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ORIGINAL ARTICLE

Identifying new drugs associated with pulmonary arterial hypertension: A WHO pharmacovigilance database disproportionality analysis

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Since the 1960s, several drugs have been linked to the onset or aggravation of pulmonary arterial hypertension (PAH): dasatinib, some amphetamine-like appetite suppressants (aminorex, fenfluramine, dexfenfluramine, benfluorex) and recreational drugs (methamphetamine). Moreover, in numerous cases, the implication of other drugs with PAH have been suggested, but the precise identification of iatrogenic aetiologies of PAH is challenging given the scarcity of this disease and the potential long latency period between drug intake and PAH onset. In this context, we used the World Health Organization's pharmacovigilance database, VigiBase, to generate new hypotheses about drug associated PAH.

Methods: We used VigiBase, the largest pharmacovigilance database worldwide to generate disproportionality signals through the Bayesian neural network method. All disproportionality signals were further independently reviewed by experts in pulmonary arterial hypertension, pharmacovigilance and vascular pharmacology and their plausibility ranked according to World Health Organization causality categories.

Results: We included 2184 idiopathic PAH cases, yielding a total of 93 disproportionality signals. Among them, 25 signals were considered very likely, 15 probable, 28 possible and 25 unlikely. Notably, we identified 4 new protein kinases inhibitors (lapatinib, lorlatinib, ponatinib and ruxolitinib), 1 angiogenesis inhibitor (bevacizumab), and several chemotherapeutics (etoposide, trastuzumab), antimetabolites (cytarabine, fludarabine, fluorouracil, gemcitabine) and immunosuppressants (leflunomide, thalidomide, ciclosporin).

Conclusion: Such signals represent plausible adverse drug reactions considering the knowledge of iatrogenic PAH, the drugs' biological and pharmacological activity and the characteristics of the reported case. Although confirmatory studies need to be performed, the signals identified may help clinicians envisage an iatrogenic aetiology when faced with a patient who develops PAH.

Protocol registration: Open Science Framework (osf.io/g2scb)

KEYWORDS
drug safety, pharmacovigilance, pulmonary arterial hypertension, respiratory medicine, vascular disease

1 | INTRODUCTION

Pulmonary arterial hypertension (**PAH**), corresponding to group 1 of the World Health Organization (WHO) clinical classification of pulmonary hypertension, is a rare and incurable disease with a prevalence ranging from 11 to 26 cases per million adults.[1] The most common symptoms are progressive breathlessness, fatigue, syncope and clinical signs of heart failure. Among the multiple identified causes of **PAH**, drugs account for approximatively 10% of cases in large registry series.[2] Since the discovery of the link between aminorex and pulmonary hypertension in the late 1960s, several other drugs have been identified as provoking, or suspected to provoke, **PAH**.[3] To date, various compounds have been associated with the onset of **PAH** including 1 protein kinase inhibitor **dasatinib**, some **amphetamine**-like appetite suppressants (aminorex, **fenfluramine**, **dexfenfluramine**, benfluorex), which have been withdrawn from the market primarily for this reason, and recreational drugs (**methamphetamine**).[1,4]

Furthermore, numerous case reports have suggested the onset or aggravation of **PAH** with other drugs and hypothesized a causative link.[4–7] However, given the scarcity of this pathology and the potential long latency period between drug intake and **PAH** onset, identifying iatrogenic aetiologies is challenging. In this context, mining large pharmacovigilance databases constituted from spontaneously reported cases of suspected adverse drug reactions (ADRs) may be an interesting way to identify drugs possibly linked to **PAH**.[8]

In this study, we used the largest pharmacovigilance database worldwide, the WHO's pharmacovigilance database, to generate disproportionality signals. All disproportionality signals were further reviewed and assessed for plausibility by experts in pulmonary hypertension, pharmacovigilance and vascular pharmacology.

What is already known about this subject

- To date, the link between dasatinib, amphetamine-like appetite suppressants or methamphetamine and the onset of pulmonary arterial hypertension has been demonstrated.
- Numerous preclinical and clinical studies have suggested a link with other drugs, but evidence is lacking.

What this study adds

- We have identified 15 new drugs likely to be related to pulmonary arterial hypertension: 4 new protein kinases inhibitors (lapatinib, lorlatinib, ponatinib and ruxolitinib), 1 angiogenesis inhibitor (bevacizumab), and several chemotherapeutics (etoposide, trastuzumab), antimetabolites (cytarabine, fludarabine, fluorouracil, gemcitabine) and immunosuppressants (leflunomide, thalidomide, ciclosporin).

2 | METHODS

2.1 | Disproportionality analysis in the WHO pharmacovigilance database

The study was an observational, post-marketing study using the ADRs reported in the WHO pharmacovigilance database, VigiBase. At the date of extraction (June 2020), >22 million of cases were reported in this database. Reports were collected from among the 134 countries participating in the WHO Programme for International Drug Monitoring since 1968.

Disproportionality analyses constitute a set of methods largely used by researchers and regulatory/drug agencies to generate *disproportionality signals*, i.e. putative links between drugs and ADRs.[9] In this analysis, we used the *Bayesian neural network method* developed by the Uppsala Monitoring Centre research team, which displays the best sensitivity and specificity among disproportionality analyses, notably for rare events.[10,11] A disproportionality signal was deemed significant if the lower boundary of the 95% credibility interval of the information component (IC025) was superior to 0.[10,12]

2.2 | Population, cases, exposure and outcomes

We first extracted from VigiBase all suspect individual case safety reports (ICSRs) of **PAH** mentioning the MedDRA Preferred Term "Pulmonary arterial hypertension".

To ensure that drugs exposures were preliminary to the onset **PAH**, all ICSRs containing a drug used to treat **PAH** (**sitaxentan**, **bosentan**, **ambrisentan**, **macitentan**, **riociguat**, **sildenafil**, **tadalafil**, **epoprostenol**, **treprostinil**, **iloprost**, **selexipag** and **nitric oxide**), a drug used in conditions associated with **PAH** (HIV, systemic scleroderma, portal hypertension, congenital heart disease or schistosomiasis) or an antecedent of **PAH** were excluded (Table S1).[13] All remaining ICSRs were included in the disproportionality analysis using the whole database as comparator (first analysis).

We anticipated that drugs already known to induce **PAH** (i.e. aminorex, **fenfluramine**, **dexfenfluramine**, benfluorex, **dasatinib**

and methamphetamine) would be associated with a significant number of reports, due to extensive media coverage, and could therefore cause a competition bias (or masking effect).[1] Indeed, drugs associated with large number of reports may hide the signals for other drugs.[14,15] Competitors were identified using the competition index at the PT level with a cut off at 5%.[16] Thus, in a secondary analysis, such drugs were removed from the dataset and we re-ran disproportionality analyses (second analysis).

Lastly, for all identified signals we performed a sensitivity analysis in modifying the comparator group to adjust for confounding induced by patients' underlying diseases and comorbidities (e.g. in comparing antineoplastic drugs against all other anticancer drugs). Methodological details are presented in supplementary material (Supplementary Method).

The protocol of the study was preregistered on Open Science Framework (osf.io/g2scb) and statistical analyses performed in Python (version 3.7.6) and R (version 3.6.2). As we used de-identified data, no ethics committee was required.

2.3 | Causality assessment

We performed a literature search to identify plausible pharmacological mechanisms for hitherto unsuspected drugs using drug names and "pulmonary arterial hypertension", "pulmonary hypertension", "vascular remodelling" and "vasoconstriction" in PubMed.

All drugs were then independently assessed for plausibility by each of the 5 authors (C.K., J.L.C., M.R., M.C.C. and D.M.) using categories adapted from the WHO causality categories (very likely/probable/possible/unlikely).[17] Criteria used to judge for causality were the signal strength (number of cases, robustness in sensitivity analyses), time to onset, evolution, patient characteristics (age, sex, underlying pathology), concomitant drugs and plausible pharmacological mechanisms. The data were synthesized and discrepancies resolved through discussion among the team.

3 | RESULTS

3.1 | Flow chart and case characteristics

We extracted 9629 ICSRs of PAH from the WHO pharmacovigilance database. After excluding cases associated with PAH treatments (i.e. cases reporting inefficacy or other adverse events), as well as patients presenting a disease known be associated with PAH, 2184 cases were included in the disproportionality analysis (Figure 1). These ICSRs were mainly reported by healthcare professionals ($n = 1891$, 86.6%), originated from France ($n = 1357$, 62%) and USA ($n = 505$,

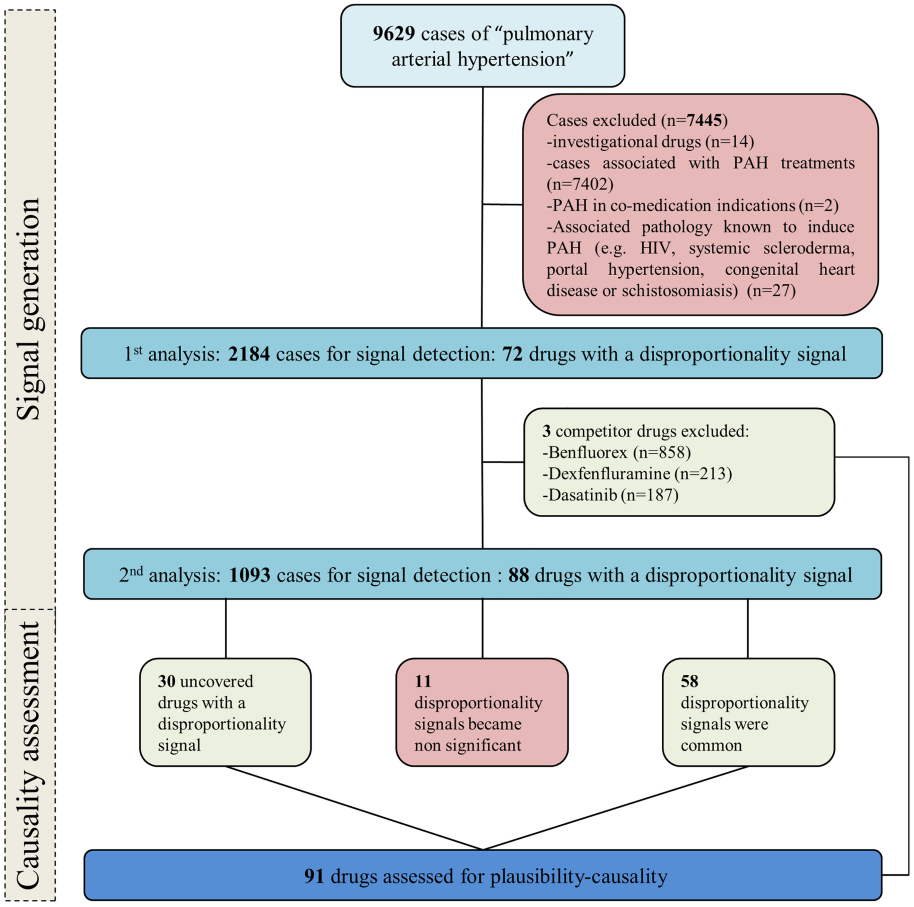

FIGURE 1 Flow chart of the study

23%), involved mostly women ($n = 1463$, 67%) and were fatal in 246 cases (11%).

3.2 | Signal generation (disproportionality analyses)

Among over 350 potentially implicated drugs, 73 displayed a disproportionality signal in the first analysis. As anticipated, large number of cases were reported with well-known drugs associated with **PAH**, such as amphetamines or **dasatinib**. After excluding the 1091 cases involving potential competitors (**dasatinib**, benfluorex and **dexfenfluramine**) the disproportionality analysis unmasked 29 new signals and 11 drugs mostly coreported with **dasatinib**, benfluorex or **dexfenfluramine** became nonsignificant (e.g. **furosemide**, **zopiclone** or **formoterol**; Figure 1). Overall, 91 drugs were assessed for plausibility. In the sensitivity analysis disproportionality signals became nonsignificant for 22 drugs, notably for antineoplastic drugs due to a higher proportion of **PAH** in cancer patients. Results of disproportionality analyses are presented in Table S2 and details on cases (age, sex, comedications, outcomes, evolution) and drug characteristics (time to onset, indication) are synthetized in Table S3.

3.3 | Causality assessment

Based on cases, drug characteristics and literature searches of putative pharmacological mechanisms, we performed a blinded evaluation for plausibility of the 91 identified disproportionality signals. The agreement between experts was acceptable (Fleiss kappa = 0.56). Among the 91 disproportionality signals, 25 were already described and considered to be very likely. Withing the remaining, 15 were quoted as probable, 29 possible and 22 unlikely (Figure 2). The main reasons for judging a drug's implication to be unlikely were the presence of an indication bias or a confounding factor (e.g. coprescription with a drug known to induce **PAH**), in utero exposure, studies and data suggesting an opposite effect on **PAH** or ruling out the link (Table S3). We notably excluded 2 **selective serotonin-reuptake inhibitors** (**paroxetine** and **sertraline**) for which most of the cases were reported after in utero exposure. A synthesis of hypothesized mechanisms by drug class is presented in Table 1.

3.4 | Characteristics of identified new signals

Altogether, 15 new drugs were identified as probable triggering factor of **PAH**. Results of disproportionality analyses and main characteristics of cases reported for these drugs are presented in Table 2. The strongest disproportionality signals were displayed by **leflunomide** (IC = 4.08 [3.54, 4.54], $n = 32$), **lorlatinib** (IC = 3.77 [2.51, 4.64], $n = 7$) and **ruxolitinib** (IC = 3.20 [2.48,3.78], $n = 19$). Median time to **PAH** onset ranged from few months (e.g. 56 days for **cytarabine** or 58 days for **ponatinib**) to several years after drug initiation (e.g. 1401 days for **leflunomide** or 462 days for **trastuzumab**). Almost all cases of **PAH** with **leflunomide** were observed with a dose of

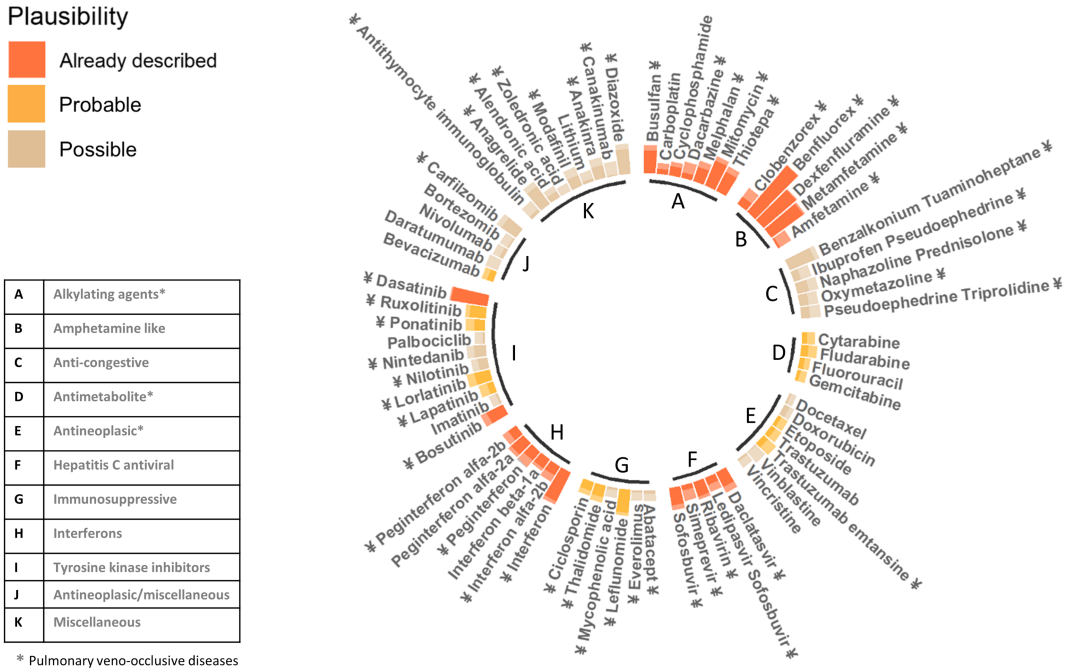

FIGURE 2 Circular bar plot presenting the results of disproportionality analyses. The bars are proportional to the magnitude of the disproportionality signals (information component values and lower 95% credibility intervals) and the colour indicates the plausibility of the signal. ¥ denotes disproportionality signals robust in sensitivity analyses

TABLE 1 Possible mechanisms in favor or against the role of identified drugs in PAH.

Drug class	Drug name	Mechanism in favour of the role of the drug	Mechanism against the role of the drug
Amphetamine-like drugs	Benfluorex Dexfenfluramine Methamphetamine Amfetamine Clobenzorex	Serotonin agonist properties.[1] Serotonin transporter substrate increasing serotonin blood concentration, contributing to vasoconstriction ($5\text{-}HT_{1B}$) and remodelling of pulmonary vasculature ($5HT_{2B}$). May induce ROS production through activation of NADPH oxidase[2]	
Tyrosin kinase inhibitor	Dasatinib	Smooth muscle cell hyperplasia and endothelial dysfunction.[3,4] Increased mitochondrial ROS production.[3,5] Src kinase inhibition (vasoconstriction and vascular remodelling)[3]	
	Bosutinib	May increase mitochondrial ROS production[6]	Frequently used after dasatinib[4]
	Ruxolitinib	Paradoxical increase in STAT3 activity (inducing proliferation and anti-apoptosis of pulmonary arterial smooth muscle cells)[7]	Used in myelofibrosis (known cause of PAH) JAK2 inhibition reduces proliferation of pulmonary arterial endothelial cells[8]
	Ponatinib	Src kinase inhibition[9]	Frequently used after dasatinib[4]
	Palbociclib		Potential role in treatment of PAH by decreasing proliferation of smooth muscle cells in idiopathic PAH with overactivation of cyclin-dependent kinases[10]
	Nintedanib		Inhibition of VEGF-R (1 and 2), PDGF-R and FGF-R (1,2 and 3) implicated in intimal and medial vascular remodelling[11] and pulmonary fibrosis[12] involved in PAH. Raf inhibitor which can reverse BMPR2 deficiency[13]
	Nilotinib	Increased mitochondrial ROS production[5]	
	Lorlatinib	2 case reports of reversible PAH after lorlatinib discontinuation with right heart catheterization[14]	
	Lapatinib	Unknown[15]	HER1/HER2 inhibitor inhibiting smooth muscle proliferation, however no benefit in PAH treatment in rat model[16]
	Imatinib		Potential role in treatment of PAH.[3] Inhibition of PDGF[16]
Hepatitis C virus antiviral	Daclatasvir Sofosbuvir Simeprevir Ribavirin	Several mechanisms could explain PAH after HCV infection and treatment: - activation of STAT-3 and NFkB by NS5A (non-structural protein of HCV)[17,18] - induction of COX-2 expression in HCV replicon-expressing cells and decrease nitric oxide synthase[18] - HCV RNA decrease during treatment could lead to rapid decrease of vasodilatory mediators[18] - HCV may reduce 5-HT blood concentration[19]	The drastic decrease of reports worldwide these last years paradoxically to the increasing number of exposed patients is in favor of a major role of the underlying pathology in PAH onset. A cohort study of 49 patients treated with hepatitis C anti-viral agents found no evidence of increased pulmonary artery pressures during treatment[20]
Alkylating agent	Busulfan Carboplatin Cyclophosphamide Dacarbazine Melphalan Mitomycin C Thiotepa	Risk factor for development of pulmonary veno-occlusive disease (PVOD), through GSH depletion, a special kind of PAH.[21] Inhibit cell proliferation, decrease of prostacyclin synthesis and limits endothelial cell repair capacity.[22,23]	

(Continues)

TABLE 1 (Continued)

Drug class	Drug name	Mechanism in favour of the role of the drug	Mechanism against the role of the drug
Immunosuppressive	Abatacept		Abatacept improves digestive involvement, prevents lung fibrosis, and attenuates PAH in SSc.[24]
	Everolimus		Inhibition of mTOR pathway has anti-angiogenic effect through downregulation of the expression of VEGF-A/VEGFR-2 and VEGF-C/VEGFR-3[25] has been used as treatment[26]
	Leflunomide	Inhibition of the src pathway, inhibition of COX-2 and dose-dependent toxicity against pulmonary endothelial cells[27]	
	Thalidomide	Endothelial cell inhibition, angiogenesis inhibition[28]	
	Mycophenolic acid		Mycophenolic acid could inhibit proliferation of endothelial cells, smooth muscle cells or fibroblasts. Reduces vascular wall thickening, improves stenosis of lumina, inhibits vascular remodeling and the development of alveolitis and pulmonary vasculitis.[29]
	Ciclosporine	Can induce endothelial damage through affecting NO function and smooth muscle cell proliferation[1]	
Platelet-reducing agents	Anagrelide		Used in polycythemia which could be a risk factor of PAH. Anagrelide is a PDE3 inhibitor which theoretically induces relaxation of smooth muscle cells, inhibits platelet aggregation and increases heart contractility.[30]
Antineoplasic	Docetaxel		Reverse pulmonary vascular remodeling in rats[31]
	Doxorubicin		Reduce pulmonary arterial wall thickness through increasing apoptosis and induce apoptosis of cultured human pulmonary artery smooth muscle cells.[32]
	Etoposide	Etoposide is a topoisomerase-II inhibitor that predominantly induces double strand breaks but also generates ROS[33]	
	Trastuzumab	Disruption of cytoskeletal microtubules and apoptosis of potentially HER2-expressing endothelial cells[34]	
	Vinblastine		
	Vincristine		
Anti-congestive	Tuaminoheptane	Similar to amphetamin like drugs[35]	
	Pseudoephedrine		
	Naphazoline		
	Oxymetazoline		
Antimetabolite	Cytarabine	Similar to alkylating agents. Case of PVOD with gemcitabine[36]	
	Fludarabine		
	Fluorouracil		
	Gemcitabine		

TABLE 1 (Continued)

Drug class	Drug name	Mechanism in favour of the role of the drug	Mechanism against the role of the drug
Proteasome inhibitor	Bortezomib		Improved PAH in pre-clinical models[37]
	Carfilzomib	Inhibition of AMPKα/mTORC1 pathways and phosphatidylinositol 3-kinase/Akt/endothelial nitric oxide synthase pathway.[38,39] Increased ROS release[40]	Improved PAH in pre-clinical models[41]
Angiogenese inhibitor	Bevacizumab	Inhibition of VEGFR-2 leading to pulmonary proliferative arteriopathy[42]	
IL-1 inhibitor	Anakinra Canakimumab		Used in Still's disease which induces PAH. IL-1R pathway is implicated in PAH pathophysiology, Anakinra and canakimumab are IL-1 inhibitors which may prevent PAH.[43]
PD-1 inhibitor	Nivolumab	Lung toxicity with checkpoint inhibitor may lead to PVOD, inflammatory PAH and increase in pulmonary arterial pressure[44,45]	
Stimulant	Modafinil		Modafinil reduces expression of endothelin-1, endothelin receptor A and KCa3.1 channel and supresses pulmonary smooth muscle cell proliferation. Expressions of Bcl-2-associated X, VEGF, TNF-α, and IL-6 are reduced in modafinil group in comparison to monocrotaline group in pre-clinical studies.[46]
Thymoregulator	Lithium		
Bisphosphonates	Alendronic acid Zoledronic acid	Zoledronic acid treatment significantly inhibited cell viability and cell migration of human umbilical vein endothelial cells, and inhibited EGFR[47]	Angiogenesis inhibitor[48]
Anti-thymocyte globulin	Antithymocyte immunoglobulin		Used in GVHD could lead to PAH[49]
CD 38 inhibitor	Daratumumab	Possible stimulation of CD38 in hypoxic pulmonary vasoconstriction[50]	Ca^{2+} release induced by Ang II is in part mediated by CD38 activation through NOX2- dependent ROS production.[50]
Interferons	Interferon alfa-2b Interferon beta-a1 Peginterferon alfa-2a Peginterferon alfa-2b	Vasospastic, procoagulant, with vasoconstrictor effects.[51] Microvascular abnormality induction such as luminal occlusion especially through IL-1 production and endothelial cell proliferation[52–54] Associated with hepatitis C infection (see hepatitis C virus antiviral) Increases serum level of endothelin-1[55]	Could induce left ventricular systolic dysfunction (secondary PAH) or interstitial lung disease[56]
Non diuretic thiazide	Diazoxide	Unknown[57]	Could reverse PAH with ABCC8 loss-of-function mutation.[58]

References of the Table are available in supplementary material.

Abbreviations: GVHD: graft versus host disease, HCV: hepatitis C virus, NS5A: Nonstructural protein 5A, SSc: Systemic sclerosis, ROS: *reactive oxygen species*, STAT-3: Signal transducer and activator of transcription 3.

TABLE 2 Results of disproportionality analyses (information component and 95% credibility intervals [CIs]), number of cases, time to PAH onset and drug dose for main signals

Drug class	Drug	Information component (95% CI)	Number of cases	Median time to onset (Q1, Q3), d	Median dose
Antimetabolite	Cytarabine	1.95 (0.78,2.78)	8	56.0 (7.0, 773.0)	3050 (2965–3135) mg/day
	Fludarabine	2.45 (1.07,3.38)	6		160 (40–200) mg/m^2
	Fluorouracil	1.58 (0.69,2.26)	13	182.0 (114.0, 311.5)	
	Gemcitabine	1.53 (0.44,2.32)	9	133.5 (45.75, 185.3)	1950 (1850–2000) mg/day
Antineoplastic	Etoposide	1.72 (0.55,2.54)	8		60 mg/kg
	Trastuzumab	1.91 (0.74,2.74)	8	562.0 (365.0, 1068.0)	346 (480–540) mg/day
	Trastuzumab emtansine	2.63 (0.89,2.71)	4	201.0 (106.0, 1125.5)	216 mg/day
Immunosuppressive	Leflunomide	4.08 (3.54,4.54)	32	1401.0 (368.0, 2238.0)	20 (20–20) mg/day
	Thalidomide	2.64 (1.79,3.30)	14	418.0 (366.0, 742.0)	50 (50–175) mg/day
	Ciclosporin	2.16 (1.31,2.82)	14		225 (212.5–237.5) mg/day
Tyrosine kinase inhibitor	Lapatinib	2.37 (1.00,3.30)	6		
	Lorlatinib	3.77 (2.51,4.64)	7	70.0 (55.0, 84.0)	100 (100–100) mg/day
	Ponatinib	3.04 (1.66,3.97)	6	58.0 (47.0, 120.5)	30 (15–45) mg/d
	Ruxolitinib	3.20 (2.48,2.78)	19	366.0 (181.0, 691.0)	20 (20–30) mg/d
VEGF inhibitor	Bevacizumab	1.79 (0.90,2.47)	13	364.0 (194.5, 725.0)	700 (525–875) mg/d

20 mg/day, lorlatinib with a daily dose of 100 mg and ruxolitinib with doses >20 mg/day.

4 | DISCUSSION

To our knowledge this is the first study that systematically retrieved and assessed all cases of PAH reported in a large pharmacovigilance database. Our approach allowed us to identify all drugs already known to induce PAH and 43 new signals, of which 15 were considered probable and 28 possible. Notably, we identified 4 protein kinase inhibitors (lapatinib, lorlatinib, ponatinib and ruxolitinib), 1 angiogenesis inhibitor (bevacizumab), several antimetabolites (cytarabine, fludarabine, fluorouracil and gemcitabine) and chemotherapeutics (etoposide and trastuzumab) and some immunosuppressants (leflunomide, thalidomide and ciclosporin). Such signals represent plausible ADR if one considers our current understanding of iatrogenic PAH, biological and pharmacological drug activity and reported case characteristics. However, these assumptions are based on the available literature, and the exact mechanisms remain to be further explored.

Understanding the mechanisms of iatrogenic PAH not only is important for exposed patients but also makes it possible to study how certain environmental factors can precipitate the onset of the disease in susceptible individuals.[6,18] While the exact mechanisms underlying the onset or aggravation of PAH are largely unknown, there is evidence that most of the known and newly identified drugs in this study may participate in the key cellular mechanisms leading to pulmonary vascular remodelling in PAH.[19] Endothelial dysfunction is the main evoked mechanism and has been hypothesized to be the cause of PAH triggered by chemotherapeutics, antimetabolites and alkylating agents but also by immunosuppressants and interferons (which also display direct vasoconstrictive effects).[20–23] Vasoconstrictive properties are also shared by several drugs through serotonin receptors, as amphetamine-like drugs, or through indirect pathways like cyclo-oxygenase-2 inhibition by leflunomide or Src inhibition by dasatinib and bosutinib.[5,24] Increasing reactive oxygen species production, which has been implicated in hypoxic pulmonary hypertension, is also a probable additional mechanism for several drugs such as interferons or tyrosine kinases inhibitors.[24,25] Lastly, angiogenesis impairment, dysregulation of the immune system and increasing proliferation/survival of pulmonary arterial smooth muscle cells have been highlighted for amphetamines and bevacizumab.[26,27] Overall, the diversity of hypothesized mechanisms and the very low proportion of patients developing PAH underly the difficulty to predict lung vascular toxicity of a drug and the necessity to lead further studies to identify clinical, biological and genetic factors driving PAH individual susceptibility.

Preclinical experiments are a valuable tool to further study drug contributions to PAH pathogenesis. The development and the extrapolation of results obtained in animal experiments is, however, challenging in PAH, due to the absence of animal models that reproduce the full spectrum of the human disease, and due to interspecies differences in drug metabolism and response.[19] For example, several experiments failed to reproduce PAH with well identified drugs such as aminorex or fenfluramine.[28,29] Nevertheless, these experiments, sometimes complemented by the use of human tissue samples from PAH patients and human primary cells, are indispensable to

understand the mechanisms of drug provoked **PAH** and have proven their importance in the exploration of recent signals of **PAH**, such as with **dasatinib** or **leflunomide**.[24,30,31]

Furthermore, the considerable advances in bioinformatic and machine learning in recent years makes it possible to mine drug, disease or *-omic* databases to find new links between drugs and **PAH**.[32,33] Combining these data with **PAH** registries, pharmacovigilance databases or epidemiological studies may represent promising approaches to discover common pathways in drug-associated **PAH** and to predict pulmonary vascular toxicities of newly marketed drugs.[34–37]

Risk assessment and identification of susceptible individuals are challenging in multifactorial and rare diseases such as **PAH**. Indeed, even in larger nationwide healthcare databases, power is insufficient to perform robust pharmacoepidemiological studies in **PAH**. However, the recent advances in common data models to create platforms allowing international collaborations across different databases at a regional scale, such as the Exploring and Understanding Adverse Drug Reactions (EU-ADR) project, the Observational Medical Outcomes Partnership (OMOP) experiment, or the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) will allow sufficient power to be reached to study rare diseases.[38–41] In addition, the methodological improvements in pharmacoepidemiological methodology to generate signals from healthcare databases or for risk quantification, notably through case-based methods, may in the future make it possible to study rare ADR.[42–44]

The ICSRs aggregated in the WHO pharmacovigilance database are spontaneously reported by healthcare professionals and patients in 134 countries around the world. This system increases power to detect scarce safety signals, but also suffers from heterogeneity in reported cases, regional drugs utilization and pharmacovigilance systems. Indeed, selective reporting of ADR and the lack of clinical data to ensure the validity of such reactions could result in misclassification of **PAH** among other PH aetiologies (e.g. when the results of right heart catheterization are missing).[9] Despite these biases, we were able to identify all drugs already known to induce **PAH**, which could be considered as positive controls. Moreover, most of the cases were reported by healthcare professionals and in a previous study we found that 75% of the **PAH** cases reported to the French pharmacovigilance network were confirmed by right heart catheterization.[45] While we tried to minimize some bias by excluding competing drugs in the second analyses, we cannot exclude that the results of disproportionality analyses may also be influenced by the extent of use of a drug, media coverage or the severity of the reaction. We also recognize that the pulmonary vascular toxicity of a drug depends on several factors (e.g., dose, sex, duration of exposure, age) and we may have incorrectly judged signals as unlikely when some benefit has been demonstrated in a study. However, we have deliberately adopted this strategy to limit the generation of false safety alerts and these judgements may change as knowledge about these drugs accumulates. Although we tried to minimize some bias by asking experts to individually judge signal plausibility, we also recognize that expert judgements are subjective and may be influenced by previous knowledge on drugs or **PAH**, and cognitive bias. Finally, the signal detection described in this work does not allow to quantify the risk of drug-induced **PAH**. Purpose-designed pharmacoepidemiological or preclinical studies are now required to confirm these possible relationships between drugs and **PAH** onset. Until then, we advise clinicians to be particularly attentive to these drugs when faced with **PAH** and to report cases to the pharmacovigilance systems.

In conclusion, we have found several drugs that were previously not known to be associated with increased reporting of **PAH** in the WHO pharmacovigilance database. Notably we identified new protein kinase inhibitors, one angiogenesis inhibitor, several chemotherapeutics and antimetabolites, and several immunosuppressants, most of which have a plausible pharmacological mechanism. Although confirmatory studies need to be performed, the signals identified may help clinicians envisage an iatrogenic aetiology when faced with a patient who develops **PAH**.

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The data supplied to VigiBase come from a variety of sources and the likelihood of a causal relationship is not the same in all reports. The information does not represent the opinions of the UMC or the World Health Organization.

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COMPETING INTERESTS

Dr Roustit reports grants from United Therapeutic outside of the submitted work. Dr Montani 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 nonfinancial support from MSD, personal fees from Chiesi, personal fees from Boerhinger, nonfinancial support from Acceleron, and personal fees from Incyte Biosciences France, outside the submitted work. Dr Humbert reports personal fees from Acceleron, grants and personal fees from Actelion, grants and personal fees from Bayer, personal fees from GSK, personal fees from Merck, personal fees from Novartis, personal fees from AstraZeneca, and personal fees from Sanofi, outside the submitted work. Dr Chaumais reports personal fees from Bayer outside the submitted work. Dr Guignabert report grants from Acceleron, Janssen and Merck outside from the submitted work and personal fees Merck. Dr Khouri, Cracowski, Hlavaty have nothing to disclose.

CONTRIBUTORS

Charles Khouri: conceptualization, methodology, investigation, formal analysis, writing—original draft, writing—review and editing; Alex Hlavaty: investigation, formal analysis, writing—original draft; Matthieu Roustit, Jean-Luc Cracowski, David Montani, Christophe Guignabert, Marc Humbert, Marci-Camille Chaumais: writing—review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from VigiBase. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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