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CASE REPORT

Transitioning intravenous epoprostenol to oral selexipag in idiopathic pulmonary arterial hypertension: a case report

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Abstract

Intravenous (i.v.) prostacyclin is the cornerstone treatment in high-risk pulmonary arterial hypertension (PAH) patients. Selexipag is an orally available prostacyclin receptor agonist. Limited data are available regarding the feasibility of transitioning from i.v. epoprostenol to selexipag. A 50-year-old woman with idiopathic PAH was diagnosed in a World Health Organization (WHO) Functional Class (FC) IV. She improved with upfront triple combination therapy, including i.v. epoprostenol. Over 2 years of follow-up, the patient remained at low risk and expressed strong preference towards oral therapies. After careful risk–benefit clinical consideration, she was transitioned from i.v. epoprostenol to selexipag. Selexipag was started at dosage of 200 μg twice daily (b.i.d.) and titrated up to 1600 μg b.i.d. over 8 weeks (up-titration of 200 μg b.i.d. every week). Simultaneously, i.v. epoprostenol was down-titrated 3.0 ng/kg/min every week from a dosage of 27.5 ng/kg/min. The transition occurred under strict medical surveillance and was well tolerated. One year after discontinuation of epoprostenol, the patient remains in WHO FC I and has no signs of clinical deterioration. Although not generalizable to most PAH patients, this case highlights that a carefully planned transition from epoprostenol to selexipag is feasible in selected low-risk patients within a shared medical decision-making framework.

Keywords Pulmonary hypertension; Idiopathic pulmonary arterial hypertension; Intravenous epoprostenol; Oral selexipag; Transition therapy; Switchback therapy

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Introduction

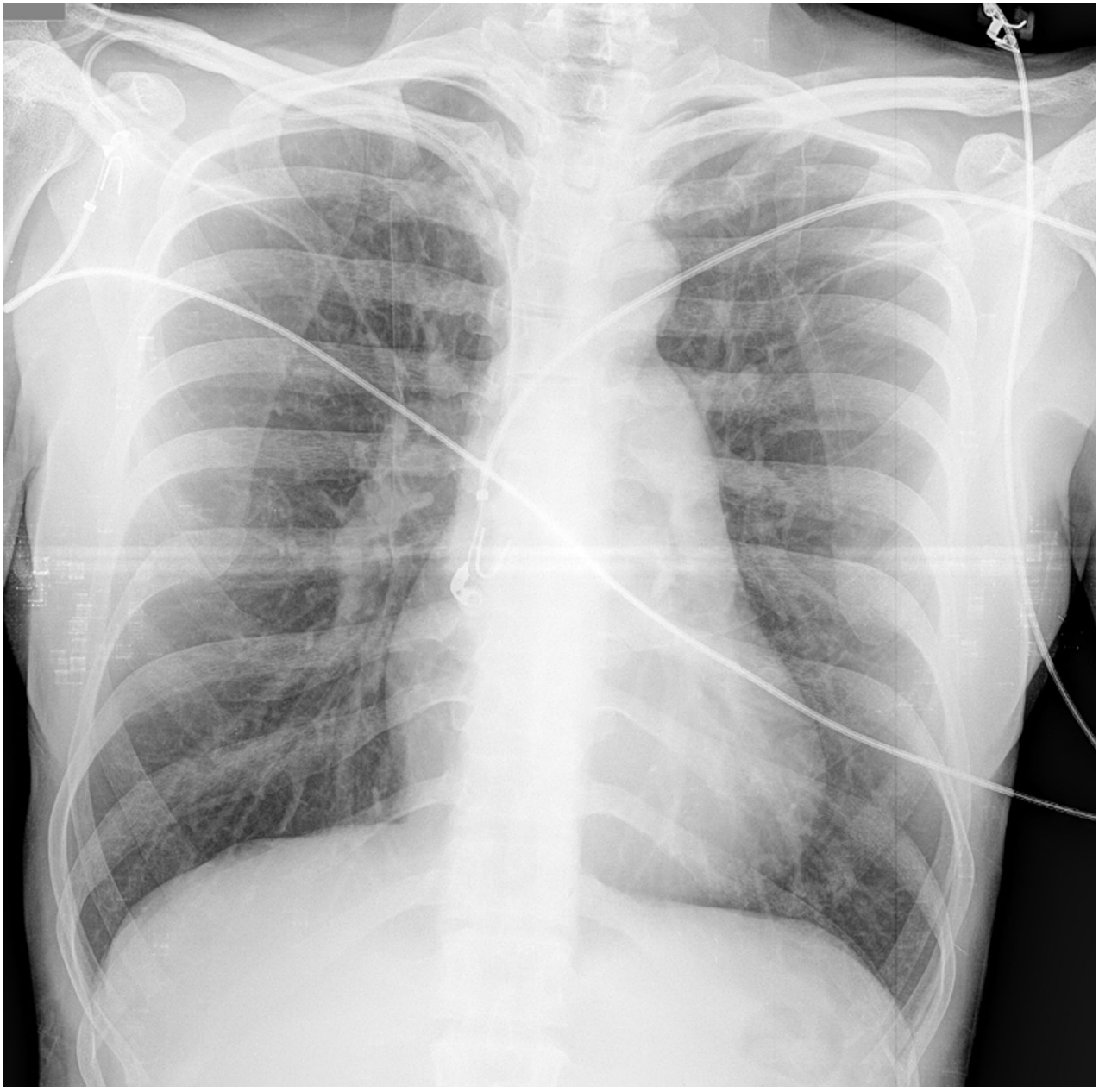
Pulmonary arterial hypertension (PAH) is a rare and progressive disease generally treated with a combination therapy targeting three distinct signalling pathways (endothelin, nitric oxide, and prostacyclin) according to mortality risk assessment.[1–3] Intravenous (i.v.) prostacyclin is the cornerstone of medical therapy in intermediate–high- and high-risk PAH.[1] Selexipag, a non-prostanoid orally available prostacyclin agonist, is approved in low- and intermediate–low-risk PAH.[1,4,5] There are limited data regarding the feasibility of transitioning from i.v. prostacyclins to selexipag in PAH patients who achieve low risk when being treated with the former drug class.[3,6–10] The purpose of this case report is to describe the careful transition process from i.v. epoprostenol to oral selexipag in a selected low-risk patient with a strong preference towards oral therapies.

Case report

A 50-year-old Caucasian woman with a history of Raynaud's phenomenon—but no history of connective tissue disease,

cardiovascular risk factors, venous thrombo-embolism, nor relevant family history—was transferred to our Pulmonary Hypertension Centre due to 6 month progressive exertional dyspnoea [World Health Organization (WHO) Functional Class (FC) IV] and severe type 1 respiratory failure. On admission, she presented a severe hypoxaemia (peripheral oxygen saturation level was 84%, and PaO_2 was 43 mmHg at FiO_2 of 21% on spontaneous breathing); thus, she was immediately started on oxygen therapy with a high-flow oxygen mask (FiO_2 of 100%). At physical examination, she was cyanotic and had an accentuated pulmonary component of the second heart sound and pulmonary auscultation was unremarkable. Blood analysis revealed polycythaemia (18 g/dL) and an elevated N-terminal pro-brain natriuretic peptide (NT-pro-BNP) (8883 pg/mL). No elevation of inflammatory parameters, renal injury, or hepatic injury was documented. The electrocardiogram showed sinus rhythm with a pulmonale P-wave and T-wave inversion in the right precordial leads. Chest radiograph showed an increased width of the vascular pedicle and a prominent pulmonary outflow tract (*Figure 1*).

Figure 1 Chest radiograph image. Chest radiograph showed an increased width of the vascular pedicle and a prominent pulmonary outflow tract, but no parenchymal consolidations, pneumothorax, or congestive signs.



Transthoracic echocardiography (TTE) raised a high suspicion of pulmonary hypertension (PH) with a mild tricuspid regurgitation and an estimated pulmonary artery systolic pressure (PASP) of 60 mmHg, mildly dilated pulmonary artery trunk (27 mm), shortening of the right ventricular outflow tract acceleration time (44 ms) with midsystolic notching, estimated pulmonary artery diastolic pressure (PADP) of 44 mmHg, flattening of the interventricular septum, right ventricle (RV) dilatation [basal diameter of 46 mm; RV/left ventricle (LV) ratio of 1.5], and RV global systolic dysfunction [tricuspid annular plane systolic excursion (TAPSE) of 17 mm; fractional area change (FAC) of 25%] (*Figure 2* and *Table 1*). No left heart disease or pericardial effusion was detected.

An urgent thoracic computed tomography (CT) angiography excluded pulmonary embolism, and high-resolution CT of the chest showed no signs of parenchymal lung disease (*Figure 3*).

Right heart catheterization (RHC) revealed mean pulmonary artery pressure (MPAP) of 75 mmHg, pulmonary artery wedge pressure (PAWP) of 17 mmHg, right atrial pressure (RAP) of 9 mmHg, cardiac index (CI) of 3.2 L/min/m^2, and pulmonary vascular resistance (PVR) of 11.8 Wood units (WU) (*Table 1*). Acute vasoreactivity testing with inhaled iloprost was negative. The increased PAWP was considered artefactual and not clinically meaningful. Other diagnostic workup as immunological study and HIV serology were negative. Abdominal ultrasound was unremarkable. TTE with bubble test excluded intracardiac shunt. Pulmonary function testing revealed an isolated reduction of the diffusing capacity for carbon monoxide measured by single-breath method (46% of predicted). Pulmonary ventilation/perfusion scan ruled out chronic thrombo-embolic PH.

The patient was diagnosed with a high-risk idiopathic PAH and was started on triple vasodilator combination therapy including a parenteral prostacyclin (macitentan, tadalafil, and i.v. epoprostenol). She slowly but steadily improved showing resolution of respiratory failure and a significant decrease in NT-pro-BNP levels (from 8883 to 360 pg/mL). She was discharged after 6 weeks on triple vasodilator therapy [macitentan 10 mg o.d., tadalafil 40 mg o.d., and i.v. epoprostenol perfusion (27.5 ng/kg/min)] with no hypoxaemia at rest and with an improvement in echocardiographic parameters (*Table 1*).

At 6 month follow-up, the patient underwent a cardiac rehabilitation programme. After completion of cardiac rehabilitation, she became physically very active (cycled 20 km/day) and it was documented a significant clinical and haemodynamic improvement (*Table 1*).

Over 2 years of follow-up, the patient remained at low risk and expressed a strong preference towards an oral therapy. After a careful risk–benefit clinical evaluation and taking into consideration the patient's quality of life, it was decided to transition i.v. epoprostenol to selexipag over several weeks. Selexipag was started at dosage of 200 μg twice daily (b.i.d.) and titrated up to 1600 μg b.i.d. over 8 weeks (up-titration of 200 μg b.i.d. every week). Simultaneously, i.v. epoprostenol was down-titrated 3.0 ng/kg/min every week from a dosage of 27.5 ng/kg/min. The transition of vasodilator therapy occurred under strict medical surveillance in 2 week intervals. The transition was well tolerated, and 1 year after discontinuation of epoprostenol, the patient remains in WHO FC I (on a regimen of macitentan, tadalafil, and selexipag 1600 μg b.i.d.) and has no signs of PAH deterioration on the regular clinical evaluations (*Table 1*).

Figure 2 Transthoracic echocardiography (TTE) raising a high suspicion of pulmonary hypertension. TTE imaging revealed a mild tricuspid regurgitation (TR) and an estimated pulmonary artery systolic pressure (PASP) of 60 mmHg, right ventricle (RV) dilatation [basal diameter of 46 mm; RV/left ventricle (LV) ratio of 1.5], and RV global systolic dysfunction (tricuspid annular plane systolic excursion of 17 mm; fractional area change of 25%). No left heart disease or pericardial effusion was detected. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

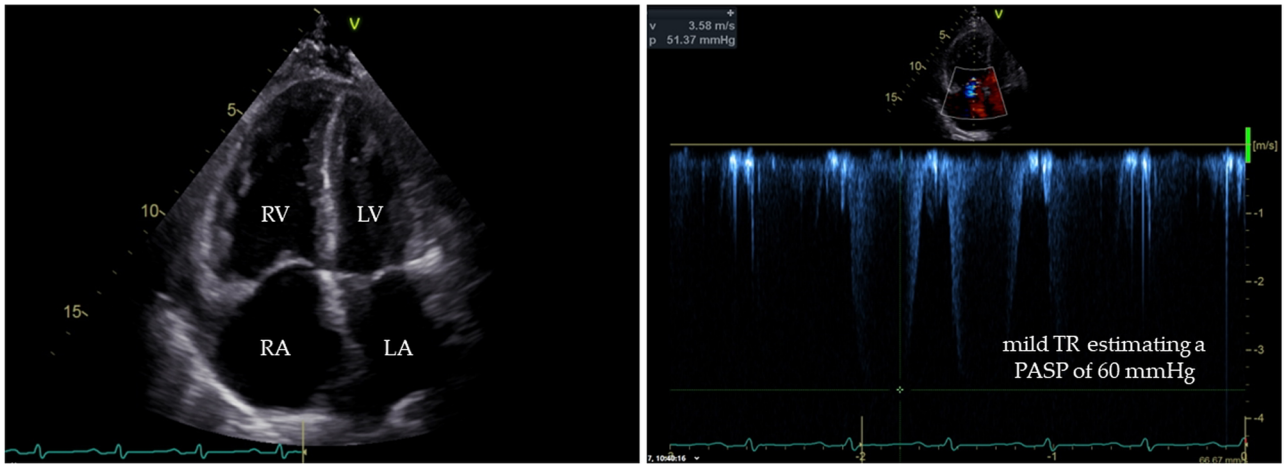


Table 1 Clinical evaluation, risk stratification, and medication at diagnosis and during follow-up

Timeline	At diagnosis	At discharge (after 6 weeks)	After CR (20 months after diagnosis)	1 year after transitioning to selexipag
WHO FC	IV	II	I[a]	I
6MWT (m)	0	312	723[a]	747
Borg dyspnoea scale	—	1	0[a]	0
NT-pro-BNP (pg/mL)	8883	360	85[a]	79
Echocardiography				
RV/LV ratio	1.5	1.0	0.7[a]	0.7
Eccentricity index	>1.1	1	1[a]	1
TAPSE (mm)	17	23	19[a]	28
FAC (%)	25	36	44[a]	48
RHC haemodynamics				
MPAP (mmHg)	75	—	35[a]	30
PAWP (mmHg)	17	—	12[a]	10
RAP (mmHg)	9	—	8[a]	6
CI (L/min/m^2)	3.2	—	3.7[a]	3.4
PVR (WU)	11.8	—	3.9[a]	3.9
CPET				
VO_2 peak (mL/min/kg)	—	—	20.0[b]	27.8
VE/VCO_2 slope	—	—	30[b]	28
Exertional O_2 desaturation	—	—	No[b]	No
Risk stratification	High	Intermediate–low	Low	Low
Medication	Macitentan Tadalafil i.v. epoprostenol	Macitentan Tadalafil i.v. epoprostenol	Macitentan Tadalafil i.v. epoprostenol	Macitentan Tadalafil Selexipag

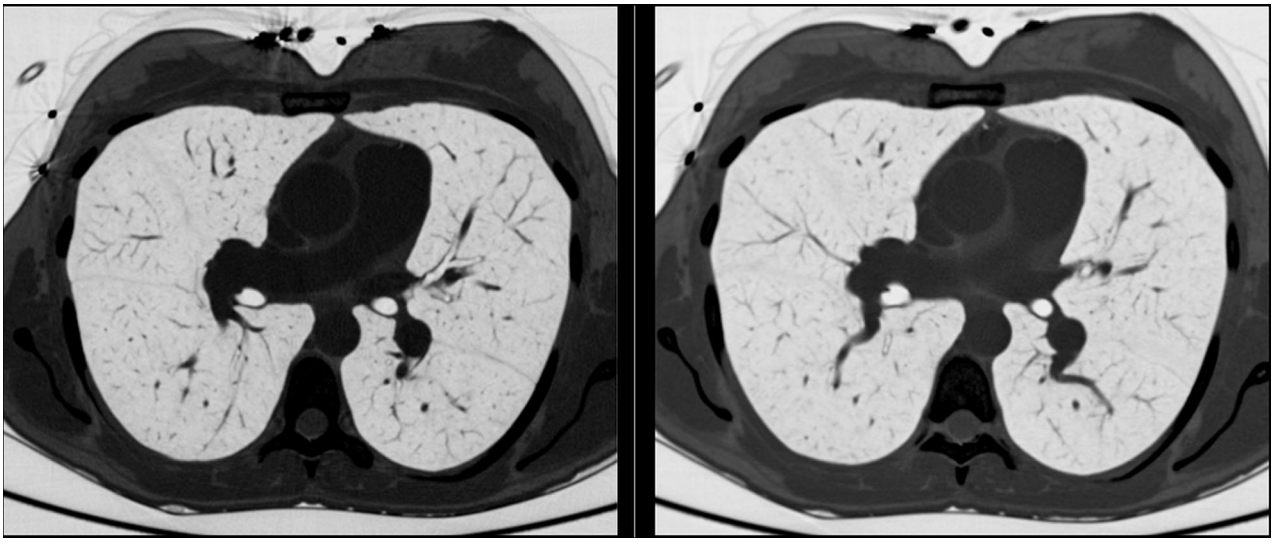
6MWT, 6 min walking test; CI, cardiac index; CPET, cardiopulmonary exercise testing; CR, cardiac rehabilitation; FAC, fractional area change; FC, functional class; i.v., intravenous; LV, left ventricle; MPAP, mean pulmonary artery pressure; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization; WU, Wood units.

Table 1 shows follow-up data (including WHO FC, 6MWT, Borg dyspnoea scale, NT-pro-BNP, echocardiography, invasive haemodynamics, CPET, risk stratification, and medication) from diagnosis to present time.

[a]Clinical evaluation, echocardiography, and RHC performed after completion of CR and at 20 months after diagnosis.

[b]CPET performed after completion of CR and at 9 months after diagnosis.

Figure 3 Thoracic computed tomography (CT) angiography and high-resolution CT imaging. Thoracic CT angiography and high-resolution CT imaging showed no signs of pulmonary embolism nor parenchymal lung disease.



Discussion

Prostacyclin medications are available in a variety of different formulations, including parenteral, inhaled, and oral.[7,11] Intravenous prostacyclin is the cornerstone of medical therapy in intermediate–high- and high-risk patients with PAH.[1] In addition to the daily life implications to patients, long-term i.v. drug administration is associated with considerable risk of severe complications, ranging from 15% to 20% and including catheter occlusion, central venous thrombosis, line infections, and catheter-related sepsis.[2] Selexipag is an orally available prostacyclin receptor agonist, which showed to reduce disease progression and hospitalizations for PAH, being approved in low- or intermediate–low-risk status.[1,4,5] Considering the aforementioned, it may be reasonable to consider switching vasodilator therapy to selexipag once high-risk PAH patients are stabilized and at lower mortality risk.[10] However, limited data are available regarding the feasibility and safety of transitioning from i.v. epoprostenol to selexipag in patients in whom parenteral prostacyclin was initially indicated.[11] The current literature exposes some contradictory reports and case series of transitions from prostacyclin analogues to selexipag.[6] Most reports lack long-term haemodynamic follow-up, and data are inconsistent due to different drugs administered before the transition (mainly subcutaneous/i.v. treprostinil or inhaled prostacyclin).[6] Furthermore, there are currently no randomized controlled trials on this topic.

In this case report, we describe an idiopathic PAH patient that was successfully transitioned from i.v. epoprostenol to selexipag using a standardized protocol in the outpatient setting. To our knowledge, this is the first published report on therapy transition from i.v. epoprostenol to selexipag in a patient who presented with severe respiratory failure and WHO FC IV. This patient tolerated the transition from i.v. epoprostenol to oral selexipag very well without any clinical decompensation and no significant change in pulmonary vascular disease severity. No adverse events interfered with selexipag up-titration. This emphasizes that successful transition from i.v. epoprostenol to selexipag is possible and feasible when patients selected for transition are at low risk of cardiac adverse events.

Nevertheless, a word of caution is needed because transitioning from i.v. epoprostenol to selexipag remains a nonstandard clinical decision taking into consideration patients' quality of life.[6] The transition can only be considered in patients unable to pursue epoprostenol for medical reasons or in very particular cases where patients express a preference for oral therapies and the mortality risk is persistently low. In addition, it should always occur under strict medical surveillance. Further research, including a sufficient number of patients, is urgently needed with regard to this therapeutic option.

In conclusion, although not generalizable to most PAH patients, this case highlights that a carefully planned transition from i.v. epoprostenol to oral selexipag is feasible and safe in selected low-risk patients within a shared medical decision-making framework.

Conflict of interest

None declared.

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Consent for publication

Written informed consent to publish this paper has been obtained from the patient. A copy of the written consent is available for review upon request.

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