Case Report

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Real-world experience with riociguat as potential bridging therapy in patients with chronic thromboembolic pulmonary hypertension: a case series

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH; World Health Organization (WHO) Group IV pulmonary hypertension (PH)) is a potential complication of acute pulmonary embolism (PE).[1,2] CTEPH is a two-compartment disease with (1) an occlusive component that may be amenable to surgical excision with pulmonary thromboendarterectomy (PTE) surgery[3] and (2) a small vessel disease and constriction, similar to that in pulmonary arterial hypertension (PAH),[4] that may be amendable to vasodilation. Riociguat, a soluble guanylate cyclase stimulator, is the only medical therapy approved by the US Food and Drug Administration for the treatment of patients with CTEPH and is indicated for patients with CTEPH who are inoperable or who have persistent/recurrent CTEPH after surgery.[4,5] Administering a treatment for PAH as a bridging therapy to PTE is supported by studies that suggest a reduction in pulmonary vascular resistance (PVR) before surgery may improve the postoperative course.[6] Since there is usually a lag time between diagnosis and being seen at a PTE center for surgical evaluation, there is a compelling case to understand whether medical therapy can benefit patients waiting for either surgery or surgical evaluation.

The current case series describes our real-world clinical experience with riociguat in 10 patients with CTEPH, identified from chart review at two PH care centers, who were either awaiting operability assessment or PTE surgery. All patients reached the 2.5 mg TID dose, except for patients 5 and 6, who reached 1.5 mg. Not all patients represented proceeded to successful PTE. No patient received balloon pulmonary angioplasty.

Case descriptions

Patient baseline hemodynamics and outcomes of treatment are summarized in Table 1.

Patient 1

An obese 58-year-old Caucasian male with a prior diagnosis of PH presented with progressive shortness of breath (WHO functional class (FC) III) and did not respond to pulmonary vasodilators. He had left popliteal non-occlusive deep vein thrombosis (DVT) a year before his presentation. Initial brain natriuretic peptide (BNP) was elevated at 476 pg/mL. Lung ventilation and perfusion (VQ) scan revealed several mismatched defects, and computed tomography pulmonary angiogram confirmed web-like eccentric filling defects. Echocardiogram confirmed right atrial and ventricular enlargement with a tricuspid annular plane systolic excursion at 1.18 cm.

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Table 1. Baseline characteristics for each patient and effects of treatment with riociguat on key parameters.

Patient	I	II	III	IV	V	VI	VII	VIII	IX	X
Age (years)	58	39	67	57	63	52	71	55	69	35
Sex	Male	Female	Male	Female	Female	Female	Male	Female	Female	Female
Ethnicity	Caucasian	Hispanic	Caucasian	Caucasian	Caucasian	Caucasian	Hispanic	Hispanic	Caucasian	Hispanic
History of PE or DVT	DVT	PE	PE	N/A	DVT + PE	PE	VTE + PE	PE	N/A	VTE + PE
WHO FC or NYHA FC	WHO FC III	WHO FC III	WHO FC IV	WHO FC III	WHO FC III	WHO FC II	NYHA FC III	NYHA FC II	NYHA FC II–III	NYHA FC III
Mean RA pressure (mmHg)	8	13	21	27	23	5–10	10	2	13	N/A
PAP (mmHg) (systolic/diastolic)	81/45	80/38	85/50	84/44	90/50	75/24	107/32	71/20	93/30	84/29
Mean PAP (mmHg)	50	52	62	57	63	39	60	37	50	47
PAWP (mmHg)	30	13	21	13	11	7	8	5	8	3
RVSP (mmHg)	34–63	74	50–55	68	70–75	N/A	N/A	N/A	N/A	N/A
Transpulmonary gradient (mmHg)	20	39	35	44	44	N/A	N/A	N/A	N/A	N/A
CO (Fick) (L/min)	4.24	6.24	4.8	4.41	4.4	2.69	5.87	5.83	5 (thermodilution)	3.2
CI (L/min/m^2)	1.77	2.45	1.71	2.96	2.5	1.44	2.49	3.43	2.24	2
PVR (Wood units)	4.7	6.25	8.6	9.97	10	11.2	8.9	8.8	8.4	13.75
PTE status	Assessed for PTE	Assessed for PTE	PTE curative	Declined PTE referral	Underwent surgery but experienced pulmonary hemorrhage during surgery and did not survive	Underwent PTE and continued on riociguat for residual PH	PTE curative	Declined PTE	Not optimal candidate for surgery	PTE curative
After treatment with riociguat										
Duration of treatment with riociguat (in months)	2	6	5	2	4	3	N/A	16	N/A	4
Dyspnea improvement	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes
ΔWHO FC or NYHA FC	WHO FC III to II	No change	No change	WHO FC III to II	WHO FC III to II	No change	NYHA FC III to II	NYHA FC II to I	No change	NYHA FC III–IV to II–III
ΔBNP (pg/mL)	N/A	−162	−136	−380	NT-ProBNP −513	N/A	+93	−2	N/A	−324
Δ6MWD (m)	N/A	+51	+88	+54	+75	N/A	N/A	+51.9	N/A	N/A

6MWD: six-minute walking distance; BNP: brain natriuretic peptide; CI: cardiac index; CO: cardiac output; DVT: deep vein thrombosis; FC: functional class; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PAWP: pulmonary arterial wedge pressure; PE: pulmonary embolism; PH: pulmonary hypertension; PTE: pulmonary thromboendarterectomy; PVR: pulmonary vascular resistance; RA: right atrial; RVSP: right ventricular systolic pressure; WHO: World Health Organization; VTE: venous thromboembolism.

A diagnosis of CTEPH (WHO Group IV and FC III) was made after right heart catheterization (RHC). The patient responded well to riociguat, with remarkable improvement in shortness of breath and transition to WHO FC II in two months. He was seen and assessed at the CTEPH center for consideration of PTE over a period of 104 days.

Patient II

A 39-year-old Hispanic female with chronic morbid obesity presented with three months of progressive shortness of breath. She was diagnosed with acute PE and started anticoagulants for six months. She was readmitted with persistent shortness of breath and thought to have ''recurrent'' PE. Pulmonary angiogram revealed occlusion of left lower lobe, lingular, right middle lobe, and right lower lobe arterial segments.

She was diagnosed with CTEPH (WHO Group IV and FC III) after confirmatory RHC, and started on riociguat. There was significant improvement in her symptoms, six-minute walking distance (6MWD), and BNP after six months of treatment (Table 1). Follow-up RHC performed at University of California San Diego (UCSD) 12 months after treatment showed mean right atrial pressure (mRAP): 12 mmHg, mean pulmonary arterial pressure (mPAP): 26 mmHg, pulmonary artery wedge pressure (PAWP): 13 mmHg, cardiac output (CO): 7.03 L/min, cardiac index (CI): 2.84 L/min, and PVR: 1.85 Wood units (WU). PTE was not performed due to normalization of hemodynamics after riociguat, and the potential risks of surgery associated with severe obesity. She is continuing on riociguat.

Patient III

A 67-year-old Caucasian male with a history of PE and IVC filter placement presented to the PH clinic with shortness of breath. VQ scan was indeterminate. RHC and pulmonary angiogram confirmed CTEPH. PAWP was elevated, which was secondary to a combination of factors—obesity, left ventricular dysfunction, left atrial enlargement, and interventricular interdependence. Right ventricle was significantly enlarged and dyskinetic. Pulmonary angiography revealed multiple filling defects with webs.

Riociguat was initiated 24 months after the onset of symptoms and continued for five months before PTE. The patient reported a reduction in dyspnea, although FC remained unchanged. Improvements in 6MWD and BNP are shown in Table 1. Hemodynamics were assessed by RHC immediately before PTE and showed mRAP: 17 mmHg, pulmonary arterial pressure (PAP): 73/38, mPAP: 50 mmHg, CO: 3.47 L/min, CI: 1.43 L/min, and PVR: 9.2 WU. After PTE, BNP had decreased by 136 points to 11 pg/mL. mRAP had decreased to 10 mmHg, PAP was 38/16 mmHg with mPAP 25 mm Hg, CO was 5.7 L/min, and PVR was 2.4 WU.

Patient IV

A 57-year-old Caucasian female with chronic rheumatoid arthritis and systemic lupus erythematosus overlap syndrome was transferred from another institution for ''acute coronary syndrome,'' chronic progressive shortness of breath (WHO FC III), and lower extremity edema. Echocardiogram revealed severe right ventricular enlargement, with pressure and volume overload signs. RHC hemodynamics are summarized in Table 1. VQ scan revealed several unmatched perfusion defects in the right lung. Final diagnosis was CTEPH, and riociguat was initiated with subsequent dramatic improvement in BNP, WHO FC, and 6MWD by two months (Table 1). The patient declined a UCSD referral for consideration of PTE for social reasons.

Patient V

A 63-year-old Caucasian female presented with dyspnea, throbbing chest discomfort during heavy exertion, palpitations, dizziness, and sleep apnea. She had a medical history of DVT and PE approximately four years before presentation and was receiving anticoagulation therapy with warfarin.

Echocardiogram showed right ventricle was thickened and moderately dilated, and right ventricular global systolic function was mildly reduced. Right atrial cavity size was also moderately dilated, and there was moderate tricuspid regurgitation. There was a small pericardial effusion. VQ scan revealed multiple perfusion mismatch defects.

Time from initial presentation to evaluation at our center was 160 days. Patient received riociguat while awaiting evaluation for PTE. She experienced an improvement in dyspnea, N-terminal pro-brain natriuretic peptide (NT-proBNP), 6MWD, and WHO FC (Table 1) after four months of riociguat 1.5 mg TID. She eventually underwent PTE complicated by pulmonary hemorrhage and did not survive.

Patient VI

A 52-year-old Caucasian female was referred to the PH clinic after transthoracic echocardiogram (TTE) depicted mild dilatation of the right ventricle with preserved right ventricular function, pulmonary arterial systolic pressure (PASP) of 75 mmHg, and right atrial pressure (RAP) of 5–10 mmHg. VQ scan depicted a high probability of CTEPH. Referral to an expert PTE surgical center resulted in initiation of riociguat; however, titration was limited due to headaches. Despite an unchanged WHO FC II, dyspnea improved before her evaluation at a PTE center.

Repeat RHC performed before PTE demonstrated a significant improvement of PVR while on treatment with riociguat (6.9 WU vs 11.2 WU before treatment). Other variables after riociguat, but before PTE, were PAP: 77/22 mmHg, mPAP: 48 mmHg, PAWP: 9 mmHg,

CO: 4.75 L/min, and CI: 2.57 L/min. The patient underwent PTE and was continued on riociguat post-PTE for residual PH (after PTE, mPAP: 27 mmHg and PVR: 4.7 WU). Time from initial abnormal TTE to CTEPH diagnosis was approximately one year. Time from CTEPH diagnosis to PTE was 90 days.

Patient VII

Patient VII was a 71-year-old Hispanic male with a medical history of multiple venous thromboembolisms (VTEs) with PE. The patient was initially evaluated by a PH clinic with concern for CTEPH in the setting of abnormal TTE (conducted at an outside facility), which depicted right ventricle with moderate to severe dilatation, moderate right ventricular hypokinesis, and RAP of 10 mmHg. He was classified as New York Heart Association (NYHA) FC III. VQ scan confirmed presence of chronic thromboemboli. Additional RHC results are found in Table 1. At a specialized PTE center, he was initiated on riociguat, titrated to 2.5 mg TID, and reported significant improvement in exertional dyspnea and improvement to NYHA FC II. Before PTE surgery, improvements in mRAP, mPAP, and PVR were observed. The patient successfully underwent PTE surgery with normalization of mPAP to 21 mmHg and PVR to 2.4 WU. Time from initial symptom onset to CTEPH diagnosis was approximately one year.

Patient VIII

A 55-year-old Hispanic female with a history of recurrent PE initially presented to a PH clinic in 2013 with a TTE showing a moderately dilated right ventricle with a mildly reduced right ventricular systolic function, mild right ventricular hypertrophy, PASP of 71 mmHg, and evidence of diastolic dysfunction. She was classified as NYHA FC II. VQ scan demonstrated a high probability for clots. Additional RHC data are presented in Table 1.

The patient was lost to follow-up and re-established care in 2016. She declined referral to a specialized PTE center because of personal preference and was started on riociguat. After 16 months of treatment with riociguat, an improvement in NT-proBNP, 6MWD, and NYHA FC was observed (Table 1). Repeat TTE in 2018 demonstrated normalization of right heart size and function.

Patient IX

A 69-year-old Caucasian female was diagnosed with CTEPH in 2007 and initially treated with sildenafil by an outside provider. Baseline values are from her initial RHC at this time, so comparisons with post-riociguat values in 2015 should be made with caution. In 2015, she was referred to a PH clinic for further management of CTEPH. TTE from the outside facility showed mild to moderate right ventricular dilatation, intraventricular septal flattening consistent with right ventricular pressure overload, a moderately dilated right atrial size, and severe elevation in PASP. No RHC was performed, as the patient was under evaluation for PTE. While the lesions were considered operable, the patient was not an optimal candidate for surgery because of severe obesity. The patient underwent RHC approximately eight months after initial evaluation (Table 1). Subsequently, sildenafil was discontinued, and the patient was started on riociguat. Repeat TTE depicted normal size and function of the right ventricle with moderate to severe PH, which was an improvement from initial TTE in 2014. During her last PH clinical visit, she reported ongoing dyspnea with exertion but had no symptoms at rest.

Patient X

Patient X was a 35-year-old Hispanic female with a medical history of recurrent VTE/PE and pulmonary Mycobacterium avium complex (MAC) infection. She has no chronic MAC, and her pulmonary function tests were normal. She was initially evaluated at a PH clinic in 2013; TTE showed an estimated PASP of 50 mmHg, a severely dilated right ventricle and right atrium, severe right ventricle dysfunction, and normal left ventricle function. VQ scan confirmed presence of perfusion defect. RHC results are shown in Table 1. Time from abnormal TTE to CTEPH diagnosis was approximately one month. Patient was initiated on riociguat. After approximately four months of treatment with riociguat, her NT-proBNP decreased (Table 1) and she reported improvement of dyspnea and edema. Time from CTEPH diagnosis to PTE was 505 days, with complete resolution of PH depicted on repeat TTE.

Discussion

We describe 10 patients with symptomatic CTEPH who initiated treatment with riociguat, either while waiting for operability assessment for PTE or for PTE surgery. In all cases, there was a prolonged period between symptom onset and evaluation at the CTEPH center. The duration of treatment with riociguat in these patients ranged from two to six months in seven of the patients, with one patient receiving riociguat for 16 months. Where data were available, all patients except for patients VI and IX experienced improvements in 2–4 outcomes (change in WHO FC, BNP, 6MWD, and dyspnea), while patients VI and IX had improvement in dyspnea only.

Conclusion

In the real world, benefit was observed as early as two months after treatment initiation with riociguat. Riociguat may be beneficial as a bridge to PTE for operable patients with CTEPH. Ongoing investigation is warranted, potentially with a clinical trial.

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Contributorship

Each author made a substantial contribution to the acquisition, analysis, and interpretation of patient cases. V.P.B. drafted the manuscript, and all authors contributed to revisions to ensure cases' accuracy. All authors approved the version to be published.

Conflict of interest

The author(s) declare the following conflicts of interest: V.P.B. receives research funding from United Therapeutics Corporation and serves as an Advisory Board member for Bayer Corporation, Gilead Sciences, Inc., United Therapeutics Corporation, and Actelion Pharmaceuticals US, Inc.

L.M.-G. is a speaker for United Therapeutics Corporation, Actelion Pharmaceuticals, and Bayer Corporation and serves on Advisory Boards for Bayer Corporation, Gilead Sciences, Inc., United Therapeutics Corporation, and Actelion Pharmaceuticals US, Inc.

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