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https://reachmd.com/programs/cme/focus-on-ctd-pah-and-rheumatology/16330/

Released: 10/31/2023
Valid until: 10/31/2024
Time needed to complete: 4h 16m

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Focus on CTD-PAH and Rheumatology

Announcer:
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Dr. Kafaja:
Do you want to tell us about your patient and what you ended up doing for the patient?

Dr. Cao:
So she had, just a reminder, she had severe precapillary pulmonary hypertension. So in light of her - I think she had WHO - she had a functional class III symptoms, because she was short of breath pretty - very easily short of breath. She had the near syncope event. So she was started pretty quickly on PH-directed therapy with subcutaneous treprostinil, as well as tadalafil. And then I think felt better like very quickly, she was able to walk to her car without taking any breaks, like go up the stairs while carrying groceries. And she ultimately proceeded to have a lung transplant about 2 years after I think she established care in pulmonary hypertension clinic.

Dr. Kafaja:
Now, what are your thoughts on - I know that you mentioned DETECT, the DETECT algorithm? And what are your thoughts? Whether we should be using DETECT in that subset of patients? Is this just mainly for scleroderma patients? What are your thoughts, Dr. Lewis?

Dr. Lewis:
Yeah, well, you know, I think the DETECT was initially proposed for scleroderma. So I mean, I personally think that that's probably where the focus should be. There have been other screening tools, there's the Australian one, which seems very simple and has been compared to DETECT. So what the Australian one does, is that uses NT-proBNP it that uses the FVC percent of a DL percent greater than 1.8 as opposed to 1.6 to send to right heart cath. And then there's also the ERS/ESC guidelines, which seem, you know, are out there, but you know, based on TR velocity and other clinical parameters. I think of the various risk strategies, DETECT and the Australian seem to come up the best. So I think whatever you use, it's reasonable to screen patients with scleroderma.

Dr. Saggar:
Yeah, I think there's, I mean, there's sort of two issues here. One is the, you know, the number - DETECT was in asymptomatic patients who had systemic sclerosis. And the idea is that I mean, this entity, the scleroderma spectrum of disease, if you will, where, you know, not all these people look alike either, right? They have - and Suzanne didn't show this, I don't think, but you know, they've homogenized how to label these people. Right? So we all think we're studying the same group, that you have to meet you know, 9 out of X number of criteria to be diagnosed with, you know, scleroderma spectrum of disease.

Once you know you have that, then because it's such a high predilection for developing pulmonary hypertension, this is why DETECT was taken on just like, okay, these patients are asymptomatic, yet, we want to figure out, you know, who may already have a problem in that setting; they have systemic sclerosis for greater than, I think it was 3 years, greater or equal to 3 years, you know, they had to be asymptomatic, they had to have a diffusing capacity that I think had to be less than 60%, and an FVC greater than 40%. So there was all

these criteria they looked at, and they had a whole number of parameters that they came out with, and they whittled it down, and they cathed everybody. So that was the beauty of it. And so, it has a pretty strong recommendation, because it took a holistic and homogenous approach, right, to these folks. And because it's such a high, you know, predilection for developing PH. And the idea is, if you treat it - the concept is if you treat it earlier, you might actually change the natural history of it. I guess that's not actually proven, but that's the concept. So I don't know.

Shelly, do you have anything to add to that? Shelley has the perspective of a cardiologist, which I've learned a lot from Shelley over the years because she has a very simple philosophy that whatever is happening in the lungs, it really doesn't matter. And it's the pulmonary hypertension is pulmonary hypertension, and she's going to treat it as such, regardless of what the lung CT looks like, but because of that, I've seen - I learned a lot actually because I think that approach is actually somewhat valid and her approach has taught us a lot from obviously, the rheumatologist focus in on these little capillaries, we focus in on the CAT scans, and Shelley's approach is look, it's bad, and we're going to treat it. And that's been helpful. I've learned a lot watching Shelley's practice. So Shelley, tell us what your thoughts are.

Dr. Shapiro:
So I think the issue is what constitutes an asymptomatic patient. And I think that's where we get very, very commonly misled. And the classic example of the mitral stenosis patients who say, 'I'm fine,' and then you ask them what they actually do. And over time, they've cut down what they do, so that what they do they feel good about, but they don't do 90% of what they used to do before. So I think getting some kind of information on what the patient actually does and thinks they're asymptomatic about, really helps you because you'll find that many of these patients who you think are just absolutely fine, are incredibly symptomatic, and they've locked themselves into a tiny little corner.

The other thing I use as a BNP and some kind of objective exercise test. So even a simple thing, like a 6-minute walk is very useful in connective tissue disease patients, because it's not very challenging. But you'll be shocked when you find out how limited they are. And then you think through additional diagnostic testing. So I think that's one thing that I would take away.

And the other point to it is that the pulmonary vascular disease has to be approached and attacked from all of the points at which you can modify the pulmonary vascular stuff, because as your right ventricle goes, you go, and what determines how your right ventricle does is the afterload and the vascular bed which it has to work with. And so I think this approach of, you know, well, we're going to go to prostacyclins first, well, I think that that's not entirely correct, we go through it pretty quickly. But you can start a PDE5 inhibitor, and even an ERA in a matter of days, and getting approval for prostacyclins, and getting people titrated up on it is not a small procedure. So if you think of making an immediate impact on patients, there are a number of things that you can do first. And that's my worldview.

Dr. Saggar:
So just to push back on that, if you - what patient, if you saw de novo, an incident case of, you know, PAH in the setting of an autoimmune disease, would you say this patient deserves a prostacyclin up front? In other words, or would you always do a dual oral approach? And then, like, how do you - how does it work in real life?

Dr. Shapiro:
So in real life, if you're seeing a patient and they're in the hospital, you can start medication that day with a PDE5 inhibitor while you're getting approval for the prostacyclin. You can start prostacyclins, but patients go completely crazy. When we used to have approval before we can even start back in the old days for Flolan, patients stayed in the ICU for days and days and days while we fought it out with the insurance company. And so we started using PDE5 inhibitors. And I actually had an abstract, which we never published because it was socially unpopular, that we're using high-dose sildenafil at that time, many of those patients left the hospital without having to initially be started on prostacyclin as an inpatient, and it was kind of remarkable, these drugs are underestimated. So I have a very low threshold for starting prostacyclins, but it's something that takes you at least a week or 2, so why not use the other things in the meantime, and see how much they improve right up front.

The other thing is volume status. It's something that hasn't really been mentioned here at all. And this is a critical part in the management of pulmonary hypertension.

Your preload, you know, is a determinant of outcome in all the guidelines, the RA pressure predicts survival dramatically. And so, getting the preload down with a diuretic, and getting some improved RV function really makes a difference in terms of how the patient does.

Dr. Saggar:
So class IV patients, Dr. Lewis, you're going to comment in a second, but class IV patients who end up in a hospital, once you diurese them and put them on maybe one or two oral drugs, particularly the PDE5 inhibitor pathway, since they're more you know, faster onset,

you can take a class IV patient and turn them into a class III patient fairly acutely. And then you can sort of figure out which way to go from there. What do you think, Dr. Lewis?

Dr. Lewis:
Yeah, I mean, I think it really depends on the patient's presentation. So I'll just give an anecdote because recently, last Saturday, I went to the wedding of a patient of mine who's age 33. I started seeing her at age 21. She had mixed connective tissue disease. She presented when she went with her friends to Disneyland, and you know, the Disneyland parking lot, as everyone knows, is huge. And she fainted twice going to the ticket office. Nevertheless, even with her friends, she still went to Disneyland. Then she told her parents when she came home and they freaked out, and the bottom line is she had an echo, which was critical. And when I heard about her, I admitted a straight to the ICU, cathetered her, her cardiac index was kind of less than 1.5. And she had critical pulmonary hypertension. We put her immediately onto parenterals. And she's done very, very well. As you suggested, that took time, we eventually weaned off parenterals and have her on three, you know, oral agents. And she's now, you know, between class I and class II, and at her wedding, even though it gave me as they say in Yiddish schpilkes, for those who understand Yiddish, watching her dance on the dance floor, because I was sitting next to a cardiologist and I was saying to him, I think she should cut back on the aerobic exercise, particularly on her wedding, but anyway, she did beautifully. And so I think it really depends on the presentation.

Dr. Saggar:
Yeah.

Dr. Shapiro:
You know, there was also the Flolan sildenafil study, where we put, at the same time they were studying sildenafil as a primary agent, they also had a subset of patients who were on Flolan and we added sildenafil to it, and a bunch of those patients came off Flolan, and then stayed off Flolan for many, many years. I have several of them that were in the original study. And so those patients were functional class IV, and they were put on Flolan at the time, because there really was no other option. But I think that sometimes we are able to modify their functional class and their status. And I think we have to go with the flow. And if any of you have seen patients chronically on prostacyclins, it's not a pretty life. And you have to think long and hard about it in terms of quality-of-life issues just from that.

Dr. Saggar:
Yeah, and I think, you know, we also are able now to transition patients from prostacyclins to the oral - to oral - well, for instance, to oral treprostinil, there's data for doing that.

Dr. Shapiro:
Or inhaled.

Dr. Saggar:
Or inhaled, yeah. Shelley, there's a question here I think that you should answer. So if you had an autoimmune disease patient, let's say systemic sclerosis, just based on the echo alone, what do you - what would make you - you're probably the wrong person to ask about this, but what would make you on an echo procedure right heart catheterization?

Dr. Shapiro:
I always do. Because many of the patients you see with connective tissue disease have other possible complicating factors like hypertension, diastolic dysfunction, whatever. And there's information from the cath that's predictive of outcome. So the cardiac index, the right atrial pressure; it provides a baseline for where they're going and a firm endpoint. And as an echocardiographer, I can tell you there's a tremendous amount of wiggle room in the interpretation of the TR velocities and how accurately they're done. And you don't just want to define it based on just that, you want to have a baseline with hard data that you can then go forward with.

Dr. Saggar:
Okay. And what do you think is the most important hard data, as we sit here today? Like give us three parameters on an echo besides TR velocity that you think are the most helpful for you? Just whether that's diagnostic or something you follow? On echo, just echo for PH.

Dr. Shapiro:
On echo? So the RV size and function, whether the RV is very large, what the IVC is. In other words, how much right atrial pressure do they have. And then there are other ways that you look at cardiac output directly and indirectly in the echo, that gives you a hint in terms of looking at whether the patient has any function. But I don't use that exclusively, and I put a heavy emphasis on things like BNP to try to improve it because many of these times you really don't get a good look at the right ventricle. We all talk about how they measure right ventricular ejection and stuff like that. But if you sit and look at them day after day, you can't see these walls very, very well. And you just don't want to be fooled when you're - especially if you're committing a patient to prostacyclin, you really want to have some hard

data.

Dr. Saggar:
Yeah. Dr. Hage, can we get a microphone. Oh, you have it. Great.

Dr. Hage:
Thank you. Tony Hage from Cedars. As Dr. Shapiro said, we get referred from rheumatologists all the time patients with rheumatological diseases, scleroderma mainly, but rheumatological. And maybe I get to cath 1 out of 10. The reason is because they are referred to us early. They are referred to us without any signs of pulmonary hypertension. For example, the case that Dr. Cao had presented here, I wouldn't think twice about right heart catheterization, she had the right ventricular hypertrophy, right bundle branch block, dilatation of the right ventricle, TR, abnormal RV. This is - you don't need even the DETECT algorithm, or the ASIG trial. I don't think we need to. It's a personalized medicine, I would go directly to cath.

Having said that, when we are referred patients without any sign, like you said, then maybe that's the patient that we need to use the DETECT trial on or sometimes even without it, if you don't see any signs of dyspnea or any sign on the EKG, simple EKG of right ventricular dilatation or abnormality in the conduction and nothing on the echo, no RV dilatation, no RV dysfunction, and a normal acceleration time, there is no point for us to go for right heart capitalization. This is the patient that I'll just follow, watch like a hawk every 6 to 12 month, and take it from there. Yeah, you absolutely can enrich it like the DETECT with BNP and anti-centromere and urates and this and that, but there is no need for them to put them through an invasive test and take the risk of cardiac right heart catheterization, which is not negligible, 1 in 1,000, to 5 in 1,000, not negligible.

Dr. Saggar:
Yeah, there was a nice – Rich, did you want to add to that? Oh, I was just going to add that there was there's a nice paper from the Belgian group looking at noninvasive ways to mate to diagnose or to get the negative predictive value for PH. And they looked at four parameters. One was, if the patient's functional class I or II, and if their resting pulse oximetry on room air is above 95%, equal to 95% or above, and if they have an NT-proBNP or a BNP that's normal, and lastly, if they have no evidence of right axis deviation, or RVH, on an 12-lead; if all of that was true, the chances of having PAH on a heart catheterization was less than 1%. So these are like I said, there was a simple algorithm that they employed in their, you know, they had a retrospective cohort, and then they validated it prospectively, which I thought was pretty helpful. Obviously, they had autoimmune disease patients in there too. But anyways, Rich you want to?

Dr. Channick:
I guess, I just thought of a second question. But, Suzanne, you know, I think anytime you hear talk on rheumatologic disease, you know, you think about immunosuppressive treatments. And obviously, I guess they haven't really panned out in PAH component of CTD. Are there any subtypes that you think might particularly be beneficial with actually immunosuppressive drugs in treating the pulmonary vascular component, or what do you think?

Dr. Kafaja:
So it's a very good question. I think the main patients that I would think about to, you know, I think as far as when it comes to vasculopathy, specifically, regardless of whether it's heart or sometimes we think the GI, although there may be other reasons for GI involvement, immunosuppression has not played - we don't think it plays a role, historically, at least in our patients in treating specifically systemic sclerosis patients. However, you know, there has been a rituximab, for instance, trial where we had high hopes for it, you know, whether it makes a difference as far as pulmonary hypertension patients. But I do think that there were also flawed - some flaws in those clinical trials. So I'm not so sure that I would actually take that to the bank and just make it - use it as a no-go for the usefulness of immunosuppression in those patients. Of course, you know, whenever we're dealing with scleroderma patients, we always want to, because they're complicated, they - because they can have aspirations, micro aspirations and so on, the use of immunosuppression, we always have to - I always tell my patients that I would be just as aggressive as your disease is. And so whenever I, you know, if I'm thinking about a patient that has - that is presenting mainly with the more vasculature component rather than ILD, for instance, it's much easier for me to say, 'Oh, yes, you have a little bit of ILD, why don't we do this?'

And you know, Rajan showed that there were some tocilizumab trials going on, which is now FDA approved for ILD for patients. So it makes it easier to kind of push and use that and see how well they do using medications that are FDA approved, for instance, or rituximab, for that matter, on top of something like MMF. But of course, there's always that component and there's the never-answered question of whether which group do they belong into? Right? Do they belong in Group I? Is this pure pulmonary arterial hypertension? Is there a component of, you know, Group 3, that is taking place there? So I - it's not a straightforward thing, it's really personal.

Dr. Saggar:
Yeah, there's a growing literature in cAMP supporting the concept that PAH, it may be a lot more inflammatory, and I know it's the buzzword, but there's a lot more active inflammation going on in pretty much in all three layers, if you will, of the pathology. And that's

really what led to the Rituxan study. I think if you look at - just like any studies that we do in PAH, they're not enriched, right? They're given to everybody. So what they found in a lot of these studies, there's people that clearly respond to these drugs. I mean, in that study, the Stanford study with Rituxan, which was an NIH multicenter study, but PI'd that Stanford was, they did find a subgroup that responded very well to Rituxan, you know, I think it was a low level of rheumatoid factor. And then they had done a whole chemokine analysis. And they I think they found IL-12 and IL-17. If they were high, you know, people have to - it's individualized stuff. I mean, at some point, there's people who respond to imatinib, there's people who respond to Rituxan, and there's people who – clearly, I mean, we've seen that in the clinical trials. The question is, how do we enrich these studies and how do we personalize the approach? So I think you haven't heard - you haven't seen the end of the anti-inflammatory sort of push, if you will, for drugs, you know, in PAH? I don't know, Rich, if you want to add to that?

Dr. Channick:
Yeah, no, I was going to actually turn it to Mike, because, you know.

Dr. Saggar:
Yeah, we were about to – I was about to.

Dr. Channick:
Yeah, the last 5 minutes, because I mean, your stem cell.

Dr. Kafaja:
Yes.

Dr. Channick:
And how many of those patients are scleroderma?

Dr. Saggar:
Mike, maybe you want to - maybe you can sort of introduce the concept of the stem cells?

Dr. Lewis:
Yeah. I mean, well, first of all, just to comment on, you know, inflammation and immune dysfunction, I mean, the pathobiology, I've just written a review paper on pathobiology of PH. It's very, very complex, and there are probably about 15 headings, so you know, clearly not everybody has everything, but you eventually will end up in the final common pathway. But these extensive data on inflammation in patients with PAH and also immune dysfunction.

So the basis for the stem cell study that many of us are involved in here was that there is an unmet need in PAH. You know, before there were therapies, and Cedars was part of the NIH registry with Spence Kerna. The median survival from the time of diagnosis was 2.8 years. Last year, Hendrickson et al, published the median survival in patients in the PAH treatment era, and in three different periods during the era, because more and more drugs became available. Basically, the median survival didn't really improve across the three periods. And that the average was 6.2 years. So you know, and it varied between 6 and 8. So, you know, even though there's been improvement, there's still, you know, pretty dismal survival.

The second thing is, if you look at the pathology in patients that either come to transplant, or maybe died of an accident, and you looked at the lungs, there's still marked, marked occlusive arteriopathy, inflammation, etc, etc., plexiform lesions, etc, etc, in patients on treatment.

And then lastly, as we all know, the RV can progress on treatment. And that's been shown by the, you know, the Dutch group very, very well. So you can actually, you know, seem to be improving in terms of symptoms and in terms of other parameters. But if you look at, you know, cardiac MRI and ejection fraction, that's going down progressively.

So, there's an unmet need and so, the cells that we use, which are cardiosphere-derived cells, they are heart-derived cells, but they - and they work not by transdifferentiating into, you know, tissues to replace, but they work by the release of exosomes which are micro vesicles, that are pretty small, 10 to 100 nanometers in size. And they contain very, very active products such as micro RNAs, non-coding RNAs, key proteins such as VEGF1 and IGF1 and all sorts of things. And even some new non-coding RNAs there, such as the YRNA and the piRNA that are exceedingly potent. So, that's kind of how they work. And they are markedly anti-inflammatory, immune modulating in terms of macrophage function, in terms of all sorts of, you know, anti-inflammatory, anti-fibrotic, angiogenic, anti-oxidative stress, etc, etc.

And so, based on animal studies, there were two that we did, one was the monocrotaline in which we gave IV CDCs, very positive study; and then another we gave intracoronary in a Sugen hypoxia model where there was RV dysfunction and failure. And there we showed marked improvement in RV function and all the kind of parameters that go wrong within the RV muscle, both immunohistochemically

and on extensive proteomic studies.

So the ALPHA study, which is a phase 1 study that's completed now, it's virtually been approved by one of the *Lancet* journals, their *Science Discovery* journal, *eBioMedicine*, we gave the CDCs once and we followed patients with endpoints at 2 months and 4 months, but follow them over a year. We looked at patients that we thought would have significant inflammatory and immune dysfunction as part of the pathobiology. So, this included IPH, HPH, PAH associated with connective tissue disease of which the majority were scleroderma spectrum, and HIV associated. That covers about 75% of PH patients. The bottom line is, we did a phase 1a, which was you know, just giving the cells and increasing the dose and then we gave phase 1b, which was double-blind placebo trial. The bottom line is, is that we, you know, found very, very encouraging efficacy signals. We did apply parametric statistics. And although we did not infer that, you know, having, you know, significant P value indicates efficacy, because this is a phase 1 study, we regard it more as keynoting, you know, highly encouraging data, you know, that warrants movement to a higher phase study where you will actually test for efficacy.

So the kind of parameters that we found, and just by the way before I mentioned that, the largest group was IPAH. But the second largest group was, as you might expect, PAH associated with connective tissue disease. So, we found significant improvement in right ventricular end diastolic volume and volume index on cardiac MR. This has been associated with survival. And so, what happened in the group getting the stem cells, it increased - I mean, it decreased significantly, and in the placebo group, it increased. So, obviously, the lower the volumes, the better. In diffusing capacity in the placebo group, it significantly went down in 2 and 4 months, and over the year. And in the CDC treated group, the diffusing capacity remained rock stable throughout. There was also a significant increase in 6-minute walk by 28 meters on average. All were on combination therapy; in fact, the majority will in triple therapy, of 28 meters. And there was a significant decrease at 4 months in serum creatinine. And then there were a 12% improvement in right ventricular fractional area change on echo. The P value was like 0.06 something, so not quite significant. And on cardiac MR, there was an 8% improvement in RV ejection fraction, which was also like P 0.06 something. And then we had encouraging signals in TAPSE. And we had also encouraging signals in the quality of life measure and the symptom score for CAMPHOR, the Cambridge quality of life measures specific for PH. And we looked at discovery proteomics, which did tend, although its pilot data this, at 2 weeks, it did tend to show that there was significant changes with regard to improving innate immune function and also a decrease in inflammation, but also a whole host of parameters.

Dr. Saggar:
That's really cool, novel stuff, Dr. Lewis, that you're engaged with. And we're, you know, really happy to be part of the study and stuff. I think there's a lot of cool stuff going on. And this is, I mean, now you're just going to enter, you know, the next phase of this in a larger format. So, it's going to be really cool to see, to see how this plays out.

Dr. Lewis:
Yeah, well just one thing to mention for the phase 2 and 3 that you guys are going to be involved in, we are going to do two things or three things. One, we're going to give repeated doses, because based on our Duchenne muscular dystrophy trial, we gave repeated doses in the kids, and they had improvements in skeletal and muscle and improvement in the heart. Because patients with Duchenne get cardiomyopathies.

The second thing we're going to do is we're going to have, as an entry criteria, patients should have some parameter, either on echo or on cardiac MR, of RV dysfunction, because I think that's an unmet group.

And thirdly, we can, within the context of the study, look and contrast scleroderma-associated PAH with IPH. And the reason we are - I think that's a good idea, is that, as we know, with scleroderma-associated PH, the outcomes tend to be worse, although there's newer data showing improvement over what was previously reported. But also if you look at the cardiac myocyte in patients with scleroderma, there's marked impairment. If we look at contractility, Ees, compared to IPH, it's significantly reduced. If you look at VA coupling in scleroderma-associated PH compared to IPH, it's significantly reduced. And then if you look take the cardiac myocytes and you do in vitro studies and look at contractility with skin myocytes, there is markedly decreased contractility indicating that the sarcomeric apparatus is completely abnormal. So, you know, this will also be a good group to study.

Dr. Saggar:
Yeah, lots to come. Lots to come.

Alright, I think we're a little bit over but let's get to lunch. And thank you. I want to thank the panel and we'll grab some lunch and thank you, everybody.

Announcer:
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