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# **Pulmonary hypertension reported with immune checkpoint inhibitors: a pharmacovigilance study**

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**Keywords**

## **Abstract**

Immune checkpoint inhibitors (ICI) restore immune response against cancer cells that can lead to immune-related adverse effects. While cardiovascular immune-related adverse effects are known to be associated with checkpoint inhibitors, recent case reports have raised concerns about the potential association with pulmonary hypertension (PH). By using the global pharmacovigilance database VigiBase, we investigated the onset of PH associated with ICI and propose a comprehensive description of the 42 cases of PH reported with ICI recorded in this database. Through this study and review of the cases published in the literature, we discuss the possible link between PH and ICI in the context of cancer in order to better understand this rare but potentially fatal event.

## **Introduction**

Immune checkpoint inhibitors (ICIs), targeting the programmed-cell-death-1 protein (PD-1), its ligand (PD-L1) and the cytotoxic-T-lymphocyte-associated-antigen-4 (CTLA-4), have improved clinical outcomes of many cancer types. Despite dramatic benefits, ICIs may promote inflammation in any organ and are associated with immune-related adverse events that may concern the cardiovascular and pulmonary systems [1–3]. As recent publications raised concerns about potential pulmonary arterial damage associated with ICIs [4–6], we faced a case of precapillary pulmonary hypertension (PH) occurring in a patient treated with nivolumab. We thus aimed at investigating the potential risk of PH associated with ICI cancer treatment through a descriptive analysis of the cases reported in VigiBase, the World Health Organization’s pharmacovigilance database.

We selected data of all serious adverse drug reactions reported with ICIs (anti-PD-1 agents: nivolumab, pembrolizumab, cemiplimab; anti-PD-L1 agents: atezolizumab, avelumab, durvalumab; or anti-CTLA-4 agents: ipilimumab) from January 2015 (after FDA approval of

nivolumab) to February 2021. PH cases were identified using a selection of MedDRA Preferred Terms (Medical Dictionary of Regulatory Activities): “pulmonary hypertension,” “pulmonary arterial hypertension” and “pulmonary veno-occlusive disease.”

From 73,032 ICI-associated serious adverse reactions reports recorded in VigiBase, we identified 42 PH cases including 11 PAH (26%). Among the 42 cases, 38 (90.5%) occurred with ICI monotherapy, including 21 (50%) patients treated with nivolumab (Table 1). Within the 36 reports where indication was available, ICIs were mainly prescribed for lung cancer (50.0%) and melanoma (22.2%). Median time to PH onset was 77 days after immunotherapy initiation. Cases were fatal in 31%. Among the 23 cases for whom associated treatments were available, no drugs identified as confirmed or possible risk factor for PAH according to Simonneau et al. were found [7]. About the co-reported adverse reactions and potential confounding factors, we found five cases of interstitial pneumonitis (12%), only one associated with PAH report, and two myocarditis associated with PH, but no case of paraneoplastic marantic embolism.

Despite the scarcity of PH reported with ICI, we provide the largest series through the analysis of VigiBase. PH is classified into five groups based upon etiology and mechanism [7]. Pulmonary arterial hypertension (PAH) is characterized by specific pulmonary arterial remodeling, represents the first group, and has various etiologies including drugs and autoimmune conditions. If few cases may result from concomitant myocarditis or ILD (group 2 and 3 PH), more than 80% of PAH cases were reported independently of another immune-related adverse effect. It is noteworthy that PAH is a very rare condition, whose exact incidence and prevalence remain unknown, but may be estimated around 5 cases/million.

Of note, half of cases described in our study received a monotherapy with nivolumab, one of the first approved ICI. To investigate a potential specific effect, we performed a disproportionality analysis of PH cases reported among ICI drugs. Doing so, we did not show any differential reporting between nivolumab versus other ICIs and between anti- PD-1/PDL-1 versus anti-CTLA-4 (data not shown). These results may support a possible class effect with ICIs.

Apart from our work, a case report of ICI-associated PAH has been recently published [5] (Table 2). Similar to the case that occurred in our center, the patient was a woman with connective tissue disease (CTD, i.e., lupus and Sjogren syndrome) who developed PAH in association with ICI. For Glick et al., CTD induced by immunotherapy remains the most likely explanation for the development of PAH in this context [5]. However, no case of ICI-induced scleroderma has been reported to date, while scleroderma is the leading CTD responsible for PAH. Furthermore, two recent small case series reported an increase in pulmonary artery diameter (PAD) on CT scans in, respectively, 59 and 24 predominantly lung

cancer patients treated by ICI, together with right ventricular dysfunction on echocardiography [4, 6] (Table 2). If these findings may suggest pulmonary vascular damage, PAD is actually a poor predictive sign for PH, a final diagnosis made in only two patients in this series of 59 cases, with no single report of PAH. Noteworthy, in the cohort of 59 patients, the authors did not demonstrate a significant association between PAD variation and the occurrence of other immune-related toxicities, notably pneumonitis.

**Table 1** Characteristics of ICI-exposed pulmonary hypertension cases reported in VigiBase® from January 2015 to February 2021

Characteristics	Pulmonary hypertension (n=42)
Age (years), median (P25-P75) (n=32)	69.0 (57.8–75.5)
Gender, n (%)	
Male	15 (35.7)
Female	27 (64.3)
Reporter type, n (%)	
Health professional	36 (85.7)
Other	6 (14.3)
Reporting year, n (%)	
2021	1 (2.4)
2020	8 (19.0)
2019	11 (26.2)
2018	12 (28.6)
2017	7 (16.7)
2016	2 (4.8)
2015	1 (2.4)
Reaction reported, n (%)*	
Pulmonary hypertension	30 (71.4)
Pulmonary arterial hypertension	11 (26.2)
Pulmonary veno-occlusive disease	1 (2.4)
Exposure to ICIs	
Monotherapy, n (%)	39 (92.9)
Anti-PD-1	28 (66.7)
Nivolumab	22 (52.0)
Pembrolizumab	6 (14.3)
Cemiplimab	0 (0)
Anti-PD-L1	8 (19.0)
Atezolizumab	3 (7.1)
Durvalumab	5 (11.9)
Anti-CTLA-4	3 (7.1)
Ipilimumab	3 (7.1)
Combination (nivolumab/ipilimumab)	3 (7.1)
Indication, n (%)	
Lung cancer	18 (42.9)
Melanoma	8 (19.0)
Renal cancer	4 (9.5)
Hodgkin's disease	3 (7.1)
Non-Hodgkin's lymphoma	1 (2.4)
Breast cancer	2 (4.8)
Unknown	6 (14.3)
Time to onset (days) (n=15)	77.0 (39.5–137.0)
Median (P25-P75)	5–232
Min-max	
Fatal, n (%)	13 (31.0)
Nivolumab	7 (53.8)
Durvalumab	3 (23.1)
Atezolizumab	2 (15.4)
Pembrolizumab	1 (7.7)

The two latter points may be considered as potential confounding biases for a causal link between ICI and PH occurrence, particularly in patients with lung cancer who may have chronic pulmonary condition and/or underlying autoimmunity. However, the description of our cases and the studies reported in the literature indicate that there is no significant association between previous independent risk factors for PH and the occurrence of PH under ICI treatment (Table 2).

**Table 2** Review of suspected pulmonary hypertension cases associated with ICI treatment

Study design	Patients, gender	Cancer type	ICI	Underlying autoimmunity	Pulmonary condition	Outcomes	Others IrAEs reported	References
Case report	n = 1 F	Lung cancer	Anti-PD-L1 (durvalumab)	SLE/Sjogren's syndrome overlap	Recurrent pleural effusions	1 PAH with RV failure	T1DM Thyroiditis Adrenal insufficiency	Glick et al. [5]
Cohort of patients with pre- and post-nivolumab CT-scans	n = 59, 36% F	Lung cancer	Anti-PD-1 (nivolumab)	Yes (13,6%) No (86,4%)	COPD (17%) CV disease (39%)	Median PAD enlargement Increasing of median PA/Ao ratio 2/59 PAH	No (81%) Yes (19%)	Fournel et al. [4]
Cohort of patients with pre- and post-ICI therapy echocardiograms	n = 24, 46% F	Lung cancer (92%) Melanoma (4%) Renal carcinoma (4%)	Anti-PD-1 (54%) Anti-PD-L1 (33%) Combination (13%)	Yes (14%)	No information	Increasing of median PA/Ao ratio 0/24 PAH	No (38%) Yes (42%) Pneumonitis (21%) Colitis (4%) Others (17%)	Mylvaganani et al. [6]
Pharmacovigilance study (VigiBase)	n = 42 64% F	Lung cancer (50%) Melanoma (22%) Other (28%)	Anti-PD-1 (67%) Anti-PD-L1 (19%) Anti-CTLA-4 (7%) Combination (7%)	Not reported	Pneumonia (17%) RV dysfunction (17%) Pleural effusion (8%) Pulmonary embolism (8%) Pulmonary fibrosis (8%) Myocarditis (8%)	30/42 PH 11/42 PAH 1/42 VOD	Pneumonitis (21%) Thyroiditis (10%) T1DM (4%) Thyroiditis (4%) Adrenal insufficiency (4%)	Our series*

Among all cases of suspected of pulmonary hypertension, we identified 30 cases of confirmed pulmonary hypertension and 13 cases of confirmed pulmonary arterial hypertension (3 published in the literature and 11 reported in the WHO pharmacovigilance database including the one reported by Glick et al.)

*Combination* with anti-CTLA-4; *COPD* Chronic Obstructive Pulmonary Disease; *CV* cardiovascular; *F* female; *PA/Ao ratio* pulmonary artery/aortic ratio; *PAD* pulmonary artery diameter; *PAH* pulmonary arterial hypertension; *PH* pulmonary hypertension; *RV* right ventricular; *SLE* systemic lupus erythematosus; *T1DM* Type 1 diabetes mellitus; *VOD* veno-occlusive disease

\*Including the case reported by Glick et al.

Other explanations may be proposed if we consider the role of the immune system in the development of PH as discussed in a recent review [8]. Interesting data in animal models and in PH patients have even suggested the implication of the immune checkpoint, with a decrease in PD-1/PDL-1 and CTLA-4 signaling responsible for T-reg dysfunction and PH [9, 10]. Indeed, the expression of PD-L1 in tissues represents a key mediator of tissue tolerance, by promoting inhibition of the activation and the expansion of effector T cells and the promotion of Treg differentiation and function. While blocking the PD-1/PD-L1 interaction restores immune control over infection, the complete absence of PD-L1 in experimentally infected mice resulted in their death, despite the increased antiviral function, thus highlighting the

necessary role of PD-L1, especially in chronic infection, to prevent the destruction of tissues that may occur during an overactive immune response and prevent the development of autoimmune diseases. We can expect the reverse to occur with potentially tissue destruction when this pathway is blocked. Furthermore, in a murine model for systemic sclerosis, an autoimmune condition associated with PH enhancing CTLA-4 signaling with abatacept was able to prevent PH [11]. In another experimental study of pulmonary hypertension based on T-reg lymphocyte deficiency, researchers found that the number of PD-L1 molecules was significantly reduced in the lungs and right ventricular tissue of female rats with pulmonary hypertension. The results of these studies suggest that in Treg lymphocytes, PD-L1 deficiency inhibits their suppressive functions, which leads to pulmonary bed damage and contributes to the development of PAH [10]. Checkpoint inhibitors by inducing an upturn in the tolerance of the immune system promote the activation, proliferation and differentiation of T cells which might play a role in pulmonary hypertension.

Importantly, tumor localization may favor the presence of a large number of cells overexpressing PD-L1 locally and may promote the occurrence of adverse reactions at this site rich in therapeutic targets. Indeed, there is an increased risk of ICI-induced pneumonitis in patients treated for lung cancer in comparison to melanoma patients [12, 13]. We think that this may also explain a potential relationship between vascular toxicities and ICI treatment in patients with lung cancer.

While our work provides the largest descriptive cohort of ICI-associated PH, we admit many limitations. First, under-reporting is an inherent limitation to the use of pharmacovigilance data: thus, reporting rate cannot be interpreted as real risk. Another limit is missing data, such as past medical history, complete work-up and invasive hemodynamic parameters using right heart catheterization. This is the major issue with the present report, deserving further studies. The precise identification of the mechanism is lacking to definitely confirm PAH since other etiological factors for groups 3/4 PH are usual in these patients, such as chronic obstructive pulmonary disease, obstructive sleep apnea or other sleep-disordered breathing, ILD, marantic emboli. It is relevant to note that more than 85% of the cases described were notified by health professionals, providing a medical validation of the precise diagnosis of the adverse effect. In order to improve the specificity of our case selection, we selected 3 specific PH-related terms instead of the standardized MedDRA query for PH which include less specific terms. Data about PH reversibility after ICI discontinuation or PAH-specific treatments were also frequently missing. However, among the 38 cases for which PH evolution was reported, more than 45% were reported as “not recovered,” 18% were “recovering” and only less than 10% were “recovered” at the time of the latest report. Successful rechallenge with nivolumab was also reported in two PH cases that were considered as “recovered,” with no further complication to date. One of the most relevant findings concerns the mortality rate of this peculiar and life-threatening event, with a fatal issue in about one third of the reported cases.

In conclusion, our study presents the largest series of PH cases reported with ICI and discusses the possibility of a causal link and underlying mechanisms. Apart from the predominant indication for lung cancer, which is consistent with the potential overexpression of anti-PD-1 or PD-L1 targets at this location, we did not find other pre-disposing factors in the cases described for the occurrence of this adverse reaction. Clinical studies with a complete work-up including right-heart catheterization in expert PH centers are also required to confirm and better characterize this possible association between PH and ICIs. Oncologists should consider the possibility of this serious and potentially fatal adverse event in case of unexplained dyspnea.

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## **Declarations**

Conflict of interest ATJM has received fees from Actelion and declares speaking fees from Astra-Zeneca, Sanofi-Aventis and BMS in the last 3 years. PG is a medical expert for LFB (Laboratoire Français du Biofractionnement) and has received fees from Abbvie, Actelion, Boehringer Ingelheim France, Bouchara-Recordati, Novartis, Pfizer, and Roche in the last 5 years. DM reports grants and personal fees from Actelion, grants and personal fees from Bayer, personal fees from GSK, personal fees from Pfizer, grants, personal fees and non-financial support from MSD, personal fees from Chiesi, personal fees from Boehringer, non-financial support from Acceleron, outside the submitted work. PF has received travel and accommodation fees from Actelion, Johnson and Johnson, BMS, Pfizer and Servier in the last 5 years. Other authors declare that they have no conflicts of interest.



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