Drug-Induced Pulmonary Arterial Hypertension: a Review.

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Drug-induced pulmonary arterial hypertension: a review

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Abstract Pulmonary arterial hypertension (PAH) is a subgroup of PH patients characterized hemodynamically by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and a PVR >3 Wood units (WU) in the absence of other causes of pre-capillary PH. According to the current classification, PAH can be associated with exposure to certain drugs or toxins such as anorectic agents, amphetamines, or selective serotonin reuptake inhibitors. With the improvement in awareness and recognition of the drug-induced PAH, it allowed the identification of additional drugs associated with an increased risk for the development of PAH. The supposed mechanism is an increase in the serotonin levels or activation of serotonin receptors that has been demonstrated to act as a growth factor for the pulmonary artery smooth muscle cells and cause progressive obliteration of the pulmonary vasculature. PAH remains a rare complication of several drugs, suggesting possible individual susceptibility, and further studies are needed to identify patients at risk of drug-induced PAH.

Keywords Pulmonary hypertension · Drug-related · Drug · Pulmonary arterial hypertension

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Introduction

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). Pulmonary arterial hypertension (PAH) is a subgroup of PH patients characterized hemodynamically by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mmHg, and a PVR >3 Wood units (WU) in the absence of other causes of pre-capillary PH such as lung diseases, CTEPH, or other rare diseases [1]. PAH leads to an increase in pulmonary vascular resistance, right-sided cardiac failure, and subsequently to death [2]. In the recent classification of PH by European Society of Cardiology (Table 1), PAH is defined as "group 1" and can be idiopathic, heritable, or associated with different conditions, including connective tissue disease, congenital heart disease, HIV infection, portal hypertension, and also exposure to toxins/drugs [3]. All these subgroups of PAH share common alterations in the signaling pathways and broadly similar histological findings, i.e., intense remodeling of non-muscularized pulmonary arteries [4]. The first "epidemic" of drug-induced PAH (DIPAH) occurred in 1965 in Switzerland, Germany, and Austria and was associated with aminorex intake, an anorexic agent [5, 6]. Eventually, with the improvement in awareness and recognition of the DIPAH, it allowed the identification of additional

Table 1 Comprehensive clinical classification of pulmonary hypertension: 1. Pulmonary arterial hypertension

1 Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1′.1 Idiopathic
1′.2 Heritable
1′.2.1 EIF2AK4 mutation
1′.2.2 Other mutations
1′.3 Drugs, toxins, and radiation induced
1′.4 Associated with:
1′.4.1 Connective tissue disease
1′.4.2 HIV infection
1″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis/or hypoxia
3. Pulmonary hypertension due to lung disease and/or hypoxemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstruction
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenosis
4.2.5 Parasites (hydatidosis)
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, oozing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Table 2 Risk level of drugs and toxins known to induce PAH

Definite	Likely	Possible
• Aminorex	• Amphetamines	• Cocaine
• Fenfluramine	• Dasatinib	• Phenylpropanolamine
• Dexfenfluramine	• L-tryptophan	• St John's Wort
• Toxic rapeseed oil	• Methamphetamines	• Amphetamine-like drugs
• Benfluorex		• Interferon-α and -β
• Selective serotonin reuptake inhibitors[a]		• Some chemotherapeutic agents such as alkylating agents (mitomycin C, cyclophosphamide)[b]

[a] Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors

[b] Alkylating agents are possible causes of pulmonary veno-occlusive disease

drugs associated with an increased risk for the development of DIPAH. The drugs and toxins are broadly classified into three categories based upon their risk of inducing PAH (Table 2): [3]

- Definite: aminorex, fenfluramine, dexfenfluramine, toxic rapeseed oil, selective serotonin reuptake inhibitors (SSRI), or benfluorex;
- Likely: amphetamines/methamphetamines, dasatanib, or L-tryptophan;
- Possible: cocaine, phenylpropanolamine, chemotherapeutic agents such as alkylating agents (mitomycin C, cyclophosphamide), or interferon alpha/beta.

The identification of drugs and toxins as risk factors for PAH poses a great challenge to the physician. In this review, we will summarize the current knowledge and recent advances on drug-induced PAH.

Pathogenesis

PAH is a complex process with progressive vasculopathy and broad imbalance between vasodilators, such as nitric oxide and prostacyclin, and vasoconstrictors like endothelin-1 and thromboxane A_2. The imbalance likely precedes the development of cellular changes and aberrant cellular proliferation [3, 4].

There have been multiple classes of drugs associated with development of PAH. The exact mechanism is unclear, but interaction between these drugs and serotonin transporter in pulmonary vasculature seems to play an important role. The interaction and uptake of multiple drugs increases proliferation of pulmonary artery smooth muscle cells (PASMC) and causes pulmonary vasoconstriction that may promote remodeling in the pulmonary arteries. Abnormal proliferation of PASMC is the earliest pathophysiological feature of vascular remodeling, which leads to muscularization and medial hypertrophy in pulmonary arteries [7]. Further, migration of smooth muscles between endothelium and internal elastic lamina leads to occlusive changes. In the advanced irreversible stages, disorganized proliferation of cells, fibroblasts, and macrophages leads to formation of a complex lumen-obliterating plexiform lesion that is commonly seen in patients with severe PAH. Additionally, abnormal proliferation and differentiation of fibroblasts and increased extracellular matrix deposition caused by several drugs could obliterate pulmonary arteries and leads to development of PAH [7].

Anorectic agents

Anorectic agents are dietary supplements or drugs that suppress appetite, hence leading to weight loss. Drugs like aminorex, fenfluramine, and benfluorex are the anorectic agents, and have been associated with PAH. These drugs have been associated with the very first outbreak of PAH in Europe as early as 1967 [6]. Almost 60% of patients during this PH outbreak were found to have a history of aminorex intake. It was reported to be associated with plexogenic pulmonary arteriopathy causing pre-capillary vascular obstruction and eventually lead to the development of right ventricular failure in 50% of the patients at 10-year follow-up. The patients usually presented to the physician within 1 year of symptom onset and had progressive worsening of disease and hemodynamics with an average survival of around 3.5 years after initial diagnosis [8]. On the contrary in the study, 12 out of 20 patients had improvement in the hemodynamics after discontinuation of drug and PAH appeared to be reversible. It has been proposed that they modify serotonin (5-HT) pathway by altering serum 5-HT levels, stimulating pulmonary artery smooth muscle cell growth, and also altering 5-HT transporter expression [9–11]. Interestingly, during the animal experiments, investigators failed to elicit aminorex-induced PH. Hence, given the different survival and disease progression patterns with lack of reproducibility in animal models, a genetic predisposition for PAH development was proposed.

Post epidemic, it was withdrawn from European market in 1972 and is currently under the list of illegal Schedule I drugs in USA. It was never available legally in US market but another agent, 4-methyl-aminorex, a central stimulant that can be easily synthesized from over the counter diet pill; phenylpropanolamine has been reported to cause similar clinical symptoms and pulmonary vasculopathy [12].

Fenfluramine

Fenfluramine is an anorectic agent that was part of anti-obesity medication in combination with phentermine. It was introduced in the US market in 1973 and withdrawn in 1997 due to reports of pulmonary hypertension. It has a racemic form, dexfenfluramine, which potentially causes vasculoproliferative effects on pulmonary vasculature by affecting the serotonergic pathways [11, 13, 14]. An active metabolite of dexfenfluramine is a 5-HT 2B receptor agonist and can activate 5-HT 2B receptor that is required for PAH development [15]. Fenfluramine and pergolide have also been shown to cause inhibition of voltage-gated K [+] channels in pulmonary arterial smooth muscle cells, leading to vasoconstriction. They inhibit serotonin reuptake that can lead to elevated plasma serotonin levels following their use and are also believed to interact with serotonin transporters in the lung, thereby increasing extracellular serotonin [16].

Amphetamines

Amphetamines were first synthesized in the late 1900s and marketed for treatment of asthma and rhinitis in 1920s. Eventually, it became a prescription drug, and by 1970 it fell under the regulation of the controlled substance act. Today, amphetamines are prescribed widely for the treatment of narcolepsy, ADHD, and treatment-resistant depression. However, illegal use of amphetamine and its derivative has become a major health problem. By 2004, rates of methamphetamine abuse reached as high as 2.2% in western and northern US states [17].

Amphetamines, methamphetamines, and cocaine are pharmacologically and structurally similar to fenfluramine and are considered to have Similar risk of DIPAH as reported in several case reports [18–21]. In a retrospective study, Chin et al. demonstrated the effect of stimulants to cause idiopathic pulmonary arterial hypertension. The authors analyzed the proportion of stimulant use in 340 patients with PAH. They revealed that 28.9% patients with idiopathic PAH had history of stimulant exposure compared to 3.8% of patients with PAH and other risk factors and 4.3% of patients with chronic thromboembolic PH. They concluded that patients with idiopathic PAH are 8–10 times more likely to have used stimulants than patients with other forms of PH [22]. Experimental data suggest that alterations in serotonin transporters (SERT) expression could play a role in development of PH. Activation of serotonin receptor plays an important role in proliferation of epithelial cells and development of PAH. Furthermore, serotonin induces proliferation of PASMC and adventitial fibroblasts. Though amphetamines and derivatives are potent norepinephrine and dopamine transport substrates compared to their activities on serotonin transporters (SERT), higher doses of METH have preferential interaction with SERT in vivo as shown by Rothman et al. [23]. These studies highlight the importance of recognizing widespread abuse of methamphetamines and obtaining an unbiased detailed history when evaluating patients with PAH.

Selective serotonin reuptake inhibitors (SSRIs)

Depression is widely prevalent throughout the world and affects 6.7% of all US adults [24]. SSRIs are considered first-line therapy for pharmacologic treatment of depression. Hypothetically, they can inhibit serotonin reuptake in the lung vasculature and lead to elevated serotonin levels following their use that play a role in PAH development. Dhalla et al. performed a population-based, nested case–control study using healthcare databases in Ontario, Canada. They observed that SSRI use was associated with an increased risk of PAH requiring pharmacologic treatment. The most common used SSRI in their cohort was citalopram. However, they attributed these findings to confounding variables including the high prevalence of psychological disorders in patients with PAH. They did not observe association between use of non-SSRI antidepressant and the risk of PAH [25].

Pregnancy is considered to be a period of high stress and antidepressants are usually not discontinued. SSRI use in pregnancy was noted to be associated with increased risk of persistent pulmonary hypertension of the newborn (PPHN). In the earlier report by Chambers et al., a total of 377 women had offspring with PAH, and 14 were using SSRI after 20 weeks of gestation [26]. Huybrechts et al. recently looked at the association between SSRI use during pregnancy and the risk of PAH in Medicaid population. They enrolled a total of 3,789,330 pregnant women in between 2000 and 2010. Out of these, 102,179 (2.7%) used an SSRI and 26,771 (0.7%) a non-SSRI antidepressant during pregnancy. After controlling for confounding factors, they observed that SSRI exposure during the late pregnancy (after 20 weeks) was associated with an increased risk of PAH. However, the absolute risk was small, and the increased risk appears more modest than suggested by Chambers et al. They also observed no increased risk of PAH with non-SSRI drug use [27].

Dasatanib

Tyrosine kinase inhibitors (TKIs) that target BCR-ABL are the mainstay treatment for chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) [28, 29]. This class of drugs includes first-generation imatinib and second-generation dasatanib and nilotinib. Imatinib also inhibits platelet-derived growth factor (PDGF) that has been demonstrated to be involved in the development of PAH and is currently being investigated as a potential treatment for PAH. Dasatinib is a second-generation TKI with a markedly higher affinity for BCR/ABL kinase (~300 times compared to imatinib) and also inhibits a number of different kinases including the Src and Eph family. Dasatinib is reserved for patients with imatinib-resistant CML, and recent data suggest that it might have better efficacy than imatinib for newly diagnosed CML. There have been multiple cases of PAH reported with the use of dasatanib [30–32].

Seven years following the first regulatory approval of dasatinib, BMS reported 41 cases of PAH in patients receiving dasatinib confirmed by right heart catheterization (RHC) [33]. Dasatinib dose usually ranged from 20 to 150 mg/day. The majority of dasatinib-induced PAH cases were females (62%) and the median age was 52 years (17–74 years). The duration of dasatinib treatment before the recognition of PAH in these cases ranged from 1 week to 75 months (mean 32.7 months; median 31.5 months). Patients most commonly presented with dyspnea, fatigue, and fluid retention. Unique to dasatinib-induced PAH, is its atypical nature and reversibility. The symptoms seem to improve after discontinuation of dasatinib suggesting that dasatinib does not cause permanent vascular changes, and it is recommended that these patients should not be prescribed dasatinib in future [33, 34]. The exact mechanism of dasatinib-induced PAH is not well understood and it is unclear why drugs in the same class have opposite effects. The most possible explanation for variable effect is so-called “off-target effects” of dasatinib that arise due to lack of selectivity of dasatinib for the vast majority of kinase and non-kinase molecules as highlighted by Mansoni et al. [34]. A broad spectrum of inhibited targets may play a role in this unusual side effect. c-Src tyrosine kinase (TK) is abundantly expressed in vascular tissue and appears to play a role in vasoconstriction and muscle proliferation. The non-specific inhibition of this class of TK could play a crucial role in development of PAH associated with dasatinib and would be of interest to investigate in future. It has also been suggested that dasatinib may promote PASMC proliferation by triggering persistent PASMC depolarization [35]. Nonetheless, complex pathways mediate this process and further studies are needed to fully understand the underlying mechanisms.

L- tryptophan

L-tryptophan is one of the standard 22 amino acids and is an essential amino acid in the human diet. Ingestion of L-tryptophan containing preparations (LTCP) was historically associated with eosinophilia-myalgia syndrome (EMS) [36]. LTCP ingestion is also associated with PAH development that is usually a component of EMS. Open lung biopsy when performed in these patients revealed extensive arteriopathy compatible with other PAH [37]. In some patients, PAH regressed with discontinuation of LTCP and administration of oral steroids. Hertzman et al. hypothesized that LTCP had several chemical impurities that could lead to EMS and PAH [38]. More recently, Smith et al. showed ingestion of large doses of tryptophan was proven to induce metabolite formation that may interfere with normal histamine degradation and development of EMS [39].

Chemotherapeutic agents

Alkylating agents were the first anticancer drugs developed and are a diverse group of agents containing six major classes: nitrogen mustards (chlorambucil, melphalan, cyclophosphamide, and ifosfamide), aziridines (thiotepa), alkyl sulfonates (busulfan), epoxides, nitrosoureas (carmustine), and triazene compounds (dacarbazine and temozolomide) [40]. The alkylating agents are frequently used in combination therapy to treat a variety of types of cancer including hematological and solid malignancies [40]. The primary dose-limiting toxicity is suppression of bone marrow function, and to a lesser degree, the intestinal mucosa with other organ systems also affected contingent on individual drug, dosage, and duration of therapy. Interstitial pneumonitis and pulmonary fibrosis are the most common pulmonary toxicities in association with alkylating agents [40]. Rarely, alkylating agents represent a risk factor for the development of pulmonary veno-occlusive disease (PVOD) [41]. PVOD is an uncommon form of PAH, accounts for about 10% of PAH cases [42]. PVOD is characterized by progressive obstruction of small pulmonary veins and a dismal prognosis. Limited case series have reported a possible association between different chemotherapeutic agents and PVOD [41]. PVOD may be a consequence of the toxic metabolites of antineoplastic chemotherapy damaging pulmonary venule endothelium. The vast majority of reported cases were in bone marrow transplant patient. Ranchoux et al. reviewed all cases of chemotherapy-related PVOD in the French PH registry network. Between 2004 and 2103, 27 cases of chemotherapy-induced PVOD were identified; 10 of them had severe PAH. Exposure to alkylating agents was observed in 83.3% of cases, mostly represented by cyclophosphamide (43.3%) followed by mitomycin (24.3%) and cisplatin (21.6%). Fifty-four percent of the patients received

additional radiation therapy. Allogeneic stem cell transplantation was proposed in 21.6% of cases. In three different experimental animal modules, cyclophosphamide induces PAH by progressive vascular injury as well as contributing to vascular remodeling and progressive interstitial fibrosis. Additionally, most of the individual case reports of PVOD in the literature were in bone marrow transplant patients who received multiple chemotherapy regimens. Henceforth, it is difficult to identify a specific association between alkylating agents and PVOD. Bleomycin carmustine (BCNU), procarbazine, and busulfan are also thought to be related to PVOD and PAH [43–46].

Interferon-associated PAH

The interferons (INFs) comprise an evolutionary conserved family of proteins that participate as extracellular messengers in a wide variety of response, including antiviral, antiproliferative, immune-modulatory, and developmental activities that act to maintain homeostasis and in-host defense [47, 48]. Type 1 INFs includes interferon-α (INF-α) and interferon-β (INF-β); are synthesized by many cell types following viral infection. They are distinguished from another glycoprotein called interferon-γ (INF-γ); sole member of type II interferon that is produced by activated natural killer (NK) cells thus appears after the induction of adaptive immune responses.

INF-α has been used in the treatment of hepatitis viruses, as well as several cancer types such as chronic myeloid leukemia, renal cell carcinoma, and melanoma [48]. The side effects of INF-α vary from mild transient flu-like symptoms to more serious effects, such as cardiac arrhythmias, cardiomyopathy, renal and liver failure, polyneuropathy, and myelosuppression [49]. Several pulmonary toxicity have been reported in association with INF-α including asthma exacerbation, pleural effusion, sarcoidosis, cryptogenic organizing pneumonia, and bilateral pulmonary infiltrates. There have been multiple reports of PAH in patients treated with INF-α for viral hepatitis, and CML [50–52]. Dhilon et al. reported four cases of PAH occurring in patients treated with INF-α for hepatitis C infection [50]. In all those cases, PAH was noted to be severe symptomatic and irreversible despite discontinuation of INF. Symptoms started 8 months–3 years after initiation of INF therapy. It was hypothesized that INF-α induces local release of cytokines and arachidonic acid metabolites that promote further smooth muscle contraction, resulting in a marked transient but reversible increase in the pulmonary vascular resistance. Over a prolonged period of time, this phenomenon may promote arterial smooth muscle hypertrophy that may lead to irreversible pulmonary artery hypertension. Additionally, HCV itself has been reported to cause an occult inflammatory reaction in pulmonary airspace that may predispose to pulmonary hypertension. Henceforth, it was suggested that INF-α accelerates the process of pulmonary hypertension that may be initiated by HCV or cirrhotic complications [50]. It has also been suggested that INF-α induces PAH by increasing the pulmonary vascular permeability through the activation of thromboxane B cascade [53]. There has been a report of a patient with melanoma who developed irreversible PAH after 30 months of INF-α and was successfully treated with sildenafil. Thus, PDE-5 inhibitors may be effective in PAH associated with interferon treatment. However, it is worth to mention that these patients were not tested genetically for hereditary causes for PAH.

Recombinant INF-β is approved for the treatment of relapsing-remitting multiple sclerosis. Up to date, there are only two cases of patients with multiple sclerosis who have developed PAH after INF-β therapy and could be incidental [54, 55]. In both cases, PAH was severe and resolved with sildenafil therapy.

Miscellaneous drugs

Sofosbuvir-induced PAH

Sofusbuvir is a selective, nucleotide inhibitor of RNA-dependent polymerase and one of the direct antiviral agent (DAA) approved for treatment of hepatitis C and is now the standard of treatment. SOF-based regimen is very well tolerated with excellent safety profile against all HCV genotype 1 to 6 [56]. SOF-based treatment has established an excellent clinical efficacy with sustained virological response (SVR) in randomized controlled trials even in old patients, patients with advanced liver disease, and those who failed previous treatment with DAA [57–59].

A recent study reported two patients being treated with SOF that developed or had worsening of pre-existing PAH. The development of clinical PAH was noted within 2–6 months after SOF therapy. They concluded that unusual severity at presentation (WHO functional class IV and low cardiac output), sub-acute presentation with 2–6 months, timing of events, rapid deterioration, and stable underlying comorbidities suggest a strong chronological link between PAH and SOF [60]. Baumann et al. reported another case of fulminant hepatic failure and pulmonary hypertension in patient treated with SOF [61].

The mechanism of SOF-induced PAH is unclear. It is postulated that suppression of HCV viral replication is achieved at the cost of acute decrease in vasodilators, which may exacerbate prior stable PAH or preclinical PAH. Until more data is available, regular monitoring may be offered to patients with stable PAH or PAH-related risk factors being treated with DAA. Development of PAH in this population should prompt urgent referral to PAH expert center and should be reported to better understand the association.

Leflunomide-induced pulmonary hypertension

Leflunomide (LFN), a disease-modifying anti-rheumatic drug, has been shown to be effective in the management of rheumatoid arthritis (RA). Although a small percentage of patients with RA develop systemic arterial hypertension while taking LFN, no other serious cardiovascular adverse reactions have been reported [62]. In 2004, first case of LFN associated PAH was reported in a patient who has recurrent appropriately treated PE with negative V/Q scan [63]. PAH developed within 13 months of initiation of LFN and resolved 1 month after withdrawal of LFN. Paulino et al. has described another possible case of LFN-induced PAH in the absence of alternative causes confirmed by right heart catheterization in a patient with stable RA where cessation of LFN and PAH therapy with bosentan plus sildenafil resulted in recovery of severe pulmonary hypertension [64].

Leflunomide inhibits the production of prostaglandin E2 (PGE2) by direct inhibiting cyclooxygenase-2 (COX-2) [65, 66]. PGE2, a known vasodilator, decreases pulmonary arterial resistance and mediate pulmonary vascular remodeling [67, 68]. Absence of COX-2 and PGE2 may further worsen hypoxia-induced PAH [69]. Based on these mechanisms, possibility of LFN precipitating PAH cannot be ignored and need further exploration.

Pulmonary arterial hypertension exacerbated by Ruxolitinib

Ruxolitinib is a JAK 1- and 2-inhibitor drug used in the treatment of myelofibrosis [70, 71]. Andrew et al. reported the first case of PAH precipitated by Ruxolitinib (RUX) recently in a patient of myelofibrosis [72]. Recent data has demonstrated the role of STAT3 signaling pathway in the pathogenesis of PAH. STAT3 activation causes up regulation of mediators that lead to proliferation and anti-apoptosis of pulmonary arterial smooth muscle. It has been thought that paradoxical activation of STAT3 could occur due to JAK inhibition and if proved, may explain possible explanation of RUX induced worsening PAH [73].

Limitations to knowledge

Even with the current advances and understanding, drug-induced PAH remains a clinical challenge. There are many questions regarding the link between the drug's use and development of PAH. It remains a great challenge to attribute the drug; as PAH is a rare side effect and affects only a small proportion of patients exposed (<1%).

There is lack of data regarding the prognosis of patients with drug-induced PAH. Although in most cases, the histopathology of pulmonary vasculature is similar between drug-induced PAH and idiopathic PAH, the disease course might be different itself. Close interactions between national drug regulatory agencies, and large registries like REVEAL might provide a possible solution to identify new potential drugs that can cause PAH. However, large multicenter studies will be required in future to better document the association between drug use and development of PAH.

In conclusion, drug-induced PAH portends a diagnostic and management dilemma for clinicians that are involved in the care of such patients. While future studies may address the clinical needs, physicians should address and document exposure to all potential drugs (including stimulants such as methamphetamines) during the work-up of PAH. Identification of association between drug use and PAH development may not only help awareness but may also help to prevent the development of this complication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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