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Interstitial Lung Disease in Scleroderma: Early Recognition and Emerging Therapeutic Options

Announcer:

Welcome to CME on ReachMD! This activity, "Interstitial Lung Disease in Scleroderma: Early Recognition and Emerging Therapeutic Options" is provided in partnership with Prova Education and supported by an Educational grant from Boehringer Ingelheim.

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Here's your host, Dr. Shira Johnson.

Dr. Johnson:

A major complication of systemic sclerosis, also known as scleroderma, is interstitial lung disease, or ILD. In fact, it's the most common cause of death in those affected with systemic sclerosis.

This is CME on ReachMD, and I'm Dr. Shira Johnson. I'd like to welcome my guest, Dr. Dinesh Khanna, to the program. Dr. Khanna is a Professor of Medicine and Director of the Scleroderma Program at the University of Michigan in Ann Arbor, Michigan. Dr. Khanna is joining me to speak further about the current management of ILD in systemic sclerosis, also called SS-ILD, and the emerging agents currently being investigated for this disease.

Dr. Khanna, thank you for being here today.

Dr. Khanna:

It's a pleasure to be on this call with you.

Dr. Johnson:

Let's start with some background information on the pathophysiology of scleroderma and its associated lung disease. What can you tell us about this?

Dr. Khanna:

Scleroderma or systemic sclerosis is a rare autoimmune disease with multisystem involvement that can affect lungs, heart, kidneys and ... It affects approximately 70,000 to 80,000 patients in US and has the highest fatality of any rheumatic disease. So, the pathophysiology of scleroderma involves complex interplay between autoimmunity, fibrosis and vasculopathy. ILD, or lung fibrosis, affects approximately 80% of patients with scleroderma based on HRCT, although the clinically significant or progressive ILD is only seen in 25 to 30% of patients. I want to highlight, ILD occurs early in the disease, usually in the first 2 to 4 years after onset of symptoms. It is largely irreversible, and therefore, early diagnosis and treatment is the key to management of ILD.

Dr. Johnson:

So, Dr. Khanna, since early diagnosis can make such a difference in patient outcomes, can you explain to our primary care clinicians how they can help achieve this goal?

Dr. Khanna:

Absolutely. This is a great question. For any orphan disease or a rare disease, there needs to be a high index of suspicion for

diagnosing that disease. What I can tell my primary care colleagues is that onset of Raynaud's phenomenon after age 30 should make them think about secondary Raynaud's phenomenon of which connective tissue disease are leading differential diagnosis. In addition, constitutional symptoms such as fatigue, joint pain and swelling, body pain and puffy fingers should prompt appropriate workup such as antinuclear antibody and rheumatoid factor and referral to a rheumatologist. I also want to highlight that digital ischemia and ulcers are not part of primary Raynaud's phenomenon and should alert the primary care doctor for referring to an appropriate subspecialist.

These symptoms develop gradually, and it usually takes a year or more until a diagnosis of connective tissue disease, including scleroderma, is entertained and confirmed. Early referral to rheumatologists with the red flags that I discussed before will help facilitate diagnosis and treatment.

Dr. Johnson:

Let's now take a look at the current management of SS-ILD. Obviously, with an autoimmune disease in context here, immunosuppression plays a major role in treatments. What therapies are currently available, and what are their limitations?

Dr. Khanna:

Yes, I want to start by stating that there are no approved therapies for scleroderma ILD. Immunosuppressive therapies, which we have borrowed from other rheumatic diseases such as mycophenolate mofetil, methotrexate, or cyclophosphamide, tend to help, although the effects are generally modest. And my statement that immunosuppressives work is supported by 2 large randomized controlled trials—SCLERODERMA LUNG STUDY I and SCLERODERMA LUNG STUDY II. The 2 trials evaluated daily oral cyclophosphamide and daily mycophenolate mofetil at 3 grams per day. The effect of these immunosuppressives, if given over a period of 1 to 2 years, is short-term, and 1-year treatment doesn't seem to impact long-term mortality and morbidity.

I want to highlight a recent data from hematopoietic autologous stem cell transplantation in early scleroderma in patients who have concomitant ILD that supported improvement in pulmonary function, improvement in symptoms and a favorable impact on survival. As we think about the patient and whether we need to treat this patient long-term on immunosuppressive therapy or not, we have to weigh the benefits versus the risks. I think if we had safer and more effective treatment, I may consider treating majority of the patients with scleroderma, and we can start to venture whether we can prevent ILD in patients with scleroderma. As I stated before, 80% of the patients have ILD on the HRCT or even start to treat very, very early ILD.

Dr. Johnson:

If you are just tuning in, you're listening to CME on ReachMD. I am Dr. Shira Johnson, and joining our discussion on the management of ILD in systemic sclerosis is Dr. Dinesh Khanna.

Dr. Khanna, you just spoke a bit about the limitations of current management for SS-ILD, such as lower response rates, high rate of side effects; but given these limitations, how does one decide who should be treated?

Dr. Khanna:

I think that's a very important question and the focus of our discussion today, and I will again start by saying early screening and diagnosis is key to the management of ILD, because ILD scleroderma is largely irreversible. Personally, once I make a diagnosis of scleroderma, I perform a high-resolution CT of the chest, including prone images, to capture early ILD, and a full pulmonary function test, or PFT. PFTs can be normal in early disease, so you need to be careful not to rely solely on PFT to make a diagnosis of interstitial lung disease. Once I make a diagnosis of ILD, the question to me is whether I should treat this patient or carefully watch the patient. There is a lack of agreement among experts on who to treat.

Here are a few features that make me consider treatment. A patient with early disease: Why early disease? I highlighted before, majority of the patients develop progressive ILD early in the course of their onset of scleroderma symptoms, so early disease along with symptoms of shortness of breath; although I want to highlight that many patients with scleroderma do not confess to having shortness of breath, and the shortness of breath can be multifactorial in scleroderma.

Having abnormal PFTs: Patients who have a forced vital capacity and a diffusion capacity below the lower limit of normal or a patient who's declining in front of you, which is beyond the measurement error of the test, or a high-resolution CT showing moderate to severe ILD early in the course of the disease. I also want to highlight that it is important to start treatment and follow PFTs every 3 to 4 months and seek stabilization of the lung fibrosis.

On the other hand, if the patient had mild ILD and no symptoms and I decide not to treat these patients, it's important for me as a sclerodermatologist to keep a close eye on the PFTs during the first 2 to 4 years when a decline in lung function is likely to happen. This makes me think in my clinical practice: What are the predictors of decline in lung function? There could be autoantibodies or blood tests, such as antiscleroderma-70 or topoisomerase I, nucleolar pattern on antinuclear antibody, or presence of diffuse cutaneous subset on examination.

Finally, I want to highlight that a declining diffusion capacity on your lung function test may be due to concomitant pulmonary vascular disease or pulmonary hypertension, and therefore, early echocardiogram and NT-proBNP are usually required in these patients.

Dr. Johnson:

Dr. Khanna, in the past years, research has clarified important pathways involved in SS-ILD pathophysiology. How has this new understanding influenced the development of the new antifibrotic agents?

Dr. Khanna:

Yes, this is a very exciting time for rheumatologists and scleroderma researchers. I think we are finally starting to understand different pathways that are important in fibrotic diseases, including scleroderma, and unravel complex interplay between inflammation, vasculopathy and fibrosis. We think that immunosuppressive therapies largely address one aspect of the disease, and with the availability of novel antifibrotic therapies such as nintedanib and pirfenidone, we now have a great opportunity to target fibrotic aspect of the disease and also to explore whether a combination therapy with immunosuppressives would be favorable in patients with scleroderma ILD.

I want to highlight the 3 ongoing trials of the antifibrotic therapies either using mycophenolate as a background therapy or as monotherapy, and these include nintedanib. It's a tyrosine kinase inhibitor that targets multiple pathways that I believe are very relevant in scleroderma. The drug is already approved for pulmonary fibrosis and has often drug designation for the treatment of scleroderma, including the ILD. I'm delighted to say that 520 patients around the globe have been recruited, and we should have the top-line data early in 2019. The trial is called SENSCIS and looked at patients with scleroderma with defined ILD on HRCT, significant impairment in the pulmonary physiology and symptoms, and the primary outcome is annual rate of decline in forced vital capacity over a period of 52 weeks.

The second drug, pirfenidone, likely inhibits transforming growth factor beta. It's again approved for idiopathic pulmonary fibrosis. And I'm one of the coprincipal investigators of SCLERODERMA LUNG STUDY III, which is combining the pirfenidone effect with mycophenolate mofetil for treatment of scleroderma-associated ILD. It's a Phase II trial. We are again taking patients with early disease, with interstitial lung disease, clear symptoms, and a forced vital capacity of less than or equal to 80%. A primary endpoint here is a change in forced vital capacity over a period of 18 months.

And finally, abituzumab is a pan alpha V beta integrin inhibitor, which prevents activation of latent TGF-beta. There's an ongoing Phase II trial—I am coordinating principal investigator—called STRATUS, and again, it's a double-blind placebo-controlled trial of abituzumab with a placebo in background of mycophenolate. The primary endpoint here is the annual rate of decline in forced vital capacity over a period of 52 weeks.

All 3 agents I want to highlight have very robust and strong preclinical data to support development in scleroderma.

Dr. Johnson:

It is a very exciting time in the research of fibrosis. We appreciate the information you just shared with us. But before we wrap up, what are some key takeaways that you want to share with our audience?

Dr. Khanna:

I think there are 3 key takeaway points that I want to highlight. The first aspect is patient management. And I want to thank our primary care colleagues who do such a fabulous job. And keep in mind that rare diseases are difficult to diagnose; therefore, you need to have a high index of suspicion. When you think a patient with Raynaud's phenomenon, consider whether the onset of Raynaud's happened after the age 30, whether they have constitutional symptoms such as fatigue, malaise, lack of energy, puffy fingers, digital ulcers. For rheumatology colleagues, early screening and diagnosis is critical in this day and age because I think early treatment does change the course of the disease.

Number 2: What is the place of new agents in therapy like nintedanib, like pirfenidone? I have to admit that the ongoing trials will dictate this. I think there is certainly the place for combination therapy with immunosuppressives or using them as monotherapy, and we are waiting the lead of the different clinical trials that have just been completed, such as Phase III trial of nintedanib, or the ongoing Phase II trials of pirfenidone and abituzumab.

And number 3: Who should be treated? I want to start by admitting that there is a lack of agreement among the experts. This is because we don't know whether every patient with scleroderma ILD will progress to develop marked decline in the lung function and severe lung fibrosis. It's also due to the side effects of the therapies that we use, and there is always a tussle whether to treat a patient or to wait and see, or to have a wait and see philosophy. I strongly believe that if we had better drugs, better way to prognosticate who will progress versus not, we may treat more patients successfully with scleroderma ILD.

Dr. Johnson:

I would like to thank my guest today, Dr. Khanna, for speaking with me and our ReachMD audience. Dr. Khanna, it was great having you on the program.

Dr. Khanna:

Well, thank you for having me. It was a pleasure to talk to you.

Announcer:

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