Pulmonary Hypertension Roundtable

Screening for PAH in Scleroderma: Identifying Hallmarks of the Disease and Optimal Treatment Strategies


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Vallerie McLaughlin, MD, Associate Professor of Medicine, Rush Presbyterian-St. Luke's Medical Center, Chicago, Illinois, conducted this roundtable discussion. The panel included James R. Seibold, MD, Professor and Director, UMDNJ Scleroderma Program. New Brunswick New Jersey; David B. Badesch, MD, Professor of Medicine and Clinical Director, Pulmonary Hypertension Center, University of Colorado Health Sciences Center, Denver, Colorado; and Virginia Steen, MD, Professor of Medicine, Georgetown University Medical Center, Washington, DC.

Dr McLaughlin: What do we think is the true incidence of pulmonary arterial hypertension in the scleroderma population?

Dr Steen: We first have to separate the different kinds of pulmonary hypertension that occur in scleroderma. Patients with limited scleroderma, or the CREST syndrome, as it is referred to, get primarily what we call vasculopathy or an isolated pulmonary hypertension unrelated to interstitial fibrosis, and it can occur in the very serious deadly form in up to as many as 20% of patients. Other patients, and it's anywhere from 10% to 30%, will have some evidence of either potential pulmonary hypertension or mild pulmonary hypertension as evidenced by abnormal findings on pulmonary function tests (PFTs) or echocardiograms. Another patient population, those with diffuse scleroderma, is more likely to have the interstitial fibrosis and they can have pulmonary hypertension related to that. And then there is the group of patients sort of in between, those who have a little bit of pulmonary fibrosis and a little bit of pulmonary hypertension, and depending on the nuances of their disease, one seems to predominate.

Dr Seibold: Scleroderma generally segregates into a rapidly evolving widespread form called diffuse scleroderma. These patients have a fairly high risk of having an inflammatory pulmonary process that looks a lot like nonspecific interstitial pneumonitis and the early onset of interstitial fibrosis. These patients develop dyspnea and impaired exercise capacity that is a mixture of their established interstitial lung disease but is clinically exacerbated by the evolution of the pulmonary vascular lesion. At the other end of the spectrum, you have limited scleroderma patients who seem to be relatively spared, although not completely, from this whole dynamic of interstitial inflammation and fibrosis but who develop an isolated vasculopathy that really starts to become clinically relevant somewhere around the 10th year or so of disease. The educated guess here is that the pulmonary vascular or arteriolar lesion is universal, and it can progress slowly and show up as pulmonary arterial hypertension alone at later stages of limited scleroderma, but it is a cofactor in the morbidity of patients with interstitial lung disease, including diffuse scleroderma.

Dr McLaughlin: David, do you have any pearls on how one might differentiate pulmonary fibrosis from

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pulmonary arterial hypertension, recognizing that in some patients they do occur simultaneously?

Dr Badesch: I would suggest looking for physical exam findings that suggest pulmonary hypertension or pulmonary fibrosis, and then using echocardiography to support or refine the diagnosis of pulmonary hypertension. A right-heart catheterization can be done to confirm the presence of pulmonary hypertension. The diffusing capacity can fall in either pulmonary fibrosis or pulmonary hypertension, but if it falls in isolation, meaning that the lung volumes are normal, it may suggest the presence of pulmonary hypertension.

Dr McLaughlin: Would the pulmonary function test then be an appropriate screening tool to perform on an annual basis in the scleroderma population?

Dr Badesch: I think it is very reasonable to follow the PFTs regularly. If you see an isolated fall in the diffusing capacity this should raise the possibility and lead to further evaluation, perhaps with an echocardiogram.

Dr Seibold: The pearls are that virtually all scleroderma patients who have pulmonary arterial hypertension have a diffusing capacity less than 55% of predicted. There are a couple of data sets that argue that when the percent of forced vital capacity (FVC) is compared with the percent of DLCO, if that ratio is elevated, it also enriches for the diagnosis of pulmonary arterial hypertension. One published series suggests a ratio of greater than 1.4. Our own data at our center suggest that that ratio might be 1.8.

Dr McLaughlin: Is there a population that should have echocardiography on a regular basis?

Dr Seibold: Yes. We might want to step back a step. Before I said that pulmonary arterial hypertension patients are typically dyspneic and sometimes clinical dyspnea on exertion is missed in rheumatologic practice. Scleroderma patients have a chronic catabolic disease; they tend to have ambulation difficulties, they tend to become very sedentary for orthopedic and musculoskeletal and peripheral vascular reasons, complicating their scleroderma. So they don't typically present complaining of dyspnea on exertion. And I think that rheumatologists probably as a rule tend to back into this diagnosis through regular performance of pulmonary function testing. And it seems quite reasonable to recommend annual pulmonary function testing as a minimum interval, across the board for all scleroderma patients, probably more frequently, if you were following someone early with active inflammatory fibrotic disease. It also follows that if the best screening test for pulmonary arterial hypertension is a Doppler echocardiogram, it is appropriate to obtain a baseline study in all patients with scleroderma, and that this test might also be repeated at some minimum interval. I don't think that we have the trial data that exactly validate what the standard of clinical practice should be. One argument should be that if you are doing pulmonary function testing and you see changes in the diffusing capacity, that might trigger repeat of the Doppler echocardiogram. Another argument might be that repeat Doppler echocardiograms might be done at about the same interval as repeat pulmonary function tests.

Dr McLaughlin: What do you do in your practice, Jim?

Dr Seibold: I look at the pulmonary function test as the outcome and turn to the Doppler echo as a measure of process. We get baseline echoes on as many patients as we can, but the decision to repeat is usually not triggered by time interval but by some index of suspicion, either clinical dyspnea or a change in the pulmonary function test.

Dr McLaughlin: And Ginny, what do you do in your practice?

Dr Steen: I think that is exactly what I do. I probably do not repeat the PFT yearly in everyone if they have normal diffusing capacity or only mildly decreased DLCO. On the other hand, if they already have a diffusing capacity of 60 to 65% and they have had 10 years of disease, then following PFT's on a yearly basis would be helpful at least to detect changes that would precipitate doing an echocardiogram. Many patients have echocardiograms that show mild pulmonary hypertension, which is in the range where the echo is difficult to interpret. Since we don't know how many of those are real pulmonary hypertension versus false positives, I think it is important to keep that in mind and to proceed to catheterization when you find mild pulmonary hypertension rather than jumping ahead and making a diagnosis of this deadly disease. I know we all have had experiences where we have an echo that says that the pulmonary artery pressures are 40 and you get all worried and nervous and you do a cath and the results are totally normal.

Dr Badesch: My impression is that follow-up and screening for pulmonary hypertension in the rheumatology and internal medicine community are probably not as stringent as what we have heard from Jim and Ginny. My sense is that by the time patients get referred to us for the evaluation and treatment of pulmonary hypertension they often have relatively advanced disease.

Dr Seibold: I agree. I think there is a disconnect between the way the true scleroderma expert approaches this and the way the community rheumatologist/internist approaches this. Lacking a pharmacoeconomic or costs of care study to actually validate it, I tend to come down in favor of a recommendation of a minimum annual interval. I agree that there are subsets of patients who don't change much over time. But if we are looking at a rate of transition from nonpulmonary hypertension to pulmonary hypertension of any level that may approach 5% of patients per year, that is a rather high incidence and I think that would justify a blanket recommendation for annual pulmonary function testing.

Dr McLaughlin: And I think this is all more an issue now that we have effective therapies. Perhaps 10 or 15 years ago rheumatologists were not screening because frankly there was

not much to do, but I think all of that has changed in the current era.

Dr Seibold: From a recent questionnaire that the Scleroderma Clinical Trials Consortium circulated to the broad community of United States and Canadian rheumatologists, it looked like echocardiography was being performed in the assessment of dyspnea only about 25% of the time.

Dr McLaughlin: I'd like to talk about proceeding with a heart catheterization to further evaluate patients who have pulmonary hypertension on an echocardiogram. One thing that is always important in looking at pulmonary hypertension patients is testing for vasoreactivity. And the scleroderma population, at least in my experience, is very rarely vasoreactive and so I am frequently asked by rheumatologists "Why do we have to cath in the first place?" Dave, do you want to comment on that?

Dr Badesch: That's a good question. Our experience mimics yours somewhat in that I think the likelihood of acute vasoreactivity is lower in the population with scleroderma than in primary pulmonary hypertension. I still think that cardiac catheterization plays an important role in evaluation of these patients. I think that establishing their baseline hemodynamics, or ruling out the rare patient with an intercardiac shunt or some other lesion that is contributing to their development of pulmonary hypertension, is important. Furthermore, in patients who are failing despite the best available medical therapy, it may be important to repeat the cardiac catheterization to confirm that it is worsening of their pulmonary hypertension that is accounting for their symptoms. In that situation, comparing the current hemodynamics to their baseline results can be very helpful. So, I still feel that right-heart catheterization plays a role in these patients, but it may not be so much in terms of evaluating vasoreactivity as in establishing a baseline, ruling out other contributing factors, and then having that information available for future comparison.

Dr McLaughlin: The other important measurement on the right-heart cath, particularly in this patient population, is wedge pressure or left ventricular end-diastolic pressure. This patient population tends to be older than the primary pulmonary hypertension population, they tend to have more concomitant illnesses, such as hypertension, and they may in fact have mild pulmonary hypertension on an echocardiogram that is really the result of systemic hypertension and left ventricular hypertrophy and elevation of LVEDP causing their pulmonary hypertension. So it is also crucial in securing the correct diagnosis and subsequently the correct treatment for these patients.

Dr Seibold: If I had to make a quick list about why one should be willing to do right- heart catheterization in scleroderma it would be 1) to confirm and to precisely quantify the diagnosis; 2) to exclude the possibility of occult left ventricular diastolic failure; and 3) to exclude a component of concomitant cardiac problems. In around 20% of the caths that we do here, we frequently find that the aortic valvular lesions are a little bit worse than was suspected, or we find mitral valve pathology, or something along those lines that truly influences our approach to therapy. Fourth on the list would be that the echo is not a perfect test. It is relatively imprecise in those that have estimated pulmonary artery systolic pressures less than 40. And there is a relatively substantial group of patients, maybe as many as 20%, who lack a tricuspid jet and one cannot get a reliable estimate of pulmonary artery systolic pressure by Doppler. So, that would be the complete list. There is no question that rheumatologists are not requesting right-heart catheterizations by their consultants frequently enough.

In patients who are failing despite the best available medical therapy, it may be important to repeat the cardiac catheterization to confirm that it is worsening of their pulmonary hypertension that is accounting for their symptoms.

Dr McLaughlin: Why don't we move along to those therapies? David, you were the principal investigator of the first trial of Pulmonary Arterial Hypertension in the Scleroderma Spectrum of Diseases with Flolan. Do you want to summarize the very impressive results of that trial for the group?

Dr Badesch: As you know, prostacyclin was initially developed for patients with primary pulmonary hypertension and we saw an improvement in exercise capacity, cardiopulmonary hemodynamics, and survival in a 12-week study. We attempted to replicate that study in the scleroderma population and what we found was that prostacyclin did in fact improve the exercise capacity and cardiopulmonary hemodynamics similarly to the way that it had in the population with primary pulmonary hypertension. We did not see a survival benefit over the three-month course of that study, but the study was not powered to detect a survival benefit. I believe that the study of prostacyclin in patients with scleroderma-associated pulmonary hypertension has led to the inclusion of such patients in the subsequent trials of therapeutic agents for pulmonary hypertension.

Dr McLaughlin: It is important to point out what the prognosis is of scleroderma complicated by pulmonary hypertension in the absence of any treatment at all. It is a horrific survival curve.

Dr Badesch: In looking at several studies done prior to the use of prostacyclin in these patients, it appears as though the two-year survival rate was in the range of 40 to 55% or so, in patients who developed pulmonary hypertension as a complication of scleroderma disease.

Dr Steen: That has certainly been our experience. But we have to remember that previously the diagnoses have been made so late that the only time the diagnosis was made really was when patients had right-heart failure and clear-cut classic clinical pulmonary hypertension. Without treatment, even to survive two years for many patients was just unheard of. With the use of prostacyclin, my patients have had a much better survival rate and quality of life, even when the diagnosis is not made until the patient has right-heart failure.

Dr McLaughlin: One of the problems that the scleroderma population sometimes has with prostacyclin is difficulty mix-

ing. Because many of them have severe Raynaud's and digital ulcers and sometimes even amputations, this can be problematic. That is one of the reasons why the subcutaneous prostacyclin analogue, treprostinil, which has recently been FDA-approved, may be useful in those patients. The scleroderma patients were included in the double-blind placebo-controlled randomized study of subcutaneous treprostinil and indeed benefited. Sometimes, however, that drug is difficult to use because of pain at the infusion site. Jim, you mentioned that there were three FDA-approved drugs. The third one is an oral therapy, bosentan. Would you like to comment on your experience with that so far? And perhaps even how the advent of an oral therapy has changed practice patterns that lead to earlier screening and diagnosis?

Dr Seibold: There is no question that the logistical convenience of an oral therapy really revolutionizes the clinical approach. Prostacyclin is expensive, it is relatively cumbersome, it has more than a certain level of day-to-day adverse effects that impact the quality of life. I agree with you that the administration of treprostinil in the whole scheme of things will be more convenient for scleroderma patients and they will be a little bit better able to handle that.

Dr Badesch: The other important thing to point out is that the mechanism of action of bosentan is considerably different from that of prostacyclin. Endothelin levels may be increased in some patients with scleroderma, and using an endothelin receptor antagonist in that situation may make particular sense, beyond even what you might expect in patients with pulmonary hypertension. So, it is particularly attractive on a theoretical basis to block endothelin in patients with scleroderma and scleroderma-related pulmonary hypertension. In a randomized and placebo-controlled study involving over 200 patients with primary pulmonary hypertension and pulmonary hypertension occurring in association with collagen vascular disease, bosentan-treated patients demonstrated better activity tolerance, as assessed by the 6-minute walk test, than patients receiving placebo. The drug seems to be relatively well tolerated although it is important to mention the side effects that have been seen to date. It can cause an elevation in liver function tests and this mandates following liver function tests on a regular basis. In fact, the FDA has mandated testing at least monthly. The drug has the potential to be teratogenic and therefore contraception is very important. It may cause male infertility and young male patients should be informed of that prior to beginning the treatment. And finally, it can cause some mild anemia and at times some fluid retention.

Dr McLaughlin: Those are important points. Dave, would you like to speculate on the results in the scleroderma subpopulation BREATHE-1 trial, compared with the scleroderma population in your trial? Granted, it was a much smaller number in the BREATHE-1 trial, but they didn't seem to obtain as much benefit in terms of exercise tolerance over the 16 weeks of that trial as the scleroderma patients treated with intravenous epoprostenol did in your trial. Any thoughts on that?

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Dr Badesch: The data suggest that in the study of intravenous prostacyclin in patients with scleroderma-associated pulmonary hypertension, there was both an improvement in the treatment group and a decline in the control group that accounted for the difference between study groups. In the BREATHE-1 study, when looking at the subgroup of patients with scleroderma-associated pulmonary hypertension, it appears as though bosentan may have contributed to the maintenance of stability while patients in the placebo arm continued to deteriorate. Now as you've mentioned, whether or not we can take away much of a message from that is a little in doubt because the relatively small number of patients with scleroderma included in the BREATHE-1 study. Whether or not bosentan can contribute to the same amount of symptomatic improvement or improvement in exercise capacity as prostacyclin in this population I think is still just little bit up in the air.

Dr McLaughlin: So, the drug has been commercially available for 7 or 8 months. Jim, Ginny, would you like to share your experience with it so far?

Dr Seibold: We were somewhat concerned when we saw the failure to improve in the scleroderma subset that was incorporated in the BREATHE-1 study, but suspect from our clinical use of the drug that that was an artifact of the relatively small sample size. We have about 65 scleroderma patients who are receiving bosentan currently. A large percentage of those patients, somewhere in the 80% range, have substantial, measurable, clinical improvement and improved exercise capacity. So we believe that more widespread use of the drug will validate that there is a positive clinical benefit from bosentan therapy.

Dr McLaughlin: That is an important point. The scleroderma population made up a very small percentage of these included in the BREATHE-1 trial and a much larger experience such as yours, Jim, is very important to delineate how effective this therapy is in this subpopulation.

Dr Badesch: I think it is important as we look toward the future to mention that we might begin to combine some of these different therapies in patients with pulmonary hypertension due to scleroderma and perhaps we will be using some form of prostacyclin preparation in combination with an endothelin receptor antagonist, a phosphodiesterase inhibitor, and perhaps oral L-arginine or a nitric oxide donor. Multimodality therapy that mimics the way we treat systemic hypertension or cancer might have a greater likelihood of a positive effect in patients with pulmonary hypertension due to scleroderma. It is important to note that my comments in this regard are speculative, and not yet supported by clinical studies.

Dr McLaughlin: I agree with that, David, and certainly combination therapy is where we are going. The scleroderma

patients were included in the BREATHE-2 trial, which looks at the combination of bosentan and prostacyclin in patients with severe pulmonary hypertension. Scleroderma patients are also being included in other clinical trails, specifically with the PDE5 inhibitor sildenafil and selective endothelin receptor antagonists. Dave, you also mentioned L-arginine; there is an international trial looking at L-arginine supplementation in patients with pulmonary arterial hypertension that also includes the scleroderma spectrum of diseases.

Dr Seibold: It should be emphasized that there is a level of scientific enthusiasm/optimism about the specificity of all these drugs in the scleroderma vascular lesion. We all recognize that scleroderma starts with vascular injury frequently expressing as dysfunctional vascular change, ie, Raynaud's phenomenon, but the endothelial injury is important very early on. One consequence is diminished nitric oxide production. A second consequence is diminished prostacyclin synthase activity and lower prostacyclin levels. A third and potentially very important tissue response is increased endothelial production of endothelin, which has vasoconstrictive effects and a variety of proliferative and proinflammatory effects that may perpetuate and worsen the structural vascular injury. So all of these agents that are being discussed, from L-arginine through prostacyclin delivery systems through endothelin antagonists may have some level of specifically addressing a key pathophysiologic derangement of scleroderma.

Dr McLaughlin: We focus so much on the existence of pulmonary arterial hypertension in the scleroderma spectrum of diseases. Are there other rheumatologic diseases that are associated with pulmonary hypertension? I have seen patients with some different rheumatologic diseases, lupus, even just Sjögren's syndrome, or polymyositis, present with pulmonary hypertension. Is that rare, or is that something rheumatologists should keep their eye out for?

Dr Steen: Well, certainly they are significantly less common than in scleroderma, but I think in the lupus population and the mixed connective disease population it is becoming more and more of a problem. In the other diseases, Sjögren's and myositis and even rheumatoid arthritis, pulmonary hypertension is well documented and we have all had these patients, but the frequency is much less.

Dr McLaughlin: Dave, have you treated a number of patients with pulmonary hypertension and interstitial lung disease? Clearly that population exists. One thing we always worry about is the potential for a worsening in V-Q mismatch, and then sometimes we just tend to treat them for their pulmonary hypertension because there is nothing else to do. I have treated a number of patients like that that and I can't say that I have seen anyone develop worsening hypoxemia because of the V-Q mismatch. How about yourself?

Dr Badesch: Initially, we excluded patients with more than mild interstitial lung disease from the prostacyclin study, because of the concern that we would worsen ventilation perfusion mismatching. I have continued to be relatively cautious in my approach to those patients, but, as I am sure other centers have done, we have broadened the group of patients we will try to treat aggressively with prostacyclin and now bosentan. I agree with you that the worsening of ventilation perfusion mismatching is probably not as much of a problem as we expected it might be early on. I would add that in the population with both interstitial lung disease and pulmonary hypertension, the early consideration of the possibility of lung transplantation is an important aspect of their care. Some of these patients may not prove to be good candidates for lung transplantation because of esophageal dysmotility and reflux and the risk of aspiration, but in the group of patients with both pulmonary hypertension and interstitial lung disease, it may be particularly important to consider the possibility of lung transplantation early on. What do you think, Jim, do you end up referring those patients for a transplant evaluation?

Dr Seibold: Dave, I really agree, but I can't find a program that will accept my patients. The problem is that somewhere between 85% and 90% of these patients have esophageal dysmotility. So there are very few centers in the United States that are doing single lung transplantation in scleroderma at all, and there is a long list of centers that have automatically excluded scleroderma from consideration.

Dr McLaughlin: Would anyone like to make any closing remarks before we finish up?

Dr Badesch: I am pleased to see that patients with scleroderma-related pulmonary hypertension are being included in most of the studies now. And as Jim mentioned earlier, the level of enthusiasm for treating these patients has increased over time. I hope that we will continue to work collaboratively on clinical trials and toward improving the timely diagnosis of pulmonary hypertension and prompt initiation of appropriate therapy.

Dr Steen: I hope that in future studies we look for patients who have what I'd term pre-pulmonary hypertension, or are borderline, or at high risk, or whatever you want to call them, and see whether by very early aggressive treatment we might totally prevent or allay or delay the dangerous deadly consequences of this.

Dr Seibold: I would just like to express my appreciation and admiration to the group of collegial, high-quality investigators in cardiology and pulmonary medicine who have pushed the field of management options in pulmonary hypertension so far and so fast, and have made available so many different options for patients with scleroderma. It has been an astounding several years of productivity.

Dr McLaughlin: The one thing I want to emphasize from our discussion is that recognizing these patients is critical. We now have something that we can do for them. Early detection of pulmonary arterial hypertension in the scleroderma population might allow us to really have an impact on this devastating disease. PH