Expanded Use of PAH Medications


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This discussion was moderated by Karen A. Fagan, MD, Professor and Director, Division of Pulmonary Medicine, University of South Alabama College of Medicine, Mobile, Alabama. Panel members included Kamal K. Mubarak, MD, Assistant Professor of Medicine, Director, Pulmonary Hypertension Clinic, Wayne State University, Detroit, Michigan; Zeenat Safdar, MD, Assistant Professor of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, Baylor College of Medicine, Houston, Texas; Aaron Waxman, MD, PhD, Associate Professor of Medicine, Harvard Medical School, Director, Pulmonary Vascular Disease Program and Pulmonary Critical Care Unit, Massachusetts General Hospital, Boston, Massachusetts; and Roham T. Zamanian, MD, Assistant Professor of Medicine, Director, Adult Pulmonary Hypertension Clinical Service, Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine, Stanford, California.

Dr Fagan: Welcome, all. We appreciate your sharing your thoughts on what is becoming an increasingly important consideration, namely, the use of PAH therapy in a broader group of patients than have been studied to date. This has important implications for the patients in question, and also for future patient groups to be targeted for treatment with PAH-specific drugs. While I am certain that we know the answer, it is important to ask, Are we using PAH-specific therapies in non-WHO group I patients, and if so, how and why are we using them?

Dr Mubarak: We have some good emerging evidence in thromboembolic disease. A recent trial with bosentan showed some benefit. In group IV patients, there may be some rationale to treat. Similarly, in the iloprost trial there was at least a small subgroup that seemed to do well, so that drug may be considered. But other drugs have not entered group IV PAH, so it is hard to say.

Dr Waxman: We have treated group IV patients with, specifically, chronic thromboembolic disease the same way we would treat group I patients, with prostanoids, ETRAs, and PDE5 inhibitors, and have found them to be just as effective.

Dr Safdar: There are some data on epoprostenol use in chronic thromboembolic disease, especially in poor surgical candidates. A recent abstract retrospectively reviewed data on sildenafil as a treatment option for patients with inoperable chronic thromboembolic disease and showed some improvement in walk distance. We have also used ETRAs and PDE5 inhibitors in this group.

Dr Fagan: Are those patients before or after surgery, or both?

Dr Waxman: I would say both—patients who were operated on and had persistent PAH and those who were not operative candidates.

Dr Mubarak: I would echo those sentiments. My patients have been treated with sildenafil, as well as with bosentan and iloprost, and I have found these fairly effective. I have not given intravenous prostanoids. It is hard to say whether they are equally effective, but my bias is also that these drugs work fairly well in this population.

Dr Safdar: We have used bosentan and sildenafil in the setting of inoperable thromboembolic disease and in those with residual pulmonary hypertension after pulmonary endarterectomy.

Dr Fagan: I have had similar experience, but the question remains that there are not many data for use of these drugs in group IV patients. Does the fact that group IV patients have primarily a vascular disease and don't have heart or other lung disease make us feel a little more confident in translating PAH group I therapies to group IV?

Dr Mubarak: When I don't have clinical trial data, I often perform a therapeutic trial. You carefully study the patient, then you introduce one therapy at a time, and then you see if there is clinical or hemodynamic benefit. If the drug seems to work for that person, you continue it, or if the drug is not working, you stop the drug.

Dr Waxman: We often take a fairly controlled approach when we start drugs as well, but also from a mechanistic standpoint these patients have something wrong with their endovascular function. For patients who have had surgery and developed PAH later, I think that is a reflection of their underlying abnormality, and we treat those patients exactly the same as group I patients.

Dr Safdar: I agree that there is an element of vas-

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cular remodeling that contributes to residual PH. In addition, there may be a component of unrecognized diastolic dysfunction in these patients.

Dr Fagan: I agree, this is a vascular disease, maybe not too unlike the vascular dysfunction we see in group I patients. So, it makes me more confident when I am talking to patients that these therapies may be appropriate.

Dr Waxman: I think the bigger group of patients where the great unknown still lies are those with pulmonary venous or group II patients where there are some biological data that some of the same mediators, both inflammatory and vasoconstrictive and vasoproliferative, like endothelin, are associated with disease progression, begging the question whether we should be treating them the same as PAH patients or not. Also with the PD-5 inhibitors where there appears to be a role for cyclic GMP and nitric oxide in left ventricular remodeling, we have been looking at that here in some small pilot studies, both in collaboration with cardiology and in our own patient populations, and still don't know if that is the right thing to do or not.

Dr Zamanian: What we can learn from clinical trials dealing with PAH, in reference to non-PAH disease processes, may be to better determine surrogates of outcomes, to better design the goals of new studies.

Dr Waxman: I can tell you that we have been looking at patients with left ventricular heart failure, both systolic and diastolic, as well as patients who have other forms of pulmonary hypertension. We have to define what we mean by pulmonary hypertension in those patients. We look much more at the transpulmonary gradient and pulmonary vascular resistance. We have been using cardiopulmonary exercise testing with a right heart catheter in place, as well as nuclear imaging of right and left ventricular function to get a sense of treatment over the long term, 6 months as opposed to the standard 3 months, to see if there is improvement in function and evidence of remodeling along with improved functional status.

Dr Mubarak: We have all seen patients we expected not to respond and they responded, or patients we expected to respond and they didn't. I think these patients are something of a mixed bag, and it is a question of separating out and predicting who is going to respond better. We don't understand that very well at this point. When you start to go outside the PAH group I category, it gets to be a complicated disease where multiple factors are responsible for PH and there are probably multiple underlying processes. We need further categorization of these patients before we can tell which ones are going to respond or not.

Dr Fagan: Do you think the need to better characterize these patients (ie, by more than just an elevated wedge pressure) applies only to patients with heart disease? Are they harder to characterize in a standard way than patients with COPD or ILD? Do we need better definitions in both groups?

Dr Zamanian: There is a body of literature showing a lack of homogeneity across patients with ILD-related PH. We've all had the mixed experience of response to vasodilator therapy for pa-tients with hypoxemia-associated PH. Some patients do well, others get worse. To better understand this, we are working with Steven Nathan at Fairfax INOVA, to correlate acute vasodilator response to long-term outcomes in pa-tients with IPF-associated PH. The ongoing IPF sildenafil study does not account for patients we may have all seen, who get more and more hypoxemic with pulmonary vasodilators, and end up doing poorly. We are attempting to better characterize patients in the catheterization lab. We are giving nitric oxide followed by sildenafil, evaluating changes in V/Q and then following patient outcomes. So, our attempt is to better understand and maybe identify patients with ILD-associated PH who would respond well to vasodilators. This approach may help in better characterizing a complex physiology.

Dr Fagan: So you are correlating their V/Q mismatch, hemodynamics, and pulmonary function testing and then looking at overall outcome, but not necessarily with specific PAH therapy?

Dr Zamanian: With regard to PAH therapies specifically, we have had patients in the catheterization lab who become more and more hypoxemic with interstitial lung disease when sildenafil or nitric oxide or epoprostenol is applied. We have always wondered whether hypoxemia begets worsening right heart failure in these patients. From our perspective, if we can categorize these patients' response to therapy and see if that predicts outcome over the long term, that might be a helpful strategy to better characterize PH in interstitial lung disease.

Dr Safdar: We have tried a different approach to test the V/Q mismatch in patients with end-stage lung disease. We monitor their oxygen saturations before and after a test dose of sildenafil, in hospital, and observe them for about 3 to 4 hours after the test dose. It is interesting in that, given the degree of lung disease, it is hard to predict which ones will develop worsening hypoxemia. It could be related to the inflammatory component or the end-stage fibrotic changes in lung parenchyma.

Dr Waxman: The difficult thing we have found with interstitial lung disease is that when we test patients in the catheterization lab we find that they are vasoreactive. If we treat them afterwards with long-term therapy, their response to treatment is often different. We use inhaled nitric oxide in the cath lab. I'm sure we are altering V/Q when we give them oral or even intravenous therapy. We have also found that over the long term there are adjustments in V/Q. I think figuring out a way to clearly phenotype these patients to know which ones will respond to therapy and which ones won't isn't going to be easy, and I don't think it's something that we can look at with just radiography or even PFTs, or even their response in the catheterization lab. It is almost something that you have to try and find out from how they do over a period of time.

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Dr Zamanian: I agree. Ardi Ghofrani has compared nitric oxide with sildenafil and it is always surprising to me (maybe it shouldn't be surprising) that patients with ILD-associated PH develop a worsening A-a gradient in response to nitric oxide, whereas with sildenafil they don't. So, I agree that we need to characterize these patients and then their response to the individual drugs we give them.

Dr Fagan: We know that PH associated with COPD and ILD predicts a worse mortality than COPD and ILD without PH, but do we know treating the PH improves mortality?

Dr Mubarak: I don't think we have the answer yet. A number of good papers show that PH is a significant problem in IPF or ILD, but actually intervening and improving that outcome has not been done. One of the ongoing trials with bosentan in IPF targets that particular pathway, but the final results are still pending.

Dr Safdar: I agree that we don't yet know whether treating PAH in COPD and ILD affects outcome, though some anecdotal data suggest that, in selected patients, treating PAH improves quality of life. Whether it improves right ventricular dysfunction and/or pulmonary vascular remodeling remains to be determined.

Dr Waxman: By the time we intervene there is already established PAH and right ventricular remodeling and change in function that is making them more short of breath. That is the clinical time point where we are now using drugs to treat PH. I suspect it is not going to affect long-term outcome, and we need to be able to intervene before the right ventricle remodels to the point of approaching cor pulmonale. Our focus needs to be maintaining normal or close to normal right ventricular function.

Dr Zamanian: That is an interesting point. Do you think right ventricular response to hypoxemic lung disease or pulmonary venous hypertension is similar to that in patients with PAH? For example, I think scleroderma patients are unique in that they have myocardial fibrosis, and maybe right ventricular modeling there is not similar to other caveats. Do you think the same phenomenon exists in non-PAH pulmonary hypertension?

Dr Waxman: I don't know. Between our animal models and what we see in humans, I think there are differences as to what is driving the remodeling. There are differences in the inflammatory pathways that are activated, as well as the vasoconstrictive and endothelial proliferative pathways. With the connective tissue diseases I think it is more of a systemic picture with RV remodeling as part of an overall process, whereas in our ILD and COPD patients it is probably more a secondary response. The longer we can maintain normal RV architecture, the longer they are going to do better.

Dr Fagan: Do you think every patient who presents with COPD or who presents with ILD, mild, moderate, or severe, should be screened for PAH and subsequently treated without having any data or evidence to say that treating it is ultimately going to change their outcome?

Dr Mubarak: We need to identify these patients as a first step, and then use that information to prognosticate survival, and perhaps even use that input for timing lung transplantation. Once you have done that, however, that patient population becomes a target for clinical trials. That is where we need to go next. We have identified that PH is a problem in ILD, and most likely in COPD as well, because the outcomes seem to be adverse when you develop PH. Then, we can use this information to counsel patients, to consider them for lung transplantation, and then to randomize them into clinical trials.

Dr Waxman: What we are striving for is a drug that is going to help prevent RV remodeling. I do not think we know yet whether, in the ILD and COPD patient, that is a vasodilator or something specific to a remodeling pathway.

Dr Fagan: But a lot of us are being pressed into action in dealing with patients who present to us with right ventricular dysfunction in the face of COPD and ILD. It can be a difficult moment in the clinic when discussing with the patient and the referring physician what the options are. How are you all addressing this, given that we agree that clinical trials are needed to ensure we're actually helping that patient population?

Dr Waxman: For us, we do try the standard PH therapies depending on how sick the patient is and what underlying side effects are already there, and by side effects I mean things like edema, that helps us decide. But having said that, I'm not impressed with the response.

Dr Safdar: We do screen COPD and ILD patients who present to our clinic for PAH, especially if their dyspnea is out of proportion to the degree of lung disease. By that I mean their CT chest and pulmonary function tests show mild to moderate disease, but they are in functional class IV, or their DLCO is severely reduced. In such situations we test to determine if they have a propensity to develop hypoxemia with a pulmonary vasodilator and then give a trial of therapy. Of course, these patients are referred for lung transplantation and encouraged to enroll in a clinical trial.

Dr Fagan: How is clinical response measured when you do treat a patient?

Dr Waxman: We do it based on a functional assessment and the 6-minute walk distance, maybe repeat echo, and on rare occasions, repeat catheterization.

Dr Mubarak: I agree with that, but when I do that in the clinic I usually pre-specify how we deal with the patient, exactly what we are going to do, and what we are going to accept as a meaningful response. If we reach that point, then I would like to continue that therapy, and if not, then these are expensive drugs with side effects, etc. At that point I would tell the patient, this is what we agreed to and

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you are not having a response, let's stop the treatment.

Dr Safdar: We have a similar approach. If a patient shows improvement in walk distance, functional class, and/or Borg dyspnea score with some improvement in quality of life, we continue therapy. We don't have a cut-off for improvement in the walk distance, and side-effects, unfortunately, can be the limiting factor in guiding therapy.

Dr Waxman: We take the same approach and try something different if we do not get the response we hoped for.

Dr Fagan: We do the same thing. My question is, when we use end points such as reported functional class or 6-minute walk distance in patients with advanced lung and/or heart disease, how do we, in patients with a progressive chronic illness (COPD, ILD, heart disease) identify whether PH treatment has had an impact? So many other factors affect these end points in addition to PAH.

Dr Waxman: We have had some limited trials that we are running in which we use cardiopulmonary exercise testing to try to define the patient's physiology and then, after a period of 3 or 6 months on therapy, reevaluate what happens with their cardiopulmonary exercise test response.

Dr Fagan: Could you tell us what features you look for in CPET?

Dr Waxman: We have a unique CPET here that we do with the right heart catheter in place, radial arterial-line, and first paths nuclear imaging of cardiac function. So we are looking at the standard alterations in VO2, VCO2, anaerobic threshold, the same thing that you would in any CPET with the added pulmonary hemodynamics and lactate thresholds based on true Fick principles. It gets pretty detailed but we have been able to get patients to go do it as a standard test and then also repeat it as part of a trial. We are looking at patients with COPD, diastolic dysfunction, and PAH to get a sense of phenotyping the patient and response to therapy.

Dr Fagan: What are other people doing in terms of addressing patients with other complicating diseases? How do you assess clinically whether they have improved or not?

Dr Mubarak: We have been interested in the circulating endothelial cells that arise from the pulmonary circulation in patients with PH. The numbers are very small, but it is possible to extract RNA from them to look for gene expression profiles within the pulmonary endothelium as you are treating them. So, that may be another way of looking at responses or categorizing patients prior to therapy into one of several groups, one of which may respond better than another.

Dr Zamanian: We all have our favorite tests and studies that we want to believe are valid or are being validated in PAH. And I think we all attempt to apply them to other populations, but we have the same difficulty everyone else has with what exactly to use. A paradigm we try to stick to is reproducibility and simplicity as a quality for outcome surrogates, if we can. We have be careful when we design studies or talk about surrogates of outcome evaluating therapies in the heterogeneous population of PH associated with ILD, COPD, or pulmonary venous diseases. Finally, once we decide on an appropriate outcome marker, we should make sure it is realistic for all study centers to perform.

Dr Fagan: In designing clinical trails in the future, what should be considered as additional end points to be studied to identify a response to treatment?

Dr Mubarak: The next one is going to be cardiac MRI, which is noninvasive and easily standardized across centers and gives you a fairly good idea of right ventricular function. Stroke volume and right ventricular ejection fraction, etc, are emerging as indices that can be used rather than, for example, hemodynamics.

Dr Fagan: We have done a lot of work in group I PAH and have categorized that patient population. What is the next big need in terms of patient populations on which we should be focusing our studies?

Dr Mubarak: I think sarcoidosis is important, since the pathophysiology appears to be similar to that of PAH.

Dr Waxman: I would add COPD, because of the sheer numbers and global health impact. These patients are in need of being better categorized since it appears there are several different subgroups of COPD patients with different severities of PH.

Dr Safdar: Sickle-cell disease patients have a high incidence of developing PAH, and PAH in these patients needs to be better defined. As you know, the study in sickle-cell patients with PAH was stopped because of poor enrollment. Chronic thromboembolic disease is another disease that is mostly excluded in clinical trials, and there is a need to better study this patient population.

Dr Zamanian: I do not think we are completely done with some of the subsegments of the population of PAH. My experience is that even within the subgroups of WHO Group I (or whatever is going to be Group I after this World Health Congress classification comes out) therapeutic efficacy is different. I don't see the same result from therapies we apply to portopulmonary versus scleroderma versus idiopathic, and I wonder if everyone here has the same perspective. It seems we categorize PAH patients all into one group and applying the same therapy may not be appropriate. As our understanding and classification of PAH continues to grow and get more complex, we should treat our subpopulations within PAH differently. For us in California scleroderma is a big deal, as is amphetamine and stimulant-associated PAH, with a huge population. In our experience, amphetamine-associated PAH patients present with severe disease and respond very well to endothelin antagonism. Also, I think we are beginning to recognize the importance

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worldwide of schistosomiasis, which was a big topic this year at the Pulmonary Vascular Research Institute meeting in Spain. We should better understand the pathophysiology and the characteristics of patients with schistosomiasis-related PAH to classify them best.

Dr Fagan: I think almost all of us may have been at the World Congress Meeting and it has been proposed to move schistosomiasis into PH Group I as opposed to being in Group V.

Dr Mubarak: Sickle cell disease has typically been ignored in the PAH category and only recently moved into the Group I category. Similarly, most of our trials have excluded portopulmonary hypertension. The data we have on portopulmonary hypertension are far less than for the scleroderma or idiopathic groups. Congenital heart disease may be different from HIV, and that may be different from, for example, Gaucher disease. Survivals are different and so responses to therapy may be just as different. There is a recent paper in the *New England Journal of Medicine,* a case report demonstrating benefit with imatinib. I have tried it and I have not found it as useful in one patient.

Dr Safdar: We had a more favorable experience with imatinib in a young woman with familial PAH receiving maximum therapy. This patient improved her walk distance, functional class, and right heart failure. Again, this is one case and the ongoing clinical trial will define the utility of this agent in PAH.

Dr Waxman: We have been looking at an endothelial nitric oxide synthetase coupler. I am very cautiously optimistic, having treated 4 patients on a compassionate use basis with very good response. When we go beyond a couple of patients to a clinical trial, which we expect to do soon, we hope it will hold up. What is interesting about even approaching it from that sort of very specific target is that when we think about vascular remodeling in the small vessel as well as the myocardium, approaching it in a pathway-specific approach makes a lot of sense. The other thing I think we have not touched on, especially regarding methotrexate, is the role of inflammation in all of these diseases, like IL-6 and targeting circulating inflammatory pathways or cellular immune responses. We know in plexogenic lesions and vascular remodeling, which is apparent in PAH and COPD and ILD, cell-mediated immunity may be playing an important role. We have not even begun to think about attacking that therapeutically.

Dr Mubarak: There is good literature on atherosclerosis and inflammation but unfortunately nobody has really looked at inflammation and pulmonary vascular disease in great detail.

Dr Safdar: A serotonin transporter inhibitor is also being tested in a clinical trial in PAH. Multiple animal studies document reversal of artificially induced PAH by serotonin transporter inhibitor. However, we have to be cautious and await result of the clinical trial to see if the animal data are replicated in humans. So if I have a depressed PAH patient, my choice of agent is a serotonin transporter inhibitor, in the hope that it will also provide some beneficial effects on vascular remodeling.

Dr Fagan: That speaks to some of the other chronic inflammatory lung diseases of which PAH is a component, like ILD or COPD. Those are pathways that mechanistically may be very important in their own subsets.

Dr Waxman: That brings up the idea of statins.

Dr Zamanian: We can learn a lot from the way we've chosen to study statins in PAH. Investigations of statins in animal models of PAH began with the pioneering experiments of our colleague, Dr Peter Kao, here at Stanford. I think the initial excitement about the utility of these compounds led to their immediate use and open-label evaluation. However, I think we learned from the statins that we cannot rush to judgment about any novel therapies. We have to undertake well-designed clinical trials to look at their efficacy. I mention this because I see a similar trend with the use of imatinib. I would suggest that with the advent of novel and exciting therapies for PAH we must hold off a rush to judgment but accelerate quickly into meaningful clinical trials.

Dr Fagan: That raises a good point in this kind of a broad grouping that we have done in assuming that all patients in that category are going to respond the same. I think we are a little more aware of that when we talk about the other groups, including heart and lung disease groups. Maybe we need to go back and suggest that we need to study even our group I patients in specific subcategories in more detail.

Dr Mubarak: I think that is important. There are so many different subsets in group I PAH. We do need detailed information on all of these. We certainly know the survival for Eisenmenger's is very different from survival with HIV. Bad liver disease is somewhere in between. For all of these diseases that we have talked about, there are probably subsets of patients in all the randomized trials for which we already have data. As an example, somebody may have just a bit of COPD or just a bit of interstitial lung disease in association with group I PAH and was in a PAH clinical trial. Perhaps that information can be pulled to give us some idea of what the effect of these comorbidities is on our trial results and conversely what the effect of these drugs is on those comorbidities. That is one place to start as we start exploring these other areas.

Dr Fagan: I think you are right, that we want to look at the patients who had forced vital capacities between 70 and 80, and between 80 and 90 and look at those data. While the data nay be limited, they may point us in interesting directions when we think about future clinical trial design. I'd like to thank everyone for a great discussion of a difficult but interesting topic. ■

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