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Switching from Phosphodiesterase-5 Inhibitor to Riociguat Improves Pulmonary Hemodynamics, In Pulmonary Arterial Hypertension Patients Under Triple Combination Therapy

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Introduction

Pulmonary Arterial Hypertension (PAH) is an angioproliferative pulmonary vascular disorder, which progressively leads to an increase of the workload of right ventricle, and right-heart failure. Drugs approved for the treatment of PAH target three main pathways participating in the pulmonary endothelial function: The endothelin pathway, which is overexpressed in PAH, as well as the prostacyclin and Nitric Oxide (NO) pathways which are under-expressed [1]. Initial oral combination therapy with an Endothelin Receptor Antagonist (ERA) and a Phosphodiesterase 5 Inhibitor (PDE5i) or a soluble Guanylate Cyclase (sGC) stimulator such as riociguat is recommended in treatment naïve, low or intermediate PAH patients [2]. If/when low risk is not achieved; addition of prostanoids is recommended [2].

There is limited evidence on the effectiveness of switching between drugs targeting different molecules in the same of pathway. The open-label, multicentre, uncontrolled study RESPITE shows that PAH patients in World Health Organization functional class (WHO-FC) III, with inadequate response to PDE5i treatment, might respond to treatment using riociguat [3]. The open label Randomized Controlled Trial (RCT) REPLACE that enrolled PAH patients receiving maintenance therapy with PDE5i with or without ERA recently demonstrated that transition to riociguat from PDE5i treatment is associated with a significant likelihood of clinical improvement [4]. We report two PAH cases with different pulmonary hemodynamic profile, who improved clinically and hemodynamically after transitioning from PDE5i to riociguat.

Case Series

Case 1

A 32 years old female, who went for follow-ups for ten years in our Pulmonary Hypertension (PH) clinic in a tertiary hospital, because of Systemic Lupus Erythematosus (SLE) -associated PAH. She was on sequential triple combination therapy including an ERA, sildenafil 20 mg TID and subcutaneous treprostinil at a final dose of 76 ng/kg/min. The combination of immunosuppressant's alongside PAH treatment resulted in patient's clinical and hemodynamic improvement consistent with low risk status, that was sustained for 5 years. However, on a routine Right Heart Catheterization (RHC), there was a decrease of Cardiac Output (CO) and Stroke Volume Index (SVI), whereas there was an increase in Pulmonary Vascular Resistance (PVR) (Table 1). The patient presented in WHO FC-II, with NT-proBNP value of 106 pg/ml and Reveal Risk Score (RRS) 4. Transition from sildenafil to riociguat was decided. The patient underwent a one-day PDE5i free period and then received riociguat at a dose of 1 mg TID, with gradual increase by 0.5 mg increments in 14 days, up to 2.5 mg TID. RHC performed one month later, showed normalization of all pulmonary hemodynamic values and an increase in SVI (Table 1), while her WHO-FC improved

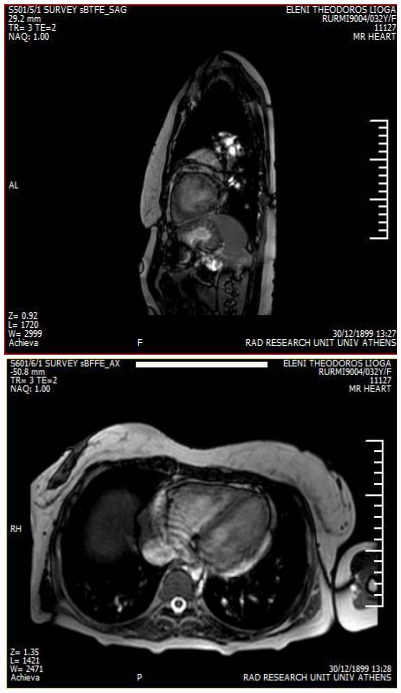

Figure 1: Cardiac magnetic resonance image of Patient #1 showing a satisfactory right ventricular function (Ejection Fraction (EF): 80%, Stroke Volume Index (SVI): 42 ml/m^2, Cardiac Output (CO): 6 L/min, Cardiac Index (CI): 3.7 L/min/m^2, Right Ventricular End Diastolic Volume Index (RVEDVi): 53.42 ml/m^2 (67 ml/m^2 to 111 ml/m^2).

to I. Moreover, echocardiography showed improved TAPSE (pre-riociguat: 1.8, after riociguat: 2), while a cardiac MRI also revealed a satisfactory RV function (Ejection Fraction (EF): 80%, SVI: 42 ml/m^2, CO: 6 L/min, CI: 3.7 L/min/m^2, Right Ventricular End-Diastolic Volume (RVEDVi): 53.42 ml/m^2) (Figure 1). There were no reported adverse events.

Case 2

Patient 2 is a 50 year old female, suffering from Idiopathic PAH (IPAH), who routinely went for follow-ups in the same PH clinic during the last 15 years. She was on triple combination therapy with an ERA, sildenafil and subcutaneous treprostinil that was progressively increased to 60 ng/kg/min. Although she presented in WHO-FC II-late, the patient's NT-proBNP value was 945 pg/ml and cardiopulmonary exercise test revealed a peak O_2 consumption of 12 ml/kg/min, which was consistent with an intermediate risk status [2], despite RRS of 5. A recent increase of treprostinil dose did not improve the patient's hemodynamic parameters (Table 1). Transition from sildenafil to riociguat, adjusted up to 2.5 mg TID, was decided RHC was performed one month after riociguat administration demonstrated significant improvement of pulmonary hemodynamics, while NT-proBNP value decreased to 634 pg/ml (Table 1) and WHO-FC slightly improved to II-early. Echocardiography also showed improved TAPSE, consistent with improved RV function. There were no reported adverse events.

Discussion

Riociguat is a sGC stimulator with mechanism of action under NO pathway. NO activates sGC, leading to the production of cyclic Guanosine Monophosphate (cGMP) in vascular smooth muscle cells, while PDE5 degrades cGMP. Inhibition of PDE5 results in the increase of intracellular cGMP, promoting vasodilatory and antiproliferative effects in the pulmonary circulation [5]. However, in PAH the effectiveness of PDE5i might be impaired, due to decrease NO synthesis. The direct stimulation of sGC by riociguat, leads to a vasodilatory effect, independently of the bioavailability of NO [6]. Therefore, there is a physiological rational of transitioning from PDE5i to riociguat in PAH patients with unsatisfactory response.

Table 1: Clinical, laboratory and hemodynamic data of patients.

	Pre-riociguat	Post-riociguat
Patient 1		
WHO-FC	II	I
NT-ProBNP (pg/ml)	106	68
RRS	4	4
6MWD (m)	450	455
RAP (mmHg)	3	3
PAP (S/D/M) (mmHg)	47/19/28.3	24/12/16
CO/CI (L/min)/CI (L/min/m^2)	3.7/2	5.8/2.6
PVR (WU)	6.3	2.2
SVI (ml/m^2)	34.2	40.2
Patient 2		
WHO-FC	II-late	II-early
NT-proBNP (pg/ml)	945	634
RRS	5	5
6MWD (m)	552	565
RAP (mmHg)	8	8
PA (S/D/M) (mmHg)	86/40/55	79/33/48
CO (L/min)/CI (L/min/m^2)	5/2.7	5.5/3
PVR (WU)	9.2	6.9
SVI (ml/m^2)	41.2	42

NT-Pro BNP: N Terminal-Pro B-type Natriuretic Peptide; WHO-FC: World Health Organization Functional Class; RRS: REVEAL Risk Score; 6MWD: 6 Minute Walking Distance; RAP: Right Atrial Pressure; PAP (S/D/M): Pulmonary Artery Pressure (Systolic/Diastolic/Mean); CO: Cardiac Output; CI: Cardiac Index; PVR: Pulmonary Vascular Resistance; WU: Wood Units; SVI: Stroke Volume Index

In the RESPITE study, PAH patients in WHO-FC III who received PDE5i and/or ERA were prospectively enrolled. Switching from PDE5i to riociguat resulted in improvement of hemodynamic parameters, cardiac biomarkers and WHO-FC [3]. The respective post hoc analysis showed that subjects had lower NT-proBNP values and RRS [7]. The subsequent REPLACE study, evaluated the transition from PDE5i to riociguat in PAH patients in WHO-FC III and intermediate risk, who received PDE5i and with or without ERA demonstrated a significant probability of clinical improvement [4].

There are several case studies and retrospective analyses providing data on transition to riociguat. Davey et al. retrospectively identified the hemodynamic benefit of switching from PDE5i to riociguat in 12 PAH patients receiving combination therapy (ERA and/or prostacyclin analogues) [8]. Another retrospective analysis of 31 patients who underwent PDE5i transition to riociguat was performed, demonstrated hemodynamic and clinical improvement [9]. Similar results were observed in three patients with Connective Tissue Disease (CTD) - associated PAH [10]. Kuroda et al. also described significant decrease of PVR in 7 patients suffering from PAH or chronic thromboembolic PH, under dual or triple combination therapy who transitioned from PDE5i to riociguat [11].

We reported two cases of PAH; the first patient suffered from SLE-associated PAH and the second suffered from idiopathic PAH, who demonstrated favorable results transitioning from sildenafil to riociguat. Both patients were in triple combination therapy that included high doses of subcutaneous prostanoid. The first patient was considered as low risk, despite the presence of CTD, decreased CO and decreased SVI [12]. The second patient was considered as intermediate risk and experienced recent hemodynamic deterioration. The goal of switching to riociguat was to improve the hemodynamic parameters, by optimizing the NO pathway. Indeed, hemodynamic status was normalized in patient #1, while significant hemodynamic improvement was achieved in patient #2. However our patients differed from those enrolled in RESPITE and REPLACE studies [3,4] as they were in triple combination therapy. Moreover we reported additional pulmonary hemodynamic parameters that were not provided in the latter study. Our results indicated that optimizing the NO pathway treatment in patients with either low (#1) or high (#2) pulmonary hemodynamic derangement, results in improvements of hemodynamic profiles, even under high subcutaneous prostanoid doses.

The alternative treatment would be switching from subcutaneous treprostinil to intravenous epoprostenol, which is a more invasive approach. In some of the retrospective analyses and case studies of PDE5i transition to riociguat, several patients were on triple combination therapy [8,9,11]. However, the improvement of hemodynamic status is not as remarkable as the improvement in our patients. In addition, to our knowledge, patient#1 is the first reported case, where normalization of mildly impaired pulmonary hemodynamic profiles was achieved under triple combination therapy.

Conclusion

Possible candidates for switching from PDE5i to riociguat might be patients without high risk parameters, who have not achieved a low risk profile and are not rapidly deteriorating [7,13]. Our patients fulfilled those characteristics, and more importantly, they were already on triple combination therapy. More trials are required in order to define whether transition between PAH therapies targeting the same pathway will be a goal-oriented strategy and to a priori identify potential responders with an impaired NO signaling. The role of this strategic option in intermediate risk patients is going to be defined in the next PH treatment guidelines.

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