Successful Transition from Phosphodiesterase-5 Inhibitors to Riociguat without a Washout Period in Patients with Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: a Pilot Cohort Study

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Summary

Transition of pulmonary arterial hypertension (PAH)-specific drugs are considered in patients with no response to combination therapy or with side effects to these drugs in those with PAH and chronic thromboembolic pulmonary hypertension. Riociguat directly stimulates soluble guanylate cyclase independently of nitric oxide. Therefore, transition from a phosphodiesterase 5 inhibitor (PDE5i), which requires nitric oxide to exert its effects, to riociguat might be effective. The length of time of washout periods for transition is important because hemodynamic instability sometimes occurs during washout periods or during transition in no washout periods. We investigated the feasibility of transition from PDE5i to riociguat without washout periods in 6 patients with PAH and 1 with chronic thromboembolic pulmonary hypertension who had already received dual or triple combination therapy. Causes of transition were due to headache caused by a PDE5i in 3 patients and an inadequate response to combination therapy in 4 patients. Transition succeeded in all patients without hemodynamic instability. Pulmonary vascular resistance (797 ± 241 to 518 ± 230 dyne/s/cm^{-5}) and systemic blood pressure (121 ± 13 to 100 ± 15 mmHg) were significantly reduced immediately after transition. There were no significant differences in the tricuspid regurgitation pressure gradient and systemic blood pressure between post-transition and follow-up. Headaches caused by a PDE5i were diminished after transition to riociguat. Transition from a PDE5i to riociguat without washout periods is safe. This transition may be a

viable option for patients with headaches caused by a PDE5i or an inadequate response to combination therapy including PDE5is.

Key words: sildenafil, tadarafil, soluble guanylate cyclase stimulator, headache

Pulmonary arterial hypertension (PAH) is a rare, life-threatening disease, which is defined by chronically elevated pressure in the pulmonary arteries. The pathophysiology of PAH is multifactorial and includes upregulation of vasoconstrictors and downregulation of vasodilators. Persistent pulmonary vascular hypertension causes remodeling of vascular structures, and results in reversible or irreversible thickened vessel walls and narrowing of the arterial lumen[1]. As this disease progresses, persistent hypertension of pulmonary vessels induces compensatory stress on right ventricular muscles, ultimately resulting in right heart failure.

Therapy for patients with PAH has progressively developed in the past decade, accompanied by clinical drug development and numerous studies for improving the efficacy of treatment strategies. Prostacyclin, endothelin receptor antagonists, phosphodiesterase 5 inhibitors (PDE5is), soluble guanylate cyclase (sGC) stimulators, and IP receptor agonists are available in treatment for PAH[2, 3]. The current treatment algorithm for PAH suggests combination therapy with PAH-specific drugs, which have different mechanisms of action[4]. In case of inadequate clinical responses to initial combination therapy or side effects of PAH-specific drugs, transition of PAH-specific drugs to other drugs with the same mechanism of action are considered[5-7]. PDE5is and sGC stimulators work on the nitric oxide (NO) pathway. PDE5is inhibit degradation of cyclic guanosine monophosphate and this results in vasodilation with NO[8, 9]. However, sGC directly stimulates cyclic guanosine monophosphate

and results in vasodilatation without NO[10, 11]. Although these drugs have the same mechanism of action, their points of action are different. Because sGC cannot be co-administered with a PDE5i because of the risk of systemic hypotension[12], transition of drugs is considered in patients with intolerance or an inadequate clinical response to PDE5is.

The length of required time for the washout period for transition is important. This is because hemodynamic instability sometimes occurs during washout periods or during transition in no washout periods. Previous study suggested that selected patients with PAH may benefit from switching from PDE5i to riociguat with washout period of PDE5i[13]. However, the feasibility of transition from a PDE5i to a sGC stimulator and washout periods required for transition have not been clearly established.

Therefore, this study aimed to investigate the feasibility of a safe transition from a PDE5i (sildenafil and tadarafil) to sGC (riociguat) without washout periods. We monitored hemodynamics under right heart catheterization in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH).

Methods

Study design

This study was a pilot cohort study. The present study was conducted according to the principles expressed in the Declaration of Helsinki and approved by Okayama University

Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital Ethics Committee (1710-002). Written informed consent was obtained from all of the patients.

Selection of patients

We selected patients with PAH and CTEPH for this study using the following criteria: 1) patients who had dual or triple combination therapy, including a PDE5i, between 2000 and 2017; 2) patients who had side effects caused by a PDE5i or those who had no adequate response with combination therapy; 4) World Health Organization functional class (WHO-FC) II or nearly III; and 5) systemic blood pressure greater than 100 mmHg. Six patients with PAH and 1 patient with CTEPH were eligible for this study.

Outcome

The primary outcome of this study was a change in mean pulmonary artery pressure (PAP) before and after transition. Secondary outcomes of this study were a change in pulmonary vascular resistance (PVR), the cardiac index (CI), systolic blood pressure (SBP), heart rate (HR), the tricuspid regurgitation pressure gradient (TRPG), tricuspid annular plane systolic excursion (TAPSE), and brain natriuretic peptide (BNP) levels. Headache, dyspepsia, diarrhea, dizziness, nasopharyngitis, vomiting, peripheral edema, and hemoptysis are the most frequent adverse side effects in patients treated with a PDE5i and riociguat. Therefore, we examined the incidence of side effects after transition from PDE5i to riociguat.

Protocol of transition

The protocol of transition from a PDE5i to riociguat is shown in Figure 1. PDE5is were stopped before the first administration of riociguat to allow a PDE5i treatment-free period of 12 hours for patients who received sildenafil and 24 hours for those who received tadalafil. Patients who received endothelin receptor antagonists and prostacyclin continued with the same dose, and other supportive drugs were also continued. Riociguat was initiated at a daily dose of 3.0 mg under hemodynamic monitoring with a Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA). Cardiopulmonary hemodynamic parameters (PAP, CI, PVR, SBP, and HR) were measured before and after riociguat administration 3 times after initiation of riociguat. The CI was calculated with Fick's method. We followed all of the patients after discharge from our hospital. At each visit, we checked medications, WHO-FC, potential side-effects of therapy, and vital signs. We increased the dose of riociguat if side effects were not observed.

Echocardiographic parameters and blood examination

The TRPG and TAPSE were measured before and 1 week after administration of riociguat and at follow-up. A blood examination, including BNP levels, was performed before and 1 month after administration of riociguat and at follow-up.

Statistical analysis

All statistical analyses were performed with SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation or median (interquartile range). Results before and after transition were analyzed using the paired t-test. Results before and 1 week after transition and at follow-up were compared using 1-way repeated ANOVA, followed by the post-hoc Bonferroni test and Wilcoxon signed-rank test. P values less than 0.05 were considered significant.

Results

Patients' characteristics

The patients' characteristics are shown in Table 1. Three men and 4 women were included in this study. The patients' mean age was 50 ± 20 years old. Two patients had idiopathic PAH, 3 patients had PAH associated with congenital heart diseases, 1 patient had PAH associated with collagen tissue disease, and 1 patient had CTEPH. Five (71%) patients had WHO-FC II and 2 patients had a WHO-FC of nearly III. Three patients were treated with sildenafil and 4 patients were treated with tadalafil. All of the patients were treated with dual or triple combination therapy. Endothelin receptor antagonists were administered in 6 patients (3 patients with bosentan, 2 patients with ambrisentan, and 1 patient with macitentan). Six patients were treated with beraprost and 1 patient was treated with treprostinil. The reason for transition from a PDE5i to riociguat was because of side effects caused by PDE5i in patient

nos. 1, 2, and 3. The reasons for transition was due to an inadequate response to combination therapy in patient nos. 4, 5, 6, and 7.

Hemodynamics during transition

Hemodynamics before and immediately after transition are shown in Figure 2. PVR significantly decreased from 797 ± 241 to 518 ± 230 dyne/s/cm^{-5} (P = 0.01). SBP also significantly decreased from 121 ± 13 to 100 ± 15 mmHg (P = 0.03). There were no significant changes in mean PAP (41 ± 9 to 39 ± 5 mmHg), the CI (from 3.3 ± 0.9 to 3.7 ± 0.9 l/min/m^2), and HR (79 ± 10 bpm to 82 ± 10 bpm).

Follow-up

Two patients were withdrawn for assessment of chronic effects. We could not confirm continuous administration of riociguat in patient no. 3 because this patient did not visit our hospital after transition for the long term. Patient no. 6 was withdrawn because we changed PAH-specific drugs from bosentan to macitentan immediately after transition from a PDE5i to riociguat. We evaluated chronic effects in 5 patients.

SBP, HR, the TRPG, TAPSE, and BNP levels at follow-up are shown in Table 2. The median follow-up period was 265 days (49–271 days). The mean dose of riociguat was 5.7 ± 2.2 mg/day at follow-up. Four patients had WHO-FC II and 1 patient had a WHO-FC of nearly III before transition. All of the patients had WHO-FC II at follow-up. There were no significant differences in the TRPG, TAPSE, BNP levels, SBP, and HR among pre-treatment,

after transition, and at follow-up.

Tolerability and safety

The most frequent side effects were not observed after transition from a PDE5i to riociguat. SBP was significantly decreased immediately after transition from a PDE5i to riociguat. However, SBP tended to increase from 97 ± 13 mmHg to 106 ± 18 mmHg at follow-up in patients who could be evaluated for chronic effects. Patient nos. 1 to 3 had a severe headache caused by the PDE5i. Severe headache was diminished in these patients after transition from a PDE5i to riociguat.

Discussion

We successfully transitioned PAH-specific drugs from a PDE5i to riociguat by our protocol without a washout period in patients with PAH and CTEPH. Transition from a PDE5i to riociguat without a washout period led to decreased PVR and SBP immediately after transition. There were no significant differences in the TRPG and SBP between post-transition and follow-up. Headache caused by a PDE5i was diminished after transition from a PDE5i to riociguat.

Some clinical studies and one case report have reported transition from a PDE5i to riociguat as follows. Hoeper et al. studied switching to riociguat in 61 patients with PAH and an inadequate response to a PDE5i (RESPITE study)[13]. Switching from a PDE5i to riociguat

significantly increased the 6-minute walk distance, decreased N-terminal-pro BNP levels, and improved the WHO-FC. Ten patients experienced serious adverse events. Ten patients had episodes of hypotension and 6 patients experienced clinical worsening. Yamamoto et al. studied the transition from a PDE5i to riociguat in 8 patients with CTEPH and an inadequate response to PDE5is[14]. BNP levels were significantly improved, and the 6-minute walk distance, mean PAP, PVR, and the CI were improved, but this was not significant. Davey et al. studied the transition from PDE5i to riociguat in 12 patients with pulmonary hypertension. The CI was significantly increased and PVR was decreased after transition from a PDE5i to riociguat[15]. One case report showed that a patient with PAH transitioned from sildenafil to riociguat[16]. This transition was well tolerated, but there were no significant changes in echocardiographic parameters. In the present study, PVR was significantly decreased immediately after transition. However, the TRPG and BNP levels tended to be decreased, but this was not significant at follow up. Transition from a PDE5i to riociguat might be beneficial in select patients with PAH and CTEPH who have an inadequate response to combination therapy. Headache caused by a PDE5i was diminished by transitioning from a PDE5i to riociguat in the present study. Therefore, transition from a PDE5i to riociguat might be beneficial in patients who have a headache caused by a PDE5i. Transition of PAH-specific drugs is not described in the present guideline of PAH. Further studies are required to confirm the effect of transition of PAH-specific drugs.

Whether a washout period should be provided is an important issue. Washout periods of 24 hours for sildenafil and 72 hours for tadarafil were used before administration of riociguat in the RESPITE study[13]. Although no clinical worsening events occurred during the washout period in this previous study, temporarily stopping PAH-specific drugs remains a matter of concern because hemodynamic and pulmonary hypertension sometimes worsen during the washout period. However, no washout periods are also a matter of concern because overlap of drug exposure might excessively cause adverse effects. In the present study, we transitioned from a PDE5i to riociguat without washout periods by monitoring hemodynamics during transition. Although SBP was significantly decreased, it was not decreased when less than 90 mmHg. There was no excess hemodynamic response during transition. Criteria for inclusion of patients in our study included WHO-FC II or nearly III, receipt of combination therapy, and SBP greater than 100 mmHg before transition. Although further study is required, transition without a washout period is feasible in patients who are satisfied with our criteria.

The present study has several limitations. First, our study was a retrospective, single-center study and the sample size was small. To confirm our findings, a multicenter, prospective study with a large sample size is required. Second, hemodynamic assessment using right heart catheterization was lacking at follow-up. Although our study has several limitations, our findings should help physicians with the treatment strategy for patients with

PAH who have an inadequate response to combination therapy or have side effects caused by PDE5is.

Conclusion

Transition from a PDE5i to riociguat without washout periods is safe. This transition may be a viable option for patients with PAH and side effects, such as headache, caused by PDE5is or an inadequate response to combination therapy including PDE5is.

Disclosures

Conflicts of interest:

S. Akagi has received lecture fees from Actelion Pharmaceuticals Japan, AOP Orphan Pharmaceuticals, Bayer Yakuhin, and Nippon Shinyaku. K. Nakamura has received lecture fees from Actelion Pharmaceuticals Japan, AOP Orphan Pharmaceuticals, Bayer Yakuhin, Nippon Shinyaku, and Pfizer Japan. H. Ito has received lecture fees from Mochida Pharmaceutical and research grants from Mochida Pharmaceutical, Actelion Pharmaceuticals Japan, AOP Orphan Pharmaceuticals, Bayer Yakuhin, and Nippon Shinyaku. The other authors have no conflicts of interest.

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Figure legends

Figure 1. Protocol of transition. Transition from phosphodiesterase-5 inhibitors to riociguat under monitoring from a Swan-Ganz catheter. The washout period was 12 hours for patients who received sildenafil and 24 hours for patients who received tadalafil.

Figure 2. Hemodynamic changes before and after transition. A. Mean pulmonary artery pressure (mPAP). B. Cardiac index (CI). C. Pulmonary vascular resistance (PVR). D. Systolic blood pressure (SBP). E. Heart rate (HR).

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Patient No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Sex	M	F	M	F	F	M	F

Table 1. Patients' characteristics.

Age	23	47	31	66	62	78	43
Diagnosis	VSD-PH	ASD-PH	PDA-PH	SSc-PH	CTEPH	IPAH	IPAH
WHO-FC	II	II	II	II	II	III	III
Pre-treatment							
PDE5i	Tadalafil	Sildenafil	Tadalafil	Sildenafil	Sildenafil	Tadalafil	Tadalafil
Dosage	20 mg	60 mg	40 mg	40 mg	40 mg	40 mg	40 mg
ERA	Macitentan	Bosentan	Ambrisentan	Bosentan	-	Bosentan	Ambrisentan
Dosage	5 mg	250 mg	10 mg	250 mg	-	250 mg	10 mg
Prostacyclin	Treprostinil	Beraprost	Beraprost	Beraprost	Beraprost	Beraprost	-
Dosage	40 ng/kg/min	120 μg	120 μg	120 μg	120 μg	120 μg	-
Side effects							
Headache	+	+	+	-	-	-	-
Joint pain	-	+	-	-	-	-	-

WHO-FC, World Health Organization functional class; PDE5i, phosphodiesterase inhibitor-5; ERA, endothelin receptor antagonist; M, male; F, female; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus, PH, pulmonary hypertension; SSc, systemic sclerosis; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension.

Table 2. Parameters before and after transition and at follow-up.

	Pre-treatment	After transition	Follow-up	P value
TRPG (mmHg)	56±21	53±10	50±7	0.27
TAPSE (cm)	15±2	13±2	15±3	0.71
BNP (pg/ml)	71 (11-86)	84 (55-134)	40 (34-110)	0.25
SBP (mmHg)	122±13	97±13	106±18	0.06
HR (/min)	76±9	78±7	85±9	0.23

TRPG, tricuspid regurgitation pressure gradient; TAPSE, tricuspid annular plane systolic excursion; BNP, brain natriuretic peptide; SBP, systolic blood pressure; HR, heart rate.