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Spotlight on Systemic Sclerosis: Pathophysiology, Presentation, & Emerging Evidence

Announcer:
Welcome to CME on ReachMD. This activity, titled *Spotlight on Systemic Sclerosis: Pathophysiology, Presentation, & Emerging Evidence*, is provided by the France Foundation. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Castelino:
Hello and welcome to our session called *The Spotlight on Systemic Sclerosis*. We'll talk about pathophysiology, the presentation, and emerging evidence. I'm Flavia Castelino. I'm an Associate Professor of Medicine at Harvard Medical School, and I direct the Scleroderma Program at Massachusetts General Hospital.

Dr. Korman:
And my name is Benjamin Korman. I'm an Associate Professor of Medicine, Allergy, Immunology, and Rheumatology at the University of Rochester, in Rochester, New York, where I lead our Scleroderma Program.

So now, to go over an outline of what we're going to be talking about and our learning objectives. We're going to start with an overview of the pathogenesis of systemic sclerosis, and specifically, we're going to describe the mechanisms underlying SSc pathogenesis with an emphasis on the vasculopathy-fibrosis axis and its relationship to clinical features. Next, we're going to have two interactive cases. The first one is going to be looking at pulmonary hypertension, the second at interstitial lung disease. And across these we're going to try to apply guideline-recommended methods to enable early and accurate diagnosis, as well as to interpret merging clinical evidence and data to optimize the treatment of SSc, PH, and ILD. And lastly, we'll talk about key takeaways and evaluation.

So first, going to that pathogenesis overview. So an overview of systemic sclerosis. This is a relatively rare disorder with an incidence of 1.5 cases per 100,000, with about 300,000 cases in the United States. It's a disease primarily of women with a 4:1 female to male ratio, and it's a complex, heterogeneous disorder that affects multiple internal organs, which has a poorly understood pathogenesis and which is heterogeneous, so not all the patients look the same. Unfortunately, it causes significant morbidity and mortality, with—these are probably older numbers—but only about a 2/3 10-year survival, and that being substantially reduced to less than 50% in patients with severe internal organ complications which can compromise things such as the heart, the lungs, the kidneys, the GI tract. And unfortunately, we don't yet have fully effective treatments, and we don't have great biomarkers for scleroderma.

So, scleroderma comes in a couple of different subtypes. We generally think of these left two, the limited cutaneous and diffuse cutaneous subtypes. The limited subtype, which is the most common, was formerly known as CREST, and this is a phenotype that will present typically with distal skin fibrosis, so things like sclerodactyly, and may present with pulmonary hypertension. It's less likely to have fibrotic complications like interstitial lung disease and renal crisis. Diffuse cutaneous disease is a less common manifestation, and usually is going to present less indolently, right? These are going to be patients who are going to present suddenly, and they're going to have more organ manifestations such as interstitial lung disease, scleroderma renal crisis, GI, cardiac disease, pulmonary hypertension.

SSc sine scleroderma is similar to the first two, but does not have skin disease. And an overlap syndrome is something that we see not infrequently, where patients will meet classification criteria for systemic sclerosis, but will also have features of other rheumatic diseases,

like lupus, polymyositis, Sjogren's, etc.

So, talking a little bit about the molecular pathogenesis of systemic sclerosis. So, we think of there being a triad, so three parts to disease pathogenesis, those being vascular disease, autoimmunity, and fibrosis. So, we think of vasculopathy, or vascular disease, as sort of the inciting trigger of disease, whereby you will have an endothelial damage that will be some sort of an insult to the endothelium, which is going to lead endothelial cells either to die, to apoptose, or to become activated and to express things like adhesion molecules, and that's going to allow immune cells to get through the blood vessel and into the tissue. The types of immune cells that we see in the tissue include B cells that make SSc-specific autoantibodies, T cells, which are primarily going to polarize towards a Th2 direction, and macrophages that are going to polarize towards an M2 direction, and then make cytokines that are going to be relevant to pathogenesis, like TGF-β, IL-6, and IL-13. The production of these things is going to take a fibroblast, which is in a resting state, and it's going to activate the fibroblast. An activated fibroblast is going to become a myofibroblast, which is then going to be able to make extra extracellular matrix, and therefore is going to lead to collagen deposition and to fibrosis.

Moving on to describe vasculopathy. So, vasculopathy in scleroderma actually comes from a number of different mechanisms. The first is that you have too many vasoconstrictive pathways. This is often mediated by things like endothelin 1, and also by alpha-adrenergic receptors. Second, you're going to have a decrease in vasodilatory mechanisms. This is going to be a result of loss of signaling from things like nitric oxide, as well as decrease in vasodilatory neuropeptides. As we already described, there's endothelial damage through oxidative stress, this is going to make it so you'll have vascular dysfunction. And lastly, you might have reduced blood flow as a result of things like increased viscosity, platelet aggregation, and the likelihood to make clots.

In terms of fibrosis, fibrosis really happens when the fibroblast gets activated into a myofibroblast, and this can be triggered by a number of different things. So, tissue injury will often lead to tissue stiffness, as well as to the production of factors like TGF-β and CTGF, which will activate the fibroblast. Once the fibroblast becomes activated, it's going to have pathways such as mechanotransduction, TGF-β signaling, which are going to lead it to produce extracellular matrix, to become less likely to undergo apoptosis, which is what happens in normal wound healing, and to, therefore, survive and persist, to allow scar formation in a vicious cycle, and therefore for us to have fibrotic disease.

Thinking about autoimmunity, one of the hallmarks of autoimmunity in systemic sclerosis is autoantibodies. 95% of patients with SSc have antinuclear antibodies, which are primarily either a centromere or a nucleolar pattern. There are three classic antibody patterns, which we see in SSc, the first being anticentromere disease, which tends to be associated with the limited cutaneous or CREST subtype, milder disease, and pulmonary hypertension later in the disease course. The second two antibodies, SCL-70 and RNA polymerase III are both seen in the diffuse subtype. SCL-70 is also associated with interstitial lung disease, as well as with severe GI and cardiac manifestations. Whereas RNA polymerase III has a different course, where it'll have more rapid skin progression, which then also can improve faster, as well as a risk of renal crisis and of malignancy.

So, many patients will present before they have a full diagnosis of systemic sclerosis. So, it's important to recognize some of the early disease manifestations. These include Raynaud's phenomenon, which is often marked by abnormal nailfold capillaries. While this is something that you can see in the clinic just by the naked eye or using something like a capillaroscopy device that is handheld, you can also perform nailfold video capillaroscopy, which is a higher magnification exam, which allows you to identify a scleroderma pattern and helps make a diagnosis. These patients will also have puffy fingers, which can be either from an edematous phase, from early signs of skin induration and tightening, or in some cases, from inflammatory arthritis. These patients will often also present with gastroesophageal reflux disease, or GERD. And if patients present with multiple features, they're very much likely to develop scleroderma within 5 years.

So that leads us to the classification criteria for SSc. So, the ACR and EULAR in 2013 published these criteria where there's a point system, and so you can see if you have skin tightening of the fingers of both hands proximal to the MCP joint, that is 9 points, which is sufficient to meet diagnosis. But, if you don't meet that criteria, there are a number of other characteristics, such as puffy fingers, digital ulcers, telangiectasias, nailfold capillaries which we just mentioned, pulmonary hypertension or interstitial lung disease, and autoantibodies, all of which give you 2-4 points. And if you have 9 points between this, then you can be classified as having systemic sclerosis.

So, thinking about the progression of disease, we mentioned that early on you're going to have vascular injury, and that's probably where you're going to present

with that Raynaud's or puffy fingers presentation. But, once you see that patient, you want to be thinking about more severe complications that may happen later. And the course of the patient is going to help you figure out, is this patient going to be more likely to have limited or diffuse skin disease, and what organ manifestations are they going to be at risk for? So, a patient with Raynaud's who

then goes on to develop digital ulcers 3-5 years later, is likely to be a patient that you want to be thinking about as a limited cutaneous patient who's at higher risk of things like pulmonary hypertension or liver disease, primary biliary cirrhosis, and that's very different from the patient whose skin gets much worse quickly, who also has some joint or muscle inflammation, who might be the patient that you're thinking about as being at risk for things like renal crisis or cardiac disease or interstitial lung disease.

So, speaking of organ manifestations, we can think of them in terms of things which are common and cause morbidity, and these include things like Raynaud's phenomenon, which is present in almost all patients, and a severe manifestation of which is digital ulcers, which is present in a minority of patients, skin disease, which is really the hallmark of disease, and you can see pictures over here on the right of a patient who really has that tight, shiny skin that we call sclerodactyly, as well as potentially digital contractures. Skin disease can be progressive, so it won't just affect the hands, especially in diffuse disease, you can have this over the entire body. GI disease, we mentioned GERD, but this motility is also very common, and in a subset of patients, you may see more severe complications, such as GAVE or malabsorption. And then musculoskeletal disease is common, so things like arthritis and myositis are not infrequent. And when we see patients, especially with diffuse disease, who present with tendon friction rubs, those are actually usually patients you worry about having more severe internal organ disease.

So, speaking a little bit more about Raynaud's phenomenon, we mentioned that this is very common, and it's a progressive micro- and macrovascular ischemic injury. Ulcers will occur in 35-50%, and from a mechanistic standpoint, this is caused by immune-mediated endothelial injury, which leads to impaired angiogenesis and vascular remodeling. And here on the bottom, you can see a patient in the bottom left who has classic Raynaud's phenomenon with two white fingers. This is usually preceded by red and afterwards the patient will have blue, and those are sort of the three phases of disease. And then a patient who has this, who has secondary Raynaud's—Raynaud's secondary to scleroderma—is going to be at risk for ulcers. And so, you can see an ulcer in A here, and in some cases, these may be associated with extra tissue, hyperkeratosis, they may be associated with calcinosis, and in severe cases, they can lead to gangrene.

Then thinking about organ manifestations that now maybe are not as common, but which present with higher morbidity and mortality. We have interstitial lung disease, which is the leading cause of mortality, which is really an inflammatory and fibrotic manifestation that we think of in that SCL-70 antibody subset, which leads to progressive loss of lung function. Pulmonary hypertension, which is a vascular complication seen in later limited disease, can lead to right heart failure and has

high mortality. Scleroderma renal crisis, which used to be the leading cause of death and presents acutely with hypertensive urgency, mostly in RNA polymerase III patients. And cardiac disease, which can have multiple manifestations, including diastolic heart failure, myocardial fibrosis, conduction abnormalities, and pericarditis.

So just a little bit more about some of these manifestations. Scleroderma renal crisis is relatively rare, present in 2-15% of patients, and this will often happen in early diffuse disease. We have an acute vascular injury which leads to a thrombotic microangiopathy, which will then result in this typical biopsy lesion that you can see on the right of onion skinning fibrosis. These patients are going to present with sudden severe hypertension, with renal failure, and a microangiopathic hemolytic anemia.

Pulmonary hypertension is most commonly seen in patients with longer standing disease, usually after 10 or 15 years. Mechanistically, this is caused by a vasculopathy or loss of the pulmonary capillary endothelium, overproduction of vasoconstrictive and underproduction of vasodilatory mediators, and pressure overload. Characteristically, these patients will present with insidious dyspnea exertion, signs of right heart failure, and they have worse outcomes and treatment response compared to patients with other causes of pulmonary hypertension.

Interstitial lung disease is more common, right, this is present in 30-50% of patients, and has the greatest risk for progression early in disease. Mechanistically, it's caused by a proliferative vasculopathy, as well as endoMT, or endothelial mesenchymal transition, where endothelial cells actually become fibroblasts, and thickening of the interstitium surrounding the pulmonary alveolar wall. Some patients don't have symptoms. If you look at the two biopsy lesions we have here, you can see in the inflammatory lesion, you have a number of immune cell infiltrating the lung tissue, whereas in the fibrotic lesion, the entire lung architecture gets ruined and replaced with collagen deposition.

All right, we're going to move to our cases. So our first case is going to be applying real-world strategies to improve the diagnosis of SSc PH. So our first case is a 66-year-old woman who has longstanding history of Raynaud's phenomenon, without ulcers, who's been managed with amlodipine, who presents to rheumatology clinic. She has some shininess to her fingers, and says her previous primary care provider told her that she has CREST, but that there was nothing to do and that she's not been followed regularly or had any labs or testing for many years. While she doesn't complain of shortness of breath, on further questioning, she notes becoming dyspnic when going up the basement stairs or walking one to two blocks. She also has been having increasing presyncopal episodes. She notes mild

lower extremity edema, and has noticed increasing red spots on her face and hands in the last year, and she was admitted last year for a GI bleed.

So, there are actually a number of red flags in this case, indicating that the patient could potentially have pulmonary arterial hypertension. These include longstanding limited cutaneous disease, older age, dyspnea on exertion, signs of poor perfusion, like presyncope, signs of potential heart failure, like the swelling that she had in her legs, increasing vasculopathy, including telangiectasias that are increasing in number and possibly having GAVE with the GI bleed, and lack of prior screening for pulmonary hypertension.

As we mentioned before, pulmonary hypertension is relatively rare, it's present in 5-15% of the patients, and has an increased risk of death compared to other causes of pulmonary hypertension. Temporally, we think of this in later-stage disease, limited cutaneous patients will have telangiectasias, severe digital ischemia or Raynaud's phenomenon, and in certain antibody subsets, like the anticentromere subset, as well as another rare one that we didn't talk about, called the Th/To subset.

So definitionally, you actually have to do a right heart catheterization in order to diagnose pulmonary hypertension. So, if you do right heart catheterization, the criteria to be classified as having pulmonary arterial—not just pulmonary hypertension—is that you have a PA pressure which is greater than 20 mmHg at rest. And it's important to note that this was actually reduced from 25 which it was recently, so we're now catching patients a little earlier with this. You also can't have left heart disease, so you have to have a wedge pressure less than 15, as well as a PVR greater than 3 Woods units.

So, there are a number of screening strategies for scleroderma-associated PH. And because this is something that is relatively common and something that can be easily missed, both the ESC/ERS, as well as the WSPH, both recommend annual screening. The DETECT algorithm is one of the ones that is recommended by both, and it utilizes a number of different modalities. There's also a second mechanism called the ASIG screening criteria, so we'll talk about these in detail.

So the ASIG screening mechanism uses PFT, as well as a blood test, the proBNP, to determine the need for heart cath. For somebody who has normal DLCO as well as an FVC to DLCO ratio and a normal BNP, then they don't likely have pulmonary hypertension and can just be screened again. But if they have either the PFT or the BNP showing some potential risk and there is suspicion, then you would either move to further testing with an echo or to a right heart cath to confirm the diagnosis. In the DETECT algorithm, there's a number of points which include many of these same things, but also include clinical criteria such as telangiectasia, centromere antibodies, uric acid, an electrocardiogram. And if you have enough points based on all of these things, then you move to phase 2, which is to perform an echocardiogram. And so at that point, you would basically be determined whether you have enough risk points to undergo right heart catheterization.

So going back to our case, our patient was found to have an elevated NT-proBNP at 500 and if you remember the DETECT algorithm, there are also points associated for risk factors, and so this patient had a centromere antibody, telangiectasias, as well as PFT suggestive of possible PH, right, so an elevated FVC to DLCO ratio. So because of that, they moved on to stage 2 of the algorithm, an echocardiogram was performed, and it showed an elevated RV systolic pressure, which indicated that they needed to go on to right heart catheterization. Right heart cath was performed, and it demonstrated a pulmonary artery systolic pressure of 35, and remember, anything greater than 20 is considered elevated, as well as a normal wedge pressure and an elevated PVR, and those things together confirmed the diagnosis of pulmonary arterial hypertension. It's important that we do this. If we don't, then we actually miss patients and outcomes are worse.

So in a study that looked at routine practice versus a DETECT algorithm, they found that the 8-year survival rate of patients who just underwent routine screening was 17%. This is of patients who had pulmonary hypertension, and this is likely because we weren't picking these patients up early enough and treating them early enough. By comparison, patients who underwent one of these detection algorithms had a survival at that same 8-year window of 64%, so you saw an almost 3 times increase in survival in patients who were screened, and so it's really important to do that screening.

So there are a number of therapeutic targets that we can look for in pulmonary hypertension, the three main ones are the endothelin, the nitric oxide, and the prostacyclin pathway. So endothelin, as you'll remember, is the vasoconstrictive pathway, and so you will want to antagonize the endothelin receptor. And so there are a number of therapies, like ambrisentan, bosentan, and macitentan, all of which do that. There are a number of different ways which we can stimulate the production of nitric oxide and prostacyclin, each of which are vasodilatory. So phosphodiesterase inhibitors, sildenafil, tadalafil, are probably the most commonly used, and these work through inhibition of phosphodiesterase to increase the production of nitric oxide, whereas guanylate cyclase stimulators, like riociguat, are going to also increase nitric oxide, but by a different mechanism. And then in terms of prostacyclin, these are both vasodilatory and antiproliferative. And there are a number of different ways that you can give these medicines orally, intravenously, inhaled. And so we have medicines that do that as prostaglandin analogs. And then, more recently, they've also developed some receptor agonists, like

selexipag.

So in terms of guidelines, the EULAR, the European League Against Rheumatism, has made guidelines on how do we go about treating patients with SSc PH. And so in the patient who has not been treated at all, we do want to do upfront combination therapy using both endothelin receptor agonist, as well as a phosphodiesterase 5 inhibitor. If the patient's already on one of those things, for example, for digital ulcers, then you may want to consider adding or switching therapies, adding things like riociguat. Then obviously you're going to reassess patients after 3-6 months, and depending on the degree of heart failure that they're in, you may want to either continue the current treatment or to add additional treatment like IV prostacyclins.

So going back to our patient, the patient was started on combination therapy with tadalafil, which is our phosphodiesterase 5 inhibitor, as well as ambrisentan, which is our endothelin receptor antagonist. However, 6 months later, they are still in class III NYHA heart failure, and therefore considered not at treatment goal, and additional therapy is considered. These therapies include things like IV prostacyclin agonists, as well as riociguat.

So we have a number of new therapies that are coming on board. In phase 3 trials right now we have seralutinib, which is a tyrosine kinase inhibitor, specifically targeting the PDGF receptor, which we're looking at in its ability to improve exercise capacity. Recently, there was an approval of an activin receptor drug called sotatercept. And so there are multiple other drugs in this activin family which are under trial. And so KER-012 is an activin ligand trap, which is currently being evaluated in phase 2 trials. And something else interesting, thinking about maybe inflammatory mechanisms, is a new drug called satralizumab, which is an IL-6 receptor monoclonal antibody, which we're looking at in, specifically patients who have immune responsive phenotypes or who have an elevated IL-6 to see if that may improve pulmonary hemodynamics.

Dr. Castelino:
All right, so let's move on to a case. So, let's talk about applying real-world strategies to improve the diagnosis of systemic sclerosis ILD. So this is our next patient, a 65-year-old female with osteoarthritis, who is status post-bilateral hip replacements, who presents with bilateral hand swelling over the last 6 months, she notes that her fingers feel puffy and swollen, and over the last several years, her fingers have been changing color in the cold. In the last few months, she's also noticed some shortness of breath with going up a flight of stairs. On physical exam, her vitals are stable. In terms of her general exam, she's in no acute distress. And on pertinent positives she has evidence of thin lips. She has some telangiectasias across her face, her lungs are clear. On extremity exam, she has some evidence of sclerodactyly, as shown here in this image on the right. And then on her skin exam, she has further evidence of telangiectasias across various digits, her nailfold capillary exam shows some capillary drop out and dilated loops, and her skin score is a 6/51, primarily affecting her fingers, the dorsal hand, and the face. On review of her labs, her CBC, her chemistry and LFTs are unremarkable. In terms of her inflammatory markers, her ESR is elevated at 40, her CRP is 14, and her antinuclear antibody is 1:640 in a centromere pattern. Her SCL-70 antibody is negative, and the remainder of her extractable nuclear antigens is negative.

So how do we go about screening for SSc ILD? So typically, the starting orders include pulmonary function testing, where we obtain a spirometry and DLCO, and a baseline high-resolution CT of the chest. And it's important to remember that ILD is detectable by high-risk CT in about 90% of patients, while PFTs can only be abnormal in about 40-75% of patients. They will have a restrictive pattern with decreased force vital capacity, normal FEV1 to FVC ratio. It's important to note that changes of 10% or more in forced vital capacity, and 15% in the diffusion capacity are significant.

And on this slide, let's review the typical high-risk CT findings in SSc ILD. So the more common pattern is that of nonspecific interstitial pneumonia. And this is shown here on the left, so you can see at the bases of the lungs, there's evidence of ground-glass opacities in a more peripheral distribution. And additionally, patients with NSIP can have subpleural and basilar predominance. The usual interstitial pneumonia pattern is seen in patients with SSc ILD as well, however, it's more rare. And this is characterized by evidence of honeycomb cysts here, as you can see in the periphery, evidence of traction bronchiectasis as well, and reticular nodular opacities.

Now, the American College of Rheumatology and CHEST published their criteria in 2023, and they developed a list of risk factors for development of SSc ILD. So, as you're evaluating a patient with systemic sclerosis, it's important to think about these particular risk factors and risk for interstitial lung disease. So, a patient with a positive SCL-70 antibody, a patient with antinuclear antibody in a nucleolar pattern, is at risk of developing SSc ILD. In addition, patients who are early in their disease in the first 5-7 years after disease onset are at risk. And then in terms of the subtypes of cutaneous subtype, a male with systemic sclerosis is at higher risk for ILD, and African American race. Patients with elevated acute phase reactants, in addition, are at risk for SSc ILD.

So moving back to our patient, so our patient undergoes pulmonary function testing, and shown here in this table are her PFT results. So, her FEV1 is 79% predicted. Her FVC is 75% predicted, with the ratio being normal at 104%. She does have a reduction in her DLCO at 52%. In terms of the echocardiographic findings, her ejection fraction is 70%, and her estimated right ventricular systolic

pressure is 30. And she undergoes a high-resolution CT. Shown here are two images with the orange arrows, we're looking at evidence of ground-glass opacities, and then the blue arrows are showing evidence of traction bronchiectasis. And this CT was read as this patient had evidence of more of a fibrotic NSIP pattern.

So as I mentioned, the 2023 ACR CHEST guidelines came out with categories of treatment for the treatment of SSc ILD, and the preferred first-line treatment has become mycophenolate mofetil. This has been chosen over cyclophosphamide, given the side effect profile. Additional considerations for first-line therapy include tocilizumab, and this can be considered, especially in patients with more early, inflammatory, diffuse systemic sclerosis with ILD. Rituximab is another potential first-line option. In terms of additional considerations, cyclophosphamide, nintedanib, an antifibrotic, or azathioprine could initially be considered, but these are not considered first-line therapy. It's important to note that glucocorticoids are strongly contraindicated in the treatment of SSc ILD.

What about patients who may progress? So if a patient progresses in terms of their ILD, if they're already on mycophenolate, then an additional agent can be considered. Either a patient can be added or switched to this therapy. For example, a patient may be switched to rituximab, or if they have more of a fibrotic component, with progression of their fibrosis, nintedanib could be considered. Tocilizumab can additionally be considered, especially if a patient is early in the disease and has high inflammatory markers. And cyclophosphamide is still an option. If a patient continues to progress, stem cell transplant referral is also indicated, and this can be considered on a case-by-case basis. It's important to also collaborate with our pulmonary colleagues and determine the need for when a lung transplant evaluation may be warranted. And again, even in progressive lung disease, it's important to remember that glucocorticoids are not indicated for the treatment of SSc ILD.

And this next slide outlines a recent paper that we published on the expert consensus on SSc ILD. So typically, what we do in practice is we initiate therapy with mycophenolate and at a dose from anywhere from 2000-3000 mg a day. We will consider an nintedanib, especially for patients who may progress. If a patient has no need for immunosuppressive medication, if their skin is stable or their skin is mild, nintedanib can be considered as monotherapy for SSc ILD. And, as I mentioned previously, the tocilizumab can be an option, especially for patients with elevated acute phase reactants and those unable to continue mycophenolate cycle phosphide or antifibrotics, for example.

In terms of monitoring progression, this varies on a case-by-case basis. At the very least, we get annual PFTs in our patients, and the high-risk CT is really determined by any changes in pulmonary function testing. Some patients with more severe disease, we'll screen them with and monitor them with pulmonary function tests, usually every 3-6 months. In terms of tapering medications, one thing to consider is, if a patient is stabilized with their medications, to consider tapering some of their immunosuppression after they've been on it for about 2 years.

So our patient was started on mycophenolate, and the dose was gradually titrated up to a dose of 1500 mg twice daily, and the patient was scheduled for follow-up every 6 months. And you can see here in this table, the changes in the pulmonary function testing, so at baseline, at 6 months, and then again at 12 months. And you can see that the pulmonary function testing has overall remained stable, with maybe some mild improvement in the diffusion capacity.

And as we're caring for our patients with SSc ILD, it's important to think about the multidisciplinary aspect. Multidisciplinary care has been shown to increase the accuracy of diagnosis, so certainly, early evaluation is key, and getting access to the various specialists that are important in the care of scleroderma patients. If you are in the community, co-management with an academic or specialist physician can be really important. And a lot of this multidisciplinary care can happen asynchronously, for example, this can happen over phone calls, through secure messaging, using the hospital system. And it doesn't have to be that you have to be that you have to be an academic center to participate in multidisciplinary care. And just want to again highlight that both the diagnosis and management of systemic sclerosis is a combined effort of many different specialists, as rheumatologists, we're lacing with pulmonologists, cardiologists, dermatologists and especially the primary care, and the radiologists and pathologists can be extremely helpful, especially if a patient has undergone imaging for ILD as well as the lung biopsy for ILD.

And in terms of patient education, one of the things our scleroderma patients tend to do is they may minimize their symptoms or attribute it to their scleroderma as a whole. So it's really important to encourage patients, one, to be active participants in their care, and to encourage telling us about symptoms that they may be feeling, that they may attribute to their scleroderma, but in fact, are related to interstitial lung disease. It's also important for patients to understand that systemic sclerosis, or scleroderma, is a multi-system disease, and it's important to monitor for any disease evolution. It's also important, as we're planning treatments for patients, to use shared decision-making, so that a patient is comfortable with the treatment options provided and the decisions made.

So let's review the newer therapies that are available in clinical trials for systemic sclerosis. As a reminder, there's no current effective treatment that combats systemic sclerosis across organ systems. So the VITALISScE study, which is a phase 2 trial looking at

avenciguat, which is a soluble guanylate cyclase activator. So this is a study that's looking in interstitial lung disease. And the primary endpoint here is a change in forced vital capacity. The secondary endpoint is a change in the skin score. And additional endpoints that are looking at include various vascular vasculopathy measures, including Raynaud's phenomena and digital ulcers. The DAISY study is the anifrolumab study, which is an anti-interferon alpha/beta receptor monoclonal antibody. And this is a phase 3 study looking at the composite response index in systemic sclerosis with secondary endpoints in forced vital capacity and the Modified Rodnan Skin Score.

So the CONQUEST study is a platform trial, where the patient may have an option of potentially being enrolled in a trial either looking amlitelimab, which is an OX40 ligand inhibitor, or nerandomilast, which is a phosphodiesterase 4B inhibitor compared to placebo. So this is a nice study in that the patient can be enrolled into one of two different drug trials while enrollment into CONQUEST. And the primary endpoint here is a change in forced vital capacity at 52 weeks. In addition to CONQUEST, there's additionally a lot of interest right now in CAR T therapy for systemic sclerosis, and there are a number of early phase studies looking at CAR T both for systemic sclerosis fibrosis and ILD.

So as you're continuing on in practice, it's important to think about the various emerging therapies, and to really refer patients early, especially if a treatment is not available at your practice. So specialty academic centers have access to various clinical trials, as well as disease-specific specialists. And then, again, I want to reiterate the importance of co-managing patients, one, with the academic centers and also with community physicians, and trying to determine a good interval for follow-up by each physician, determining which aspects of the care will be managed by each physician, and important to also monitor patients for disease progression and modify treatment as needed.

Time for discussion in terms of management. So how can you improve access to therapies that are not necessarily available where you practice? Dr. Korman, I don't know if you want to give your thoughts on on how you handle this at your practice.

Dr. Korman:
Yeah so I think it's really important that you be plugged in, both with specialists locally and nationally, in the individual domains that we're treating. So you probably want to have access to, particularly since we're talking about ILD and PH, the pulmonary colleagues who have access to these medications. So if you're not at a place where those are things that are available, then that's particularly important. But for people who don't have these drugs or don't use them regularly, certainly referring to a tertiary center and a place that focuses on scleroderma, makes a lot of sense.

Dr. Castelino:
Yes, and certainly also with the newer drugs, it's important to have that support for the prior authorizations to make sure patients are getting the drugs approved. And oftentimes at these academic specialist centers, you know, they have the resources and the ability to get a lot of these drugs approved.

So in terms of patients who are progressing, what is your typical practice style? Or what do you do next?

Dr. Korman:
It's something that needs to be somewhat individualized. In some cases, you can just go through approved therapies in sort of a stepwise fashion, especially if the person is progressing maybe slowly, or you have reason to believe that a different mechanism might make sense. But in cases where you're struggling, where the patient's really not doing well, you certainly want to, you know, collaborate with, you know, both your specialists as well as people at other centers, and think about referring patients for clinical trials.

Dr. Castelino:
Absolutely. And again, this goes back to the academic centers. There's a lot of different clinical trials in the pipeline, as we've talked about, so getting a patient early into a clinical trial can be helpful just to improve, one, their access to care and potentially have access to a newer drug that might be effective for their ILD.

All right, so let's close with some of the key points that we've discussed in our lecture today. So vasculopathy, immune dysregulation, and fibrosis can occur simultaneously and self-perpetuate to cause the symptoms and complications of systemic sclerosis. As we've talked about, the leading cause of mortality in systemic sclerosis is interstitial lung disease. And recently, there have been development of various guideline recommendations to both aid with screening patients and treating patients with SSc ILD and pulmonary hypertension. Important to remember that to collaborate with the various specialists, this can improve patient care, and additionally provide access to newer therapies. And practice tips to take home include that it's important to screen patients with Raynaud's phenomenon or puffy fingers for systemic sclerosis, and to really screen all our patients with SSc for pulmonary hypertension and interstitial lung disease. Think about applying the guideline recommendations for screening, diagnosis, and treatment, and again, co-manage these patients with the various multidisciplinary specialists.

Announcer:
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