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Soluble Guanylate Cyclase Stimulators and Activators: Novel Therapies for Pulmonary Vascular Disease or a Different Method of Increasing cGMP?

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Abstract Pulmonary arterial hypertension (PAH) is a progressively worsening disorder characterized by increased pulmonary vascular resistance leading to increased afterload, right ventricular hypertrophy, and ultimately right heart failure and death. Current pharmacologic treatments primarily act to reduce pulmonary vascular resistance (PVR) and provide some benefit but do not cure PAH. Canonical vasodilator therapy involving the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cGMP pathway has demonstrated efficacy, but in pathologic states, endothelial dysfunction within the pulmonary vasculature leads to the reduced synthesis and bioavailability of NO. Acting downstream of NO, sGC stimulators and activators restore the endogenous functions of NO and exploit the positive effects of sGC stimulation on various organ systems, including the heart. Riociguat (BAY 63-2521) is the first agent in a class of sGC stimulators to receive FDA approval for the treatment of PAH and chronic thromboembolic hypertension (CTEPH). Riociguat has demonstrated significant benefit as assessed by 6MWD, PVR, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, time to clinical worsening, World Health Organization (WHO) functional class, and other quality of life measures in clinical trials as a monotherapy and in combination with endothelin receptor antagonists or non-intravenous prostanoids. Riociguat is the first FDA-approved treatment option for inoperable or persistent CTEPH and adds a new effective drug to available treatment options for pulmonary hypertension (PH). The question of whether riociguat is superior to other available treatment options is unanswered at the present time and requires further study.

Keywords Soluble guanylate cyclase stimulator · Riociguat (BAY 63-2521) · Pulmonary hypertension (PH) · Pulmonary arterial hypertension (PAH) · Chronic thromboembolic hypertension (CTEPH)

Introduction

Pulmonary hypertension is a disorder characterized by progressive degeneration and remodeling of the pulmonary vasculature, leading to a progressive rise in pulmonary vascular resistance, right heart failure, and death [1, 2]. The World Health Organization (WHO) classifies pulmonary hypertension (PH) into five groups (Table 1). In this review, we will primarily focus on the treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic hypertension (CTEPH), groups one and four respectively, and discuss the role of soluble guanylate cyclase modulators such as the soluble guanylate cyclase (sGC) stimulator riociguat and the sGC activator cinaciguat for PH therapy.

PAH is a debilitating chronic disease with 1- and 3-year mortalities at 15–17 and 32–42 %, respectively [4, 5]. CTEPH is also associated with increased risk of mortality, 1- and 3-year mortality is 18 and 30 % for those with inoperable disease, and 1- and 3-year mortality is 1 and 6 % for those with residual PH after pulmonary thromboendarterectomy (PTE) undergoing medical treatment [6]. Treatment goals in PAH and CTEPH are to improve quality and length of life, and clinical benefit is assessed by improvements in functional class (WHO FC), exercise capacity (6MWD), right ventricular (RV) size and function, cardiopulmonary exercise parameters,

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Table 1 WHO pulmonary hypertension taxonomy

WHO group	Description
Group 1 PAH	- Idiopathic, heritable, toxin-, and drug-induced or associated with conditions such as connective tissue disease, congenital heart disease, liver disease, HIV infection, schistosomiasis, or portal hypertension
	- Common obstruction and adverse remodeling of the small pulmonary arteries
Group 2	- Common elevation of left atrial pressure
Left heart related	- Due to systolic or diastolic left ventricular dysfunction or left-sided valvular disease
Group 3 Lung related	- Secondary to chronic lung diseases (e.g., chronic obstructive pulmonary disease, interstitial lung disease), chronic hypoxia, or sleep disordered breathing
Group 4 CTEPH	- Due to unresolved thromboemboli in the pulmonary arterial circulation
Group 5 Other	- Unclear multifactorial mechanisms

Pulmonary hypertension groups exhibiting similar pathophysiology as defined by the World Health Organization [3]

plasma brain natriuretic peptide (BNP) or N-terminal of the prohormone BNP (NT-proBNP) levels, and survival [7].

The various subgroups of PAH at the molecular level share similar pathology: endothelial dysfunction, inflammation, increased cell proliferation, impaired apoptosis, and disordered metabolism in the pulmonary vasculature and right ventricle [8–15]. This results in a loss of arterial vascular volume, increased vasoconstriction, and impaired vascular compliance, leading to increased pulmonary vascular resistance (PVR) and RV afterload [1, 16•]. Increases in afterload are associated with remodeling and phenotypic changes of the RV, ultimately culminating in RV failure and death [9].

PAH patients frequently exhibit dysregulation of prostaglandin levels favoring constrictors over vasodilators, attenuation of the nitric oxide (NO) signaling pathway, and elevation of endothelin-1 [8, 17–19]. Prostacyclin analogues or prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 (PDE-5) inhibitors effectively target these imbalances, but vasodilatory agents alone have not proven to reverse pulmonary arterial vasculature dysfunction or normalize right ventricular function [20, 21]. The apparent mechanisms underlying disease pathophysiology and approved therapeutics do not seem to match [2, 22].

Soluble guanylate cyclase is a heterodimer composed of one α-subunit and one heme-binding β-subunit that catalyzes the formation of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate [23]. Nitric oxide normally stimulates sGC, but NO production may be reduced in the occlusive vasculopathy present in PH [8]. The NO-sGC-cGMP signaling pathway may be further attenuated by the inactivation of NO by reactive oxygen species and oxidation of the sGC heme moiety, reducing NO sensitivity [24, 25]. Inhaled NO or drugs releasing NO and organic nitrates are associated with noteworthy therapeutic shortcomings such as the development of tolerance and a lack of efficacy in certain disease states [26–32].

Soluble guanylate cyclase stimulators such as riociguat (BAY 63-2521) require the presence of a reduced heme moiety and both sensitize sGC to NO by stabilizing NO-sGC binding and directly stimulate sGC independently of NO [24]. Soluble guanylate cyclase activators such as cinaciguat (BAY 58-2667) are heme mimetics that bind and replace the endogenous heme in sGC catalyzing the production of cGMP in a NO- and heme-independent manner [33–35]. These novel sGC modulators maintain efficacy in conditions in which endogenous NO production, NO bioavailability, and sGC redox status are compromised, providing a potential theoretical advantage over existing PDE-5 inhibitor therapy in certain patient populations. Unfortunately, current sGC modulators lack specificity for the pulmonary vasculature and cause dose-dependent reductions in systemic blood pressure [36]. Significant systemic hypotension is poorly tolerated in many PAH patients due to an inability to increase cardiac output owing to reduced right ventricular reserve as a result of intrinsic right ventricular disease, reduced pulmonary arterial cross-sectional area, and reduced compliance of the pulmonary arterial vasculature [22].

In animal models, sGC modulators have demonstrated positive effects on the pulmonary vasculature and hemodynamics [37–46]. These agents have other notable effects on the heart and vasculature mediated by sGC including anti-fibrotic [47–51], antiproliferative [52], and anti-inflammatory effects [47]. Direct pharmacological stimulation of sGC demonstrated a cardioprotective effect on several preclinical studies in different animal models of pulmonary hypertension [47, 48, 53, 54].

Clinical Trials

Riociguat for PAH

The Pulmonary Arterial Hypertension sGC Stimulator Trial 1 (PATENT-1) was a multicenter, randomized, placebo-controlled trial ($n = 443$, primarily WHO FC II or III) evaluating the safety and efficacy of riociguat to treat group 1 PAH in therapy-naïve patients (50 %) and patients receiving ERAs

(44 %) or non-intravenous prostanoids (6 %) as background therapy [55•]. At week 12, the placebo-adjusted 6MWD within the experimental group increased 36 m with a baseline 6MWD of 363 m. Improvements in secondary endpoints such as PVR, improvement of NT-proBNP levels, WHO FC, time to clinical worsening, and Borg dyspnoea score were significant in the riociguat individual titration group (to maximum dose of 2.5 mg tid) vs. placebo. Drug-related serious adverse events (SAEs) included syncope (1 %) and single cases of increased hepatic enzyme levels, dizziness, presyncope, acute renal failure, and hypotension (0.4 %). Drug-related adverse events (AEs) that led to discontinuation included esophageal pain and esophageal swelling, supraventricular tachycardia, hypotension, generalized edema, and neck pain.

Riociguat for PAH Long-Term Extension Trial

Pulmonary Arterial Hypertension sGC Stimulator Trial (PATENT-2) is an ongoing long-term, open-label extension trial ($n = 396$, 97 % WHO Functional Class II or III) of PATENT-1 evaluating the safety and efficacy of riociguat as monotherapy (50 %), and as a combination therapy for patients receiving ERAs (43 %), non-intravenous prostanoids (6 %), and ERAs with non-intravenous prostanoids (1 %) [56•]. Improvements were noted in mean 6MWD (+51 m compared with the PATENT-1 study baseline), and benefits observed in WHO FC (94 % improved or stable), NT-proBNP levels, and Borg dyspnoea scores were maintained at 1 year with an estimated survival rate of 97 % [56•]. Two-year data was released in an abstract with mean 6MWD increasing by 47 m compared with the PATENT-1 study baseline, and 91 % of patients had improved or stable WHO FC and 93 % survival [57].

Drug-related AEs were reported in 54 % of patients; the most common were dizziness (9 %), headache (8 %), and dyspepsia (8 %). Drug-related SAEs were reported in 7 % of patients. The most common drug-related SAEs included syncope (2 %) and worsening PAH (1 %). Two cases of hemoptysis/pulmonary hemorrhage were considered study-drug related by the investigators though the exposure-adjusted rate of hemoptysis/pulmonary hemorrhage was lower in the PATENT-2 study compared with PATENT-1 [56•].

The subgroup of patients in the PATENT studies with PAH-associated corrected congenital heart disease ($n = 35$, a subgroup with limited existing clinical data) was determined to exhibit similar safety and efficacy to the composite study population in a retrospective study [58].

Combination Therapy with Riociguat and PDE-5 Inhibitors

PATENTplus was a blinded, placebo-controlled, randomized extension study ($n = 18$) to study the safety and efficacy of adding riociguat to background sildenafil (20 mg tid) therapy in PAH patients [59•]. No significant benefits were observed with combination therapy in exploratory efficacy variables, and high rates of adverse events and discontinuation resulted in study termination [59•]. As a result, riociguat should not be used in combination with phosphodiesterase type-5 inhibitors.

Riociguat for CTEPH

The Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (CHEST-1) was a multicenter, randomized, double-blind, placebo-controlled trial ($n = 261$, primarily WHO FC II or III) evaluating the efficacy and safety of riociguat in patients with inoperable group 4 CTEPH (72 %) or persistent or recurrent PH after pulmonary thromboendarterectomy (28 %) [60•]. After 16 weeks, treatment was associated with a significant increase in placebo-adjusted mean 6MWD (+46 m), decreases in PVR (-249 dyn · sec/cm^5), decreases in mPAP (-5 mmHg), and improvements in cardiac output, NT-proBNP levels, and WHO FC when compared to placebo. Drug-related SAEs in the riociguat group included syncope (2 %) and gastritis, acute renal failure, and hypotension (1 % for each). Four (2 %) AEs and three (2 %) SAEs of hemoptysis were reported in the riociguat group during CHEST-1 [61•].

Riociguat for CTEPH Long-term Extension Trial

CHEST-2 is a long-term, open-label extension trial ($n = 237$) which included patients from CHEST-1 [61•]. At 1 year, 6MWD increased 51 m in the total patient population compared with baseline and NT-proBNP significantly decreased. WHO FC improved or remained stable in 96 % of patients, and the estimated survival rate was 97 %. Riociguat was well tolerated, and 6 % of patients withdrew due to AE and SAE. The most common drug-related AEs were dizziness (10 %), dyspepsia (8 %), and hypotension (5 %), while drug-related SAEs were reported in 5 % of patients. The most common drug-related SAEs were syncope (2 %) and hypotension (1 %). During CHEST-2, eight (3 %) AEs and four (2 %) SAEs of hemoptysis were reported.

Riociguat for Group 2 PH with Left Ventricular Dysfunction

Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) was a phase IIb double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study ($n = 201$) evaluating the clinical utility of riociguat in patients with heart failure resulting from PH caused by systolic left ventricular dysfunction [62]. The primary endpoint was not met as the drop in mPAP was not statistically different from placebo. Cardiac index, stroke volume index, pulmonary, and systemic vascular resistance were significantly improved without significant

changes in heart rate or systemic blood pressure. Riociguat also reduced the Minnesota Living with Heart Failure score. Treatment-emergent drug-related AEs were reported in 43 and 22 % of patients in the riociguat 2 mg and placebo groups, respectively. Treatment-emergent drug-related SAEs in the riociguat 2 mg group included cardiac failure, ventricular tachycardia, syncope, and hypotension (6 % in total).

Riociguat in Patients with Group 2 PH Associated with Diastolic Heart Failure

Acute Hemodynamic Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Diastolic Heart Failure (DILATE-1) was a double-blind, randomized, placebo-controlled, parallel-group study ($n = 36$) examining the effects of single-dose riociguat in clinically stable patients receiving standard HF therapy with heart failure with preserved LV ejection fraction (HFpEF) and PH [63]. There was no significant change in peak decrease in mPAP up to 6 h after treatment with riociguat. Stroke volume and cardiac index significantly increased, and systolic BP and right ventricular end-diastolic area significantly decreased without significant changes in heart rate, pulmonary arterial wedge pressure, transpulmonary pressure gradient, or PVR. The majority of AEs were of mild or moderate intensity. Drug-related SAEs (30 %) were one case of decreased cardiac output and three cases of decreased MAP.

Effect of Riociguat on Right Heart Size and Function

In a study ($n = 39$) of patients drawn from the PATENT, PATENTplus, CHEST, and the Expanded Access Program (EAS) trials, the long-term effects of riociguat on right heart size and function were evaluated [16•]. Echocardiography, 6MWD, and further clinical parameters were analyzed at baseline and after 3, 6, and 12 months. Mean right ventricular (RV) area significantly decreased after 3, 6, and 12 months compared to baseline with 30.7 % of patients going into normal ranges after 1 year. Right atrial area significantly decreased after 12 months with 26 % of patients going into normal ranges after 1 year, and tricuspid annular plane systolic excursion (TAPSE) significantly improved after 6 and 12 months. RV wall thickness and 6MWD significantly improved after 3, 6, and 12 months. Invasive hemodynamics also significantly improved after 3 months.

Riociguat for Group 3 PH with Associated Lung Disease

An exploratory, non-randomized, non-blinded, non-controlled pilot study ($n = 22$) by Ghofrani et al. examined the acute single-dose effects of riociguat (1 and 2.5 mg) in borderline or manifest PH associated with chronic obstructive pulmonary disease (COPD) [64]. Acute riociguat treatment in the 2.5 mg group led to significant dose-dependent improvements in mPAP (−4.83 mmHg), PVR (−123.8 dyn · sec/cm^5), and cardiac output (+1.61 L/min) without relevant changes in lung function or gas exchange with minor drug-related AEs [64]. These effects are generally more pronounced than those observed after the administration of inhaled NO [2, 65].

In an open-label, uncontrolled pilot trial ($n = 22$), patients received oral riociguat for the treatment of interstitial lung disease (ILD) associated with PH [66]. PH can arise as a significant problem in ILD patients with approximately 30–40 % of patients with ILD developing PH [67–72]. Riociguat appeared to be well tolerated by the majority of patients with PH-ILD, and after 12 weeks of therapy, mean cardiac output and 6MWD increased, PVR decreased, and mPAP remained unchanged compared with baseline. Frequently reported drug-related AEs were dyspnoea (27.3 %), peripheral edema (27.3 %), dyspepsia (13.6 %), headache (13.6 %), and feeling hot (13.6 %). Reported drug-related SAEs included syncope (4.5 %), dyspnoea (13.6 %), pancytopenia (9.1 %), respiratory disorder (4.5 %), and respiratory failure (4.5 %).

Cinaciguat Clinical Trials

In the first non-randomized, uncontrolled study of cinaciguat in patients with acute decompensated heart failure, cinaciguat had formidable preload- and afterload-reducing effects, increasing cardiac output and preservation of renal function. The drug was reportedly well tolerated, with hypotension reported in 10 % of patients [73]. A subsequent unpublished study (NCT00559650) was terminated, and the COMPOSE series of trials (COMPOSE 1, COMPOSE 2, and COMPOSE EARLY) were terminated early due to systemic hypotension and difficulty enrolling patients [74].

Discussion

Riociguat is administered orally tid, requires dose titration to lessen the risk of systemic hypotension, and does not alter prothrombin time when combined with warfarin. Riociguat is contraindicated in patients receiving PDE-5 inhibitors, nitrates, or nitric oxide donors and is listed as pregnancy category: X [75].

It is our opinion that riociguat is a useful addition to the available treatment options for PH in the current time particularly for patients who may not respond to existing therapies or have issues with their respective side effects. The question of whether riociguat is superior to other treatment options is unanswered and requires further study. We concur with the conclusions reached by Dasgupta et al. that the sGC stimulator riociguat is similar in safety, tolerability, and efficacy to existing oral medicines for the treatment of PAH [22]. Sufficient evidence is not present in the literature to determine

the preferred initial therapy for therapy-naïve patients, or preferred combination therapy for more advanced patients. The results, to date, from the PATENT-2 study indicate that Riociguat serves as an acceptable choice for monotherapy and in combination with ERAs and non-intravenous prostanoids for PAH [56•]. Given that CTEPH does not self-resolve and the excellent results of PTE, eligibility for surgical management should be assessed as soon as possible. Medical management of CTEPH appears to be of benefit to inoperable patients, those with recurrent or persistent PH following PTE, and may be beneficial as a bridge to surgery. The sGC activator cinaciguat has shown to be limited in its utility in the clinical setting due to a lack of specificity for the pulmonary vascular bed and systemic hypotension, to a greater extent as compared to riociguat [74].

Most PH patients present with a severely enlarged right heart with increased right ventricular (RV) and right atrial (RA) areas and impaired cardiac output at diagnosis. Previous studies have shown that right heart function is the key determinant of outcome in PAH and CTEPH patients [7, 76]. More specifically, RA area has been shown to be one of the most important independent prognostic factors in PAH patients [77–79]. Direct sGC pharmacological stimulation by riociguat has demonstrated to reverse right heart dilatation and hypertrophy and to improve systolic function in several preclinical studies [48, 53, 54]. In PAH and CTEPH patients, Marra et al. demonstrated a decrease in right heart size after riociguat therapy [16•]. These data are tremendously promising for this high-risk patient population.

The role of vasodilators in the treatment of WHO groups 2 and 3 PH is controversial, with present treatments primarily targeted towards the underlying causes. Initial studies of riociguat in group 2 PH failed to meet the primary endpoint of a reduction in mPAP, but produced benefits in some secondary measures and appeared to be well tolerated [62, 63].

Deficient NO-sGC-cGMP signaling results from endothelial dysfunction and may underlie impaired cardiac relaxation/distensibility in HF-PH patients. In preclinical and small clinical studies, NO-sGC-cGMP signaling was demonstrated to be involved in impaired cardiac relaxation/distensibility, though a study by Reinke et al. showed that neither riociguat nor cinaciguat at clinically relevant levels exerted any positive inotropic effects on isolated cardiac myocytes despite an increase in cGMP levels [80–82]. It must be noted that cardiac myocytes and smooth muscle cells differ markedly in the regulation of contraction and relaxation as well as in the composition of regulatory and structural proteins [83]. This may explain a lack of significant change in ventricular filling pressure in DILATE-1 patients. Riociguat may however provide a benefit by unloading the heart and improving stroke volume and cardiac output in group 2 PH patients.

Riociguat appears to be well tolerated in both completed single-dose studies in group 3 PH patients [64, 66]. The estimated prevalence of PH-associated COPD is wide ranging (30–70 %), depending on the PH definition used [84–87]. Risk of worsening gas exchange associated with COPD is a problem with many available vasodilators, but riociguat was well tolerated [88]. Riociguat may be useful in combination with other established therapies in the treatment of group 3 PH, but further studies are needed to determine if it can improve function or survival in this patient population.

The future of sGC modulator research for PH should focus on the mechanisms that underlie their effect on right heart size and function. As stated above, the right atria and ventricle are integral to patient outcomes. The non-vasodilatory effects of sGC modulators, such as the anti-fibrotic, antiproliferative, and anti-inflammatory effects, open up new possibilities in treating the overall picture of PH. Recent research has identified the increasingly important role of cell proliferation in PH and its similarities to neoplasia [89]. Although, the first trial of the antineoplastic agent, imatinib, in the treatment of PH failed to meet expectation due to a lack of efficacy and increased side effects [90], it is possible that other approaches to inhibiting cellular proliferation, such as stimulation of sGC, may prove helpful.

Conclusion

Riociguat is the first sGC stimulator approved for the treatment of PAH and CTEPH. Current evidence suggests that riociguat is suitable as a monotherapy and in combination treatments with ERAs and non-intravenous prostanoids. The question of whether riociguat is superior to other available treatment options is unresolved at this time. It is our opinion that riociguat is a useful addition to the medical armamentarium, and further studies and development of this novel class of drugs is a worthwhile pursuit.

Compliance with Ethical Standards

Conflict of Interest Drs. Koress, Swan, and Kadowitz declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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