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Exploring Risk Assessment Strategies and a Treatment Option for Pulmonary Arterial Hypertension

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Exploring Risk Assessment Strategies and a Treatment Option for Pulmonary Arterial Hypertension” is sponsored by the Janssen Pharmaceutical Companies of Johnson & Johnson, the marketer and distributor of UPTRAVI® (selexipag). Please see the full Prescribing Information at www.uptravihcp.com. The following program is intended for US healthcare professionals only and is not certified for continuing medical education. Our guest today is Dr. Raymond Benza, who is a paid consultant for the Janssen Pharmaceutical CompaniesofJohnson & Johnson. Before we get started, let’s review some Important Safety Information about UPTRAVI.

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.[1]

Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.[1]

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 example, gemfibrozil) with UPTRAVI is contraindicated.[1]

And, now here is your host Dr. Paul Doghramji, a paid consultant for ReachMD.

Dr. Doghramji:
Pulmonary arterial hypertension, or PAH, is a rapidly progressive disease with no known cure.[2-4] While the need for timely and regular risk assessment in PAH is widely acknowledged, real-world evidence indicates that risk assessment in the clinical setting may be suboptimal for some physicians given barriers, including complexity of tools and invasive procedures.[5,6] But could a recently developed risk assessment tool help reduce this burden?

This is ReachMD, and I’m Dr. Paul Doghramji. Joining me to discuss a non-invasive PAH risk stratification tool, referred to as REVEAL Lite 2.0, is Dr. Raymond Benza, who’s a professor of medicine at The Ohio State University Wexner Medical Center.

Dr. Benza, thanks for being here today.

Before we dive into the specifics of REVEAL Lite 2.0, let’s talk about the goal of risk assessment in PAH. Can you explain why this is so important?

Dr. Benza:
That’s a really great way to start off this conversation. Although we’ve done a great job with medications and management, we need to be able to risk stratify patients in order to characterize their disease better, to know how to intelligently implement their medications, and know when to refer them for lung transplantation. For patients with PAH, risk assessment is necessary to evaluate disease progression, and inform treatment decisions based on patients’ prognosis.[2,7]

According to the 2015 European Society of Cardiology and European Respiratory Society Guidelines, also referred to as the ESC/ERS Guidelines, and proceedings of the sixth World Symposium on Pulmonary Hypertension in 2018, the overall treatment goal for PAH patients is achieving and maintaining low-risk status, which has been associated with improved outcomes.[2,7]

A low-risk status means that the risk of any individual patient for succumbing to this disease is less than 5% at one year.[2] The 2015 ESC/ERS Guidelines stress that risk assessment should be made at PAH diagnosis, and at regular intervals during follow- up.[2] The results of these assessments should be used to guide management, including treatment decisions.[2]

Findings from the Registry to Evaluate Early and Long-term PAH Disease Management, or REVEAL, which was a registry developed in the United States, has suggested that a variety of variables, including functional class, is significant in ascertaining to predict risk.[8]

For example, Functional Class II patients are as likely to clinically worsen within one year, as is Functional Class III patients, 43% versus 45%, respectively.[9]

Therefore, frequent reassessment on all patients with PAH is essential towards escalating treatment as indicated to help delay disease progression.[7]

Dr. Doghramji:
So now that we know what the goal is, Dr. Benza, what can you tell us about the history of risk assessment in PAH and how the strategies have evolved over time?

Dr. Benza:
I think what we have learned over the last two decades is that not any single variable really paints the whole picture.[2]

The first risk assessment algorithm that we use to predict prognosis was derived purely from hemodynamic data, collected by the National Institutes of Health Primary Pulmonary Hypertension Registry Investigators.[10] This was the first attempt to really give us a pattern on how patients survived with this disease. Subsequently, almost a decade later, additional information showed that collections of variables may be better than singular variables in predicting risk.[8] And based on this sentinel paper, investigators in the REVEAL Registry, from which I was part of, developed the REVEAL risk calculator, and this was derived from a registry, of over 3,000 patients.[8,9]

More recently, investigators have developed additional risk assessment strategies, using primarily newly diagnosed patients, and these came from several European registries: from Sweden, which was the Swedish Pulmonary Arterial Hypertension Registry; from Germany and other European countries; from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension or COMPERA; and then from the French Pulmonary Hypertension Registry.[12-14] And these risk assessment strategies are made up on the basis of thresholds that were defined in four to eight variables and that were published in a table in the 2015 Guidelines.[2]

Now, we also came up with a refined calculator based on the original REVEAL calculator I mentioned earlier. And it was always our purpose, when developing that original US calculator, that periodic refinements, including the reassessing of cut points, and adding the number of points assigned to existing variables, and perhaps adding new variables that came out in the literature, was always built into that progression. This led to the development of the REVEAL 2.0 calculator, which estimates PAH prognosis by assigning scores to thirteen variables.[15]

Now to help expedite risk assessment in the clinical setting, we tried to develop simple calculators, based on the original REVEAL 1.0 and 2.0 calculators, and these were called the REVEAL Lite 1 and REVEAL Lite 2 calculators.[16] Both are validated using validated variables from the REVEAL 2.0 calculator, but in an abridged form.[16] What I mean by this is we only use the modifiable factors that were in REVEAL 2.0 and those factors that can be easily collected at every clinic visit.[16] This is a tool that we can now use in clinic on an everyday basis.[16]

Dr. Doghramji:
So with that being said Dr. Benza, how is REVEAL Lite 2.0 different from other tools out there, and how can it improve risk-stratification in patients with PAH?

Dr. Benza:
Thank you for that question. REVEAL Lite 2.0 was developed to provide clinicians with a simplified risk calculation method that can be routinely implemented in clinical practice, where data for patients may lack and be time-constrained.[16] It provides discrimination between patients at low, intermediate and high risk, using six non-invasive variables with potential applicability to remote telehealth.[16]

It is an abridged version of the REVEAL 2.0 risk calculator that uses six, rather than thirteen, exclusively non-invasive and modifiable variables.[16] The variables include functional class, vital signs, both systolic blood pressure and heart rate, 6-minute walk distance, BNP or NT-proBNP levels, and renal insufficiency by estimating the glomerular filtration rate.[16] It was validated in a series of analyses, including Kaplan-Meier, Concordance Index, Cox Proportional Hazard Models and multi-variable analyses.[16]

Data show that REVEAL Lite 2.0 provides greater discrimination than the French and Bologna risk assessment strategies.[16] The most highly predictive parameter included in REVEAL Lite 2.0 was the BNP or NT-proBNP levels, followed by 6-minute walk distance, and functional class.[16]

However, it's important to note that the tool does have some limitations.[16] Because a derivative cohort, ie, REVEAL cohort, was used to confirm findings in REVEAL Lite 2.0, and must be validated in a non-derivative cohort, and as needed in other WHO group populations.[16]

Additionally, patients in REVEAL were treated at specialized PAH centers within the United States.[16] Therefore, our results, using data exclusively from REVEAL patients, may not be applicable to PAH patients who received treatment in different clinical settings.[16]

Dr. Doghramji:
For those just tuning in, you're listening to ReachMD. I'm Dr. Paul Doghramji, and Dr. Raymond Benza is here with me today to talk about REVEAL Lite 2.0, which is a risk assessment tool for pulmonary arterial hypertension, or PAH. This program is sponsored by the Janssen Pharmaceutical Companies of Johnson & Johnson. So Dr. Benza, now I'd like to get your perspective on the implementation of this new tool. How do you see REVEAL Lite 2.0 impacting long-term prognosis in PAH?

Dr. Benza:
Thanks very much for that question. REVEAL Lite 2.0 can be used as a relatively quick and simple method for accurately identifying patients predicted to have a low-risk status.[16]

A potential advantage of using REVEAL Lite 2.0 is, like its predecessor, REVEAL 2.0, REVEAL Lite 2.0 uses weighting of variables.[16] Weighting is achieved by assigning an integer score to a risk factor. This score is proportional to its contribution to the overall risk rating. The use of weighting improves the degree of agreement between the predicted and the observed risk.[16]

Other risk assessment tools, like the French, COMPERA, and the Bologna methods, either do not use weighting of variables, like the French or Bologna method, or use only equal weighting – COMPERA – rather than assigning different weight based on predictive value and performance by statistical model incorporated in REVEAL risk assessment tools.[16]

REVEAL Lite 2.0 may also be adopted to use in remote telehealth, especially in the current COVID-19 environment.[16] Efforts to further improve the usability of REVEAL Lite 2.0 are ongoing, including potential incorporation of the tool into electronic medical records.[16]

Announcer:
The full REVEAL 2.0 score should be used at baseline, 4-6 months and during yearly evaluations in treatment-naïve patients.[1 6] The abridged REVEAL Lite 2.0 may be used in between these time points to project trajectory using a simpler three component system.[16] REVEAL Lite 2.0 is intended to complement rather than replace REVEAL 2.0.[16]

Dr. Doghramji:
Now as we wrap up, I'd like to ask you one final question. You've explained that the REVEAL Lite 2.0 risk calculator is an abridged version of the REVEAL 2.0 calculator. With that understanding, can you tell us how the prognostic ability of REVEAL 2.0 has been investigated?

Dr. Benza:
Yes, that's a great question. I'd like to explain that particularly in two parts.

One, REVEAL 2.0 has been investigated and validated in several large registries, including the Australian and and New Zealand registry, as I mentioned.[17] But importantly, it's been also validated in several clinical trials, and one of the pivotal trials that we utilized to validate REVEAL 2.0 was the GRIPHON trial. For the sake of simplicity, I'd like to describe a bit about the GRIPHON trial.[18]

GRIPHON assessed the efficacy and safety of UPTRAVI, or selexipag, an oral selective prostacyclin receptor agonist, in 1156 patients, nearly all of which were Functional Class II or III at baseline. UPTRAVI reduced the risk of disease progression by 40% versus placebo, which was highly statistically significant, and the exposure of UPTRAVI in this trial was up to 4.2 years, with a 1.4 year median duration.[1]

As many people remember, the primary composite endpoint in GRIPHON was defined by several things, including the time of the first morbidity and mortality event, up to the end of treatment, and these events could be hospitalization for PAH, or initiation of parenteral prostacyclin therapy or chronic oxygen therapy, PAH worsening, resulting in a need for lung transplantation or balloon atrial septostomy, or other disease progression events, based on a 15% decrease in baseline, and the 6-minute walk distance, and worsening of functional

class, or a need for PAH-specific therapy or finally, death.[1] At baseline, the majority of enrolled patients were on background therapy, about 80%. 15% were being treated with endothelin receptor antagonist monotherapy, and 32% were being treated with a PDE-5 inhibitor monotherapy, and 33% were being treated with both.[1] The 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.[1]

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.[1] Other disease progression was experienced in 6.6% of the UPTRAVI group subjects, compared to 17.2% of the placebo group.[1] Death occurred in 4.9% of the UPTRAVI group versus 3.1% of the placebo group.[1] Parenteral prostacyclin or chronic oxygen therapy was needed for 1.7% of the UPTRAVI group, compared to 2.2% of the placebo group.[1] And lastly, PAH worsening, resulting in the need for lung transplant, or atrial septostomy occurred in 0.2% of the UPTRAVI group versus 0.3% of the patients within the placebo group.[1]

Dr. Doghramji
Thanks, Dr. Benza. And now let's go over some Important Safety Information.

Announcer:
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 that occurred more frequently than in the placebo group (≥3%) are headache (65% vs 32%), diarrhea (42% vs 18%), jaw pain (26% vs 6%), nausea (33% vs 18%), myalgia (16% vs 6%), vomiting (18% vs 9%), pain in extremity (17% vs 8%), flushing (12% vs 5%), arthralgia (11% vs 8%), anemia (8% vs 5%), decreased appetite (6% vs 3%), and rash (11% vs 8%).[1]

These adverse reactions are more frequent during the dose titration phase.[1]

Hyperthyroidism was observed in 1% (n=8) of patients on UPTRAVI and in none of the patients on placebo.[1]

Now in this pivotal GRIPHON trial, which is the largest PAH trial studied to date, a post hoc analysis was done to evaluate the relationship between risk profile and long-term morbidity/mortality outcome in the GRIPHON population. The analysis described here is post hoc, and exploratory.[18] That's important to remember, because GRIPHON was not powered to assess treatment effects and interactions in subgroups defined by risk status.[1,8] These post hoc observations cannot be used to determine treatment effect on individual components of the REVEAL 2.0 risk calculator and should be interpreted with caution. Additionally, GRIPHON did not assess the treatment effect on all the individual parameters of the REVEAL 2.0 risk calculator, and only NT-proBNP, 6-minute walk distance, and absence of clinical worsening of functional class were evaluated endpoints in GRIPHON.[1]

The REVEAL 2.0 risk assessment criteria included WHO Group I subgroup, which is the etiology of PAH, and the functional class, 6-minute walk distance, NT-proBNP, age, gender, estimated glomerular filtration rate or renal insufficiency, systolic blood pressure, heart rate, pericardial effusion, mean right atrial pressure, pulmonary vascular resistance, and all-cause hospitalization within the previous six months.[15] Patients were required to have at least seven parameters available for inclusion in this analysis.[19]

Per REVEAL 2.0, patients are grouped into 3 categories.[15] A score between zero and six was considered low-risk, a score of seven or eight was considered intermediate-risk, and a score of nine or higher was considered high-risk.[15]

Of the 1156 patients in GRIPHON, 48% were categorized as low-risk, 25% as intermediate-risk, and 28% as high-risk at baseline, when using the REVEAL 2.0 risk score.[18]

Aside from these parameters used to classify risk, baseline characteristics were generally balanced between the subgroups.[18] Patients in REVEAL 2.0 low-risk category tended to be younger than the higher-risk patients.[18]

The treatment effect of UPTRAVI to first disease progression event was consistent, regardless of the risk category baseline, with 42% risk reduction for low-risk patients, 53% in intermediate-risk patients, and 29% in high-risk patients.[18]

The following tables summarize the primary composite endpoint by each subgroup.

The following table summarizes adverse events, greater than or equal to 3%, associated with UPTRAVI during the post hoc analysis.

In evaluating change from baseline by REVEAL 2.0 risk category, 14.6% of UPTRAVI patients and 8.2% of placebo patients were in a lower risk category at week 26 compared to baseline.[18] While 65.3% of patients on UPTRAVI, and 69.9% of patients on placebo

remained unchanged, 20% of patients on UPTRAVI and 21.8% of patients on placebo were in a higher risk category at week 26 compared to baseline.[18]

Patients receiving UPTRAVI were 84% more likely to be in a lower REVEAL 2.0 risk score category from baseline to week 26, compared with patients receiving placebo, with an odds ratio of 1.84, and a 95% confidence interval of 1.41 to 2.40.[18]

As a reminder, these results are from a post hoc analysis, and should be interpreted with caution. These post hoc observations cannot be used to determine the long-term treatment effect of UPTRAVI on survival or on individual components of the REVEAL 2.0 risk calculator.

Dr. Doghramji:
And before we close, Dr. Benza, what are some takeaways you'd like to pass on to our listeners?

Dr. Benza:
PAH is a silently progressive disease, and risk assessment can help detect disease progression that patients themselves cannot see, which has important implications for patient care, including guiding treatment decisions and potentially improving outcomes.[9]

Limitations in data availability, as well as time constraints, may make a risk assessment strategy that assesses fewer variables, such as REVEAL Lite 2.0, more practical than existing methods, and regular risk assessments with REVEAL Lite 2.0 may be incorporated into routine clinical practice to help clinicians identify modifications in disease progression and offer therapy to meet the specific needs of each patient.[16]

Dr. Doghramji
I'm Dr. Paul Doghramji. Please stay tuned for some important safety information.

Announcer:
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.[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 dose up to twice of UPTRAVI 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 microgramsonce 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 the full Prescribing Information at www.uptravihcp.com.

Dr. Doghramji:
Thanks for summing all that up for us, Dr. Benza, and as that brings us to the end of today's program, I want to thank you for helping us better understand the development and clinical implementation of REVEAL Lite 2.0.

Dr. Benza, it was great speaking with you today.

Dr. Benza:
It was really an honor to be here today, and, thank you so much.

Announcer:
This program was brought to you by the Janssen Pharmaceutical Companies of Johnson & Johnson. If you missed any part of this discussion visit reachmd.com/pah-perspectives. This is ReachMD. Be part of the knowledge.

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