



# Combination therapy with riociguat and inhaled treprostinil in inoperable and progressive chronic thromboembolic pulmonary hypertension



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### List of abbreviations:

cGMP

cyclic guanylate monophosphate

CTEPH

chronic thromboembolic pulmonary hypertension

FDA

Federal Drug Administration

NO

nitric oxide

PAH

pulmonary arterial hypertension

PDE5

phosphodiesterase 5

PEA

pulmonary endarterectomy

## ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by formation of chronic, organized thrombus in pulmonary arteries resulting in development of pulmonary hypertension. We describe the favorable recovery of a patient with inoperable CTEPH treated with combination riociguat and inhaled treprostinil.

The patient is a 77 year old female who presented with bilateral pulmonary emboli and was anti-coagulated with warfarin for six months. One year later the patient developed recurrent dyspnea and multiple bilateral pulmonary emboli were again noted. Pulmonary arterial pressure (PAP) was estimated at 91 mmHg by echocardiography. The patient was treated with warfarin and sildenafil. Eighteen months later the PAP was estimated at 106 mmHg with significant right ventricular enlargement. The patient was referred to our center for pulmonary hypertension consultation. Right heart catheterization confirmed severe pulmonary hypertension with preserved cardiac output. The patient was not a candidate for thromboendarterectomy due to the peripheral location of chronic obstructing thrombi. Systemic prostacyclin therapy was declined by the patient. Inhaled treprostinil was added to sildenafil and warfarin. The patient maintained good performance status for 2 years, but then developed progressive activity limitation with depressed cardiac output on right heart catheterization. Systemic prostacyclin therapy was declined again. Sildenafil was replaced with riociguat, and 1 year later the patient demonstrated significant recovery of functional capacity and improved hemodynamic profile.

We describe significant recovery in a patient with inoperable, progressive CTEPH treated with riociguat and inhaled treprostinil after failing sequential addition of sildenafil and inhaled treprostinil to warfarin. The reported benefits may relate to riociguat's ability to directly stimulate production of cyclic GMP independent of nitric oxide levels in pulmonary artery smooth muscle. There may also be a unique interaction between riociguat and treprostinil that enhanced treatment outcome. Further investigation of this combination of agents may be warranted.

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## 1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a consequence of blood flow limitation by persistent, organized

thrombus in the pulmonary arterial circulation following pulmonary thromboembolism. CTEPH is categorized as WHO Group 4 in the World Health Organization classification of pulmonary hypertensive diseases [1]. Historically, treatment options for CTEPH have included surgical thromboendarterectomy or off-label use of pulmonary arterial vasodilators approved for the treatment of WHO Group I pulmonary arterial hypertension (PAH). Pulmonary endarterectomy (PEA) can significantly improve pulmonary vascular resistance and functional capacity [2]. However, many patients are

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not candidates for surgical treatment, and some experience persistent pulmonary hypertension after PEA [3]. While several agents have been approved by the Federal Drug Administration (FDA) for treatment of PAH, FDA-approved options for medical therapy of CTEPH remain limited to one agent, riociguat [4]. There have been far fewer clinical trials designed to examine the efficacy of targeted therapies in CTEPH. Further, although there is heightened interest in a combination therapy approach to treating PAH, the potential role of combination pharmacotherapy in the treatment of CTEPH is largely unknown.

We report the favorable outcome of a patient with inoperable CTEPH who was treated with combination riociguat and inhaled treprostinil after disease progression on sildenafil alone and with combination sildenafil and inhaled treprostinil.

**2. Case report**

Our patient was a 77 year old female who was diagnosed with moderate pulmonary hypertension (estimated right ventricular systolic pressure 50–60 mmHg) by echocardiography at the time of an initial thromboembolic event resulting in bilateral pulmonary emboli. She was anticoagulated with warfarin for 6 months and regained normal functional capacity. She developed exertional dyspnea one year following the initial thromboembolism. Multiple bilateral pulmonary emboli were identified once again, and treatment with warfarin reinitiated. After this second event, the patient’s estimated pulmonary artery pressure was markedly elevated at 91 mmHg by echocardiography. Three months later there were no clinical improvements in dyspnea, echocardiographic or radiologic findings. The patient reported NYHA functional class 4 symptoms. Sildenafil was added to warfarin (Month 0, Fig. 1). The patient experienced some improvement in dyspnea (NYHA functional class 3) in the following months. Echocardiography was repeated after 18 months of treatment with sildenafil and warfarin. The estimated pulmonary artery pressure was even higher at 106 mmHg and right ventricular enlargement had become apparent. At this point, the patient was referred to our center for a pulmonary hypertension consultation.

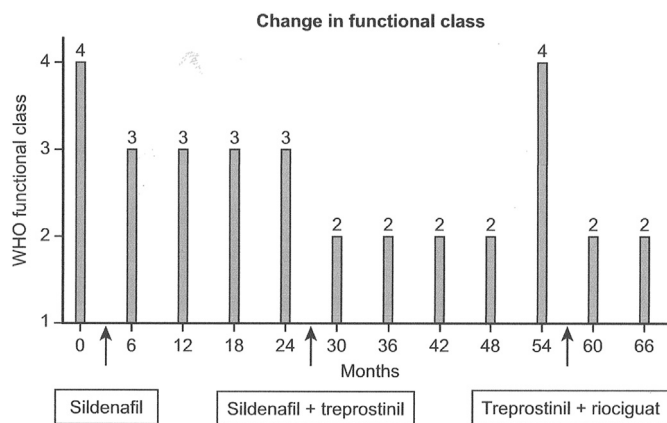


Fig. 1. Change in NYHA functional class.

During the initial pulmonary hypertension evaluation, the patient reported NYHA functional class 3 symptoms and was able to walk 405 m in 6 minutes. A ventilation perfusion scan revealed persistent peripheral perfusion defects. Right heart catheterization was performed confirming severe pulmonary hypertension. The pulmonary artery pressure was severely elevated at 102/34/58 mmHg, although cardiac output and cardiac index remained within normal range (Table 1, Sildenafil alone). In light of right ventricular enlargement noted by echocardiography and the severe degree of pulmonary artery pressure elevation, systemic prostacyclin therapy was recommended. The peripheral perfusion abnormalities on ventilation perfusion scanning were not considered amenable to thromboendarterectomy. The patient expressed reluctance to systemic prostacyclin treatment, so inhaled treprostinil was added to sildenafil (Month 24, Fig. 1).

The addition of inhaled treprostinil to sildenafil resulted in significant improvement in functional class over the next 24 months (Fig. 1). Six minute walk distance increased to 475 m over the next 6 months. The patient suffered a toe fracture and was unable to complete a 6 minute walk for several months thereafter. She began to report more exertional dyspnea and activity limitation after 24 months on the sildenafil-inhaled treprostinil combination. By month 30 on this combination she was unable to perform a 6 minute walk due to severe breathlessness and fatigue. She reported NYHA functional class 4 symptoms (Fig. 1) and was requiring continuous use of supplemental oxygen.

Right heart catheterization was repeated (Table 1, Sildenafil + Treprostinil). Although the PA pressure was similar to the previous study, there had been a substantial decline in cardiac output and index. Systemic prostacyclin therapy was again recommended, but the patient remained reluctant. As an alternative, riociguat was substituted for sildenafil on a trial basis.

After the initiation of riociguat-inhaled treprostinil, the patient experienced a significant improvement in activity tolerance (Fig. 1). The patient regained NYHA functional class 2 activity tolerance and by 12 months was walking 400 m in 6 minutes. Right heart catheterization was repeated at 12 months on the riociguat-inhaled treprostinil combination. Improvements were noted in pulmonary artery pressure, cardiac output and cardiac index as noted in Table 1 (Treprostinil + Riociguat). This combination of agents effected improvements in activity tolerance and hemodynamics after failure on sildenafil-inhaled treprostinil.

**3. Discussion**

In this report we describe the outcome of a patient with non-operable and progressive CTEPH who was initially treated with sildenafil. Sildenafil provided some relief of symptoms and seemed to limit progression for a period of time. However, signs of progression began to appear on echocardiogram leading to the addition of inhaled treprostinil to sildenafil. This treatment regimen resulted in improvement of functional capacity, but ultimately progression of the disease process was noted with significant right ventricular compromise. The substitution of the soluble guanylate cyclase stimulator, riociguat, for sildenafil subsequently led to improvement in functional class, 6 minute walk distance and

Table 1 Treatment effects.

|  | 6 MW (m) | FC | RA (mmHg) | PA (mmHg) | CO (L/min) | CI (L/min/m2) |
|--|----------|----|-----------|-----------|------------|---------------|
| Sildenafil alone 24 months(Treprostinil added)                     | 405      | 3  | 12        | 102/34/58 | 6.5        | 3.2           |
| Sildenafil + treprostinil 30 months(Riociguat replaced sildenafil) | 0        | 4  | 16        | 101/36/59 | 4.02       | 2.04          |
| Treprostinil + riociguat 12 months                                 | 400      | 2  | 15        | 92/28/49  | 4.5        | 2.28          |

hemodynamics.

Riociguat is a soluble guanylate cyclase stimulator approved by the FDA for treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) in 2013. This agent is the first in a new PAH treatment class. Riociguat is the first and only treatment agent approved specifically for treating CTEPH to date. The pathogenesis of PAH is known to depend, in part, on the pulmonary vascular nitric oxide pathway [5]. Nitric oxide is an endogenous vasodilator produced by the conversion of arginine to nitric oxide under the influence of nitric oxide synthase in pulmonary vascular endothelial cells. Nitric oxide diffuses to the vascular smooth muscle where it catalyzes the formation of cyclic guanylate monophosphate (cGMP) by guanylate cyclase. Cyclic GMP then effects smooth muscle relaxation and regulation of cellular proliferation and inflammation in the vessel wall [6]. The pathogenesis of PAH is known to involve a deficiency of nitric oxide synthase in pulmonary vascular endothelial cells. The resulting deficiency of NO production limits vascular smooth muscle relaxation and regulation of other cellular activities in the vessel wall.

Riociguat enhances the formation of cGMP in pulmonary vascular smooth muscle similar to the effect of endogenous nitric oxide (NO) although by a different mechanism. This effect is achieved by directly stimulating guanylate cyclase and by making guanylate cyclase more sensitive to NO [7]. Phosphodiesterase 5 (PDE5) inhibitors have been shown to augment the effect of low NO production in PAH by preventing the degradation of cGMP [8]. As such, the impact of PDE5 inhibitor action on the nitric oxide pathway is dependent on the amount of NO produced, whereas, riociguat action is independent of endogenous NO production.

Our patient had been treated with the PDE5 inhibitor, sildenafil, initially. As her disease progressed, inhaled treprostinil was added to sildenafil. This combination resulted in significant, but temporary, improvement in the prognostic indicators, 6 minute walk distance and WHO functional class. Hemodynamic parameters did not improve. In fact, both functional and hemodynamic parameters deteriorated over time. The substitution of riociguat for sildenafil resulted in a restoration of functional capacity, oxygenation and improvement in hemodynamics. While systemic prostacyclin therapy was recommended after progression on the combination of sildenafil and inhaled treprostinil, the effects of combination riociguat and inhaled treprostinil allowed delay of this more complicated form of treatment.

Recent literature has reported benefit when agents from the different pathways known to effect the pathophysiology of PAH are combined. As an example, the addition of sildenafil to long-term intravenous epoprostenol therapy has been shown to improve exercise capacity, hemodynamics, quality of life and time to clinical

worsening [9]. We saw an initial benefit when treprostinil was added to sildenafil, although the effect faded with time. We then observed significant clinical improvements when riociguat was substituted for sildenafil in the combination regimen with treprostinil. Hoepfer et al. have reported improvements in 6 minute walk distance, hemodynamics, NT-proBNP levels, and WHO functional class in PAH patients with an inadequate response to PDE5 inhibitor therapy and then transitioned to riociguat [10]. Further, patients in the Patent 1 trial demonstrated significant improvement when riociguat was added to existing prostacyclin therapy [11]. The improvements our patient experienced were clearly associated with the substitution of riociguat in the treatment regimen and provided clinical benefit not achieved with the combination of sildenafil and inhaled treprostinil. The clinical improvements in our patient after substitution of riociguat for sildenafil were likely due to the fact that riociguat is not dependent on endogenous NO levels, but rather provides an effective substitute for the effect of NO on cGMP production. Further investigation of riociguat-prostacyclin combination therapy in CTEPH treatment may be warranted as there are many patients who are not candidates for surgical endarterectomy.

The patient described in this report provided consent to publish an account of her experience with chronic thromboembolic pulmonary hypertension and its treatment.

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