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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Results of an Expert Delphi Consensus Survey on Clinical Scenarios Considered When Initiating Oral Prostacyclin Pathway Agents for Pulmonary Arterial Hypertension

Announcer:
For ReachMD, this is AudioAbstracts. Today's episode is sponsored by Actelion Pharmaceuticals US, Inc.

Pulmonary arterial hypertension, or PAH, is a severe chronic disease characterized by markedly elevated pulmonary vascular resistance which, over time, can induce right heart failure. The exact cause of PAH is unknown, and while treatable, it has not been cured.[1]

Numerous innovations have improved exercise capacity and delayed the risk of disease progression for people living with this disease. There are three drug classes that target one of the three pathways in the pathogenesis of PAH: endothelin receptor antagonists, or ERAs, prostacyclin pathway agents, or PPAs, and phosphodiesterase-5 inhibitors, or PDE5 inhibitors.[2]

The objective of the PIXEL (Prostacyclin International Expert Panel) was to develop consensus opinions on clinical scenarios considered when adding oral PPA to WHO functional class II and III PAH patients on ERA and PDE5 inhibitor background therapy.[3] These opinions do not address all possible clinical scenarios nor do they account for additional individual patient factors not specifically stated. The PIXEL was not a consensus conference such as one held by a task force convened for the purpose of developing treatment guidelines. The results are not intended to be formal treatment guidelines or recommendations. The PIXEL opinions cannot replace assessment and/or clinical decision-making by a qualified healthcare practitioner for an individual patient.

This panel's report was presented at the CHEST Annual Meeting 2019.

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Consensus opinions were formed utilizing the RAND/University of California Los Angeles Appropriateness Method, which incorporates the Delphi method and nominal group technique. To create the survey, panelists ranked clinical factors that they typically use to make routine treatment decisions regarding the initiation of oral PPAs, with the following considered in order of importance (within each functional class): hemodynamics (based on thresholds defined by the 2015 European Society of Cardiology and European Respiratory Society guidelines3), PAH-associated hospitalization within the prior 6 months, right ventricular (or RV) function, BNP/NTproBNP levels, and 6-minute walk distance. These factors were then used to develop survey questions for patients with either idiopathic, heritable, drug- or toxin-induced, repaired congenital heart disease-associated PAH (all considered as one etiological group called IPAH+) or connective tissue disease-associated PAH (or CTDPAH), who were on an ERA and PDE5 inhibitor.[3]

The PIXEL showed consensus that for patients with IPAH+ or CTDPAH on dual oral therapies with high-risk hemodynamics, the treatment of choice was intravenous or subcutaneous prostacyclin, irrespective of other factors. The PIXEL then developed consensus opinions on when they considered adding marketed oral PPA UPTRAVI® (selexipag) to an ERA and PDE5 inhibitor.[3]

UPTRAVI is indicated for the treatment of pulmonary arterial hypertension (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%). Concomitant use of strong inhibitors of CYP2C8 (for instance, gemfibrozil) with UPTRAVI is contraindicated.[4]

For IPAH+ patients, the panel considered the following clinical scenarios when initiating UPTRAVI in those receiving dual oral ERA/PDE5 inhibitor therapy[3]:

1-2. Patients with functional class II symptoms, low-risk hemodynamics and hospitalization for PAH within the last 6 months; or if they have not been hospitalized and have moderate to severe RV dysfunction.
3. Patients with functional class II symptoms and intermediate-risk hemodynamics.
4. Patients with functional class III symptoms and low-risk hemodynamics.
5-6. Patients with functional class III symptoms, intermediate-risk hemodynamics and no hospitalization for PAH within the last 6 months; or if they have been hospitalized and have normal or mildly impaired RV function.

For CTDPAH patients, the panel considered the following clinical scenarios when initiating UPTRAVI in those receiving dual oral ERA/PDE5 inhibitor therapy[3]:

1-2. Patients with functional class II symptoms, low-risk hemodynamics and hospitalization for PAH within the last 6 months; or if they have not been hospitalized and have any degree of RV dysfunction and abnormal BNP/NTproBNP levels. Panelists noted that some patients in this category may benefit from parenteral therapy, specifically those with moderate-to-severe RV dysfunction and 6-minute walk distance at or below 440 meters. However, patients with CTDPAH may have difficulty managing parenteral therapy due to the necessity of manipulating pumps and a higher incidence of adverse events compared to patients with IPAH+; UPTRAVI offers an alternative therapy in such situations.
3. Patients with functional class II symptoms and intermediate-risk hemodynamics.
4-5. Patients with functional class III symptoms, low-risk hemodynamics and hospitalization for PAH within the last 6 months; or if they have not been hospitalized and have at least one of the following: abnormal RV function, BNP/NTproBNP levels, or 6-minute walk distance at or below 440 meters.
6-7. Patients with functional class III symptoms, intermediate-risk hemodynamics and hospitalization for PAH within the last 6 months, and normal or mildly impaired RV function; or if they have not been hospitalized within the last 6 months.

These expert opinions may serve as a template for future investigations, however, they must be validated with rigorous prospective studies.[3]

Warnings and Precautions associated with UPTRAVI include Pulmonary Veno-Occlusive Disease (PVOD). Should signs of pulmonary edema occur, consider the possibility of associated Pulmonary Veno-Occlusive Disease, or PVOD, if confirmed, discontinue UPTRAVI.[4]

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.[4]

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.[4]

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.[4]

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.[4]

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.[4]

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).[4]

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.[4]

UPTRAVI tablet strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 micrograms.[4]

Please see full Prescribing Information at www.uptravihcp.com.[4]

This has been a presentation of Audio Abstracts, sponsored by Actelion Pharmaceuticals. To revisit this episode and discover more about the PIXEL, visit ReachMD.com/AudioAbstracts. This is ReachMD. Be Part of the Knowledge.

References

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4. UPTRAVI® (selexipag) full Prescribing Information. Actelion Pharmaceuticals US, Inc.