

Phosphodiesterase type 5 inhibitor to riociguat transition is associated with hemodynamic and symptomatic improvement in pulmonary hypertension

Ryan Davey¹, Raymond L. Benza², Srinivas Murali² and Amresh Raina²

¹Division of Cardiology, Western University, London, Ontario, Canada; ²Cardiovascular Institute, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA

Abstract

Riociguat is a soluble guanylate cyclase stimulator approved for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. We studied the clinical and hemodynamics effects of transitioning 12 pulmonary hypertension patients from Phosphodiesterase type 5 inhibitor (PDE5i) to riociguat, and demonstrated a significant increase in cardiac index, fall in pulmonary vascular resistance, and improvement in functional class with this switch. Switch from PDE5i to riociguat appeared to be safe and fairly well tolerated in most patients.

Keywords

hemodynamics, pulmonary arterial hypertension, riociguat, transition

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Introduction

Phosphodiesterase type-5 inhibitors (PDE5i) are a widely-used class of pulmonary vaso-remodeling agents in the treatment of pulmonary arterial hypertension (PAH)^{1,2} and have also been used in some patients with inoperable or residual chronic thromboembolic pulmonary hypertension (CTEPH).^{3,4} Recently, a novel soluble guanylate cyclase (sGC) stimulator, riociguat, has been approved for use in patients with PAH and CTEPH.^{5,6} Riociguat impacts the nitric oxide (NO) pathway, but its mechanism of action differs from PDE5i in that riociguat has NO dependent and independent effects.^{7,8} As such, riociguat may be a more potent agent compared to the PDE5i.

Riociguat cannot be co-administered with PDE5i⁹ and so has been used in treatment-naïve patients or in place of PDE5i in patients with intolerances or inadequate clinical responses to these agents. However, the benefit of switching from PDE5i to riociguat in PAH and CTEPH patients has not been clearly established. In this study, we sought to investigate the clinical and hemodynamic effects of switching PAH patients and patients with residual CTEPH after pulmonary thromboendarterectomy

previously treated with PDE5i to riociguat in a real-world clinical setting.

Methods

Study population

We retrospectively screened our pulmonary hypertension (PH) database to identify participants aged 18–80 years who had been switched from PDE5i to riociguat for the treatment of PAH or residual CTEPH after pulmonary thromboendarterectomy for a clinical indication. For inclusion, participants were required to have a right heart catheterization (RHC) prior to initiation of PDE5i therapy but were also required to have repeat RHC and clinical evaluation after a minimum of 12 weeks of therapy on PDE5i and then another repeat RHC and clinical evaluation after a

Corresponding author:

Amresh Raina, Pulmonary Hypertension Program, Section of Heart Failure/Transplant/MCS & Pulmonary Hypertension, Allegheny General Hospital, Temple University School of Medicine, 320 East North Avenue, Pittsburgh, PA 15212-4772, USA.

Email: amresh.raina@ahn.org



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minimum of 12 weeks on riociguat therapy. The protocol was approved by the institutional review board at our institution (protocol RC-5841).

Study design

This study followed a standard retrospective format with data extracted between August 2005 and February 2015 at a single tertiary PH referral center. Clinical, invasive hemodynamic, and imaging parameters were compiled at three pre-specified points: before starting on PDE5i therapy; before switching PDE5i therapy for riociguat; and after reaching steady-state therapeutic effect of riociguat after a minimum of 12 weeks of therapy at a maximally tolerated dose.

Statistical analysis

Paired t-testing was undertaken to determine differences between the pre-PDE5i and the pre-switch cohorts and also between the pre-switch and post-switch cohorts. Covariate analysis was performed with a view to controlling for the length of time on PDE5i therapy and as to whether PH therapies were intensified at the time of or prior to riociguat transition.

Results

We identified 26 patients treated with riociguat during the inclusion period. Of these, 18 had previously been treated with a PDE5i and six of these were found to have incomplete records; thus 12 patients were ultimately included in this analysis (mean age = 58 years, 83% female).

Most patients had PAH (six idiopathic, two connective tissue disease associated, one congenital heart disease associated) although three (25%) had residual CTEPH after

pulmonary thromboendartectomy. At baseline prior to PDE5i therapy, pulmonary vascular resistance (PVR) ($760 \text{ dynes/s/cm}^{-5}$) and mean PA pressure (48 mmHg) were significantly elevated but cardiac index was largely preserved (2.4 L/min/m^2). There was no significant differences in baseline or post-riociguat mean PA pressure between PAH and CTEPH patients (baseline = 49 ± 13 versus 47 ± 17 mmHg, $P=0.86$; post riociguat = 44 ± 13 versus 43 ± 7.0 mmHg, $P=0.84$) and similarly no difference in PVR among the two groups (baseline = 735 ± 428 versus 835 ± 805 dynes/sec/cm⁻⁵, $P=0.85$; post-riociguat = 563 ± 403 versus 394 ± 218 , $P=0.38$). The reason for the PDE5i to riociguat switch was clinical worsening in nine patients, side effects of PDE5i therapy in one patient, and approval of riociguat for CTEPH in two patients.

With respect to the data points specified, there were no significant differences in clinical parameters between the pre-PDE5i and the post-PDE5i groups after mean treatment duration of 172 weeks. Specifically, 6-minute walk distance (6MWD) was similar, and there were no significant differences in echocardiographic metrics of RV function (Table 1). There was a trend towards improved functional class (FC) post PDE5i therapy (3.1 versus 2.8, $P=0.07$). At baseline, 17% (2/12) of patients were on endothelin receptor antagonists (ERA) and none were on prostacyclin analogues (PC). Post-PDE5i, 75% were on ERA and 33% were on PC therapy meaning that 67% of patients had other PH therapies added or intensified. Two patients in the study had an ERA discontinued during the follow-up period while on riociguat.

The mean dose of riociguat achieved was 2.4 ± 0.1 mg three times daily, with a mean treatment duration of 34 weeks. Comparing the post PDE5i to post-riociguat time points, there was again no significant change in 6MWD or echocardiographic metrics of RV function. Clinician assessment of FC did improve significantly after this switch from a

Table 1. Comparison of clinical and laboratory parameters post treatment with PDE5i with post switch to riociguat.

	Pre-PDE5i	Post PDE5i	P value*	Post riociguat	P value†
Laboratory findings					
Creatinine (mg/dL)	1.2 ± 0.4	1.1 ± 0.2	0.60	1.2 ± 0.2	0.78
6MWD (m)	X	332 ± 22		337 ± 25	0.84
RVEDD (mm)	49 ± 8	48 ± 4	0.87	50 ± 2	0.62
TAPSE (mm)	18 ± 10	18 ± 2	0.79	17 ± 2	0.44
Concomitant medications					
ERA	2	8	P = NS	6	P = NS
Prostacyclin	0	5	P = NS	7	P = NS
Clinical characteristics					
WHO FC	3.1 ± 0.5	2.8 ± 0.1	0.07	2.5 ± 0.2	0.018

Values reported as mean \pm standard deviation.

*For comparison between the pre-PDE5i and post-PDE5i time points.

†For comparison between post-PDE5i and post-riociguat time points.

6MWD, 6-minute walk distance; RVEDD, right ventricular end-diastolic dimension; TAPSE, tricuspid annular plane systolic excursion; ERA, endothelin receptor antagonist; WHO FC, World Health Organization functional class; X, missing data.

mean FC of 2.8 ± 0.1 to 2.5 ± 0.2 ($P=0.018$). 6MWD was not examined at the pre-PDE5i time point due to missing historical 6MWD data.

Hemodynamic changes from pre-PDE5i to post-PDE5i and from post-PDE5i to post-riociguat are detailed in Table 2. There was no significant change in hemodynamics from pre- to post-PDE5i therapy, with non-significant trends to lower right atrial pressure (11 versus 8 mmHg, $P=0.21$), PVR (760 versus 649 dynes/sec/cm⁻⁵, $P=0.33$), higher cardiac index (2.4 versus 2.6 L/min/m², $P=0.20$), and higher systolic blood pressure (132 versus 141 mmHg, $P=0.07$). However, in comparing hemodynamics from post-PDE5i to post-Riociguat, cardiac index increased significantly (2.6 versus 3.1 L/min/m², $P=0.026$), PVR decreased significantly (649 versus 524 dynes/sec/cm⁻⁵, $P=0.037$), and systolic blood pressure decreased (141 versus 119 mmHg, $P=0.001$). Systolic and mean PA pressure did not change significantly.

Seven patients in this cohort received acute vasoreactivity testing with inhaled NO at 20 ppm in the catheterization laboratory, in part as an investigational tool to determine whether vasoreactivity to inhaled NO might predict hemodynamic response to chronic riociguat therapy. In these patients, mean PVR decreased by 37% acutely during inhaled NO administration whereas with long-term riociguat therapy, PVR in this cohort dropped by 15%. By means of comparison, patients who did not receive inhaled NO during right heart catheterization ($n=5$) had a 24% fall in PVR on long-term riociguat therapy. There was no significant correlation between fall in PVR with inhaled NO and drop in PVR with riociguat ($r=0.031$, $P=0.943$) in patients who received acute vasoreactivity testing. On covariate analysis, there was no significant impact of time of riociguat therapy or the addition of other PH therapies at the time on the hemodynamic endpoints post riociguat (i.e. cardiac index, PVR, MAP). In terms of side effects, both

headache and lowering of blood pressure (mean decrease in systolic blood pressure = 22 mmHg) were commonly reported with the switch from PDE5i to riociguat, but did not require discontinuation of riociguat in this cohort.

Discussion

The treatment algorithm for PAH continues to evolve with numerous new treatment options now available as well as the more frequent use of early combination therapy.^{10,11} Our study demonstrates that the switch to riociguat in place of PDE5i in patients mainly treated with combination therapy appears to have a hemodynamic and potentially a symptomatic benefit. This study is the first published work, to our knowledge, to detail the clinical and hemodynamics effects of switching a PDE5i to riociguat in a mixed cohort of PAH and CTEPH patients on background combination therapy.

We demonstrated a statistically significant but also clinically meaningful increase in cardiac index and a concomitant decrease in PVR. Though PA systolic and mean pressures were slightly lower after riociguat therapy, these changes were not significant. There are two potential explanations for this finding. The first is the well-described phenomenon that incremental PH therapies may increase pulmonary blood flow without changes in pressure by trading flow for resistance. The second is merely that our sample size was too small to adequately detect a relatively modest decrease in PA pressure with this switch.

This study also demonstrated an improvement in FC after switch to riociguat, but this did not correlate with improvement in 6MWD. In this cohort, acute vasoreactivity to inhaled NO during catheterization was not associated with the degree of decrease PVR on long-term riociguat therapy. Therefore, our data do not support using vasoreactivity to inhaled NO as a metric to predict clinical

Table 2. Comparison of hemodynamics pre treatment and post treatment with PDE5i and post treatment with riociguat.

	Baseline	Post PDE5i	P value	Post riociguat	P value
RAP (mmHg)	11.2 ± 1.5	8.4 ± 1.0	0.21	9.8 ± 1.0	0.36
PAs (mmHg)	80.6 ± 7.1	80.9 ± 5.8	0.77	69.8 ± 5.9	0.06
PAd (mmHg)	30.1 ± 2.9	27.6 ± 3.7	0.44	25.3 ± 2.5	0.40
PAm (mmHg)	48.2 ± 3.8	47.1 ± 4.8	0.68	43.6 ± 3.1	0.37
PCWP (mmHg)	11.8 ± 1.2	12.5 ± 1.6	0.60	11.7 ± 1.0	0.61
FCI (L/min/m ²)	2.44 ± 0.28	2.64 ± 0.19	0.20	3.05 ± 0.22	0.026
PVR (dynes-s/cm ⁵)	760 ± 145	649 ± 103	0.33	524 ± 102	0.037
SBP (mmHg)	132.3 ± 5.7	141.0 ± 6.3	0.07	119.2 ± 6.8	0.002
DBP (mmHg)	74.4 ± 5.6	81.3 ± 3.7	0.34	67.2 ± 3.4	0.007
MAP (mmHg)	93.9 ± 4.6	101.0 ± 4.6	0.19	81.6 ± 3.5	0.001

Values reported as mean ± standard deviation.

RAP, right atrial pressure; PAs, pulmonary artery systolic pressure; PAd, pulmonary artery diastolic pressure; PAm, pulmonary artery mean pressure; PCWP, pulmonary capillary wedge pressure; FCI, Fick cardiac index; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SVR, systemic vascular resistance.

response to riociguat therapy and, as such, acute vasoreactivity testing in the catheterization laboratory is not recommended for this purpose. Lastly, our data suggest that switching to riociguat in PAH and residual CTEPH patients previously treated with a PDE5i is safe and fairly well tolerated.

Limitations

This was a retrospective cohort study and, as such, is subject to the same limitations as any retrospective analysis. This cohort included both PAH patients and patients with residual CTEPH after pulmonary thromboendarterectomy surgery to reflect “real-world” clinical practice, but as such these patients’ pathophysiology, though potentially sharing common features, might also be subtly different. There was a variable amount of time between the pre- and post-PDE5i assessments, and in many patients, background therapy was changed or intensified which may have impacted the hemodynamic and clinical assessments. Another inherent limitation is that neither clinicians nor patients were blinded to the switch in treatment, allowing for potential bias in symptom reporting. Lastly, the study sample size was relatively small and some clinical and laboratory data were not available (e.g. BNP, troponin levels) or were incomplete at the various time points.

Conclusion

We conclude that switching from a PDE5i to riociguat may be a viable option for PAH patients with worsening clinical status and is associated with a significant increase in cardiac index, fall in PVR, accompanied by an improvement in FC. Acute vasoreactivity to inhaled NO in the catheterization laboratory was not associated with hemodynamic response to long-term riociguat therapy and is not recommended for this purpose. The switch from PDE5i to riociguat appeared to be safe and fairly well tolerated in most patients. Published results from the RESPITE trial¹² may shed additional light on the efficacy of this switch in PAH.

Conflict of interest

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