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

Exploring Earlier Initiation of Treatment for Pulmonary Arterial Hypertension

Announcer:
Welcome to ReachMD. This medical industry feature, titled "Exploring Earlier Initiation of Treatment for Pulmonary Arterial Hypertension" is sponsored by Actelion Pharmaceuticals US: the marketer and distributor of UPTRAVI®, or selexipag. The following program is intended for US healthcare professionals only and is not certified for continuing medical education. Your host today is Dr. Jennifer Caudle, a paid consultant for ReachMD, and your guest is Dr. Richard Channick, who is a paid consultant for Actelion Pharmaceuticals US, Inc. Please see the full Prescribing Information at www.uptravihcp.com.

Dr. Caudle:
Pulmonary arterial hypertension, or PAH, is a progressive disease that falls under the broader category of pulmonary hypertension, or PH.[1] Newly diagnosed patients with PAH have a poor prognosis and disease progression is eventually inevitable.[2-5] Enormous strides have been made over the past two decades in advancing understanding and treatment of the disease.[2] This is ReachMD and I'm your host Dr. Jennifer Caudle. Joining me to discuss data that provides support for earlier initiation of treatment in patients with PAH is Dr. Richard Channick. Dr. Channick is a Professor of Medicine and the Director of the Pulmonary Vascular Disease Program at UCLA Medical Center.

Dr. Channick, thanks so much for being here today.

Dr. Channick:
Thanks for having me.

Dr. Caudle:
Well we are excited that you are here. You know, as a physician specializing in treating patients with PAH, can you share a little bit about the disease?

Dr. Channick:
Absolutely, so PAH, or pulmonary arterial hypertension, is a form of PH, which is pulmonary hypertension and there is a hemodynamic definition for PAH that is a mean pulmonary artery pressure of at least 25 millimeters of Mercury at rest, pulmonary artery wedge pressure, which measures the left sided pressures of less than or equal to 15, along with a pulmonary vascular resistance, which is a calculated number that's greater than 3 wood units.[3] That is the definition. Now there are many causes for PAH and one of the problems with this disease in general is that the symptoms are pretty nonspecific and can include worsening shortness of breath with exercise, chest pain, lightheadedness, even fainting and because these symptoms are often pretty mild and pretty nonspecific, and can be associated with a lot of other common conditions, misdiagnosis or delay in diagnosis is a big problem and that delay can even go on for years before the proper diagnosis is made.[4] And this is really a critical problem because, as we know, the longer it takes to make the diagnosis and start treatment, the worse the patient does.[4]

Dr. Caudle:
That is interesting. You know, let's talk a little bit about prognosis. What is the prognosis for patients diagnosed with PAH?

Dr. Channick:
Without treatment, we know prognosis is really dismal and we have known that for years. But, fortunately over the last couple of decades, we now developed multiple drugs to treat this condition that targets specific pathways within the blood vessels that cause

pulmonary hypertension and we really can target those pathways effectively. So, the prognosis has improved with the development of treatment.[3]

Dr. Caudle:
Right, and you know, to that point exactly, you know, given that the prognosis can be so poor in certain situations, what should clinicians who treat PAH be doing to help patients?

Dr. Channick:
Well I think there are several things that physicians can do. Risk assessment, I think, is a very important part of that approach, determining what risk your patient falls into[2,3] and actually a couple of different large organizations, one European Society of Cardiology and European Respiratory Society, in a document put out in 2015 really codified this, this concept of risk assessment.[3,7] This is also referred to in the Sixth World Symposium on pulmonary hypertension in 2018 and both of these documents really emphasize that treatment goals for patients with PAH really should be achieving and maintaining a patient in low-risk status[3], that it's not acceptable to wait for patients to deteriorate and take this sort of, you know, late approach in managing this disease and so this risk assessment, comprehensive risk assessment, really should look for a variety of things, like is there clinical deterioration, what is right ventricular function, biomarkers like BNP levels, exercise capacity, and these various measures really should be done at every follow-up appointment for patients. Which one to use in particular, you can debate, but any patient who you are treating and following for PAH, should have this sequential risk assessment and always looking at whether you are meeting the goals of therapy.[8]

Dr. Caudle:
Right, right.

Dr. Channick:
And in practice, what we do, is really a combination of a number of things we look at, a number of metrics. So, we assess measures of right ventricular function for instance, echocardiography, BNP levels, we look at exercise capacity, using a 6-minute walk test, so a simple test that can be done seeing how far a patient can walk in six minutes. We look at hemodynamics so we may look at what the pulmonary hemodynamics have done in response to treatment or how severe they are. We can look at functional capacity. So how limited a patient is. All of these things help us determine what our treatment regimen should be.[8]

Dr. Caudle:
That makes a lot of sense and you mentioned risk assessment, so let's talk a little bit more about that. You know, what role does risk assessment play in forming treatment decisions?

Dr. Channick:
Yeah, it plays a critical role and again, if you look at those guidelines from the ESC and ERS, with the goal of achieving low-risk status, as well as the Sixth World Symposium recommendation, that really informs treatment and so these treatments are often combination therapies used early on, additional therapies and so options like UPTRAVI or selexipag, you know is the latest in our armamentarium, and you know, I would certainly encourage clinicians to look at the full prescribing information for UPTRAVI to get more information.[3,9]

Announcer:
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 example gemfibrozil) with UPTRAVI is contraindicated. [9]

Dr. Caudle:
So, speaking about UPTRAVI. So what role can UPTRAVI play in the treatment continuum for PAH?

Dr. Channick:
Well, the role of UPTRAVI has really been developed based on the GRIPHON Trial. The GRIPHON Trial was a pivotal trial, randomized placebo-controlled trial of UPTRAVI, which is an oral prostacyclin pathway agent that works in one of the prostacyclin receptors. This was a study of over 1100 patients, about half receiving UPTRAVI and half on placebo. This in fact, was the largest randomized, multicenter, double-blind, placebo-controlled, outcomes trial ever conducted in patients with WHO Group 1, or PAH. And this trial found about a 40% risk reduction in the primary event, which was a morbidity/mortality, a composite end-point. So a 40% reduction, the

likelihood of having one of those morbidity/mortality events compared to placebo. Now, other important aspects… these patients were mostly, almost all class II and III functionally and this was a true long term study. The trial went up to 4.2 years and in fact, there was a median duration of exposure of 1.4 years. So this really did evaluate long term efficacy and safety of oral UPTRAVI in PAH.[9,10]

Announcer:
In the GRIPHON trial, the primary composite endpoint was defined by time to first morbidity/mortality event up to the end of treatment, including death or hospitalization for PAH, or initiation of parenteral prostanoid therapy or chronic oxygen therapy, or PAH worsening resulting in need for lung transplantation or balloon atrial septostomy, or other disease progression based on a 15% decrease from baseline in 6-minute walk test plus worsening of functional class or need for additional PAH-specific therapy. At the baseline, the majority of enrolled patients (80%) were being treated with a stable dose of endothelin receptor antagonist (ERA) monotherapy (15%), a PDE5 inhibitor (32%), or both (33%). Primary endpoint events were captured up to the end of treatment, with 27% of the UPTRAVI group experiencing an endpoint event versus 41.6% of the placebo group.[10]

Among the trial participants, hospitalization for PAH represented the most frequently recorded primary endpoint, experienced in 13.6% of the UPTRAVI group versus 18.7% of the placebo group. Other disease progression, defined as a 15% decrease in 6-minute walk test plus worsening of functional class or need for additional PAH specific therapy, was experienced by 6.6% of the UPTRAVI group subjects compared to 17.2% of the placebo group. Death occurred in 4.9% of the UPTRAVI group versus 3.1% of the placebo group. Parenteral prostanoid or chronic oxygen therapy was needed for 1.7% of the UPTRAVI group compared to 2.2% of the placebo group. Lastly, PAH worsening resulting in the need for lung transplantation or atrial septostomy occurred in 0.2% of the UPTRAVI group versus 0.3% of patients within the placebo group.[10]

Warnings and Precautions include Pulmonary Veno-Occlusive Disease (PVOD). Should signs of pulmonary edema occur, clinicians should consider the possibility of associated Pulmonary Veno-Occlusive Disease, or PVOD, and if confirmed, discontinue UPTRAVI.[9]

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.[9]

Dr. Caudle:
Is there any additional data exploring the use of UPTRAVI in patients with PAH?

Dr. Channick:
Yes there is. So we did a post-hoc analysis, of that GRIPHON Trial, where we explored the association between time from diagnosis and treatment response, and so it is important to point out that these subgroups weren't prespecified for evaluation of their primary end-point, this did not compare patients treated within six months with patients treated after six months directly, so we need to consider sample size, and really approach these results with caution. But having said that, we categorize patients on time from diagnosis at baseline using the six-month threshold. So patients treated earlier were defined as those who got treatment within six months of the diagnosis and those who were treated later after six months.[11]

One of the things we looked at were what were the characteristics of those two groups and how did they differ? Interestingly, when we looked at the patients treated within six months of diagnosis, we found them to be younger, more likely to be class II, either to be treatment naïve, in other words on no background therapy, or just a PDE5 inhibitor monotherapy, and interestingly, more likely to be from Asia or Eastern Europe compared to the overall GRIPHON population. The patients treated after six months conversely were more likely from Western Europe, Australia, North America and had a longer mean time from diagnosis compared to the overall population.[11]

Patients who had PAH who received UPTRAVI within six months of diagnosis, had a 55% risk reduction in morbidity/mortality end-point compared to placebo, while patients receiving treatment after six months had a 30% risk reduction versus placebo. Now we adjusted these results for functional class, sex, race, age, etiology of PAH, geographical region, six minute walk distance, NTproBNP, what we found was that the adjusted risk reduction was 53% in patients treated earlier and 26% in those who were treated later, again compared to placebo. So pretty, pretty impressive findings.[11]

Announcer:
Irrespective of time from diagnosis, the most frequently reported adverse events for UPTRAVI-treated patients were headache, diarrhea, and nausea. No differences in safety profile were observed between the two subgroups.[11]

Dr. Caudle:
Excellent. So Dr. Channick, you know, what would you consider the most clinically significant implication from this discussion and really

for the future prognosis for patients with PAH?

Dr. Channick:
I think, again, it gets down to proper diagnosis and risk assessment. Risk assessment really is essential for guiding the decision making and how we treat PAH patients, regardless of what tool one uses, this sequential repeated risk assessment.[2,3,7] I think the fact that there are increasing data showing medications like UPTRAVI can delay disease progression in PAH, to me is very exciting as we continue to progress in this condition and this very serious disease and unfortunate patient population.[9-11]

Dr. Caudle:
Understood. Well, you know, that is a really great way to round out our discussion on this topic and I would like to really thank you, Dr. Channick, for really helping us understand better considerations for earlier initiation of treatment in functional class II and III patients with PAH. Dr. Channick, it was great speaking with you today.

Dr. Channick:
My pleasure.

Announcer:
Please note: In this post-hoc review of the GRIPHON trial, results were adjusted for the following baseline covariates: PAH therapy (categorized as yes/no), WHO functional class, sex, race, age (categorized as <65/≥65 years), etiology, geographical region, 6-minute walk test and NTproBNP: Hazard Ratio 0.47 (95% confidence interval) (0.33-0.65) in those treated earlier and 0.74 (95% confidence interval) (0.57-0.96) in those treated later (versus placebo).[11]

In the subgroup treated within six months of diagnosis, 207 patients received UPTRAVI while 197 patients received placebo. 27% of the UPTRAVI group experienced an endpoint event compared to 50.3% of the placebo group, with hospitalization for PAH representing the most frequently reported event experienced in 11.6% of the UPTRAVI group versus 19.8% of the placebo group. Other disease progression was reported in 7.2% of the UPTRAVI group compared to 24.4% of the placebo group. Death occurred in 6.8% of the UPTRAVI group versus 5.1% of the placebo group. Parenteral prostanoid or chronic oxygen therapy was needed for 1.9% of patients from the UPTRAVI group compared to 1% of patients from the placebo group. No patients from either group experienced PAH worsening resulting in the need for lung transplantation or atrial septostomy.[12]

In the subgroup treated after six months of diagnosis, 367 patients received UPTRAVI while 385 patients received placebo. 26.7% of the UPTRAVI group experienced an endpoint event compared to 37.1% of the placebo group, with hospitalization for PAH representing the most frequently reported event experienced in 14.7% of the UPTRAVI group versus 18.2% of the placebo group. Other disease progression was reported in 6.3% of the UPTRAVI group compared to 13.5% of the placebo group. Death occurred in 3.8% of the UPTRAVI group versus 2.1% of the placebo group. Parenteral prostanoid or chronic oxygen therapy was needed for 1.6% of patients from the UPTRAVI group compared to 2.9% of patients from the placebo group. 0.3% of patients from the UPTRAVI group versus 0.5% of patients from the placebo group experienced PAH worsening resulting in the need for lung transplantation or atrial septostomy.[12]

Adverse reactions notably different from the overall population were also monitored in two subgroups of patients: those treated within six months of diagnosis, and those treated beyond six months of diagnosis. In the subgroup treated within six months of diagnosis, extremity pain was reported in 14% of UPTRAVI users versus 2% of placebo users. Arthralgia was also reported in this subgroup, experienced in 12.6% of the UPTRAVI group versus 5.6% of the placebo group.[12]

Within the subgroup of patients treated after six months of PAH diagnosis, 48.1% of patients receiving UPTRAVI experienced diarrhea compared to 21.5% from the placebo group. Jaw pain was reported by 31% of participants in the UPTRAVI group versus 7.6% of the placebo group.[12]

These adverse reactions are only those occurring ≥3% on UPTRAVI compared to placebo and with a placebo-corrected difference of ≥3% in both those treated within six months of diagnosis, and those treated beyond six months of diagnosis versus the overall population.[12]

Irrespective of time from diagnosis, the most frequently reported adverse events for UPTRAVI-treated patients were headache, diarrhea, and nausea. No differences in safety profile were observed between the two subgroups.[11]

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 administration of UPTRAVI with strong inhibitors of CYP2C8 is contraindicated.[9]

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.[9]

Concomitant administration with an inducer of CYP2C8 and UGT 1A3 and 2B7 enzymes (rifampin) halved exposure to the active metabolite. Increase dose up to twice of UPTRAVI when co-administered with rifampin. Reduce UPTRAVI when rifampin is stopped.[9]

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.[9]

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).[9]

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.[9]

UPTRAVI tablet strengths: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 micrograms.9

Please see the full Prescribing Information at www.uptravihcp.com.[9]

Announcer:
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