Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/pulmonary-arterial-hypertension-and-connective-tissue-disease/16512/

Released: 11/30/2023
Valid until: 11/30/2024
Time needed to complete: 4h 49m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Pulmonary Arterial Hypertension and Connective Tissue Disease

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Cuttica:
So I am going to present the pulmonary arterial hypertension and connective tissue disease, and move forward. We're going to review the current knowledge of pulmonary vascular disease in patients with connective tissue disease, and focus on screening, diagnosis, and treatment of CTD-PAH. Alright, so we know PH is a progressive debilitating disease associated with significant morbidity and mortality, as we've talked about. It will eventual leading to right-sided heart failure and death.

So this is data from again, that REVEAL registry we've talked about; a large registry of patients with Group 1 PAH from the United States. And this just shows the distribution of the types of the subgroupings of PAH that were identified in the REVEAL registry. About half of these patients had idiopathic PAH, but you can see as we're going to talk about today, a quarter of the patients in REVEAL had - as the underlying ideology of their PAH, underlying connective tissue disease. And we saw the prevalence that we've talked about of PAH within the rural population. But again, we're going to focus mainly on ,or only on CTD, so our connective tissue disease-associated PAH.

So I like this slide that he put together, looking at the different WHO groups and highlighting where connective tissue disease fits into this. Alright, this is again a review that we saw in the earlier slides or the earlier sections of how we categorize pulmonary hypertension with group 1 pulmonary arterial hypertension being primarily the vascular disease of the lung, group 2 heart disease, group 3 lung disease-related PH, clotting in group 4, and then the multifactorial mechanisms in group 5. And as we think about connective tissue disease-associated PH, what we usually first thing got this group 1, right, that's what we're always worried about in our scleroderma patient population, or other connective tissue disease is the risk of these patients developing pulmonary arterial hypertension or the primary vasculopathy. Oops, sorry, I jumped ahead. This is what we talked about, destruction of lungs, he's just reviewed, or we're reviewing here, the underlying ideologies of this, and that as we think about connective tissue disease, right, group 1 pulmonary arterial hypertension, the one we really worry about. But we know as we approach this patient population, they're at risk for all different types of pulmonary hypertension. So as our case highlighted and we talked about before, we know these patients are at risk for underlying cardiac disease that can put them at risk for group 2. And then the underlying interstitial lung disease that can develop in patients with connective tissue disease can put them at risk for group 3. So as we approach these patients from a diagnostic and treatment standpoint, we want to keep in mind all the different ways they can develop PH, and make sure they're categorized appropriately. And we can't again, forget about group 4 PH and this population, because we know patients with underlying connective tissue disease like lupus, at higher risk for antiphospholipid antibody syndrome, clotting risk associated with lupus. So we always, always want to think about chronic thromboembolic disease when we're working up with patients with pulmonary hypertension.

So again, we're going to talk primarily about PAH and connective tissue disease. The thought process behind this connection between

autoimmune disease and connective tissue disease is this intersection between immune dysfunction and the vasculature - in the pulmonary vasculature, right? When we think about what drives group 1 PAH, we think about vasoconstriction, we think about clotting risk, we think about proliferative vasculopathy, and then we think about inflammation as sort of the four major drivers of the vasculopathy. And connective tissue disease sort of drives many of those and that with this immune dysfunction. We know under pathologic studies, vascular lesions of connective tissue disease-associated PAH are often indistinguishable from those with idiopathic PAH. We know that many patients with idiopathic PAH eventually go on to be diagnosed with autoimmune diseases down the road, so this sort of known interaction. And then we know that survival and clinical outcomes tend to be worse in patients with connective tissue disease-associated PAH compared to idiopathic PAH, especially those who have scleroderma, as their underlying connective tissue disease.

So specifically in scleroderma, we know the prevalence of this is about 8 to 12%. So about 8 to 12% of patients with scleroderma will develop group 1 pulmonary arterial hypertension during the course of their disease. We know there are disturbances in angiogenesis and elevated levels of these angiogenic factors. There's an association with certain autoantibodies in scleroderma. And we know that the hemodynamic profiles of patients with PAH are similar to those with idiopathic PAH, but less hemodynamic impairment.

And this is a paper that highlighted the comparison between those with idiopathic PAH and scleroderma-associated PAH. And you can see, although the outputs are generally about the same, the scleroderma patients tended to have lower mean pulmonary pressures and lower pulmonary vascular resistance; two things that you would think would be associated with better long-term outcomes, but we know in scleroderma patients, they tend to have worse outcomes than patients with idiopathic PAH.

This is a publication that looked at survival of patients with group 1 PAH comparing the different subcategorizations. And you can see that green, connective tissue disease patients' survival curves being significantly lower than those with both idiopathic PAH and CTEPH, approaching sort of the same survival curves as those with portal pulmonary hypertension, only being better than those with pulmonary veno-occlusive disease.

This is a graphics that also shows survival comparing scleroderma-associated PAH with non-scleroderma-related connective tissue disease that highlights again that of all the connective tissue diseases, those with scleroderma tend to have the worst outcomes. And why is this? Well, this probably has to do with RV adaptation in patients with scleroderma compared to PAH. And we know that even though that hemodynamic profile appears to be better when you look at just the pressures, that patients with scleroderma tend to have worse right ventricular function parameters when you look at these metrics like RV, ejection fraction, elastance measurements, and volume measurements. Their RVs tend to be sicker even with less abnormalities in their hemodynamics.

And then as we talked about, those interesting data with looking at mean PAP, or the change in pulmonary pressure and cardiac output as the exercise-induced PH, this is looking at change in pressures and cardiac output – or mean PAP and cardiac output looking at different subgroups of patients. And we see that patients with scleroderma-associated PAH have the worst markers of right ventricular function. And this is comparing across normal, which is the boxes along the bottom. We look at scleroderma idiopathic PH and scleroderma patients with borderline PH, and those with pulmonary hypertension have the worst outcomes or the worst marker of RV function.

The risk factors for the development of PAH are limited to patients with limited cutaneous scleroderma as opposed to diffuse cutaneous, late age at the onset of their scleroderma, the length of time they've had scleroderma. So at some point in their course, having Raynaud's and digital ulcers, as well as the number of telangiectasias and then, again, as in our case highlighted, right, as from a screening standpoint and identification of these patients, a isolated reduction of the diffusing capacity or the FVC to DLCO ratio that's elevated, another way of saying an isolated reduction in diffusing capacity, can be predictive of those at risk for developing PAH with scleroderma. Increased BNP and in the presence of autoantibodies, right. So all of these things, as we think about this high-risk patient population, where there are guidelines that recommend aggressive screening of these patients, these are things we should be thinking about to identify those that we're really worried about developing PAH.

Val had mentioned this before in one of the talks where saying that there is a validated screening tool called DETECT, which is available in use and centers for try to take patients through an algorithm to identify who needs to get echo, who needs to get cathed in this higher risk patient population. So you can see it's a pretty nice tool. There's a QR code that you can scan and get to this site and you enter in your parameters for your patients and it walks you through step 1, where it looks at lung function, physical exam, like the presence of telangiectasias, their antibody status, the NT-proBNP, urate, and EKG changes. So, right, all non-invasive testing for the most part, that we can look at that, gives you a score. If the score is above 300, recommended that you get an echocardiogram. And step 2, in the scleroderma screening, you can get the echocardiogram again, put it into their algorithm and it tells you whether or not the patient needs to have a right heart catheterization. So it's a nice stepwise approach.

This is an example of going through and putting in the parameters into these patients and showing your scoring system, echo recommended or not. And then after the echo is done, looking at the parameters telling you whether or not you should proceed to a right heart catheterization. So a nice validated tool that's available online for your scleroderma patients to be able to go through and determine whether or not we should be cathing them. And that's the QR code that takes you to the DETECT website, which I think is available for you outside of this.

And then screening echo, right, we've talked about this both in the guidelines. We saw some nice pictures of this, showing that, you know, we have moved - should have moved beyond the idea of just measuring the estimated pressure. I think sometimes the echo reading guidelines need to catch up to the clinical practice where we still see these echo reads come back and say, hey, the pulmonary artery pressure is 60, consistent with severe pulmonary hypertension, but the RV looks normal and all the other parameters look okay. So PA, SP, or RVSP on the echo is one piece of the puzzle that you want to look at. But you really always want to interpret that number in the context of the structure and function of the right ventricle. Is the right ventricle enlarged? Is the right atrium enlarged? Is the function of the right ventricle reduced? Are there left-sided abnormalities that could account for some of the elevated pressures inside the lungs? So using that ESC/ERS guideline table that looks at all those nice ways of thinking about the echocardiogram, I think is really important, especially in a high-risk patient population like scleroderma patients.

This is another publication that looked at the MRI imaging of the heart. And again, I think it highlights basically what we're talking about as far as looking at structure and functional changes of the right side of the heart and not just relying on the pressure estimate.

And then the last section here for the last 2 minutes, we're going to talk about treatment in scleroderma-associated PH or connective tissue disease-associated PAH. So I think this is the first time this image has shown up today in a talk, and I'm sure it will probably show up about four or five more times, you can't have a PH symposium where we don't look at this picture. This is a really nice, I think the original publication was in this *New England Journal* article way back 100 years ago, but it basically highlights are three treatment pathways that we think about that are currently available for targeting patients with PAH. The endothelin pathway, which is – endothelin is a potent vasoconstrictor that tends to be overproduced in patients with PAH, so we target it by blocking endothelin. The nitric oxide pathway, a potent vasodilator which is underproduced, underutilized in patients with PH. So we target either preventing the destruction of nitric oxide or tweaking that pathway to promote vasodilation. And prostacyclin pathway. Prostacyclin is again, potent vasodilators underproduced in patients with PAH. So we give that back through prostacyclin analogues to promote vasodilation.

This is a really nice picture that highlights all the different ways we deliver these drugs, right. We've talked about these in the guideline talk. But these range from inhalational therapies to oral therapies to continuous IV infusion and sub-q infusion. So we want to make sure all treatment pathways are available to patients as we treat them.

And then we're going to talk to the last two slides, he highlighted two I think really important and interesting concepts in the world of PAH, specifically connective tissue disease, which is the role of immunosuppression, right, we're in a PH conference, we're talking about pulmonary vasodilators, really good data, you know, showing us or guiding us how we should treat with upfront combination versus triple therapy in these patients. But these are connective tissue disease patients, right? They're always treated with steroids and other immunosuppressive agents. How do they impact PAH? And this is I think, as he highlights here, important to sort of split this into, well, what's the underlying connective tissue disease? How should we think about this? Are we talking about primarily lupus patients? Or are we talking about scleroderma patients?

So again, this looks at - this is a clinical trial that was done, this is in the early 2000s that it was in a lupus patient population using cyclophosphamide to treat patients with probably lupus-associated PAH. And what this showed was through - with a lupus population with immunosuppression, they showed improvements in the hemodynamic profiles. There have been other publications out of Europe showing similar findings where with active lupus, if you treat the lupus with immunosuppression, the PAH can get better. So if you have a lupus population, you still want to think about treating them with traditional pulmonary vasodilator therapy but making sure their lupus is under control is important. And then this, in specifically the scleroderma patient population, this was an interesting thought-provoking, question-generating trial that was led by Roham Zamanian, looking at rituximab in patients with – or the use of rituximab in patients with systemic sclerosis-associated PAH. Now ultimately, this was a negative trial. It didn't hit the endpoint to say that Rituxan worked, but it raised some interesting questions about the effect on 6-minute walk test with treating with Rituxan. But again, a negative trial. And to date, nothing consistently showing that treating scleroderma patients with immunosuppression actually affects the PAH. So, in a scleroderma patient population, you really want to focus on pulmonary vasodilator therapy early and aggressive, as we've talked about, to try and keep their RV happy and healthy. And then we can talk to rheumatology about the role of immunosuppression for other scleroderma issues that arise in them. Maybe more to comment this pathway and things to talk about in the years to come, but as of now, a negative study.

So in summary PH in patients with CTD is associated with impaired clinical outcomes despite similar hemodynamic profiles. Early

recognition is key.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, LLC. and is part of our MinuteCE curriculum.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.