Complete Therapeutical Approach in Pulmonary Arterial Hypertension: from Vasodilators to Lung Transplantation - Case Report

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ABSTRACT
We present the case of a 37 years old patient with idiopathic pulmonary arterial hypertension (PAH). After initial treatment with calcium channel blockers (CCB), based on a positive vasoreactive response at right heart catheterization, due to disease progression, major vasodilator therapies were introduced in a sequential strategy: sildenafil, bosentan and treprostinil. Finally, the patient received double-lung transplantation with eventually favourable evolution despite immediate postoperative significant complications.

Markers of disease progression were monitored before the transplant, and after the intervention the patient was screened according to a specific protocol for bronchiolitis obliterans and infections.

According to our knowledge, this case represents a premiere in Romanian medicine, being the first lung transplant in a PAH patient.

This case represents a model of PAH with a documented evolution of 8 years. We present the progression of the disease and the effective therapeutic strategies according to the current guidelines. This case reinforces the need for upgrading the Romanian National PAH Program with the inclusion of prostanoid therapy, as an option for severe patients.

Keywords: pulmonary arterial hypertension, pulmonary vasoreactive test, vasodilator combination therapy, lung transplantation

INTRODUCTION
Pulmonary hypertension (PH) represents a heterogeneous family of disorders, characterized by a mean pulmonary arterial pressure (mPAP) above 25 mmHg, determined by right heart catheterization (RHC). According to the latest clinical classification, Dana Point 2008, pulmonary arterial hypertension (Group 1), groups a number of rare diseases characterized by precapillary PH (pulmonary wedge pressure, PWP <15 mmHg), with similar clinical picture and similar pathological changes in the...
pulmonary circulation. Idiopathic PAH accounts for almost 40% of the PAH group (1,2).

Epidemiologic data suggest a PAH prevalence between 15 cases/million (French registry) to 50 cases/million (Scottish registry) and an incidence of 2.4 cases/million/year (3,4).

The condition is marked by a severe prognosis with an estimation of mean survival, without treatment, of 2.8 years from diagnosis (5). Recent data from the French cohort confirm a 3 year survival of only 67% in the treated population (6).

The therapeutic options consist of medical treatments (7-13) and surgical interventions (Table 1). They imply a step-up approach from monotherapy to sequential combination therapy (prostanoids and oral medication), according to markers of disease progression: clinical – NYHA functional class (New York Heart Association Classification) and syncope, exercise tolerance – 6 minute walking test (6MWT) and cardiopulmonary exercise testing, echocardiography - pericardial effusion, tricuspid annular plane systolic excursion (TAPSE) and right atrial (RA) enlargement, brain natriuretic peptide (BNP) levels and ultimately cardiac output and right atrial pressure on RHC (1,2).

**CASE REPORT**

We present the case of a female patient, 37 years old (at diagnosis), non-smoker, active nurse, without previous significant medical history.

The first medical presentation was in 2005 for progressive dyspnoea on exertion, for the past 2 years, and recently associated with syncope. The clinical evaluation identified a NYHA functional class III and a modified clinical examination with mild lower limb oedema and the presence of a systolic tricuspid murmur. Cardiac ultrasound revealed a significant pulmonary hypertension (estimated systolic PAP of 97 mmHg) with enlarged right heart chambers (RA 46 mm and RV 42 mm), normal left heart and paradoxical interventricular septum motion.

The etiological evaluation was done according to the PH classification, Venice 2003 (14). A thorough diagnostic workup evaluated the 4 major PH groups: chronic thromboembolic PH, hypoxic PH and left heart disease were ruled out and from the PAH Group 1, neither an associated condition nor a familial form were identified, with a final diagnosis of idiopathic PAH.

RHC confirmed the pulmonary hypertension: sPAP 100 mmHg, dPAP 31 mmHg, mPAP 60 mmHg with a cardiac index (CI) of 2.4l/min/m². The vasodilator test with ilomedin decreased the mPAP to 39 mmHg. According to the guidelines (14), a positive test is defined by a lowering of mPAP with more than 10 mmHg and below 40 mmHg without a decrease of cardiac output, and signals a probability for clinical response to CCB. Diltiazem was introduced and uptitrated to high doses with good clinical benefit and tolerance.

At her first visit in our clinic, in 2005, the patient was clinically stable, functional class I, with complete remission of symptoms soon after CCB introduction. The clinical examination showed absence of tachycardia and preserved systemic blood pressure. The 6MWT distance at that time was 582m and lung function tests confirmed normal volumes and flows with only a mild decrease of DLCO to 61% of predictive. The chest radiograph showed a typical pattern of PAH without cardiomegaly (Figure 1A). The ECG presented sinus rhythm, P pulmonale – RA strain, right QRS deviation and RV strain.

The clinical evolution was marked by disease progression. After 8 months of CCB therapy, the patient presented a clinical deterioration to FC III and also an episode of syncope on exertion and thus she was considered a non-responder to CCB therapy. The treatment was switched to sildenafil 25 mg TID with a transitory clinical aggravation. After 4 months of persistent FC III, treatment was upgraded to double oral therapy, adding bosentan 125 mg BID, with good clinical and hepatic tolerance. In 2008 a marked clinical aggravation occurred, with dyspnoea at rest, repeated syncopeces on mild exertion and overt right heart failure. The patient was admitted to the intensive-care unit and treatment was started with high doses of intravenous furosemide and dobutamine.

Due to this major clinical deterioration, in a PAH patient on a double oral vasodilators combination, we considered the remaining therapeutic options: prostanoid treatment and listing for lung transplantation. Balloon atrial septostomy, another possible surgical intervention, was not considered in this case. This procedure is available only in a few experienced centres, none in Romania; it offers only a short relief in symptoms for some selected patients.
and might be used as a “bridge” to transplant for NYHA IV patients with severe syncopal symptoms.

Treprostinil was started (by continuous subcutaneous pump injection) with a slow uptitration process, permitting the weaning of inotropes and the switch to oral diuretics. Presence of local side effects – pain on infusion site – was the major issue for dose-progression. At the same time the case was presented to the Vienna (Austria) transplant team. After obtaining the required approvals, the patient was listed for double-lung transplantation. The triple vasodilator therapy induced a mild amelioration to FC III. Due to the plateauing of treprostinil to 10 ng/min/kg because of side effects, the patient deteriorated further.

The patient was evaluated periodically before the transplant intervention. The parameters that correlated well with the clinical status were 6MWT distance which decreased steadily to a value of 280 m, and NYHA functional class, which progressed from FC I to FC IV (Figure 2). Also, a good correlation was observed with investigations that monitored the dilatation of the heart, such as chest radiograph (Figure 1B.), showing significant increase of cardiac index, or echocardiography, with dilation of RA and RV. Among parameters that showed no correlation with disease progression we emphasise DLCO and estimation of sPAP from the velocity of the tricuspid regurgitant jet, parameters which were fairly stable for the entire period.

On echocardiography and computed tomography (CT) severity markers were the pre-
sence of pericardial effusion and ascites and major dilation of the RA. In addition, there were no arguments for veno-occlusive disease noted on the CT (lung parenchyma septal lines and nodules, mediastinal adenopathies). Unfortunately RHC was not available for follow-up.

The indication for lung transplantation was established according to international standards (15) and was based on disease progression despite triple therapy, young age and disease severity, with survival estimated to less than 2 years.

Our patient required an extensive list of investigations for inclusion on a lung-transplant list, according to the the practice of the transplant center (AKH Vienna) and international recommendations. The workup detailed the specific etiology and lung function and it also evaluated the complete medical status of the patient (screening for possible contra-indications – Table 2). For the donor-recipient compatibility the main parameters were blood group and thoracic morphometric measurements. The HLA typing and the presence of anti-HLA antibodies may indicate the risk of organ rejection. Due to significant deconditioning, we recommended the inclusion in a local rehabilitation program before the transplantation in order to improve survival.

In March 2010 lung transplantation was performed and vasodilator treatment was stopped. The transplant procedure was performed in Vienna General Hospital. According to the protocol for PAH patients, extra-corpo-real membrane oxygenator (ECMO) was used during the intervention. The postoperative evolution was difficult due to poor clinical status at the time of the operation, with 9 days of mechanical ventilation, 35 days in the intensive-care unit, haemodialysis for renal failure and gas tropareisis. A rehabilitation protocol was implemented when the patient was able to perform physical exercise and the patient was discharged after 4 months in a stable clinical condition.

Treatment after lung transplantation used immunosuppressive drugs (mycophenolate mofetil, tacrolimus and prednisone), and infection prophylaxis (valganciclovir for CMV and inhaled amphotericin for aspergillus). Functional follow-up included screening for bronchiolitis obliterans syndrome and also bronchial biopsies aiming to detect both organ rejection and chronic lung infection.

3 years after lung transplantation, the patient is in stable clinical status with persistence of moderate microcytic anaemia, chronic renal failure with stable creatinine levels, and mild restrictive pattern on pulmonary function tests. The pulmonary hypertension relapse is not an issue and the severe remodelated heart, with important dilation and hypertrophy of the right chambers and compression of the left ventricle, presents a reverse remodelling process.

**DISCUSSION**

Idiopathic PAH is a complex and severe disease that requires a specific investigational protocol. The diagnosis implies a multidisciplinary team and should be performed in dedicated centres. RHC is required for diagnosis and also should be used for severity evaluation.
Due to low survival in naive patients and persistence of increased mortality in treated patients, follow-up parameters such as clinical data – NYHA functional class and syncope, 6MWT, echocardiography and ideally RHC are very important. DLCO and PAP are not markers of disease progression.

CCB are indicated only in positive vasoreactive patients and should be continued only in responders (approx. 7% of all PAH patients).

Vasodilator treatment may require combination therapy in patients with disease progression. New therapies should be added not switched, in order to avoid the risk of rebound. Sequential treatment strategy (1,2), validated in clinical trials, is usually recommended. In patients with markers of severity at baseline combination treatment may be started up-front.

All major treatments used by the presented patient (sildenafil, bosentan and treprostinil), were started as donations, due to lack of therapeutic options in Romania at that time. Starting 2008, the patient received sildenafil and bosentan through the Romanian National Program for PAH. Presently, in Romania, over 50 patients receive double oral combination therapy and almost half of them still present markers of severity. Treprostinil and all other prostanooids are still not available in Romania.

There is no indication for heart-lung transplant even in cases of severe heart failure.

Lung transplantation is still not performed in Romania, although it represents the ultimate option for severe young patients with PAH and other lung diseases. According to our knowledge, this case represents a premiere in Romanian medicine, being the first lung transplant for a PAH patient.

CONCLUSION

This case represents a model of PAH with a documented evolution of 8 years. We present the progression of the disease and the effective therapeutic strategies according to the current guidelines. This case reinforces the need for upgrading the Romanian National PAH Program with the inclusion of prostanoid therapy as an option for severe patients.

Conflict of interests: I undersign, certificate, that I was a consultant, speaker and investigator in clinical studies for Actelion, Pfizer and GlaxoSmithKlein companies.

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