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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 No haemodynamic assessment during follow-up
Caravita [6], 2011	1 (female)	MS	1 year	None	Improvement on PDE-5i No haemodynamic assessment during follow-up
Savale [10], 2014	5 (females)	MS	4–10 years	One atrial septal defect	Non-reversible cases 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 One death
Anderson [10], 2014	1 (female)	HCV	12 months	Advanced liver fibrosis	Improvement on ERA No haemodynamic assessment during follow-up
Savale [11], 2014	48 (14 females and 34 males)	47 HCV 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.

In order to provide further clinical evidence to support a causal link between IFN exposure and the development of PAH, detailed analysis of IFN-induced PAH in patients without concomitant risk factors for PAH is required, together with analysis of long-term outcomes after IFN discontinuation. Thus, the case report by Prella and colleagues and two further cases published recently are very interesting. In all three cases, severe PAH suspected to be induced by IFN-β occurred in patients without other PAH risk factors [7, 8]. The analysis of disease evolution after IFN discontinuation provides additional support for a causal role of IFN. Spontaneous and complete reversal of PAH was seen in two cases [7, 8] and in the third case, near normalisation of haemodynamics occurred after 6 months of therapy with an endothelin antagonist and phosphodiesterase-5 inhibitor.

Considering these three cases, the number of PAH cases associated with IFN-α or IFN-β exposure confirmed by right heart catheterisation and reported in the literature now total 55 and 10, respectively (table 1). Interestingly, all PAH patients exposed to IFN-β were females, and clinical and functional improvements were usually observed after IFN withdrawal. However, some patients required targeted PAH treatment. Reversible PAH has only been described in patients without concomitant PAH risk factors.

As indicated previously, initiation of IFN therapy in patients with known PAH often results in clinical and functional worsening. Interestingly, PAH worsening is usually transient even in the absence of reinforcement of PAH therapy [11]. When IFN therapy is considered mandatory in a patient with PAH, we recommend a complete baseline clinical and haemodynamic assessment, optimisation of PAH treatment prior to cautious initiation of IFN treatment, and close clinical monitoring during and after IFN therapy.

Clinical experience has been recently enriched by basic science research on this topic demonstrating that IFN is involved in both human and experimental pulmonary hypertension [12]. The effects of IFN are regulated by IFN receptor 1, and could induce IP10 and endothelin-1 release leading to pulmonary endothelial dysfunction.

In conclusion, accumulating clinical and experimental data argue for a link between IFN therapy and PAH. Awareness of drug-induced PAH allows better pharmacovigilance and reporting of possible drug-induced cases. Close interactions between drug regulatory agencies, pharmaceutical companies and healthcare professionals as well as systematic reporting of potential drug-induced PAH cases are key to provide robust information to the community [13].

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Accumulating clinical and experimental data argue for a possible causal link between IFN therapy and PAH http://ow.ly/Ttsqv

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