Positioning Newer Agents: Riociguat, Selexipag, and Oral Treprostinil in the Current Landscape

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The availability of newer oral agents for therapy of pulmonary arterial hypertension entails both opportunity and uncertainty. There is the opportunity for less intrusive therapy and the potential to further lessen risk of disease progression, but there is also uncertainty regarding optimal role of these agents, concern about their expense, and risk of preventable deterioration if these agents are used in settings that clearly warrant parenteral prostanoids. Among the newer agents, the evidence is strongest for the use of the prostacyclin receptor agonist selexipag, which has been shown to reduce events in functional class II and III patients, even in the setting of background therapy with a phosphodiesterase type 5 (PDE5) inhibitor and an endothelin receptor antagonist. Riociguat is a soluble guanylate cyclase stimulator that has been shown to be beneficial, including in combination with an endothelin receptor antagonist, and may be a useful alternative to a PDE5 inhibitor in properly selected patients. It has also been shown to be beneficial in inoperable or residual thromboembolic pulmonary hypertension. Oral treprostinil has been shown to improve 6-minute walk distance as monotherapy, and has been used to transition from inhaled or parenteral treprostinil in carefully selected patients also on other agents. Herein we discuss the mechanisms of action, side effect profiles, and clinical trial data for these agents, followed by a practical approach to their use, integrating the available data with real-world experience.

The panoply of agents available for therapy of pulmonary arterial hypertension (PAH) creates both opportunity and uncertainty. Properly applied, there is the opportunity to individualize therapy to maximize benefit while minimizing intrusiveness, side effects, risk, and cost. Achieving these goals is made more difficult by the limited comparative data for available approaches and combinations, the variable trial designs, and strength of the evidence for these agents. Herein we discuss the mechanisms of action, side effect profiles, and clinical trial data for these agents, followed by a practical approach to their use, integrating the available data with real-world experience of the author. Accordingly, the discussed approach is not intended to be strictly guideline based, and should be considered as one reasonable approach in the context of an imperfect and evolving landscape. In implementing a particular strategy for a particular patient, the practitioner will do well to keep in mind the advice of a mountain sojourner: getting off the trail is forgivable; not realizing it and promptly defining a change in course can be fatal.

When considering next steps in PAH therapy, it is useful to consider the range of factors shown in Figure 1. These factors need to be viewed in light of both intermediate and long-term individual patient goals and expectations. Is long-term survival an important goal, or is avoidance of intrusive therapy and potential for side effects a greater goal? Is short-term avoidance of intrusive therapy and side effects worth the risk of future physical suffering and shortened survival due to progression of right heart failure? A wise clinician integrates a detailed understanding of their patient's goals and degree of acceptance of the burdens of therapy with their risk profiles. When combined with knowledge of the evidence for the available therapeutic approaches, an optimal strategy can be achieved.

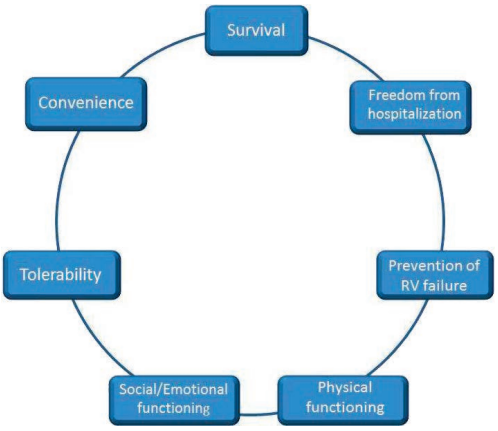

Figure 1: Patient-centered medicine – considerations.

Riociguat, selexipag, and oral treprostinil have been shown in randomized clinical trials (of varying robustness and endpoints) to have some degree of ef-

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Table 1. Comparative Considerations for These Therapies

Medication	Monotherapy	Sequential Dual Combination	Sequential Triple Combination
Selexipag			
Riociguat			*
Inhaled Treprostinil	**		
Oral Treprostinil			

Green: Positive event-driven trial. Yellow: Positive 6-minute walk-driven trial. Orange: Clinical experience, nonrandomized data, or trends in randomized data suggest possible benefit.

*Cannot utilize with phosphodiesterase type 5 inhibitor; experience with prostanoids is thus far limited. **Rarely used as monotherapy.

ficacy as monotherapy in PAH and, for riociguat and selexipag, also in combination therapy) (Table 1).[1-3]

However, given their cost, need for titration, and potential for side effects, their use as initial therapy in PAH has thus far been limited. Given the strength of the available evidence, riociguat or selexipag are generally preferred to oral treprostinil in patients requiring combination therapy. Nonetheless, some patients seem to do well with oral treprostinil in combination therapy. The nonrandomized studies of transition from parenteral treprostinil to oral treprostinil in highly selected, well-compensated patients included almost exclusively patients on combination therapy, and indeed this approach can be effective in some patients.[4] It must be emphasized that those patients were very highly selected and managed at expert centers; the risk of deterioration with such a transition must be kept top of mind by both the practitioner and the patient. Patients have also been successfully transitioned from inhaled prostanoids to oral treprostinil, thereby avoiding the inconvenience of qid inhalation therapy.[5,6]

Riociguat is the first-in-class Food and Drug Administration (FDA)-approved soluble guanylate cyclase (sGC) stimulator, approved for treatment of Group 1 PAH and inoperable or residual Group 4 pulmonary hypertension (PH)—the first drug with adequate evidence in chronic thromboembolic pulmonary hypertension (CTEPH) to achieve labeling for this indication. By directly stimulating sGC, and amplifying the sGC responsiveness to nitric oxide, it drives increased production of cyclic guanosine monophosphate (cGMP), the second messenger that mediates the nitric oxide vasodilatory response. It cannot be used in combination with a phosphodiesterase type 5 (PDE5) inhibitor due to risk of excessive systemic vasodilation that could result in hypotension and syncope. Riociguat has been shown to improve 6-minute walk distance, pulmonary vascular resistance, N-terminal pro b-type natriuretic peptide (NT-proBNP) levels, World Health Organization (WHO) functional class, time to clinical worsening, and Borg dyspnea score in PAH.[2] About 44% of the patients were on background therapy with an endothelin receptor antagonist (ERA), and a few were on nonparenteral prostanoids. Dizziness, hypotension, headache, peripheral edema, and dyspepsia were the adverse events that were predominantly greater in the treatment compared with placebo groups.

Selexipag is the oral, first-in-class, FDA-approved selective prostacyclin (IP) receptor agonist. Selexipag has been shown in a robustly designed endpoint-driven trial to be an effective agent in PAH, either as monotherapy or in addition to a PDE5 inhibitor or ERA or both.[3] The combined clinical endpoint was predominantly driven by reduction in PAH-related hospitalizations, and by prevention of clinical worsening. The starting dose of 200 ucg bid can be uptitrated at weekly or longer intervals depending on tolerability and blood pressure, to achieve a maximal approved dose of 1600 ucg bid, the top dose in the randomized study. Most patients develop one or more significant prostanoid-like side effects (headache, lightheadedness, diarrhea, muscle aching, jaw claudication, lower-extremity neuropathic pain). Avoiding rapid titration (eg, in patients experiencing significant side effects, advancing the evening dose by 200 ucg for a week and then advancing the morning dose by 200 ucg) and continuing slow but steady titration may ultimately be more successful in achieving a higher maximally tolerated dose. The side effects tend to subside when the dose levels off, but some patients need to reach a dose higher than their ultimate dose in order to really establish maximal tolerated dose. Stopping attempts at titration too readily may result in an ineffective dose being achieved. The patient must be counseled prior to starting treatment that side effects are to be expected, and to stick with it until reaching the proper individualized dose. Close contact between the patient and the care team at regular intervals is essential to success, just as it is for parenteral prostanoids. It is critical to institute parenteral prostanoid therapy rather than utilizing selexipag if high-risk patient characteristics are present; selexipag is NOT equipotent vis-à-vis parenteral prostanoids.

Most commonly, selexipag is added to the combination of PDE5 inhibitor and ERA in a patient failing to achieve treatment goals, rather than in lieu of one of the other agents, unless there are patient intolerances to one of those agents. This approach has been taken partly because of preexisting treatment patterns. Some practitioners argue that targeting the prostanoid pathway earlier

is desirable. A randomized clinical trial of up-front triple therapy with selexipag or placebo, and an ERA combined with a PDE5 inhibitor or riociguat, will help to answer this important question (The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension [TRITON]; ClinicalTrials.gov NCT02558231).

In treatment-naïve PAH patients at low to moderate risk, accordingly an initial treatment plan of a PDE5 inhibitor or ERA followed rapidly by addition of the other agent if inadequate response, or started simultaneously as shown in the AMBrIsentan and Tadalafil in patients with pulmonary arterial hypertensION (AMBITION) study is reasonable.[7] Bosentan is not preferred in combination with sildenafil given drug interactions (reduction in sildenafil levels, increase in bosentan levels) and the negative results of the Effects of the Combination of Bosentan and Sildenafil Versus Sildenafil Monotherapy on Pulmonary Arterial Hypertension (Compass-2) study.[8] Nonetheless, some patients historically have done satisfactorily with this combination, and bosentan can be used in combination with tadalafil without concern regarding drug interactions. Although use of riociguat as first-line therapy is certainly supported by the clinical trial data, and indeed with stronger clinical trial evidence than what is available for PDE5 inhibitor, for reasons of cost-effectiveness, simplicity, and tolerability, an initial strategy of combined PDE5 inhibitor and ERA seems preferable, pending any new data regarding relative merits of riociguat plus ERA vis-à-vis PDE5 inhibitor plus ERA.

A common scenario in PAH is the patient who is not meeting treatment goals on a combination of a PDE5 inhibitor and an ERA. Options in this setting are shown in Table 2. This table incorporates considerations of efficacy, safety, and tolerability; is meant as a general guide; and is not intended as a substitute for full consideration and understanding of the PH guidelines with regard to strength of the evidence and indications for therapy. It includes parenteral prostanoids to emphasize that the newer agents forming the focus for this discussion are not as potent and should not be utilized as substitutes for parenteral prostanoids in more advanced disease.

Table 2. Comparative Considerations for Patients Not Meeting Treatment Goals Despite PDE5 Inhibitor + ERA

	Efficacy	Tolerability	Convenience	Safety
+ Intravenous Epoprostenol	+++++	+++	++	+++
+ Intravenous Treprostinil	+++++	+++	++	+++
+ Subcutaneous Treprostinil	+++++	+++	++	++++
+ Selexipag	++++	++++	++++	+++++
+ Inhaled Treprostinil	+++	++++	+++	+++++
ERA + Riociguat*	+++	+++++	+++++	+++++
Oral Treprostinil**	++	+++	++++	+++++

*Cannot combine riociguat with PDE5 inhibitor. **Oral treprostinil has not met endpoints in randomized combination use.

The relative effectiveness of riociguat vs a PDE5 inhibitor has not been studied in a randomized controlled study. Since nitric oxide production can be variably deficient in PAH, it could be that in some patients riociguat will more maximally leverage the nitric oxide pathway than a PDE5 inhibitor. This concept was tested in the open-label phase 4 Riociguat in Patients with PAH and an Inadequate Response to Phosphodiesterase 5 Inhibitors (RESPITE) study.[9,10] Patients with suboptimal clinical status on PDE5 inhibitor (nearly three quarters also on background ERA) were converted from PDE5 inhibitor to riociguat. Endpoints included functional class, 6-minute walk distance, NT-proBNP level, and hemodynamics, all of which improved. Given the open-label nature of this study, it must be considered hypothesis generating, but the author's (limited, anecdotal) clinical experience with conversion from PDE5 inhibitor to riociguat is indeed consistent with some patients benefiting. Efforts in the RESPITE study to predict which patients would respond based on plasma markers eg, cGMP levels, were unsuccessful. Additional work in this area, perhaps looking at urinary cGMP, may be warranted.

The author has noted some patients with vasodilatory response to nitric oxide in the catheterization laboratory (though at time of PAH diagnosis not sufficient to warrant calcium channel blocker therapy) to have residual response to repeat nitric oxide challenge despite being on a PDE5 inhibitor. This has seemed to correspond with a favorable clinical response to riociguat; whether this approach will further enhance prediction of response to conversion requires additional study. This was not part of the approach in RESPITE, and certainly should not be considered as a necessary component in a decision to convert from PDE5 inhibitor to riociguat in patients with suboptimal PDE5 inhibitor response.

Accordingly, in patients not meeting treatment goals on ERA plus PDE5 inhibitor, consideration can be given to switching to riociguat from PDE5 inhibitor rather than adding yet a third agent. The side effect profiles, cost, and/or inconvenience of a third agent need to be carefully considered. If a switch to riociguat is made, it is incumbent on the practitioner to reassess, and if insufficient improvement is achieved, move ahead with incremental therapy.

Riociguat seems to have more tendency to lower systemic blood pressure than a PDE5 inhibitor, as the dose is advanced and can result in lightheadedness, particularly in patients with relatively low systemic blood pressure. In a patient with low systemic blood pressure or orthostatic hypotension who is not meeting treatment goals on PDE5 inhibitor plus ERA, but not yet in need of parenteral prostanoids, switching to riociguat may be problematic. If the achievable dose of riociguat is likely to

be low, it may be unlikely to be more effective than the PDE5 inhibitor, and at increased cost.

Among the nonparenteral agents, selexipag has the strongest evidence for use in reasonably stable patients not meeting treatment goals on a combination of ERA and PDE5 inhibitor, including both functional class II and III patients. Accordingly, this is the most obvious approach in such patients. The opportunity to protect even functional class II patients from risk of disease progression is an important finding in the selexipag study, and it is anticipated that an increasing number of class II patients will be treated with selexipag with this opportunity in mind.

None of the patients in the selexipag pivotal study were on riociguat during the randomized portion of the study. Clinical experience suggests that in patients with relatively low blood pressure who are receiving riociguat, titrating selexipag can be more challenging due to low blood pressure and lightheadedness. In such patients, alternative approaches should be considered, such as addition of inhaled treprostinil or iloprost. Reduction of the riociguat dose can also be considered, in order to make more room for the selexipag titration. Addition of midodrine to support systemic blood pressure can also be considered, while monitoring carefully for development of supine hypertension.

RIOCIGUAT IN INOPERABLE/ RESIDUAL CTEPH

Patients with inoperable or residual CTEPH have been treated with virtually every available PAH therapy over the years despite lack of clinical trial evidence for such practice. These therapies can be effective in some patients (eg, there are patients who have survived a decade or more on parenteral prostanoid therapy), though outcomes of inoperable CTEPH have historically been poor. Riociguat has been shown to improve 6-minute walk distance, functional class, hemodynamics, and NT-proBNP levels in inoperable/residual CTEPH.[11] It can be used prior to pulmonary balloon angioplasty (PBA); by improving hemodynamics in this setting it is felt that it may facilitate safe completion of PBA, though is certainly not uniformly utilized in patients undergoing PBA. In patients without suitable targets for PBA, or with residual PH following PBA, riociguat can be useful. A clinical trial comparing riociguat to PBA in inoperable CTEPH is underway in France (clinicatrials.gov identifier NCT02634203). Given the FDA approval of riociguat for inoperable/ residual CTEPH, it has become more difficult in the United States to use other agents, including decisions by payers to require conversion from a PDE5 inhibitor even in a patient doing well on that therapy and despite the increased cost incurred by such a decision. With letters of appeal and cajoling, approval to use other agents can still sometimes be obtained. Certainly if a patient is not doing well enough on riociguat, other agents should be added in an effort to use best clinical judgment to achieve improvement. Topline results of the randomized placebo-controlled Macitentan in thE tReatment of Inoperable chronic Thromboembolic pulmonary hypertension (MERIT) study indicate that the ERA macitentan can also improve 6-minute walk (placebo-corrected improvement of 34 m), with improvement in pulmonary vascular resistance and NT-proBNP levels. These data have not yet been published in peer-reviewed form, but it is hoped this will result in another proven therapy for inoperable CTEPH. The ultimate roles of medical therapy and PBA will no doubt evolve in the years ahead as more experience is gained on both fronts.

SELEXIPAG OR INHALED TREPROSTINIL?

Some patients view inhaled treprostinil as excessively inconvenient (qid inhalations) and express interest in maintaining an exclusively oral medication approach. In addition, the quality of the evidence for selexipag is stronger than that available for inhaled treprostinil. It must be acknowledged that this difference may simply reflect relative trial design. Nonetheless, inhaled treprostinil can have the advantage of selective delivery to the pulmonary bed, with low systemic blood levels, and some patients have a robust improvement with inhaled treprostinil.[12] Patients with migraine headaches or substantial gastrointestinal issues may be more likely to tolerate inhaled treprostinil than selexipag. Patients with cirrhosis and portopulmonary hypertension with hepatic dysfunction and tendency to ascites can do well with inhaled treprostinil, without the concern for issues of hepatic metabolism and potential for aggravation of ascites that may accompany use of selexipag or oral treprostinil. The addition of inhaled treprostinil to an appropriately dosed and monitored ERA has been a useful approach in appropriately selected patients with portopulmonary hypertension.

ORAL TREPROSTINIL

Oral treprostinil is FDA approved based on a monotherapy trial demonstrating modest improvement in 6-minute walk distance and Borg dyspnea score.[1] The clinical trials examining oral treprostinil in combination with an ERA or a PDE5 inhibitor that have thus far been completed failed to meet their primary endpoint of 6-minute walk distance.[13,14] This may reflect difficulties in those studies with starting doses, difficulty of tolerability in bid dosing that limited achieved dose, and limitations in achieving improvement in 6-minute walk distance within a short time frame in patients on background therapy, or a simple lack of efficacy. However, an interesting additional analysis provides some additional suggestion of benefit, particularly if dosed to adequate extent.[15] Experience with oral treprostinil, which originally was dosed in bid fashion and beginning at relatively high starting doses, suggests that tolerability can be enhanced with low starting dose (eg, 0.125 mg), tid dosing, and care to take it with sufficient food, allowing enhanced titration to doses more likely to be effective. An additional event-driven trial, FREEDOM-Ev (Early Combination of Oral Treprostinil With Background Oral Monotherapy in Subjects With Pulmonary Arterial Hypertension, clinicaltrials.gov identifier NCT01560624), that allows tid dosing is underway, which, if positive, will enhance the evidence base for oral treprostinil in combina-

tion therapy. Open-label experience with transition from parenteral to oral treprostinil in patients who were well compensated on parenteral therapy and who were on background ERA and/or PDE5 inhibitor suggests that this can be accomplished successfully in highly selected patients.[4] Transition from inhaled prostanoids to oral treprostinil has also been reported.[6]

Oral treprostinil thus is in the difficult position of having a weak evidence base for its use, yet some practitioners (including the author) have been successful in utilizing it to good effect in some patients, including those on other background therapy. There is the sense that the treprostinil molecule is an effective pulmonary vasodilator, and it is hoped that the ongoing trial will further establish the efficacy and tolerability of oral treprostinil in combination therapy.

CONCLUSION

The availability of additional oral agents for treatment of PAH is a welcome advance. Optimal use of these agents must take into consideration the strength and nature of the available evidence, the risk profile of the patient, individualized considerations of goals of therapy, and probability of tolerability of the various approaches. Regardless of the approach taken, it is critical to reevaluate regularly, be ready to change course as needed, and have a low threshold for referral if any doubt about adequacy of therapy is present.

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In this, the second of two issues on "Guidelines Gaps," we are pleased to provide additional insightful articles and commentary on the challenges of following guidelines for the management of pulmonary arterial hypertension (PAH) and its heterogeneous group of underlying disorders at a crucial time in the evolution of medical treatments. We present these in the context of the sections of the European Society of Cardiology and European Respiratory Society's guidelines 2015 treatment algorithm (as presented in Figure 2 on page 16 of this publication).

As we stated in the previous issue, challenges remain—and will remain—regarding optimal treatment of patients with this rare disease. Not only are we adding to our armamentarium of new drugs, but daily we are gaining knowledge from our patients about the effects of different routes of administration, mono- versus combination therapy, and quality-of-life considerations as we try to balance the risks and benefits of newly-available tools to add to evidence in treating this unique population.

We urge you, the clinician reader, to consider these two issues together as a source of more knowledge for you to apply as you optimize management for your patients. In addition to the actual guideline documents that have been offered by various organizations as means of guidance to practitioners, we offer the experience and perspective of leading clinicians in these two issues. We urge you to consider the challenges of guideline writing as described by Dr James Klinger in the previous issue along with topics including calcium channel blocker therapy, the state of monotherapy, and introduction of newer agents as you read in this second issue about combination and infusion prostacyclin therapies offered by Drs. Schilz and Myung Park. Plus, Drs. Nicole Ruopp and Harrison Farber present the gaps and controversies that factor into the uncertainties still remaining despite great gains in this field. As a wrap-up to the two issues, we offer a transcript of a lively discussion among Drs. Burger, Robert Bourge, Richard Channick, and Srinivas Murali, moderated by Dr Schilz, that touches on a multitude of experiences gained in treating PAH patients over more than two decades including risk assessment, treatment strategies, goal setting, escalation of therapy, and application of guidelines. We hope you will find these two issues to be thought-provoking and useful.

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ERRATUM
The abstract to Frantz, RP: Positioning newer agents: Riociguat, selexipag, and oral treprostinil in the current landscape on page 193 of *Advances in Pulmonary Hypertension,* Volume 15, number 4 contained an error. The sentence beginning in line 10 should read: "Riociguat is a soluble guanylate cyclase *stimulator* that has been shown to be beneficial, including in combination with an endothelin receptor antagonist, and may be a useful alternative to a PDE5 inhibitor in properly selected patients.