**Transcript Details**
This is a transcript of an educational program accessible on the ReachMD network. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/when-were-oral-ppas-considered-for-pah-patients-in-common-clinical-scenarios/11479/

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When Were Oral PPAs Considered for PAH Patients in Common Clinical Scenarios?

Announcer:
You're listening to ReachMD. This Medical Industry Feature, titled "When Were Oral PPAs Considered for PAH Patients in Common Clinical Scenarios?" is sponsored by Actelion.

Here is your host, Dr. Jennifer Caudle.

Voice over (VO):
UPTRAVI® (selexipag) is indicated for the treatment of pulmonary arterial hypertension (or PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).[1]

Concomitant use of strong inhibitors of CYP2C8 (for instance, gemfibrozil) with UPTRAVI is contraindicated.[1]

The Prostacyclin International Expert Panel was not a consensus conference such as one held by a task force convened for the purpose of developing treatment guidelines. The Prostacyclin International Expert Panel opinion survey statements are not intended to be formal treatment guidelines or recommendations, and survey results presented here must be validated with rigorous prospective studies.[1] **The Prostacyclin International Expert Panel opinion survey statements cannot replace assessment and/or clinical decision-making by a qualified healthcare practitioner for an individual patient. These statements do not address all possible clinical situations, nor do these statements account for additional individual patient factors not specifically stated.**[2]

Funding for the Prostacyclin International Expert Panel was provided by Actelion to support the use of independent providers of Delphi methodology expertise and nominal group technique, survey creation, data analysis, medical communication, and meeting management. Actelion played no role in the literature search and analysis, development of surveys used to gather consensus, or data analysis. No Actelion employees were present at the face-to-face meeting during which consensus statements were finalized. The current manuscript was drafted, critically reviewed, and edited solely by the authors with support from an independent professional medical communications agency. Actelion reviewed the final manuscript only to ensure accuracy of treatment background information; no edits were made to the manuscript based on this review.[2]

Dr. Caudle:
Pulmonary arterial hypertension, or PAH, is a serious, progressive disease with a variety of etiologies and has a major impact on patients' functioning as well as their physical, psychological and social wellbeing. There is currently no cure for PAH, and it is often fatal. Treatment of PAH has evolved substantially over the past two decades and varies according to etiology, functional class, hemodynamic parameters and other clinical factors.[3,4]

This is ReachMD and I'm your host, Dr. Jennifer Caudle. Joining me from Los Angeles is Dr. Victor Tapson, professor of medicine at Cedars-Sinai Medical Center. Dr. Tapson is here to discuss results from the Prostacyclin International Expert Panel Consensus survey on common clinical scenarios in which they considered adding oral prostacyclin pathway agents, or P-P-As, in patients with P-A-H. Dr. Tapson was a panelist and co-author of the publication and serves as a paid consultant for Actelion Pharmaceuticals US, Inc. Dr.

Tapson, thank you so much for being with us today.

Dr. Tapson:
Thank you for having me, Dr. Caudle.

Dr. Caudle:
So, what was the objective and the purpose of the panel, and what was your personal interest in being involved?

Dr. Tapson:
Well, the original question we set out to answer was broadly when to consider oral P-P-As, that is, prostacyclin pathway agents, in adult patients with P-A-H. But after the group's initial input into the presurvey, the focus was narrowed to look at only functional class II and functional class III PAH patients on dual background therapy. There are a number of data out there in the medical literature that look at different forms of oral PPA therapies in the management of PAH. Most clinicians tend to first use a phosphodiesterase inhibitor, a PDE-5 inhibitor, and endothelin receptor antagonists or ERA in patients and the next agent's usually an oral PPA, which we have UPTRAVI or selexipag and oral treprostinil as approved therapies. So, based on a detailed literature review and our collective input we summarized available published evidence, ranked clinical factors and then used these factors to develop these clinical scenarios and we evaluated the clinical scenarios using Delphi methodology in a face-to-face meeting, which resulted in a total of 14 consensus opinions in which the addition of oral PPAs to an ERA and PDE-5 inhibitor was considered. So, I was personally interested in being part of this project, this, very seasoned group of physicians, drawing on our long-term clinical experiences with these folks, and many physicians often have limited time, so these consensus opinions really provide insights from those of us who have been treating PAH patients for a long time and offer a starting point for further investigation.

VO:
Warnings and Precautions associated with UPTRAVI include Pulmonary Veno-Occlusive Disease (PVOD). Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue UPTRAVI.[1]

Adverse reactions more frequent on UPTRAVI than on placebo by ≥3% are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia, anemia, decreased appetite, and rash. These adverse reactions are more frequent during the dose titration phase. Hyperthyroidism was observed in 1% of patients on UPTRAVI and in none of the patients on placebo.[1]

Dr. Caudle:
Nineteen physicians participated in the panel. So, can you tell us about the collective clinical experience this panel had.

Dr. Tapson:
Well, it was a very qualified international panel with a lot of experience with patient care and research, and beyond the US and we had representation from other countries: Ireland, Canada, and France among others, so, to kind of give you a sense of the collective experience, several of us were involved way back in the Intravenous Epoprostenol (Prostacyclin) study that we published in The New England Journal in 1996. So, these are people that really know this disease and have a significant amount of background and clinical experience. The depth of knowledge of the participating physicians was really important to be able to rank these 1,620 clinical scenarios and come to consensus about when oral PPAs might be considered for functional class II and III PAH patients on dual background therapy.

Dr. Caudle:
I have to say, that's actually – it's quite impressive. Could you describe the methodology used by the panel to form the consensus opinions.

Dr. Tapson:
Sure. So, we ranked in descending order of importance the clinical factors we typically use to make routine treatment decisions regarding, the initiation of oral PPAs. So, these factors were then used to develop clinical scenarios about patients who were on an ERA and PDE-5 inhibitor with functional II or III – functional class II or III symptoms. And we evaluated the clinical scenarios by completing two rounds of Delphi surveys and utilizing the nominal group technique during a face-to-face meeting. And I think the face-to-face meeting really added to the validity of the method. I think it helped improve the participation among the authors and created an accountability to keep us all in – on track to achieve final consensus opinions and, as I mentioned, there were quite a lot of clinical data, so focus and commitment to all the detail was really important.[2]

In the first Delphi round, we evaluated 1,620 clinical scenarios and assigned each scenario a score from one to nine evaluating the risk-to-benefit ratios. This is a really rigorous approach to the literature search and analysis. And in Delphi round 2, we determined which clinical scenarios met the predetermined threshold for preliminary consensus and advanced to a face-to-face meeting at that point. And

we used the nominal group technique to obtain consensus on the draft consensus opinions, developed based on Delphi round 2, and each draft consensus opinion was discussed and voted on using a computerized system.

In terms of criteria, we looked at the addition of oral PPAs to dual background therapy in two different patient groups, including idiopathic, heritable, repaired congenital defect, and drug or toxin-induced PAH, which was considered one etiological grouping, IPAH+, and then also, patients with connective tissue disease associated PAH or PAH-CTD. And, so, patients with functional class II and III symptoms were looked at in both of these two groupings.[2]

Dr. Caudle:
The panel was asked to rank factors that they used to make routine treatment decisions regarding the addition of oral PPAs to dual background therapy. What was the panel's collective thinking around this?

Dr. Tapson:
Well, to create the scenarios, we ranked clinical factors that are typically used to make routine treatment decisions regarding the treatment or the use of oral PPAs with the following considered in descending order of importance within each functional class, including hemodynamics, PAH-associated hospitalization within the prior six months, right ventricular function, BNP or NT-proBNP levels, and six-minute walk distance. And these factors were then used to develop clinical scenarios evaluated in the Delphi survey for patients with either IPAH+ or PAH-CTD who were on an ERA and PDE-5 inhibitor.

Dr. Caudle:
Now to the results of the survey. In which common clinical scenarios did the authors consider adding UPTRAVI, an oral PPA? Were there any surprises with this?

Dr. Tapson:
Well, for the IPAH+ patients, we considered adding UPTRAVI to dual oral ERA PDE-5 inhibitor therapy for the following clinical scenarios. I'll first mention four for the IPAH+ patients. Patients with functional class II symptoms, low-risk hemodynamics and hospitalization for PAH within the last six months, or if they'd not been hospitalized and have moderate to severe RV dysfunction. Next, patients with functional class II symptoms and intermediate-risk hemodynamics, irrespective of other factors. And then patients with functional class III symptoms and low-risk hemodynamics, irrespective of other factors. And, finally, patients with functional class III symptoms, intermediate-risk hemodynamics, and no hospitalization for PAH within the last six months, or if they'd been hospitalized and had normal or mildly impaired RV function.

Now, for the PAH connective tissue disease patients, we considered adding UPTRAVI to dual oral ERA PDE5 inhibitor therapy in these scenarios. Patients with functional class II symptoms, low-risk hemodynamics, and hospitalization for PAH within the last six months, or if they'd not been hospitalized and had any degree of RV dysfunction and abnormal BNP or NT-proBNP levels. Next group was patients with functional class II symptoms and intermediate-risk hemodynamics, irrespective of other factors. And then patients with functional class III symptoms and low-risk hemodynamics, and hospitalization for PAH within the last six months, or if they'd not been hospitalized and have at least one of the following: abnormal RV function, abnormal BNP or NT-proBNP levels, or a six-minute walk distance at or below 440 meters. And then, finally, patients with functional class III symptoms, intermediate-risk hemodynamics, and hospitalization for PAH within the last six months and normal or mildly impaired RV function, or if they'd not been hospitalized within the last six months.

There was one consensus opinion in which prostacyclin therapy, that is parenteral prostacyclin therapy, was considered the preferred treatment option for IPAH+ or PAH connective tissue disease on dual oral therapies, and those were the patients with high-risk hemodynamics, irrespective of any other factors.

Dr. Caudle:
Overall, in your opinion, what is the most important aspect of these consensus opinions for the PAH and medical community?

Dr. Tapson:
Well, in my opinion, I believe these consensus opinions may help provide additional insights for physicians treating patients with PAH. There's great variability in practice when considering oral PPAs and while individual factors should be considered, these opinions may offer further perspective to determine when an oral PPA like UPTRAVI may be appropriate. Though these consensus opinions are not Level 1 evidence, they provide a perspective into clinical scenarios when adding an oral PPA in those patients currently on dual background therapy. It's important to note that the opinions are not considered treatment guidelines and can't replace assessment or clinical decision making by a qualified physician. They're opinions only and the results in the publication must be validated with rigorous prospective studies.

VO:

Important Safety Information Continued

UPTRAVI drug interactions include CYP2C8 inhibitors and CYP2C8 inducers. Concomitant administration with gemfibrozil, a strong inhibitor of CYP2C8, doubled exposure to selexipag and increased exposure to the active metabolite by approximately 11-fold. Concomitant use of UPTRAVI with strong inhibitors of CYP2C8 is contraindicated.[1]

Concomitant administration of UPTRAVI with clopidogrel, a moderate inhibitor of CYP2C8, had no relevant effect on the exposure to selexipag and increased the exposure to the active metabolite by approximately 2.7-fold. Reduce the dosing of UPTRAVI to once daily in patients on a moderate CYP2C8 inhibitor.[1]

Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase UPTRAVI dose, up to twice, when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped.[1]

Recommended starting dose is 200 micrograms twice daily. Tolerability may be improved when taken with food. Increase by 200 micrograms twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 micrograms twice daily. If dose is not tolerated, reduce to the previous tolerated dose.[1]

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose is 200 micrograms once daily. Increase by 200 micrograms once daily at weekly intervals, as tolerated. Avoid use of UPTRAVI in patients with severe hepatic impairment (Child-Pugh class C).[1]

When co-administered with moderate CYP2C8 inhibitors (for example, clopidogrel, deferasirox and teriflunomide), reduce the dosing of UPTRAVI to once daily. Revert back to twice daily dosing frequency of UPTRAVI when co-administration of moderate CYP2C8 inhibitor is stopped.[1]

UPTRAVI tablet strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 micrograms.[1]

Please see full Prescribing Information at www.uptravihcp.com.[1]

Dr. Caudle:
Well, that's a great way to round out our discussion on this topic. Dr. Victor Tapson, thank you so much for helping us better understand the consensus opinions from the Prostacyclin International Expert Panel.

Dr. Tapson:
Well, thanks again for having me, Dr. Caudle.

Announcer:
This program was brought to you by Actelion Pharmaceuticals. If you missed any part of this discussion visit ReachMD.com/PAHPerspectives. This is ReachMD. Be part of the knowledge.

**References**

[1] UPTRAVI® (selexipag) full Prescribing Information. Actelion Pharmaceuticals US, Inc.
[2] McLaughlin V, et al. *CHEST*. 2020;157(4):955-965.
[3] Howard L, et al. *Eur Respir Rev*. 2014;23:458-468.
[4] Galiè N, et al. *Eur Heart J*. 2016;37:67-119.