REGULAR ARTICLE

Rapid Transition From Oral Selexipag to Intravenous Treprostinil in a Patient With Severe Pulmonary Arterial Hypertension

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Purpose: Certain patients may require transition from selexipag to intravenous (IV) treprostinil due to clinical deterioration or worsening pulmonary arterial hypertension. However, consensus on how to transition between these agents is lacking.
Summary: Herein, we report a 44-year-old woman diagnosed with pulmonary arterial hypertension treated with oral triple therapy (sildenafil 40 mg 3 times daily, bosentan 125 mg twice daily, and selexipag 1600 mg twice daily), who required transition from oral selexipag to IV treprostinil due to worsening clinical parameters. Right heart catheterization revealed mean right atrial pressure of 3 mmHg, mean pulmonary artery pressure of 48 mmHg, mean pulmonary capillary wedge pressure of 5 mmHg, pulmonary vascular resistance of 12 WU, and cardiac index (indirect Fick) of 2.12 L/min/m^2. Upon admission to the intensive care unit, selexipag was weaned down over 3 days while IV treprostinil was up-titrated to 35 ng/kg/min. Our patient experienced improvements in echocardiographic parameters as well as clinical symptoms after the transition was completed.
Conclusion: In this case report, we demonstrate the feasibility of faster transition without increasing the risk of adverse effects, if performed in a monitored setting.

INTRODUCTION

Selexipag is an oral selective prostacyclin receptor agonist (IP-receptor) indicated for patients who have World Health Organization (WHO) functional class (FC) II–III pulmonary arterial hypertension (PAH). It has increasingly been used based on its efficacy, favorable adverse effect profile, and availability as an oral formulation.[1] Despite this, conversion to parenteral prostacyclin therapy may be indicated for patients who have rapid progression or high-risk PAH. Published data on transitioning from oral selexipag to parenteral treprostinil are limited, and no formal guideline recommendations exist, despite this conversion being commonly performed at pulmonary hypertension centers. In this case report, we outline the rapid transition from selexipag to intravenous (IV) treprostinil at a specialized pulmonary hypertension center.

CASE REPORT

A 44-year-old woman with WHO Group 1, FC IV idiopathic PAH underwent a planned admission to transition from oral selexipag to IV treprostinil due to worsening parameters on echocardiogram and right heart catheterization (RHC). Her past medical history was significant for renal artery stenosis successfully treated with balloon angioplasty with resolution of her systemic hypertension. The patient was diagnosed with PAH at the age of 32 after she presented with progressive dyspnea on exertion. Through the years, she required treatment escalation of her PAH medications due to declining FC and right ventricular function, with reasonable, short-lived improvement after each escalation. She was also resistant to the idea of IV prostacyclin when it was first recommended, several years after diagnosis, and with disease progression on sildenafil and bosentan. She eventually agreed to oral prostacyclins. At the time of current admission, she was on sildenafil 40 mg 3 times daily, bosentan 125 mg twice daily, and selexipag 1600 mg twice daily. The patient had received selexipag for approximately 5 years.
The triple regimen was generally well tolerated with occasional mild headaches (treated with acetaminophen) and constipation. Other medications included spironolactone 50 mg daily and torsemide 10 mg twice daily. Her 6-minute walk distance (6MWD) on dual therapy before selexipag initiation was 336 m. Her 6MWD on triple therapy and prior to transition was not available. A transthoracic echocardiogram on this regimen identified a D-shaped interventricular septum suggestive of elevated right-sided pressure as well as a moderately dilated right ventricle with moderately reduced function. She did not have a sufficient tricuspid regurgitation jet to estimate right ventricular systolic pressure. Subsequently, she underwent a RHC which showed a mean right atrial pressure of 3 mmHg, mean pulmonary

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Table 1. Hemodynamic Values Before, During, and After Initiation of Intravenous Treprostinil Administration

Day	6MWT (m)	HR (beats/min)	RA mean (mm Hg)	PA (mean), (mm Hg)	PCWP mean (mm Hg)	PVR (WU)	CO (L/min)	CI (FICK), (L/min/m^2)
2 mo prior to treprostinil infusion (on triple therapy)	NA	54	7	89/34 (53)	19	11.97	2.84	1.74
Day 0 (upon admission), prior to initiation of treprostinil infusion	NA	69	3	75/32 (48)	5	12	3.39	2.12
Titration of treprostinil to 10 ng (day 2)	NA	60	3	63/28 (40)	5	8.19	4.27	2.58
Titration of treprostinil to 25 ng (day 3)	NA	69	1	64/32 (42)	5[a]	10.45[b]	3.54	2.19
Titration of treprostinil to 30 ng (day 4)	NA	72	3	54/29 (38)	5[a]	9.5	3.88	2.38
4 months after target dose of 40 ng/kg/min was achieved	549	68	1	52/25 (35)	4	8.05	3.85	2.46

Abbreviations: 6MWT indicates 6-minute walk test; CI, cardiac index; CO, cardiac output; HR, heart rate; NA, not available; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVT, pulmonary vascular resistance; RA, right atrium.

[a] Unable to obtain PCWP from Swan-Ganz; therefore, estimated from right heart catheterization.

[b] Estimated.

artery pressure of 48 mmHg, mean pulmonary capillary wedge pressure of 5 mmHg, pulmonary vascular resistance (PVR) of 12 WU, and cardiac index (CI, indirect Fick) of 2.12 L/min/m^2 (Table 1). Based on these findings, a decision to undergo transition to IV treprostinil was made. A subcutaneous route of administration was offered. However, the patient refused due to the potential for injection site reactions.

On admission, the patient had a brain natriuretic peptide of 21 pg/mL, with normal liver and kidney chemistries, and a total body weight of 56.7 kg (body mass index = 21.46 kg/m^2). She was hemodynamically stable with an oxygen saturation of 99% on room air. She was admitted to the intensive care unit (ICU), and a Swan-Ganz catheter was placed. Down-titration of selexipag was started by 400 mcg every 12 hours until 400 mcg was reached from her initial dose of 1600 mcg (Table 2). Then it was decreased by 200 mcg until completed (on day 3). Concurrently, IV treprostinil was titrated rapidly by 5–7.5 ng/kg/min every 12 hours until 25 ng/kg/min was reached. Subsequently, the rate of titration was lowered to 2.5 mg/kg/min every 12 hours until a final dose of 35 ng/kg/min was reached. Overall, this transition occurred over the course of 3 days and was generally well tolerated except for complaints of minimal headaches and constipation. She did not endorse any muscle pains, flushing, flulike symptoms, symptomatic hypotension, diarrhea, nausea, or vomiting. No significant changes in heart rate or blood pressure were noted during the transition process. She did not require any vasopressor support or fluid administration and was maintained on her home diuretic regimen of spironolactone 50 mg daily and torsemide 10 mg twice daily during the in-patient treatment. Via the Swan-Ganz catheter, a decrease in PVR was seen from 12 to 10.5 WU over these initial 3 days. The remainder of the hospital stay was insignificant, and the patient was discharged home on day 8 after teaching and logistics of home therapy were in place. Treprostinil was up-titrated as an outpatient over several weeks to reach a target dose of 40 ng/kg/min (see details in discussion). Her functional capacity continued to improve, and she continued to work full time. A follow-up RHC at 4 months after achieving the target dose of 40 ng/kg/min showed continued improvement in her hemodynamics, as demonstrated in Table 1. Notable findings include an overall decrease in PVR from 12 to 8.05 WU as well as an increase in CI (via indirect Fick) from 2.12 to 2.46 L/min/m^2. Her echocardiogram at 4 months showed resolution of the previously seen D-shaped interventricular septum with an associated improvement of right ventricular function (Figure 1). The REVEAL Lite 2 risk score improved from 7 at baseline to 2 at week 16, representing a shift from intermediate- to low-risk strata.[2]

DISCUSSION

In this case report, we describe the rapid transition from oral selexipag to IV treprostinil therapy due to disease progression despite oral triple regimen. Transition was safely completed over 3 days in an ICU, without the patient experiencing any significant adverse effects. Our patient experienced improvements in echocardiographic parameters as well as clinical symptoms after the transition was completed. WHO FC improved from IV to I, and she reported increased endurance at work. We acknowledge that some of the hemodynamic numbers obtained throughout this process such as PVR were variable, which may be in part due to the limitations of an indirect Fick.

Selexipag is an oral prostacyclin receptor agonist with a nonprostanoid structure approved for patients with PAH who have WHO FC II and III.[1] The starting dose of selexipag is 200 mcg twice daily titrated to a maximum dose of 1600 mcg twice daily.[3] It achieves rapid absorption with maximum plasma concentration achieved within 1–2 hours, bioavailability of 49%, and a terminal half-life of 0.8–2.5 hours.[3] In the landmark GRIPHON

Table 2. Doses of Selexipag and Intravenous Treprostinil, Vital Signs, Side Effects, and BNP Levels During the Transition

Day	Selexipag AM (mcg)	Selexipag PM (mcg)	Treprostinil AM (ng/kg/min)	Treprostinil PM (ng/kg/min)	Blood pressure (MAP range)	Adverse effects	BNP	Titration comments
0	1600	1600	0	0	NA	NA	NA	NA
1	1600	1200	0	5	74–89	None	21	Increase treprostinil by 5 ng/kg/min every 12 h
2	800	400	10	17.5	80–107	None	NA	Increase treprostinil by 7.5 ng/kg/min every 12 h
3	200	NA	25	27.5	70–102	Mild headache and constipation	NA	Increase treprostinil by 2.5 ng/kg/min every 12 h
4	NA	NA	30	32.5	70–101	Constipation	NA	Increase treprostinil by 2.5 ng/kg/min every 12 h
5	NA	NA	35	35	87–102	Mild headache and constipation	<10	NA

Abbreviations: BNP indicates brain natriuretic peptide; MAP, mean arterial pressure; NA, not available.

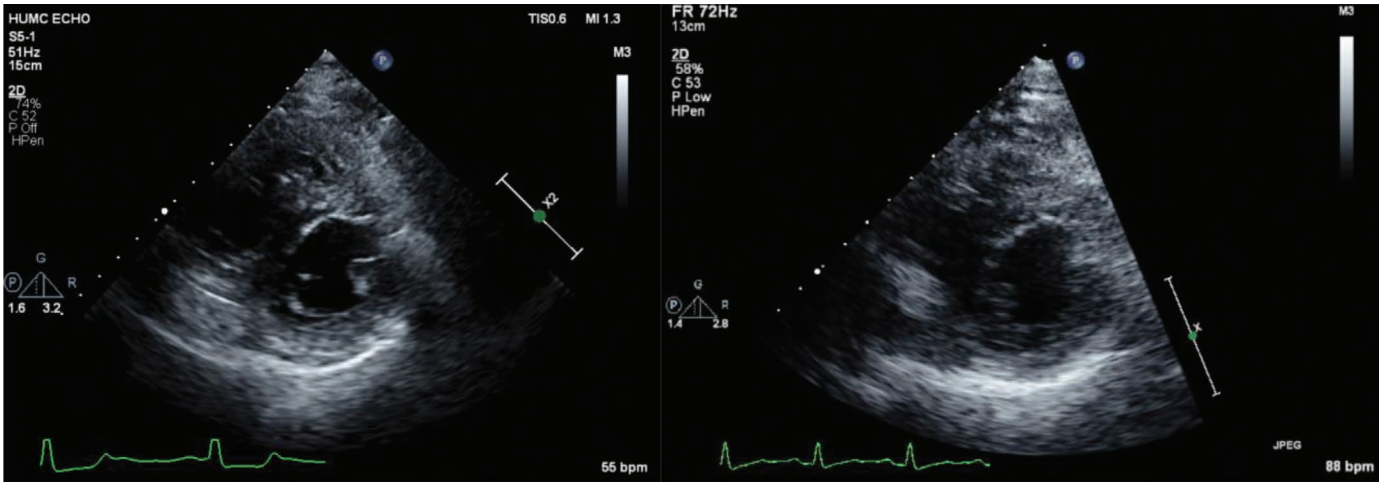

Figure 1: Echocardiogram 2 months prior to the transition and 4 months after intravenous treprostinil administration.

trial, selexipag was associated with a reduction in hospitalization and slower disease progression.[1] A reduction in all-cause mortality was not observed.[1] Treprostinil is a prostacyclin analog with a half-life of 2–4 hours and achieves 100% bioavailability with IV administration.[4] Since they both target the prostacyclin pathway, they share common adverse effects including headache, diarrhea, nausea, flulike symptoms, and flushing. The IV route of treprostinil is also associated with bloodstream infections.[4]

Despite receiving maximum doses of selexipag, our patient demonstrated disease progression requiring transition from oral selexipag to IV treprostinil. We found no standardized dose conversion strategy for transitioning from oral selexipag to IV treprostinil. Several case reports have been published describing transition from selexipag to subcutaneous treprostinil due to patient preference but lack consistent practices.[5,6] Cases of transition to IV treprostinil are limited to 1 report.[7] Since considerably less guidance is available for conversion between selexipag and IV treprostinil, we were challenged with optimal titration rate for achieving a rapid response while minimizing adverse effects. Additionally, it was difficult to extrapolate previous conversion schedules since dose requirements vary between patients, making it difficult to know an individual's target therapeutic dose ahead of time when the predominant reason for transitioning is typically worsening symptoms. We derived our conversion strategy based on a previous study in which authors estimated dose equivalency of selexipag

200 mcg twice daily to subcutaneously treprostinil 5 ng/kg/min.[5] Using this conversion strategy, the corresponding equivalent dose of IV treprostinil dose would be 40 ng/kg/min. In the present case, 40 ng/kg/min dosage of IV treprostinil improved hemodynamics parameters better than the 1600 mcg twice daily dosage of selexipag.[8] Despite its proven efficacy, selexipag has relatively low oral bioavailability at approximately 49%. The patient's favorable response to an equivalent dose of IV treprostinil may be better explained by the consistent drug delivery of the IV formulation, which reduces the fluctuations associated with oral dosing. This practice is in line with previous reports in which authors have suggested that the route of administration may influence treatment efficacy.[5] Low-risk patients seem to tolerate oral agents compared with patients that experience deterioration requiring IV therapy. Another explanation for improved hemodynamics may lie in the dose equivalency that was used in this case. In contrast with the previous article, Furukawa et al[8] have suggested selexipag 1600 mcg twice daily provides vasodilating effects that are roughly equivalent to parenteral treprostinil 20 ng/kg/min. The discrepancy in dose equivalency adds to the confusion on how to safely transition between the 2 agents and highlights the need for additional literature.

The duration over which the transitions are implemented has also varied across studies.[5–12] Most reported conversions occurred over several days to a few weeks, depending on the setting (inpatient versus outpatient). However, in one study, a rapid transition was completed over 30 hours in a patient with mixed-etiology PAH who was receiving therapy with selexipag 1600 mg twice daily and macitentan 10 mg daily.[12] During the rapid escalation of treprostinil, the patient experienced minor adverse effects.[12] Authors of most reports have suggested titrating parenteral treprostinil by 5 ng/kg/min once daily, with corresponding selexipag dose reduction by 200 mcg twice daily.[5,9] We created an individualized, rapid titration approach for our patient after having an extensive discussion among the treating team, including the pulmonary hypertension attending and advanced practice provider, ICU intensivist, pulmonary fellow, and a critical care pharmacist. A discussion on the risk to benefit profile of rapid titration was addressed, including hypotension and other relevant side effects. Thereafter, we derived our titration protocol to involve reducing the dose of selexipag by 400 mcg twice daily, which is double the previously recommended reduction in selexipag dosing. Our patient tolerated it quite well without any major adverse effects. Prior exposure to a prostacyclin therapy likely contributed to both the rapid titration and overall tolerability, as noted in a previous report.[13] Given the variability in response, a one-size-fits-all approach may not be practical; instead, an individualized approach should be attempted based on tolerability, especially in a monitored inpatient setting.

This case report is novel, as it provides a faster transition strategy without complications, allowing for a shortened ICU and hospital length of stay. This is critical in an era when hospital beds are in dire need and rapid turnover of beds is desired. None of the authors of previous reports described this faster rate of titration considering the target dose of treprostinil required in our patient. At our institution, patients requiring de novo prostacyclin therapy or any dose titrations must be cared for in an ICU for monitoring purposes. Additional data are needed to add to the literature regarding the safety of rapid conversion from selexipag to IV treprostinil.

Despite increased use of oral prostanoids, certain patients will require transition to IV prostanoid therapy. Guidance on how to transition between these agents is an unmet need. In this case report, we add to the current literature by providing a faster strategy on transitioning from oral selexipag to IV treprostinil that was well tolerated.

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