



## Case Report

# Interferon-Beta and Pulmonary Artery Hypertension: Case Reports and Review of the Literature

Lanzillo G<sup>1,2</sup>, Scelsi L<sup>1</sup>, Bergamaschi R<sup>3</sup>, Greco G<sup>3,4</sup>, Breviario F<sup>1,2</sup>, Turco A<sup>1</sup>, Greco A<sup>1</sup>, Oltrona Visconti L<sup>1</sup>, Ghio S<sup>1</sup>

<sup>1</sup>Division of Cardiology, IRCCS Policlinico San Matteo, Pavia, Italy

<sup>2</sup>Department of Molecular Medicine, University of Pavia, Pavia, Italy

<sup>3</sup>Multiple Sclerosis Centre, IRCCS Mondino Foundation, Pavia, Italy

<sup>4</sup>Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

\***Corresponding Author:** Stefano Ghiode, Division of Cardiology, IRCCS Policlinico San Matteo, Pavia, Italy.

**Received:** 20 December 2021; **Accepted:** 04 January 2022; **Published:** 20 May 2022

**Citation:** Lanzillo G, Scelsi L, Bergamaschi R, Greco G, Breviario F, Turco A, Greco A, Oltrona Visconti L, Ghio S. Interferon-Beta and Pulmonary Artery Hypertension: Case Reports and Review of the Literature. Archives of Clinical and Medical Case Reports 6 (2022): 388-397.

### Introduction

Interferon Beta (IFN $\beta$ ) was the first developed drug for Multiple Sclerosis (MS) treatment. Its discovery and introduction to clinical practice, revolutionized the landscape of a disease that was thought to be incurable, being the driver of a paradigm shift in MS, from symptomatic management into disease modifying long-term therapy, with a tangible change in prognosis. Although newer, more effective and easier to manage drugs are now

available, IFN $\beta$  is still widely used as a first line treatment for MS, mostly because its safety and tolerability has been well known for many years. Common side effects include injection site reactions (erythema, pain, pruritus) and flu-like symptoms such as malaise, fever, headache, myalgia, chills; those are generally reported as mild or moderate at worst, although they often hinder treatment compliance [1-4].

A rare, albeit extremely severe complication of IFN treatment is Pulmonary Arterial Hypertension (PAH), historically defined as mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg at rest, measured by right heart catheterization (RHC) [5]. Among the clinical classification of PAH, a specific category is reserved for drug- and toxin-induced PAH, which is subdivided in two groups: definite association to PAH, with data based mostly on large multicentre studies, and possible association to PAH, where correlation has been described in multiple case series. The latter category includes IFNb.

**Keywords:** Hypertention; dyspnea; Pain; Pruritus

## 1. Case Report 1

We report the case of a 31-year-old woman, who was diagnosed with Multiple Sclerosis (MS) in 2014. She was started on IFNb. Disease course was mild since then, with no evidence of disease activity, both clinically and radiologically, and very good tolerance of the drug. In early 2021, she developed progressive dyspnoea on exertion, weakness, and fatigue. She was then admitted to the Cardiology Department, where a transthoracic echocardiogram (TTE) showed pericardial effusion, hypertrophic and dilated right ventricle (RV) with mild systolic dysfunction (Tricuspid annular plane systolic excursion [TAPSE] 13 mm, Fractional Area Change [FAC] 30%), and severe pulmonary hypertension (Figure 1A).



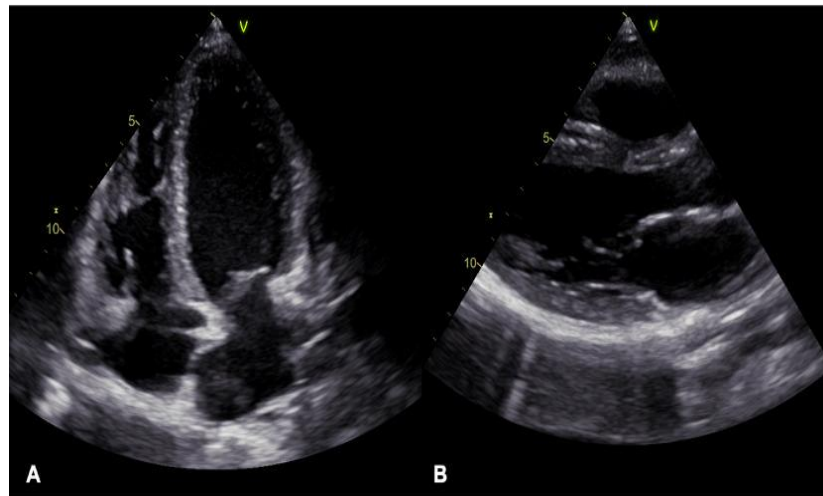
**Figure 1A:** First clinical case: patient's baseline echocardiographic findings. Panel A: apical four-chamber view. Panel B: parasternal long axis view. TTE shows pericardial effusion, hypertrophic and dilated right ventricle.

The ECG showed sinus tachycardia with right bundle branch block (RBBB). Pulmonary CT was negative for parenchymal alterations, including fibrosis or signs of pulmonary thromboembolism. Blood work was unremarkable, and ultrasound scans ruled out other causes

of right heart congestion, including liver disorders. RHC showed severe pre-capillary PAH: pulmonary artery pressure [PAP s/d/m] was 99/43/63 mmHg; pulmonary artery wedge pressure [PAWP] was 9 mmHg, cardiac index [CI] was 2 L/min/m<sup>2</sup>; pulmonary vascular resistance (PVR)

was 17 WU and right atrial pressure [RAP] was 15 mmHg. Vasoreactivity test with inhaled nitric oxide was negative (Table 1). IFNb was immediately discontinued. After IFNb withdrawal, the patient was started on double combination therapy with tadalafil (a PDE5 inhibitor) + ambrisentan (an endothelin receptor antagonist), and furosemide 25 mg OD, with progressive improvement of her symptoms. Oral

anticoagulation with warfarin was also started. After 3 months the patient was stable in WHO class IIa. TTE showed a mildly dilated RV (Right ventricular outflow tract - Parasternal long axis [RVOT-PLAX]: 26 mm vs 34 mm) with preserved systolic function (FAC 40%, TAPSE 29 mm, S' 18 cm/s) (Figure 1B).



**Figure 1B:** First clinical case: patient's echocardiographic findings at 3-months follow-up. Panel A: apical four-chamber view. Panel B: parasternal long axis view. TTE shows a mildly dilated RV with no pericardial effusion.

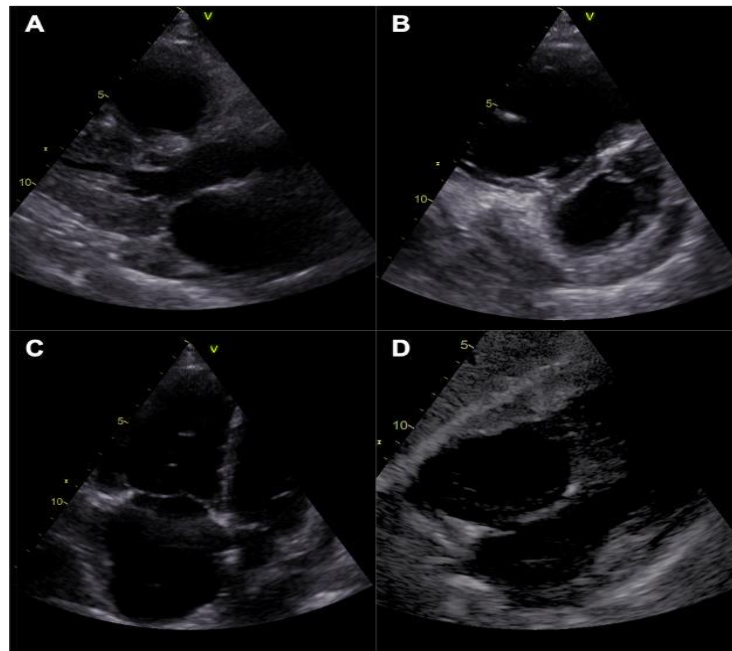
	<b>Baseline RHC</b>	<b>3-months RHC</b>
PAP s/d/m (mmHg)	99/43/63	46/19/30
PAWP (mmHg)	9	8
CI (l/min/m <sup>2</sup> )	2	3.91
RAP (mmHg)	15	6
PVR (WU)	17	3

**Table 1:** First clinical case: patient's RHC at baseline and after 3 months of dual combination therapy (tadalafil + ambrisentan) Abbreviations: PAP= pulmonary artery pressure; PAWP= pulmonary artery wedge pressure; CI= cardiac index; RAP= right atrial pressure; PVR= pulmonary vascular resistance.

At the RHC (Table 1), PAP was sharply reduced (46/19/30 mmHg), CI was normal (3.91 L/min/m<sup>2</sup>) as well as RAP (6 mmHg); PVR were 3 WU. Genetic testing for the main variants associated with PAH was performed, and it did not show any significant result. MS disease course remained stable, and a brain and spinal cord MRI confirmed disease inactivity. She was therefore switched to Dimethylfumarate, reducing diuretic therapy. Double combination therapy was confirmed.

## 2. Case Report 2

The second case report refers to a 53-year-old woman who was diagnosed with MS in 2009. She was started on IFN $\beta$  with very good tolerance of the drug until 2015, when she developed dyspnoea at rest, and fatigue. The ECG showed sinus tachycardia with signs of right ventricle overload. At TTE RV was dilated and hypertrophic, with compression of left ventricle (Figure 2A).



**Figure 2A:** Second clinical case: patient's baseline echocardiographic findings. Panel A: parasternal long axis view. Panel B: parasternal short axis view. Panel C: apical four-chamber view. Panel D: subcostal four-chamber view. TTE shows hypertrophic and dilated right ventricle, with compression of left ventricle.

At RHC precapillary PAH was observed (PAP s/d/m 84/40/56 mmHg, PAWP 4 mmHg, CI 1.24 L/min/m<sup>2</sup>, PVR 23 WU and RAP 8 mmHg) (Table 2). Double combination therapy with tadalafil and ambrisentan was started, adding low dose of frusemide and VKA antagonist. IFN $\beta$  was discontinued. After 3 months the patient referred dyspnoea in WHO class II but with worsening peripheral oedema: ambrisentan was then switched to macitentan (endothelin-2

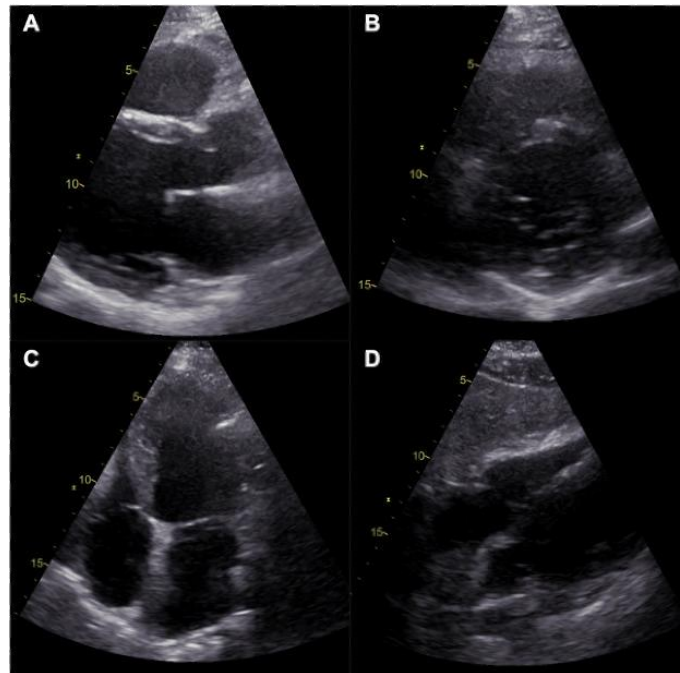
receptor antagonist). The control RHC did not show any improvement: tadalafil was therefore stopped and riociguat (soluble guanylate cyclase stimulator) was started. In June, 2017 RHC (Table 2) showed a worsening of PAH (PAP s/d/m 108/44/65 mmHg, PAWP 14 mmHg, RVP 17 UW, RAP 20 mmHg), that led to a triple combination therapy with treprostinil (prostacycline vasodilator).

	Baseline RHC	3-months RHC
PAP s/d/m (mmHg)	84/40/56	108/44/65
PAWP (mmHg)	4	14
CI (l/min/m <sup>2</sup> )	1.24	1.26
RAP (mmHg)	8	20
PVR (WU)	23	17

**Table 2:** Second clinical case: patient's RHC at baseline and after 3 months of dual combination therapy (tadalafil + ambrisentan). Abbreviations: PAP= pulmonary artery pressure; PAWP= pulmonary artery wedge pressure; CI= cardiac index; RAP= right atrial pressure; PVR= pulmonary vascular resistance.

After 2 years of relative clinical stability, the patient's conditions deteriorated to WHO class IV. Moreover, frequent infections at infusion site led to switch from treprostinil to epoprostenol (intravenous prostaglandin). Considering the young age of the patient, the absence of major comorbidities, the labile hemodynamic stability in the absence of alternative pharmacological treatments, the

patient was listed for lung transplant (National Emergency Program) on March 2019. In July, 2019 she underwent uncomplicated double-lung transplantation. At 2-year follow-up the patient was in WHO class I. TTE showed a non-dilated RV, with normal systolic function without indirect signs of pulmonary hypertension (Figure 2B).



**Figure 2B:** Second clinical case: patient's echocardiographic findings at 2-years follow-up, after lung transplantation.

Panel A: parasternal long axis view. Panel B: parasternal short axis view. Panel C: apical four-chamber view. Panel D: subcostal four-chamber view. TTE shows non-dilated, non-hypertrophic right ventricle, with no signs of compression of left ventricle.

Genetic testing for the main variants associated to PAH was performed, and did not show any significant result. MS disease course remained stable (on therapy with dimethylfumarate since 2015). Diuretic and anticoagulation therapies were stopped, while low-dose of beta-blocker was continued (bisoprolol 1.25 mg OD).

### 3. Review of literature and Discussion

We searched the literature for reports of PAH in MS patients treated with IFN-b. The first patient was reported in 2009 [6], and since then, several case reports highlighted the association, for total of 18 patients [6-17]. All patients are female, which is only partly expected, as incidence of

PAH is fourfold higher in women than in men [5], while MS incidence is threefold higher in women than in men [18]. Development of PAH seems to be a somewhat slow process, as median treatment duration before PAH presentation was 6 years, with the only notable exception being one patient [13] who developed PAH after just one year of IFN-b treatment. Cardiac measurements at presentation are generally rather severe (Table 3). Mean PAP at presentation was 57.7 mmHg ( $\pm$  16.1), mean cardiac output 3.4 L/min ( $\pm$  1.9), mean PVR 14.8 was WU ( $\pm$  9.2). This is consistent with the natural history of the disease, which can be insidious at first and manifests when pathology is well ahead of the clinical picture.

References	Number	Sex (F=female)	Age	Treatment duration (years)	Outcome	mPAP (mmHg)	Cardiac Output (L/min)	PVR (Wood Units)
Fok et al.	1	F	50	7	Lung transplantation	50	4.7	8.27
	2	F	50	7	Improved	44	2.8	15.8
Savale et al.	3	F	41	5	Improved	52	9.3	3.1
	4	F	45	6	Improved	52	3.8	11.7
	5	F	48	7	Improved	69	4.4	11.3
	6	F	39	9	Dead	70	1.5	43.3
	7	F	57	4	Dead	62	3.6	15.9
Lerche et al.	8	F	46	5	Improved	66	1.5	18.6
	9	F	53	8	Improved	52	1.5	18
Ledinek et al.	10	F	26	3	Improved	47	3.4	12.3
Caravita et al.	11	F	59	1	Improved	69	NA	NA
Prella et al.	12	F	72	15	Improved	48	2.3	14.5
Govern et al.	13	F	45	5	Improved	52	NA	NA
Piroddi et al.	14	F	47	6	Improved	109	NA	NA
Demerouti et al.	15	F	32	6	Improved	40	2.3	7.8
Gibbons et al.	16	F	45	3	Improved	47	3.25	13.5
Anthi et al.	17	F	32	6	Improved	53	3.3	13
Baghizadeh et al.	18	F	39	7	Improved	NA	NA	NA
Mean ( $\pm$ SD)			45.8 (10.7)			57.7 (16.1)	3.4 (1.9)	14.8 (9.2)

**Table 3:** Clinical and hemodynamic characteristics of patients with MS and PAH: review of the literature

Abbreviations: mPAP= mean pulmonary artery pressure; PVR= pulmonary vascular resistance.

To date, PAH occurrence in IFN $\beta$  treated patients is considered very rare. The largest study to provide reliable numbers retrospectively examined 20,113 subjects treated with interferon  $\alpha$  or  $\beta$  therapy for either hepatitis C or multiple sclerosis<sup>19</sup>. Pertinent to this article, patients with MS treated with IFN- $\beta$  were 7190; among those, 11 developed PAH. Epidemiological data show that the incidence of PAH ranges from 2.0 to 7.6 cases per million adults per year<sup>5</sup>; considering total numbers of IFN- $\alpha$  and - $\beta$  patients and correcting for follow-up years, the authors

concluded that the risk of developing PAH in patients receiving interferon  $\alpha$  or  $\beta$  therapy is several folds higher than expected compared to the general population. Moreover, the combination of such severe clinical pictures and the young age of patients elicits further considerations on whether there should be some genetic predisposition for developing PAH, which might then be triggered by IFN- $\beta$  treatment. The two patients described by Lerche et al. were screened for a panel of gene variants associated with PAH. One of them was found to have a nonsense variant in the



recently described PAH gene ATP13A320; in the other patient, a missense variant in the CYP1B1 gene was recorded, and recent studies have described its role as a mediator of toxin induced PAH21. Notwithstanding the rarity of the association, these embryonic data show promise to suggest a possible genetic predisposition in some MS patients to develop PAH during IFN $\beta$  therapy. A crucial point is whether PAH developed because of IFN is reversible or not. MS patients are generally quite young and, at least early in disease course, relatively free of disability. Therefore, a diagnosis of PAH, given its generally severe prognosis, could become a much heavier burden on their life expectancy than MS. A vast majority of the patients reported (15 out of 18) showed some improvement; the only patient who underwent lung transplantation, did not switch from IFN $\beta$  therapy until several years after PAH presentation<sup>8</sup>. Two patients in the report by Savale et al. died<sup>15</sup>, although disease course was not reported.

Most interesting aspects of our case reports derive from the great likeness of presentation and the absolute difference in terms of disease progression:

- Both patients were young female with no severe comorbidities
- Both patients had stable MS course, on IFN $\beta$  therapy for 6 years and in both cases, it was discontinued as soon as diagnosis of PAH was made
- Both patients started the same double combination therapy with ambrisentan and tadalafil
- In both patients genetic testing for the main variants associated to PAH did not show any significant result

According to our case reports, a discrepancy in terms of clinical outcomes can be noted, given the need for lung transplantation in the second patient, even in the presence of a correct diagnosis and a rapid and aggressive therapeutical work-up.

These findings, although preliminary, may suggest the presence of other modifying factors not known to date, such as new genetic variants related to PAH or polymorphisms that affect IFN $\beta$  metabolism, that may heavily interfere with the prognosis of IFN $\beta$ -related PAH.

#### 4. Conclusions

IFN $\beta$  is generally considered a very safe treatment for MS, albeit more effective drugs are available. However, it is important to raise awareness of PAH, a rare but potentially fatal complication. Close attention to early signs of PAH, such as dyspnea, reduced exercise capacity, exertional syncope, particularly in female patients after a few years of treatment exposure, is key. Timing of drug discontinuation is crucial and early treatment with PAH targeted therapies can improve functional outcome and help symptoms management and long-term prognosis. Nonetheless, a variability in clinical response has to be taken into account.

New studies are needed to foresee clinical course of these patients, and a close follow-up is mandatory.

#### References

1. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular Interferon Beta-1a for Disease Progression in Relapsing Multiple Sclerosis. *Ann Neurol* 39 (1996): 285-294.



2. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Suncutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon  $\beta$ -1a in relapsing/remitting multiple sclerosis. *Lancet* 352 (1998): 1498-1504.
3. Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): A randomised, phase 3, double-blind study. *Lancet Neurol* 13 (2014): 657-665.
4. Filipi M, Jack S. Interferons in the treatment of multiple sclerosis: A clinical efficacy, safety, and tolerability update. *Int J MS Care* 22 (2020): 165-172.
5. Thenappan T, Ormiston ML, Ryan JJ, et al. Pulmonary arterial hypertension: Pathogenesis and clinical management. *BMJ* 360 (2018).
6. Ledinek AH, Jazbec ŠŠ, Drinovec I, et al. Pulmonary arterial hypertension associated with interferon beta treatment for multiple sclerosis: A case report. *Mult Scler* 15 (2009): 885-886.
7. Piroddi IMG, Barlascini C, Nicolini A. Severe Respiratory Failure Due to Interferon Beta-Related Pulmonary Hypertension. *Am J Ther* 23 (2016): 1275-1276.
8. Fok A, Williams T, McLean CA, et al. Interferon beta-1a long-term therapy related to pulmonary arterial hypertension in multiple sclerosis patients. *Mult Scler* 22 (2016): 1495-1498.
9. Lerche M, Eichstaedt CA, Hinderhofer K, et al. Mutually reinforcing effects of genetic variants and interferon- $\beta$  1a therapy for pulmonary arterial hypertension development in multiple sclerosis patients. *Pulm Circ* 9 (2019).
10. Prella M, Yerly P, Nicod LP, et al. Pulmonary arterial hypertension in patients treated with interferon. *Eur Respir J* 46 (2015): 1849-1851.
11. Anthi A, Stagaki E, Rallidis L, et al. Is pulmonary arterial hypertension associated with interferon- $\beta$  therapy for multiple sclerosis reversible? A case study to explore the complexity. *ERJ Open Res* 6 (2020): 00328-02019.
12. Baghizadeh S, Sahraian MA, Ghahari M. Reversible Pulmonary Artery Hypertension in Association with Interferon-Beta Therapy for Multiple Sclerosis Iranian Journal of Neurology 15 (2016).
13. Caravita S, Secchi MB, Wu SC, et al. Sildenafil therapy for interferon- $\beta$ -1a-induced pulmonary arterial hypertension: A case report. *Cardiology* 120 (2012): 187-189.
14. Gibbons E, Promislow S, Davies R, et al. Reversible Pulmonary Arterial Hypertension Associated with Interferon-Beta Treatment for Multiple Sclerosis. *Can Respir J* 22 (2015): 263-265.
15. Savale L, Sattler C, Günther S, et al. Pulmonary arterial hypertension in patients treated with interferon. *Eur Respir J* 44 (2014): 1627-1634.
16. Govern EM, Judge EP, Kavanagh E, et al. Interferon beta related pulmonary arterial hypertension; An emerging worrying entity? *Mult Scler Relat Disord* 4 (2015): 284-286.
17. Demerouti E, Karyofyllis P, Athanassopoulos G, et al. Pulmonary arterial hypertension associated with interferon-beta treatment for multiple sclerosis. Case report and literature review. *Mult Scler Relat Disord* 28 (2019):273-275.
18. Bove R, Chitnis T. Sexual disparities in the incidence and course of MS. *Clinical Immunology* 149 (2013): 201-210.

19. Papani R, Duarte AG, Lin YL, et al. Pulmonary arterial hypertension associated with interferon therapy: A population-based study. *Multidiscip Respir Med* 12 (2017).
20. Barozzi C, Galletti M, Tomasi L, et al. A Combined Targeted and Whole Exome Sequencing Approach Identified Novel Candidate Genes Involved in Heritable Pulmonary Arterial Hypertension. *Sci Rep* 9 (2019): 1-9.
21. West J, Cogan J, Geraci M, et al. Gene expression in BMPR2 mutation carriers with and without evidence of Pulmonary Arterial Hypertension suggests pathways relevant to disease penetrance. *BMC Med Genomics* 1 (2008):1-11.



This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC-BY\) license 4.0](https://creativecommons.org/licenses/by/4.0/)