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Case Report

Safe and successful transition from oral selexipag to subcutaneous treprostinil in a patient with idiopathic pulmonary arterial hypertension treated with triple combination therapy

Shiro Adachi (MD, PhD) [a,*], Itsumure Nishiyama (MD) [b], Kenichiro Yasuda (MD) [a], Masahiro Yoshida (MD) [a], Yoshihisa Nakano (MD, PhD) [b], Takahisa Kondo (MD, PhD) [c], Toyoaki Murohara (MD, PhD, FJCC) [b]

[a] Department of Cardiology, Nagoya University Hospital, Nagoya, Japan
[b] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[c] Department of Cardiology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

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ABSTRACT

Some patients with pulmonary arterial hypertension (PAH) might undergo transition to parenteral prostacyclin analogs due to inadequate response to oral combination therapy. However, there is no consensus on how transition from oral selexipag to subcutaneous treprostinil should be performed. Herein, we report a 56-year-old woman diagnosed with idiopathic PAH that was treated with initial combination therapy (10 mg of macitentan, 40 mg of tadalafil, and 3.2 mg of selexipag daily). Mean pulmonary arterial pressure (PAP) improved from 63 to 39 mm Hg. Transition to parenteral prostacyclin analog was required because cardiac index was below 2.5 L/min/m^2. The selexipag was tapered off while subcutaneous treprostinil was titrated up to 30 ng/kg/min over 19 days. Hemodynamic parameters were slightly better than those before the transition. The mean PAP improved to 32 mm Hg by further gradual increases of subcutaneous treprostinil up to 60 ng/kg/min. Therefore, the patient having idiopathic PAH with inadequate response to oral triple combination therapy experienced successful transition from selexipag to subcutaneous treprostinil. Hemodynamic parameters were slightly more improved at a dose of 30 ng/kg/min of subcutaneous treprostinil than at a dose of 3200 μg daily of selexipag in the midst of disease progression.

Learning objectives: There is limited evidence for transition of pulmonary vasodilators, especially from oral selexipag to subcutaneous treprostinil. Detailed change in hemodynamic parameters before and after transition and the way of performing transition in patients with idiopathic pulmonary arterial hypertension with exacerbations despite treatment with oral triple combination therapy may provide useful information for better management in the clinical setting.

Introduction

Subcutaneous treprostinil, a prostacyclin analog, improves exercise tolerance and possibly survival in patients with pulmonary arterial hypertension (PAH), which is a devastating disease that could lead to right heart failure [1–3]. There are four routes of administration of prostacyclin analogs, including oral, inhalational, subcutaneous, and intravenous. Treprostinil is the only approved prostacyclin analog that is administered subcutaneously in Japan. Some patients with idiopathic PAH (IPAH) might undergo transitions from oral or inhalational to intravenous or subcutaneous routes due to inadequate responses to initial therapy. However, there is no consensus on how these transitions should be performed, especially from oral selexipag, a selective prostacyclin-receptor agonist, to subcutaneous treprostinil.

Herein, we report a case of successful transition from selexipag to subcutaneous treprostinil due to inadequate response to oral triple combination therapy.

Case report

A 56-year-old woman was hospitalized because of acute heart failure. Right-sided heart failure due to pulmonary hypertension was suspected, which warranted her referral to our institution. Lung perfusion scintigraphy performed at presentation was normal. There were

* Corresponding author at: Department of Cardiology, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan.
E-mail address: sadachi@med.nagoya-u.ac.jp (S. Adachi).

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Table 1
Changes in hemodynamic parameter values before transition, after transition at 30 ng/kg/min and 60 ng/kg/min of subcutaneous treprostinil.

	Before transition at 3200 μg of selexipag, 10 mg of macitentan and 40 mg of tadalafil daily	After transition at 30 ng/kg/min of sc Tre, 10 mg of macitentan and 40 mg of tadalafil daily	After transition at 60 ng/kg/min of sc Tre, 10 mg of macitentan and 40 mg of tadalafil daily
PAP (mm Hg)	69/23 (39)	74/23 (40)	54/19 (32)
PAWP (mm Hg)	7	7	7
RAP (mm Hg)	5	5	5
CI (L/min/m^2)	2.30	2.75	3.61
PVR (wood unit)	7.9	6.7	3.9

PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; sc Tre, subcutaneous treprostinil; RAP, right atrial pressure.

no signs of connective tissue disease, liver cirrhosis, lung disease, or left heart disease. The patient underwent right heart catheterization (RHC), and was diagnosed with IPAH with World Health Organization (WHO) functional class III. Hemodynamic parameters at diagnostic RHC were as follows: pulmonary arterial pressure (PAP), 96/46 (63) mm Hg; pulmonary arterial wedge pressure (PAWP), 9 mm Hg; cardiac index (CI), 1.23 L/min/m^2; and pulmonary vascular resistance (PVR), 23.2 wood unit (WU). Oral macitentan (10 mg once daily), tadalafil (40 mg once daily), and beraprost (60 μg three times daily) were sequentially administered within three months after the diagnostic RHC. Additionally, re-evaluation of the RHC was performed seven months after the previous RHC. Mean PAP (mPAP) and CI improved to 41 mm Hg and 2.50 L/min/m^2, respectively, resulting in a PVR of 7.3 WU. The WHO-functional class improved to II. Beraprost was switched to oral selexipag, as further improvements were expected. About 175 days were required to reach a maximum selexipag dose of 1600 μg twice daily. The RHC was used to evaluate the additional effects of selexipag two years after the diagnostic RHC; it revealed an mPAP of 39 mm Hg, CI of 2.30 L/min/m^2, and PVR of 7.9 WU (Table 1). Although brain natriuretic peptide (BNP) levels were at 17.3 pg/mL, peak oxygen consumption (VO_2) measured by the cardiopulmonary exercise test was 15.3 mL/kg/min which has a predictive value of 64%. Moreover, a distance of 423 m in six-minute walk test and minimal pericardial effusion on echocardiography were noted. Right ventricular ejection fraction (RVFAC) was also reduced to 15% on echocardiography, indicating severe right ventricular dysfunction. These findings suggested that adequate improvements were not achieved despite switching from beraprost to selexipag. Therefore, an intravenous or subcutaneous prostacyclin analog was considered. However, the patient preferred the subcutaneous route; hence, subcutaneous treprostinil was initiated at 1.0 ng/kg/min (day 0) and this was gradually up-titrated to 14 ng/kg/min (day 11) while maintaining 3200 μg of selexipag (Fig. 1). Although infusion site pain was observed when subcutaneous treprostinil started, it was made tolerable by using oral analgesics, including tramadol hydrochloride and acetaminophen, or loxoprofen sodium hydrate. On day 10, down-titration of selexipag was started at 400 μg per day. Treprostinil was concurrently titrated up to 30 ng/kg/min at 2 ng/kg/min per day, and selexipag was terminated on day 17. On day 19, treprostinil was increased to 30 ng/kg/min, and facial flushing developed for the first time on day 21. The RHC performed on day 23 showed the following: mPAP, 40 mm Hg; CI, 2.75 L/min/m^2; and PVR, 6.7 WU with 30 ng/kg/min of treprostinil (Table 1). The treprostinil dosage was further increased by 2 ng/kg/min per week. Diarrhea developed on interim, however, the symptoms were mild and transient, which required no treatment. On day 79, the treprostinil dosage was increased to 60 ng/kg/min. The RHC performed on day 286 after the transition to treprostinil revealed improvements in hemodynamic parameters: mPAP, 32 mm Hg; CI, 3.61 L/min/m^2; and PVR, 3.9 WU (Table 1). Improvement in cardiomegaly on chest radiography, and right ventricular dilation and compression of left ventricle on echocardiography were observed (Fig. 2). Additionally, pericardial effusion resolved with the increase of RVFAC from 15% to 33%. Although exercise tolerance was not measured since the puncture site was at the mid-thigh, her WHO functional class improved to class I, and a low-risk profile was obtained. Treprostinil (60 ng/kg/min) was continued to maintain the patient's low-risk profile.

Discussion and conclusions

This report describes a beneficial transition from selexipag to subcutaneous treprostinil in a patient with IPAH due to inadequate response to oral triple combination therapy. Selexipag has been shown to reduce the composite end point of death or complications related to PAH compared to placebo [1]; however, in that study, there was no significant difference in mortality between the two groups. Since oral triple combination therapy did not improve the patient's hemodynamics

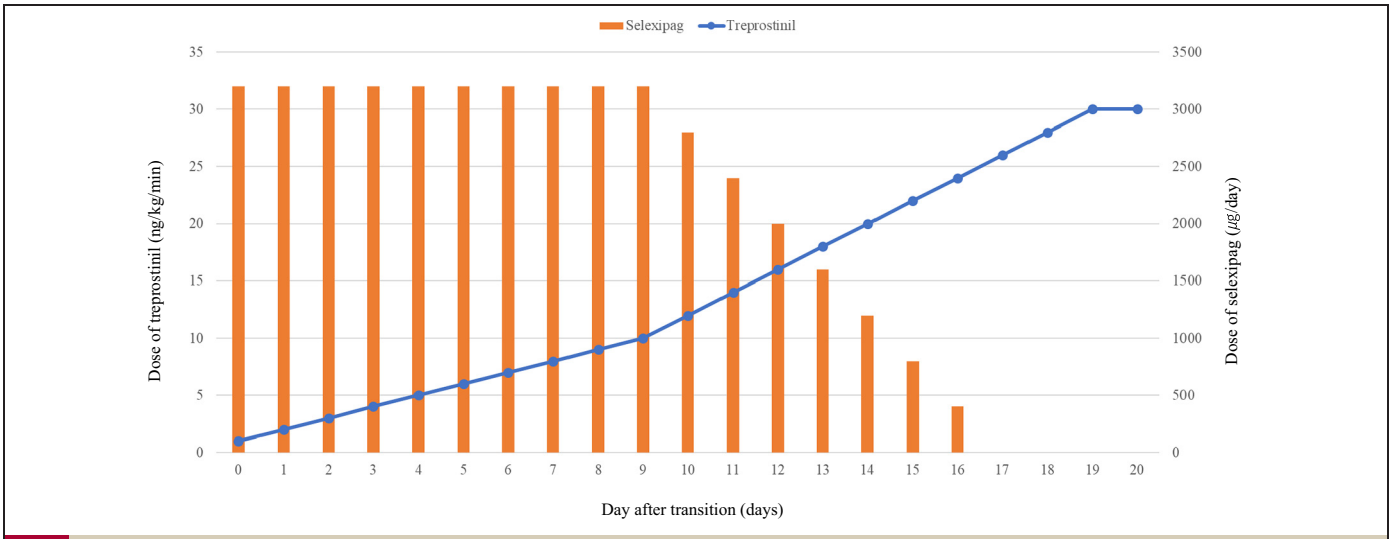

Fig. 1. Doses of selexipag and subcutaneous treprostinil administered during transition.

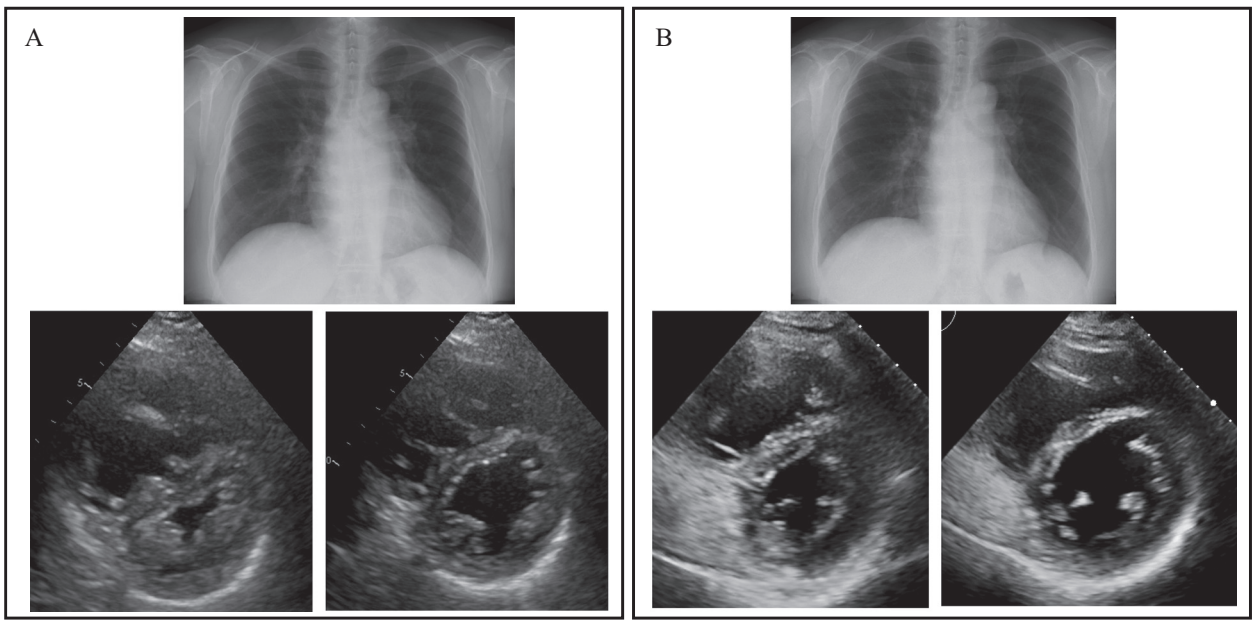

Fig. 2. Changes in chest radiography and echocardiography findings before and after the transition. (A) Before transition. (B) After transition (60 ng/kg/min of treprostinil). The cardio-thoracic ratio improved from 53.4% to 47.6% after transition. Left ventricular compression during the systolic and diastolic phase was improved after transition.

parameters substantially, we decided to change from oral or inhalational to intravenous or subcutaneous routes of administration. Long-term efficacy in terms of survival, as well as short-term efficacy in terms of exercise capacity in patients with PAH who receive subcutaneous treprostinil therapy has already been reported [3,4]. However, little is known about transitioning from oral selexipag to subcutaneous treprostinil. Additionally, we report the hemodynamic details of RHC before and after this transition. Some patients may choose subcutaneous rather than intravenous prostacyclin analogs due to the lower risks of complications, such as catheter-related systemic infection and fewer life restrictions related to its longer half-life (4.6 h), and due to the depot effect of subcutaneous prostacyclin analogs compared to that of intravenous analogs. Cases of transition from intravenous epoprostenol to subcutaneous treprostinil due to catheter-related life-threatening complications have been reported [5]. Additionally, a case series also reported transitions from intravenous or subcutaneous treprostinil to selexipag due to complications and problems during parenteral administration of prostacyclin, such as bloodstream infection and injection-site pain [6]. In that study, one of the four patients who had recurrent syncope underwent transition from subcutaneous treprostinil (35 ng/kg/min) to selexipag (1000 μg twice daily) within eight days; that patient complained of diarrhea and headaches during this transition. In the present case, selexipag (3200 μg) was gradually switched to subcutaneous treprostinil (30 ng/kg/min) within 19 days, and RHC was performed before and after transition to adjust the dose of treprostinil. The effects of selexipag at a dosage of 1600 μg twice daily were reported to be equivalent to those of subcutaneous treprostinil at a dose of 20.1 ng/kg/min [7]. In the present case, 30 ng/kg/min dosage of subcutaneous treprostinil improved hemodynamic parameters slightly better than 1600 μg twice daily dosage of selexipag.

Since the patient's condition deteriorated with oral triple combination therapy, transition from selexipag to treprostinil was performed for further treatment. In contrast, a previous case reported withdrawal of treprostinil after improvements in PAH [7].

Furthermore, 60 ng/kg/min of subcutaneous treprostinil was clearly more effective than selexipag. After the transition, typical adverse effects were observed, such as facial flushing, headache, and diarrhea. Some adverse events were related to the treprostinil administration, including infusion site pain and reactions. Therefore, collectively, this case report suggests that subcutaneous administration should be considered when oral combination therapy has suboptimal efficacy.

A patient with IPAH with inadequate response to oral triple combination therapy experienced successful transition from selexipag to subcutaneous treprostinil. Hemodynamic parameters were slightly more improved at a dose of 30 ng/kg/min of subcutaneous treprostinil than at a dose of 3200 μg daily of selexipag in terms of disease progression.

Declaration of competing interest

Yoshihisa Nakano and Takahisa Kondo belonged to the endowed department of Actelion Pharmaceuticals Japan (now Janssen Pharmaceutical K.K.) until March 2021. All of the other authors declare they have no conflict of interest to disclose.

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Availability of data and materials

All data supporting conclusions of our case report are included in this published article.

Consent for publication

A written consent was obtained from the patient to publish the information contained in this case report.

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