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# Pulmonary arterial hypertension in patients treated with interferon

*To the Editor:*

We read with interest the article by Savale *et al.* [1] reporting pulmonary arterial hypertension (PAH) associated with treatment with interferon (IFN) in 53 patients from the French PAH registry. As noted by the authors, patients receiving IFN-α have confounding factors such as portal hypertension or HIV infection that may classify them in group 1.4.3 or 1.4.2, respectively, according to the 2013 updated pulmonary hypertension classification [2]. Therefore, "pure" cases, such as those treated with IFN-β for multiple sclerosis are important to identify in order to strengthen the causal relationship between the suspected drug and PAH.

We briefly report here the case of a 72 year-old woman who was diagnosed with multiple sclerosis back in 1992. Starting from 1999, she was treated regularly with IFN-β subcutaneously every other day (Bayer AG, Zurich, Switzerland) without significant interruption. Additional diagnoses included cigarette-induced chronic obstructive pulmonary disease (COPD) with a post-bronchodilator forced expiratory volume in 1 s of 79% predicted, together with a type 2 diabetes mellitus. During the previous 2 weeks her dyspnoea had rapidly increased from New York Heart Association (NYHA) class 2 to 4 and she was admitted to the intensive care unit (ICU) with mild hypoxaemia (arterial oxygen tension of 59 mmHg) and clinical signs of right heart failure. A transthoracic echocardiography revealed a dilated right ventricle with severe systolic dysfunction (tricuspid annular plane systolic excursion (TAPSE)=11 mm), a small pericardial effusion (4 mm) along the right cavities, and a three-quarters tricuspid regurgitation with maximal jet velocity of 3.77 $m \cdot s^{-1}$ (maximal right ventricular/right atrial gradient of 57 mmHg). There was a D-shape deformation of the interventricular septum but the left ventricular systolic function was otherwise normal. Haemodynamic measurements collected at the ICU confirmed a precapillary pulmonary hypertension with a pulmonary pressure of 72/34–48 mmHg (systolic/diastolic–mean) and a pulmonary wedge pressure of 13 mmHg (table 1). The cardiac index was measured at 2.3 $L \cdot min^{-1} \cdot m^{-2}$, and the pulmonary resistance was calculated at 14.5 Wood Units. No vasoreactivity was observed after inhalation of 20 ppm nitrous oxide. A ventilation/perfusion ratio ($V'/Q'$) scan and a computed tomography (CT) scan angiography ruled out thromboembolic disease and lung interstitial disorder. Emphysematous alteration of the lung parenchyma was minimal. In the work up for PAH group 1, HIV serology returned negative, there was no clinical or biological sign for liver cirrhosis or connective tissue disorder, and the history for familial PAH was negative. The severity score according to the REVEAL registry was 12 out of 22, corresponding to a very high risk [3]. We concluded that this patient had PAH associated with chronic intake of IFN-β (group 1.3, 2013 classification [2]) and this medication was stopped. She was treated with an upfront dual oral regimen including a phosphodiesterase-5 inhibitor (sildenafil) and an endothelin receptor antagonist (macitentan), allowing regression of the dyspnoea from NYHA class 4 to 3 after 3 weeks. Follow-up at

TABLE 1 Haemodynamic measurements

| | Baseline | Follow-up | |
|---|---|---|---|
| | | 3 months | 6 months |
| **NYHA functional class** | IV | II | II |
| **NT-proBNP ng·L$^{-1}$** | 1208 | 436 | 203 |
| **TAPSE mm** | 11 | 15 | 18 |
| **Systolic/diastolic/mean PAP mmHg** | 72/34/48 | | 39/18/25 |
| **Wedge pressure mmHg** | 13 | | 11 |
| **PVR Wood Units** | 14.5 | | 2.8 |

NYHA: New York Heart Association; NT-ProBNP: N-terminal pro-brain natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance.

3 months showed a significant improvement in exercise capacity (NYHA class 2), a drop of N-terminal pro-brain natriuretic peptide levels from 1208 to 436 ng·L$^{-1}$, and an increase of diffusing capacity of the lung for carbon monoxide from 34 to 55% predicted. A new echocardiography again revealed a dilated right ventricle with a moderate dysfunction (TAPSE=15 mm) and a tricuspid maximal jet velocity of 3.16 m·s$^{-1}$. After 6 months a complete work-up was repeated including haemodynamic measurements (table 1): clinical, laboratory and haemodynamic data continued to improve, with all the parameters within the range of a controlled PAH, except the 6-min walking test that was not assessable due to the neurological diagnosis.

With the five cases described by Savale *et al.* [1], and the two previous case reports in the literature (and not 10 as erroneously reported by Savale *et al.* [1]), there were eight reported cases previously treated with IFN-β who developed PAH [1, 4, 5]. Meanwhile, an additional ninth case has been published by McGovern *et al.* [6]. It is interesting to note that all cases are women. Our case also illustrates the very long delay that may occur between initiation of IFN-β therapy and diagnosis of PAH (15 years in our case as compared with 4–10 years in the study by Savale *et al.* [1] and 5 years in the case from McGovern *et al.* [6]). The mild COPD diagnosed on pulmonary function tests, with minimal emphysema on the CT scan and a moderate decrease in diffusing capacity of the lung for carbon monoxide, is an unlikely explanation for the severe clinical presentation and haemodynamic parameters. However, the marked improvement after cessation of IFN-β and introduction of a double specific therapy clearly emphasises the primary influence of PAH in this patient's dyspnoea. Similarly to others, the response of our patient to PAH treatment was at the upper range to what can be expected for idiopathic PAH, as near normalisation of haemodynamic parameters is rarely achieved except for in vasoreactive cases. It is therefore likely that the interruption of IFN-β played a significant role in this improvement. However, it is as yet unknown whether PAH specific medications could be eventually stopped after a prolonged surveillance [6]. As already emphasised, it is critical for all pulmonary hypertension centres to report to pharmacovigilance networks and regulatory agencies any suspected drug-induced PAH case.

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**Suspected drug-induced PAH cases should be reported to pharmacovigilance networks and regulatory agencies** http://ow.ly/TthdY

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*From the authors:*

We read with interest the correspondence by Prella and colleagues reporting yet another case of pulmonary arterial hypertension (PAH) suspected to be induced by long-term interferon (IFN)-β therapy in a patient with multiple sclerosis. As discussed by Prella and colleagues, IFN-α and IFN-β are regarded as "possible" risk factors for PAH [1]. This was justified by the publication of case reports of IFN-induced PAH in the past decade [2–10] and the experience recently reported by the French Referral Centre for Pulmonary Hypertension [11]. Despite strong clinical and temporal suspicion, it remains a great challenge to definitively confirm the causal role of IFN in the development PAH because many patients (especially those treated with IFN-α for hepatitis C) have concomitant PAH risk factors such as portal hypertension and/or HIV infection. In these patients, IFN therapy may potentially act as an additional trigger for portopulmonary and/or HIV-associated PAH.

TABLE 1 Literature search for cases of pulmonary arterial hypertension (PAH) induced by interferon (IFN)-α and -β and confirmed by right heart catheterisation

| First author [Ref.], year | Cases n (sex) | Indication for IFN therapy | Delay in PAH diagnosis | Other PAH risk factors | Management and outcome |
|---|---|---|---|---|---|
| **IFN-β** | | | | | |
| Ledinek [4], 2009 | 1 (female) | MS | 3 years | None | Improvement on PDE-5i and ERA<br>No haemodynamic assessment during follow-up |
| Caravita [6], 2011 | 1 (female) | MS | 1 year | None | Improvement on PDE-5i<br>No haemodynamic assessment during follow-up |
| Savale [10], 2014 | 5 (females) | MS | 4–10 years | One atrial septal defect | Non-reversible cases<br>Two deaths at short term |
| Prella, 2015 | 1 (female) | MS | 15 years | None | Near normalisation of haemodynamics on ERA and PDE-5i at 6 months |
| McGovern [7], 2015 | 1 (female) | MS | 5 years | None | Reversible case at 2 years |
| Gibbons [8], 2015 | 1 (female) | MS | 3 years | None | Reversible case |
| **IFN-α** | | | | | |
| Fruehauf [2], 2001 | 1 (male) | CML | 6 months | None | Reversible |
| Jochmann [3], 2005 | 1 (female) | Melanoma | 2.5 years | None | Improvement but non-reversible at 6 months on PDE-5i |
| Dhillon [5], 2010 | 4 (3 males and 1 female) | HCV | 8–32 months | Liver cirrhosis in 3 cases | Non-reversible<br>One death |
| Anderson [10], 2014 | 1 (female) | HCV | 12 months | Advanced liver fibrosis | Improvement on ERA<br>No haemodynamic assessment during follow-up |
| Savale [11], 2014 | 48 (14 females and 34 males) | 47 HCV<br>1 CML | 6–88 months | Portal hypertension and/or HIV infection in 47 cases | Improvement on specific-PAH therapies but non-reversible cases |
| Ko [9], 2015 | 1 (male) | HCV | 2.5 years | Occurred after liver transplantation | Improvement but non-reversible at 6 months on PDE-5i, beraprost and treprostinil |

MS: multiple sclerosis; PDE-5i: phosphodiesterase-type 5 inhibitor; ERA: endothelin receptor antagonist; CML: chronic myeloid leukaemia; HCV: hepatitis C virus.