Primary pulmonary hypertension (PPH) is a rare, progressive disease with poor prognosis. Until only a few years ago, treatment consisted of supportive care, calcium antagonists and lung transplantation (LTx). However, transplant dysfunction because of rejection remains a major complication. For transplantations performed between 1991 and 1995 in the Netherlands for pulmonary hypertension, 2-yr survival is limited to ~50% [1, 2].

Over the last few years, treatment of PPH with prostacyclins has proven effective [3]. Initially considered as a bridge to transplantation, it is now thought that prostacyclins enable postponing of transplantation for a longer period of time, possibly even indefinitely [4]. This case report describes the course of a patient who underwent single LTx for PPH at the time when prostacyclins were not available for long-term treatment.

Case report

A 35-yr-old female was diagnosed with pulmonary hypertension in late 1993. Secondary pulmonary hypertension was ruled out using laboratory and pulmonary function tests, high-resolution computed tomography, ventilation-perfusion scintigraphy and echocardiography. Although the patient had taken an undocumented dose of dexfenfluramine as a teenager, the final diagnosis was PPH. In 1995, further investigation was carried out, including acute vasodilator testing. During this test, the pulmonary artery pressure (PAP) decreased from 95/35/68 mmHg to 80/28/48 mmHg (-29%) after increasing doses of epoprostenol. There was no beneficial response on high levels of oxygen. Because of the diagnosis of PPH and subsequent deterioration of the patient’s condition under supportive treatment with oxygen, oral anticoagulants and digoxin, the patient was listed for LTx. At that time, only single LTx was performed for PPH in the Netherlands. Within a year after listing, an uncomplicated transplantation of the right lung was performed. Postoperative PAP was 36/11/19 mmHg. Ventilation-perfusion scintigraphy revealed an equal distribution of ventilation over both lungs, but 89% of the blood flow passed through the transplanted lung.

Immunosuppressive therapy consisted of antithymocyte globulins for induction, and corticosteroids, cyclosporin and azathioprine as maintenance therapy. Nevertheless, very frequent episodes of acute rejection occurred. Within 8 months after transplantation, the first signs of bronchiolitis obliterans were found in an open-lung biopsy. More aggressive immunosuppression with corticosteroids, tacrolimus and mycophenolate mofetil resulted in reduction of the frequency of acute rejections, but failed to halt the progression of bronchiolitis obliterans. Four and a half years after transplantation all functionality of the transplanted
vascumlar resistance. # during reversibility testing; PAP: pulmonary artery pressure; TPVR: total pulmonary resistance was started with an initial dose of 4.7 ng eprostenol (table 1). Long-term eprostenol therapy was considered. However, in the time that had passed since transplantation, eprostenol had been registered in the Netherlands for use in PPH. At right heart catheterisation, a PAP of 111/36/61 mmHg was found without any acute response on epoprostenol (table 1). Long-term epoprostenol therapy was started with an initial dose of 4.7 ng·kg⁻¹·min⁻¹ (500 mcg·24 h⁻¹), followed by an average monthly increase of 1 ng·kg⁻¹·min⁻¹. Within a month, the patient was less dyspnoeic and the 6 MWD had increased of 1 ng·kg⁻¹·min⁻¹. Within a month, the patient was less dyspnoeic and the 6 MWD had increased by 325 m. After 3 months, supplemental oxygen was discontinued, without negative effect on the exercise capacity. In the following months, the 6 MWD remained stable at ~350 m, but eventually increased to 503 m (fig. 2). Blood gas analysis showed a Pao₂ of 10.9 kPa (82 mmHg) without supplemental oxygen after 17 months of epoprostenol therapy. The patient is now classified as NYHA functional class 2 and generally feeling well. No right heart catheterisation was performed during the follow-up period, considering the fact that the findings would not affect the therapy in any way.

Table 1. – Haemodynamic measurements before transplantation (BT), after complete donor lung rejection (LR) and after 17 months of epoprostenol therapy (ET)

| Haemodynamic measurements | BT       | LR       | ET       |
|---------------------------|----------|----------|----------|
| PAP mmHg                  | 95/35/68 | 111/36/61|          |
| Lowest PAP mmHg           | 80/28/48 | 105/27/58|          |
| Cardiac output L·min⁻¹     | 4.6      | 2.4      | 3.5      |
| Stroke volume mL          | 61       | 31       | 46       |
| TPVR dyne·s·cm⁻³           | 1182     | 2033     |          |

PAP: pulmonary artery pressure; TPVR: total pulmonary vascular resistance. #: during reversibility testing; *: measured by catheterisation; #: measured by magnetic resonance imaging velocity mapping.

Discussion

Findings at the histological examination of the explanted right lung were consistent with the diagnosis of PPH, stage IV–V: intima proliferation, media hypertrophy and plexiform lesions were seen. According to present standards, this patient should have been considered reversible at the vasodilator test before transplantation, as the decrease in PAP was >20%. The decision to list this patient for LTx immediately, without attempting treatment with calcium-channel blockers first, was not fully justified. Lack of experience with this rare disease and perhaps some confusion due to the difference in response on oxygen and epoprostenol may well have lead to this decision. The rapid deterioration under supportive care alone made listing for LTx a logical choice at that time. Whether single or bilateral LTx is most beneficial for patients with PPH in general remains uncertain. Although some authors have noted that bilateral LTx has a somewhat better survival [6] and single LTx may result in significant ventilation/perfusion mismatches [7], single LTx is a well accepted modality [8–9]. More than 5 yrs after transplantation, chest imaging of the patient showed a fully sclerotic, collapsed donor lung, as a result of ongoing bronchiolitis obliterans and transplant vasculopathy. The patients survival on a prostacyclin-treated native lung enabled the development of a severe stage of bronchiolitis obliterans in...
the transplant, which is unusual and obviously not compatible with life.

To the best of the authors’ knowledge, no literature was available on the use of epoprostenol after LTx and subsequent rejection. The decision to start this therapy rather than listing for retransplantation was therefore based upon the general treatment algorithm for PPH patients [10] as follows: 1) no response during vasodilator testing, 2) NYHA functional class III or IV, and 3) no listing for transplantation unless epoprostenol therapy fails. This case demonstrates that epoprostenol treatment can be effective after single LTx and subsequent rejection. Furthermore, it is demonstrated that patients who are initially not treated with prostacyclins, can still benefit from that form of treatment in a later stage of their disease, even with only one lung with severe PPH.

With hindsight, several therapeutic decisions concerning this patient have been controversial at best. The use of single lung transplantation as an unexpected bridge to epoprostenol treatment did however result in a long survival (>8 yrs after the diagnosis) and a good exercise capacity.

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