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REVIEW

Evaluating Riociguat in the Treatment of Pulmonary Arterial Hypertension: A Real-World Perspective

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Abstract: Pulmonary hypertension (PH) is a broad term describing the mean pulmonary artery pressure, as measured by right heart catheterization, exceeds 20mmHg. Pulmonary arterial hypertension (PAH) exists when PH is accompanied by a normal wedge pressure and elevated pulmonary vascular resistance. PAH is typified by dysmorphic and dysfunctional pulmonary arterial vasculature. Attempting to restore the functionality of the pulmonary artery is a hallmark of care to the PAH patient. Riociguat is a powerful stimulator of soluble guanylate cyclase and increases blood flow through the pulmonary arteries by dilating vascular smooth muscle cells. This review examines the pharmacology of riociguat, the fundamental clinical trials applying it to PAH patients, practical aspects when selecting its use, and future directions for its utilization.

Keywords: pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, riociguat, soluble guanylate cyclase stimulator

Introduction

"Pulmonary hypertension" (PH) is an umbrella term that describes patients with pulmonary artery pressures exceeding 20mmHg on right heart catheterization.[1] PH is a disease highlighted by an increased resistance to blood flow through the pulmonary arterial system. Though the factors responsible for the development of this vasculopathy are unknown, it is clear that over time hypertrophy of the medial layer of the vascular bed, thickening of the adventitia, and fibrosis of the intima leads to dysregulation of the signaling pathways responsible for vasoreactivity and autoregulation of blood flow through the pulmonary artery.[2]

Because PH is a disease of dysmorphic and dysfunctional pulmonary arteries, attempting to restore the functionality of the pulmonary artery is a tenement of modern medical management. However, the causes of PH are myriad and often overlapping. The World Health Organization (WHO) established a categorization system in 1973 to organize research priorities around PH and help establish evidence-based treatment approaches for clinicians. The latest update of this classification system occurred at the 6th meeting of the World Symposium on Pulmonary Hypertension in February 2018 and organizes PH into five groups: Pulmonary arterial hypertension (Group 1), PH due to left heart disease (Group 2), PH due to underlying lung disease or chronic hypoxemia (Group 3), PH attributable to chronic thromboembolic pulmonary hypertension (Group 4), and PH due to unknown, or overlapping, mechanisms (Group 5).[1]

Pulmonary arterial hypertension (PAH) is termed "pre-capillary" disease because of the pathological vascular changes that occur prior to the pulmonary capillary bed as it delivers blood to the pulmonary venous system. PAH occurs when elevated pulmonary artery pressures are accompanied by normal wedge pressure (less than 15mmHg) and elevated pulmonary vascular resistance (greater than 3 Woods units). This vasculopathy of the pulmonary arteries and arterioles often warrants a combination of vasodilatory therapies to reconstruct vascular functionality. Though recent trial results challenge assumptions that group 2 and 3 diseases are without disease-specific interventions, PH consensus guidelines emphasize that addressing underlying heart and lung disease is the primary treatment approach to these patients.[3,4] Group

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4 is the only curable form of PH and is potentially reversible either by invasive surgery pulmonary endarterectomy or minimally invasive pulmonary artery balloon angioplasty.[5] Diagnostic and therapeutic plans are challenging to construct in group 5 patients. It is recommended that such patients are referred to PH centers of excellence to address their care needs.

There are currently 14 drugs approved for the treatment of group 1 pulmonary arterial hypertension. Riociguat, a potent stimulator of soluble guanylate cyclase (sGC) and inducer of nitric oxide (NO), is an approved therapy for PAH and is the only medication approved by the European Committee for Medicinal Products for Human Use (CHMP) and the American Food and Drug Administration (FDA) for use in patients with inoperable or persistent group 4 PH. The purpose of this manuscript is to provide an up-to-date review of the clinical uses of riociguat. A conversation about the drug's pharmacology, the fundamental clinical trials justifying its role in PAH, practical aspects important in selecting its use, its application to diseases other than PAH, and future directions for its utilization are overviewed.

The NO-sGC-cGMP Pathway

Because riociguat is a potentiator of nitric oxide activity, it seems reasonable to briefly overview the role of nitric oxide in the pulmonary vasculature before pursuing a robust conversation regarding its clinical uses.

Nitric oxide (NO) is a lipophilic gas that is a valuable contributor to homeostasis. It is employed as a regulator of blood pressure, a neurotransmitter, an inhibitor of platelet activation, and a versatile participant in the inflammatory pathway. The dysregulation of the nitric oxide pathway is associated with numerous pathophysiological processes, including pulmonary hypertension.[6–8]

Nitric oxide is synthesized from L-arginine by nitric oxide synthase (NOS) (Figure 1). The byproduct of this reaction is the production of L-citrulline. Nitric oxide synthetase exists as three isoforms in the human body: neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS). As the name suggests in the latter, eNOS is expressed in the cardiovascular endothelium (though it is also present in the endocardium and in platelets). Nitric oxide's lipophilic nature allows for easy diffusion of the molecule into vascular smooth muscle cells where it is biologically active.[9] The half-life of NO is on the order or milliseconds and is easily degraded by erythrocytes.[10] Free heme, such as that released during hemolytic processes, will generate reactive oxygenation species that serve as an active scavenger of NO and may explain the risks of developing pulmonary hypertension in sickle cell disease and other hemolytic anemias.[11] Production of NO is tightly regulated as a result of its volatility and value to the cardiovascular system.

Soluble guanylate cyclase (sGC) is the signaling target of NO in the smooth muscle. NO has a strong affinity for sGC and its binding results in the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP).

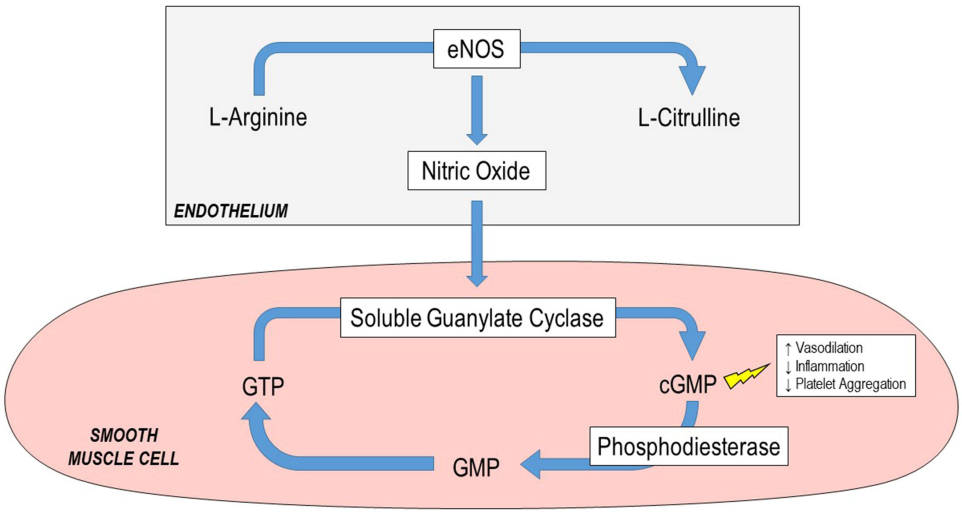

Figure 1 The NO-sGC-cGMP pathway.
Abbreviations: cGMP, cyclic Guanosine Monophosphate; eNOS, endothelial; GMP, Guanosine Monophosphate; GTP, Guanosine Triphosphate; NO, Nitric Oxide; sGC, soluble Guanylate Cyclase.

This, in turn, activates protein kinase G (PKG), causes the sequestration of intracellular calcium into smooth muscle sarcoplasm and results in vasomotor relaxation. Beneficial downstream effects of this pathway include inhibition of platelets as well as downregulation of the inflammatory cascade. cGMP is enzymatically hydrolyzed by phosphodiesterase 5 (PDE5) in cardiomyocytes and is eventually recycled back into GTP.[9] Of note, pharmacological inhibition of PDE5 by the drug sildenafil results in the potentiation of NO's signaling effect, vasodilation of the pulmonary artery, and serves as a foundational treatment of pulmonary arterial hypertension.

Mechanism of Action of Riociguat

sGC is a heterodimer that exists in both a "reduced" and "oxidized" form. The reduced form (so named because it carries Fe^{+2}) contains heme on the β-subunit and is the receptor for NO. Riociguat is termed a "stimulator" of sGC as it is able to activate and provoke the protein into upregulating cGMP production. In addition, Riociguat also acts as a potentiator of NO activity and therefore works synergistically with cGMP. The net effect of these actions is that riociguat works by two NO-dependent, heme-dependent, mechanisms to increase sGC activity and causes vasodilation of the cardiovascular system.

The oxidized form of sGC (carries Fe^{+3}) is unable to bind NO and is considered pathological. There are a number of cardiovascular diseases associated with the production of reactive oxygenation species that may lead to the oxidation of sGC and its inactivation. This may explain the cardiovascular dysregulation typically seen in diseases such as pulmonary hypertension and heart failure. Newly developed sGC "activators" (cinaciguat) work independently of NO availability and are able to activate sGC even in its reduced form. sGC activators are the subject of active investigations as researchers attempt to apply the benefits of their properties to combat cardiovascular disease.

Pharmacological Profile of Riociguat

Riociguat possesses a very short half-life and is administered three times a day. Dosing ranges from 0.5mg to a maximum of 2.5mg. Patients are generally started at a low dose and titrated every two weeks until either the highest tolerable or recommended maximum dose is achieved. The drug is teratogenic and female patients of reproductive age should test for pregnancy prior to drug initiation, test at regular intervals across the arc of drug administration, and register with an approved risk evaluation and mitigation strategy (REMS) program. It is recommended that breast feeding patients should not take riociguat.

In the original manuscripts that looked at riociguat's efficacy (PATENT-1 and CHEST-1 trials; as discussed below), side effects were reported in upwards of 92% of patients (versus 86% in placebo arms).[12,13] Approximately 25% of patients experienced headaches and/or dizziness with only 2% of study patients reporting a syncopal event. It is rationalized that these side effects reflect the systemic effects typical with the administration of potent vasodilators and echo the possible risks of other medications used to treat PAH such as sildenafil and the prostanoid analogues.

These reported trial results reflect our own group's experience with the drug. Fortunately, many of these reported side effects are managed with over-the-counter medications for symptomatic control and wax in their severity with acclamation over time. In cases of poor tolerability or extreme side effects, we recommend slowing titration schedules perhaps longer than the recommended 2 week increases. As a last effort before discontinuing completely, we often consider titrating down to a lower dose before stopping the drug.

Any patient with profound side effects from riociguat must first have a thorough medication reconciliation completed. Specifically, riociguat should not be administered concomitantly with a PDE5 inhibitor or a nitrogen-based product. Because PDE5 inhibitors prevent the breakdown of cGMP, they are dependent on the presence of cGMP and NO. Riociguat, by directly stimulating sGC is free of this constraint and it is easy to rationalize a synergistic effect with oral nitroglycerin, sildenafil, or tadalafil. Investigators in the PATENT PLUS trial (discussed below) demonstrated that the simultaneous use of riociguat with a PDE5 inhibitor detrimentally potentiates postural hypotension without evidence of improved clinical outcomes.[14] Patients demonstrating side effects, particularly hypotension, with the initiation of riociguat should be re-evaluated to ensure proper cessation of PDE5 inhibitors and/or any nitrogen-based medications.

Riociguat is metabolized by the cytochrome system of enzymes. Patients actively taking strong cytochrome P450 inhibitors (such as the azole antimycotics or protease inhibitors for human immunodeficiency virus) are at risk for having

overt side effects and need close observation.[15–17] In the modern era, it is important to be mindful that ritonavir (along with nirmatrelvir) is active component in Paxlovid™, the only oral antiviral approved for outpatient use in the treatment of COVID19. Because ritonavir is a potent inhibitor of cytochrome P450, Paxlovid is contraindicated in patients taking riociguat. Finally, it is worth noting that tobacco consumption upregulates cytochrome monooxygenase CYP1A1. Therefore, patients consuming tobacco products may have a poor response to riociguat and require higher than anticipated doses of the drug to reach a clinical effect.[18]

Use of Riociguat in Group 1 Pulmonary Hypertension

Riociguat gained approval from the FDA and CHMP on the strength of the PATENT-1 (Pulmonary arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1) and CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1) trials.[19] Both were multi-center, randomized, placebo-control studies evaluating the use of riociguat to treat patients with group 1 PAH and group 4 CTEPH, respectively. Given the relevance to the topic at hand, the PATENT-1 trial is reviewed below while the CHEST-1 trial is discussed deeper in the text. Table 1 summarizes the seminal clinical trials associated with the application of riociguat to the pulmonary hypertension patient population.

In PATENT-1, 443 patients with group 1 pulmonary arterial hypertension were randomized to receive either placebo or a maximum dose of 1.5mg versus 2.5mg of riociguat in a 2:4:1 fashion, respectively. Patients receiving the maximum dose of 1.5mg three times a day were not pooled with the final analysis of the 2.5mg group and were used to explore the potential benefits of lower riociguat doses. Half of the patients that participated in this study were on background therapy

Table 1 Clinical Trials Pertinent to the Use of Riociguat

Trial (Year)	Lead Author	Study Description	Patient Population	Summary of Pertinent Findings
CHEST-1 (2013)	Ghofrani HA et al[12]	Multi-center, randomized, double-blind, placebo-controlled	261 patients with inoperable or recurrent Group 4 PH	-6MWDT improved net 45 meters compared to placebo -PVR decreased by net 249 dyn·sec·cm
PATENT-1 (2013)	Ghofrani HA et al[13]	Multi-center, randomized, double-blind, placebo-controlled	443 patients with Group 1 PH	-6MWDT improved net 36 meters compared to placebo -No change in PVR
PATENT-2 (2015)	Rubin LJ et al[20]	Open label extension of PATENT-1	324 patients with group 1 PH	-Results from 12-week PATENT-1 study were maintained upwards of 1 year
RESPITE (2017)	Hoeper MM et al[24]	Multi-center, open label, uncontrolled	51 patients with group 1 PH	-31-meter increase in 6MWDT
REPLACE (2021)	Hoeper MM et al[28]	Multi-center, randomized, prospective, open-label	224 patients with group 1 PH on background PDE5 inhibitor with intermediate risk of 1-year mortality	-Switching from PDE5 inhibitor to riociguat safe and may be used for treatment escalation
RISE-IIP (2019)	Nathan SD et al[48]	Multi-center, randomized, double-blind, placebo-controlled	147 patients with group 3 PH from idiopathic interstitial pneumonia	-Study terminated early due to increased serious adverse events in treatment arm
SETOUCHI-PH (On-going)	Akagi et al[44]	Multi-center, prospective, open-label, randomized, controlled equivalence	Actively recruiting	-Forthcoming; primary end point is change in PVR in patients on macitentan and either riociguat or selexipag

Abbreviations: 6MWDT, 6-Minute Walk Distance Test; PDE5, Phosphodiesterase 5; PH, Pulmonary Hypertension; PVR, Pulmonary Vascular Resistance.

with a large majority receiving an endothelin receptor antagonist (46%). Like the CHEST-1 trial, the primary end point of this study was a measurement of change in 6-minute walk distance. The demographics for each experimental group were evenly represented.[13]

PATENT-1 yielded robust results with many of its primary and secondary end points successfully reached and sustained in a long-term extension (PATENT-2).[20] Patients receiving riociguat had a net improvement in their 6-minute walk distance by 36 meters (least-squares mean, 95% confidence interval: 20–52m, $p < 0.001$) compared to the placebo group. In addition, patients receiving riociguat also significantly demonstrated improvements in their pulmonary vascular resistances ($p<0.001$), N-terminal pro B-type natriuretic peptide (NT-proBNP, $p<0.001$), WHO functional status scores ($p<0.003$), standardized evaluations of their dyspnea (ie, Borg score, $p<0.002$), and time to clinical worsening ($p< 0.005$). Similar results were seen in subgroup analysis of patients with subvariants of PAH caused by portopulmonary hypertension and connective tissue disease.[21,22] Riociguat was well tolerated in the treatment arm of PATENT-1, with 10% of patients experiencing hypotension despite an 8-week titration phase of the study. Reported side effects in the PATENT-1 trial mirrored those reported in CHEST-1.

Beyond PATENT-1: Practical Aspects of Riociguat Use in Patients with Group 1 Pulmonary Hypertension

Studies subsequent to CHEST-1 and PATENT-1 led to expanded roles for riociguat in the pulmonary hypertension population. By the time that riociguat received approval from both the FDA and CHMP in 2014, consensus guidelines had already established a place for PDE5 inhibitors as a cornerstone of PAH treatment plans. Yet, riociguat shares an influence on the NO-SGC-sGC pathway similar to the PDE5 inhibitors and the concomitant use of tadalafil or sildenafil with riociguat is contraindicated.[23] Therefore, the impressive success of the PATENT-1 trial raised real-world questions about the place of riociguat amongst the longstanding (and generic) therapeutics.

The first trial to address this issue came from the Riociguat clinical Effects Studied in Patients with Insufficient Treatment responses to PDE5 inhibitors (RESPITE) study.[24] Patients on therapy with a phosphodiesterase 5 inhibitor can fail to reach target therapeutic goals or reduce adjudicated risk scores that predict progression of PAH.[25] RESPITE investigators hypothesized that a reduction in NO availability, as is seen in PAH, may explain this occurrence and could potentially improve with the use of a sGC stimulator in place of a PDE5 inhibitor.[7,26] In a 24-week uncontrolled study that enrolled 61 patients, RESPITE investigators sought to prospectively evaluate whether patients that failed to achieve treatment goals with either sildenafil or tadalafil could safely switch to riociguat with measurable clinical benefit. Researchers demonstrated that after a designated titration period, patients moved to riociguat had a 31 meter increase in 6-minute walk distance and improvements in NT-proBNP and functional status.

Despite these encouraging results, RESPITE was not without its criticisms and its clear application to bedside clinical practice was difficult to discern. By design, the exploratory nature of the trial involved a small sample size and did not have an identifiable primary end point. Additionally, of the 61 patients originally enrolled in the study, only 51 completed the 24-week study period. Dropout in RESPITE was higher than that observed in PATENT-1 and 52% of enrolled patients reported side effects. Most importantly, the uncontrolled design of the study introduced the possible influence of bias upon the trial's small sample size.[27]

To reconcile these limitations, researchers undertook the Riociguat rEplacing PDE5 inhibitor therapy evaluated Against Continued PDE5 inhibitor thErapy (REPLACE) study as a prospective, open-label, randomized control trial.[28] 41% of patients moved to riociguat versus 20% of patients followed in the PDE5 inhibitor group met a composite endpoint of clinical improvement. The study recruited patients with an intermediate risk of 1-year mortality which reflected a patient profile of significant relevance to the practicing physician. Subsequent publications endorsed the safety and potential benefit of switching to riociguat since REPLACE.[29–35] Risk calculator scoring models, such as the REVEAL 2.0 risk assessment, have been used as practical clinical tools to predict treatment response to riociguat and disease progression.[36] A recent Delphi consensus of expert opinion supported considerations for treatment escalations and for switching from a PDE5 inhibitor to riociguat in PAH patients not achieving treatment goals or at high-risk of progression.[37] Such a strategy may be helpful and safe in pediatric patients faced with progressive or difficult to control disease.[38]

In the developing interim from RESPITE to REPLACE to the present, a greater emphasis is now placed on offering dual - or even triple – upfront therapy to patients with PAH.[39–41] Riociguat clearly has a place in this conversation especially as half of patients in PATENT-1 and 82% of patients enrolled in RESPITE were on background therapy. Recent studies indicate that the inclusion of riociguat in upfront combinations of PAH medications with sister drug classes is an appropriate treatment strategy.[42,43] The SETOUCHI-PH (Effects of Dual Initial Combination Therapy With Macitentan Plus Riociguat or Macitentan Plus Selexipag on Hemodynamics in Patients With Pulmonary Arterial Hypertension) trial is an open label trial actively recruiting patients to determine the proper combination of agents used in therapy.[44] The primary outcome of interest in the trial is change in pulmonary vascular resistance, a definitive marker of pulmonary vascular health. Results from this trial may provide much needed insight into the proper approach to establishing initial therapies for patients with PAH.

Use of Riociguat in Diseases Other Than Group 1 Pulmonary Hypertension

Early successes in treating PAH and CTEPH with the use of riociguat promoted interest in its application to alternative disease processes. To be clear, riociguat is only approved for use in patients with group 1 and 4 pulmonary hypertension. However, given the impressive results of CHEST-1 and PATENT-1 as well as research advancing the understanding of the NO-sGC-cGMP pathway and its involvement in a litany of disease states, an emerging cohort of trials are attempting to find novel clinical uses for riociguat.

Group 2 Pulmonary Hypertension and Heart Failure

Despite the introduction of recent therapeutics, heart failure remains a leading cause of worldwide hospitalizations with a profound burden on morbidity and mortality. Perturbation of the NO-sGC-cGMP pathway is seen in models of heart failure and is associated with excessive vasoconstriction and potentiation of inflammation.[22] Researchers have looked to the sGC stimulators to repair this pathway with varying degrees of success. Studies using riociguat to treat either heart failure with reduced or preserved ejection fraction (HFrEF and HFpEF, respectively) largely failed to meet their primary end points but did not negatively impact markers of cardiac function.[45,46] Vericiguat is a sGC stimulator related – but distinct – to riociguat. Its use in patients with progressive HFrEF despite background therapy showed benefit in reducing death and hospitalization despite increased rates of anemia.[47] These results are provocative and lay the groundwork for conversations and investigations into the use of the sGC stimulators to treat heart failure patients.

Group 3 Pulmonary Hypertension and Interstitial Lung Disease

"Interstitial lung disease" (ILD) or "pulmonary fibrosis" are synonymous terms that encompass a diversity of diseases arising from systemic diseases, environmental exposures, genetic, or idiopathic causes. Hypoxemia is a cardinal feature of ILD and can lead to PH. The largest group of diseases under the ILD canopy are the idiopathic interstitial pneumonias; of which, idiopathic pulmonary fibrosis stands as the most represented member.

Given the limited number of treatment options available to this patient population and its poor prognosis, the Riociguat In patients with Symptomatic PH associated with Idiopathic Interstitial Pneumonias (RISE-IIP) study group sought to evaluate the possible use of riociguat as a therapeutic tool in the war against pulmonary fibrosis.[48] Unfortunately, patients in the treatment arm of RISE-IIP showed no clinical benefit and an increased mortality, leading to early termination of the study. A post hoc subgroup analysis by the study organizers subsequently showed that patients with combined pulmonary fibrosis and emphysema (CPFE) and those with a greater radiographic burden of emphysema had worse outcomes than other members of the cohort. Patients with CPFE enrolled in the treatment arm were two times more likely to die than patients with pulmonary fibrosis alone.[49] Future trials that wish to examine riociguat's role in treating patients with pulmonary fibrosis will need to account for the heterogenous nature of the ILD population in their design.[50]

Group 4 Pulmonary Hypertension and Chronic Thromboembolic Disease

Chronic thromboembolic pulmonary hypertension (CTEPH) occurs in approximately 2–4% of cases of pulmonary embolism.[51,52] CTEPH is by and large a surgical disease with improvements in pulmonary artery pressures, pulmonary

vascular resistance, and patient ambulation seen after invasive pulmonary artery endarterectomy and less invasive (but less studied) balloon angioplasty. Medical intervention is considered in CTEPH patients deemed poor operative and procedural candidates and in those that remain symptomatic even after intervention.

CHEST-1 assessed the use of riociguat in the management of patients not appropriate for pulmonary endarterectomy or had persistently elevated right-sided pressures following endarterectomy.[12] In this 16-week trial, 261 patients were assessed for change in 6-minute walk distance after receiving either riociguat or placebo. Patients in the study arm demonstrated a net increase in 46 meters of walk distance as well as a reduction in pulmonary vascular resistance and NT-proBNP levels. In addition, patients receiving riociguat also demonstrated an improvement in their WHO functional status scores.

Group 5 Pulmonary Hypertension and Sarcoidosis

Sarcoidosis is typified by the systemic deposition of granulomas and is associated with PH in 2.5–10% of patients.[53,54] The causes of PH in sarcoid patients are myriad and largely misunderstood. As such, PH in sarcoid patients receives a group 5 designation under the current WHO classification system. In 2022, Baughman et al sought to investigate the role of riociguat in this patient population.[55] Using pooled outcomes of hospitalization, death, lung transplant, and decline in 6-minute walk distance, patients received either riociguat or placebo over 48 weeks. Patients in the placebo arm showed a significant progression in disease as defined by time to clinical worsening. This trial enrolled a small sample size (16 patients in total) and excluded patients with a reduced forced vital capacity less than 50% of predicted, a marker of relevant pulmonary fibrosis. The implication these results on clinical practice is unclear but provides justification for a larger Phase 3 study.

Use of Riociguat in Diseases Other Than Pulmonary Hypertension

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disease caused by mutations that occur at the cystic fibrosis transmembrane conductance regulator (CFTR) gene whereby 90% of patients are effected at Phe508del.[56] Because preclinical studies suggested that promotion of NO production with administration of a PDE5 inhibitor showed improvement in chloride transport function,[57] researchers from the Rio-CF study group sought to evaluate the role of riociguat in treating cystic fibrosis patients carrying a homozygous PHe508del mutation to the CFTR protein.[58] In a placebo-controlled study, cystic fibrosis patients randomized to receive 1.0mg of riociguat three times a day demonstrated no changes in sweat chloride concentration and forced expiratory volume in one second (FEV1) across 28 days. This study was terminated before a planned open-label second part was undertaken and it would appear that riociguat does not have a place in the treatment of patients with cystic fibrosis.

Systemic Sclerosis

Sclerosis is a systemic disease highlighted by fibrotic deposition most commonly in the dermis but potentially also present in the gastrointestinal, renal, pulmonary, and cardiovascular systems.[59] Preclinical data from animal models of dermal fibrosis implied a possible role for the reversal of skin thickness and reduced myelofibroblastic activity with riociguat.[60] Towards these ends, a Phase 2, placebo-controlled study attempted to evaluate non-PH outcomes with the use of riociguat in patients with early (less than 18 months) diffuse cutaneous systemic sclerosis.[61] This trial was conducted over one year but failed to meet its primary end point of observed changes from a standardized assessment of skin thickness (Rodnan skin score) when compared to placebo. Despite this disappointment, patients receiving riociguat showed a trend towards reduction in digital ulcerations and an improvement in Raynaud's phenomena.

Future Directions for the Use of Riociguat

There is a rising interest amongst investigators and clinicians to better understand the effects of PAH medications on RV health. Riociguat and selexipag (an oral prostacyclin receptor agonist) both received FDA approval for the treatment of PAH based on noninvasive surrogate makers (the later used a composite of death and complications related to PAH as its

primary end point[62]) of cardiovascular health. However, because the final stages of terminal PAH are marked by RV failure, there is an interest in identifying early markers of PAH's impact on RV function. Advances in cardiac magnetic resonance imaging (MRI) and its integration with right heart catheterization techniques may someday augment biomarker and noninvasive data to present a fuller picture of pulmonary artery compliance and its impact on RV functionality.[63] This data, could in turn, hopefully be used to identify patients most likely to derive benefit from the use of riociguat.

Conclusion

Riociguat, a powerful stimulator of soluble guanylate cyclase, increases blood flow through the pulmonary arteries by dilating vascular smooth muscle cells. It is used to treat patients with group 1 pulmonary arterial hypertension as a primary agent or in place of phosphodiesterase 5 inhibitors such as sildenafil or tadalafil. The side effects associated with riociguat are stereotypical for drugs that promote systemic vasodilation. The place of riociguat's usage in disease outside group 1 and 4 pulmonary hypertension is of unclear efficacy. More and more studies are being undertaken to apply riociguat to diseases outside of PAH that demonstrate a malfunctioning NO-sGC-cGMP pathway. Moreover, more sGC stimulators and activators are coming into development. It is with great hope that perhaps these drugs will find an expanded role place in the treatment of maladies common to the general population and not just those suffering from PAH.

Abbreviations

CFTR, Cystic Fibrosis Transmembrane Conductance Regulator; CHMP, Committee for Medicinal Products for Human Use (Europe); cGMP, cyclic Guanosine Monophosphate; CPFE, Combined Pulmonary Fibrosis and Emphysema; CTEPH, Chronic Thromboembolic Pulmonary Hypertension; eNOS, endothelium Nitric Oxide Synthase; FEV1, Forced Expiratory Volume in One Second; FDA, Food and Drug Administration (USA); GTP, Guanosine Triphosphate; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; ILD, Interstitial Lung Disease; MRI, Magnetic Resonance Imaging; iNOS, inducible Nitric Oxide Synthase; nNOS, neuronal Nitric Oxide Synthase; NO, Nitric Oxide; NOS, Nitric Oxide Synthase; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAH, Pulmonary Arterial Hypertension; PDE5, Phosphodiesterase 5; PH, Pulmonary Hypertension; PKG, Protein Kinase G; RV, Right Ventricle; sGC, soluble Guanylate Cyclase; WHO, World Health Organization.

Disclosure

The authors report no conflicts of interest in this work.

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