[MUSIC PLAYING]

CHESTER ODDIS: Hello, my name is Dr. Chet Oddis. I direct the myositis center here at the University of Pittsburgh, and I'd like to give you a update on inflammatory myopathy or myositis.

These are my disclosures. Essentially, none of the agents that I'll discuss today are really FDA approved for myositis. These are the three objectives that I'd like to cover, that is to discuss some selected clinical features of myositis classification.

I'd like to talk about the spectrum of autoantibodies seen in patients with myositis in their clinical associations and then I'd like to discuss selected treatment aspects of myositis. But it will be difficult to talk about a lot of treatment aspects given some of the other topics in this lecture.

But we'll talk about some aspects of myositis particularly autoimmune interstitial lung disease, which is a challenging problem that we have in myositis. So this is a well known classification of myositis, that includes adult polymyositis, dermatomyositis, along with juvenile myositis.

We'll just touch briefly on some of these today because of the time factor. Malignancy associated myositis is another subset along with myositis and overlap with another autoimmune disease, but we will not be discussing inclusion body myositis today.

When you look at the diagnostic criteria, there's an old set of criteria the Bohan and Peter criteria many years ago, it includes symmetrical weakness and elevated muscle enzymes that are listed there, along with a myopathic EMG, some that had normal features on a muscle biopsy, and the cutaneous features of myositis which sets dermatomyositis apart from the other subsets.

Now, the problem with the Bohan and Peter criteria is that there is really no good way to exclude other myopathies. And many patients are misclassified as having inclusion body myositis or polymyositis.

So really it's been a shift in the past that a lot of what we called PM may have been inclusion body myositis and the other factor is that each one of these criteria are not explicitly defined.

So the initiative over the past few years and it really took a long time to get this going and it was led by Doctor Ingrid Lundberg in Sweden. Is that there was a combined EULA that's European League Against Rheumatism and ACR initiative to look at classification criteria for adult and juvenile myositis subsets.

And it is a very difficult and tedious process and I'm only really able to talk about this in a superficial fashion. But basically, what happens is that there are [INAUDIBLE] variables that were assembled from a lot of published criteria and from expert opinion.

And this data collected was really from rheumatologist, a dermatologist, neurologists, and even pediatric rheumatologist around the world. And these new criteria were derived and each item which is different from before was given a weighted score, so that the total score course, corresponds to a probability of having idiopathic inflammatory myopathy analysis called that myositis for the rest of this talk.

Very complicated slide, but basically, this is the different criteria that I'm talking about. And as you can see here if you have a biopsy that's done or if you don't have a biopsy that's done you get a different weight or a different number points for different criteria.

And like I said, I cannot go through all of these but they include clinical features, skin manifestations, other clinical manifestations, and then laboratory findings. And there's actually a calculator that's been developed to use these criteria.

And what you end up seeing is basically, the criteria that gives you the weighted score that I talked about. And the bottom line is and I guess the way that I would summarize this without going through all of the details is that. If a patient does not have a classic DM rashes the recommendation is that you do a muscle biopsy, and you get points for doing that muscle biopsy.

But if a patient has a classic dermatomyositis rash without muscle involvement then you probably should verify it with a skin biopsy. And then like I said, these criteria provide a score and a probability for having myositis really for clinical trial purposes.

Now, when a patient sits across you and has one of these classic rashes and there are many rashes of dermatomyositis. Gottron papules here with sparing of the interphalangeal area and more involvement over the knuckles and the PIP joints.

This is Gottron papules over the knee. This is a rash that may look like Psoriasis but it's a rash of dermatomyositis. This is an ulceration a vascular manifestation, and this is the malar rash of dermato, and you can see that it does not spare the nasal labial area as you would see with lupus.

And this is an example of what's called the holster sign or the lateral aspect of the thigh again that patient's hand is lying next to their thigh. Classic heliotrope, classic V neck, and then the shawl sign so a lot of different rashes of dermatomyositis.

So when you make the diagnosis of dermatomyositis it's not difficult when you have the classic rash OK, it's easy. But that being said it doesn't mean that the management is easy because sometimes the skin disease can be one of the most dominant features of patients with myositis. And this is just a couple of slides on the severity, of scalp involved.

But this is a patient I saw many years ago, significance scalp involvement this woman had such severe scalp involvement that she was almost suicidal. And then this woman could even put on her glasses because it just irritated right over the area above the ear and underneath the hairline there. So very significant scalp involved here.

So when I look at patients with skin disease, they sometimes end up being treated as aggressively as some of the more serious manifestations that we see in myositis. So we start off with classic measures, protection of the sun, topical agents, sometimes topical calcineurin agents, antimalarials may be effective but oftentimes they are not, and them then of course steroids.

And if you get a response, well that's good. With steroid alone you can a ride and see what happens. But what happens many times is the skin rash is refractory and we treat these patients as you can see here much like we would treat significant myositis or the other more serious manifestations that we see in myositis.

And I had pictures but I had to cut some of these out. What I had now is a fourth line and what we actually reported in these two articles here is the use of tofacitinib. We reported a handful of patients that were quite refractory to all of these agents, gave them Xeljanz or tofacitinib and there was a very nice response.

Similarly, we have a case report of a patient that was refractory to a lot of different agents. Actually, the dermatologist got approval for apremilast which is Otezla given for psoriasis and this patient had a dramatic response. So now we even have a fourth line that we can go to in patients with dermatomyositis.

So let's move now to polymyositis which is problematic over the past few years. And why do I say that it's problematic? Well, as I said earlier, if you make a diagnosis of polymyositis there's a little bit more difficult because you've got to worry about mimics.

This is an entire lecture in its own right but there are many mimics of polymyositis which include endocrine problems, toxic myopathy, metabolic, evens forms of dystrophy, infectious problems, paraneo plastic issues, and even overlap with other connective tissue disorders.

So there are a lot of mimics which means and which moves us to the fact that, you got to get a muscle biopsy in a patient with polymyositis. If you've got those classic rashes that we talked about earlier that we showed here maybe you don't have to do the EMG and muscle biopsy if they are weak. But in these patients where there are the potential for mimics as you see here, muscle biopsy is a must.

Why is it a must? Because what we have actually learned over the years last several years, maybe even the last decade or two is what we used to call polymyositis. In some cases we now call necrotizing myopathy. So we've got a new kid on the block here when it comes to the diagnosis or classification of myositis.

This is not a typo. What has happened over the years is that, we are calling patients with polymyositis less frequently. And we are not really decreasing what we call dermato and some of the other subsets.

But clearly, We are decreasing our termi patients with polymyositis and I can tell you that when this article came out, gosh, almost 20 years ago now from the neurology literature where it was stated that, polymyositis is an over diagnosed entity.

Many of us said, wow, I can't believe that these neurologists are telling us what we can call them we can't call our patients. But indeed I believe that many of those investigators were correct.

And the reason is it's a matter of semantics. And there's much less pure adult polymyositis these days because they're probably shifting into this category of myositis in overlap with another autoimmune disease. And what is made is real to us is antibodies that we have identified through the years which allows us to move away from that designation of just pure adult polymyositis.

Let me give you an example of that. So these are real cases I have I think three cases here. This is a 67-year-old woman who had some medical comorbidities. And I put this up here and this is the lady I'm still following.

But I put this up because I want you to look at the dates. So she actually and we put these people down she actually got started on atorvastatin in July of 2004. And look at the time frame here, four years later she tolerates this medication fine but four years later she starts to develop the insidious onset of lower extremity weakness.

And then a year later she's having difficulty walking up steps, getting stuff out of the cupboard the closet, raising her arms above her head, and her daughter actually goes online over 10 years ago and says, mom I think you have to stop this stuff, this astorvastatin is Lipitor.

But she stops it like her daughter said but she doesn't get any better. If she goes through the summer and she sees her PCP and believes that she's just getting older and then she says, look she shows up in September.

Really, which is probably a year and a few months after the onset of weakness. And she says, there's something going on and he says, OK, I'll check a CK and he gets it, CK at 6,400 and then he says, well I think that's probably not correct.

So he waits a couple of weeks and it's up to 9,000 the patient gets admitted to the hospital. She has a muscle biopsy and it shows what's called myonecrosis. But no inflammation, no vasculitis.

So this is what this is about her biopsy in this came from a report in the literature but this is what it showed-- not a lot of lymphocytic inflammation but necrosis and very little lymphocytic inflammation throughout the biopsy described as and characterized as a necrotizing myopathy.

But what happens with this lady? She gets treated with prednisone, high dose followed by methotrexate and Imuran and later the addition of IVIg and she normalizes her muscle strength. Normalizes after being in her late 60s and actually gets better with IVIg.

Now, what happened later on is that, we didn't have that test to look for HMG-CoA reductase antibodies. But later on when this test became available indeed this patient was anti-HMGCR autoantibody positive.

So what do we know about these really significant patient, the patients would get significantly weak on statins. Remember, most of the statins in the statin used does not cause a necrotizing myopathy. But these patients that get the necrotizing biome from a standard and manifest or develop anti-HMGCR autoantibodies.

They're pretty sick, they're pretty weak, and there's data out there now published by Andrew Mammen a few years ago in the New England Journal that suggests, that IVIg is really first line therapy for these statin associated autoimmune necrotizing myopathy.

So just a little bit of a IVIg I told you I'd sprinkle some treatment in here. IVIg is a pretty effective drug and it's interesting that I can't really report all the data. IVIg was recently reported in dermatomyositis in a important session at the American College of rheumatology and it was quite effective. And this data is going to be made available to the public very soon in the form of a manuscript.

But just to review it IVIg briefly, there's a lot of data on IVIg out there. It's pretty safe with tolerable adverse events, you have to worry about propensity for blood clotting in patients. It's clearly steroid sparing that's very nice in the setting of infection.

Because it's immunomodulatory and not really immunosuppressive. And it's quite effective in the esophageal involvement or dysphasia and it's very good for acute complications or if a patient is rapidly progressing. And we find it to be very effective for the refractory graft and like I said in these days it may be the drug of choice in statin associated necrotizing myopathy.

Well, there is another necrotizing myopathy. That brings us to the consideration of an autoantibodies subset called anti-signal recognition particle or anti-SRP. These patients also have the onset of severe weakness, high CK maybe than myalgias and they look the same.

They have this necrotizing myopathy used to be called a PM phenotype but now we know that it's really a necrotizing myopathy. They don't get the rash of dermatomyositis, they rarely have interstitial lung disease, which we'll talk about later on.

And they also have a poor response to therapy with a variable prognosis. And when I saw these patients many, many years ago they were quite bad when they were untreated or undertreated and they almost looked as though they had muscular dystrophy.

Now, if you look at this, muscle pathology is similar to what we looked at in the patients with IMN or immune mediated necrotizing myopathy. That is they lack, lymphocytic, inflammation, but they have necrosis. You can see the areas of necrosis here but not a lot of interstitial inflammation in this biopsy.

So these are tough patients as I said before. So what else do we do? What else can we do besides IVIg and the necrotizing myopic patients? Well, we and others have actually reported on the use of B cell depletion in the form of rituximab in SRP positive necrotizing myopathy.

And we use that in our large clinical trial, which we did called the rim study or the rituximab in myositis study, but also the group from Hopkins actually reported on the use of open-label reduction map and they found a decrease an improvement in the MMT and a decrease in the CK.

And six out of eight patients that they reported improved. And our patients with SRP who were included in the reduction at trial also improved. So now as I said before this classification that I said earlier has now expanded and not only do we have necrotizing myopathy but we've got to autoantibodies subsets in that group of necrotizing myopathy.

Well, the classification gets even a little more complicated with the addition to what is termed a myopathic dermatomyositis to the subset of adult dermatomyositis And again, this is a lecture in its own right.

But just summarizing one particular autoantibodies we said we would be talking about these particular autoantibodies. Well, what occurred in the Asian literature, Jesus, long as 15 years ago and then extending more recently is in Japan.

There was these reports of amyopathic dermatomyositis with rapidly progressive interstitial lung disease. And then it showed up in China acute, subacute, interstitial pneumonitis, dermatomyosis patient. And then there were similar phenotypes in other Asian populations.

And they identified this 140 number here means it's a 140 kilodalton protein to which the autoantibody was directed against. So they called it anti-CADM, clinically amyopathic dermatomyositis 140. And it was later identified as anti-MDA-5.

What is MDA-5? Well, MDA-5 is actually a cytoplasmic protein that senses viral RNA. It induces production of a type 1 interferon. So it's involved in the innate immune defense against viruses. So it's natural that you would say, well, if you've got an antibody against a cytoplasmic protein that senses viral RNA then maybe it supports the role of a viral trigger. And, indeed, a lot of these patients become so sick so quickly that it does look like an infectious trigger.

But MDA-5 is even more interesting because it has a characteristic cutaneous phenotype. And these patients reported by Dave Fiorentino many years ago have palmar papules and cutaneous ulcerations. And this is vasculitis where you get a necrotic fingertip in association with a vascular culture. And these are taken from Dr. Fiorentino's article.

So this brings us to case 2. And again, this is somewhat before some of these antibodies became more well known. And I, again, want to point you to the chronology in this second case, which is a patient who develops a photosensitive rash, a 58-year-old woman, in the summer of 2012. And by January of 13, she's got a polyarthritis, mild muscle weakness and a rash. She has a normal CK, a Jo-1, which we'll talk about later. Most of you know about is an antibody that was negative. ANA was negative. SSA and B were negative. And she gets better on low dose prednisone and methotrexate.

And then she was referred to me, just to get another opinion, from one of our Fellows who is working in the Erie, Pennsylvania, area. So I see her in May, and her DM rash is a little worse. And it's interesting. When I'm listening to her and talking to her, I put my stethoscope on her chest, and I hear some basilar crackles. I said, that's unusual. I said, do you have any problems, any pulmonary symptoms? Nothing.

In fact, she says, I, kind of, walk up the steps when I go to work. And that's, kind of like, my gauge as far as my muscle weakness. And she had mild weakness. And I said, OK, well, I think you ought to increase your prednisone a little bit, and let's add Mycophenolate Mofetil for the rash and the weakness.

But I'll tell you, I said, I want you to get a CT scan of your chest. And I want you to get a pulmonary function test. And I passed that on to the referring physician and look at this. So this is May 2013. Well, she gets her-- she's in no hurry. A month later, she gets her CT scan. And this is not normal, but there's changes in the pleural area. There's little ground-glass opacities and some interstitial and reticular changes, as you can see here, and note the time. When I saw her, it was May, and this is in June.

And then I get a call around the 4th of July, one month later, from the referring doctor. And says, this patient's in the emergency department short of breath, and we can't adequately oxygenate her. And they sent me the eventual scan. So remember June, July, one month later.

And in retrospect, this patient ended up having anti-MDA-5. MDA And, unfortunately, she died in three days, three to five days after presenting around the 4th of July with refractory hypoxemia. And in retrospect when we looked at her blood, she, indeed, had the anti-MDA-5 autoantibody.

And this is a tough antibody. This is an antibody that's associated with a poor outcome. And this is data that we published just a few years ago from Dr. Moghadam-Kia who was a fellow and now a faculty member. And as you can see here, this is data where we had a fairly good cohort. We had a group of MDA-5 positive patients and a group of MDA-5 negative patients. This is the survival in the negative patients. This is a survival in our MDA-5 cohort.

I must mention that not all of our MDA-5 patients do poorly. Many of them do OK. But clearly, this is a bad prognostic autoantibody with a significantly different survival compared to those who were MDA-5 negative.

And then interestingly, as I said before, these patients have cutaneous manifestations. And this is just, simply, two other patients that I saw, patients referred to me with MDA-5. This patient did not have any lung involvement, interestingly. But look what happened to her fingers over three months. She gets necrotic. This is vasculitis. This is a vasculopathy.

And this is another patient. And I put here-- look at the little finger. I outlined that here. Two months later, this is her fifth finger, where she has now become necrotic. This is a vasculitis. Interestingly, both of these patients-- this one had mild lung disease. This one had no lung disease. So it can be variable, but, yet, MDA-5 is a vasculopathic-type presentation.

Well, we're talking about antibodies. We've talked about necrotizing myopathy. We've talked about amyopathic, where you get MDA-5. We talked about these two antibodies. Well, there's another whole subset of antibodies called the anti-synthetase antibodies. And the anti-synthetase syndrome is defined clinically as a homogeneous type of syndromes. It has some classic manifestations of fever, myositis. Arthritis that's oftentimes, early on-- whenever you have joint dominant disease, it can actually be misdiagnosed as RA because it can look like rheumatoid arthritis, symmetric inflammatory small joint arthritis.

These patients can develop Raynaud phenomena. They can have mechanics hands. But the real problem is with interstitial lung disease. In this goes-- this is mechanics hands. It goes over the clinical features. This is also mechanics hands. This is a patient with long standing, Jo-1 arthropathy. It looks like RA. And this is a patient with Raynaud phenomenon. And of course, the dreaded complication of interstitial lung disease.

But as I say that, the skin rash and the myositis can be very subtle in these patients. And sometimes, they present with what's called lung dominant disease. So this is another example of a patient. This is the third case. And, again, look at the dates here.

This is a patient that I saw two decades ago. She was in her late 30s at that time. She was hospitalized with an FUO. That was her symptom, her presenting symptom. She's in the hospital with an FUO. She's got a low titer ANA, and she's got basilar pulmonary fibrosis. And we are consulted on her because of the ANA and some non-specific-- well, actually, we were consulted for the fever.

So two months later, I see her in the office on follow up because she signs out AMA because nobody can figure out what she had. She got frustrated and says, I'm going home. So she goes home, and two months later, she's got worsening myalgias and arthralgias. She's got small pleural effusions. Her fever came back. She develops Raynaud phenomena.

And I say, you've got something going on. We're going to call this undifferentiated connective tissue disease. And she gets empirically treated with prednisone. But what we did at that time is that we, oftentimes, got blood samples. And we stored those blood samples in our own research laboratory.

And what happens is that one month later this patient then calls me and says, I'm short of breath. And I can't walk up the steps. And she gets a CT scan. And she's got diffuse pulmonary infiltrates. She's got those very subtle Gottron changes over her knuckles. And she ends up having an antibody called anti-PL-12.

Now, the course of this case-- and I, kind of, summarized it and compressed it, is that she gets worsening infiltrates. And back 20 years ago, these were her PFTs. These are not good PFTs for a person in their late 30s. FVC of 56%, a low FEV-1 and a low diffusion capacity, but she gets better with steroids and a medication called tacrolimus.

And the reason I used it back then is that I had the opportunity to use this anti-transplant drug in collaboration with some of the transplant doctors here. And I figured I wanted to try to use this drug to see if it could help some of these serious manifestations of inflammatory myopathy.

So her skin rash, joint symptoms and fever, they never returned. This patient never developed myositis. And her PFTs, just a couple of years ago, you can see they nicely improved back to where she was. Because I'll tell you what, I was not encouraged when I saw these. And I really did not think the outcome was going to be very good here. But she really has done well. She's on no oxygen, no pulmonary hypertension.

I tried to take her off tacrolimus because I was afraid of long-term tacrolimus and complications. And she says, well, if you take me off, I better not get worse. So she worsened a little bit, and she's on tacrolimus now. No prednisone again, and she's doing pretty well.

So this brings us to the concept of making the diagnosis of autoimmune interstitial lung disease. Because not everybody is going to have that classic anti-synthetase syndrome, where they get their fever, they get polyarthritis, they get lung problems, and they have myositis. This patient never developed myositis.

So let's look at our synthetase cohort a little bit more in depth. So these are the eight different synthetase antibodies. And you can see that they all target one particular tRNA synthetase. The common one, Jo-1, that most people know about targets histidyl tRNA synthetase.

And this is our cohort from a few years ago. I haven't updated this. This is what we used to publish data. Because I wanted to look at this synthetase cohort because it looked to me like the patients with Jo-1 were acting differently than the patients with the other anti-synthetase. So we really looked at the six major anti-synthetases.

So this is a very large cohort of synthetase positive patients, which went into a nice publication that Dr. Aggarwal and I did a few years ago. And this is what I want to point out. I want to look at the Jo-1-- now remember, this is all anti-synthetase. This isn't the other antibodies. So I want to look at the Jo-1 cohort and the non-Jo-1 cohort.

And what we found, and what we often try to look at in our patients, is what is the first disease that they are really diagnosed with. As you can see in the Jo-1 group, we called more polymyositis back then, but you can see that these patients had really predominantly myositis. A few had overlap. But flip over to the first diagnosis in the non-Jo-1 cohort, which is a nice cohort of 80 patients. Half of them undifferentiated or overlap. Some dermato, some poly, some even presented with scleroderma. This is scleroderma.

So you can see here that there's a lot of heterogeneity in that non-Jo-1 cohort. The point here is that, in fact, there's a statistically different diagnoses initially in these patients. 83% of Jo-1 had myositis. Only 39% non-Jo-1 have myositis. And you can even see here some of the other things that I've talked about. And that's a significant difference in that cohort regarding the initial connective tissue disease diagnosis.

What we also looked at in that cohort is survival over time. And we've got good data, long-term longitudinal data, on these patients. And you can see here that the non-Jo-1 cohort actually does worse in terms of outcome over time. With lower survival being-- with survival being worse in the non-Jo-1 compared to the Jo-1 patients.

And in fact, if you look a little more-- take a deeper look at why, you can see that the diagnosis delay is different. What is the diagnosis like? In the Jo-1 patients, they get diagnosed in 0.4 years, a few months. In the non-Jo-1 group, they're not diagnosed for a mean of one year. And that's a significant difference, statistically significant difference, in the delay to diagnosis in the Jo-1 versus the non-Jo-1.

But if you look at the-- what I did here is I look at the death in the entire cohort that is Jo-1 and non-Jo-1. And you can see that these patients are dying pulmonary deaths, as you can see here. Now, even these patients that died of other diseases did have significant lung disease. So clearly, in the synthetase positive patients, pulmonary disease was the most dominant cause of death.

So what do you summarize from that group? Well, the summary is that these non-Jo-1 patients frequently present with non-myositis symptoms, and they may never manifest myositis. Secondly, the diagnosis of a specific connective tissue disease is delayed in the non-Jo-1 group, and perhaps, that leads to the worsening survival. As the lung disease may go untreated for a longer period of time. And then third, the synthetase positive patients, whether they're Jo-1 or non-Jo-1, have an increased pulmonary morbidity and mortality.

So since we're talking about it, and as I said earlier we're going to sprinkle some treatment in here, how do you treat these patients? This is some of the more severe and significant patients that we see, and we do have non-biologic treatment of myositis-ILD. Steroids is the initial treatment. We talked about that earlier. Cyclophosphamide and azathioprine were used early or in steroid resistant cases with variable results, even intermittent pulse cyclophosphamide. There's a lot of data now that's accumulated on mycophenolate mofetil both in myositis autoimmune ILD, as well as other CTD ILD, and that's listed here.

And then finally, I mentioned earlier in the one patient that I spoke of, the use of cyclosporine and tacrolimus. So let's talk a little bit about that because these are anti-T cell agents. So is the anti-T cell therapy rational in patients with myositis ILD? It sure helped the first patient-- not the first one, but the most recent one that I talked about with anti-PL-12.

And if you look at some of the literature, there might be an indication as to why T cells might be a reasonable therapeutic target in myositis associated ILD. First of all, pathologically, they form these lymphoid follicles in the lung. These infiltrating lymphocytes and myositis non-specific interstitial pneumonitis revealed activated CD8 positive T cells. These CD8 positive and activated T cells were also increased in the bronchoalveolar fluid of a subset of myositis patients. Further, there's a decrease in regulatory T cells. And we know that regulatory T cells are a good thing in treating or in tempering autoimmunity.

So this implicates activated CD8 positive T cells in myositis associated ILD, which brings us to an article that we wrote many years ago, over 15 years ago now, where we looked at tacrolimus in myositis and ILD in a retrospective study. More than just a couple of patients-- we had a 13 patient synthetase cohort. 12 of them had Jo-1.

And what we found was that these pulmonary parameters got significantly better in patients with tacrolimus. And, in fact, the CK got better. Muscle disease got better, and it was steroid sparing. So this is a reasonable medication to consider. And indeed, after we reported it, you can see that over the past-- a few years after that, there were other reports on the use of data reporting the efficacy of tacrolimus and the other anti-transplant drug, cyclosporine, in myositis-associated ILD.

Given that, we then wanted to move on and say, OK, well, anti-T cell therapy works. We now have a biologic that targets the T cell and that's abatacept. So we are in the process of looking at our data and finishing up a trial on assessment of abatacept for the treatment of myositis-associated interstitial lung disease. And this is a proof of concept study, smaller study, in a few different centers. And we'll be looking at that data over the next year or so.

Well, another drug that has gained a lot of interest over the past many years, not just from our trial looking at rituximab called the RIM Study, but looking at rituximab lab in anti-synthetase syndrome-related ILD, again, that tough subset that I talked about.

And I'm just going to go over a few slides on a nice study. It's a retrospective study, but it was a nice study done five years ago. And this was, again, a large cohort of snythetase positive patients. 34 of whom were treated with rituximab. 30 had severe ILD. And they had acute ILD in half the patients. And they had pretty good follow up with these patients. The other thing to remember here is that this was not monotherapy with rituximab, and many of these patients received cyclophosphamide.

But let's look at the data. And the data here is that looking at these patients over time, looking at PFTs, this is the increase from the baseline of these PFT parameters. For example, pre-rituximab, post-rituximab, significant increases in FVC, significant increase in FEV1, and an increase in the DLCO. Again, the increase from baseline.

What happened to their CT scans? Well, I'm not going to go into the grading. But they looked at a grading system demonstrating parenchymal involvement on the CT. And this is the pre- and this is the post-. And what was looked at was they had pre- and post-rituximab scans in 23 or 24 patients. And the grading, the scale went from a 50% involvement to a 33% involvement on the HRCT, which is a significant drop. And actually, in five, the ILD extent dropped greater than 60%. And in only one patient did the HRCT worsen, and that patient got transplanted.

After that, and we've also contributed to some of this data over the past few years, is that there has been more reports of the efficacy of rituximab in anti-synthetase positive patients. And this just outlines literature. This was a study that we did in conjunction with the group at Harvard, Massachusetts General Hospital. So rituximab seems to work in patients with synthetase positive ILD.

So I just put this up here. I mean, I'm not going to go through this. We published this a couple of years ago outlining our approach to myositis-associated ILD. You can see that there's an induction phase, almost, that I kind of talked about. But if the patient has severe disease, you're giving them steroids and Cytoxan or rituximab. And then you're going on with maintenance therapy. And then, of course, we talked about some of the more experimental agents that are being studied in clinical trials. So I put this in there as a reference for those who are interested.

Just a few remaining slides on the classification of myositis, back to that, and talking about malignancy-associated myositis. And I put this in here because one has always been interested in the autoantibody markers that identify patients with malignancy-associated myositis. And, indeed, we now have an autoantibody. We talked about MDA-5 and some of the synthetases. Well, this is an antibody against a doublet protein. Again, looking at the kilodalton of 140, 155 and the auto antigenic target is transcription intermediary vector 1 gamma. And this is the target auto antigen.

Interestingly, we didn't talk about much today regarding juvenile dermatomyositis, but this is a common autoantibody in juvenile dermatomyositis. So it occurs in adult and juvenile. And when you see it in kids-- it's actually probably in 20% to 25% or even up to 30% of JDM patients. And they can have skin involvement, and it can become severe. In an adult, there's this malignancy association. And this is just a doublet here. These are patients in the 155, 140 across or 155, 140.

So just a quick summary of this. In adults, these patients can have cutaneous dermatomyositis and cancer. Clearly, not all of these patients develop cancer. And, in fact, this autoantibody, anit-TIF1 is one of the most-- really, is probably the most common antibody that I see, and most of these patients do not have cancer.

Interestingly, the kids, the juvenile dermatomyositis, they get cutaneous involvement, ulceration, edema, and calcinosis. They do not get cancer. And even if you follow these JDM kids out farther, they don't develop cancer. So it's an interesting difference between adult and JDM patients regarding this autoantibody.

So, again, just summarizing things, you can only cover so much in a lecture like this. How do we approach these patients in the future regarding therapy? Well, you can take out the heterogeneity of myositis and look at disease subsets, but it's probably better, as I likely made the case today, to look at these in terms of autoantibody subsets rather than clinical subsets. And maybe if you look at these autoantibody subsets, you'll be able to identify certain cytokines or even microarrays that might indicate what might be turned on in these patients that have these autoantibodies. So you can almost kind of determine if there's an interferon mechanism that needs to be targeted.

The other approach that we oftentimes don't talk about is a sequential approach using different agents. Maybe there are certain times in the course of a patient where one particular cytokine may dominate, so you have to, kind of, do a targeted approach.

And the other thing that I did not talk about in myositis that there's a whole literature on is improving exercise in these patients. It used to be that we put patients with myositis at rest. Oh, we don't do that anymore. And we actually want them to become and maintain more activity.

So this is our Myositis Center here. We have Drs. Aggarwal, Moghadam-Kia, and Dr. Dana Ascherman, who's our division chief. We've got a lot of collaborators, and we've got a strong research coordinator group and a lot of collaborations that are important for us, as you can imagine. The pulmonary collaboration is very important. And I've done a lot of collaboration over the years with a superb neuromuscular pathologist Dr. David Lacomis.

Just one plug that we wrote a book on managing myositis. It's a very nice practical guide to managing myositis. Rohit Aggarwal and I are editors of this book, and it's available, and it really-- we've got world class contributors to this book that really gives you a practical approach to myositis. So thank you. And, hopefully, this provided some background for you on the inflammatory myopathies.