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Long-Term Experience and Safety of Transitioning from Subcutaneous Treprostinil to Oral Selexipag in the High-Risk Pulmonary Hypertension Patient: A Case Report

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Key Words: Heart failure • Hemodynamics • Pulmonary hypertension

Abbreviations	
BID	Twice daily
BNP	Brain natriuretic peptide
IV	Intravenous
QD	Once daily
PAH	Pulmonary arterial hypertension
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
SC	Subcutaneous
TID	Three times daily
6MWD	6-minute walk distance

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and grave disease that affects the lungs and heart.[1,2] The primary goal of treatment is to delay disease progression, and as such, currently available treatments target one of the three pathways believed to be implicated in the pathophysiology of PAH: the endothelin, nitric oxide, and prostacyclin pathways.[1]

Selexipag is an oral selective agonist of the prostaglandin I_2 receptor that reduces the risk of morbidity and mortality in patients with PAH, and lowers the treatment burden for patients compared with parenteral therapy.[1,2] However, when transitioning from parenteral to oral therapy, care needs to be taken to ensure that adequate prostacyclin agonist activity is maintained; the parenteral prostacyclin analog may be tapered, whilst up-titrating the oral therapy.[3,4]

Currently, there is no definitive guidance on how to effectively transition a patient with PAH from parenteral to oral prostacyclin therapy and little evidence supports the long-term safety.[4] This case report characterizes the speed of tapering treprostinil with simultaneous up-titrating selexipag under the careful guidance of repeated hemodynamic monitoring to successfully transition from parenteral to oral prostacyclin therapy in a World Health Organization (WHO) functional class IV PAH patient.

CASE

A 61-year-old woman with WHO functional class IV PAH and comorbid paroxysmal atrial fibrillation admitted to our hospital presented with dyspnea and chest tightness over the preceding week. This patient was diagnosed with PAH in 2010 and sequential combination therapy with bosentan 62.5 mg twice daily (BID) and sildenafil 20 mg three times daily (TID) were administered. Subcutaneous (SC) treprostinil was added in 2013 due to progressed hypoxia and dyspnea. Bosentan was changed to macitentan in 2014. During this period, she

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suffered from all kinds of adverse drug reactions, including severe headache, diarrhea, nausea, vomiting, persistent infusion site pain, pruritis, low back pain, general soreness, and myalgia. Depression was diagnosed with frequent suicidal ideation. Because of above intolerable side effects, SC treprostinil had been shortly changed to inhaled iloprost, with sildenafil replaced by riociguat in August, 2015. However, dyspnea exacerbated soon after the transition, and her functional class deteriorated from functional II to III. Intravenous (IV) treprostinil was resumed and she was on the list of lung transplantation. We soon changed IV treprostinil to SC form in 2016 because of central line-associated infection and septic shock. Although her condition improved, the above-mentioned adverse effects persistently afflicted her. Her functional class still slowly progressed to III-IV but she refused further dose escalation because of intolerable side effects and she strongly requested to give up the therapy. Transition from SC treprostinil to oral selexipag was therefore considered. After we comprehensively explained the risk of transition and possible adverse effects,[5] the transition was scheduled.

At the time of switching in 2017, the patient was undergoing SC treprostinil 46 ng/kg/min via ambulatory pump. Her vital signs and the incidence of adverse effects were continually monitored while the patient received selexipag (200 μg BID). Weeks later, the dosing of selexipag was up titrated to 400 μg BID and treprostinil was tapered to 36 ng/kg/min (2017-03-23 in Figure 1). However, patient reported dizziness and headaches. Because acceptable plasma brain natriuretic peptide (BNP) level, 262 pg/mL, was reported, selexipag was gradually uptitrated to 800 μg BID with treprostinil reduced to 34 ng/kg/min over the following 2 months (2017-05-04 in Figure 1). Nevertheless, the patient began to experience dyspnea, chest tightness and epigastric pain. She also exhibited bilateral swelling in her legs and tarry stools. Her hemoglobin level was 6.2 g/dL and her BNP level further elevated (379 pg/mL), suggesting worsening of her condition. At this time, she was also being administered oral riociguat (2.5 mg TID) and macitentan [10 mg once daily (QD)]. After the correction of anemia, selexipag was uptitrated to 1000 μg BID and treprostinil tapered to 32 ng/kg/min (2017-05-11 in Figure 1). To clearly delineate the disease status, we performed right heart catheterization (RHC) (2017-05-19 in Table 1) and found that cardiac output, 5.40 L/min, was actually improved rather than worsened. We confirmed her dyspnea was hemodynamic unrelated by RHC. The transition was therefore accelerated with treprostinil rapidly and confidently tapered at a rate of 2 ng/kg/min each day. When selexipag was uptitrated to 1600 μg BID, treprostinil was withdrawn (2017-06-01 in Figure 1). A repeated RHC showed relatively normal cardiac output and stable hemodyna-

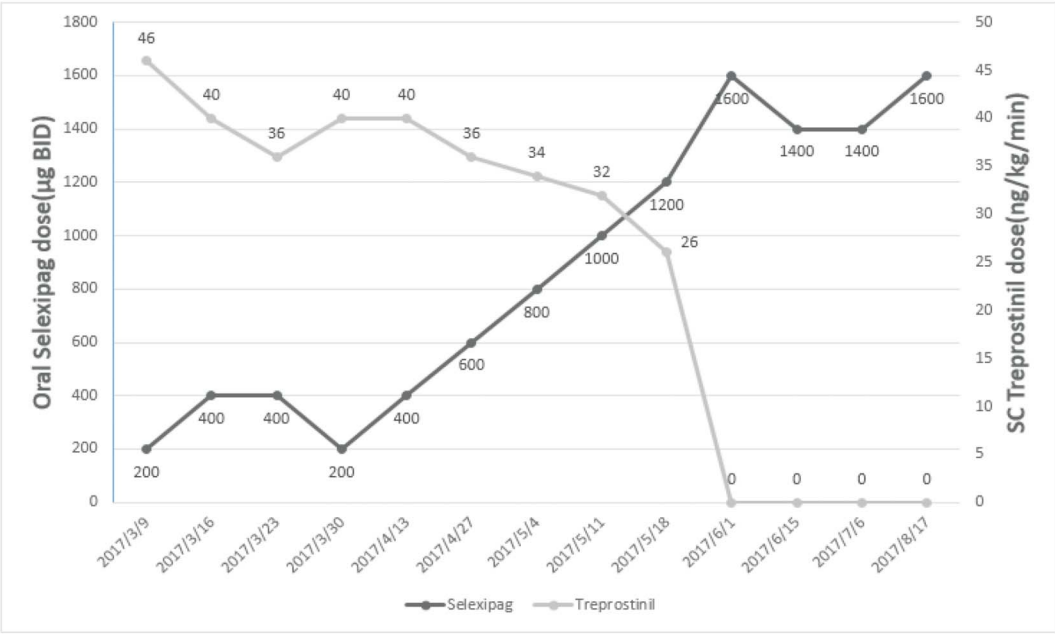

Figure 1. *Time course of the transition from SC treprostinil to oral selexipag. BID, twice daily; SC, subcutaneous.*

mic (2017-06-02 in Table 1). The patient was discharged from hospital with regularly monitoring as a cardiology outpatient. The patient had been being well tolerated and her dyspnea improved. Six months after the transition, a further RHC confirmed mid-term stability with relatively normal cardiac output and stable hemodynamic. Her WHO functional class had improved from IV to II (2018-01-23 in Table 1). Subsequent sequential RHC reported decreasing pulmonary vascular resistance (PVR) with stable hemodynamics at 1-year and 2-year follow-up (2018-06-26 and 2019-05-31 in Table 1). Plasma natriuretic peptide levels also maintain stable status up to 3.5-year follow-up (2020-12-31 in Figure 2). She remained functional class II without significantly worsening 6-minute walk distance (6MWD) and experienced the much better quality of life with little inconvenience and suf-

Table 1. Hemodynamic profile of the patient across time

Parameter	2010-04-06	2015-05-12	2017-05-19	2017-06-02	2018-01-23	2018-06-26	2019-05-31
Treatment	Nil	S+M+T	R+M+T+Se	R+M+Se	R+M+Se	R+M+Se	R+M+Se
RV failure	Yes	Yes	Unknown	No	No	No	No
Hemoptysis	Yes	No	No	No	No	No	No
Syncope	No	No	No	No	No	No	No
WHO FC	IV	II	IV	II	II	II	II
6MWD, m	–	306	–	266	261	256	318
Plasma BNP, pg/mL	1110	94	325	147	198	321	–
Plasma NT-proBNP, pg/mL	–	–	–	–	430	352	343
RA area, cm^2	–	–	15.7	18.4	20	18.6	17.4
Hemodynamics							
RAP, mmHg	15	3	3	1	7	4	2
CI, L/min/m^2	1.63	1.92	4.53	3.67	3.93	3.39	4.92
SvO_2, %	45	46	58	80	57	46	58
mPAP, mmHg	96/35 (55)	63/14 (33)	76/22 (40)	75/16 (36)	82/34 (50)	70/28 (42)	77/24 (42)
PVR, WU	18.0	8.7	4.7	4.3	6.0	5.83	5.25
PAWP, mmHg	10	8	9	13	15	13	10
CO, L/min	2.5	2.88	5.40	5.36	5.78	4.98	6.10

BNP, brain natriuretic peptide; CI, cardiac index; CO, cardiac output (Fick's); M, macitentan; mPAP, mean pulmonary artery pressure; NT-proBNP, N terminal pro B type natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; R, riociguat; RA, right atrium; RAP, right atrium pressure; RV, right ventricle; S, sildenafil; Se, selexipag; SvO_2, mixed venous oxygen saturation; T, treprostinil; WHO FC, World Health Organization functional classification; WU, wood units; 6MWD, 6-minute walk distance.

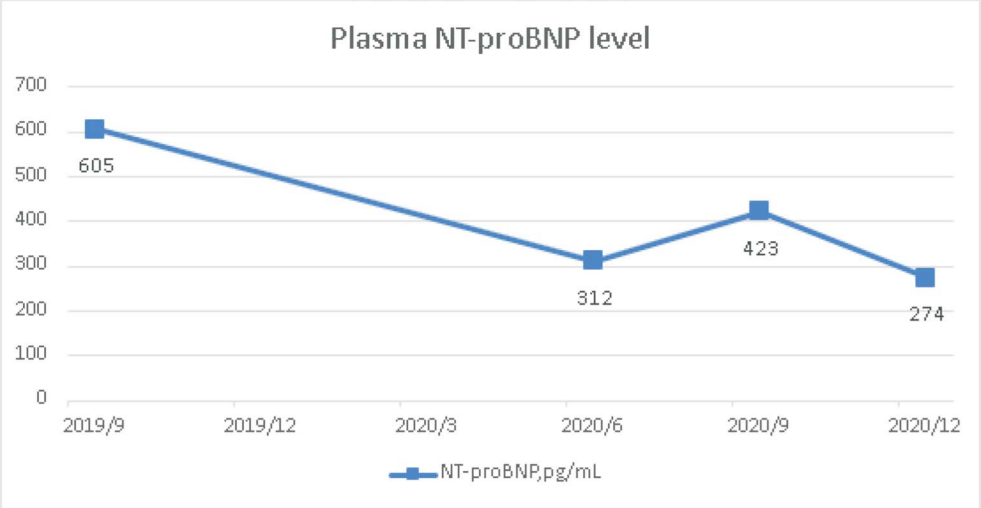

Figure 2. *Plasma NT-proBNP level on routine blood exam follow-up for 3 years. NT-proBNP, N terminal pro B type natriuretic peptide.*

fering caused by those parenteral prostacyclins. Besides, there had been no PAH-related complications or hospitalizations in long-term follow-up.

DISCUSSION

There are many approved PAH-targeted therapies, including prostacyclin analogs, endothelin receptor antagonists and phosphodiesterase type-5 inhibitors. These targeted therapies can be used as a monotherapy or in combination according to the risk stratification.[6] The Taiwan Society of Cardiology guidelines for the management of PAH recommend parenteral prostacyclin in patients with functional class IV.[7] While treprostinil is effective for treating PAH, SC or IV route can be inconvenient and is associated with a high injection burden, infusion site pain, infection and reduced quality of life.[3,7,8] In this case, treprostinil was also not tolerated by the patient, so oral selexipag therapy, which was approved of treatment for PAH by the US Food and Drug Administration in December 2015, was considered because of its efficacy and convenience.[1,2,5] However, there is no internationally recommended procedure for transitioning a patient with PAH from a parenteral prostacyclin regimen to an oral regimen and the evidence of long-term outcome after transition was scanty. In this case, off-label prescription is administered with ethical approval received from institutional review board because of specific condition mentioned above.

To date, there are several reports of transition from parenteral prostacyclins to selexipag. However, there has been limited reports about long-term outcome after transition, not to mention the transition in a patient with functional class IV. Transition therapy from SC treprostinil to selexipag 1600 μg BID was reported in a 38-year-old woman with WHO functional class III PAH because of poor tolerability, but the transition began from a much lower dose of treprostinil (20.1 ng/kg/min) than our case and merely 5-month outcome was reported.[9] The TRANSIT-1 study[10] reported a successful transition in 34 patients, but it was from inhaled treprostinil to selexipag. Different from above-mentioned studies, our case initiated the transition at a more critical baseline with a relatively higher dose of treprostinil and was followed up for a much longer duration (3.5 years).

Of particular note, during the transition period, dyspnea and chest tightness developed, which were initially presumed to be parenteral prostacyclin tapering related clinical worsening. Instead of the expected hemodynamic worsening, RHC contrarily demonstrated a high normal cardiac output, which may result from the combined activity of overlapping high-dose treprostinil and selexipag therapy during the transition period. Dyspnea and chest tightness were caused more likely by dual prostanoid over-stimulation than by PAH clinical worsening. Alternatively, the dyspnea and chest tightness may arise from myalgia, a known adverse reaction, which can increase chest discomfort and stimulate dyspnea. Moreover, dyspnea and chest tightness may issue from anemia, a notorious adverse effect of many PAH targeted drugs. As presented in our case, many clinical symptoms or even laboratory data may mimic PAH clinical worsening that prohibits the further transition. To clarify the genuine hemodynamic status, RHC is considered the gold standard for the evaluation in patients with PAH, and thus, is of supreme importance in the transition protocol. Relying on RHC to assess the efficacy and tolerability, we keep transition even encountering clinical-worsening-like complaints. The RHC-guided transition may improve the probability of success. On the other hand, if our patient could not have tolerated transition from parenteral treprostinil to oral selexipag, the alternative therapeutic plan would have been a challenge. Because our patient could not tolerate parenteral treprostinil, switching back to parenteral treprostinil might not have been feasible for our patient. Therefore, supportive care may be another therapeutic option if the patient is not a potentially eligible candidate for lung transplantation.

LEARNING POINTS

We reported a patient who had WHO functional class IV PAH and a history of intolerance to parenteral prostacyclin therapy, which was successfully transitioned from parenteral treprostinil to oral selexipag in a 3-month period. RHC-guided transition protocol was able to facilitate the transition and improve the likelihood of success. Repeated or even periodical RHC may be needed to ensure the long-term stability after the transition,

particularly for those who had a critical baseline and treated with high-dosed IV or SC prostanoids before the transition. Although we reported a successful case with a favorable long-term outcome, transition from IV or SC prostanoids to oral selexipag is still generally discouraged until more solid evidence is available. Last but not least, current guidelines still support the use of parenteral prostanoids in patients with WHO functional class IV PAH, which have stronger evidence.[2] As a result, extreme caution should be exercised while the transition is inevitable with a justifiable reason.

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DECLARATION OF CONFLICTS OF INTEREST

To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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