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Using Advanced Pulmonary Hypertension Therapies in Children

On July 8, 2011, Editor-in-Chief **Erika Rosenzweig** convened a discussion among a group of physicians who work daily with pediatric PH patients to share their thoughts and experiences related to using new therapies with children. Contributing to the conversation were guest editor **Dunbar Ivy, MD**, Professor of Pediatrics, University of Colorado; **Jeffrey A. Feinstein, MD, MPH,** Associate Professor, Stanford University School of Medicine; **Tilman Humpl, MD, PhD**, Associate Professor, Pediatrics, University of Toronto; and Professor **Maurice Beghetti,** Head of Pediatric Subspecialties Division and Head of Pediatric Cardiology Unit, Children's University Hospital, Geneva, Switzerland.

Dr Rosenzweig:

Good morning and thank you all for joining this roundtable panel today to discuss how we use advanced pulmonary hypertension therapies in children with PAH. Before we begin, I would like to welcome each of our roundtable experts to this panel discussion. We have Dr Dunbar Ivy joining us from Colorado, Dr Jeff Feinstein from Stanford, Dr Maurice Beghetti from Geneva, and Dr Tilman Humpl joining us from Toronto. As you may know, the last roundtable discussion for *Advances* that was focused on pediatric issues was published 5 years ago. At that time, the oral agents were relatively novel. And, other than nitric oxide, inhaled agents were not being used much at all for children. So my first question to the expert panel is: With the emergence of several novel agents for the treatment of pulmonary arterial hypertension, how has your approach to treating childhood PH changed over the last 5 to 10 years? Dunbar?

Dr Ivy:

Well, I think our initial approach to the evaluation of children with pulmonary hypertension is similar. We continue to try to perform a complete evaluation and then treat any potential causes that we can find before starting vasodilator therapy. I would say that with the advance in oral therapies there may be a few patients that were started on oral therapy more recently that we would have started on intravenous therapy in the past. So, for example, in the child without heart failure who is nonreactive to vasodilator testing, we do consider starting oral therapies; whereas in the past we would have started intravenous therapy. Since there are so many available oral therapies, the real challenge is to decide which one you begin with. This challenge is even more complex in the more recent couple of years with the addition of other available therapies. So now we have available bosentan and ambrisentan as endothelin-receptor antagonists as well as sildenafil and tadalafil for type 5 phosphodiesterase inhibitors.

Dr Rosenzweig:

So there are clearly a lot more choices. And how about you, Maurice?

Dr Beghetti:

I completely agree with Dunbar. It does facilitate the treatment of children, but, indeed, in some ways it also complicates it a little bit. Now we have to discuss with families the different options sometimes, especially with oral therapies. Because, as Dunbar said, there are 2 or 3 different possible first therapies, so you have the possibility to discuss and to see what are the potential advantages and disadvantages of the different oral therapies for the child. I would say this is really something completely different from 5 years ago where we had difficulties

even starting therapy. Here now we have choices. And the problem of the choice is that we don't have any comparisons between therapies, and we do not have any data supporting that the use of one or the other is better. So, personally, sometimes it is difficult to answer the parents when they ask which one to choose. It's really an open discussion with the parents, which I assume some of my colleagues have also, depending on what therapies are available in their own countries—which sometimes is also a problem.

Dr Rosenzweig:

Very good points. Jeff, have you had a similar experience as well?

Dr Feinstein:

I have, and it's an interesting dilemma. Sometimes you complain about having no therapies and now we have the issues of having too many therapies; the decisions are tough to make. I agree completely with Maurice and Dunbar. One of the other things I think complicates the issue of having oral therapies available is the decision-making with regard to how long you leave somebody on oral therapies before becoming more aggressive or advancing to inhaled or IV therapies. I think some of the issues we're seeing are with kids who present to us fairly late in the process; they've been on oral therapies with other providers or other institutions, and it is a tough decision as to when to actually move forward with more aggressive therapy. I think the other thing that has been a nice advantage to us is the addition of inhaled therapies. One of the particular groups for which we think this is a great advantage is the Eisenmenger population. In the past, I've been reluctant to use intravenous therapy in those patients because of the concern about thromboembolic events; the availability of a prostanoid for the Eisenmenger population has been a nice advantage for us.

Dr Rosenzweig:

Yes, I think you highlight some really important points, and I echo those comments in that this is a new challenge; I think the challenge of the next 5 or 10 years will be trying to figure out how to best navigate through the new therapies. With the limited data, as Maurice said, in terms of pediatric trials, it's hard to say one drug is better than the other. Jeff, you brought up a good point about patients who are started on oral therapy first. When do you bite the bullet and say that we need to escalate to IV? And how long do you wait? I think that's a very important question as these oral medications are available in smaller clinics that may not have experience with IV/SQ therapies. Also, how do you go about reassessing the children? I'd be interested in hearing comments on when you all decide to escalate therapy versus

when you decide you need to go to IV therapy from the very beginning.

Dr Beghetti:

I think that for me that's one of the most difficult points. We are currently trying to work on that because the adults have a treatment goal approach, which we should also have in pediatric patients. The problem is it's difficult to extrapolate the goals that the adults have to the pediatric population. We need treatment goals for pediatric patients—and maybe a scoring system also for pediatric patients—to try to discriminate the patient that requires more aggressive follow-up and more aggressive therapy, because there are clearly different groups of patients. Probably what happens now is that we all have our own clinical approach including all the different testing that we do—most of them noninvasive. Personally, I group echo, exercise capacity, quality of life, NT-BNP or NT-proBNP—all these things together. And when I have a real problem assessing the patients, I do an invasive hemodynamic assessment (catheterization) before starting another drug. We should come up with something that is more similar in all the different expert centers to try to deliver to the community some scoring and some endpoints for the pediatric population. I think that's also what we should do in the next few years.

Dr Rosenzweig:

I think that's critical, particularly with the children where we know they have a more rapidly progressive natural history when left untreated. I think reassessment after 2 to 3 months of starting a first-line therapy is critical for them. Again, if there is no improvement—or certainly if there is progression—you change or escalate the therapy sooner than later. These aren't patients that you can say, “let's see you in 6 months or a year and see how you are doing.” Any other comments?

Dr Ivy:

I would agree with Maurice that it would be nice to have some goals for therapy in children. And as he alluded to, I think these goals will be different from the goals in adults because children tend to have less heart failure than adults, and they tend to walk farther on the 6-minute walk test. So to use the adult criteria and apply them to children really would lead to under treatment of some children. We do need to look at large registries and try to develop an idea of what value of cardiopulmonary exercise test or 6-minute walk test or even catheterization variables to define targets for therapy.

Dr Rosenzweig:

I certainly think for children, at least in my practice, we tend to be more aggressive to get them to lead the most active lives that they can, so other functional measures are important. You bring up the point of hemodynamics, which I believe is an important point for children when we sometimes can't assess how they're doing functionally. How much do you all rely on the hemodynamics for monitoring your patients?

Dr Feinstein:

I rely on hemodynamics a great deal. We are probably one of the more aggressive programs as far as follow-up and doing catheterizations fairly routinely. We do, in general, annual cardiac catheterizations at a minimum. As you mentioned, we do follow-up caths in kids who are borderline shortly after starting oral therapy. I think there are certainly some pitfalls with cath and what those numbers represent, so we've also actually started using, as Maurice mentioned, other sorts of quality of life measures, and, in some of our cases, MRI values as well to try to get a better look at RV function overall. But, we are fairly aggressive about getting hemodynamic data and using those data as they relate to changing therapies.

Dr Beghetti:

I agree. I'm not doing invasive hemodynamics in all my patients, but for all the patients that I'm not satisfied with, clearly we perform another catheterization before changing therapies. I need to be sure of that. One of the problems is that historically we think that cardiac catheterization has been considered very high risk. But, and I think Dunbar can probably also mention a study in the US, we also have data coming now from registries showing that when the cath is done in expert centers with an expert team, especially expert anesthetists, it seems that the risk of death and complications are not so high. That's probably also why most of the new trials with new drugs in pediatrics are considering using hemodynamics as a primary endpoint. So, I think hemodynamics remains something important for what I would call a hemodynamic disease.

Dr Feinstein:

That's an excellent point, Maurice. Of course, the biggest problem with all of this is the fact

that the kids who need the cath the most are usually the sickest. It's great when you get to cath the healthy ones, but the ones who have the highest risk are, of course, the sickest.

Dr Rosenzweig:

On that note, I just want to rewind a little bit back to the comment about selection of therapy. Do you think the pendulum has swung too far the other way in that we are so reluctant to start IV therapy because we have other less invasive agents available? We talk about right heart failure as an indication for IV therapy in children but—even Dunbar alluded to this—the symptoms of right heart failure are not as often present as they are in adults. Are there any other red flags that the panel uses to indicate that you should go right to IV/SQ prostanoid therapy from the start?

Dr Ivy:

Certainly I think we could all agree that in the patient who presents with right heart failure and is very symptomatic, IV therapy should be strongly encouraged to the family. I think for me the other group that sometimes I'm more aggressive with is the younger child with severe disease. There are some data, although not well proven in the literature, that the young child with severe disease that's started on IV therapy may be the most likely to be able to come off of IV therapy and to have some remodeling of the pulmonary vasculature. And Erika has written a recent paper about patients who have been able to come off of the intravenous therapy if their hemodynamics are very favorable. So that group, in particular, I try to encourage the family to consider more aggressive therapy because I think we may be able to change the natural history. In the adolescent that presents with severe disease, I'm not quite so optimistic with the family that once you really need to start IV therapy that there is a good chance you're going to come off.

Dr Beghetti:

I think that's a good point, Dunbar. That's why before, when we were discussing endpoints, I put together scoring and endpoints. I think what we would like to have when we diagnose a patient or when we follow up a patient after 3 or 6 months of the first introduction of oral therapy are values such as a combined score that would tell you this patient should not wait to switch to IV because the risk of dying or the risk of progression, rapid progression, is really there. If we could find that we could really discriminate the small group that has a very aggressive disease and needs really aggressive therapy from a group that sometimes remains stable for a long time and would be okay on one or a double-combination oral

therapy, that would be a major step for the community to approach the pediatric patient this way.

Dr Rosenzweig:

That is a very good point. While we are discussing therapy selection, I'd like to ask about using monotherapy versus combination therapy. Are you all routinely using combinations in the children and is there a particular combination that you like best?

Dr Feinstein:

I think, obviously, that combination therapy is a lot more frequently used than it had been in the past. One of the big issues that we now face is the concept of swapping therapies or adding therapies. If you start a therapy and you don't see very much change, either in symptoms or in hemodynamics, is there a benefit in actually continuing that therapy? And I think quite honestly, as we've all alluded to, those data just don't exist yet. But if you look at our practices overall, the use of combination therapy is fairly common. I think the use of 2 oral agents or an IV agent plus an oral agent is a lot more common than it was, obviously, even just a few years ago. And this is simply because we quite frankly don't know exactly which agent works best for which patient yet. And we all believe that attacking the disease in multiple pathways is probably a good idea. Now one of the things that we've looked at here, and Dunbar has helped with this, are adverse events with therapies as reported to the FDA. Hopefully, those data will come out soon. But the interesting thing, just as a snapshot of the population we treat, is that of the reports that were submitted to the FDA, basically 70% of pediatric patients were on monotherapy. And that goes along with a lot of the adult data. So certainly the general practice for many is not to use multi-therapy at this time. That may be due to drug availability and maybe even clinician comfort; and it may simply be lack of awareness of the potential benefits of multiple therapies simultaneously.

Dr Rosenzweig:

I think that's a good point, in particular for children, where there is a lack of data on appropriate treatment selection and the use of combination therapy; some practitioners may be even more uncomfortable using combination therapy in children.

Dr Ivy:

That gets back to the goals that Maurice brought up. My goal for children is that they live many decades. So with that in mind, I tend to be more aggressive; and I think some of the registry data suggest that most pediatric pulmonary hypertension practitioners do use more combination and more triple therapy than in adults. My guess is that's because we feel that there is a value of pressure and resistance that if we can lower the pulmonary hypertension to that level that the child may do well for a very long time. Unfortunately, we don't have absolute data to support that, but I think that the registry data do suggest that most children are on more therapies than adults are.

Dr Beghetti:

Yes, I agree. You know that we are also working on this in the worldwide registry called TOPP. It depends clearly on the country where you live and the possibility that you have to treat your patient with 2 or 3 drugs due to the price of these drugs. But when you have this availability, usually most of the children tend to be on at least double oral if not triple drugs. So I agree. I think one of the things that we did not discuss for the moment is that for some of the drugs we still have a problem of dosage and delivery of the drugs and having really good data to be sure that the dose we give to the children is the good one. That's also something probably that needs to be worked on, but the studies are currently being done to be sure that we are really giving the right dose to the pediatric patients. We have seen that with the endothelin receptor antagonists (ERAs), sometimes the dose may not be exactly what we thought it should be. So we have to think about that also to improve the treatment with the current drugs that we have.

Dr Rosenzweig:

I think that's another important point. Maurice, would you like to make a comment about some of the upcoming work that will be done so that these data will exist in the future?

Dr Beghetti:

Yes, with one of the ERAs, bosentan, there has been a pharmacokinetics (PK) study. But there will be some other PK studies going on to see if children are really comparable to adults or if they need maybe different dosages. There is also work with different doses of these drugs on specific pediatric formulations, because sometimes it's difficult to deliver the drug to very young children because they are not able to swallow the tablets that are currently on the

market, which are not really adapted to very young patients. Most of the pediatric studies that are currently done for approval will have different doses of these different drugs to see if there is something with regard to plasma levels or side effects with different doses so that we can have really good data to treat our patients.

Dr Rosenzweig:

I agree that it will be very important to obtain data on pharmacokinetics to determine optimal dosing in children with PAH.

Dr Ivy:

So most of these studies, as Maurice said, do have a pharmacokinetic evaluation of children at different doses and some attempt at a correlation between the PK and efficacy. The real difficulty is that in order to get the maximum data, there are not really enough patients in these trials to optimally determine the dose per age. I think that is going to be a challenge that we face as these trials will give us some data on pharmacokinetics, some data, for efficacy, and many of them will have a subgroup of hemodynamic endpoints. But in order to really put this all together we would need hundreds of patients per trial.

Dr Beghetti:

I could not agree with you more. That's exactly the problem we have: the number of patients is small and also these studies are quite difficult for our patients. The PK studies are difficult studies because you need to stay in hospital and have a lot of different blood work. So it's not an easy study for our population. We have to face that pulmonary hypertension is an orphan disease with difficult studies.

Dr Ivy:

We're also finding that for some of these, most of the studies that are coming out are on drugs that are already approved by the EMEA or FDA, and patients that are already on that therapy are excluded. So since the drugs are already approved in adults and used in children, we're not able to enroll children because they're already on that therapy.

Dr Rosenzweig:

Right. I think these are unique challenges that we face. But you both highlight the importance of getting these data even if it's in a limited fashion so that we can learn as much as we can about dosing in children. As we all know, kids are not just small adults, so there are differences in metabolism that may have important clinical implications. Hopefully these data will emerge over the next several years.

I have just one more question about the use of combination therapy: I am interested in this panel's experience in using dual or even triple therapy in children. I know the French have had experience at least in adult PAH patients with starting upfront triple therapy at the time of diagnosis. You all mentioned that we tend to be more aggressive with children because we're thinking about prolonging survival for decades. Has that been an approach that any of you have tried yet or something you've thought about doing—where we induce a “remission” or “remodeling,” and then you pull back therapy or de-escalate therapy later down the road? Or is there another approach to combination therapy that you favor?

Dr Beghetti:

Clamart's group in France has just presented that data a few months ago with some data findings that are quite strong in adults. As a small center, I did not have patients like that coming to my center recently. But I would say that having patients coming in class IV, severely sick, I would tend to do that, especially in pediatric patients. And from what I understand from Dunbar, I'm sure that they would be not so far from doing the same thing: starting IV plus two orals and then just see what happens in the next few weeks or months as maybe you can then either wean or stop the IV. But I think being aggressive in our class IV patients would probably be a good approach.

Dr Rosenzweig:

I would agree with that. Dunbar?

Dr Ivy:

I'd be curious to hear Jeff's opinion as well. We have not started immediately with triple therapy, but we have started double therapy with IV and a PDE-5 inhibitor based on the adult data in the PACES study. We've not started immediately with triple therapy, but in some of those very sick patients, it's not long before we get to triple therapy.

Dr Rosenzweig:

Yes, I think we may tend to escalate a little more quickly as well. How about you, Jeff?

Dr Feinstein:

We rarely actually start more than monotherapy, but we do escalate fairly quickly. I think one of the things that I try to get a feel for is— in fact, since we don't have any definitive data, often—which drug they respond to. I think in the case of a class IV, obviously the IV prostanoid therapy is the first line initiated and then the question is how do you add others? Whether it's side effects or symptomatic improvement, I like to get a feel for which drug causes what and which one drug they are responding to. So it wouldn't be unusual for me to add an oral therapy to an IV therapy within a couple of weeks, but I do generally try to do either oral therapy and then wait a month or 2 months before adding another oral therapy or IV and then adding oral therapy behind it. While I appreciate that essentially they all work on different targets, in a very sick patient I think we will all agree that the overwhelming bang for the buck comes from the IV therapy. So I don't feel particularly badly about waiting a few weeks before adding an oral therapy to get the IV therapy titrated up without the worry of concomitant side effects and not knowing which therapy it is.

Dr Beghetti:

I'm quite interested by what you say, Jeff. Do you see many of the patients that would not respond to one of the oral but have a very nice and extraordinary response to another one? So do you mean really that there are patients that do respond well to one drug and not the other?

Dr Feinstein:

Yes, I think we've actually seen that both symptomatically and clinically. It's really very interesting. And I was very surprised by this. So we have probably 3 or 4 kids who, when they got sildenafil, for example, told us that there was nothing different at all. But when they ended up on bosentan, there was a huge improvement in symptoms. In fact, we had one particular patient in whom during the acute post-op phase for back surgery, the bosentan made a huge difference. Alternatively, you can extend that to other kids where they've taken bosentan and it's like they're taking placebo. Then you give them sildenafil and they feel dramatically different. I think one of the huge challenges for us is to figure out exactly which drug for which kid.

Dr Rosenzweig:

Right. I would agree that response clearly varies from patient to patient, and that is probably where the pharmacogenetics come in between drug classes. We've even seen that sometimes within the same class of drug in adult patients and sometimes in children where they'll report that they feel better with one ERA versus the other or one PDE-5 inhibitor versus the other. Jeff, you mentioned earlier about understanding why certain children respond to one over another and believe it's back to the wiring and the mechanism of their disease. I am unaware in terms of pharmacogenetics that this is currently being studied in children. Are any of you familiar with any trials currently addressing this issue in children?

Dr Beghetti:

I think that in one of the trials with one of these drugs, blood will be kept for such a study in the future. It's asked in the consent for use in the future in order to have a sort of blood bank for further evaluation if needed.

Dr Rosenzweig:

I agree that it is important as these trials are being designed; maybe, as you suggest, to store now for when we know more later, particularly given the small numbers of patients. We may not know now what these markers are, but sometime in the future we'll have the ability to go back and look at them.

Dr Feinstein:

This is a perfect question for Tilman. If you think about the work he did with sildenafil in the catheterization lab where he showed that in a large percentage—I think it was almost 50%—of the kids you don't detect sildenafil and you don't get changes in cyclic GMP. So there is clearly a wiring difference among the kids and Tilman is at least starting the process of investigating that.

Dr Humpl:

Yes, thank you, Jeff. In our study we were able to show suboptimal absorption of sildenafil in about half the children undergoing acute hemodynamic testing in the catheterization laboratory. In some patients we detected a “therapeutic” or “valuable” level of sildenafil in the blood, but the effect of sildenafil on pulmonary vasodilation was not much different from that of inhaled NO even though we had noticeable differences in cGMP levels. This suggests possible variations in responses or mechanisms of both drugs. Interestingly, the response to sildenafil was also seen despite “undetectable” blood levels. This may point to the fact that the therapeutic range for some children might be different than in the past described for adults.

Dr Ivy:

In unpublished data, we previously compared response to therapy with endothelin levels, cyclic AMP, and cyclic GMP levels, but there were no good correlations.

Dr Beghetti:

Well, I think we also have quite a heterogeneous group. In our pediatric population, even if sometimes—and I know there is discussion about that—we classify patients in the same group to improve the number of patients, there are a lot of differences among patients. I'm not sure that congenital heart disease patients and idiopathic or connective tissue disease patients are exactly the same with regard to the response they may have to the different drugs. Sometimes, because we have very few patients in studies, we try to group our patients and maybe that's why we have such scattered results with some of the measurements.

Dr Rosenzweig:

I think that's a great point, particularly in pediatrics where many of these “groups” of patients, like those with congenital heart disease and those with lung disease, are very heterogeneous. And, this has been the rationale for trying to update the classification system in pediatrics. Since you mentioned congenital heart patients, let me ask then if any of you believe there is a role for these novel therapies in patients other than classic Eisenmenger patients. Perhaps we can discuss single ventricle patients (Fontan). And, have you been using any of these agents in other groups that are not classic group I patients?

Dr Beghetti:

I reviewed all the literature on Fontan recently and I think with the Fontan, for example, if we talk about heterogeneity, we have a huge heterogeneity because you face a lot of different anatomies. Then you have patients who underwent a Fontan when they had increased pulmonary blood flow before surgery and some who had decreased. And then you try to put all these patients together in a study and use the drug and look at the results. So, I think this is one of the first problems. So far there is, I think, no real good study showing the effect of targeted therapies in Fontan patients. That's why the results are a little bit controversial. And, as usual, the successful ones are only case reports. But I think there is a good rationale, because, for example, with a Japanese group, we showed that in failing Fontan there is increased staining of endothelium in the lung vessels. So, I think we should pursue that, because this a hemodynamic circuit that probably will not last for a whole life. I believe it would be worthwhile to try to understand what is happening in the single ventricle/Fontan pulmonary vascular bed of these patients and see if these drugs may have a role. It would be a major progress.

Dr Ivy:

I would strongly agree. And I think this group of single ventricle patients is really ready for an interventional trial. I think that you could get many centers involved nationally and internationally, and really learn something definitive about the role of these therapies in the single ventricle patient.

Dr Rosenzweig:

I would agree with that as well. And, in addition, in terms of patients who are borderline candidates for completion of their Fontan, we've had some experience, and there are a

handful of case reports of lowering PVR in those patients and making them more suitable candidates. So I agree this is an area of study that will emerge in the future and that we will need to collaborate on to determine the best approaches.

Dr Ivy:

I think one of the other things that's interesting that Maurice brought up is the whole fact that these are patients with a single right or left ventricle We haven't really talked about the drugs' effect on the ventricles. Certainly there are data out there that would suggest that sildenafil has an effect on the right ventricle, but we don't really know what the effect is on the left ventricle as well. So certainly there are different kids with different diseases with different ventricles, and this is going to make our job even more difficult because they are so different and so complex.

Dr Rosenzweig:

In terms of the heterogeneity of the group, what about the neonates and children with chronic lung disease? Have you all had experience with treating some of these patients with targeted PH therapy as well?

Dr Ivy:

Because these patients with chronic lung disease have multifactorial etiologies of the disease, most centers are very aggressive in trying to treat any underlying problems such as reflux or aspiration, reactive airways disease, or obstructive sleep problems before beginning pulmonary vasodilator therapy. We have seen some impressive responses in the child with bronchopulmonary dysplasia. The difficulty for most of us is that a lot of children come to us already on therapy, so we need to try to decide when to stop it. If the child really has a nice response over 6 months to a year and the echo looks normal and the BNP is normal and the child is doing well, we'll stop therapy and then consider a repeat catheterization several months later to be sure that there's been resolution.

Dr Beghetti:

I think the lung disease group is probably underdiagnosed for the moment. I think there are some data confirming this in the current pediatric registries. I'm not sure that all of these patients are really addressed for this particular problem, because they are not always referred to the centers that are able to diagnose the pulmonary vascular problem in this population; and, as Dunbar said, that's why they really need to have clearly overt problems to be sent to the PH centers, and usually are already on treatment. What we should really know is the percentage of, for example, premature babies that will have PH associated with bronchopulmonary dysplasia.

Dr Rosenzweig:

I agree. And I think you're right this is a group that often doesn't make it to the major centers. And it's also the group that probably, as you say, could wean off therapy at some point. I sure would hate to have children on therapy longer than they need to be, and so these children do need to be followed closely in terms of resolution of the pulmonary hypertension and the possibility of weaning them off as well.

Another question for the panel: Are you using inhaled prostanoid agents more so for the children with chronic lung disease because of the issue of V-mismatch or are there any other particular groups— Jeff, you mentioned the Eisenmenger patients—where you favor using inhaled prostanoids?

Dr Feinstein:

For me it ends up being mostly the Eisenmengers. We have not used a lot of inhaled therapies. I know there is a lot more experience out there than we have, but we have not used it in the neonates with chronic lung disease. Dunbar, you probably have some experience with that and some of the side effects as it relates to pulmonary function. But we have not used much of it except in the Eisenmenger's patients, where I like it actually quite a bit.

Dr Ivy:

Most of our patients with BPD are too young for inhaled therapy. In the acute setting there is interest in inhaled prostanoids and there are ongoing studies. We tend to use the inhaled prostacyclins as the third agent in a child over 5 or 6 who is on 2 therapies and may not have right heart failure, but still has exercise limitation and the parents are very hesitant to consider subcutaneous or IV therapy.

Dr Beghetti:

Yes, I agree. My opinion is that these inhaled therapies are probably better in the acute setting currently than for chronic use because of the difficulties delivering the drug to this population. Also, in the data that we published together with some of the centers in the US, that Dunbar published in the *Journal of the American College of Cardiology*, you see that clearly that's an add-on therapy to 1 or 2 others but rarely a single therapy approach.

Dr Humpl:

We had very similar experiences, but we have use inhaled therapies, eg, prostacyclin, if we had a compliant patient but the parents do not want to go with intravenous therapy for individual reasons. This reflects only a very small number of patients; however, it may work for some.

Dr Rosenzweig:

I'm going to ask one final question: How do you envision the next 5 to 10 years moving ahead, and what are the top priorities for us in terms of treating pediatric PAH? Also, are there any other novel agents or pathways that you think are particularly promising for children in the future?

Dr Beghetti:

I can start. I see 3 points. First is that we should better use the drugs that we have and be sure that we have reached the maximal potential of the drugs we have, because I think we can still improve that. Second, I think we should find a way to define the point that we raised about which patient may respond to one drug versus another. This is definitely something that is very important. Third, there is currently a new pathway that will be studied in children if the adult study is positive; it is the pathway of the PDGF inhibitors. So, I do not see in the pipeline currently a completely new drug that should change everything in the next 3 to 5 years.

Dr Ivy:

We really need to optimize current therapy by determining the appropriate dosing and to define better endpoints for clinical trials in children. The 6-minute walk test is not very reliable as a primary endpoint. Time to clinical worsening may be a very good endpoint, but the trials will be very long in duration. We need to develop goals of therapy so that we can more rationally decide when to add an additional drug. Hopefully our registries will allow us to come up with some of these endpoints, which I think are going to be different from adults.

Dr Rosenzweig:

Thank you, Jeff?

Dr Feinstein:

From my perspective, I completely agree with Maurice and Dunbar, and we're all talking about the same general thing, which is it's time to add even more science to what we do. A lot of what we do is anecdotal. A lot of what we do is personal preference. And I think that in the next 3 to 5 to 10 years it's going to be critical to add science and add quantitative values—whatever those values happen to be—to what we do to try to actually be able to look back 10 years from now and say, “Okay, here's what we've been doing; here are the data; here's what works and here's what doesn't work.” My biggest fear is that we continue to march along the “I do what feels right” path and then not have the data to be able to make informed decisions 5 or 10 years from now. I think, as Dunbar and Maurice both mentioned, the ability to find rational endpoints, the ability to find trials that are going to answer key questions, the use of registries, and some version of a protocol on how to use therapies is going to be critical.

Dr Humpl:

As Maurice mentioned earlier, the TOPP registry may be able to answer some of the questions as we have a more “global” way to look at diagnosis and treatment in children with pulmonary hypertension. This relates to mono or combination therapy as well as access to drugs and follow-up. And again, defining clear endpoints for our patient population is vital.

Dr Rosenzweig:

I would support these comments. It seems that we all have similar concerns. It's a theme that is worldwide when it comes to treating children with PAH. It sounds like some of the highlights of our discussion are trying to better understand how to optimize current therapies and trying to define how we assess the children, because they are not necessarily the same endpoints as far as clinical trials or even goals of therapy as we have for adults. We are trying to achieve, as Dunbar said earlier, decades of wellness and survival and so we do tend to be more aggressive in the children, but as Jeff said, we need the science to support the decisions and hopefully that will be a focus of the future.

I want to thank you all for your participation in this panel discussion. This has been a wonderful discussion and undoubtedly very valuable for the pediatric PAH community.

Comments

Related Resources

- Pulmonary Hypertension In Children With Sickle Cell Disease
- TOPP: The First Multinational Registry in Pediatric Pulmonary Hypertension
- Hemodynamic Characterization at Diagnosis in Children with Pulmonary Hypertension (PH): Insights from the Global TOPP Registry (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension)
- Quality of Life and Parental Functioning in Pediatric Pulmonary Hypertension
- Acute Hemodynamic Effects of Inhaled Treprostinil and Nitric Oxide in Children with Pulmonary Arterial Hypertension.

Vallerie McLaughlin, MD

Kim A Eagle Endowed Professor of Cardiovascular Medicine
University of Michigan, Ann Arbor, Mich.
Distinguished Advisor, PHA Scientific Leadership Council

801 Roeder Road, Ste. 1000, Silver Spring, MD 20910
301-565-3004 | PHAOnlineUniv@PHAssociation.org