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

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Focus on Lung-Disease Associated PH

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**Dr. Saggar:**
So let's go to the panel. That's what's next, right? Okay. All right. So I think like they did for the CTEPH, we could probably kind of go back to the case real quick. And Houda, maybe we can start with you. So, in your case, when you went to the CT, I was pretty impressed with the amount of fibrosis that was in there. What were your thoughts about, you know, how that - if that patient was limited by their PH? Or I mean, did you – you must have had a thought before you considered therapy?

**Dr. Boucekkine:**
Sure. Yeah, the fibrosis was definitely pretty impressive on his CT, which obviously could explain his limitations, his hypoxemia that he was experiencing. I think it's hard just looking at the imaging alone, to figure out what is the predominant factor that is contributing to the limitation, whether it's the pulmonary vascular resistance, the PH, or the fibrosis itself. I think looking at that scan, I could have easily – I thought to myself, it's mainly the fibrosis, just given how significant it was. But then looking at that, once I saw the echo, and saw that RV dysfunction, it seemed to be a little more mixed at that point.

**Dr. Saggar:**
So with that in mind, Yuri, what do you think about RV dysfunction? I mean, it comes in different flavors. We use this term as, we just throw it out there, does the patient have RV dysfunction? As if it's binary. You probably see a lot of - I assume you see a lot of fibrosis patients who have stable, mild RV dysfunction going over years when they're referred to you, for instance, as opposed to someone with much more significant RV dysfunction. And once you answer that question, maybe you can let us know what are the metrics you use for RV dysfunction?

**Dr. Matusov:**
Yeah, so there are probably two ways to look at this. So if you have a temporal trend, right, so if you have a temporal trend of echocardiograms, over time, it can be - this question is much more made much more easy for you, right? Because you can sort of figure out, if they've developed RV dysfunction over time, and they're becoming, in tandem, they're becoming more symptomatically limited, then it's probably the RV dysfunction that's driving it, they probably should treat their PH. If you just have a static echo, right, where you don't know what's been going on in the past, you can use things like you know, TAPSE to sPAP ratio. You know, you can use sort of other, you know, other measures of objective RV dysfunction. And, but the reality is that, you know, you have to really figure out in your mind what you think the - as you mentioned, what you think the predominant driver of this patient's symptomatology is. And if you can do a CPET, that's great. But oftentimes, as you mentioned, you can't do that. And I do think that sometimes these patients merit a trial of therapy. And that therapy is usually prostacyclin-based therapy, rather than sort of talking ourselves out of treating them simply because they have significant fibrosis.

**Dr. Saggar:**
Yeah. So Siva, what do you think about treating these patients? I think, I mean here, we do quite a bit of that parenteral approach. I think if you - I mean, I've done this, and I've gone around the country and talked to a lot of people and they think we're crazy for doing parenteral prostacyclins in patients like the one Houda just showed. I mean, what are your thoughts on what should be offered and maybe what you offer in your practice?

**Dr. Ganesh:**
So I also deal with a lot of lung transplant patients. So we see about 50 to 60% of the lung transplant evaluation patients have moderate to severe PH. When they come to us, they have high oxygen requirements and moderate to severe PH. What do you do with severe RV dysfunction most of the time? Transplant surgeon will always be skeptical about transplanting this patient without having to address the RV dysfunction. So we - I prefer parenteral because that's, one, in my mind, it's short-acting, if they develop side effects, we can always scale back and discontinue, and also we see the improvement in a short time of duration so that we can decide whether this is helping the patient or not. Not in terms of actually RV dysfunction will get better, at least the patients symptomatically improve or not improve in a shorter period of time compared to oral medications or even inhaled medications. The difficulty I have like even though FDA approved inhaled medications are available, I do still struggle with my patient population because not much of an improvement in the symptoms of the patient. And to the point, actually, they can be considered for any - towards transplant or not, but - and also the side effects. I see a lot of side effects in terms of respiratory side effects, which made very exacerbated on inhaled vasodilator therapy compared to parenteral. I know everyone does differently, but I - my preference is parenteral. Actually severe PAH patients, we have done parenteral therapy until transplant and bridge them towards transplant successfully. Most of the time, I would say, yeah. But as you guys did a study, we have now not done like any internal study to assess like, what's the outcome of our patient population? But I think that's one of the ways we approach our patients too.

**Dr. Saggar:**
Yeah, I think the two things that people are concerned about, and for good reason, is they're worried about making gas exchange worse; and the people that were ending up treating are already very perturbed with their gas exchange. So they're already requiring a significant amount of oxygen at rest, but particularly on exertion. I mean, some of these people as outpatients are on 10-15 liters of oxygen. So that's scares folks for giving a parenteral therapy or a systemic therapy where you might have diffuse vasodilation in the lung and cause worsening V/Q mismatch.

And then the other thing I think that scares folks, again, appropriately, is the pathology. The pathology does suggest that there's venopathy and capillary duplication. And we do know that this PCH/PVOD sort of spectrum, you know, tends to have a negative response, if you will, and significant worsening and the potential for worsening, you know, when we treat them with systemic vasodilators. In that context, we started treating a lot of these patients in house because we also were worried, but again, our clinical experience has been I think, knock on wood, relatively good.

Does - I'll just throw this out here, if you have a fibrosis - if I showed you a fibrosis patient with, you know, severe hemodynamics, severe fibrosis, you know, RV dysfunction, the whole story, and I told you they were idiopathic - some of the questions coming through here are like, you know, are these - and then I changed the story and I said, actually this patient has scleroderma. You know, does that change what you do, if they have an autoimmune disease, a defined autoimmune disease or an autoimmune flavor, and let's say you were blinded to that piece of information, does that change your threshold to offer therapy? Or what do you think, Yuri?

**Dr. Matusov:**
So I think that if you have significant fibrosis and you have significant RV dysfunction, those patients should be offered therapy, irrespective of the underlying cause. My threshold is lower for scleroderma patients. So in my opinion, sort of scleroderma patients, if they have any suggestion of pulmonary hypertension, you should treat the pulmonary hypertension. In people who have IPF, that's a little bit - it's a little bit more difficult to sort of make that statement. But I think that if you have significant RV dilation, you know RV dysfunction and significant fibrosis even with IPF, I would usually admit them and I would try parenteral prostacyclin.

**Dr. Saggar:**
And not to belabor this point, but if you - when we call someone IPF, we assume that we've done some workup, right, to label them idiopathic by virtue of the fact that it's exclusionary diagnosis. Well, you have a classic CAT scan, but we all know the classic CAT scan, you know, we can see patients with a classic CAT scan for IPF, but it turns out to have an etiology. So I guess the question is, do you think – how – what is - do we - do you have a standardized approach to sort of your serologic evaluation, your physical exam? I mean, there's a whole bunch of things that I think we - and I can say this because I'm obviously a pulmonary person too, that we don't really - we sort of label people idiopathic, but we don't take a very great environmental history. We don't do a standardized serologic approach. You know, I've seen patients in the clinic that have come to me with severe pulmonary hypertension labeled idiopathic and they have

obvious sclerodactyly, and that starts up a whole cascade of events. So do you find that - do you have a - is your panel of serologies, Siva, changed over time? Like do you check? Are you very aggressive with this whole interstitial pneumonia with autoimmune features?

**Dr. Ganesh:**
Yes. All patients, we do have the full panel of CTD workup we do before actually we label them IPF. Most of them come to us like, as all of us know, as IPF. But like when you go into the details and do the panel and the whole workup that we do for lung transplants, you realize, okay, most of the time the IPFs have some other reason to have the fibrosis. So that dictates like how we are going to actually address the pulmonary hypertension part. And it makes it a little bit easier for us to actually have confidence in treating the PH compared to not knowing what's the etiology for the PH. So especially the CTD-associated PH, we all see actually good improvement in their outcomes as well as functionality when you aggressively treat the pulmonary hypertension compared to not treating anything.

So I definitely do the whole workup for most of the IPF patients, actually all IPF patients come through to transplant, we do whole workup to diagnose what's the etiology. And then like depends on like what we find, then we segment into other details, hypersensitivity pneumonitis workup and other types of workup for the ILD etiology, but definitely CTD workup.

**Dr. Saggar:**
Yeah, obviously the devil's in the details, because I bet you we all have different panels that we probably send. And, you know, it's I personally think it should be standardized. Shelley, do you have a question?

**Dr. Shapiro:**
- approach to this problem. I think, you know, the data on the PDE5s were done in very low doses, that initial study was done on 20 mg, which is really quite low. And when you're looking at patients who already have a very complicated life, a trial of PDE5 inhibitors, is actually very gratifying. And at the VA, where we have a huge number of patients with underlying lung disease, we start this up because you can get it immediately, it's well tolerated, and patients actually do get better. They don't get great, but every little bit that you can make in improving them, gives them a little bit of margin.

The other thing that we use, which hasn't been mentioned at all is DIG, which is when you have RV dysfunction, digoxin is an effective drug to improve myocardial function. And this is very much load dependent. And that's one of the reasons that we see variability in the echoes over time; they come in with hypoxia and worsening pulmonary hypertension, and the RV goes to stool, and then you treat them and then the RV gets a little better and you feel better. And then it goes back and forth. It's not that the RV is basically defective, it's the load that's put on it. So anything that you can do to improve RV contractility and reduce the size, helps. So those are my suggestions, which is yes, it's very nice to use parenteral prostacyclins. But it's really a very big jump for patients, and the downside risk of using a PDE5 inhibitor is extremely minimal.

**Dr. Saggar:**
Yeah, good points.

**Male:**
Yeah. You know, with regard to IPF, I think there's probably a difference if you're bridging somebody to transplant versus some of these elderly IPF patients that have comorbidities but also have PH and RV dysfunction. So if people could address that?

The other thing I would suggest is, I think that the time is ripe, you know, in appropriate patients to compare and contrast in a study, you know, high-dose inhaled treprostinil with parenteral treprostinil in appropriately chosen cohorts.

**Dr. Saggar:**
Yeah, I think for the for the first question regarding like, the older IPF patient who happens to have some PH and RV dysfunction, again, I think the devil's in the details, right, exactly how much how bad their situation is and how frail they are. And, and I think that goes back to Shelley's point, which is, you know, I hope the takeaway message here is not that we should be using parenteral treprostinil in all these patients, that's not the message. But I think in the severe - I was hoping I stressed this, but it was it's for the more advanced group of patients. For the mild to moderate cases, it's a judgment call, it has to do with the patient's, you know, understanding of what they want out of the rest, if they want to take a trial of therapy, are they happy with their quality of life? On your end, you're saying, hey, this is associated with survival, so we should try to do something about it. Again, keeping in mind, it's an association is not necessarily a cause and effect. So I think all those factors play into sort of that phenotype, the older patient who has some PH and some RV dysfunction. And then as you know, a lot of these people have comorbidities, they have diastology, they have other issues playing into this as you work them up.

As far as your second question, which was?

**Male:**

You know, was regarding doing a trial? Compare and contrast, yeah. And also, are you guys using inhaled Tyvaso? So, you know, like Steve Nathan is pushing? Or are you not?

**Dr. Saggar:**
Yeah. Yeah, I think the main message from this - hopefully this other main message came through, is that inhaled treprostinil is the FDA approved medication. This is what we're doing, this is what's been approved, and we're certainly doing that as well. Again, we kind of reserve the parenteral approach for the more severe cases. And I think one of the issues with inhaled treprostinil that we've run into is that a lot of our patients are presenting as inpatients; and getting inhaled treprostinil as an inpatient has been a bear, to say the least, because - just because of how ill they are, it's not inconceivable. And I would, I'm sure you guys appreciate this, that a lot of these patients end up with us as inpatients; and in that setting, it's really tough to sort of – you know, you want to treat them. So that's where we're using a lot of sildenafil, maybe some inhaled nitric oxide, and then we're sort of stuck, if you will, you know, starting at a parenteral approach, and then we might transition to inhaled or transition to, you know, make that sort of move. So that's the other issue I think that we've run into.

There are some questions here surrounding lung transplantation, just for a second is like, and Siva, maybe you can comment on this, and then in terms of is, do you have a goal of trying to treat patients to the point - in other words, do you - at UCLA, we have an issue with double versus single based on the degree of pulmonary hypertension, which I think most centers tend to offer double lung transplants when there's significant pulmonary pretension. Again, every center has a different threshold. But do you try to treat their PH also in an effort to get them a single lung, because you feel single is a more sort of a safer procedure or less morbid, if you will?

**Dr. Ganesh:**
Yeah. So the very severe pulmonary hypertension with ILD patients, that's the group - actually, I agree with your statement saying that I try the parenteral actually on our moderate to severe PH patients. So that patient group, actually we tried to treat to do single or double; that increases the chance for the patient to get the transplant. If we wait for the dual lung transplant, the wait time can be very long. So that's one of the reasons we aggressively treat at that short period so that we can get the RV dysfunction to get better.

**Dr. Saggar:**
Do you ever have a – sorry, to interrupt, but do you have a threshold over at USC for what you - when you offer the single?

**Dr. Ganesh:**
Yeah, actually, we have done severe pulmonary hypertension patients on ECMO.

**Dr. Saggar:**
Single?

**Dr. Ganesh:**
On single, yes. We put them on VA ECMO, bridge them to transplant, and do the single lung transplant. And when they come out, their RV function is back to normal as well as their outcomes are pretty good. When they have really no time like only way to actually support the RV as well as get the get them to transplant is VA ECMO. So we have done single-lung transplant on severe PH patients, PA pressures like more than hundreds. And VA ECMO, bridge to transplant, single lung transplant. But otherwise, the preference is actually double lung transplant. If the PA pressure is above 60, that's our threshold for the surgeons. If the systolic pressure is above 60 and your cardiac index is like borderline, 1.8 to 2, they prefer to do double lung transplant if we have the time to wait on the patient.

**Dr. Saggar:**
So it does play into what you offer the patient.

**Dr. Ganesh:**
Correct, yes.

**Dr. Saggar:**
Okay.

**Dr. Matusov:**
You know, just as an additional comment from the transplant staff point of view, you know, you have these patients sometimes where they are kind of - they meet criteria for transplant and they should be transplanted, but they're too functionally limited. And I think you alluded to this earlier, Siva, you know, sometimes you can get those people to be more functional with a course of treating the PH.

**Dr. Ganesh:**
Correct.

**Dr. Matusov:**
And then they actually - we've seen this happen, we've had this happen ourselves where people go from being not candidates because they're too immobile and too frail to actually being very robust because the PH is treated and now they're better transplant candidates.

**Dr. Saggar:**
Yeah, so there may be two things going on here. One is to potentially bridge someone to a single instead of a double.

**Dr. Ganesh:**
Right.

**Dr. Saggar:**
Which is it's just, I mean, considered a less morbid procedure for good reason. And then there's also a role for, you know, actually getting a stronger, more physically rehabilitated person to transplant, which is always also, you know, there's plenty of data showing frailty and bad outcomes equals bad outcomes or worse outcomes. So we want to make people as functional as possible before we do a transplant. That makes good sense.

I think - let me just see if there's any more questions here. There's some question here about imaging and biomarkers. Obviously CPET is brought up by this question as well, it's not, you know, it's not easy to do on these, at least right now, we don't have any data on the severely hypoxic patients, but any role of brain natriuretic peptide? Does that buy you anything? Or do you sometimes forget to do it, it's an afterthought?

**Dr. Ganesh:**
We regularly do NT-proBNP. But we always actually also do cardiac MRIs, a lot of these patients to more predict what's the RV dysfunction is, as well as you can get the RVEF on the cardiac MRI, so that can guide us like is it going to be safely be able to be transplanted one single lung transplant or double lung? We sometimes use the cardiac MRI RVEF to determine that as well. NT-proBNP we do regularly but like do we make decisions, like main decisions? Probably not.

**Dr. Saggar:**
Yeah. With the MRI, we have a heart rate issue?

**Dr. Ganesh:**
Yes .

**Dr. Saggar:**
Do you guys actually beta block those people to get the MRI?

**Dr. Ganesh:**
We do. We do actually.

**Dr. Saggar:**
You're bold. It's bold that you –

**Dr. Ganesh:**
We do.

**Dr. Saggar:**
Yeah, it's a great study.

**Dr. Ganesh:**
Yes.

**Dr. Saggar:**
But it obviously has its –

**Dr. Ganesh:**
Its limitations. Yeah, it's practical limitations. But we tried to get that done so that we can determine like whether we can go with a single or double with the number that we have in front of us.

**Dr. Saggar:**
I just want to take 10 seconds here to just let everyone know that we actually have at UCLA an animal model for Group 3 PH, which Dr. Hong and others, Eghbali and Soban Umar have mastered, it's actually the only Group 3 PH model, an animal model, that's available in the literature. This uses a combination of bleomycin and hypoxemia to create a fibrosis PH phenotype with RV dysfunction. It's very

elegant.

And there's a few papers looking at that. And I think it's primed for, you know, studying the next generation of drugs, for instance. So for instance, with what sotatercept can offer to this population or, you know, whatever, you know, there's a pan-ROCK inhibitor that's being looked at right now, there's a whole bunch of different ways of, obviously different pathways being looked at. So I just wanted to bring that up, because some good science is being done here at UCLA in that regard to with a Group 3 sort of PH, you know, and sort of looking at it the bench level.

Any other questions from the audience? Okay. All right, I think we'll conclude. Thank you. Thanks, everybody.

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