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SSc-ILD: The Importance of Early Diagnosis, Patient Centered Communication and Evidence Based Treatment

Announcer:
Welcome to CME on ReachMD. This activity titled, *SSc-ILD: The Importance of Early Diagnosis, Patient Centered Communication and Evidence Based Treatment*, is provided in partnership with National Jewish Health and is supported by an independent educational grant from Boehringer Ingelheim pharmaceuticals, incorporated. Before starting this activity, be sure to review the disclosure statement as well as the learning objectives.

Dr. Yunt:
Hello, and thank you for joining us for this program titled Systemic Sclerosis Interstitial Lung Disease: The Importance of Early Diagnosis, Patient-centered Communication, and Evidence-based Treatment. I'm Dr. Zulma Yunt, pulmonologist at National Jewish Health, and I'll be guiding you through the first part of this presentation.

I'd like to give a "thank you" to Boehringer Ingelheim for helping to fund this educational activity.

Please take a moment to review the Accreditation Council statement.

Listed here are our disclosures as presenting faculty.

And now let's take a moment to introduce our faculty: Dr. Amy Olson, pulmonologist in the Interstitial Lung Disease Program and associate professor at National Jewish Health; myself, Dr. Zulma Yunt, pulmonologist in the Interstitial Lung Disease Program at National Jewish Health; and our esteemed colleague Dr. Virginia Steen, Chief of the Division of Rheumatology and professor at Georgetown University.

These are our learning objectives for today's program. First, we will apply the best practices in diagnosis based on clinical symptoms, pathophysiology, and disease course in systemic sclerosis ILD. Second, we will utilize evidence-based decision-making to determine the best treatments for patients with this complex condition. Finally, we will apply strategies for longitudinal management in systemic sclerosis ILD acknowledging that this typically involves multiple specialists with a multidisciplinary approach, and it commonly involves close communication with patients.

The first part of this talk we will review diagnosis, pathophysiology, and the evaluation.

So, systemic sclerosis, as I mentioned, is a complex condition. It is a systemic condition, it is autoimmune, and it's one of the connective tissue diseases. It is characterized clinically by overproduction and deposition of collagen into the skin and visceral organs, and this leads to a wide variety of disease manifestations. Two general predominant forms of clinical disease are recognized: limited cutaneous disease and diffuse cutaneous disease. And we'll talk a little bit more about those particular presentations.

It is very critical to understand that the lung is commonly involved in systemic sclerosis, and it manifests in 2 ways: interstitial lung disease and pulmonary arterial hypertension. It's important to recognize that these can both occur or one or the other can occur in any one patient. They don't necessarily or commonly even occur at the same time. Lung involvement is so common in systemic sclerosis that it is actually part of the latest diagnostic criteria.

So the diagnostic criteria for systemic sclerosis, or scleroderma, were updated in 2013, and the diagnosis is now made using a scoring system. The elements of the scoring system reflect 3 ultimate hallmarks of systemic sclerosis. The first of these is vasculopathy, the second is autoantibodies, and the third is fibrosis of the skin or organs. And under this diagnostic system, a score of greater than or equal to 9 points gives a definitive diagnosis of scleroderma. This scoring system was tested against other autoimmune conditions and was found to have a very high sensitivity and specificity of greater than 90% for both. You'll note that the presence of lung disease earns 2 points on the scoring system.

In patients diagnosed with scleroderma, 2 general disease subsets are recognized. I mentioned this earlier. These are the limited cutaneous scleroderma and diffuse cutaneous scleroderma, and the nomenclature here really reflects the extent of skin involvement.

In limited cutaneous systemic sclerosis, skin involvement occurs gradually, and it involves the distal extremities. It may involve the face and the neck and the upper chest, but it generally spares the trunk and the central part of the body. Esophageal dysmotility is common, and interstitial lung disease is common. It occurs in 17–35% of patients. Pulmonary arterial hypertension is common in this condition and is generally more severe, generally occurs later in the course than in diffuse cutaneous disease. The anti-centromere, or ACA, antibody is common. It is seen in 70–80% of cases.

Diffuse cutaneous disease is generally regarded as the more severe and aggressive form of scleroderma. In this condition, thickening of the skin occurs early, and it can manifest throughout the entire body. Esophageal dysmotility is common, and so is intestinal disease often with malabsorption. In diffuse cutaneous scleroderma, ILD is very common, occurring in 53–73% of patients. Pulmonary arterial hypertension can be seen as well, though it's a bit less frequent than in limited disease. The classic antibody associated with diffuse cutaneous scleroderma is the anti-topoisomerase I antibody, much better known as Scl-70. We'll talk more about antibodies a little bit later on.

In terms of the prevalence of this disease, it's rather uncommon. Its prevalence is 7–44 per 100,000 people, and the incidence is somewhere between 0.6–5.6 per 100,000. It is recognized that the disease occurs more commonly in certain populations. In particular, in the US and Australia, it occurs more frequently than in Europe and Asia. It's actually quite uncommon in Asians. The disease occurs more frequently, quite notably, in African-Americans and in females. Unfortunately, there is certainly a mortality associated with this disease. Ten-year survival is 65–73% in Europe and 54–82% in North America. ILD is present in 70–80% of patients with scleroderma, so it is extremely common. The ILD is progressive in 25–30% of patients, so you'll note that not everybody has aggressive or progressive ILD, but it's extremely common, and many do.

The pathogenesis of scleroderma is very complex. Broadly speaking, pathogenesis involves an initial vascular injury that then triggers inflammation and an autoimmunity. This leads to recruitment of fibroblasts. Fibroblasts differentiate into myofibroblasts, and this lays down collagen and scar. Let's take a moment to see how this happens in the lung.

Systemic sclerosis is a complex autoimmune disorder associated with abnormal humoral and innate immunity. Disease manifestations may occur in multiple organs, including the lung. Disease manifestations in any one individual are likely determined by environmental, genetic and epigenetic factors in addition to autoimmunity.

Microcirculatory abnormalities are the earliest and most ubiquitous pathogenic findings in systemic sclerosis. Within the lung, early disease findings include microvascular injury but also interstitial and alveolar inflammation or alveolitis. This commonly occurs together with fibrosis in the early stages of disease.

In systemic sclerosis ILD disease pathogenesis, injury to lung endothelium and epithelium is followed by abnormal repair. The precise insults that trigger injury are not known. However, autoimmunity, environmental factors, aspiration and pathogens may play a role.

As in IPF, genetic factors predispose some individuals to abnormal repair following injury. However, the specific gene polymorphisms associated with fibrosis in systemic sclerosis differ from those in IPF.

Repetitive injury to lung endothelial and epithelial cells activates innate and adaptive immune responses. This leads to release of TGF-β thrombin, Wnt/β-catenin and other fibrogenic proteins. TGF-β is involved in multiple important pathogenic processes. These include inhibition of alveolar epithelial cell proliferation, increased MMP-7 expression, myofibroblast activation, and extracellular matrix accumulation. Thrombin potently induces several pathogenic cytokines, chemokines, and growth factors, as well as extracellular matrix proteins. Thrombin is mitogenic for fibroblasts and enhances fibroblast proliferation. Monocyte-macrophage crosstalk and IL-6 also appear to be important.

At the cellular level, immune activation leads to epithelial cell alteration. This may include epithelial-mesenchymal transformation and/or apoptosis. Loss of epithelial cell integrity leads to secretion of glycoproteins into the circulation, including surfactant protein-D and KL-6, which have been studied as biomarkers in systemic sclerosis ILD. Persistent lung injury further induces recruitment and activation of

lung fibroblasts with anti-apoptotic features. These cells play a central role in extracellular matrix formation.

In systemic sclerosis ILD characterized by progressive fibrosis, fibroblasts transform into myofibroblasts, which secrete increased levels of matrix components furthering scar formation. Myofibroblasts in association with matrix proteins and soluble factors drive ongoing fibrosis.

By the end of these multiple profibrotic processes, fibrosis has been established destroying the alveolar unit, the interstitium beyond it and the endothelial cells. This process is generally not reversible and tends to lead to more fibrosis.

Dr. Yunt:
Now that we've reviewed the pathogenesis, let's see how this translates to clinical presentation.

So, when you as a pulmonologist or a clinician see somebody with scleroderma, recognize that whether they have limited or diffuse cutaneous scleroderma, ILD can occur, and it may be severe. Generally, in patients that have ILD, they'll be recognized within the first 5 years of their diagnosis. Patients with ILD in scleroderma most commonly have the Scl-70 antibody or an ANA nucleolar pattern. It is important that this can be seen in either diffuse or limited cutaneous disease.

In terms of symptoms, it's important to recognize that not all patients that present with scleroderma ILD actually notice respiratory symptoms. Many patients may have subclinical disease or very mild disease when it's recognized. Common symptoms include cough and shortness of breath. The cough is often a dry cough and, as with many patients, can be multifactorial, but in patients with scleroderma due to the rather significant involvement of the esophagus with esophageal dysmotility, it's important to remember that that is commonly an important contributor to cough.

In terms of the physiology on pulmonary function testing, a restrictive pattern is classic, but because disease may be mild, it may be normal in some cases. Also remember that a reduced DLCO can reflect ILD, but it can also reflect pulmonary arterial hypertension, and in some patients it may indicate both.

To really assess patients and understand their initial clinical presentation as well as management going forward, it's important to get baseline studies, and this includes pulmonary function tests, an oxygen assessment typically with a 6-minute walk test, and an HRCT.

Let's review some of the clinical presentation in systemic sclerosis ILD. On HRCT, which is a very critical and important tool in the initial evaluation of such patients, NSIP is by far the most common pattern that's seen. This pattern is notable for being basilar predominant and peribronchovascular, so more central in location. Classically, NSIP has some subpleural sparing to it on imaging, and you might see ground glass opacities, which are non-fully-consolidative opacities that can be seen through such that the structures underneath that opacity can be seen. Reticulation is more classic of fibrosis, and it's common, particularly in fibrotic NSIP. Traction bronchiectasis results from a pulling of the airways due to surrounding fibrosis in the lung, so that can be seen, particularly, of course, if patients are more fibrotic. Honeycombing is not seen with an NSIP pattern commonly at all.

Other patterns that may be seen include a UIP pattern, basilar and peripheral predominant pattern that does include honeycombing. It can look exactly like other conditions, even IPF. Pleuroparenchymal fibroelastosis, or PPFE, is not common at all in systemic sclerosis but does indicate a poor prognosis. This is characterized by pleural and subpleural consolidation, an apical predominance of the disease often with evidence of volume loss, and due to that, upper lobe disease. Very importantly, we should recognize that the radiologic pattern does not predict mortality.

Let's think about bronchoscopy and how this might present or how this might be helpful. Somewhat surprisingly, there is no significant lymphocytosis or really much abnormality in many bronchoscopies in patients with systemic sclerosis ILD. Some studies have indicated that a granulocytosis is associated with worse outcome, but in many cases the BAL lavage will be largely normal.

In terms of pathology, a study on 80 systemic sclerosis ILD patients identified that 78% had an NSIP pattern on pathology. Only 8% had UIP. Both cellular and fibrotic NSIP can be seen, but again, it's important to know that in terms of pathology, there is not a relationship to mortality based on the pathology.

We have talked about the fact that ILD is very common in scleroderma. We've also talked about the fact that the disease can be severe and progressive in either diffuse or cutaneous disease. But then how do we know who to be most concerned about? There are risk factors that have been recognized for patients with systemic sclerosis ILD, and it's important to review these. Being of male gender or older age is associated with worsening disease and risk of progression, being African-American is itself also a risk factor, and having diffuse cutaneous disease over limited cutaneous—though, as I've mentioned, it can be seen in both.

It's very important to recognize that early disease is generally when you see the most progression in interstitial lung disease. It's when you see it present and when you see it get worse, so within the first 5 years of diagnosis, one has to be quite vigilant for the possibility of

this. In addition to this, autoantibodies are very helpful. The Scl-70 antibody and a nucleolar pattern ANA, which is indicative of other antibodies outlined on this slide, are particularly associated with a more severe and progressive course. We'll talk more about tools that pulmonologists can use to better assess who might have a worse prognosis related to HRCT and to lung physiology, in particular FVC.

It's important to understand that pulmonary fibrosis is now the leading cause of mortality in systemic sclerosis. This was not the case decades ago. The blue arrows here indicate the percentage of deaths in scleroderma related to pulmonary fibrosis. If you look on the left, from 1972–1976, they were actually a minority of the cause of death. The renal crisis was actually the greatest cause of death at that time. Shifting over to 1997–2001, on the right side you can see that renal crisis is no longer a major cause of mortality, and instead, pulmonary fibrosis is the leading cause. You'll notice that pulmonary arterial hypertension is the second leading cause, so certainly the pulmonary system is important to be monitoring and managing in these cases. Thirty-five percent of systemic sclerosis-related deaths are due to pulmonary fibrosis. In light of this, all patients who are diagnosed with scleroderma should be screened with an HRCT at the time of diagnosis.

So, what can we do with an HRCT to better glean information and understand how we might manage these patients? In 2008, a very important paper was published by Goh and colleagues that help us stage systemic sclerosis ILD using HRCT and pulmonary function data. Under this system a designation as limited versus extensive disease was found to predict mortality, so let's look at this system. It's actually quite simple. There are only 2 steps in this. In the first step you assess whether there is less than 20% or greater than 20% of disease on HRCT. If it's unclear, then you use a cutoff of 70% on the FVC to determine whether one as limited disease or extensive disease. Let's go through an example.

These CT scans outline and demonstrate the extent of fibrosis on a patient with scleroderma ILD. In the upper lobes, the 2 pictures on the left, there is really not very much disease that you see, and on the right there appears to be reticulation in the periphery predominantly at the bases. If you review it, you might say, "Yeah, this definitely has less than 20% disease," or you might be a little bit more on the fence. So, let's say that we're not certain.

Then we look at the FVC. Based on the HRCT, we fall into the indeterminant category, and saying that this person's FVC was 82% of predicted, this would then indicate that the patient would be categorized as having limited disease, and this is very important in understanding prognosis and mortality for this patient. As outlined in this graph, patients with limited disease have much better survival than patients with extensive disease with a hazard ratio of 3.46, so it's important to go through this exercise in patients with a new diagnosis of scleroderma and ILD. And in this study they found that it was very reproducible. They actually had a group of medical students with only 10 minutes of training in reading HRCTs perform this, and they actually very commonly came up with the same answers as expert radiologists and pulmonologists, so the nice thing about this is that it's quite simple and very reproducible despite your training level.

How else can we use clinical data from the pulmonary field to determine mortality in these patients? Well, pulmonary function testing trends at 1 year also predict mortality. This was another paper published by Goh and colleagues, this one in 2017, and in this study they looked at survival based on decline in FVC. They looked at a greater than or equal to 10% relative decline in the forced vital capacity over a year, and this led to a hazard ratio of 1.84 for increased mortality in patients that met this criteria versus patients that had less than 10% decline.

In another aspect of this study, they examined the CCD index, which looks at a 5–9% relative decline in FVC and greater than 15% relative decline in DLCO, and if you can meet those criteria, the patients grouped in that category had increased mortality with a hazard ratio of 1.96.

Generally speaking, we tend to use the FVC decline because it's a quite straightforward analysis that we can do, so looking for a greater than or equal to 10% relative decline in FVC is an important thing that one can do with their scleroderma ILD patient.

So let's think again about the disease course in scleroderma ILD. Let's remember that ILD typically develops within the first 5 years of the first non-Raynaud's phenomenon or the scleroderma manifestation. Most FVC decline occurs in the first 4 years after scleroderma is diagnosed. That's why it's so critical in that first period of the first 5 years to really be mindful and watchful for the possibility that the disease could progress.

It's important to understand that the disease course is variable though. Some patients have stable disease and really don't seem to progress, others may experience slow gradual progression, and some progress rapidly, which is why we need to be mindful and try to really identify who to watch closely and who to treat.

So, if you're a pulmonologist, the concerning features for a patient presenting to you would be a recent diagnosis of scleroderma, the presence of certain auto antibodies, particularly the Scl-70 antibody, the absence of an anti-centromere antibody, declining forced vital capacity, as we just saw with a greater than 10% decline per year—remember that on physiology seeing an isolated decline in DLCO

could indicate pulmonary arterial hypertension, so that's another thing as a pulmonologist to be looking for—and then extent of disease on HRCT using that strategy of categorizing patients with extensive or limited disease. This should be evaluated and examined in every patient that presents with scleroderma ILD, and depending on which of these criteria patients meet, that should really guide management decisions.

As I mentioned, scleroderma is a complex condition requiring a multidisciplinary approach, so now we'll hear from Dr. Virginia Steen with regard to the rheumatologist's approach to managing these patients.

Dr. Steen:
Thank you, Dr. Yunt. I think those are very important points that you made for our pulmonologists. As a rheumatologist who's been specializing in scleroderma, I have a little bit different approach to this problem because I'm seeing these patients much earlier than most of the pulmonologists. And yes, we do separate scleroderma into limited cutaneous and diffuse cutaneous, but it's important to remember that though these subsets are associated with extent of skin involvement and certain organ involvement, that certainly lung fibrosis can occur in both of these patient populations.

This is just a schematic which shows the time of the course of the disease on the bottom and the extent of skin involvement on the left-hand side and then when the organ involvement is happening, and as you can see, in both the diffuse cutaneous and the limited cutaneous, pulmonary fibrosis is occurring generally early in the disease. So, what I think is really important as far as the lung fibrosis in our patients is the relationship of the disease to the autoantibodies. The autoantibodies really are very important markers for the type of lung disease that our patients have. So the classic limited cutaneous antibody, anti-centromere antibody, is one that's really rarely associated with interstitial lung disease and, as we all know, has a high association with pulmonary arterial hypertension. The Scl-70 or anti-topoisomerase, again the classic antibody for diffuse cutaneous, is the one that has the highest occurrence of pulmonary fibrosis, but about 25–35% of these patients may have only limited cutaneous disease. Some of the other very important antibodies are ones that aren't easily obtained except that they have a nucleolar pattern ANA, and these are at the bottom of this slide. The U3-RNP, or fibrillarin, the Th/To and the Pm/Scl, and sometimes the only way you can tell that they may be present is because the antinuclear antibody is a nucleolar pattern.

So I think there are important caveats for all of us to consider, that the fibrosis occurs early but can stabilize, and in many circumstances our patients will totally stabilize and not have progressive disease. The antibodies are really helpful in deciding who's going to have the likelihood of progressive fibrosis. And importantly, just because they have some fibrosis doesn't necessarily mean that they require treatment. It really depends on the extent and the rapidity of change. And again, new shortness of breath does not always mean that they have severe fibrosis.

Another thing that I think is quite different between pulmonologists and rheumatologists is that we rarely use steroids. Again, most of my patients don't have a lot of symptoms when I treat them, and so steroids really have no benefit to them, and we've not shown that steroids, certainly nothing in high doses or anything, have any long-term benefit. There are a few patients that some short courses of lowest-dose steroids might be helpful for their pulmonary symptoms. And importantly, I think it's important to remember that anti-centromere antibody is actually protected of having severe fibrosis. The other thing is that, unlike in idiopathic pulmonary fibrosis, in scleroderma an isolated decreased DLCO is really not—it cannot be used automatically as a sign of early interstitial lung disease. I did a study that looked at a large number of isolated DLCOs in scleroderma, and only 4% of those patients went on to develop severe fibrosis as opposed to 20% of them developing pulmonary vascular disease. Another feature is that pleural effusions is not related at all in scleroderma to having pulmonary fibrosis, and we actually have found more cancers in patients that have pleural effusions.

Treatment of scleroderma ILD, particularly in our hands, has been strongly associated with immunosuppressive agents, and we've been working on this for many, many years and have conducted several scleroderma lung studies, the first of which was a double-blind, placebo-controlled cyclophosphamide versus placebo, and these patients… It was about 150 patients, and we showed that the FVC had a small but definite statistical difference between those that received the drug and those who did not. We realize that it did not correlate with the BAL. We were doing BALs as well as HRCT, and really, the only thing that the improvement or the worsening correlated with was the extent of fibrosis. So the unfortunate thing is that after the 1 year of Cytoxan, during the second year of the study, they lost effectiveness that the Cytoxan had given them in the first year, and by the end of 10 years, there was no survival difference.

This is the FVC from the Scleroderma Lung Study, and you can see there was actually even further improvement between 1 year and 18 months. And unfortunately, during that second year, during the placebo, the Cytoxan group lost effectiveness of the Cytoxan and ended up right where the placebo group was, but as you can see in this slide, it really was the more fibrosis that you had if you were on placebo the worse you got, and you had improvement with the Cytoxan, again correlated with the extent of fibrosis that you had.

So this is the symptoms, the Mahler, which I'm sure you're all familiar with, the TDI, and it showed that the patients that were on Cytoxan not just had that little small amount of increase in their FVC, they also had improvement in their symptoms, and I think that is really

important to remember.

In Scleroderma Lung Study II, we decided to compare cyclophosphamide for 1 year with a placebo versus 2 years of 3 grams of mycophenolate. We had hoped that we would show that mycophenolate was superior to Cytoxan, but it was a comparison trial. This study had 142 patients. They were mostly diffuse cutaneous, but again, as you see, 40% were limited. They had a mean of 2.5 years of symptoms. Their forced vital capacity was 66% predicted, and they had 26% of their CT scan had fibrosis as done by the quantitative methods by Jonathan Goldin.

Again, here was the effect of the study on the forced vital capacity. You can see there's improvement in both of the groups. Again, the Cytoxan was 2 mg/kg for 1 year followed by a placebo, and the MMF was 3 grams, and there was no superiority in the MMF group, but there was no difference in the outcomes between the 2 drugs.

This was the effect where you can see that not only did they just have that little bit of improvement, which we saw of 3%, 65–75% of the patients had improvement in their forced vital capacity up to 15%. And again, they also had improvement in their pulmonary symptoms, and they had improvement in their scleroderma symptoms, particularly the skin score. The important thing that we also found is that patients were much more readily able to tolerate the MMF, and as this slide shows, the patients that were on Cytoxan were much more likely to withdraw from toxicity, particularly cytopenias and infections. Surprisingly, our patients tolerate the MMF with little difficulty and do not have a lot of infections and also surprisingly don't have a lot of GI complications from it, although it certainly does occur.

The guidelines at this point done by the EUSTAR and European guidelines group has said that patients with early scleroderma, particularly those with interstitial lung disease, should be treated with immunosuppressive agents first, and this is certainly in the United States the standard of care. It has been shown to improve lung function as well as symptoms as well as skin and well-being in the patients, and as we showed, mycophenolate is better tolerated and has shown to have improvement in lung function.

We've talked about how the immunosuppressive treatment in scleroderma early interstitial lung disease is very important, and now Dr. Olson is going to tell us how working with pulmonary and rheumatologists and other groups as well as additional medications and treatments are also very important in the management of interstitial lung disease in scleroderma. Thank you.

Dr. Olson:
Thank you, Dr. Steen. In addition to immunosuppressive therapy, we also need to discuss antifibrotic therapy. Let's think back to the pathophysiology of systemic sclerosis-associated interstitial lung disease that Dr. Yunt presented earlier. In some patients there is the ultimate development of progressive lung fibrosis despite immunosuppressive therapy.

So, in 2014, the FDA approved 2 agents for idiopathic pulmonary fibrosis, which has a pattern of usual interstitial pneumonia on either histopathology or on imaging. Both slowed down the rate of FVC decline by approximately 50% over 1 year. One of these agents was nintedanib, which is a triple kinase inhibitor. The most common side effect from this drug was diarrhea. The dose is 150 mg orally twice daily, and you do need to monitor LFTs. Pirfenidone was the other drug that was approved at that time. It's an antioxidant, has anti-inflammatory properties, and also has antifibrotic properties. The most common side effects we see include nausea, weight loss, photosensitivity. The dose is 801 mg orally 3 times a day, and we do have to monitor the liver function tests.

So, nintedanib was then used in systemic sclerosis, and the trial was called SENSCIS. It was published in the *New England Journal* in 2019. It enrolled 576 patients with systemic sclerosis, and they were randomized to either nintedanib or placebo for 1 year. Patients had to have greater than 10% fibrosis on imaging, disease onset within 7 years, an FVC of greater than 40%, and a diffusion that ranged between 30–89%. Patients could be on background therapy with mycophenolate, methotrexate, or low-dose prednisone, and in fact, 48% of the patients were on background mycophenolate mofetil therapy.

The primary outcome was the adjusted annual rate of decline of FVC in ml per year. They saw no differences in the symptoms or the clinical signs of systemic sclerosis. The adverse events, which included diarrhea, were more common in the treatment group than placebo, and there were slightly more LFT elevations in the treatment group than placebo. Nintedanib was discontinued in about 16% of those on treatment versus 8.7% of those on placebo. Interestingly, the placebo group lost 93.3 ml per year versus the nintedanib group, which lost only 52.4 ml per year, or a difference of 41 ml per year, and that graph is shown here on the right.

Our next graph is the decline in FVC over time. You can see the nintedanib group on the top versus the placebo group on the bottom, and you can see what happens over that 52 weeks of time. Interestingly here, we start to notice the change at 24 weeks of therapy.

So, effective therapies to treat interstitial lung disease include cyclophosphamide and mycophenolate mofetil, and in this study, the SENSCIS study, 48% of patients did receive background therapy with mycophenolate mofetil. If we look at all patients, and what we just talked about, there was a difference of 41 ml per year. If we look at patients on background mycophenolate mofetil therapy alone, there seems to be maybe less of a benefit versus those that were not on mycophenolate mofetil where it seems there may have been more of

a benefit to the therapy.

However, the authors caution against overinterpreting multiple subgroup analyses as means at identifying independent predictors of treatment response, and I think down the road there will be more information about the true effects with those on MMF versus those who are not on MMF therapy and on nintedanib.

The next study included the INBUILD trial and used nintedanib in progressive fibrosing lung disease, but this also included systemic sclerosis. There were 663 patients with progressive fibrosing lung disease, or PF-ILD, other than IPF, and they were randomized to nintedanib or placebo. Their FVC had to be greater than 45%, their diffusion ranged from 30–80%, and their HRCT had to have greater than 10% fibrosis in their lungs. They were ultimately stratified by a UIP pattern or without a UIP pattern. They did have to have progression within the past 2 years and a relative decline of 10% of the predicted value or a relative decline between 5–10% of predicted value and increased symptoms or increased extent of fibrosis.

So the primary outcome was the annual rate of decline in the FVC. There was no background therapy allowed initially, but it could be added if there was further progression over the first 6 months. Of this group, 25.6% had connective tissue disease, and of that, 23% had systemic sclerosis-associated interstitial lung disease.

This is the data from the INBUILD trial, and as you can see, the top line is nintedanib therapy versus the bottom line is placebo, and you can see over time in terms of a fall in the FVC, the nintedanib group does better. In fact, the adjusted rate of decline with nintedanib was -80.8 ml per year versus placebo, which lost 187 ml per year. The adjusted rate of decline in those patients with UIP alone on imaging revealed that nintedanib patients lost 82.9 ml per year versus placebo, which lost 211 ml per year.

Finally, pirfenidone, the second agent we talked about earlier, has been studied in systemic sclerosis. There was a phase II trial of the safety and tolerability of pirfenidone in patients with scleroderma-associated lung disease called the LOTUSS trial, and as you can see, the first author was Dr. Khanna.

So the phase II trial of pirfenidone in systemic sclerosis-associated interstitial lung disease had 63 patients over 18 sites and in 3 countries. All subjects received pirfenidone. The time course was 16 weeks total, and each patient was titrated to 2,403 mg per day. They were randomized to 2- versus 4-week titration schedules.

The most common treatment-emergent adverse event included nausea, headache and fatigue. Again, mycophenolate mofetil was used in the background and was found to be used in 63.5% of patients. It did not seem to affect the tolerability of the pirfenidone. Eight-nine percent of the people completed the study. Six withdrew due to treatment-emergent adverse events, 5 in the 2-week titration group and 1 in the 4-week titration group. Treatment-emergent adverse events occurred more often during titration than maintenance. Severe treatment-emergent side effects were seen in 19% of subjects, and most of these occurred at full dose. There was no change in lung physiology, dyspnea, skin tightness, or quality of life indicators at 6 weeks. The conclusion was as follows: that pirfenidone had similar tolerability as seen in the IPF trials, and it was well-tolerated with mycophenolate mofetil.

Given the results of this trial, there is now the ongoing Scleroderma Lung Study III trial. It's a phase II, randomized-controlled trial that will be assessing the effects of pirfenidone and mycophenolate mofetil versus placebo and mycophenolate mofetil. The goal is to enroll 150 patients. The primary endpoint will be the change in FVC predicted over 18 months. Second endpoints will be the change in skin scores, extent, and total fibrosis on high-resolution CT scan.

So, in summary, not all rules are absolute. ILD should be suspected in anyone diagnosed with systemic sclerosis-associated interstitial lung disease. Initial evaluation should include assessment of respiratory symptoms, clinical examination including lung crackles, pulmonary function testing, high-resolution CT imaging, gas exchange markers and screening for pulmonary hypertension.

And in summary, as Dr. Steen said, consider early immunosuppressive therapy in those with high risk of progression or present with clinically significant disease and then consider antifibrotic therapy with nintedanib therapy in those who show evidence of progression despite immunosuppressive therapy.

So now I'm moving on to the longitudinal management of systemic sclerosis-associated interstitial lung disease. So, for longitudinal monitoring, Dr. Khanna and others have said that universal screening is paramount in identifying patients early. Fifty percent of general rheumatologists screen, and 66% of subspecialists screen, so let's screen and come up with our longitudinal monitoring plan.

So, as we can see here, we assess patients for underlying interstitial lung disease, and if they don't have it—and we move to the left of this chart—what we do want to do is monitor them closely for every 4–6 months for approximately 3–5 years to determine if they develop underlying interstitial lung disease, especially those in the high-risk groups we've talked about earlier. If patients then have changes in their FVC or diffusion or they have new symptoms, then we want to obtain a new high-resolution CT scan and go back and determine if they have interstitial lung disease on HRCT imaging.

So, if they do have underlying interstitial lung disease, we then go to the left and determine if this is subclinical disease. Do they have minimal or mild disease on HRCT imaging? Are their FVCs and diffusions preserved? Have they had minimal change in their FVC or diffusion which just may be measurement error? And do they have any symptoms? If they don't have symptoms and they appear relatively stable and that this is subclinical interstitial lung disease, then we typically continue to follow these patients until they possibly have the development of clinical interstitial lung disease.

Special thought may be given to those patients with a high-risk phenotype with subclinical disease. Some of those patients we may want to treat with immunosuppressive therapy early. And if the patient has evidence of clinical interstitial lung disease, as we see on the right side of the screen, with evidence of more severe disease on HRCT imaging or has had falls in their lung function or is clinically more symptomatic, then those patients are also treated with immunosuppressive therapy.

If a patient has worsening respiratory symptoms, we have to think of several different things besides just ongoing interstitial lung disease or worsening of their underlying interstitial lung disease. As we've talked about earlier, these patients do have pulmonary hypertension that may complicate the disease and may need to be screened for that. If they do have evidence of pulmonary hypertension, we recommend that they be referred to a pulmonary hypertension expert center. On the other hand, we also want to think about other things that may be causing worsening lung disease in these patients besides interstitial lung disease. Patients may have neuromuscular disease. They may have thoracic restriction. And commonly we see aspiration from their gastroesophageal reflux disease and esophageal dysmotility and even components of deconditioning. And I think given that a lot of these patients are on immunosuppressive therapy, we always need to ensure that they don't have evidence of infection driving this worsening symptom complex.

So, our longitudinal monitoring summary is as follows. We want to ensure that we do an excellent clinical examination and assess for worsening breathlessness or cough and then try to determine what's causing that. We also want to assess for extra pulmonary symptoms that may be occurring with this disease. We want to go ahead and complete pulmonary function testing, oxygen titration and HRCT imaging. How often should we do CT imaging? Some recommend that perhaps just routine CT imaging, not high-resolution CT imaging, may be performed annually to assess for lung malignancies. Again, at the onset of the evaluation, we want to ensure that there is not pulmonary hypertension, and so, therefore, they'll have an echocardiogram at baseline, and then if they have worsening symptoms, we want to consider pulmonary hypertension as a cause for these worsening symptoms. We also want to ensure that laboratory monitoring for patients on pharmacotherapies has been completed. And how often? Again, we clinically want to monitor at approximately 3- to 4-month intervals for the first 3–5 years or in those patients with evidence of progression, and we want to see any patient sooner for worsening pulmonary symptoms.

So, how do we do this? We need a multidisciplinary team. That's how we're going to provide an overall approach to care. So we need our primary care physician to help coordinate the care of all the subspecialists these patients may require. For the systemic sclerosis, we're going to need to work closely with a rheumatologist. For the underlying interstitial lung disease, it takes a pulmonologist that's been trained in interstitial lung disease along with a radiologist and even potentially a pathologist. For the pulmonary hypertension part of the disease, we want to have a pulmonologist that's trained in pulmonary hypertension or a cardiologist that's trained in pulmonary hypertension. And because we see so much gastroesophageal reflux disease and esophageal dysmotility, we typically need a gastroenterologist on our team. For renal disease and renal crisis, we'll need a nephrologist, for cardiac disease, a cardiologist, and for any neuromuscular disease, neurology. And because there are so many other possible complications, we may need a number of practitioners on our team. Again, I want to highlight that a lot of these patients have gastroesophageal reflux disease and esophageal dysmotility. I think this is very important as it leads to symptoms of breathlessness and cough.

When we go to other complications and how we may need another number of practitioners on our team, this is a patient that I had that had severe Raynaud's with necrosis of her fingers and presented like this to clinic on a Friday afternoon. We needed infectious disease, as a number of her fingers were infected. We needed to talk to the vascular surgeons to see if there was anything else we could do. We also talked to our pulmonary hypertension team to determine if there are medications we could give her to help save these fingers. And the good news is that while she lost a little bit of her fingertips on some of these necrotic fingers, she's using her hands very well today with minimal disability.

So we have talked a lot about pharmacotherapies, and now I want to touch base on nonpharmacologic therapies. So we need to educate patients about the disease and the comorbidities of the disease, and this will come up over and over as education is so important for the patients to understand their disease and what to be looking for. If any patients are smokers, we need them to stop smoking. We need the appropriate nutrition, either for those who are overweight or those who are underweight due to their disease condition. We need to determine the need for supplemental oxygen, and in my notes I always say at rest, with ambulation, during exercise and during sleep, so we need to check them during all these different activities to ensure they are getting adequate oxygen.

Patients also need supportive care, and not just for the patients but also for their caregivers. Support groups are excellent in helping patients and their caregivers. The Scleroderma Foundation is also another excellent resource. And for those patients that continue to progress despite everything we've done, there's always the option of palliative care. We do use nursing support all of the time to assess for new or worsening symptoms when patients call in, and our nurses do an excellent job at therapeutic monitoring and monitoring for side effects of any of the agents that we are using. Pulmonary rehabilitation makes people feel better, makes them be able to exercise longer, improves their quality of life, and we recommend that for patients who are able to do it. We want them to have vaccinations and ongoing healthcare maintenance and lung transplantation if required. Observational studies have shown that lung transplantation is relatively tolerated in this patient population and are very encouraging at this time. And finally, we want to ensure that if patients are interested in clinical trials, that we allow patients to go into clinical trials so that we have better answers for this disease process.

So now we're going to see a patient in a patient video and hear her perspective of having systemic sclerosis-associated interstitial lung disease.

I would say I am probably, um, 20% of capacity. A lot of it has to do with mobility in my joints, chronic headaches, chronic stomach issues, and, um, fogginess, um, just not being able to focus because of pain, and my pain daily is, uh, anywhere from 6 to 8, and then, um, sometimes it can go to a 10 at night. It's caused mostly by—I don't know if you can see—but by the joint. This is my full grip, and then also just being able to dress myself, put my earrings on, get in the bathtub. Uh, walking is (clears throat) very painful. (clears throat) Excuse me, my voice has been affected as well. It's tightened, and, uh, it makes it hard a lot of times for swallowing and for just talking in general. It's just... It has completely taken over, and just your normal things, I mean, it has affected all of that.

And the hardest part with the medicines is you know that they're working, but they have their different side effects. Just being be able to—to hold it to go to the bathroom if you're in a public setting, it pretty much... You're living as if you're living your last days. You're searching always, whether it's Googling or reading or, uh, talking with a support group or talking with your doctors, and I have—goodness, I probably have 6 doctors who are around me now. You have to put your life on hold to get your life back, and you have to be your advocate. There's so much unknown, but I'm so blessed and thankful that at this time there's been so much research done in the last few years, just a couple years, that they're understanding what scleroderma—how it affects the lungs and why it affects the lungs. And people don't understand. You look... You look your normal self, but inside you feel so bad.

The support group is helpful. It gives you, um, grace for yourself to understand that, um, this isn't something made up. People understand what you feel. Just talking about your feelings is the biggest deal because it does bring on, um, a depression, and it does bring on a sense of, um, a sense of quality of life. You know, where do I go from here? Not everyone is the same. The disease is not the same for everyone, and for the doctors to listen to your patient, listen to the colleagues, listen to the research, and, um, but—but individualize your patient because it's webbed out so many different ways.

Dr. Olson:
That was very insightful, and I'd like to move on about the patient in systemic sclerosis-associated interstitial lung disease.

So, what we want to talk about here is patient-centered communication. If we look at the right side of the screen, we have physician priorities, and this is the stuff that we go to clinic with and we know we're going to do. We're going to assess for risk of progression, look at pulmonary function testing, check their HRCT scan and look at the extent of fibrosis, identify comorbidities, develop a management plan with our multidisciplinary team, have ongoing monitoring and try to maximize survival. But if we look and listen and understand what the patient priorities are, these are actually patient priorities from a patient advocate from the Scleroderma Foundation, and I think these are really important, and these themes come up over and over again. For patients it's very important to minimize uncertainty. They really need to understand their disease and understand the treatment options. While they want to seek assistance from their partner, family and friends, they also want to maintain independence. They want to maintain their energy and stamina, and they want to maintain social participation. Finally, some patients need to address their self-identity issues with the disease that they have and not the disease having them.

So, how do we maximize all of this then? We listen and understand the patient, and we come up with a treatment plan together. It requires that we establish a strong patient/physician relationship, that we're attempting to reduce symptoms for the patient, we choose effective and well-tolerated treatments together, and we maximize the patient's quality of life.

So, if we go back to patient priorities, I think education again comes up so often in the literature, and I think one of the other things in addition to discussing the disease and the therapeutic options that we're going to use is to use the Scleroderma Foundation as a resource, and I've included their website here.

So, in summary, we want to screen to identify systemic sclerosis-associated interstitial lung disease. We want to monitor closely for

progression, especially in those with increased risk, and early on in disease course. We want to treat those with a high risk of progression or with clinical symptoms, and we start with immunosuppressive therapy, and we do want to consider antifibrotic therapy with ongoing progression. We want to develop a multidisciplinary team for the patient, and this will include their primary care physician, their subspecialists and support teams. We want to use patient-centered communication to address their concerns with a complex disease and devise an optimal treatment plan for each individual patient.

And with that I want to thank you. Please remember to fill out your post-test and your evaluation for CME credit. Thank you.

Announcer:
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