Case Report

Riociguat use in sickle cell related chronic thromboembolic pulmonary hypertension: A case series

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Abstract
Adults with sickle cell disease can develop pulmonary hypertension from a multitude of etiologies. Classified as WHO Group 5, there are no therapies approved for the treatment of sickle cell disease-pulmonary hypertension. Thromboembolic disease is prevalent in sickle cell disease and can lead to pulmonary hypertension. The only approved medical therapy for chronic thromboembolic pulmonary hypertension is riociguat. We report the experience, safety and tolerability of riociguat use in a series of sickle cell disease patients with chronic thromboembolic pulmonary hypertension.

Keywords
sickle cell disease, chronic thromboembolic pulmonary hypertension, riociguat

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Introduction
Sickle cell disease (SCD) is the most common autosomal recessive genetic disorder worldwide, affecting 100,000 in the United States alone. Adults with SCD can develop progressive vasculopathy with pulmonary artery endothelial dysfunction, and intimal and smooth muscle proliferation, leading to pulmonary hypertension.1 Recent hemodynamic studies report 6.2–10.4% of SCD adults develop pulmonary hypertension,2,3 with reduced functional capacity and increased mortality.4 Venous thromboembolism is a common complication of SCD, leading to chronic thromboembolic pulmonary hypertension (CTEPH) in some patients.

Despite advances in therapies for pulmonary arterial hypertension (PAH), a significant unmet need remains for sickle related pulmonary hypertension. The Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy (Walk-PHaSST) trial, the largest randomized control study of vasodilator therapy in SCD, was halted for safety. Sildenafil is considered unsafe in SCD, and other medications targeting the nitric oxide (NO) pathway are considered scrupulously. Treatment of CTEPH, however, is warranted regardless of underlying comorbidities.5 Riociguat is the first soluble guanylate cyclase stimulator approved by the Food and Drug Administration (FDA) for treatment of PAH and CTEPH. We describe the first experience of riociguat use in a sickle related CTEPH case series.

Case presentations

Case #1
A 42-year-old woman with frequent vaso-occlusive pain crises (VOCs) without history of acute chest syndrome (ACS) (Table 1) had concomitant rheumatoid arthritis treated with prednisone, methotrexate, etanercept and hydroxychloroquine. Baseline pulmonary pressures were mildly elevated a year earlier with pulmonary artery mean pressure of 23 mmHg. She presented in 2014 with subacute dyspnea and desaturation. Echocardiogram (ECHO) revealed elevated right ventricular systolic pressure (RVSP), and computed tomography (CT) angiogram (Table 2) demonstrated
bilateral pulmonary emboli with deep vein thrombus of left lower extremity. She was treated with enoxaparin and permitted travel after two months’ treatment.

Three months later, she returned complaining of pleuritic chest pain and dizziness off anticoagulation and was placed on unfractionated heparin. ECHO (Table 3) showed severely dilated right sided chambers with septal flattening. CT angiogram demonstrated progression of bilateral emboli. Failing to improve with unfractionated heparin, thrombolysis was administered, along with diuresis. Her hemodynamics improved, and she was discharged on apixaban.

ECHO seven months later showed persistent septal flattening. Right heart catheterization (RHC) was performed (Table 4). She was started on riociguat 0.5 mg three times daily (TID) a year after her initial pulmonary embolism, with dose titration gradually to 2.5 mg TID. Close monitoring for signs and symptoms related to her SCD, both subjectively and objectively with laboratory testing, revealed no adverse effects. Repeat ECHO showed resolution of septal flattening and normalization of pressures. Repeat RHC performed 48 months after drug initiation revealed significant improvement. There were no hospitalizations or ED visits related to VOC during riociguat therapy. Thromboendarterectomy was declined by a surgical center, therefore no pulmonary angiogram was performed. He discontinued riociguat after 18 months’ therapy due to intractable headaches.

**Case #3**

A 54-year-old woman presented in 2006 with dyspnea and hypoxemia and was diagnosed by RHC to have severe pre-capillary pulmonary hypertension with preservation of cardiac output. No history of ACS or thromboembolism was noted at presentation. V/Q was high probability suggestive of CTEPH and she was initiated on warfarin, hydroxyurea, supplemental oxygen, and bosentan. Anticoagulation was discontinued after one year due to recurrent vitreous hemorrhages. She responded well to therapy, with improvement of dyspnea, resolution of hypoxemia, and other objective markers. Her pulmonary hypertension was stable for seven years until 2013, when she developed acute dyspnea, and CT angiogram showed acute pulmonary embolism with ECHO evidence of acute right ventricular failure requiring intensive care unit (ICU) admission for inotropic support.

The patient was discharged home improved on bosentan, enoxaparin, hydroxyurea, home oxygen, and diuretics. Because of progressive dyspnea, repeat RHC was performed showing significant progression of her pulmonary hypertension. Therapy was escalated to include subcutaneous treprostinil (maximal dose 20 ng/kg per min) and riociguat, which was titrated to 2.5 mg TID. She tolerated riociguat without adverse events or VOCs. No hospitalizations or ED visits related to riociguat occurred during the dose titration. There was improvement in N-terminal pro-brain natriuretic peptide (NT-proBNP; 1022 to 713) and World Health Organization (WHO) functional class dyspnea scale III to II.

Unfortunately, 18 months later she travelled by airplane without her medications or supplemental oxygen and experienced worsening dyspnea but did not seek medical attention. Returning home, she presented in right heart failure. CT angiogram demonstrated new pulmonary embolism with evidence of chronic pulmonary embolism as well. ECHO revealed worsening right heart failure with moderate to 1.5 mg TID due to headaches. Repeat RHC could not be performed due to concomitant medical problems. Thromboendarterectomy was declined by the surgical center; therefore, pulmonary angiogram was not performed. He discontinued riociguat after 18 months’ therapy due to intractable headaches.

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**Table 1. Baseline clinical characteristics of patients.**

| Characteristic | Case #1 | Case #2 | Case #3 | Case #4 | Case #5 | Case #6 |
|---------------|---------|---------|---------|---------|---------|---------|
| Race          | Black   | Black   | Black   | Black   | Black   | Black   |
| Age           | 42      | 61      | 54      | 37      | 22      | 64      |
| Genotype      | SS      | SC      | SS      | SS      | SS      | SS      |
| Gender        | Female  | Male    | Female  | Male    | Male    | Female  |
| Comorbidities | RA; LAC+| COPD    | –       | –       | ESRD, OSA| CKD, RA, LAC+|

CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ESRD: end stage kidney disease; LAC+: positive lupus anticoagulant; OSA: obstructive sleep apnea; RA: rheumatoid arthritis.

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**Case #2**

A 61-year-old man with history of stroke, priapism and moderate VOCs presented in 2015 with progressive exertional dyspnea, dizziness and chest pain. ECHO revealed new evidence of right heart strain and oxygen desaturation. Ventilation perfusion scan (V/Q) was high probability. Anticoagulation and diuresis were initiated for three months without improvement in ECHO. RHC was consistent with pre-capillary pulmonary hypertension. Riociguat was initiated and titrated very slowly due to side effects, namely headache, dizziness, and sleepiness. He was closely monitored with biweekly clinic visits. Dyspnea and chest pain improved significantly, and laboratory testing showed stable SCD parameters. No hospitalizations or ED visits related to VOC occurred. After one year, dose was reduced to 1.5 mg TID due to headaches. Repeat RHC could not be performed due to concomitant medical problems. Thromboendarterectomy was declined by the surgical center; therefore, pulmonary angiogram was not performed. He discontinued riociguat after 18 months’ therapy due to intractable headaches.
pericardial effusion. The patient was again admitted to the ICU for inotropic support and diuresis, and discharged home improved. She declined pulmonary thromboendarterectomy and transplant evaluation. Pulmonary angiogram was therefore not performed. She received riociguat for three years. At the writing of this manuscript she has passed away from progressive right heart failure.

**Case #4**

A 37-year-old man with minimal VOCs presented in 2015 with his first ACS. Shortly thereafter, he presented hypoxic and dyspneic. V/Q scan was high probability for pulmonary embolism and anticoagulation was initiated; however, the patient remained significantly dyspneic and RHC showed severe pulmonary hypertension. Therapy including riociguat was started and he tolerated titration dose to 2.5 mg TID, being followed closely to ensure no side effects, subjectively and objectively. Given the severity of his disease, macitentan was added, which he tolerated. He had no clinical or laboratory evidence of worsening VOC, with no hospitalizations or ED visits during titration or maintenance phase of riociguat. Attempts were made to refer for thromboendarterectomy but failed due to lack of insurance. He has received riociguat for over two years.

**Case #5**

A 22-year-old man with history of stroke, recurrent priapism, and chronic kidney disease on dialysis presented with progressive dyspnea and near syncope. ECHO showed large pericardial effusion with severe pulmonary hypertension. He underwent emergency dialysis and subsequent RHC. V/Q scan confirmed chronic pulmonary emboli. Anticoagulation and riociguat were initiated, the latter at 0.5 mg with slow escalation due to renal failure. Repeat testing was performed on 0.5 mg TID. Periembolic effusion had resolved. The only side effect reported was brief gastroesophageal reflux, which resolved over a few weeks. No subjective or laboratory evidence of worsening or maintenance phase of riociguat. Attempts were made to refer for thromboendarterectomy but failed due to lack of insurance. He has received riociguat 1 mg TID for over a year.

**Case #6**

A 64-year-old woman with frequent VOCs, ulcers and chronic kidney disease was admitted with worsening right heart pressures. V/Q scan was consistent with CTEPH, which revealed pulmonary hypertension. Upon referral to RHC, which revealed pericardial effusion, ECHO was notable for rising right heart pressures. Riociguat was initiated for a minimum of three months prior to RHC, which revealed pulmonary hypertension. Riociguat was increased and very slowly increased due to diuresis was consistent with CTEPH. Anticoagulation therapy for a year was started and he tolerated titration dose to 5 mg TID. Periembolic effusion had resolved. The only side effect reported was brief gastroesophageal reflux, which resolved over a few weeks. No subjective or laboratory evidence of worsening or maintenance phase of riociguat. Attempts were made to refer for thromboendarterectomy but failed due to lack of insurance. He has received riociguat 1 mg TID for over two years. The patient was again admitted to the ICU for inotropic support and diuresis, and discharged home improved. She declined pulmonary thromboendarterectomy and transplant evaluation. Pulmonary angiogram was therefore not performed. She received riociguat for three years. At the writing of this manuscript she has passed away from progressive right heart failure.

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**Table 2. Clinical data of patients prior to and after initiation of riociguat.**

| Case #1 | Case #2 | Case #3 | Case #4 | Case #5 | Case #6 |
|---------|---------|---------|---------|---------|---------|
| Characteristic | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat |
| V/Q | Intermediate | High prob. | High prob. | High prob. | High prob. | High prob. | High prob. | High prob. | High prob. | Intermediate |
| CTPA | Saddle PE | Resolved PE | No PE | No PE | Acute PE | Acute PE | Chronic PE | No PE | No PE | Intermediate |
| PAH therapy | None | Riociguat 2.5 mg TID | None | Riociguat 2.5 mg TID | Bosentan, SQ treprostinil | Bosentan, SQ treprostinil | No | None | Macitentan, riociguat 2.5 mg TID | Sildenafil, Riociguat 0.5 mg TID |
| SCD therapy | HU 12 mg/kg | HU 12 mg/kg | HU 15 mg/kg | HU 15 mg/kg | HU 14 mg/kg | HU 14 mg/kg | HU 43 mg/kg | HU 43 mg/kg | HU 43 mg/kg | HU 25 mg/kg |
| Other therapy | Diuretic | Diuretic | Diuretic | Diuretic | Oxygen, diuretic | Oxygen, diuretic | Oxygen, diuretic | Oxygen, diuretic | Oxygen, diuretic | Diuretic |
| Anticoagulation | Apixaban, Apixaban | Warfarin, Warfarin | Enoxaparin, Enoxaparin | Enoxaparin, Enoxaparin | Rivaroxaban, Rivaroxaban | Rivaroxaban, Rivaroxaban | None | Apixaban, Apixaban | Apixaban, Apixaban | Apixaban, Apixaban |
| Hb, g/dL | 8.2 | 9.3 | 8.8 | 9.8 | 11 | 11.9 | 7.5 | 8.6 | 7.7 | 8.8 |
| Hb, F% | 20% | 24% | 1.6% | 1.1% | 27% | 30% | 16.1% | 24.7% | 7.4% | 5.3% | 1.7% | 2.0% |
| ProBNP, pg/mL | 481 | 57 | 1681 | 885 | 1022 | 713.5 | 317 | 107 | 57284 | 1974 | 1974 | 2783 | 5708 |

CTPA: computed tomography pulmonary angiogram; CTPA: continuous positive airway pressure; Hb: hemoglobin; HU: hydroxyurea; PAH: pulmonary arterial hypertension; PE: pulmonary embolism; prob.: probability; ProBNP: pro-brain natriuretic peptide; SCD: sickle cell disease; TID: three times daily; V/Q: ventilation-perfusion scintigraphy

*Pro-BNP not available from time of assessment. Taken from prior assessment > 1 year prior.*
Table 3. Echocardiogram and six-minute walk data pre and post riociguat therapy.

| Characteristic | Case #1 | Case #2 | Case #3 | Case #4 | Case #5 | Case #6 |
|----------------|---------|---------|---------|---------|---------|---------|
|                | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat | Pre-riociguat | Post-riociguat |
| ECHO           |         |         |         |         |         |         |
| Three months   | 3.0     | 2.7     | 4.27    | 3.6     | 4.09    | 4.00    | 4.3      | 3.4      | 4.1      | 2.9      | 3.4      | 3.4      |
| Two months     | 4.27    | 3.6     | 4.09    | 4.00    | 4.3     | 3.4     | 4.1      | 2.9      | 3.4      | 3.4      | 3.4      | 3.4      |
| One month      | 4.09    | 4.00    | 4.3     | 3.4     | 4.1     | 2.9     | 3.4      | 3.4      | 3.4      | 3.4      | 3.4      | 3.4      |
| Six months     | 4.3     | 3.4     | 4.1     | 2.9     | 3.4     | 3.4     | 3.4      | 3.4      | 3.4      | 3.4      | 3.4      | 3.4      |
| RV, m/s        | 41      | 34      | 78      | 62      | 81      | 79      | 85       | 57       | 87       | 39       | 55       | 61       |
| RA area, cm²   | 11      | --      | 35      | --      | Markedly enlarged | Moderately enlarged | Moderately dilated | Dilated | Severely dilated | Mildly dilated | Dilated | Mildly dilated |
| (normal <18)   |         |         |         |         |         |         |         |         |         |         |         |         |
| RA pressure    | 5       | 5       | 5       | 10      | 15      | 15      | 10       | 10       | 20       | 5        | 10       | 15       |
| LA area, cm²   | 20      | --      | 30      | --      | Mildly dilated | Mildly dilated | 45       | 53       | 62       | 48       | 35       | 36       |
| (normal <22)   |         |         |         |         |         |         |         |         |         |         |         |         |
| WHO FC         | 3       | 1       | 4       | 3       | 3       | 2       | 2        | 1        | 4        | 2        | 3        | 2        |
| 6MWD, m        | 390m    | 458m    | 203m    | 365m    | 240m    | 260m    | 526      | 533      | 483      | 510      | 232      | --       |
| Borg dyspnea:  | 2; 4    | 1; 1    | 1; 10   | 0; 7    | 1; 3    | 1; 3    | 0; 2     | 0; 1     | 3; 0     | 1; 4     | 0; 2     | --       |
| pre; post      |         |         |         |         |         |         |         |         |         |         |         |         |
| O₂ sat. on air:| 98%; 92%| 99%; 94%| 100%; 96%| 100%; 87%| 92%; 82%| 95%; 88%| 100%; 100%| 100%; 99%| 100%; 100%| 100%; 95%| 100%; 98%| --       |
| pre; post      | 65; 123 | 81; 145 | 98; 125 | 87; 128 | 99; 120 | 99; 110 | 78; 145  | 65; 117  | 83; 109  | 102; 139 | 95; 133  | --       |

6MWD: six-minute walk distance; ECHO: echocardiogram; HR: heart rate; LA: left atrial; O₂ sat.: oxygen saturation; RA: right atrial; RVSP: right ventricular systolic pressure; TRV: tricuspid regurgitant velocity; WHO FC: World Health Organization functional class.
gastroesophageal reflux. The dose was escalated to a maximum of 1.5 mg TID, at which she experienced increased VOC. Dose was reduced to 1 mg TID with improvement in VOC but persistent gastrointestinal effects. Repeat objective testing at four months revealed lack of improvement; riociguat was terminated and after much discussion sildenafil was initiated and titrated. Aside from the VOC experienced at the 1.5 mg dose, she had no increase in VOC frequency or severity at other doses. Laboratory measures of SCD stability were closely monitored and confirmed absence of increased hemolysis. She has declined repeat RHC.

**Discussion**

This report represents the first description of riociguat experience in a sickle cell case series with CTEPH. Riociguat use is well established in the medical management of CTEPH patients unable to undergo surgery, or in patients with persistent pulmonary hypertension after pulmonary endarterectomy. In such patients riociguat improved six-minute walk distance (6MWD) and cardiac output and significantly lowered pulmonary venous resistance. Thromboembolic disease is well established in SCD; however, no SCD patients have been included in the clinical trials of riociguat, and no medical literature has been published on the use of this medication in this population. Herein, we report our experience with the use and the safety and tolerability of riociguat use in six adults with SCD and CTEPH. Riociguat was safe and was well tolerated in four out of the six patients.

Pulmonary hypertension in SCD is associated with increased morbidity and mortality. The etiology of SCD-pulmonary hypertension (SCD-PH) is often multifactorial, including hypoxia, oxidative stress, high cardiac output, chronic thromboembolism, left-heart disease, hemolysis, dysregulated NO metabolism, surgical splenectomy or functional asplenia, renal insufficiency, increases in vasoactive mediators such as endothelin-1 and placentinal growth factor, and genetic factors. The relative contribution of each of these mechanisms to SCD-PH in individual patients is variable and remains unknown. Each patient has a variety of these contributing factors and can have a combination of WHO Group sub-classifications, including CTEPH. No publications to date have examined the role of riociguat in CTEPH patients with SCD.

Venous thromboembolism (VTE) affects approximately 25% of SCD adults and is a risk factor for death. Incidental VTE occurs in 17% of severe SCD by age 40, and recurrent VTE is reported in 37% at five years. The etiology of increased VTE risk is multifactorial, with in situ thrombosis contributing to disease but not always being distinguished. Both traditional factors, such as central venous catheters, frequent hospitalization, orthopedic surgeries, and many SCD-specific factors, such as thrombophilic defects, genotype, and splenectomy, may modify the risk of VTE; most importantly sickle hypercoagulability contributes considerably to VTE. CTEPH has been noted in patients with SCD. One study reported 6/27 SCD patients with pulmonary hypertension having high probability V/Q scans, three (12%) of which were consistent with patterns observed in CTEPH. A small autopsy study reported up to 50% of pulmonary hypertension patients (defined as having right ventricular hypertrophy) had evidence of proximal vessel pulmonary thrombi. Underlying hypercoagulability may also contribute to the pathogenesis of elevated pressures in SCD-PH patients without chronic thromboembolic disease. Autopsy studies of SCD patients have demonstrated diffuse in situ thrombi in the pulmonary vessels of a majority of patients with pulmonary hypertension, which could represent a pathogenic link between small vessel thrombi seen in SCD patients with pulmonary hypertension and VTE.

To date, there have been no studies to inform anticoagulation practices in patients with SCD. Small pilot studies

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**Table 4. Baseline hemodynamic data before riociguat therapy.**

| Hemodynamics | Case #1 | Case #1 follow-up two years after initiation | Case #2 | Case #3 | Case #4 | Case #5 | Case #6 |
|--------------|---------|---------------------------------------------|---------|---------|---------|---------|---------|
| PAPs, mmHg   | 54      | 42                                          | 64      | 101     | 87      | 85      | 45      |
| PAPd, mmHg   | 26      | 20                                          | 32      | 34      | 31      | 55      | 20      |
| PAPm, mmHg   | 35      | 28                                          | 43      | 62      | 52      | 70      | 32      |
| RAPm, mmHg   | 10      | 9                                           | 17      | 18      | 12      | 26      | 8       |
| PCWP, mmHg   | 12      | 9                                           | 12      | 7       | 7       | 30      | 15      |
| TPG, mmHg    | 23      | 19                                          | 31      | 55      | 45      | 40      | 17      |
| Cardiac output, L/min | 6.05 | 5.6                                         | 7.75    | 8.16    | 5.49    | 9.0     | 3.6     |
| Cardiac index, L/min per m² | 4.0 | 3.2                                         | 3.7     | 4.26    | 2.82    | 4.5     | 2.4     |
| PVR, Wood U  | 3.8     | 3.39                                        | 4.0     | 12      | 8       | 4.4     | 4.72    |

All cardiac outputs were determined by Fick measurements.
PAPd: diastolic pulmonary artery pressure; PAPm: mean pulmonary artery pressure; PAPs: systolic pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; TPG: transpulmonary gradient.
have investigated anticoagulant agents such as warfarin, acenocoumarol, and heparin to prevent complications such as VOC in SCD,\(^{18}\) but trials evaluating anticoagulation for VTE treatment and prevention are lacking. Anticoagulation management of symptomatic VTE, therefore, currently relies on established general guidelines for VTE management.\(^{19}\) Management of CTEPH in SCD is similarly poorly understood with very few publications addressing it. First, one prescribes the recommended treatment of SCD-PH in general, which is primarily maximal therapy for SCD, either through hydroxyurea or transfusion therapy.\(^{20}\) Other supportive treatment measures include supplemental oxygen to maintain a saturation of 90%.\(^{20}\) Diuretics are used to reduce right ventricular volume overload,\(^{21}\) without causing volume depletion, which can induce erythrocyte sickling. Only then can pulmonary hypertension therapy be proposed.

The literature for SCD-PH therapy is equally limited. Two trials compared treatment with bosentan to placebo in SCD patients with RHC-defined precapillary pulmonary hypertension (ASSET-1) or post-capillary pulmonary hypertension (ASSET-2).\(^{22}\) After randomization of 14 subjects and 12 patients respectively, the trials were prematurely terminated due to withdrawal of support. Although few patients were enrolled, there were no apparent toxicity issues. The third trial, Walk-PHaSST,\(^{23}\) compared the safety and efficacy of sildenafil with placebo in SCD patients with a tricuspid regurgitant velocity \(\geq 2.7\) m/s. After enrolling 74 (of a targeted 132) subjects, the study was prematurely discontinued due to an increase in serious adverse events in the sildenafil group, primarily hospitalization for pain.\(^{23}\)

Riociguat is a suitable vasodilator for SCD-PH since it does not rely on NO.\(^{24}\) Free hemoglobin acts as a scavenger of NO which can exacerbate SCD-PH.\(^{25}\) Given the common pathway of NO and cyclic guanosine monophosphate (cGMP) between riociguat and sildenafil, a phosphodiesterase type 5 inhibitor, there is naturally concern about similar side effects with riociguat as seen in the Walk-PHaSST trial. In our case study, there was an increase in VOC in one patient who was not on hydroxyurea but on transfusion therapy, observed at higher doses, albeit in renal insufficiency. In other patients whose SCD was well managed, no increase in VOC or other pain was noted, subjectively or objectively. However, this remains a retrospective report of a case series; prospective large population trials will be needed to appropriately address this issue.

These six patients clearly had moderate to severe pulmonary hypertension based on their RHC, with history of thromboembolic disease and CTEPH based on consensus definition (abnormal V/Q scan with abnormal RHC or ECHO despite anticoagulation for three months or longer). Administration of riociguat resulted in significant improvement in functional class, exercise capacity, NT-proBNP, and RVSP in half of the patients. Subjective and objective response in this population of CTEPH patients, as measured by the biomarker NT-proBNP, ECHO and clinical measures (functional class and 6MWD), is important as these are gauges deemed essential by patients, caregivers, researchers, and drug manufacturers. These are also the endpoints commonly studied in pulmonary hypertension clinical trials, along with hemodynamics and biomarkers such as NT-proBNP.\(^{5,7}\)

There are many limitations to the current report, most noticeably, given a small case series, its retrospective nature and the lack of follow-up RHC data. In comparing the response of these patients to riociguat, it is appropriate to compare them with other CTEPH patients and not to Group 1 or Group 5 clinical trials. Our first two patients had 68-m and 162-m improvements compared with our remaining patients, who had 20-m, 7-m and 27-m improvements, the 7-m increase due to preserved baseline 6MWD. The patient intolerant of riociguat did not repeat the six-minute walk test prior to switching therapies. Our series had an average meter improvement of 56.8 m (SD 63.07, SEM 28.2, median 27). This cannot be compared to the average 39-m change in the Chest-1 trial prompting FDA approval of riociguat;\(^{7}\) however, it is worthy of mention. Moreover, 5/6 patients also had improvements in RVSP, functional class and NT-proBNP similar to the Chest-1 study.\(^{7}\)

Referral for thromboendarterectomy remains standard of care for CTEPH regardless of comorbidity or age. Recently a large successful surgical experience for milder hemoglobinopathies was published.\(^{26}\) That cohort reported hemodynamics similar to ours. Our patients were all referred for surgery while initiating vasodilator therapy. The majority were declined for inoperable disease and/or comorbid illness. Anticoagulation in this cohort was administered using a variety of therapies, including direct oral anticoagulants. Effective long-term anticoagulation in SCD is difficult and these agents are a welcome addition.

In conclusion, this is the first description of the use of riociguat in SCD related CTEPH. This therapy was overall safe and well tolerated, as well as effective at the approved dose in carefully selected patients with SCD and pulmonary hypertension related to chronic thromboembolic disease. Longer term studies in SCD with CTEPH will be needed to ensure that the significant benefits of riociguat persist over time. The authors caution health care providers to ensure that eligible sickle CTEPH patients not be deprived of evaluation for pulmonary endarterectomy, a potentially curative surgical procedure, simply because of the convenience of a modestly effective oral medication.

**Key points**

Riociguat is FDA approved for CTEPH but no sickle cell patients have been included in the trials investigating the safety and tolerability of this drug. Thromboembolic disease and pulmonary hypertension are both prevalent in sickle cell disease. This is the first report of safety and tolerability of riociguat use in sickle cell related CTEPH.
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AM and NAW were responsible for the idea of the manuscript and the integrity of the paper. DL, AC, NAW and AM collected the data and reviewed the manuscript. AM and NAW wrote and analyzed the data.

Declaration of conflicting interests

DL has served as a consultant for Gilead Sciences, Actelion and Bayer Pharmaceuticals. NAW has served on advisory board for Gilead Sciences. AC has no disclosures.

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