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Transitioning selexipag to oral treprostinil in patients with pulmonary artery hypertension

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ABSTRACT

There are no prospective studies or guidelines describing transition between selexipag and oral treprostinil. We present two different transition strategies from selexipag to oral treprostinil, one started inpatient and then completed at home, and one completely under outpatient settings. Neither patient experienced worsening prostacyclin-type adverse effects; both were rigorous in their attention to a 7–8 hour administration schedule for oral treprostinil, and both experienced objective clinical benefit at follow-up. Prospective studies are needed to help guide clinical decisions when patients remain intermediate risk after a trial of either drug.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive and often fatal pulmonary vascular disease [1]. Prostacyclin and its analogues have vasodilator, anti-platelet, anti-proliferative, and anti-inflammatory properties [2]. Parenteral prostacyclin therapy is clearly preferred for many intermediate- or high-risk patients [3], but patients often prefer oral options. There are currently two FDA approved oral prostacyclin therapies available, selexipag [4], a selective prostacyclin IP receptor agonist, and treprostinil [5], a prostacyclin analogue. Oral prostacyclin therapy [4,5] helps improve symptoms, right ventricular function, and clinical outcomes. There are no prospective studies describing transition from one drug to the other. We present two different methods (inpatient and outpatient) with successful transition of two patients from selexipag to oral treprostinil; each had improvement in REVEAL 2.0 risk assessment [6].

2. Case 1

A 70 year old female with idiopathic PAH was taking ambrisentan 10 mg daily, tadalafil 40 mg daily, and selexipag 1600 mcg twice daily before presenting to our clinic with persistent symptoms in New York Heart Association (NYHA) Functional Class III. A right heart catheterization completed 6 months prior to her visit showed pulmonary arterial hypertension with increased vascular resistance despite being on triple vasodilator therapy (Table 1). She was unable to do a 6-Minute Walk Test (6MWT) at her initial visit and had a REVEAL 2.0 risk assessment of 10. She did not have evidence of decompensated heart failure on exam and was not taking diuretics. Her echocardiogram showed a moderate-severely enlarged right ventricle with reduced function. After discussing therapeutic options, she elected hospitalization and transition to oral treprostinil with a brief intravenous treprostinil bridge. She took her last dose of selexipag 1600 mcg the evening prior and started intravenous treprostinil the next morning at 6 ng/kg/min with increases of 2 ng/kg/min every 8–12 hours until 20 ng/kg/min. Her in-hospital walking ability and symptoms of breathlessness improved with IV treprostinil; we then transitioned to oral treprostinil at a dose of 4 mg every 8 hours [7]. She had no difficulty with prostacyclin adverse effects during this

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transition. We initiated low dose torsemide and spironolactone in the hospital, and her weight was unchanged at discharge. She did not want to repeat a right heart catheterization while hospitalized. She continued titration of treprostinil at home, reaching FC II symptoms at a dose of 7.25 mg every 8 hours in two months. At 6 month follow-up, she walked 329m and her REVEAL 2.0 risk score dropped to 7 (Table 1). Her right ventricle has improved on echocardiogram and is now mild-moderately enlarged with minimal septal dyskinesia. Over the last 18 months, she has maintained clinical improvements without hospitalization or need for urgent provider follow-up; she declined our suggestion for repeat catheterization.

3. Case 2

A 60 year old male with idiopathic PAH and morbid obesity (BMI of 40 kg/m²) was using tadalafil 40 mg daily and selexipag 1200 mcg twice daily. Due to nasal congestion, he could not tolerate endothelin receptor antagonists or higher selexipag dosing. He was on stable doses of torsemide and spironolactone without clinical evidence of fluid retention. He had worsening dyspnea on exertion within NYHA Functional Class II. A right heart catheterization (RHC) revealed residual pulmonary arterial hypertension with increased resistance (Table 1), and his Reveal 2.0 risk score was 7. We recommended switching selexipag to oral treprostinil therapy with hospitalization and an IV treprostinil bridge as above. Because of the COVID-19 pandemic, the patient declined admission. He took his last dose of selexipag the evening prior, and the following morning he started treprostinil 0.75 mg every 8 hours. On careful phone follow-up, he denied worsening breathlessness, lightheadedness, presyncope, chest pain, or edema. He was able to titrate up by 0.125 mg every 72 hours until 1.75 mg but stopped further titration because he experienced prostacyclin side effects including flushing and nasal congestion. He reported clear symptom improvement within FC II. His 6MWT increased by 67 m, and his Reveal 2.0 risk score fell to 5. At 6 month follow up, his echocardiogram showed a mildly enlarged right ventricle with preserved systolic function and minimal septal dyskinesia (Table 1).

4. Discussion

We report two strategies for transitioning selexipag to oral treprostinil and observed objective clinical benefit in two patients. Neither patient experienced worsening prostacyclin adverse effects; both were rigorous in their attention to a 7–8 hour administration schedule for oral treprostinil. Close follow up of right ventricular function is important during transitions, and we recommended repeat catheterizations but both patients declined in light of reassuring echocardiograms.

Parenteral prostacyclins have been shown to improve exercise capacity, functional class, and hemodynamics [3]. Despite the impressive efficacy of these drugs, the complex delivery systems limit use. Selexipag and oral treprostinil may be more acceptable to patients and allow earlier introduction of this therapeutic class. The GRIPHON study showed a delay in clinical worsening for PAH patients on any (or no) background therapy; its twice daily schedule is easier for patients [4]. On the other hand, the Freedom-EV study demonstrated that oral treprostinil not only delayed clinical worsening but also improved symptoms and NT-pro-BNP in PAH patients who recently started monotherapy [5]; the rigorous three times daily schedule is a limitation for some. There are no direct comparisons between the two drugs, and different clinicians (and patients) will likely have different preferences [8]. There is no direct calculation to switch from selexipag to treprostinil. We were conservative on our initial treprostinil dose with the possibility of residual selexipag in their system, but a dose of ~0.75–1 mg every 8 hours is likely a safe starting point for a patient on higher dose selexipag. Further studies are needed to confirm that. We also found the Reveal 2.0 risk assessment [6] useful when measuring therapeutic responses.

Outpatient transitions have not previously been reported. There is a single case report of 24 year old male transitioning from selexipag 1600 mcg twice daily to oral treprostinil 7.5 mg every 8 h [9] during a 10 day hospitalization. Our approach with IV

Table 1
Transition table before and after Oral Treprostinil.

Case 1	Baseline (Selexipag)	3–6 Months Post Treprostinil
Hemodynamics		
RA (mmHg)	4	–
mPAP (mmHg)	42	–
PVR (dynes/sec/cm-5)	608	–
CI (L/min/m ²)	2.2	–
NT-pro BNP (pg/ml)	<50	<50
6-Minute Walk Test (m)	–	329
NYHA FC	III	II
REVEAL 2.0	10	7
Case 2		
Hemodynamics		
RA (mmHg)	7	–
mPAP (mmHg)	50	–
PVR (dynes/sec/cm-5)	462	–
CI (L/min/m ²)	2.26	–
NT-pro BNP (pg/ml)	164	82
6-Minute Walk Test (m)	420	487
NYHA FC	III	II
REVEAL 2.0	7	5

RAP: right atrium pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CI: cardiac index.

treprostinil as a bridge provided a faster transition. Both of our patients enjoyed clinical improvement with lower REVEAL 2.0 risk scores; this could be attributable to treprostinil's broader prostanoid receptor profile [2]. We emphasize the importance of careful phone and office follow-up with any transition. Repeat right ventricular assessment (echo, cMRI, or right heart catheterization) is mandatory, and we have a low threshold to repeat hemodynamics as previously recommended [7]. Given the large number of patients using these drugs who still have an intermediate risk profile and the increasing attention to achieving low risk [10], prospective transition studies following a prescribed protocol would be valuable.

Declaration of competing interest

This case series did not receive any funding. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript. R. Jim White (RJW) does research with United Therapeutics (UT); he has no personal financial relationship, and all funds go to the University of Rochester. Daniel Lachant (DJL) has served as a paid consultant to UT and does research with UT (funds to University of Rochester). Carlo Arevalo (CA) declares no conflict of interest.

References

- [1] M. Humbert, M.T. Lau Edmund, D. Montani, et al., Advances in therapeutic interventions for patients with pulmonary arterial hypertension, *Circulation* 130 (24) (2014) 2189–2208.
- [2] B.J. Whittle, A.M. Silverstein, D.M. Mottola, et al., Binding and activity of the prostacyclin receptor (IP) agonists, treprostinil and iloprost, at human prostanoid receptors: treprostinil is a potent DP1 and EP2 agonist, *Biochem. Pharmacol.* 84 (1) (2012) 68–75.
- [3] N. Galiè, M. Humbert, J.-L. Vachiery, et al., ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, *Eur. Respir. J.* 46 (4) (2015) 903, 2015.
- [4] O. Sitbon, R. Channick, K.M. Chin, et al., Selexipag for the treatment of pulmonary arterial hypertension, *N. Engl. J. Med.* 373 (26) (2015) 2522–2533.
- [5] R.J. White, C. Jerjes-Sanchez, G.M. Bohns Meyer, et al., Combination therapy with oral treprostinil for pulmonary arterial hypertension: a double-blind, placebo-controlled study, *Am. J. Respir. Crit. Care Med.* (2019).
- [6] R.L. Benza, M. Gomberg-Maitland, C.G. Elliott, et al., Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-Based risk assessment strategies, *Chest* 156 (2) (2019) 323–337.
- [7] M.M. Chakinala, J.P. Feldman, F. Rischard, et al., Transition from parenteral to oral treprostinil in pulmonary arterial hypertension, *J. Heart Lung Transplant.* 36 (2) (2017) 193–201.
- [8] V.V. McLaughlin, R. Channick, T. De Marco, et al., Results of an expert consensus survey on the treatment of pulmonary arterial hypertension with oral prostacyclin pathway agents, *Chest* 157 (4) (2020) 955–965.
- [9] I. Oriaku, A. Patel, Z. Safdar, Transition from selexipag to oral treprostinil in a patient with pulmonary arterial hypertension, *Pulm. Circ.* 10 (1) (2020), 2045894019898032.
- [10] J. Weatherald, A. Boucly, S. Sahay, et al., The low-risk profile in pulmonary arterial hypertension. Time for a paradigm shift to goal-oriented clinical trial endpoints? *Am. J. Respir. Crit. Care Med.* 197 (7) (2018) 860–868.