 who have limited cutaneous scleroderma (formerly known as CREST syndrome) are more likely to have PAH than those patients who have diffuse cutaneous systemic sclerosis. PAH may be the result of the same processes that cause damage to small blood vessels in the systemic circulation of patients with scleroderma. The lining cells of the blood vessels (endothelial cells) are injured and excessive connective tissue 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 may have PH because they have significant scarring (fibrosis) of their lungs. 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 PULMONARY HYPERTENSION?

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, lightheadedness or fainting, palpitations (heart racing or fluttering), and swelling.

HOW IS PULMONARY HYPERTENSION DIAGNOSED?

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 DLCO 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 lung fibrosis, if the DLCO is less than 50 percent of its predicted value, this is a clue that PH may be present. Another test commonly used to screen patients for 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. Right heart catheterization is the "gold standard" for diagnosing PAH.

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. Studies now suggest that patients identified with mild or early PAH will fare better if drug therapy is started before symptoms and exercise capacity worsen.

WHAT IS THE TREATMENT OF PAH?

Supplemental oxygen and diuretics are often important parts of general treatment measures for PAH. If the oxygen level at rest, with exercise, or during sleep is low, supplemental 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 amlodipine, diltiazem or nifedipine) can help a small proportion of patients with PAH. Such treatment is successful in only a minority of scleroderma patients with PAH.

PAH SPECIFIC MEDICATIONS

The list of drugs for treating PAH continues to expand and include the following FDA-approved drugs: epoprostenol (generic, Flolan®, and Veletri®), treprostinil SQ or IV (Remodulin®), treprostinil inhaled (Tyvaso®), treprostinil oral (Orenitram®), iloprost (Ventavis®), bosentan (Tracleer®), ambrisentan (Letairis®), macitentan (Opsumit®), sildenafil (generic, Revatio®), tadalafil (Adcirca®), riociguat (Adempas®), and selexipag (Uptravi). Each of these drugs falls within one of four separate categories based on different mechanisms of action. These drugs are used alone or in combination with drugs in one or more other classes. Each will be briefly reviewed below.

Prostacyclin Analogs

Epoprostenol

Epoprostenol (generic, Flolan®, Veletri®) is a potent vasodilator that 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 and 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 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 dose-related. The use of subcutaneous treprostinil may be

limited by infusion site pain and redness. Treprostinil is approved for intravenous or subcutaneous delivery for the treatment of patients in Functional Class II, III, and IV PAH. Inhaled trepostinil (Tyvaso®), when administered four times daily, has been shown to improve exercise capacity in patients with Class III PAH. An oral form of treprostinil (Orenitram®) was approved by the FDA in December 2013.

Iloprost

Iloprost (Ventavis®) is a prostacyclin analog delivered by inhalation 6–9 times daily that has been shown to improve a composite measure of exercise capacity and functional class. Inhaled iloprost has been studied in patients who remain symptomatic while on stable ERA (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.

Selexipag

Selexipag (Uptravi®) is an oral prostacyclin receptor agonist that has been shown to delay disease progression and reduce the risk of hospitalization for PAH. Side effects are similar to that of prostanoids and include headache, flushing, jaw pain, nausea, diarrhea, and bone pain

Endothelin Receptor Antagonists (ERA)

Bosentan

Bosentan (Tracleer®) is an oral endothelin receptor antagonist (ERA). 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 study confirmed improvement in exercise capacity and showed a reduction in clinical worsening. 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 an FDA-approved ERA drug treatment for patients with PAH. To be taken once daily for patients in Functional Class

II or III, this drug has shown improvement in exercise capacity. 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.

Macitentan

Macitentan (Opsumit®) is the latest drug in the ERA class to be approved to treat PAH. Macitentan is approved for treatment of PAH to delay disease progression defined as death, initiation of intravenous (IV) or subcutaneous prostacyclin drugs, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). The need for PAH hospitalization was also reduced. Like other ERA drugs, macitentan is contraindicated in pregnancy because it may harm the developing fetus, and females of reproductive potential should be counseled on the use of reliable contraception and have a negative pregnancy test prior to initiating therapy and monthly thereafter.

Phosphodiesterase-V (PDE-V) Inhibitors

Sildenafil

Sildenafil was previously approved for the treatment of erectile dysfunction under the trade name of Viagra®. It is also approved for the treatment of PAH, under the trade name of Revatio® (a generic preparation is now also available). 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®) is approved as a once-daily oral therapy for the treatment of PAH, and is indicated to improve exercise capacity in PAH patients. Side effects include headache, stomach upset, back pain, muscle pain, stuffy or congested nose, flushing, pain in arms or legs, or vision change.

Guanylate Cyclase Stimulators

Riociguat

Riociguat (Adempas®) is the first in a new class of drugs to be approved for treatment of PAH, including scleroderma patients with PAH, as well as for treatment of chronic thromboembolic pulmonary hypertension. Drugs in this new class act to dilate

blood vessels, thus reducing pulmonary vascular resistance and improving PAH. Riociguat has been shown to significantly improve exercise capacity, functional class, time to clinical worsening, and dyspnea score. Riociguat should not be used in pregnant women because it can harm the developing fetus.

LUNG TRANSPLANTATION

Lung transplantation may be an option for patients with severe PAH who do not respond to 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 PAH. Not all patients are suitable candidates for lung transplantation. Gastro-esophageal 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 patients with scleroderma. Interstitial lung disease (ILD), also called pulmonary fibrosis, is another potentially 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, and your pulmonologist or 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 Badesch, 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:

- We budget at least $1 million annually for research.
- 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 awareness activities.

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 member benefits.

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Join Now!

Your tax-deductible gift of $25 or more makes you a member.

The Scleroderma Foundation's three-fold mission focuses on Support, Education and Research.

Support – We help patients and their families cope with scleroderma through various support programs, peer counseling, physician referrals and educational information offered by our nationwide network of chapters and support groups.

Education – We promote public awareness and education through patient and health professional seminars, in scleroderma-related literature and in publicity campaigns. A toll-free information line is available as well as patient education information and a website with relevant medical articles, research updates and support information.

Research – We aim to stimulate and support research that is focused on improving treatment and ultimately finding the cause and a cure. We are the leading nonprofit supporter of scleroderma research, and our peer-review based program annually funds over $1 million in scleroderma-related research.

Membership: For only $25 a year, you can become a member, support our mission and receive our quarterly magazine, *Scleroderma Voice*, which regularly features information like the following:

- Updates on the latest scleroderma research and treatments
- Articles by leading doctors and other healthcare professionals
- Answers to medical questions by healthcare professionals
- Practical tips on coping with scleroderma
- Heartwarming stories about people living with scleroderma and how they faced their challenges
- Articles about what the Scleroderma Foundation is doing for you—funding new research, advocating on Capitol Hill for more federal research funding, and working nationwide, year-round to raise public awareness of scleroderma and its impact on individuals and their families

It's easy to give! Here are a few options:

1. **Call the Scleroderma Foundation toll-free** at 1-800-722-4673 and make your gift via credit card.
2. **Give online** via our secure server. Visit our website at www.scleroderma.org and click on the Donate box on the upper right side.
3. **Mail your gift** (check or credit card) to the Scleroderma Foundation at the address below.
4. Give through **payroll deduction** at work through the Combined Federal Campaign (CFC), United Way or your employer's workplace giving program. Our CFC # is 2615.

Thank you for your support!

Literature & Awareness Items Order Form

Scleroderma Foundation
300 Rosewood Dr, Ste 105
Danvers MA 01923
800-722-4673(HOPE)
Fax: 978-777-1313

Please call for international shipping costs before placing order!

Literature	$_____
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