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## Emerging Treatments: Diagnosis and Treatment of Chronic Fibrosing ILD with a Progressive Lung Disease Phenotype

Narrator:

Welcome to CME on ReachMD. This activity titled *Emerging Treatments: Diagnosis and Treatment of Chronic Fibrosing ILD with a Progressive Lung Disease Phenotype*, is provided by National Jewish Health and supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Incorporated. This replay of a live broadcast focuses on identifying patients with progressive fibrosing interstitial lung disease. Here are your panelists, Dr. Kevin Brown, Dr. Kevin Flaherty and Dr. Rebecca Keith.

Dr. Brown:

Well, welcome to this educational opportunity in interstitial lung disease. We are going to talk about emerging treatments really focused on the diagnosis and treatment of fibrosing interstitial lung disease with a progressive phenotype.

I want to thank the supporter of this opportunity with an independent educational grant from Boehringer Ingelheim.

This is an accredited opportunity. It's accredited by National Jewish Health. The details are provided as noted on this slide.

And I want to introduce the faculty. I'm Kevin Brown. I'm a lung doctor from Denver at National Jewish Health, and I'm joined by colleagues that I'm delighted to share the virtual podium with: Rebecca Keith, who's an associate professor with me here at National Jewish Health in the Division of Pulmonary Critical Care and Sleep Medicine—she's really focused in the interstitial lung disease program and is a critical component of that—and an international expert, Kevin Flaherty, who's a Professor of Medicine at the University of Michigan, a colleague for more than 20 years who's really been instrumental in the development both of this concept and of our interventional investigation associated with it.

Here are our disclosures. All these are potential conflicts of interest. You will see that Dr. Flaherty, Dr. Keith and I all have and have received fees from Boehringer Ingelheim among a number of other companies. Please consider our comments in the light of these potential conflicts.

So let me comment on the learning objectives. We're going to talk about progressive fibrosing interstitial lung disease. We're going to identify those conditions that are associated with PF-ILD and describe their impact both on the lung and on how the lung itself affects both symptoms, pulmonary physiology or function, and long-term outcome or mortality. We are going to try to describe to you the best practices for an early and accurate diagnosis of the disease and how to follow up those patients who are at risk for developing the progressive phenotype, and we want to discuss the evidence-based strategies for those treatments that are currently available for its treatment.

So I'm going to talk about both the concept and the underlying, hopefully, mechanisms responsible for this form of diffuse lung disease that's characterized by progression with worsening symptoms, increasing chest imaging abnormalities, worsening physiology and shortened survival.

So, when you think about the universe of fibrosing forms of interstitial lung disease, that's a huge and broad group of disorders, but we know a number of things about this, and we've known them for a number of years. For more than 30 years, we've understood that there

were differences in some of these forms of interstitial lung disease. This is data from Professor Moises Selman from years ago that talks about underlying chronic bird breeder's disease and how that differentiated itself from idiopathic pulmonary fibrosis. This separation clearly shown in these Kaplan-Meier curves with a much shorter survival for those with IPF is characterized by an underlying UIP pathologic pattern versus the top curve, which is the chronic pigeon breeder's lung disease. There was this interesting group of patients who had a UIP pattern who also had significant bird exposure that wasn't really well understood at that time, but we also understood and have understood for a long time that if you do a surgical lung biopsy on patients with underlying fibrosing interstitial lung disease, that those with a particular pattern, this UIP or usual interstitial pneumonia pattern, have a significantly shorter survival than those with any other pattern regardless of treatment.

So, because we understood these differences and because idiopathic pulmonary fibrosis, or IPF, is associated with the presence of a UIP pathologic pattern surgically, that we understood that we could draw this circle in the middle of this universe of fibrosing interstitial lung diseases, and we actually could draw a bright line around it, and we could call this IPF, and calling this IPF required us to create very strict diagnostic criteria to allow us to differentiate it from these other forms of fibrosing interstitial lung disease, so we called these basically not IPF. But we understand that there are a wide variety of underlying diseases that are associated with the development of fibrosing forms of interstitial lung disease, progressive forms of fibrosing interstitial lung disease, including connective tissue disease, fibrosing forms of nonspecific interstitial pneumonia, undifferentiated forms of lung disease, hypersensitivity pneumonitis, occupational drug-related disease—even ARDS and sarcoid—can all be complicated by fibrosis and progression thereof.

So we tried this process to separate those things that are IPF from not IPF. So a patient with underlying fibrosis comes to see you, and the first thing you ask is, Is there an identifiable cause or association? If the answer is yes, that is by definition not idiopathic pulmonary fibrosis. If there is no identifiable cause or association, we look at the underlying high-resolution CT scan pattern. We know that there is a pattern also called UIP because it predicts the presence of an underlying pathologic pattern of UIP that allows us to obviate the need for surgical lung biopsy. That by definition is IPF. However, at least half and often more of those patients will not have a characteristic HRCT pattern. One needs to decide whether surgical lung biopsy or some other form of tissue acquisition is necessary and then determining that underlying pattern. If it's not UIP, it's not IPF. If it's a UIP pattern, you're left with the diagnosis of IPF. This is the short scheme and how we approach diagnoses of fibrosing lung disease.

However, we know that there are a number of problems associated with this schema. Just looking at identifiable causes and association, we know that there is a significant overlap with forms of chronic hypersensitivity pneumonitis, for example. We know that there are patients who have features of an underlying autoimmune disease but do not meet diagnostic criteria. We've called this interstitial pneumonia with autoimmune features, or IPAF, but just another characteristic problem with trying to separate those with identifiable causes or associations. We know that the interpretation of high-resolution CT scan is difficult. It is challenging. The kappa values associated with interpretation even among experts can fall below that level that we consider significant. We understand that there are UIP patterns, but there are a variety of other patterns, including probable UIP, indeterminate UIP, and those with alternative diagnoses. And unfortunately, exactly the same problem exists under the circumstances with surgical lung biopsy. This requires interpretation, kappa values can be quite low, and it remains uncertain in a large number of cases, whether these patients meet diagnostic criteria for IPF or another disorder.

Recognizing this, Professor Athol Wells has been a big proponent of understanding the importance of disease behavior, and he has convinced me, and I hope both he and I can convince you. I want to describe just one paper that helps us understand this. This is a group of patients with idiopathic pulmonary fibrosis, i.e. those with an underlying surgical lung biopsy pattern of UIP, versus those with a fibrotic form of NSIP. This is a beautifully done study from a number of years ago that shows exactly what we would expect. Under treatment, those with fibrotic NSIP live significantly longer than those with a diagnosis of idiopathic pulmonary fibrosis.

If you mix up those patients and throw them all together and have just baseline information and ask, What predicts survival? How long are these patients going to live? those things that we would expect fall out. Age is a very strong predictor of how long you will live. Underlying diffusing capacity, the lower the value, the shorter your survival, and a surgical lung biopsy diagnosis of NSIP are all predictors, NSIP diagnosis predicting a much longer survival.

However, if you have additional information... Now, if you have information from as little as 6 months later, what continues to predict shorter survival? So, gender, we know that women live longer than men. It is true in this disorder as well. We know that underlying initial diffusing capacity also predicts survival, lower the shorter survival.

However, what you also see is that a 6-month change in FVC is the most confident and potent predictor of survival than any of those baseline values, so the longitudinal addition of information provides powerful additional prognostic information.

And most importantly, once you have additional information at 6 months, what is no longer relevant? The underlying pathologic diagnosis of NSIP. So, regardless of the initial diagnosis, a declining FVC at 6 months is a much more potent predictor than any

baseline value.

We also understand that acute exacerbations occur not only in IPF but basically all other forms of fibrosing interstitial lung disease.

And this led to the following concept. This is a paper that Professor Flaherty and Wells and I were lucky enough to participate in. We talked about the underlying concept of fibrosing interstitial lung disease and how progression of that underlying fibrosis is really more important than any name we might provide to an individual disorder.

There were both clinical evidence, including evidence that chronic hypersensitivity, rheumatoid arthritis, IPAF patients, those with drug-induced disease, all exhibit IPF-like behavior, i.e. they are likely to progress, they are likely to worsen, and they are likely to die early. There is now also significant pathologic, underlying biologic, mechanistic data that support common mechanisms responsible for the progression of that underlying fibrosis.

So we were lucky enough—and many times one is not when comes up with these hypotheses—to actually be able to test this hypothesis in prospectively developed data. And I'll show you one slide here where we were able to compare patients in the INPULSIS study, those focused on IPF, the use of nintedanib in patients with idiopathic pulmonary fibrosis, and then compare their longitudinal behavior as measured by FVC in the group in the INBUILD study, those with non-IPF progressive fibrosing interstitial lung disease, and hopefully what you're able to see here and hopefully what I'm able to convince you of is that these curves overlap, that the decline in FVC over 52 weeks in the IPF patients was nearly identical to the overall INBUILD population, it was virtually identical to the UIP-like pattern in the INBUILD population, and only slightly greater than that in the non-UIP-like pattern behavior.

And as importantly, and maybe more importantly, when you broke down each of the individual diagnoses that made up the INBUILD population, what you can see is a general consensus that decline over time in FVC was the pattern that we see, recognizing that this, the INBUILD study, was not powered for any of these individual diagnoses, but again, the overall pattern is what we were looking for.

So, what I think we can say today is that we recognize that there's a universe of fibrosing interstitial lung disease. We recognize that there is a group of patients that we call IPF, that we can define well and understand its natural history, but we also now can understand that a whole variety of other forms of fibrosing lung disease share characteristics at baseline but more importantly over time in terms of their natural history.

Thank you very much. Now, before I hand over the podium to Professor Keith, let's hear from a patient.

Patient Speaker:

So I first noticed the problem in November 2018. I drove to a little town called Rio Rancho to go to court and represent my client, and I parked in the parking lot. Um, I walked from the parking lot into the courthouse, kind of a brisk walk, met up with my client, and I could not—I could not breathe. I couldn't capture my breath, and my client even saw me and thought I was going to pass out. And I went to the ER room. They did a series of tests, spent several hours there. They couldn't figure out what was wrong with me. And ultimately, I made appointments with my pulmonologist and my cardiologist. I didn't get a formal diagnosis of scleroderma systemic and ILD until April 2019.

I think the biggest challenge with living with it, um, is the same as thinking about it in my mind, is that it's not reversible, and the lung disease itself is debilitating if you let it get to you, if it stops you from daily activities, and it really isolates you if you let it do it. I tried my best to normalize my life despite the limitations by, you know, dragging around the oxygen tanks and still going to the office and still going to courts and, um, but—but it was certainly challenging because it takes away what we take for granted in terms of ability just to get up and go somewhere. You just have to be strong and counter it with the idea of getting up and doing the things you, um, normally are accustomed to doing. You may not do them as—as good or as fast or as much, but doing something is better than nothing.

In terms of medication, um, so, what we did was we put together a dietary plan—my wife did—would secure the—the type of food that would be helpful. At the time I was taking the medications twice a day, one in the morning, one at night. So, from the OFEV perspective, I suffered a little bit of the GI stuff but overcame, uh, the secondary side effects of the medication. In terms of the mycophenolate and the—and the OFEV, certainly makes your—your immune system, uh, weak, and so for that I suffered, still do, a lot of chest colds constantly with trying to maintain the hoarseness of the voice, may be attributed to the cough, but it could also be the—the medications. I don't know. We've never figured out exactly which one contributes, um, more to that issue.

Dr. Keith:

Thank you for sharing your experience with progressive interstitial lung disease. It is so important to hear from our patients. Now let's move to the next part of our presentation. I'd like to present best practices to make an early and accurate diagnosis of ILD with progressive phenotype and manage over time.

So, what is interstitial lung disease? Well, interstitial lung disease is a diverse group of disorders, about at least 150, that result in

inflammation and scarring of the pulmonary parenchyma. It's difficult to differentiate between these diseases because they often present with a similar phenotype. With progressive shortness of breath, a dry cough, they have abnormal pulmonary physiology and abnormal chest imaging.

When we think about these 150 different disorders, I often group them into 3 main categories: the IIPs, of which idiopathic pulmonary fibrosis is the most common, autoimmune lung disease, and hypersensitivity pneumonitis. There are other groups as well, including sarcoidosis and then other interstitial lung diseases. The diseases highlighted in bold are the ones that can become progressive over time. Again, the classic one is idiopathic pulmonary fibrosis, but you'll see highlighted rheumatoid arthritis interstitial lung disease and systemic sclerosis as well.

So, when do I suspect interstitial lung disease? I think about interstitial lung disease when I have a patient present to my clinic with shortness of breath or a dry cough. I often start with a detailed history, and then I go to a physical exam. I think one of the most important things to do on a physical exam is to auscultate the lungs. It's important to listen way down low at the bases of the lungs because that's where we hear dry, inspiratory crackles that can clue us in that there's an interstitial lung disease. I often order pulmonary physiology, which I expect to be restrictive in interstitial lung disease, and I may order a chest x-ray or perform additional testing. One of the tests I think is most important to perform is an ambulatory oxygen test because many of our patients with interstitial lung disease may have normal oxygen saturations at rest, but once they start to move, their oxygen saturation drops. If I have any hint that there may be an interstitial lung disease, I order a high-resolution chest CT because that will give me the fine detail I need to determine which type of interstitial lung disease they may have.

So I've diagnosed interstitial lung disease. Great. But then which ILD is it? There's over 150 different kinds. So, what I do is I like to use this algorithm by the ATS to help me think about the steps that are needed to make this diagnosis. So I have a patient with ILD, and so I stop at the first step, and that's to exclude known causes of interstitial lung disease. So, if I can identify a known cause of interstitial lung disease, then it cannot be IPF. For example, if my patient has rheumatoid arthritis, they have rheumatoid arthritis-associated interstitial lung disease and not idiopathic pulmonary fibrosis.

So, in order to do that, I need to become a detective. I need to take a full history, do a complete physical exam, perform pulmonary physiology, closely evaluate my radiography, and sometimes I need a surgical lung biopsy.

So, what are the clues I may find? If I have a patient that presents for typical IPF, they are usually older than 50 years of age, male, and they may present with exertional dyspnea and that dry cough, and they may have fatigue or other symptoms, but they should have no extrapulmonary symptoms. They shouldn't have synovitis or other things that may suggest that they may, in fact, have a different disorder, such as a rheumatologic disease.

What are the findings that may clue me in that I have a connective tissue disease? Well, for rheumatoid arthritis, I may have morning stiffness or active inflammation in my joints. For systemic sclerosis, it may be a younger patient, and they may have Raynaud's or their fingers may turn white and then blue in the cold. They may have skin tightening or telangiectasias over their face and hands. For Sjogren's, I may have a patient with dry eye or dry mouth, and they may have an abnormally high number of dental caries because they don't have the normal amount of saliva to protect their teeth. Finally, for dermatomyositis or polymyositis, I may see Gottron's papules. But the one I think is most interesting is, when patients have drying and cracking over their hands, that's mechanic's hands, and that's a clue to me that I need to be thinking about dermatomyositis or polymyositis.

Patients, where they live and work, are important factors in determining what may contribute to their interstitial lung disease, so occupational history is important. If your patient worked with asbestos, silica, coal or beryllium, those are clues that might lead us to what is contributing to their interstitial lung disease. Even their hobbies are important. So, if your patient is a woodworker, they may have hypersensitivity pneumonitis. Talking about their home environment is also key, so I ask patients, do they have a hot tub. Especially indoor hot tubs can contribute to hypersensitivity pneumonitis. Any water or mold damage, certainly pets like birds or even down in comforters or pillows can contribute to an interstitial lung disease like hypersensitivity pneumonitis.

Back to the physical exam, it's very important to do a detailed physical exam and with special attention to auscultating the chest and listening for crackles way down low at the bases but also listening at the apices. In hypersensitivity pneumonitis, which can impact the airways, we may hear inspiratory squeaks or other noises that may key us in to other diagnoses besides idiopathic pulmonary fibrosis. We spend a lot of time looking at the joints for any evidence of synovitis, or the skin for telangiectasias, or those mechanic's hands I talked about previously. I often order blood work, like serologies, to look for any evidence that a patient may have autoimmunity, because often autoimmunity can turn up in the lung before we see any systemic evidence. I've had patients myself who have a positive CCP and suggestion that they may have rheumatoid arthritis interstitial lung disease but only presented with joint findings 5–10 years after their initial diagnosis of interstitial lung disease. What about serum precipitins? I don't find them that helpful in my clinic because they have limited sensitivity and specificity for diagnosing hypersensitivity pneumonitis. I use them when there may be multiple

exposures and I'm trying to differentiate which one may be the key driver for their hypersensitivity pneumonitis.

Back to the hands, these images help us remember what we're looking for in the hands. So the first image is of Gottron's papules, which may suggest that there is a polymyositis or dermatomyositis. That second picture shows kind of drying and cracking along the palmar surfaces, and that's an example of mechanic's hands. The next image over shows a classic swan neck deformity that we often see with rheumatoid arthritis. On the bottom row, there's an example of clubbing and an example of skin tightening and telangiectasias that we see in systemic sclerosis. And finally, often in our clinic we may perform nail bed capillaroscopy, and this image shows what we might expect to see, dilated capillary loops that can clue us in that there's an autoimmune condition that we need to investigate further.

**Physiology:** When we perform physiology in interstitial lung disease, we expect that our physiology is restrictive, and that is a low total lung capacity and a symmetrically low FVC and FEV1. However, some patients can have mixed physiology and may have a form of COPD plus interstitial lung disease, and then we can see either normal pulmonary physiology with a low DLco or an obstructive pattern. Whatever the pulmonary physiology it is, those initial tests are your baseline from which we'll follow that patient for evidence of progression as time moves on.

Back to an evaluation of gas exchange, I cannot emphasize enough how important it is to not only test a resting oxygen saturation but an ambulatory oxygen saturation. Our patients with interstitial lung disease often have a low DLco, and so their oxygen saturation may be normal at rest, but as soon as they start to walk or move, their oxygen saturation will drop, and it's important to identify that so we can provide supplemental oxygen, which can increase their exercise capacity. When we're doing a radiologic evaluation, I get a high-resolution chest CT, and that means that these are thin slices of only about a millimeter to a millimeter and a half thick. This allows us the resolution to see those fine details of what's going on in the interstitium. The CT does not have IV contrast, and I often request both supine and prone images to be able to see the bases of the lungs clearly and identify early interstitial lung changes. Finally, I get both inspiratory and expiratory images. Those expiratory images are key to help us look for mosaic attenuation that we may find in hypersensitivity pneumonitis.

In idiopathic pulmonary fibrosis as well as some other collagen vascular diseases, such as rheumatoid arthritis and scleroderma or systemic sclerosis, we often see a UIP pattern, and that's a subpleural, basilar predominant pattern with reticulation and honeycombing. There can be traction bronchiectasis, and there are the absence of other features that would suggest an alternate diagnosis. The picture here is a classic UIP pattern with honeycombing, and notice the absence of micronodules or ground-glass.

We use bronchoalveolar lavage in our diagnostic algorithm. It is not that helpful in idiopathic pulmonary fibrosis, but it can be helpful in looking for other diagnoses, such as sarcoidosis or hypersensitivity pneumonitis. We may see lymphocytic inflammation, and I'll talk more about this when we talk about hypersensitivity pneumonitis later. Sometimes when we can't decide what we think the diagnosis is after a multidisciplinary discussion, we often go to a surgical lung biopsy, and that pathology can help us make an official diagnosis or a clinical consensus diagnosis.

So let's spend some time talking about the most common interstitial lung diseases that become progressive over time. Again, the classic progressive pulmonary fibrosis is idiopathic pulmonary fibrosis. That tends to affect men more than women. Generally, patients are greater than 50 years of age. Smoking is considered the largest risk factor. And patients often present with exertional dyspnea and a dry, nonproductive cough. They may report fatigue as well. There should be no extrapulmonary features to suggest an alternate diagnosis. Patients who have synovitis or other autoimmune features, you should be thinking of a different diagnosis from idiopathic pulmonary fibrosis. The presence of a UIP pattern on high-resolution chest CT can be diagnostic of IPF when there's no other cause of this interstitial lung disease, and often we do not need a surgical lung biopsy to make this diagnosis of IPF.

Next, let's talk about connective tissue-related ILD. Now, this is a large number of different types of disorders, and they are more common in women than in men, and they tend to impact younger patients as opposed to older patients. Most patients with connective tissue disease have some form of associated interstitial lung disease, but it can come in various different forms. Patients that have progressive fibrotic lung disease often have rheumatoid arthritis, systemic sclerosis, polymyositis, dermatomyositis, or antisynthetase syndrome. The prognosis for connective tissue disease-related interstitial lung disease is often better than that of idiopathic pulmonary fibrosis. The most common pattern that we see in most connective tissue disease-related ILD is actually NSIP, or nonspecific interstitial pneumonia. However, in rheumatoid arthritis, the most common pattern is that of UIP, which we also see in idiopathic pulmonary fibrosis.

So, what is NSIP, or nonspecific interstitial pneumonia, depicted in this picture here? It's often subpleural and basilar predominant. There are reticular changes in traction bronchiectasis. There should not be any honeycombing. We can see ground-glass opacities, and the key feature is that we generally see subpleural sparing or that the interstitial changes in ground-glass does not go all the way to the pleural surface.

In hypersensitivity pneumonitis, this is a disease that's triggered by exposures or things in the environment. Often birds or mold or water damage or other exposures are key triggers for development of this disease. Thirty percent of cases we are never able to find an antigen, and that can make diagnosis of this disorder tricky. When we look at imaging for this disease, it can have a UIP pattern much like idiopathic pulmonary fibrosis. However, often the fibrosis is upper lobe predominant. It is key to look at expiratory images because that can be the largest clue that this is hypersensitivity pneumonitis. Expiratory images generally can show lobular air trapping or mosaicism, and when we see this on imaging, we should be thinking about hypersensitivity pneumonitis. We can use bronchoscopy to help us make this diagnosis, and when we do a lavage, we should see lymphocyte predominance. And often transbronchial biopsies can be helpful as they can show poorly formed granuloma, which can help us key into this diagnosis.

Sarcoidosis is another fibrotic lung disease that can become progressive over time. This is a rare granulomatous lung disease of unclear etiology. Genetics are thought to play a part, and HLA type can be a driver for sarcoidosis. About 20% of patients with sarcoidosis can develop a progressive fibrotic lung disease. Sarcoidosis itself can affect multiple organs, including the heart and the lungs.

So, how do I know if my interstitial lung disease that I diagnosed has become progressive? Well, what happens with interstitial lung disease over time? Every patient is different, so it can be difficult to predict in any single patient, and here, looking at this graph, there is a period of subclinical progression until a patient becomes symptomatic. Once a patient is symptomatic, they can have a slowly progressive course or a rapidly progressive course. Even patients on a slowly progressive course can develop an acute exacerbation or worsening of their interstitial lung disease, and so a patient can go from having not needing oxygen to needing a portable oxygen concentrator to needing high flow oxygen over a period of weeks to a month, and this can be a devastating change. So, when I meet a patient for the first time, they often want to know, "Doc, what's going to happen with my situation?" And it's hard to tell patients because I don't know if they are going to be a slow progressor or a rapid progressor or if they are going to have an acute exacerbation, and so, in my practice I try to follow patients closely over time and have them partner with me to identify any early symptoms that may suggest that they are having a change in their lung status. I tend to see my patients every 3–6 months and order a pulmonary physiology so I can follow that FVC and DLco and see if there are any hints that my patient may be progressing. I tend to use CT sparingly to avoid the radiation exposure, but I will get a repeat CT at a year so that I can compare to prior, and I will get a repeat CT if patients have a change in their symptoms or a worsening of their FVC.

Unfortunately, there are no single criteria for defining progression. Here is a table that shows some of the different ways people have defined progression in research studies in the past.

I tend to like the INBUILD criteria because I think it is straightforward, and I kind of understand what they are looking for. The INBUILD study—and we'll talk about this more in Dr. Flaherty's talk—defines progression as a change in FVC of at least 10% of the predicted value, or you could have a lesser degree of change, a 5–10% of the predicted value, plus worsening of respiratory symptoms or an increase of extent of fibrosis on that high-resolution chest CT. Finally, if your patient just had worsening symptoms and an increase in the extent of fibrosis without a change in their FVC, that can be evidence of progression as well. And if we're following patients closely over time with interval pulmonary physiology at 3–6 months, we should be able to identify these changes early so that we can quickly identify progression and think about doing something about it.

Once we identify progression, we need to think about, Well, why is my patient progressing? And not all patients progress for the same reason. Fibrosis sometimes begets additional fibrosis, but sometimes inflammation can trigger more fibrosis, so in idiopathic pulmonary fibrosis as depicted in patient 1, that is a fibrotic process that's thought to be driven in the absence of any inflammation, so certainly, my patient who's progressing with idiopathic pulmonary fibrosis, fibrosis is begetting more fibrosis, and I should think about using an antifibrotic medication when my patient is progressing. But what about collagen vascular disease? That can be tricky. If I have a patient with rheumatoid arthritis and they are progressing, I need to think about what's going on with that patient and with that disease state. If my patient with rheumatoid arthritis has really active synovitis and evidence of systemic inflammation, I may think about increasing their immunomodulatory medicines to address their progressive fibrosing interstitial lung disease. I might think about adding a lung-targeted medication like rituximab. However, if my patient, as in patient #3, has progression of their fibrosis without any evidence of systemic inflammation and they have a UIP pattern, I may think about targeting that progression with an antifibrotic.

Now this is just my practice, and certainly there's a lot of research and data to come about how we think about these questions over time. We should also think about in hypersensitivity pneumonitis the same thing applies. Sometimes inflammation is a driver for progression in hypersensitivity pneumonitis, and sometimes it's just fibrosis getting more fibrosis.

So let's look at this video to help summarize everything Dr. Brown and I have talked about and to help understand how fibrosis can progress over time.

Female Speaker:

Some patients with a fibrosing interstitial lung disease are at risk of developing a progressive fibrosing phenotype. This phenotype often leads to worsening respiratory symptoms, loss of lung function, increasing extent of fibrosis on chest imaging and early mortality. Idiopathic pulmonary fibrosis is the classic form of a fibrosing ILD with a progressive phenotype. However, many other forms of ILD can present with a progressive phenotype, including connective tissue disease-associated ILD; hypersensitivity pneumonitis; idiopathic, nonspecific interstitial pneumonia; occupational lung disease; sarcoidosis; and unclassifiable ILD. All progressive fibrosing ILDs are thought to share some common pathogenic mechanisms that drive self-sustaining fibrosis. In IPF, and perhaps other progressive fibrosing ILDs, lung injury appears to target the alveolar epithelial cells and results in their death and subsequent reprogramming of neighboring alveolar epithelial cells triggering an aberrant wound healing response. In some ILDs, such as collagen vascular disease-associated ILD, the triggering event for lung injury is thought to be an autoimmune mechanism. In others the triggering event is largely unknown.

Alveolar epithelial cells themselves may have or require features that makes them more susceptible to injury, such as an underlying genetic predisposition and/or aging. This epithelial injury ultimately results in fibroblast activation and transformation, matrix deposition and scar formation. The end result of multiple, often overlapping profibrotic processes is the loss of the alveolar unit and destruction of the interstitium beyond it, recognized histologically by collagen deposition and architectural distortion. This process is currently not reversible, tends to lead to more fibrosis and may ultimately lead to the progressive fibrosing phenotype.

Dr. Keith:

So, in summary, interstitial lung diseases are a diverse group of disorders that can have similar clinical presentation, and that can make it hard to differentiate between all of those 150-plus diseases, but spending the time to be a good detective is important. Determining which ILD you're dealing with can help you determine the prognosis and the potential therapeutics. Close patient monitoring is key to determine if an interstitial lung disease is becoming progressive. If we're not following our patients closely over time, there is no way we can know that they are progressive. We also need to partner with our patients, and patients need to be active, because if they notice a change in their function, like they used to be able to exercise at a certain level and now they can't, that's a great reason for them to call us and for us to investigate further. When we have identified progression of interstitial lung disease, we need to be really thoughtful about considering all the potential drivers for that progression in an individual patient or in a disease process, and these thoughts can help us guide the potential therapies over time.

So I'd like to thank you for your time, and I'd like to pass over to Dr. Flaherty so he can conclude our presentation today.

Dr. Flaherty:

Thank you, Dr. Keith. Now we're going to talk about evidence-based strategies and emerging therapies for the pharmacologic treatment of progressive fibrosing interstitial lung disease.

As we've already heard about, there are a myriad of interstitial lung diseases, and our first task is to make an accurate diagnosis and assign appropriate initial therapy. With that approach some diseases will stabilize or improve. However, as we know, many of these develop progressive fibrosis, the phenotype of progressive fibrotic interstitial lung disease.

I'm going to show 2 studies today that looked at these diseases in different ways. The first study is nintedanib in progressive fibrosing interstitial lung diseases, or the INBUILD trial. This was a trial that was 1:1 randomization of nintedanib compared to placebo with patients treated for at least 52 weeks with the primary endpoint being change in forced vital capacity at 52 weeks. Patients were continued on blinded study treatment longer than 52 weeks until the last subject enrolled had completed 52 weeks of data, so that provided additional safety and efficacy data for patients that were enrolled early in the study.

The key inclusion criteria included a physician diagnosis of interstitial lung disease other than idiopathic pulmonary fibrosis. Nintedanib had already been studied and had approval to treat patients with IPF, so we didn't want to enroll patients with IPF into this trial. The patients had to have diffuse fibrosing lung disease with at least 10% fibrosis in extent on HRCT, and this was centrally read. Forced vital capacity was greater than 45% of predicted, and DLco was between 30% and 80% of predicted.

We've already seen, but to reinforce the criteria for progression in this study, was that in the 24 months prior to screening, patients had to meet 1 of the following criteria, and they could meet more than one. They could have a relative decline in FVC of at least 10%, a relative decline of FVC between 5% and 10% if it was combined with worsening respiratory symptoms or combined with increased extent of fibrosis on HRCT, or they could have worsening symptoms associated with worsening extent of fibrosis on CT.

Shown on this slide are the baseline characteristics where we can see between nintedanib and placebo the overall age, race distribution and pulmonary function were similar. As I mentioned, these were patients that had interstitial lung diseases other than idiopathic pulmonary fibrosis. The different types of interstitial lung disease were not specified by the study.

So, what types of ILDs were enrolled by the study centers? Well, about 25% of patients had chronic hypersensitivity pneumonia, around

the same proportion had autoimmune disease-associated interstitial lung disease, around 20% or so had idiopathic nonspecific interstitial pneumonia, around 15% had unclassifiable idiopathic interstitial pneumonia, and the other group were a mixture of other types of interstitial lung diseases. Those could be occupational, asbestosis, sarcoid. These were ILDs that by individual count had small numbers, and they were grouped together, so we had relatively 5 equal categories to look at later.

The primary endpoint was change in FVC at 52 weeks, and whether we looked at the overall population or the population which about 60% of patients had a UIP-like pattern on HRCT or the other fibrotic patterns, there was a statistically significant slowing in the decline in FVC in patients treated with nintedanib compared to patients treated with placebo.

The adverse events in this study were similar to the adverse events that we see in treating patients with idiopathic pulmonary fibrosis. Diarrhea and other GI things like nausea were by far the most common adverse events and more common with nintedanib compared to patients receiving placebo.

The second study I want to share with you is a phase II trial of pirfenidone in patients with progressive fibrosing unclassifiable interstitial lung disease. So, unlike the INBUILD trial we just talked about, which included lots of different types of interstitial lung disease, the inclusion criteria for this study included only patients that had unclassifiable interstitial lung disease, and that was unclassifiable after having a multidisciplinary team discussion. Age was 18–85 years, forced vital capacity was greater than 45% of predicted, DLco greater than 30% of predicted, there had to be at least 10% fibrosis on HRCT within the previous 12 months, and progressive disease in the prior 6 months included either an absolute decline in forced vital capacity of at least 5% or symptomatic worsening that was not explained by other causes, such as cardiac or other causes of worsening dyspnea.

The primary endpoint was change in forced vital capacity measured by daily home spirometry. Secondary ends points were change in FVC, DLco and walk distance, and change in patient-reported outcomes, such as dyspnea, cough and quality of life. Progression-free survival and safety were also evaluated.

The baseline characteristics to the patients treated with pirfenidone and placebo looking at age or other demographics as well as lung function were similar.

I mentioned that the primary endpoint was based on home spirometry. Unfortunately, due to intrasubject variability, this primary endpoint ended up being unanalyzable, so the primary endpoint of the trial could not be analyzed in the study technically with primary endpoint unanalyzable was negative.

There were secondary endpoints that looked at onsite spirometry, and if you looked at changes from baseline to 24 weeks by the site spirometry, categorical changes of either 5% or 10% were statistically lower for patients treated with pirfenidone compared to the subjects treated with placebo.

Adverse events with pirfenidone compared to placebo were similar to what we see in our patients with idiopathic pulmonary fibrosis with GI being more common with pirfenidone than placebo.

So, if we put this all together, how might we approach these patients with interstitial lung disease? So we start and recognize that our patients' symptoms of cough, dyspnea, fatigue, are due to interstitial lung disease. We do appropriate diagnostic testing, and we use a multidisciplinary team approach to make the diagnosis. If the diagnosis is idiopathic pulmonary fibrosis, we assume that that disease will be progressive from the beginning. We know that immunosuppressive therapy is likely harmful, and we can have a discussion with that patient about potential initiation of antifibrotic medications. If the interstitial lung disease is not idiopathic pulmonary fibrosis—say it's related to an autoimmune disease or hypersensitivity pneumonia—we should assign the best appropriate therapy at that time, perhaps immunosuppression for patients with autoimmune disease-related ILD, antigen avoidance with or without immunosuppression in patients with hypersensitivity pneumonia, and then we can evaluate what happens. If that initial approach to therapy causes our patient to be stable or actually improve, we can have discussions with that patient about either continuing therapy or maybe even at some point stepping down therapy and through those decisions continuing to monitor the patient's disease course. Are they still getting better? Are they the same? Or are they progressing? If, however, our initial approach for these non-IPF-ILDs does not work and patients are not stable and those patients are developing progressive fibrosis, we can have another discussion. Perhaps the discussion is we need to further augment your immunosuppressive therapy or try other treatments, and one of those other treatments could be consideration of antifibrotic therapy.

Thank you for joining us. Please complete the posttest and evaluation.

Narrator:

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