To the Editor:

Interferon (IFN)-β has been classified as a drug that is possibly associated with development of pulmonary arterial hypertension (PAH), a devastating disease that can lead to right heart failure and premature death [1]. Drug- and toxin-induced PAH is a well-known entity in the field of pulmonary hypertension (PH) since the epidemic of idiopathic PAH occurred in the central Europe, between 1967 and 1971, following the use of anorexigens. The Sixth World Symposium on Pulmonary Hypertension, based on recent data, proposed a simplified characterisation of PAH associated with drugs and toxins into two subgroups (definite and possible) to help physicians to identify drugs requiring specific surveillance. According to this framework, and supported by case series and case reports, IFN-β is classified as a drug with possible association with PAH development [2].

In the literature, there are several cases of patients with multiple sclerosis (MS) on treatment with IFN-β who were diagnosed with PAH associated with the IFN-β exposure [3–9]. The need to identify and present related cases has been highlighted [4, 5].

We report a case of a patient with MS on treatment with IFN-β who subsequently developed PAH. The initial suspicion of PAH, the subsequent diagnosis and management, and the final outcome are presented in order to underline the reversibility of PAH following IFN-β discontinuation and specific PAH therapy administration, and the emerging need to early detect similar cases.

A 32-year-old female was diagnosed with relapsing remitting MS on 2010 with an Expanded Disability Status Scale score of 1 and negative immunological indices. She had received therapy with IFN-β for 6 years when she presented to our PH clinic with a 4-month history of dyspnoea on exertion, fatigue, dizziness and episodes of presyncope. She thought her symptoms were MS-related. Her past medical history was otherwise unremarkable, with no known risk factors for PAH.

Upon admission to the hospital, in New York Heart Association functional class (NYHA-FC) III, she was unable to complete the 6-min walking test (6MWT) due to a presyncopal episode during the fourth minute of the walk.

A transthoracic echocardiography demonstrated right ventricular dilatation and systolic dysfunction, tricuspid regurgitant jet velocity of 4 m·s⁻¹, and left ventricular ejection fraction of 60%. Flattening of the intraventricular septum during both systole and diastole was also noted. High-resolution computed tomography and angiography of the lungs revealed dilatation of the right heart ventricle and an enlarged pulmonary arterial trunk (3.8 cm). There were no lung lesions nor signs of pulmonary embolism. A perfusion lung scan was unremarkable. Pulmonary function tests were normal with a mildly reduced diffusion capacity of 72% pred. Baseline blood work was normal, including thyroid function tests.

The possible causal relationship between interferon-β exposure and pulmonary arterial hypertension development requires close follow-up of patients on treatment with interferon-β http://bit.ly/2OOGSVP

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immunological tests and serology. The patient underwent right heart catheterisation (RHC) that confirmed the presence of severe precapillary PH (table 1), explaining her severely impaired functional class and the presyncopal episode during exercise.

Based on reported cases [3–9], IFN-β was discontinued and the patient received glatiramer acetate for 2 years. After a severe optic neuritis, she is currently treated with natalizumab.

In addition, upfront dual specific PAH treatment was initiated with ambrisentan and tadalafil, uptitrated to a daily dose of 10 mg and 40 mg, respectively, 2 months later [10].

The patient was followed closely, and showed gradual improvement of her symptoms and functional status. 1 year later she had a NYHA-FC of II and walked 513 m on 6MWT, while the follow-up RHC demonstrated a significant improvement to all the haemodynamic parameters (table 1). At the end of the second year, the patient’s functional status and pulmonary haemodynamics derived from a third RHC (table 1) showed maintenance of the obtained improvement. However, there was no complete reversal of PAH, and the patient remains on double specific PAH therapy 4 years after PAH diagnosis and IFN-β discontinuation.

In the recent literature, there are a few PAH cases associated with IFN-β therapy for MS, which have shown significant clinical and haemodynamic improvement following cessation of IFN-β and initiation of specific PAH therapy. PRELLA et al. [4] reported a case with marked haemodynamic improvement near normalisation 6 months after cessation of IFN-β and introduction of a double specific PAH therapy including sildenafil and macitentan. GIBBONS et al. [6] described a fully reversible case after discontinuation of IFN-β and upfront combination therapy with ambrisentan and tadalafil, with complete resolution of pulmonary haemodynamics to normal values (which was sustained even with discontinuation of PAH therapy). MCGOVERN et al. [7] also described a fully reversible case after discontinuation of IFN-β and initiation of PAH therapy with ambrisentan and sildenafil. Similarly, DEMEROUTI et al. [8] recently reported a reversible case of PAH following cessation of IFN-β and initiation of PAH therapy with ambrisentan and tadalafil. The normalisation of haemodynamic parameters and clinical condition were documented and sustained 5 months after discontinuation of PAH therapy.

However, it appears that the reversal of PAH after discontinuation of IFN-β is not always possible, while PAH can be very severe leading to death or lung transplantation. SAVALE et al. [3] reported the fatal outcome of two patients with severe PAH and a history of IFN-β therapy for MS. FOK et al. [9] reported a case where the continuation of IFN therapy together with triple specific PAH therapy, including intravenous epoprostenol, resulted in PAH worsening and pulmonary transplantation. The histopathological findings described in this case were similar to those observed in idiopathic PAH.

At present, we do not know why in some patients, we observe complete reversal of PAH following IFN-β cessation and initiation of specific PAH therapy, while in some others, this outcome does not occur, requiring continuation of PAH therapy. It is possible that the reversal of PAH following IFN-β cessation is related with the duration of IFN-β exposure, the delay of PAH diagnosis and the severity of the disease at the time of diagnosis. In the literature, the time from exposure to IFN-β to the PAH diagnosis ranged from 1 to 15 years; however, the longer exposure time was not clearly associated with adverse outcome [2–5, 8, 9].

### Table 1

Functional status and right heart catheterisation at baseline, as well as 1 and 2 years after discontinuation of interferon-β and initiation of pulmonary arterial hypertension-specific therapy

|                         | Baseline | 1 year | 2 years |
|-------------------------|----------|--------|---------|
| 6MWT m                  |          |        |         |
| NYHA-FC                 | III      |        |         |
| RAP mmHg                | 5        | 6      | 3       |
| PAP syst/diast/mean mmHg| 74/42/53 | 49/21/30 | 41/20/27 |
| PAWP mmHg               | 10       | 7      | 6       |
| CO L·min⁻¹              | 3.3      | 6.5    | 6.3     |
| CI L·min⁻¹·m⁻²          | 1.9      | 3.8    | 3.7     |
| PVR Wood units          | 13       | 3.5    | 3.3     |

Vasoreactivity testing during the first right heart catheterisation with intravenous epoprostenol up to 12 ng·kg⁻¹·min⁻¹ was negative. 6MWT: 6-min walking test; NYHA-FC: New York Heart Association functional class; RAP: right atrial pressure; PAP: pulmonary artery pressure; syst: systolic; diast: diastolic; PAWP: pulmonary artery wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance.

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Based on reported cases, following IFN-β cessation, most patients were treated with other therapies for MS; to our knowledge, until now, there have been no reports connecting PAH development with these other drugs.

PAH is a rare disease. PAH is also a rare event in patients receiving IFN therapy. A population-based study, using a large commercial insurance database, intended to determine the incidence of PAH in a patients cohort treated with IFN. They identified 20113 patients who received IFN therapy during the study period (April 2001 to December 2012); pulmonary hypertension occurred in 71 patients. Although the incidence of PAH in this population is low, in comparison with the general population it appears significant. Notably, the risk of developing PAH in patients receiving IFN therapy is several-fold higher than in the general population [11].

Finally, a recent study supports the hypothesis that MS patients who receive IFN-β therapy might be at higher risk for PAH development if they carry a pathogenic variant or sequence variant genetically predisposing to the disease. It should be noted though that these findings are based on two patients [12].

Some questions arise: are patients with MS on treatment with IFN-β “at risk” of PAH? Can IFN-β work as a "second hit" for patients prone to PAH development? Could IFN-β be upgraded to a definite risk factor for PAH in the future, depending on the available information? Certainly, at this point, we do not have enough data to answer these questions. However, there is an emerging need to follow patients on treatment with IFN-β closely, to recognise PAH symptoms early and to act accordingly. In this respect, we feel that an annual transthoracic echocardiogram and clinical assessment of all patients on IFN-β therapy might be of assistance. In this context, we should also emphasise that some symptoms of PAH (dyspnoea on exertion, fatigue and dizziness) are not specific and can be misinterpreted as MS related. Timely PAH diagnosis and effective management are both key factors for better outcome.

Our case adds to the group of reported PAH cases related to IFN-β treatment for MS, underling that PAH associated with IFN-β is not always reversible after IFN-β cessation. Moreover, there is a need to raise awareness for early detection of these cases and evaluate the patients with caution, since as mentioned, symptoms such as fatigue and dizziness could be interpreted as MS related. Finally, it is essential to report all similar cases in order to get a complete picture of IFN-β-induced PAH for future recommendations.

Anastasia Anthi1,2, Eleni Stagaki1, Loukianos Rallidis1,3, Dimitrios Konstantonis1,2, Maria-Eleftheria Evangelopoulos4, Konstantinos Voumvourakis5, Apostolos Armaganidis1,2, and Stilianos E. Orfanos1,2

1 Pulmonary Hypertension Clinic, “Attikon” Hospital, Athens, Greece. 2 2nd Dept of Critical Care, National and Kapodistrian University of Athens, “Attikon” Hospital, Athens, Greece. 3 2nd Dept of Cardiology, National and Kapodistrian University of Athens, “Attikon” Hospital, Athens, Greece. 4 Demyelinating Diseases Unit, Dept of Neurology, National and Kapodistrian University of Athens, Eginition Hospital, Athens, Greece. 5 2nd Dept of Neurology, National and Kapodistrian University of Athens, “Attikon” Hospital, Athens, Greece.

Correspondence: Anastasia Anthi, 2nd Department of Critical Care, Attikon University Hospital, 1, Rimini St, 12462, Haidari Athens, Greece. E-mail: anastasia.anthi1@gmail.com

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