One on One Interview

Seeking a Consensus on PH: Challenges Left by the Venice Symposium

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The Venice Symposium was a unique assemblage of physicians and scientists representing a variety of disciplines ranging from pulmonary medicine to cardiology, rheumatology, pathology, genetics, molecular biology, and surgery, all with a common interest in pulmonary vascular disease. The state-of-the-art overviews provided not only a perspective of where we are and how we got there, but also glimpses into the future of new and exciting directions in basic and translational research. The opportunity for basic investigators, clinical researchers, and representatives from industry to interact and explore new avenues to pursue will undoubtedly lead to fruitful collaborations and innovative approaches to the understanding, and ultimately the cure, of hypertensive pulmonary vascular disease. It is remarkable that, despite the attendance by several hundred individuals, a consensus on major issues was reached, including the adoption of a revised nomenclature. - Lewis Rubin, MD, University of California at San Diego.

Commentary on the Venice Meeting, featuring an interview of Nazzareno Galiè, MD, one of the organizers of the Third World Symposium on Pulmonary Hypertension. Victor Tapson, MD, is Editor-in-Chief of *Advances in Pulmonary Hypertension*.

Dr Tapson: Nazzareno, would you give us an overview of this meeting and how you would compare it with other sessions?

Dr Galiè: This meeting was a challenge because we tried to combine the concepts of the Evian meeting based on task force discussions with more conventional scientific presentations in front of a larger audience. It was a challenge because the plenary presentations to a wide audience were really prepared during the task force meeting. This was difficult because the time allowed was not infinite and we forced competitive scientists with different ideas to reach a consensus on "hot" topics and to have this consensus written and definite before the plenary presentation. The real success was this: we forced and we obtained this consensus between the task force members because during the plenary presentation only attending people asked additional questions. There was not additional discussion among the task force members. This means that the consensus was reached.

Dr Tapson: Did you think there were any big surprises or controversies with the meeting that were difficult to resolve?

Dr Galiè: I don't think so. There were challenges because in some task forces—for example, genetics, we put together people who were "scientifically" competing among themselves for the last 3 or 4 years. This has been important because they had consensus to collaborate, to define some common research strategies for the future. This was another success. Another surprise was the consensus we reached on the treatment algorithm. I thought it would have been very difficult to get a consensus between people in Europe and the United States because the approved drugs and experiences are somewhat different. Nevertheless, we reached a good compromise in the treatment algorithm.

Dr Tapson: Despite initial differences, it's impressive to make those agreements when practices can be quite different. There are certain obvious things like the use of inhaled prostacyclin, iloprost in some countries. Were there any international differences that were really significant in terms of diagnosis and treatment?

Dr Galiè: The main difference is that in the United

States subcutaneous prostacyclin (treprostinil) is approved whereas this is not approved in Europe. And in contrast, iloprost is already approved in Europe. It was adopted as "off-label" use in some German-speaking countries. Now we have the official approval of the EMEA (European Agency for Evaluation of Medicinal Products) that will become fully operative in a few months. In the United States you have the availability of subcutaneous treprostinil that we have utilized only in patients enrolled in clinical trials. The lack of availability of treprostinil in the clinical setting limits our experience with the use of this drug. This is the main difference. Otherwise, epoprostenol is approved in most European countries, as is bosentan.

Dr Tapson: Did you get a sense from the task force on pathology and pathobiology that there is any one disease mechanism that people seem to agree is the most important or that there is any trend in priorities of the most important mechanism?

Dr Galiè: No, we didn't find a particular mechanism that can be considered more important than any other. We have the problem related to the endothelial dysfunction, to all the changes in the NO, prostacyclin, or endothelin pathways. We have the serotonin hypothesis. This is coming back because of the genetics. Serotonin transport can explain some differences in the development of pulmonary hypertension in subgroups such as those with HIV or people with portal pulmonary hypertension. I think also the TGF-beta pathway has been studied a lot because of the mutations found on that type of receptor. But I haven't found a pathway that has been more explored than any other.

Dr Tapson: So the concept of combination therapy is still going to be important in the future?

Dr Galiè: Yes, this is the rationale for the combination therapy. It is linked to the multiple changes in the different pathways. The concept of combination therapies is quite complex because you combine drugs but you also can combine side effects. We cannot forget that all the drugs we are using in pulmonary hypertension are also systemic vasodilators. So you combine many systemic vasodilators and this combination may be detrimental for blood pressure. In any case, this is a problem that can be addressed by an appropriate dosing and timing strategy.

Dr Tapson: Along the lines of treatment, one of the tough topics for me has been the timing of transplantation. Do you think we came to any more consensus?

Dr Galiè: This is another challenge that is linked to the length of the waiting list. If we could rely on a definite mean time for the waiting list (for example 6 months) we could wait until the patient's condition has deteriorated to the level at which the expected survival is approximately 6 months. But this is not the case. You know that the waiting list is usually longer than 12 months and up to 18 to 24 months. This is why it is difficult to include in a treatment algorithm the lung transplantation intervention. How can you decide to put a patient on a waiting list 18 to 24 months before the transplantation? Anything can happen in 18 to 24 months. Despite this, the long-term experience with Flolan published recently by Vallerie McLaughlin (Chicago) and by Olivier Sitbon (Paris) showed that the people who have not shown an adequate hemodynamic or exercise capacity improvement after 3 to 4 months of therapy need to be listed for lung transplantation. For example, if the patient cannot walk more than 350 meters, he or she should be considered for listing for lung transplantation because this is a negative prognostic factor. This is probably what we will implement in the future. Maximized medical treatment, including combination therapy. If you cannot obtain a good hemodynamic profile and an exercise capacity above a defined level, they are likely candidates who should be listed.

Dr Tapson: Let's backtrack for a second. In terms of genetics, do you have a sense of who should be tested for BMPR-2 mutations? Do you test families or do you have a sense of what we should do?

Dr Galiè: I don't think we have a consensus about this. It's still a matter of research. Genetics is still a research tool, not something you can use in clinical practice. Even if you identify a mutation in family members who do not have pulmonary hypertension, you do not know if they will ever develop pulmonary hypertension. And in any case, if you tested such patients who are otherwise healthy and you reported to them that they have the mutation you can completely change their lives. For scientific and ethical reasons, we believe that genetic testing does not currently play a role in clinical practice for pulmonary hypertension.

Dr Tapson: That seems to be the consensus of most. It sounds like most people think we should be careful about how we're using genetic testing at this point. It was a fantastic meeting. What does the future hold?

Dr Galiè: We look forward to the proceedings being published. We will not have another meeting for some time. It's like the Olympics. We need to wait maybe another 4 years. ■