

# Epoprostenol discontinuation in patients with pulmonary arterial hypertension: a complex medical and social problem

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To the Editor,

Pulmonary arterial hypertension (PAH) is a severe disease characterized by pulmonary vascular remodeling, leading to an increase in pulmonary vascular resistance (PVR) and causing exertional dyspnea, right heart failure, and eventually death. Prostacyclin analogs and prostacyclin receptor agonists (epoprostenol, treprostinil, iloprost, selexipag), endothelin receptor antagonists (bosentan, ambrisentan, macitentan), and phosphodiesterase type-5 inhibitors (sildenafil, tadalafil) are the main drugs to treat PAH.<sup>1</sup> Besides improving symptoms, exercise capacity, and hemodynamics,<sup>2</sup> intravenous epoprostenol is the only drug shown to reduce mortality in PAH.<sup>1</sup> However, it is administered by continuous intravenous infusion via a long-term central venous catheter and is therefore cumbersome, expensive, and prone to mechanical and infectious complications. In France, an activity-based financing system, known as T2A (*tarification à l'activité*), is implemented for the funding of public and private hospitals, based on diagnosis-related categories in which the cost of the drugs is included.<sup>3</sup> However, in order to be covered, expensive drugs such as epoprostenol need to be prescribed with respect to the clinical guidelines. We report herein three cases of patients with PAH from an expert center, in whom epoprostenol treatment was stopped for non-respiratory purposes. These cases highlight the complexity of a holistic approach in the care of these patients.

The first patient (Table 1) was a 70-year-old woman diagnosed with anorexigen-associated PAH. She received sildenafil and inhaled iloprost, switched one year later to intravenous epoprostenol due to clinical and hemodynamic deterioration. Five years later, she developed cognitive impairment and depression leading to less hygienic care of the central venous catheter and subsequent infections.

Epoprostenol had to be permanently discontinued to avoid further complications and because of the additional workload devolved upon psychiatry nurses who were not qualified for epoprostenol manipulation. The patient was therefore transitioned to ambrisentan. The patient experienced progressive clinical worsening of PAH and died three years later of sudden cardiac arrest.

The second patient (Table 1) was a 60-year-old woman diagnosed with PAH associated with congenital heart disease (CHD). Her medical history included a cerebral tumor at the age of 14 years treated with radiotherapy without histological data. CHD consisted of a 16-mm ostium secundum atrial defect with bidirectional shunt. The pulmonary flow over systemic flow (Qp/Qs) was measured at 1.3 suggesting a moderate left-to-right shunt. The alveolar–arterial gradient in hyperoxia was high (62 kPa) in favor of a strong right-to-left shunt. Mean pulmonary arterial pressure (mPAP) was measured at 50 mmHg, cardiac index (CI) was at 4 L/min/m<sup>2</sup>, and PVR was at 6.1 Wood units. After multidisciplinary discussion and case referral to the National Reference Center for PAH, closure of the atrial defect was refused. The patient was initially treated with bosentan and tadalafil then switched to intravenous epoprostenol 3.5 years later because of worsening dyspnea (NYHA class IV) and hemodynamic severity (CI = 1.6 L/min/m<sup>2</sup>). Five years later, she had an ischemic temporal stroke, revealing cerebral cavernomatosis secondary to cerebral irradiation. The patient had no prior anticoagulant treatment. Sequelae included aphasia, epilepsy, and

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**Table 1.** Characteristics of patients with PAH in whom epoprostenol was discontinued.

	Patient 1	Patient 2	Patient 3
Age at diagnosis (years)	69	54	54
Associated condition	Anorexigen	Congenital heart disease	Systemic sclerosis
Previous PAH treatment (duration in months)	Sildenafil (15) Inhaled iloprost (12)	Bosentan (6) Tadalafil (34) Treprostinil not tolerated	Ambrisentan (30) Tadalafil (5) Inhaled iloprost (14)
Time from last RHC to epoprostenol discontinuation (months)	23	8	14
Last RHC before epoprostenol discontinuation			
mPAP (mmHg)	26	58	48
CI (L/min/m <sup>2</sup> )	3.6	2.9	2.8
PVR (Wood units)	4.8	10.9	7.5
Epoprostenol dose (ng/kg/min)	30	17	35
Time from initiation to discontinuation (years)	5	5	2
NYHA class before epoprostenol discontinuation	III	III	IV
Survival status	Died after 3 years	Alive after 1 year	Died after 2 days
Cause of death	Right heart failure	N/A	Right heart failure
PH biomarkers (before/after epoprostenol discontinuation)			
BNP (ng/L)	123/745	40/150	1009/not done
6MWD (m)	255/230	245/300	120/not done
RVEF (%)	45/38	15/13	45/not done
TAPSE (mm)	22/18	18/14	10/not done

RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; BNP, brain natriuretic peptide; 6MWD, 6-min walking distance; RVEF, right ventricle ejection fraction as measured by tomographic scintigraphy; TAPSE, tricuspid annular plane systolic excursion.

transient confusion. Because of the lack of clinical recovery of the neurological condition, epoprostenol was stopped in order to facilitate the patient's admission to a long-term care unit and to avoid any risky manipulation of the venous catheter. No additional PH treatment was initiated. Six months later, the patient was alive with no clinically relevant worsening signs of PAH.

The third case (Table 1) involved a 59-year-old woman with PAH associated with systemic sclerosis. She had a history of lower-limb amputation secondary to antiphospholipid syndrome. She was initially treated with ambrisentan, tadalafil, and inhaled iloprost. Epoprostenol was started two years after diagnosis. Despite this treatment, the patient had persistent class IV NYHA dyspnea and suffered from several side effects (diarrhea, headache, and jaw pain) significantly altering her quality of life. The decision to discontinue epoprostenol and other PAH oral drugs was taken in order to transfer the patient in a long-term care facility. Unfortunately, she developed fatal acute respiratory failure two days after epoprostenol withdrawal. In all three patients, the decision to withdraw epoprostenol was made during an extended meeting with practitioners and nursing staff.

The patients were informed about the purpose of the decision and its inherent risks.

Social problems affect patients' health and treatment effectiveness.<sup>4</sup> These three cases underline the complex problem of epoprostenol discontinuation in patients with an established medical indication for this treatment, in the presence of independent medical or social situations rendering it difficult to maintain. At the time of epoprostenol initiation, all three patients had PAH with severe clinical and hemodynamic features. Obstacles to continuation of epoprostenol appeared several years later and were all non-PH in nature. Although the use of intravenous epoprostenol is not well established in PAH associated with CHD, we decided to treat patient 2 with epoprostenol due to the worsening of PAH after the failure of a combination oral therapy and the intolerance to subcutaneous treprostinil. Several studies have shown a beneficial effect of intravenous epoprostenol in patients with CHD-PAH without aggravation of gas exchanges or major side effects.<sup>5,6</sup> The financial aspect of epoprostenol use needs to be considered, especially in long-term care facilities, where the nurse/resident ratio is generally low, and paramedics unprepared to manage this

drug, which may also prove time-consuming. As the discontinuation of epoprostenol can sometimes lead to clinical deterioration, the decision may be ethically challenging for chest physicians. In a recent retrospective study, epoprostenol withdrawal was done in eight patients with PAH (mainly portopulmonary PAH and PAH associated with HIV) based on the patient's request (and not because of major side effects).<sup>7</sup> These patients had persistent improvement of clinical and hemodynamic status (NYHA class I or II, CI > 2.5 L/min/m<sup>2</sup>, stable dose of epoprostenol over the last three months, and lower mPAP and PVR). All patients completed the transition; half of them experienced mild hemodynamic deterioration without the need to reinstitute epoprostenol. Two other studies have described transition from epoprostenol to oral agents in nearly 70% of patients with stable PAH.<sup>8,9</sup> However, the cases described in our letter did not share the same severity profile as they had worsening clinical and/or hemodynamic features of PAH at consecutive evaluations. After epoprostenol withdrawal, two patients experienced clinical worsening and their death could be attributed to PAH, although the timeframe was largely variable (2 days – 3 years). After epoprostenol discontinuation, only one patient was switched to another PH treatment. However, the remaining two patients had already been treated with endothelin receptor antagonists and phosphodiesterase type-5 inhibitors.

Patient choice is another essential factor in epoprostenol discontinuation. Our patients were informed about the possibly life-threatening consequences of epoprostenol discontinuation. Despite a probably shorter life expectancy, their acceptance was based on the improvement of their quality of life, with less secondary effects, less hospitalizations for catheter removal and/or infection, and a higher probability of being accepted in long-term care facilities. In our center, when patients with similar conditions refuse epoprostenol withdrawal, the drug is maintained with respect to patient's choice. Collaboration with geriatric assessment teams, palliative care teams, and hospital ethics committee may be useful. A multidisciplinary approach is even more valuable when considering the changing demographic picture of PAH. Reports from PAH registries have increasingly shown a rise in the proportion of elderly patients,<sup>10</sup> who have a higher burden of co-morbidities.<sup>11,12</sup> The diagnostic and therapeutic approach in these patients is critical, particularly when the administration of epoprostenol is considered.<sup>13</sup> A global geriatric assessment is required before the prescription of PAH drugs. The main therapeutic objective in the elderly is the improvement of symptoms, which depends on autonomy level and exercise ability. The benefit–risk balance of such treatment should be clearly discussed with the patients and their family, and help should be sought from other medical specialties such as cardiogeriatrics. In conclusion, while epoprostenol discontinuation may be feasible in patients with stable PAH and concomitant therapy, caution is required in patients with severe PAH because epoprostenol withdrawal may lead to clinical deterioration and death.

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