Heart & Lung xxx (2017) 1–2

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.org

# Subcutaneous treprostinil was effective and tolerable in a patient with severe pulmonary hypertension associated with chronic kidney disease on hemodialysis

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ARTICLE INFO

*Article history:*
Received 22 December 2016
Received in revised form
10 January 2017
Accepted 10 January 2017
Available online xxx

*Keywords:*
Pulmonary hypertension
Treprostinil
Chronic kidney disease
Hemodialysis
Infection

ABSTRACT

*Background:* Pulmonary hypertension (PH) is a life-threatening complication in patients with chronic kidney disease on hemodialysis (CKD-HD).
*Objectives:* To determine whether subcutaneous infusion of treprostinil was effective and tolerable CKD-PH.
*Methods and results:* A 57-year-old man was admitted to our hospital due to presyncope and dyspnea during exercise with a history of CKD-HD. Cardiac catheterization revealed high pulmonary arterial pressure (PAP) of 53/24/32 mmHg and pulmonary vascular resistance (PVR) of 11.2 w.u. Upfront combination therapy with bosentan and sildenafil was started. However, 6-month therapy did not attenuate his symptoms, probably due to the high PAP and PVR (60/19/30 mmHg and 5.9 w.u.). We added subcutaneous treprostinil. Surprisingly, 9-month treprostinil (50 ng/kg/min) normalized hemodynamics (PAP: 25/4/13 mmHg and PVR: 1.9 w.u.). His symptoms during excise disappeared without any adverse effects.
*Conclusion:* This is the first report that subcutaneous treprostinil was very effective and tolerable in a PH patient with CKD-HD.



## Introduction

Pulmonary hypertension (PH) is a life-threatening complication in patients with chronic kidney disease on hemodialysis (CKD-HD).[1,2] Endothelin receptor antagonist and phosphodiesterase 5 inhibitor have been reported to be effective in PH associated with CKD-HD.[3] In contrast, the therapeutic efficacy of intravenous prostacyclin analogue, epoprostenol has not been established due to a potential high risk of the bloodstream infection in these patients with an arteriovenous fistula.[4,5] Recently, treprostinil, a subcutaneous formulation of prostacyclin, has been reported to improve exercise capacity, hemodynamics and survival in severe pulmonary arterial hypertension (PAH).[6,7] It did not require any hospitalizations for the treatment of bacteremia or sepsis in 26 PAH patients during 1 year of follow-up.[8] We here present a case of severe PH associated with CKD-HD, in which subcutaneous infusion of treprostinil was effective and tolerable.

## Case report

A 57-year-old man was admitted to our hospital due to presyncope and dyspnea during exercise. He had a history of a horseshoe kidney and end-stage CKD-HD via an arteriovenous fistula for 22 years. Right ventricular (RV) catheterization revealed pulmonary arterial pressure (PAP, systolic/diastolic/mean) of 53/24/32 mmHg, cardiac index (CI) of 1.5 ml/min/m$^2$, pulmonary vascular resistance (PVR) of 11.2 w.u., and pulmonary wedge pressure (PCWP) of 4 mmHg (Fig. 1 and Table 1). Based on these data and history, he was diagnosed as severe PH associated with CKD-HD and upfront combination therapy including bosentan (125 mg/day) and sildenafil (30 mg/day) was started. After 6 months of treatments, 6-min-walk distance was prolonged from 186 to 430 m and plasma BNP level decreased from 885 to 199 pg/ml (Table 1). However, his symptoms such as dyspnea and presyncope during exercise did not change which might be due to elevated PAP and

Disclosure Statement: The authors report no financial relationships or conflicts of interest regarding the content. We thank Masahiko Oka for helpful comments.

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http://dx.doi.org/10.1016/j.hrtlng.2017.01.004

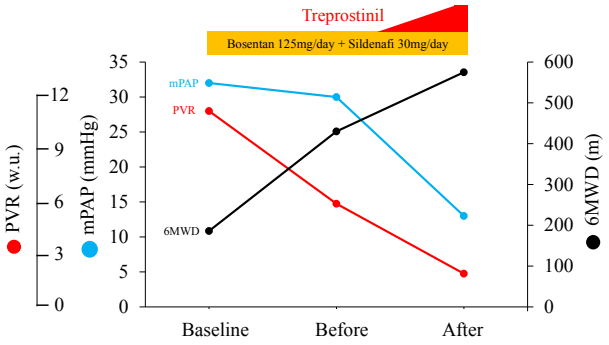


**Fig. 1.** Time course of hemodynamic and exercise capacity before and after the administration of subcutaneous treprostinil. Pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP) assessed by right heart catheterization and 6-min-walk distance (6MWD) are shown. Before: before treatment of treprostinil. After: after 9-month-treatment of treprostinil.

**Table 1**
Hemodynamic and functional parameter values at the baseline, before and 9 months after subcutaneous treprostinil treatment.

| | Baseline | Before | After |
|---|---|---|---|
| Pulmonary arterial pressure, mmHg (s/d/m) | 53/24/32 | 60/19/30 | 25/4/13 |
| Mean pulmonary capillary wedge pressure, mmHg | 4 | 4 | 3 |
| Cardiac index, l/min/m$^2$ | 1.5 | 2.7 | 4.0 |
| Pulmonary vascular resistance, w.u. | 11.2 | 5.9 | 1.9 |
| 6-min walk distance, m | 186 | 430 | 575 |
| WHO functional class | IV | III | I |
| Plasma BNP, pg/ml | 885 | 199 | 12 |
| Serum uric acid, mg/dl | 6.4 | 6.7 | 3.2 |
| Drugs | | | |
| Bosentan, mg/day | | 125 | 125 |
| Sildenafil, mg/day | | 30 | 30 |
| Subcutaneous treprostinil, ng/kg/day | | | 50 |

s, systolic pressure; d, diastolic pressure; m, mean pressure; w.u., Wood unit; WHO, World Health Organization; BNP, brain natriuretic peptide.

PVR (60/19/30 mmHg and 5.9 w.u., respectively) (Fig. 1 and Table 1). We first tested a short-term effect of intravenous epoprostenol on hemodynamics in this patient. Surprisingly, the administration of epoprostenol (10 ng/kg/min) for 10 days dramatically reduced PAP to 43/12/23 mmHg and PVR to 2.9 w.u without affecting systemic arterial pressure. We then added a long-term treatment of subcutaneous treprostinil. Subcutaneous injection of treprostinil (50 ng/kg/min) for 9 months further improved 6-min-walk distance to 575 m, decreased plasma BNP to 12 pg/ml and serum uric acid from 6.7 to 3.2 mg/dl, and normalized hemodynamics (PAP: 25/4/13 mmHg; CI: 4.0 ml/min/m$^2$; PVR: 1.9 w.u) (Fig. 1 and Table 1). His symptoms during excise disappeared without any adverse effects including infection and infusion site pain.

## Discussion

The pathogenesis of CKD-PH is complicated because the feature of the disease includes precapillary (Dana point group 1; PAH) and postcapillary PH (group 2; left heart disease). Therefore, CKD-PH has been categorized as group 5; PH with unclear multifactorial mechanisms. Our case was considered as group 1 rather than group 2 PH due to normal PCWP value (4 mmHg). According to 2015 ESC/ERS guideline,[9] treprostinil and epoprostenol have been recommended for the treatment of severe PAH. However, a central venous catheter may increase the risk of sepsis in CKD patients dialyzing through arteriovenous fistula.[4] It is therefore reasonable to avoid the intravenous epoprostenol in these patients. There have been no clinical trials reported to determine the chronic effects of prostacyclin analogues on CKD-PH. Our case shows that subcutaneous treprostinil is very effective and tolerable in such patient. Further clinical evaluation is needed for this clinical setting of severe PH.

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