Review Article

Riociguat: Something new in pulmonary hypertension therapeutics?

Elangovan Shanmugam, Amrita Jena, Melvin George

Department of Cardiology, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India

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ABSTRACT

Pulmonary hypertension (PH) continues to be a disease that is associated with woeful outcomes. The search for an ideal drug molecule for PH led to the discovery of riociguat, which is a first-in-class drug molecule that activates soluble guanylate cyclase. We conducted a systematic literature search using databases such as PubMed, Science Direct, Springer, Cochrane Reviews and Google Scholar to gather evidence generated from published clinical trials on the efficacy, safety, pharmacokinetics and regulatory status of riociguat. CHEST-1 and the PATENT-1 were phase-3 pivotal clinical trials that showed that riociguat was able to significantly improve the 6-min walk distance with 16 weeks of therapy as compared with the placebo arm. The drug also showed improvement in secondary outcome measures such as improvement in the pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide levels, World Health Organization functional class, time to clinical worsening and Borg dyspnea score. The drug had a modest safety profile, with hypotension being the most bothersome adverse effect. These findings led to various regulatory agencies around the world granting approval for riociguat for the treatment of pulmonary arterial hypertension (PAH) and inoperable chronic thromboembolic pulmonary hypertension (CTEPH). The entry of a new class of drug for PAH and CTEPH therapy portends some hope for patients with a disease that is traditionally linked with a poor prognosis.

Key words: Chronic thromboembolic pulmonary hypertension, guanylate cyclase, pulmonary arterial hypertension, riociguat

INTRODUCTION

Pulmonary hypertension (PH) can be described as a complication caused by progressive obstruction and obliteration of the pulmonary arteries, ultimately leading to a progressive rise in pulmonary vascular resistance (PVR) and right ventricular (RV) failure and death.[1] PH may be classified into five categories: Group 1 - pulmonary arterial hypertension (PAH), which includes idiopathic, sporadic, familial, drug-induced, HIV infection; group 2 - PH due to left heart disease; group 3 - PH due to lung disease; group 4 - chronic thromboembolic pulmonary hypertension (CTPH); and group 5 - PH with multifactorial mechanisms.[2,3] Smooth muscle medial hypertrophy, intimal proliferation, *in situ* thrombosis and the development of plexiform lesions are some of the pathological changes observed during this condition. The incidence of PAH is roughly said to be 1–2 per 1,000,000.[4]

Prostanoids, endothelin receptor antagonists and phosphodiesterase type V inhibitors are principally used in the drug therapy of PAH. Prostanoids include epoprostenol,

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Address for correspondence:
Melvin George, Department of Cardiology, Division of Cardiac Clinical Trials and Research, SRM Medical College Hospital and Research Centre, Kattankulathur, Kancheepuram, Chennai - 603203, Tamil Nadu, India. E-mail: melvingeorge2003@gmail.com

teprostinil, iloprost and beraprost. The use of epoprostenol is fraught with a myriad of drug delivery issues such as requirement of the patient to be familiar with the techniques of sterile drug preparation, operation of the pump and skill in using intravenous catheter that is surgically implanted, catheter-related infections and pump malfunction. Teprostinil is associated with a high rate of gram negative infections. Iloprost requires frequent administration via the inhalational route. Beraprost, which is only approved in Japan, has also been shown to lose its effectiveness over 1 year. Endothelin receptor antagonists such as bosentan, ambrisentan and sitaxsentan have similar efficacy. Peripheral edema and hepatotoxicity are disconcerting features associated with their usage.[5-7] The limitations with the current crop of molecules has spurred the quest for a better drug molecule for PAH. Riociguat is the most recent drug approved by the United States Food and Drug Administration for the treatment of PAH. This review highlights the key features of this novel first-in-class drug molecule.

An electronic search was performed using databases such as PubMed, ScienceDirect, Cochrane Library, Google Scholar and Springer Database. The search term used for the literature search was "Riociguat and PAH and CTEPH." The literature search was limited to human studies only. Riociguat associated with animal studies, pediatric studies, diabetic, anemia, renal dysfunction, hypertension and obesity were excluded. *In vitro* studies, poster presentations, conference proceedings, abstracts and editorials were also excluded. Some papers from references were also retrieved so as not to miss important information. All original papers were included for the systematic review [Figure 1].

Mode of action of riociguat

Riociguat is a first-in-class agent that belongs to the class of molecules termed as soluble guanylate cyclase stimulators. In PH, there is a breakdown in the signaling mechanisms of nitric oxide-soluble guanylate cyclase and cyclic guanosine monophosphate (cGMP) coupled with a reduction in the nitric oxide synthesis. By virtue of its ability to stimulate guanylate synthase independent of nitric oxide, riociguat is able to increase cGMP that causes vasodilation and a fall in the pulmonary arterial pressure. cGMP also has additional anti-fibrotic and anti-proliferative actions.[8,9]

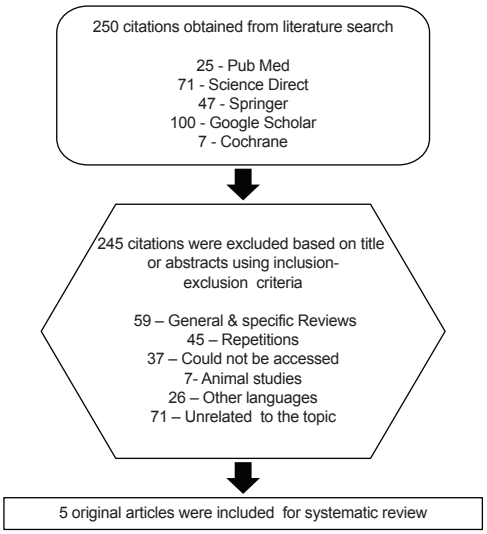

Figure 1: Flowchart depicting systematic review for riociguat

Clinical trials

Gofhrani *et al.*[10] conducted a 12-week, prospective, open-label, dose-titration (according to systolic blood pressure) phase II study. They included 42 patients with chronic thromboembolic PH and 33 patients with PAH according to the World Health Organization (WHO) functional classes II/III. Safety, tolerability and feasibility of individual titration of riociguat according to peripheral systolic blood pressure (SBP) were the primary end points of the study, combined with secondary end points like change from baseline (week 0) in exercise capacity (6-min walk distance [6MWD], modified Borg dyspnea score and WHO functional class [assessed after 12 weeks]). Riociguat treatment increased exercise capacity as measured by 6MWD. A significant median improvement by 55 m (20.0–107.0; $P < 0.0001$) was observed after 12 weeks of treatment in the total population, which was 359.0 m (300.0–420.0) at baseline before treatment. 6MWD was 390.0 m (330.0–441.0) at baseline in the CTEPH group, which improved by 55 m (17.0–105.0) ($P < 0.0001$) following 12 weeks of riociguat treatment. More significant improvement was observed in the PAH group than in the CTEPH group. Greater improvement by 57.0 m (25.0–117.0) ($P < 0.0001$) was observed in the PAH group, which was 337.0 m (215.0–406.0) at baseline.

The PATENT-1 and CHEST-1 studies provided clinching evidence to justify the approval of riociguat in PAH therapy. The Pulmonary Arterial Hypertension Soluble GuanylateCyclase–Stimulator Trial 1 (PATENT-1) was a phase 3, double-blind study in which 443 patients with symptomatic PAH were recruited and received placebo and riociguat in individually adjusted doses of upto 2.5 mg three times daily (2.5 mg - maximum group) or riociguat in individually adjusted doses 1.5 mg three times daily (1.5 mg - maximum group). The primary endpoint of this study was to observe the changes from baseline to the end of week 12 in the distance walked in 6 min. The change in PVR, N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, WHO functional class, time to clinical worsening, score on the Borg dyspnea scale, quality-of-life variables and safety were the secondary end points included in the study. The results of the study showed that riociguat had increased the 6MWD by week 12 to a mean of 30 m in the 2.5 mg – maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% confidence interval, 20–52; $P < 0.001$). It also showed significant improvement in

secondary end points, such as PVR ($P < 0.001$), NT-proBNP levels ($P < 0.001$), WHO functional class ($P = 0.003$), time to clinical worsening ($P = 0.005$) and Borg dyspnea score ($P = 0.002$).[11]

The Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group was a phase IIb, double-blind, randomized, placebo-controlled, dose-ranging hemodynamic study that included 201 patients with heart failure resulting from PH caused by systolic left ventricular dysfunction. They were randomized to double-blind treatment with oral placebo or riociguat (0.5, 1 or 2 mg three times daily) for 16 weeks in four parallel arms. Their primary outcome was the placebo-corrected change from baseline at week 16 in mean pulmonary artery pressure. However, the decrease in mean pulmonary artery pressure in the riociguat 2 mg group (-6.1 ± 1.3 mmHg; $P < 0.0001$ versus baseline) was not significantly different from placebo ($P = 0.10$), but the cardiac index (0.4 $L \cdot min^{-1}m^{-2}$; 95% confidence interval, 0.2–0.5; $P = 0.0001$) and stroke volume index (5.2 mL/m^2; 95% confidence interval, 2.0–8.4; $P = 0.0018$) were significantly increased without changes in heart rate or systemic blood pressure compared with placebo. It also reduced the Minnesota Living with Heart Failure score ($P = 0.0002$). Riociguat was well tolerated in patients with PH caused by systolic left ventricular dysfunction and improved cardiac index and pulmonary and systemic vascular resistance, even if the primary end point was not achieved.[12]

The CHEST-1 (Chronic Thromboembolic Pulmonary Hypertension Soluble GuanylateCyclase–Stimulator Trial -1) is a phase 3, multicenter, randomized, double-blind, placebo-controlled study. Here, they randomly recruited 261 patients with inoperable chronic thromboembolic PH or persistent or recurrent PH after pulmonary endarterectomy to receive placebo or riociguat. The change from baseline to the end of week 16 in the distance walked in 6 min was their primary end point, and changes from baseline in PVR, NT-proBNP level, WHO functional class, time to clinical worsening, Borg dyspnea score, quality-of-life variables and safety were included as secondary endpoints. The 6-min walk by week 16 had increased by a mean of 39 m in the riociguat group as compared with a mean decrease of 6 m in the placebo group. Riociguat showed significant improvements in the NT-proBNP level ($P < 0.001$) and for the WHO functional class ($P = 0.003$).[8]

A study was conducted by Grimminger *et al.*[13] to evaluate the safety, tolerability and efficacy of riociguat in patients with moderate to severe PAH. Of the19 patients who were enrolled in the study, four patients were given an hourly incremental dose of riociguat, five patients underwent single dosing regimen of 1 mg and 10 patients were given a 2.5 mg single dose of riociguat. All patients underwent nitrous oxide inhalation for 10 min. Oral administration of riociguat was effective as there was a clinically significant reduction in mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), systolic blood pressure (SBP) and systemic vascular resistance (SVR) from baseline triggered by both riociguat 1 mg and 2.5 mg doses. The cardiac index also increased significantly with both doses (*P*-value between 0.0151 and < 0.0001).

Safety

Administration of riociguat in study patients did show some adverse effects. The most common serious adverse event in the placebo group and the 2.5 mg – maximum group was syncope (4% and 1%, respectively) in the PATENT study.[11] In the CHEST-1 study, the observed serious adverse events were RV failure (in 3% of patients in each group) and syncope (in 2% of the riociguat group and in 3% of the placebo group).[11] The most common adverse events in the riociguat 2 mg group were diarrhea (18% versus 7% with placebo), dizziness (16% versus 10% with placebo) and nausea (16% versus 7% with placebo) in the LEPHT STUDY.[12] Majority of the episodes of hypotension occurred during the titration phase and were handled by down-titration of dose. Treatment-emergent drug-related serious adverse effects like cardiac failure, ventricular tachycardia, syncope and hypotension were reported in four patients (6%) in the riociguat 2 mg group and ventricular tachycardia and lobar pneumonia, syncope and hypotension were seen in two patients (3%) in the placebo group.[8]

Pharmacokinetics

Riociguat is a soluble guanylate cyclase stimulator. It is an orally administered, first-in-class drug for the treatment of PAH. The drug reaches its maximal concentration after approximately 0.5–1.5 h. Food does not interfere with the absorption of riociguat. The drug is 95% bound to plasma protein. The high plasma protein binding feature of riociguat prevents it from being dialyzable. Riociguat follows three routes of elimination in humans; 27–71% of the dose gets eliminated by oxidative biotransformation, 13% (up to 44%) gets excreted as unchanged drug in feces and 6% (up to 19%) gets excreted as unchanged drug in urine via glomerular filtration. The elimination process shows inter-individual variability based on the CYP1A1 activity status. The drug has a mean terminal half-life of 6.8 h. In elderly healthy subjects, the mean half-lives are prolonged to 12 h.[14]

Current status

The United States Food and Drug Administration and the Health Canada approved riociguat as the first direct soluble guanylate cyclase stimulator in October 2013 for using it on patients with CTEPH and PAH. It was launched in the UK in March 2014. In the same month, it was approved in the EU for the treatment of CTEPH and PAH. The drug is to be started

at a dose of 1 mg thrice daily, and the dose is escalated every 2 weeks by 0.5 mg until a maximum dose of 2.5 mg thrice daily at 6 weeks.[15]

Limitations

Riociguat cannot be used for treatment in females with pregnancy and it is also to be avoided in patients with renal failure.[14] The drug should not be used concurrently with NO donors such as nitroglycerine due to the increased proclivity to develop hypotension with syncope. Hence, it may not be a viable option for PAH patients with co-existing coronary artery disease.[16] The drug has not yet been compared on a head-to-head basis with the currently approved drug molecules for PAH. Nevertheless, the improvement in 6MWD makes it a compelling prospect in PAH therapy.

CONCLUSION

PAH continues to be a disease linked with a dismal prognosis. The current battery of drugs available in the market has not really made a significant impact in improving the long-term outcomes, besides tolerability issues. Riociguat is a new drug that is approved for PAH and CTEPH based on the evidence generated from two pivotal trials, CHEST-1 and PATENT-1. It is a direct sGC stimulator and has shown improvement in the primary end points as measured by 6MWD from short-term studies, besides other secondary end points. It is also the first non-surgical therapy that is approved for CTEPH and appears to offer some respite, especially to the one-third of candidates who are inoperable and do not have any other alternate modalities of treatment. Thus, riociguat could be described as nothing short of breakthrough for CTEPH. Although hypotension and bleeding require careful monitoring, the drug appears to have a reasonable safety profile. Nevertheless, there is a definite need to continue monitoring the drug for its long-term outcomes and to compare it with the existing drug molecules before it becomes a front-line option in PAH drug therapy.

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