Case report: Stepwise transition from subcutaneous treprostinil to epoprostenol in high-risk pulmonary arterial hypertension

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Background
Idiopathic pulmonary arterial hypertension is associated with high morbidity and mortality. In recent years, the use of targeted therapies has led to an improvement in prognosis. Prostacyclin analogues treprostinil and epoprostenol require continuous subcutaneous or intravenous infusion and are generally administered in a stepwise approach. However, there are no clear recommendations for transition in high-risk patients requiring high doses of prostacyclin analogues.

Case summary
In this report, we describe the case of a 20-year-old woman under combined treatment with sildenafil, macitentan, and treprostinil who required transition from subcutaneous treprostinil therapy to intravenous epoprostenol due to erratic drug absorption and functional class progression. The transition was performed over 48 h in a stepwise approach reducing treprostinil dose 4 ng/kg/min every 3 h while increasing epoprostenol infusion 2 ng/kg/min until achieving a maintenance dose of 32 ng/kg/min. There were no side effects requiring changes in the infusion rate.

Discussion
Patients with advanced pulmonary arterial hypertension may necessitate switching from subcutaneous treprostinil to epoprostenol. Although many protocols have been used to date, there are no guidelines to direct this process safely. This 48-h scheme based on the pharmacokinetic properties of each drug was successful and well-tolerated.

Keywords
Case report • Idiopathic pulmonary hypertension • Prostacyclin analogues • Treprostinil • Epoprostenol

Learning points
- Treprostinil and epoprostenol are prostacyclin analogues that need to be administrated by continuous infusion and cannot be discontinued abruptly due to the potential for rebound pulmonary hypertension.
- Currently, there are no established protocols to guide switching from one drug to another.
- This case describes a 48-h protocol that resulted in a safe and well-tolerated transition from one prostacyclin analogue to another in a high-risk patient.
Introduction

Pulmonary arterial hypertension (PAH) is a relatively rare disease with an incidence of five to ten cases per million adults per year. It is characterized by precapillary involvement leading to an increase in pulmonary vascular resistance. The consensus resulting from the 2018 6th World Symposium on Pulmonary Hypertension redefined it as a medium pulmonary arterial pressure greater than 20 mmHg and a pulmonary vascular resistance greater or equal to 3 WU. Conditions classified within this group share haemodynamic characteristics and treatment strategies. Nevertheless, the prognosis and clinical presentation may be widely variable. Idiopathic pulmonary arterial hypertension (IPAH) represents the most frequent type of sporadic PAH and has no identifiable risk factors.

In Argentina, data from the RECOPILAR registry show a prevalence of 6.7% for this subgroup. The prognosis of IPAH, particularly in patients with WHO functional Class III/IV, has improved in recent years due to specific therapy.

The goals of treatment are to reduce symptoms, improve functional capacity, and slow down the progression of the disease by avoiding remodelling and subsequent failure of the right ventricle. It includes general support measures and specific drugs to target the major pathophysiological pathways: calcium channel blockers, phosphodiesterase-5 inhibitors, endothelin antagonists, and prostacyclin analogues (prostanoids). Combination treatment is widely extended, mainly in the advanced forms of the disease (WHO functional Class III and IV).

Epoprostenol and treprostinil are synthetic prostacyclin analogues that stimulate the IP receptor—a Gs protein-coupled receptor—leading to vasodilation, inhibition of platelet aggregation, and anti-proliferative and anti-inflammatory effects.

These drugs are titrated up to a maximum according to tolerability. Continuous intravenous epoprostenol therapy has demonstrated an impact on survival; however, there are no established protocols for transitioning from subcutaneous (SC) treprostinil to intravenous (IV) epoprostenol.

Case presentation

We present a 20-year-old woman (body weight, 55 kg; height, 1.60 m) with a history of IPAH diagnosed at the age of 16 after developing episodes of syncope. She initiated combination therapy with sildenafil and bosentan, which was switched to macitentan due to hepatotoxicity. Along the clinical course of the disease, the treatment was escalated to subcutaneous treprostinil due to a suboptimal response to dual therapy. Chronic adjuvant therapy included spironolactone and anticoagulation with acenocoumarol.

High-risk categorization was based on clinical variables (WHO functional class 3/4); biochemical markers [Pro-B-type natriuretic peptide (BNP): 3000 ng/mL, age-related reference value <450 pg/mL; echocardiographic parameters (right atrial area: 43.2 cm², right atrial volume: 113 mL/m², and a moderate pericardial effusion measuring 15 mm); and pulmonary catheterization (right atrial pressure: 17 mmHg)]. As a result, switching to intravenous infusion of epoprostenol was decided in accordance with local and European guidelines.

The patient was admitted to the cardiac intensive care unit for placement of a tunnelled central line (Hickman) and epoprostenol dose titration.

Vital signs recording on admission showed sinus tachycardia at 110 b.p.m., blood pressure 102/70 mmHg, and 97% SpO₂ on room air. Cardiovascular physical examination revealed a loud and fixed S₂ splitting, palpable parasternal lift at second left intercostal space with dullness on percussion, and mild peripheral oedema.

For target dose calculation, we used an approximate equivalent dose ratio of treprostinil to epoprostenol of 2:1 based on the equimolar potency of epoprostenol and the experience of other longer protocols in which the final dose reached this proportion. Thus, the target dose of epoprostenol was estimated at 32 ng/kg/min.

Drug titration began after central line placement. The infusion rate of each drug was based on its half-life and adjusted every 180 min. Treprostinil dosage decreased 4 ng/kg/min every 3 h while epoprostenol increased 2 ng/kg/min. Epoprostenol was titrated up under close monitoring of respiratory rate, heart rate, blood pressure, and blood oxygen saturation. Dosage was reduced to the previous

Timeline

| Time       | Intervention                                      |
|------------|--------------------------------------------------|
| Day 1      | Admission to the Cardiac Intensive Care Unit; placement of a Hickman line |
| Day 2      | Start of drug transition                          |
| Day 3      | End of drug transition                           |
| Day 4      | Transfer to cardiology ward                       |
| Day 5      | Non-pruritic macular rash                         |
| Day 6      | Skin rash spontaneous disappearance               |
| Day 7      | Hospital discharge                                |
| Day 14     | Follow-up visit: Persistence in functional Class III/IV; right-sided heart failure. Reference for pre-transplant assessment. |
| Day 47 post-discharge | Orthotopic double lung transplantation              |
| Day 77     | Discharge                                         |
titration step if side effects developed. The transition from SC treprostinil to IV epoprostenol lasted 48 h. There were no adverse events. Pro-BNP level at the end of titration was 2928 pg/mL.

The patient was transferred from the cardiac intensive care unit to the cardiology ward 4 days after titration. On the fifth day, she developed a non-pruritic macular rash of the limbs that faded spontaneously within hours without any dosage change and was discharged from hospital 2 days later. There were no significant changes in cardiac ultrasound parameters during hospital stay.

Despite the well-tolerated infusion of epoprostenol, absence of serious adverse events, and short length of stay, persistence in WHO functional class 3/4 and signs of right-sided heart failure on a 7-day follow-up appointment prompted referral to pre-transplant assessment. At this stage, a new echocardiogram showed a pulmonary artery systolic pressure (PASP) of 95 mmHg, impaired right ventricular systolic function, and persistent moderate pericardial effusion.

Orthotopic double lung transplantation was performed 47 days after discharge, with marked echocardiographic improvement 1 month later (PASP = 31, preserved right ventricular function, and absence of pericardial effusion).

Examination of the explanted lungs revealed medial wall thickening and muscularization, obliteration of small arteries, intimal fibrosis, and plexiform lesions consistent with IPAH.

**Discussion**

Epoprostenol is the only drug with demonstrated impact on the survival of patients with PAH. This evidence comes from a randomized study conducted in patients with functional class III/IV, which showed a statistically significant improvement in survival at three months compared with conventional therapy.9

In comparison to other prostanoids, epoprostenol also showed better results in the 6-min walk test, functional class improvement, and lower all-cause mortality in a meta-analysis of 14 randomized clinical trials.10

Therefore, the change in the strategy for treating this patient seems to be appropriate. However, the pharmacokinetic properties of both drugs may explain why epoprostenol is not the first option when starting a patient on prostanoids therapy.

As epoprostenol has a short half-life of approximately 2–6 min, it is only indicated for continuous infusion by intravenous route. Therefore, it requires the placement of a central venous catheter with strict hygiene precautions for manipulation and the correct use and control of an infusion pump. Moreover, abrupt interruption of the infusion can induce rebound pulmonary vasoconstriction that may result in haemodynamic instability and death.

On the other hand, treprostinil is a prostacyclin analogue developed after epoprostenol that can be administered by SC infusion due to its longer half-life (3–4 h). Currently, there are also implantable subcutaneous systems that reduce the daily burden of external pump handling. For this reason, treprostinil results are superior to epoprostenol in terms of patients’ satisfaction and quality of life.10,11 These characteristics explain why treprostinil is prioritized despite the lack of evidence in terms of improved survival or long-term outcomes.

In the present case, treprostinil therapy was ineffective at the maximum tolerated dose, either due to progression of disease or pain and reactions at multiple infusion sites over several months, which are common side effects of the drug.12 Thus, the clinical status of the patient made the transition necessary.

To our knowledge, there are no practical guidelines in literature for the transition between these prostacyclin analogues or 48-h high dose titration.

In a systematic review carried out in 2017,13 the authors reported on three studies involving a total of 18 patients in which transition from SC or IV treprostinil to epoprostenol had a success rate of 67%.

Reisbig et al.14 presented a stepwise transition protocol limited by signs of under-dosage or excessive pharmacological effects. The dosage of treprostinil was reduced to 5 ng/kg/min, while epoprostenol was increased every 4 h in a variable range depending on the occurrence of side effects. The total transition time was 62 h.

Alkukhun et al.15 reported four cases of transition from SC treprostinil to epoprostenol with different protocols. The maximum incremental dose of epoprostenol was 2 ng/kg/min. None of the patients exceeded a final epoprostenol dose of 20 ng/kg/min or a basal treprostinil dose of 30 ng/kg/min. These figures differ from those used in the present case.

Lastly, a recent publication16 suggested a transition scheme that could result in less titration time but with different adjustment intervals for each drug.

**Conclusion**

This 48-h protocol resulted in safe and well-tolerated transition from one prostacyclin analogue to another in a high-risk patient. Moreover, switching to epoprostenol enabled a more realistic assessment of the disease and timely referral to lung transplantation.

**Lead author biography**

Graduated from the University of Buenos Aires in 2015. Nowadays finishing my Cardiology residency at Hospital General de Agudos “Dr. Cosme Argerich” Buenos Aires, Argentina.

**Supplementary material**

Supplementary material is available at *European Heart Journal* - Case Reports online.

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References
1. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010;137:376–387.
2. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
3. Echazarreta D, Perna E, Coronel M, Diez M, Lescano A, Atamanuk N et al. Registro Colaborativo de Hipertensión Pulmonar en Argentina (RECOPLAR). Rev Fed Arg Cardiol 2014;43:146–149.
4. Farber HW, Miller DP, Poms AD, Badesch DB, Le-Rouzic EM, Romero AJ et al. Five-year outcomes of patients enrolled in the REVEAL registry. Chest 2015;148:1043–1054.
5. Oudiz RJ, Farber HW. Dosing considerations in the use of intravenous prostanooids in pulmonary arterial hypertension: an experience-based review. Am Heart J 2009;157:625–635.
6. Sociedad Argentina de Cardiología. Guías argentinas de consenso en diagnóstico y tratamiento de la hipertensión pulmonar. Rev Arg Cardiol 2017;85 (suplemento 3).
7. Galie N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Heart J 2016;37:67–119.
8. Gomberg-Maitland M, Tapson VF, Benza RL, McLaughlin VV, Krichman A, Widlitiz AC et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med 2005;172:1586–1589.
9. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296–301.
10. Zhang H, Li X, Huang J, Li H, Su Z, Wang J. Comparative efficacy and safety of prostacyclin analogs for pulmonary arterial hypertension: a network meta-analysis. Medicine (Baltimore) 2016;95:e2575.
11. Minai OA, Parambil J, Dweik RA, Davila GH, Peterson L, Rollins KD et al. Impact of switching from epoprostenol to IV treprostinil on treatment satisfaction and quality of life in patients with pulmonary hypertension. Respir Med 2013;107:458–465.
12. Sadushi-Kolic R, Skoro-Sajer N, Zimmer D, Bonderman D, Schemper M, Klepetko W et al. Long-term treatment, tolerability, and survival with subcutaneous treprostinil for severe pulmonary hypertension. J Heart Lung Transpl 2012;31:735–743.
13. Sofer A, Ryan MJ, Tedford RJ, Wirth JA, Fares WH. A systematic review of transition studies of pulmonary arterial hypertension specific medications. Pulm Circ 2017;7:326–338.
14. Reisbig KA, Coffman PA, Fiorenani AA, Bultsma CJ, Olsen KM. Staggered transition to epoprostenol from treprostinil in pulmonary arterial hypertension. Ann Pharmacother 2005;39:739–743.
15. Alkukhun L, Bair ND, Dweik RA, Tonelli AR. Subcutaneous to intravenous prostacyclin analog transition in pulmonary hypertension. J Cardiovasc Pharmacol 2014;63:4–8.
16. Mourtaglou SA, Pasialis A, Feloukidis C, Karvounis H, Giannakoulas G. Transition protocol from subcutaneous treprostinil to intravenous epoprostenol in deteriorating patients with pulmonary arterial hypertension. Int J Cardiol 2020;306:187–189.