Idiopathic pulmonary arterial hypertension: could we obtain a hemodynamic near normalization? Clues from three long-term survivors on epoprostenol treatment

Abstract

Pulmonary arterial hypertension is a disease with a poor prognosis characterized by right ventricular failure, due to an increase in pulmonary vascular resistance and pulmonary arterial pressure. The introduction of specific treatments in the past decade has dramatically changed the management of the disease, and the addition of parenteral prostanoids to oral therapy has shown to improve survival in responding patients, as demonstrated by the clinical cases exposed in this paper: three female patients with moderate or severe pulmonary arterial hypertension and advanced NYHA functional class at diagnosis were able to overcome a 10-year survival along with a significant improvement in clinical and hemodynamic status thanks to the introduction of intravenous epoprostenol treatment.

Keywords: pulmonary arterial hypertension, epoprostenol, survival

Abbreviations: CI, cardiac index; iNO, inhaled nitric oxide; iPAH, idiopathic pulmonary arterial hypertension; NYHA, New York heart association; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricular; TAPSE, tricuspid anular plane systolic excursion; WHO, world health organization; WP, wedge pressure; WU, wood units; 6MWD, 6-minute walking distance

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by an increase in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) leading to right ventricular failure and ultimately death. The past decade has witnessed major advances in PAH management, due to the introduction of specific therapies. Furthermore, oral drugs have been available in the last decade consenting a more wide treatment of the disease among clinicians’ community. ET (endothelin)-receptor antagonists and PDE-5 (phosphodiesterase-5) inhibitors showed to improve exercise capacity, NYHA functional class, hemodynamics and progression of disease in several clinical trials. However, many patients have clinical worsening during oral treatment. Thus, addition of prostanoids represents an important chance to reach clinical improvement for these patients. During a 16-year period of activity in our referral center we treated almost 500 severe PH patients, and near 100 patients represented an important chance to reach clinical improvement for these patients. During a 16-year period of activity in our referral center we treated almost 500 severe PH patients, and near 100 patients were exposed to parenteral prostanoids. In this paper we describe the clinical course of 3 long-term survivor patients (>10years), as they could be considered to have had an exceptional good response to treatment.
mild side effects due to prostanoids (flushing and tolerable jaw pain). We had to reposition the central venous catheter (CVC) twice due to local infection (6 and 10 years after the first implantation).

**Patient 2** is a 47-year-old woman who received a diagnosis of iPAH in 1999 after progressive dyspnoea and reduction of the exercise capacity in the last 2 years and syncope in the last months. At first evaluation at our centre, the patient was in NYHA/WHO functional class III and had jugular distension, hepatomegaly and peripheral oedema. The 6MWD revealed a marked reduction of effort capacity (270m), ECG showed RV strain Figure 2A, echocardiography showed marked right heart dilatation with severe RV free wall hypokinesia (TAPSE 12mm) (Table 1). The RHC revealed a severe pulmonary hypertension (mPAP 57mmHg, WP 3mmHg, CI 2.2l/min/m², PVR 16.4 WU), with no response to the acute vasoreactivity test (iNO, 20ppm) (Figure 2). Thus, she was started on bosentan 62.5 mg bid, increased to 125 mg bid after 4 weeks. In the first 10 months the patient had an improvement in NYHA/WHO functional class (from III to II), in effort tolerance (from 270m at baseline to 360m after 3 months of treatment) and a regression of systemic congestion. At that time RHC confirmed ahemodynamic improvement. During the following year, she had a new reduction of exercise capacity and returned to III NYHA/WHO functional class. A RHC, performed after 2 years of treatment, showed a deterioration of pulmonary hemodynamics (mPAP 50 mmHg, CI 3.6 l/min/m², PVR 12.8 WU) (Figure 3).

On the basis of these results we started iv infusion of epoprostenol. The patient met a rapid improvement of NYHA/WHO functional class (from III to II after 2 months of treatment) and effort tolerance (6MWD from 240m before epoprostenol to 380m after 2 weeks, 445m after 4 months, 485 after 1 year and above 500m after 4 years of treatment, (Figure 3)). Four years later (epoprostenol 37 ng/Kg/min), RHC showed a considerable improvement of hemodynamic assessment (mPAP 37 mmHg, CI 3.5 l/min/m², PVR 6.5 WU), reversing PH to a mild stage. Thirteen years after starting epoprostenol, patient is still NYHA/WHO functional class II, 6MWD is stable on 500m; echocardiography (Table 1) and ECG Figure 2A-B show an improvement of RV eccentricity index and RV strain, respectively. The last catheterization shows a near normalization of pulmonary pressure and a mild elevation of PVR (mPAP 27 mmHg, CI 3.5 l/min/m², PVR 4.4 WU) (Figure 3). Patient’s side effects during follow-up were essentially limited to flushing, jaw pain and episodic diarrhoea.

**Patient 3** is a 48-year-old woman who received a diagnosis of iPAH in 1999. Since 1998 she had dyspnoea and progressive reduction of effort tolerance, and these symptoms worsened during the last 2 months of pregnancy. Just few days after the delivery she had an echocardiographic evaluation that showed an estimated systolic PAP of 100 mmHg, so she was referred to our center. At first evaluation, the patient presented jugular distension (1-2/4), hepatomegaly and mild peripheral oedema; she was NYHA/WHO functional class III and showed a decreased exercise capacity (6MWD 330m, (Figure 4)); ECG showed right ventricular strain; respiratory function tests, perfusion lung scan and autoantibiotic assessment were normal. The patient underwent RHC that confirmed the diagnosis of moderate-severe precapillary PH with positive response to acute vasoreactivity test with iNO 20 ppm (mPAP from 46 to 36 mmHg, CI from 2.8 to 3.6 l/min/m², PVR from 7.8 to 4.7 WU) (Figure 4). According to these results, the patient was started on a calcium channel blocker (nifedipine 90 mg/die; it was not possible to increase the dose because of severe peripheral oedema). After 1 year of treatment, the patient showed a substantial increase in effort tolerance (6MWT from 330 to 470m, (Figure 4) and improvement of NYHA/WHO functional class (from III to II), but in the following 3 months exercise capacity.
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Discussion

PAH is a progressive disease, with a very poor prognosis if left untreated. In the last decade we witnessed the introduction of specific therapies which showed to improve exercise capacity, NYHA functional class, hemodynamics and progression of disease in several clinical trials.6-8,11-13 Despite the number of PAH patients on treatment is increasing worldwide, there are no data published on patients with a very long survival and a good hemodynamic response. In this paper we report three iPAH cases with a very long survival (>10years), impressive hemodynamic response (almost normalization of PVR) and reverse remodelling of the RV. This response to specific treatment is uncommon and is similar to the results obtained in the minority of patients who could be treated with calcium channel blockers (CCB). Among our cases, only one patient was vasoreactive, but she had limited benefit by CCB; after few months she had a severe deterioration as she lost pulmonary vasoreactivity. Thus our patients had “fixed” PVR when epoprostenol was started, and the very significant reduction in PVR after long–term treatment raises the question if it is possible to achieve the regression of the pulmonary arteriopathy responsible of the clinical syndrome. Several studies demonstrated that prostanoids have antiproliferative effects in vitro13-16 and can prevent or reverse the pulmonary arteriopathy in animal models of pH. A similar mechanism could be present in human, as suggested by the fact that patients, who did not have acute hemodynamic benefit during acute vasodilator challenge, had clinical and hemodynamic benefit during chronic epoprostenol treatment. The results of our patients are even more impressive with the near normalization of PVR, RV anatomy and function. In our opinion, the magnitude of this improvement suggests that in a small subgroup of non-vasoreactive patients with iPAH it might be possible to obtain a reverse remodelling of the obstructive arteriopathy. This hypothesis should be confirmed by the analysis of large registries which are currently ongoing,19–21 and it should foster collaborative studies among referral centers looking at these patients with a particular good response to therapy.

Acknowledgements

None.

Table 1 Patient 2: Echocardiographic parameters variations during follow-up

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<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
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Legend – El, eccentricity index; RA, right atrium; TAPSE, tricuspid anular plane systolic excursion
Conflict of interest

The author declares no conflict of interest.

References