Connective tissue disease associated with pulmonary arterial hypertension: management of a patient with severe haemodynamic impairment

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Despite the availability of specific therapies targeting multiple pathways involved in the development and progression of pulmonary arterial hypertension (PAH), and the improved survival observed in PAH patients in recent years, it remains a progressive, devastating disease [1]. Some encouraging evidence regarding the use of upfront triple-combination therapy in the management of patients with advanced disease has been previously reported [2]. This article reports the management of a patient diagnosed with severe PAH (New York Heart Association (NYHA) functional class IV) who was referred to the national pulmonary hypertension reference centre. The article highlights important considerations for timely and accurate diagnosis of PAH and exhaustive aetiological evaluation. It provides key insights into the management of patients presenting with severe disease, with particular focus on their treatment with multiple PAH-specific therapies.

This is the case of a 20-year-old female patient who was seen by her general practitioner with symptoms of inflammatory arthralgia (fingers, wrists and knees), which she had been experiencing for several months (since December 2010), associated with a long history of Raynaud's phenomenon. The patient was a nonsmoker, was not on any therapy (except the oral contraceptive pill), and did not have a history of taking appetite suppressants. She had no family history of PAH. A rheumatological assessment was initiated, and despite tests for rheumatoid factor and anti-cyclic citrullinated peptide being negative, rheumatoid arthritis was initially suspected. Treatment with nonsteroidal anti-inflammatory drugs followed by methotrexate proved to be ineffective and was stopped in September 2012 after 21 months.

In February 2013, the patient presented with a 1-month history of worsening dyspnoea following exertion, dizziness and palpitations. Her general practitioner referred her to a cardiologist for an ECG which revealed sinus tachycardia, thus, she was prescribed a β-blocker. The patient's clinical status rapidly deteriorated and

Received: Sept 29 2014 | Accepted after revision: Oct 14 2014

Conflict of interest: Disclosures can be found alongside the online version of this article at err.ersjournals.com

Provenance: Publication of this peer-reviewed article was sponsored by Actelion Pharmaceuticals Ltd, Allschwil, Switzerland (principal sponsor, *European Respiratory Review* issue 134).

she was referred to a university hospital (Centre Hospitalier Universitaire, Saint-Etienne, France) where she presented with dyspnoea when resting along with chest pains. A physical examination performed at the emergency department reported the following: body mass index 19.7 $kg \cdot m^{-2}$; blood pressure 100/60 mmHg; heart rate 82 $beats \cdot min^{-1}$; arterial oxygen saturation measured by pulse oximeter 96%; jugular distension; hepatalgia; hepatomegaly; and loud P2 heart sounds. Her blood haemoglobin level was 13.2 $g \cdot dL^{-1}$, sodium was 139 $mmol \cdot L^{-1}$, creatinine was 72 $\mu mol \cdot L^{-1}$, and her aspartate aminotransferase and alanine aminotransferase levels were approximately twice the upper limit of normal. Prothrombin time was 60%, D-dimer levels were elevated (>6000 $\mu g \cdot L^{-1}$), brain natriuretic peptide (BNP) levels were 1128 $ng \cdot L^{-1}$ and β-human chorionic gonadotropin was negative.

A chest radiograph performed at the emergency department showed dilatation of the main pulmonary artery and also a degree of cardiomegaly. High-resolution computed tomography of the chest showed enlargement of the main pulmonary artery, dilation of the right atrium and right ventricle (with compression of the left ventricle), and dilation of the hepatic veins. No signs of proximal or distal pulmonary embolism or parenchymal abnormalities were seen. Transthoracic echocardiography showed: normal left heart function (ejection fraction 50%) with no atrial or ventricular defect; right atrial and right ventricle dilation; impaired right ventricle function (tricuspid annular plane systolic excursion 12 mm, S wave 8 $cm \cdot s^{-1}$); paradoxical septal motion; estimated right ventricle systolic pressure ~89 mmHg (tricuspid regurgitant jet velocity ~4.30 $m \cdot s^{-1}$ and estimated right atrial pressure (RAP) ~15 mmHg); and moderate pericardial effusion.

The patient was referred to the national pulmonary hypertension reference centre (Centre de Référence de l'hypertension pulmonaire sévère, Hôpital Bicêtre, Université Paris-Sud, Le Kremlin-Bicêtre, France) and was immediately admitted to the intensive care unit as she was in NYHA functional class IV, had severe right heart failure, normal blood pressure (98/60 mmHg), and 98% arterial oxygen saturation measured by pulse oximeter on room air. The patient was treated with high-dose intravenous diuretics (250 mg furosemide drip for 24 h), small-dose dobutamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and anticoagulants (low-molecular-weight heparin). Blood tests were negative for HIV and hepatitis B and C virus, no coagulation disorders were present (no antiphospholipid antibodies) and rheumatoid factor testing was negative. However, antinuclear antibodies were positive (1/1280), with elevated anti-ribonucleoprotein levels (357 IU).

The completed work-up included a lung ventilation/perfusion scan that showed normal lung perfusion and no evidence of pulmonary thromboembolism. Abdominal ultrasonography was also performed to check for liver diseases and portal hypertension, but these were negative. Pulmonary function tests showed normal volume and flow, and included forced vital capacity (FVC; 74% predicted), forced expiratory volume in 1 s (FEV_1; 70% predicted), FEV_1/FVC (82%) and total lung capacity (81% predicted). Diffusing capacity of the lung for carbon monoxide (D_{LCO}) was low (40% predicted). When corrected for alveolar volume, D_{LCO}/alveolar volume was 70% predicted. Arterial blood gases reported an arterial oxygen tension and arterial carbon dioxide tension of 89 mmHg and 28 mmHg, respectively. After a few days of *i.v.* diuretics and inotropic drugs, the 6-min walking distance (6MWD) was 220 m, including two stops; with a high Borg score of 6, no desaturation and no increase in heart rate; the patient's BNP level was still elevated (802 $ng \cdot L^{-1}$).

Right heart catheterisation after withdrawal of dobutamine therapy indicated that haemodynamic parameters were severely impaired, with a RAP of 12 mmHg, mean pulmonary arterial pressure (mPAP) of 57 mmHg, pulmonary artery occlusion pressure of 4 mmHg, low cardiac output of 2.40 $L \cdot min^{-1}$, low cardiac index of 1.60 $L \cdot min^{-1} \cdot m^{-2}$, high pulmonary vascular resistance (PVR) of 22 Wood units and a mixed venous oxygen saturation of 49%. Acute vasodilator testing (inhaled nitric oxide) was negative with no change in mPAP (58 mmHg). Following these assessments, the patient was diagnosed with severe PAH in association with mixed connective tissue disease (CTD), was in NYHA functional class IV with right heart failure at presentation and was non-vasoreactive. The diagnosis of mixed CTD was based on the patient's clinical presentation with arthralgia and Raynaud's phenomenon, and the presence of a very elevated anti-ribonucleoprotein level.

Based on the risk assessment from the 2009 European Society of Cardiology/European Respiratory Society guidelines [3], it was determined that this patient was unstable and deteriorating, and had a poor prognosis (table 1). Upfront triple-combination therapy with *i.v.* epoprostenol (12 $ng \cdot kg^{-1} \cdot min^{-1}$) was initiated in addition to bosentan (125 mg twice daily) and tadalafil (40 mg once daily). Additional immunosuppressive therapy was started in order to improve pulmonary vascular disease in the form of oral corticosteroids (prednisone 0.5 $mg \cdot kg^{-1} \cdot day^{-1}$) and *i.v.* cyclophosphamide pulses (600 $mg \cdot m^{-2}$ every 4 weeks, reassessed after six pulses). After 6 months, the patient was assessed and, compared with baseline, improvements included a change in NYHA functional class from IV to I, an improvement in 6MWD from 220 to 487 m, and normalisation of haemodynamic parameters: RAP (12 to 7 mmHg), mPAP (57 to 20 mmHg), cardiac output (2.4 to 6.6 $L \cdot min^{-1}$) and PVR (22 to 1.4 Wood units).

DOI: 10.1183/09059180.00009214

TABLE 1 Patient risk assessment

Parameter	Stable and satisfactory		Stable and not satisfactory		Unstable and deteriorating	
	ESC/ERS guidelines	Current case	ESC/ERS guidelines	Current case	ESC/ERS guidelines	Current case
Clinical RV failure	No				Yes	Yes
Rate of progression	Slow				Rapid	Rapid
Syncope	No	No			Yes	
NYHA FC	I, II		III		IV	IV
6MWD m	>500[#]		300–500		<300	220
V'_{O_2peak} mL·min^{-1}·kg^{-1}	>15		12–15		<12	Not determined
BNP/NT-proBNP	Normal/near normal		Elevated		Very elevated/ increasing	Very elevated
Echocardiography findings	No PE and TAPSE >2.0 cm		TAPSE 1.5–2.0 cm		PE and/or TAPSE <1.5 cm	PE and TAPSE 1.2 cm
Haemodynamics	RAP <8 mmHg and CI ⩾2.5–3.0 L·min^{-1}·m^{-2}		RAP 8–15 mmHg or CI 2.0–2.5 L·min^{-1}·m^{-2}	RAP 12 mmHg	RAP >15 mmHg and/or CI ⩽2.0 L·min^{-1}·m^{-2}	CI 1.6 L·min^{-1}·m^{-2}

ESC: European Society of Cardiology; ERS: European Respiratory Society; RV: right ventricular; NYHA: New York Heart Association; FC: functional class; 6MWD: 6-min walking distance; V'_{O_2peak}: peak oxygen uptake; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; PE: pericardial effusion; TAPSE: tricuspid annular plane systolic excursion; RAP: right atrial pressure; CI: cardiac index. [#]: depending on age, height, weight, aetiology of pulmonary arterial hypertension and presence of comorbidities. Adapted from [3] with permission from the publisher.

To summarise, this case described the disease course and management of an adult patient who presented with severe PAH (NYHA functional class IV) associated with mixed CTD. Pulmonary hypertension has been reported in 3–32% of patients with mixed CTD [4–7], with PAH reported in only 1% [4], and has been shown to persist despite treatment [7]. Inflammation is thought to play an important role in the development of PAH in CTD patients [8]. Autoantibodies have been implicated in the immunopathological processes involved [9]. It has been recognised that the immune and inflammatory mechanisms implicated in CTD-associated PAH support the use of immunosuppressants for its treatment, although the evidence to date is variable [10, 11]. Patients with mixed CTD who are suspected to have cardiopulmonary involvement should be referred as early as possible to expert pulmonary hypertension centres for right heart catheterisation, as pre-capillary PAH should be confirmed prior to the initiation of PAH-specific therapies [10]. The patient presented here was treated by combining three PAH-specific therapies upfront, in addition to immunosuppressant therapy for the treatment of the underlying inflammatory processes.

In patients with severe PAH, targeting more than one of the three known pathological pathways of PAH is common. In heart failure and malignant hypertension, or in diseases where mortality rates are high, an upfront pre-emptive approach is standard [12, 13]. The evidence for combining treatments upfront is increasing in PAH, but is still very limited with regard to upfront triple-combination therapy [14]. The 5th World Symposium on Pulmonary Hypertension indicated that initial combination therapy may be considered (grade of evidence IIb–C) in patients in NYHA functional class III/IV [15]. More recently, a pilot study has investigated the benefit of upfront triple-combination therapy in 19 patients with PAH in NYHA functional class III/IV [2]. Patients with idiopathic and heritable PAH received upfront bosentan, sildenafil and *i.v.* epoprostenol. In 18 out of 19 patients, major improvements in NYHA functional class, 6MWD and haemodynamic parameters (including cardiac index, mPAP and PVR) were observed after 4 months and were sustained long-term. Moreover, all patients were still alive and in NYHA functional class I or II after a mean follow-up period of 41±13 months.

Several case studies [16–20] and some larger retrospective studies [8, 21–23] have reported positive outcomes for patients with lupus- or mixed CTD-associated PAH treated with immunosuppressive therapy alone or in association with PAH-specific therapies. However, immunosuppressive therapy alone does not appear to be sufficient in patients with more severe haemodynamic impairment [8, 10, 22]. The case reported herein provides further weight for combining immunosuppressive therapy with triple-combination PAH therapy in treating a patient with severe mixed CTD-associated PAH.

Another important consideration that this case brings to light is how this patient, now in NYHA functional class I on immunosuppressive and triple-combination therapy, should be managed. In patients who respond favourably to treatment, an immunosuppressive maintenance regimen has been suggested [8].

There is also a need to determine if patients, such as the current case, should continue to receive *i.v.* epoprostenol or if, in specific patients, they can be weaned off this treatment. Varying outcomes following weaning of *i.v.* epoprostenol have been reported in adult patients with PAH. While some patients have been successfully weaned from epoprostenol to be maintained on oral or inhaled therapies, others have deteriorated, requiring re-initiation of *i.v.* epoprostenol [24–37]. Unfortunately, factors that may predict a patient's clinical response following epoprostenol weaning are difficult to define.

In conclusion, patients with complex pulmonary vascular diseases should be referred to expert centres as soon as possible in order to provide patients with the most appropriate treatment; close monitoring is essential. Upfront triple-combination therapy in conjunction with immunosuppressive therapy may provide benefit in patients with severe PAH associated with mixed CTD. Further evidence is needed to determine the optimal maintenance regimes for these patients.

Acknowledgements

Medical writing support was provided by Lynda McEvoy (apothecom scopemedical ltd, Sevenoaks, UK), which was funded by Actelion Pharmaceuticals Ltd (Allschwil, Switzerland).

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