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**Going Rogue: Forgoing Riociguat for inhaled Treprostinil in a patient with CTEPH and sickle cell disease.**

Yaqoob M, Anguiano RH, Feld C, Fraidenburg DR

*University of Illinois At Chicago, Chicago, IL*

**Background:** Sickle cell disease (SCD) is a common genetic disorders with venous thromboembolism affecting a quarter of adults with SCD. Chronic thromboembolic pulmonary hypertension (CTEPH) has been noted in at least 12% of SCD patients with pulmonary hypertension. While medical therapy for pulmonary arterial hypertension and CTEPH has been well established, patients with sickle cell disease can have varied responses and unique adverse effects of these medications. We present a patient with SCD and CTEPH who had an adverse response to initial therapy with riociguat and was successfully managed with inhaled treprostinil.

**Methods:** A 46 year old woman with sickle cell disease, ESRD on peritoneal dialysis, recurrent pulmonary embolism, and severe precapillary PH was diagnosed with CTEPH after identifying multiple large perfusion defects on ventilation-perfusion scan. She declined evaluation for pulmonary thromboendarterectomy and riociguat was started as first line medical therapy. She had two hospitalizations after starting riociguat and was unable to tolerate dose escalation due to multiple adverse effects, including increased joint pains. Alternative pulmonary vasodilator therapies were discussed with her and she was started on inhaled treprostinil. The dose was titrated to 11 breaths four times per day over a course of 8 months. Supportive treatment with anticoagulation and volume control with dialysis was continued. Echocardiogram showed improvement in her right ventricular function. Her tricuspid regurgitant jet velocity decreased from 6 m/s to 4.69 m/s, with improvement in the right ventricular systolic pressure from 152 mmHg to 103 mmHg. Her walk distance and BNP both improved while hospitalizations decreased. Her prognosis remains guarded given her poor functional class and severely deranged pulmonary hemodynamics, yet her quality of life has significantly improved.

**Results:** Riociguat is the only FDA approved medical therapy specifically targeting CTEPH though its use for PH in SCD is not well-established. A trial of sildenafil in SCD associated PH was stopped early as increased painful episodes and hospitalization occurred in the treatment arm. While riociguat has therapeutic effects through the same molecular pathway, it is unknown if the same adverse effects will be encountered. Our patient reported increased pain and had recurrent hospitalizations while on riociguat possibly in the setting of ESRD and altered drug metabolism, yet conclusions cannot be drawn from this single experience. More interesting is her impressive response to inhaled treprostinil therapy. The use of inhaled treprostinil has been published in only five subjects with SCD and PH, none of which were diagnosed with CTEPH. In addition to the pulmonary vasodilating effects of treprostinil, antiplatelet effects may be of particular benefit in this population. SCD patients have increased platelet activation which is thought to contribute to both vaso-occlusive pain crises and thrombosis.

**Conclusions:** Our case represents the first known report on the successful use of inhaled treprostinil in a patient with SCD and CTEPH. The pharmacologic effects of treprostinil suggest that this therapy may be particularly effective in similar patients.



*Presented at the 2019 Pulmonary Hypertension Association (PHA) Pulmonary Hypertension Professional Network (PHPN) Symposium.*