University of Pittsburgh & UPMC Scleroderma Center

COLLAGEN CONNECTION

Fall 2023

Updated Therapies for SSc-ILD

by Eleanor Valenzi, MD

Interstitial lung disease (ILD), often referred to as pulmonary fibrosis, is the most frequent lung complication of systemic sclerosis (SSc), and may have significant effects on quality of life for those who develop it. ILD refers to inflammation and scarring that develops in the lungs, blocking the movement of oxygen from the small air sacs of the lung into the bloodstream. Lower oxygen levels and/or stiffened lungs that are unable to take large breaths may cause people with ILD to feel short of breath, especially during physical activity. Cough and fatigue are also common in some patients with systemic sclerosis-associated ILD (SSc-ILD). For patients with SSc, lung disease is primarily diagnosed and monitored by pulmonary function testing (breathing tests) and CT scans of the chest. Most research studies for treatment of SSc-ILD focus on results of pulmonary function testing in those receiving the medication versus those not receiving it.

Treatment of SSc-ILD

While there is no one best treatment approach for SSc-ILD, additional medications approved by the US Food and Drug

Continue on Page 2

Dr. Eleanor Valenzi is a pulmonologist specializing in autoimmune interstitial lung diseases (ILD) at the University of Pittsburgh. She obtained her BA from the University of Pennsylvania, followed by her MD at the University of Alabama School of Medicine. After internal medicine residency training at the University of Chicago, she moved to Pittsburgh to completer her pulmonary/critical care fellowship at the University of Pittsburgh, and joined the faculty in 2019. Working with Dr. Robert Lafyatis of the Scleroderma Center since 2017, Dr. Valenzi's translational research program focuses on determining the molecular mechanisms and DNA structural changes underlying systemic sclerosis-associated interstitial lung disease. She and Dr. Lafyatis have advanced the community's scientific knowledge of the cell-specific changes occurring in SSc-ILD through their work examining the RNA expression changes in individual cell types utilizing a novel technology known as single-cell RNA-sequencing. They published the first studies utilizing these techniques in SSc-ILD: ***Single-cell analysis reveals fibroblast heterogeneity and myofibroblasts in systemic sclerosis-associated interstitial lung disease.*** Valenzi E, Bulik M, Tabib T, Morse C, Sembrat J, Trejo Bittar H, Rojas M, Lafyatis R.Ann Rheum Dis 2019 Oct;78(10):1379-1387. doi: 10.1136/annrheumdis-2018-214865. Epub 2019 Aug 12, allowing this data to be shared with and used by others studying scleroderma. Dr. Valenzi's work is supported by the NIH, National Scleroderma Foundation, Pulmonary Fibrosis Foundation, and the Francis Family Foundation. She also participates in clinical trials for ILD. Outside of work she enjoys spending time with her husband and two young children exploring the nature trails, restaurants, and theatre in Pittsburgh.

IN THIS ISSUE

Administration (FDA) for use in SSc-ILD in the last several years have increased the options available and hopefully outcomes for those living with SSc-ILD. For some patients with mild and/or stable lung disease, monitoring lung function and symptoms without medication is appropriate. For others who require treatment, medications that act by suppressing the immune system such as mycophenolate mofetil, cyclophosphamide, or azathioprine are used.

Patients may also be offered the opportunity to participate in a clinical trial for new medications in addition to their other prescribed treatments if an appropriate trial is ongoing at the time.

Tocilizumab

In 2021, the FDA approved tocilizumab (actemra) for the treatment of SSc-ILD. Tocilizumab is an anti-interleukin (IL)-6 receptor antibody biologic therapy given as subcutaneous injection once a week. In SSc, high IL-6 levels in the blood are predictive of worsening ILD, suggesting patients may benefit by blocking this protein. Clinical trials performed in patients with early SSc who met specific inflammatory marker parameters (high CRP levels) found that tocilizumab slowed the rate of pulmonary function decline. In the phase 3 clinical trial of tocilizumab, most patients receiving the medication experienced stable lung function while those receiving placebo had a decline in their lung function testing- indicating worsening of their lung disease. Like most immunosuppressive medications, there is a risk of increased infections while taking the medication, and patients also require blood test monitoring while taking it.

Nintedanib

Another option for some patients with SSc-ILD is the "anti-fibrotic" medication nintedanib (ofev). This medication was first used in a different form of ILD, idiopathic pulmonary fibrosis, and is now approved for use in SSc-ILD as well based on clinical trials in patients with scleroderma. Nintedanib is an oral medication primarily used in those with worsening lung disease despite immunosuppressive medication. It can be used in addition to other ongoing immune system-directed treatments, though is typically not started at the same time. Nintedanib acts as an inhibitor of multiple tyrosine kinases, important enzymes that act in cellular signaling pathways involved in fibrosis. Nintedanib does not reverse the already present fibrosis/scarring, but rather slows down the progression of the lung disease in some patients. The most common side effects are gastrointestinal, and it does require blood test monitoring as well while taking the medication. Neither nintedanib nor tocilizumab have been shown to have significant effects on skin disease in SSc, and at the current time are used only in those with ILD.

Other Treatments

Supplemental oxygen (when indicated), pulmonary rehabilitation, smoking cessation, routine vaccinations, and management of other scleroderma affected organs are also important aspects of the treatment of SSc-ILD for all patients. Many patients may need oxygen with significant physical activity (such as climbing stairs or exercising), but not require it when sitting or doing light activity. Lung transplantation is also an appropriate treatment for some people with severe SSc-ILD. For these patients, early evaluation by a lung transplant center is important as the process involves a series of appointments and medical testing to provide extensive information about transplantation and determine if they are an appropriate candidate.

To schedule an appointment with Dr. Valenzi, please contact The Simmons Center for Interstitial Lung Disease at the UPMC Comprehensive Lung Center at 412-802-3275.

University of Pittsburgh
Systemic Sclerosis Center of Research Translation

On June 9th, 2023, Dr. Robert Lafyatis, the Director of Systemic Sclerosis Center of Research Translation (CORT), along with Robyn Domsic, CORT associate director, held the Annual Scientific and Advisory Committee Meeting at the University of Pittsburgh. CORT funding is provided by the National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS) at the National Institutes of Health (NIH). The purpose of this funding is to have a team of scientists and physicians carry out interactive and coordinated research projects to address the challenge of understanding and treating systemic sclerosis from a translational approach. Translational research is the process of applying knowledge and discoveries obtained through basic laboratory research into development of new treatments and therapies

To study such a complex multi-organ disease like systemic sclerosis it is important to take a systematic targeted approach to project design. In this Systemic Sclerosis CORT, led by Dr. Lafyatis, there are three major projects specific to significant clinical complications of the disease each run by highly accomplished and respected field leading scientists.

Dr. Lafyatis is leading Project 1 which investigates skin complications and disease progression. He presented the data generated from the first year Project 1. The long-term goals of this project are to discover biomarkers permitting more efficient testing of novel drugs for SSc patients, to dissect the cellular source and progenitors of cells expressing biomarkers in SSc skin, and to study how genes uniquely expressed by myofibroblasts regulate myofibroblast differentiation.

Dr. Oliver Eickelberg from The University of Pittsburgh Pulmonary, Allergy and Critical Care Medicine, is a world renown investigator in pulmonary fibrosis and interstitial lung disease. He presented the data from Project 2. Dr. Daniel Kass, a pulmonologist and director of the Simmons Center for ILD is the Associate Director of this project. This project incorporates assaying many archived tissues collected from UPMC Scleroderma patient lung transplants and evaluating these tissues for protein and proteomic analysis.

Dr. Steven Chan presented the data from Project 3 which focuses on pulmonary arterial hypertension (PAH In systemic sclerosis, PAH is a leading cause of morbidity and mortality. Moreover, patients with SSc-PAH have a poorer prognosis than patients with idiopathic PAH. To improve treatment options for SSc-PAH, a better understanding of SSc-PAH pathogenesis is needed. Dr. Chan's project includes a novel PET imaging trial where a unique tracer is used to identify vascular changes present in patients with SSc-PAH. Dr. Chan's study also includes control patients without lung disease for comparison. Dr. Sruti Shiva is the Associate Director of this project, her work focuses on platelet cells in the blood and their role in disease.

Dr. Domsic presented the Clinical & Biospecimen Core. The Clinical Core provides prospectively collected, longitudinal clinical data and associated bio-samples on a well-characterized cohort of SSc patients. It is extremely important for each project to have the resources it needs to effectively pursue their goals.

The Annual Advisory Meeting is an opportunity for the project investigators to present their ongoing research and goals to an external committee of industry experts in clinical researchers and highly respected specialized clinicians to make recommendations of the projects and discuss opportunities to improve the work being done. Some committee members traveled as far as the London to participate. This year the Advisory Committee included expert physicians in Pulmonary Fibrosis, Pulmonary Hypertension, Fibrotic Skin Disease, Genomics, as well as the CEO of the National Scleroderma Foundation and a Patient Advisory. Caroline Graettinger is a scleroderma patient as well as the leader of the local Scleroderma Foundation Support Group.

At the meeting's end, Caroline addressed the room.
"While we patients navigate our personal journeys with this condition, it's truly heartening to know this international team is working tirelessly on our behalf. What I heard today gave me renewed hope – a feeling I sincerely wish for every scleroderma patient".

CLINICAL DRUG TRIALS AND OBSERVATIONAL STUDIES

Our Scleroderma Center is committed to participating in clinical trials. We feel it is a vital step in working together to find treatments for scleroderma. Without clinical trials, our field will not advance. If you are interested in participating in a trial or would like additional information, please contact Maureen Laffoon at 412-648-7871 or laffoonm@pitt.edu.

CURRENTLY ENROLLING:

A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Ifetroban in Patients with Systemic Sclerosis-Associated Pulmonary Arterial Hypertension

The purpose of this study is to find out if Ifetroban is effective and helps reduce symptoms associated with systemic sclerosis.

Approximately 34 adults will take part in this study. Half of the participants in this study will receive Ifetroban and half will receive placebo. Ifetroban/Placebo is in capsule form and will be taken for up to 1 year. Participants will be required to come to our Center for 6 visits. There will also be check-in phone calls in between these visits. The study drug and medical care related to the study will be provided at no cost to you.

Study visits will include a blood draw, cardiac MRI, Echocardiogram, Pulmonary Function Test, Six minute walk test, and you will be asked to complete questionnaires.

Participant compensation and travel reimbursement are provided to eligible participants.

A Double Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of PRA023 in Subjects with Systemic Sclerosis Associated with Interstitial Lung Disease (SSc-ILD)

The purpose of this study is to help understand how safe and effective PRA023, the study drug, is in treating Systemic Sclerosis Associated with Interstitial Lung Disease (SSc-ILD) when compared to placebo over the course of 50 weeks. PRA023 is a monoclonal antibody that has the potential to be both an anti-inflammatory and an anti-fibrotic agent.

Patients will receive PRA023 or placebo Intravenously (IV) on Week 0, Week 2, and then every 4 weeks thereafter until Week 50. After completion of 50 weeks of treatment, you have the option to continue in the open-label extension phase of the study where you will receive PRA023 IV every 4 weeks.

Study visits will include blood draws, ECGs, Chest CT scan, Pulmonary Function Test, and you will be asked to complete questionnaires.

Participant compensation and travel reimbursement are provided to eligible participants.

A Phase 1b Randomized, Double-Blind, Placebo-Controlled, Multiple-Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of ACE-1334 Plus Standard of Care in Participants with Systemic Sclerosis

The purpose of this study is to determine if ACE-1334 will be a safe treatment for reducing lung function loss, skin thickness, and other symptoms in people with systemic sclerosis.

Participants will be seen at our Center every 2 weeks for 6 months. You will have a 1 in 4 chance of receiving placebo. For each dose of study drug/placebo, you will be given one or more injections under the skin, in your outer thigh, upper arm, or stomach.

Study visits will include blood draws, ECGs, Skin Biopsy, Pulmonary Function Test, and you will be asked to complete questionnaires.

Participant compensation and travel reimbursement are provided to eligible participants.

Tocilizumab Observational Study in Skin Complications in Systemic Sclerosis

The purpose of this study is to see how tocilizumab affects the cells in your skin and how it is likely affecting the cells in your lungs.

In this study, skin biopsies will be performed at two of your regularly scheduled clinic visits.

The first biopsy will be taken before you start taking tocilizumab and 12 weeks after taking tocilizumab.

You will also be asked to complete questionnaires. The questionnaires will take approximately 5 minutes and will assess your skin status.

Tocilizumab is prescribed by your treating rheumatologist as part of your clinical care. It is not dispensed as part of the study.

Participants will be compensated.

Study of a topical gel (without active drug) to evaluate the acceptability of the formulation in patients with systemic sclerosis

The purpose of this study is to obtain information from patients using a topical gel to assist in the design of a future study of this same gel with an active drug for treatment.

This study does not involve any active drug but will hopefully lead to a potential drug in the future.

A participant will apply the gel to the front and back of your right forearm and will be asked to complete a questionnaire regarding your assessment of the gel. You will then do the same to your left forearm and complete a questionnaire.

This study typically only requires one visit to our Center. Study participants will be compensated $100 for the completion of all study related procedures. The payments will be made on a reloadable debit card.

Systemic Sclerosis Skin Biopsy Research Repository

The purpose of this study is to establish a systemic sclerosis (SSc) skin biopsy research repository in which tissue specimens are stored and used for scleroderma research.

The researchers are also maintaining a SSc longitudinal database of computerized medical information and allows continued research into the complications, causes, and advancement of treatments for SSC.

This study involves procedures such as skin biopsies, blood collection, and measurement of skin elasticity. Participants may also be asked to complete questionnaires.

Participants will be compensated $50 to $150 depending on the amount of biopsies taken and payment will be made on a reloadable debit card.

PLEASE JOIN US

UPMC Scleroderma Educational Event
Saturday, October 28, 2023
8:30 a.m. check-in & breakfast
Seven Spring Mountain Resort
777 Waterwheel Drive
Seven Springs, PA 15622

The Mid-Atlantic Chapter of the National Scleroderma Foundation is proud to partner with the University of Pittsburgh Medical Center to present its 2023 Scleroderma Educational Event.

PRESENTERS

Dr. David Levinthal, Gastroenterologist

Dr. Belinda Rivera LeBron and Dr. Kevin Gibson, Pulmonologists

Dr. Cassie Torok, Pediatrician Scleroderma Specialist

Dr. Robyn Domsic, Scleroderma Specialist and Researcher

A buffet breakfast will be offered at 8:30 am with the live program starting at 9 am and concluding at 12:30 pm. The admission fee to attend is $25 a person. *

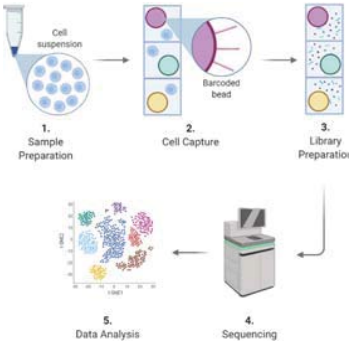
Rooms at Seven Springs Mountain Resort will be available at a discounted rate for interested attendees. Guests can call 855-947-0438 every day from 8am-5pm MT. Please reference the group code (S7SNSF23) or the group name (National Scleroderma Foundation).

*Admission Fee is to help offset costs. Scholarships are available for the admission fee. For more information contact JoAnne LaPergola at 609-707-8651. jlapergola@scleroderma.org

Pediatric Research News

Single-Cell Analysis Identifies Subclusters with Inflammatory Fibroblast Responses in Localized Scleroderma

Singe-cell RNA sequencing (scRNA seq) is a new technique that can provided detailed information at the cellular level. Multiple scRNA seq studies have been conducted in systemic sclerosis populations, but few have been conducted detailing localized scleroderma populations. In conjunction with an adult scleroderma group, our lab explored the scRNA seq data of LS patients versus healthy controls.



The root of LS is skin fibrosis, making fibroblast activity a key target of scientific investigation for our lab group. With this study, they identified 3 subclusters of cells that were significantly up-regulated in localized scleroderma compared to healthy controls. After gene analysis, these subclusters appear to play a role in immune response pathways, wound healing pathways, and cell growth regulation. Of note, 2 subclusters also appeared commonly among SSc patients, however, 1 subcluster was unique to LS only.

The end goal of these studies is to identify proteins and pathways that are up-regulated in LS as targets of therapeutic agents. With this paper, the lab found an excess production of a protein called IL-6 which is known to exist in a fibrotic pathway. IL-6 inhibitors are used in some systemic sclerosis therapies, but may eventually be tested in LS.

Links to Publications:

1. Werner G, Sanyal A, Mirizio E, Hutchins T, Tabib T, Lafyatis R, Jacobe H, Torok KS. **Single-Cell Transcriptome Analysis Identifies Subclusters with Inflammatory Fibroblast Responses in Localized Scleroderma.** Int J Mol Sci. 2023 Jun 6;24(12):9796. doi: 10.3390/ijms24129796. PMID: 37372943; PMCID: PMC10298454.
2. Baghdassarian H, Blackstone SA, Clay OS, Philips R, Matthiasardottir B, Nehrebecky M, et al . **Variant STAT4 and Response to Ruxolitinib in an Autoinflammatory Syndrome.** *N Engl J Med.* 2023 Jun 15;388 (24):2241-2252. doi: 10.1056/NEJMoa2202318. Epub 2023 May 31. PMID: 37256972.
3. Stefancic S, Robinson A, Havrilla H, Branton S, Sood V, Torok K. **Performance of the UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 Instrument in a Juvenile Systemic Sclerosis Cohort**. *Arthritis Rheumatol.* 2023; 75 (suppl 4).

TRIOS (Spit Study) and STAT4 Mutation

Many patients that are enrolled in the National Registry for Childhood Onset Scleroderma (NRCOS) have also participated in our TRIOS study. This study collects spit from patient and both parents so that we can isolate the DNA to check for any mutations observed in the patient. With each family, we typically observe about 15-30 different variants in patient DNA. We then send these variants to our friends at the National Institutes of Health (NIH) to find out if any of these mutations are contributing to the patient's disease.

One such mutation that was discovered last year, is a mutation in a gene that encodes the signal transducer and activator of transcription (STAT) 4. STAT4 mutation was discovered in 3 patients with pansclerotic morphea.

In biology, a lot of cellular activity is mediated through something called a signaling cascade, meaning that one protein activates another protein and so on until we reach our desired cellular product. STAT 4 is a protein that is mediated by a Janus kinase (JAK), the protein before STAT4 in this cascade. If we inhibit JAK, we can in theory, stop the expression of the mutated STAT4. Luckily for us, a drug called Ruxolitinib, a known JAK-inhibitor, already exists. Pansclerotic morphea patients treated with Ruxolitinib showed improvement over the course of therapy!

Performance of GIT Survey Abstract Acceptance

New clinical research assistant, Sophie Stefancic, explored the performance of the UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract Instrument (GIT). This survey is given to our systemic sclerosis patients at each visit to monitor for underlying gastrointestinal system conditions that are not always brought up during the patient's visit. Sophie saw that the GIT has the same efficacy in pediatric patients as in the adult cohorts. It was also found that distension and reflux scores were highest for patients and that GI scores correlate to overall patient quality of life indexes. This means that a lot of pediatric systemic sclerosis patients experience bloating and acid reflux, and that a strong presence of GI symptoms decreases the quality of life of our patients. Research like this allows us to develop effective pharmacotherapies to improve a patient's quality of life and disease progression.

2023 National Scleroderma Conference - Recap

The National Scleroderma Foundation holds a patient education conference for systemic sclerosis and localized scleroderma patients annually. This year's conference was held at the Signia Hotel in Orlando, FL from July 14-16th.

Patients, families, scleroderma doctors and researchers alike came from all over the United States and Puerto Rico to attend the conference.

Conference attendees were also encouraged to see what's up and coming in scleroderma research. The research session consisted of poster presentations from some of the top specialists and research faculty. Each poster highlighted the work their respective labs are doing to help better understand scleroderma and ultimately find a cure.

SAVE THE DATE:
NATIONAL SCLERODERMA CONFERENCE 2024
BELLEVUE, WASHINGTON
JULY 19-21

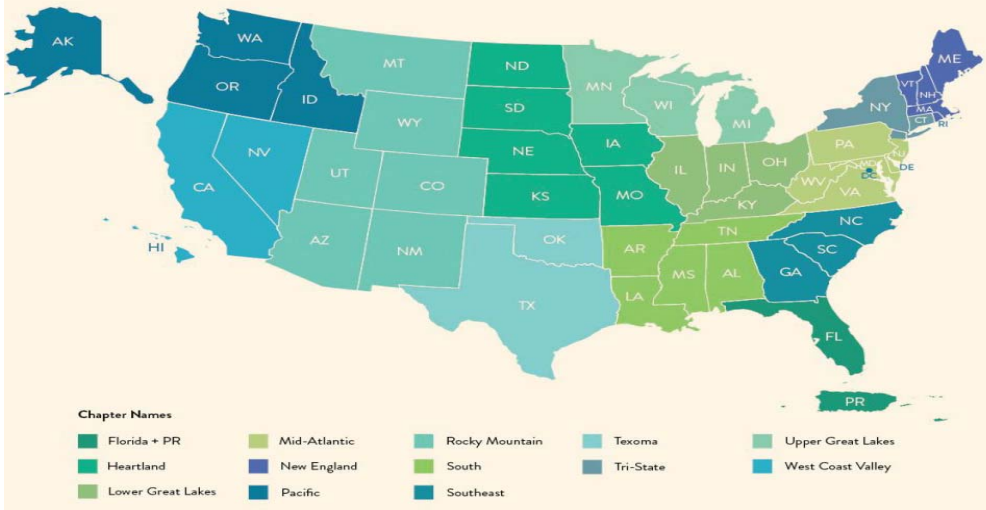
The Scleroderma conference not only brings members of the community together, but it provides patients and their families with the tools necessary to manage a scleroderma diagnosis.

Patients were invited to attend numerous discussion sessions over the course of the conference. The sessions included topics such as understanding and treating scleroderma, medications, pain management strategies, and even happiness practices.

Dr. Eleanor Valenzi, Nina Morse and Liz Evans

Whether you were a first timer or a conference veteran, the knowledge and shared experiences are invaluable.

We hope to see you at next year's National Scleroderma Conference!



The National Scleroderma Foundation has recently announced a new chapter alignment in hopes to provide even further outreach to our Scleroderma community.

The new alignment includes 13 reestablished chapters across the country. Our chapter, formerly known as the Western PA chapter, will now be identified as the Mid-Atlantic Chapter.

Pittsburgh Area Support Group Meeting Schedule

Oct 28, 2023	Jan 27, 2024	Apr 27, 2024
Nov 18, 2023	Feb 24, 2024	May 25, 2024
Dec 30, 2023	Mar 30, 2024	Jun 29, 2024

For more information, contact **sfgrouppitt@gmail.com**

Scleroderma Center
University of Pittsburgh
3500 Terrace Street
BST South 7th Floor
Pittsburgh, PA 15261

Scleroderma Research Faculty & Staff

Robert Lafyatis, MD
Professor of Medicine
Center Director

Thomas A. Medsger, Jr., MD
Professor of Medicine Emeritus

Robyn T. Domsic, MD, MPH
Associate Professor of Medicine
Clinical Director

Kathryn S. Torok, MD
Associate Professor of Pediatrics

Patrizia Fuschiotti, PhD
Assistant Professor of Rheumatology

Eleanor Valenzi, MD
Assistant Professor of Pulmonary

Cristina Padilla, MD
Postdoctoral Scholar & Clinical Instructor

Anna Papazoglou, MD
Clinical Instructor of Medicine

Mengqi Huang, PhD
Instructor of Medicine

Leigh Freno, CRNP
Clinical Care

Christina Morse, BS
Laboratory Manager

Maureen Laffoon, BS
Clinical Trial Coordinator

Eileen Roth, MT (ASCP)
Biorepository Manager

Leah Wunsch, BS
Research Assistant

Elizabeth Evans, BS
Clinical Research Coordinator

Erika Benson, BS
Clinical Trial Coordinator